

Literatur zum Thema Medizinisches Cannabis und Dronabinol zur Behandlung schwerer Erkrankungen

zusammengestellt von Dr. Joachim Hartinger (Immunologe und Neurobiologe),
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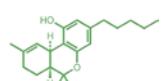
Diese Literaturliste behandelt in vier Fällen Umfrageergebnisse und in geringem Umfang Informationen aus der Tages- und Nachrichtenpresse zum Umfeld der THC Pharm GmbH The Health Concept und der Herstellung von Dronabinol, sowie dem sozialen-politischen Umfeld von Dronabinol bzw. medizinisch genutztem Cannabis. Ansonsten finden sich – bis auf drei Ausnahmen – humane klinische Daten. Ergebnisse von Tierversuchen und in vitro-Experimenten finden sich höchstens als Co-Daten hauptsächlich in Reviews, und auch Effekte von anderen synthetischen Cannabinoiden als Dronabinol und/oder Cannabidiol sowie von Endocannabinoiden sind (wegen des Umfangs) ebenfalls nur in Ausnahmefällen als Zusatzdaten enthalten – auch wenn gerade diese Daten wichtige Informationen zum biologischen Wirkmechanismus und möglichen Gefährdungspotential liefern.

Literatur zum hedonistischen Freizeit-Konsum von Cannabisprodukten wird ebenso nur am Rande und den hier besprochenen, medizinischen Bedarf betreffend, mit angegeben. **Hervorhebungen** und **Einschübe** wurden durch mich vorgenommen.

Aufgeführt sind Literaturzitate aus Medline (Pubmed), ScienceDirect und Deutsche Nationalbibliothek Frankfurt. Leider fehlt aus finanziellen Gründen noch eine größere Menge an relevanter Literatur: die vom Deutschen Institut für Medizinische Dokumentation und Information [DIMDI] (ab 2003) und die vom Fachinformationszentrum Karlsruhe (komplett) gelistet ist.

Die Qualität der meisten Veröffentlichungen lässt sich an der Positionierung im ISI Science Citation Index und daran, dass fast alle peer-reviewed sind, auch ohne medizinische Fach-Ausbildung überprüfen.

Ein Abhängigkeitspotential durch medizinischen Gebrauch von Dronabinol, Cannabis oder Marihuana scheint, nach Suchen auf Deutsch, Englisch und Französisch (beim Menschen) nicht zu existieren. Deswegen konnte ich dazu auch keine Zitate aufführen.



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(1995) "Deglamorising Cannabis." [Editorial] *Lancet* **346** (8985): 1241.

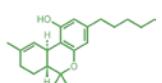
The smoking of cannabis, even long term, is not harmful to health. Yet this widely-used substance is illegal just about everywhere. There have been numerous calls over the years for the legalisation, or at least decriminalisation, of soft drugs, among which cannabis remains the most popular with all social groups. In this highly contentious area, the Dutch attitude has been often mentioned as the voice of sanity. In the Netherlands, customers of coffee shops can buy up to 30 g of cannabis for about 10 pounds (\$15) although the drug is technically illegal. The shops are not allowed to advertise, or to sell cannabis to individuals aged under 16 years.

Prominent among those currently calling for legislative reform -- and going further by making constructive proposals -- are police chiefs and city medical officers, people who know only too well that the existing policies in most countries are ineffective and unworkable.

Meanwhile, politicians have largely remained silent, seemingly afraid of offending powerful segments of the electorate or merely of being perceived as weak in the face of rising crime figures. When the occasional politician raises her head above the parapet -- as the British opposition MP Clare Short did recently in calling for a fresh debate on decriminalisation of cannabis -- the response is tediously predictable: widespread condemnation from political colleagues and overwhelming support from those who have to cope with the end result of political inertia.

In the case of Ms. Short, not only was she speedily reprimanded by the party leader, but also party officials claimed that their non-legalisation stance was entirely logical since legalisation of cannabis would "increase the supply, reduce the price, and increase the usage". According to a Home Office report earlier this year, the number of people taking cannabis has doubled in a decade -- without any help from "liberal" measures. Perhaps the politicians' real fear was that freedom to use soft drugs would automatically progress to increased use of substances such as cocaine and heroin. If so, they must have overlooked the recent Dutch government review which pointed out that decriminalisation of possession of soft drugs has not led to a rise in the use of hard drugs.

If the Dutch approach is so successful, why are changes afoot in The Hague to tighten up that country's drug policy? First Amsterdam's mayor proposed closing down half the city's coffee shops that sell cannabis, and in doing so he rejected a report by his health department in favour of legalisation of soft drugs. Then the Dutch government, which had made an election promise to legalise cannabis, last month issued a discussion paper which mirrored the Amsterdam plan. If, as expected, the Dutch parliament agrees the latest proposals, half the country's 4000 cannabis-selling coffee shops will close and the amount that can be sold to an individual will be cut to 5 g. Since the government's own review provides no ammunition for such a change in policy, the real reason behind the new measures must lie elsewhere. One need look no further than the Netherlands' neighbours and co-signatories of the Schengen agreement, which introduced a border-free zone between the Netherlands, France, Germany, Spain, Luxembourg, and Belgium. When France, in particular, threatened to end the agreement, claiming that the Netherlands was the major supplier of Europe's drugs, some action had to be taken and the coffee shops became the scapegoat.



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Leaving politics aside, where is the harm in decriminalising cannabis? There is none to the health of the consumers, and the criminal fraternity who depend for their succour on prohibition would hate it. But decriminalisation of possession does not go far enough in our view. That has to be accompanied by controls on source, distribution, and advertising, much as happens with tobacco. A system, in fact, remarkably close to the existing one in Dutch coffee shops. Cannabis has become a political football, and one that governments continually duck. Like footballs, however, it bounces back. Sooner or later politicians will have to stop running scared and address the evidence: cannabis per se is not a hazard to society but driving it further underground may well be.

(1999) "Cannabis: When will it become a medicine?" Pharmaceutical Journal **263** (7068): 681-682.

(1999) "THC for Tourette's syndrome." Harvard Mental Health Letters **16** (5): 6.

(2001) "Marihuana auf Rezept. " Hanf! Special – Gesund mit Hanf **08/2001**: 75.

Dr. Christian Steup erklärt, was Patienten und Ärzte über die Verordnung von Dronabinol wissen sollten. Ein querschnittgelähmter Biochemiker leidet unter auftretenden Spasmen. Zur Linderung seiner Beschwerden nimmt er Cannabis und macht positive Erfahrungen. Er erzählt dies seinen Freunden. So entsteht die Idee, Dronabinol zu synthetisieren und als Rezeptur auf den Markt zu bringen. 1996 ist es dann soweit. Die Frankfurter THC-Pharm GmbH wird gegründet. Unternehmensziel ist die legale Erforschung und Bereitstellung von dringend benötigten Medikamenten aus Cannabis und anderen Rohstoffen für eine Vielzahl von medizinischen Indikationen.

(2001) "Ratschläge hinter verschlossenen Türen." Der Standard **99** (13.02.01).

Cannabis gegen Schmerzen

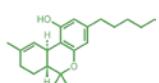
Frankfurt/Main - Hinter geschlossenen Praxistüren geben Schmerztherapeuten ihren Patienten bisweilen ungeheuerliche Ratschläge: "Fahren Sie nach Holland und kaufen Sie sich Haschisch oder Marihuana - und bitte nicht nur ein paar Gramm", rät so mancher Kollege, wie Mediziner zugeben. "Es gibt chronische Schmerzpatienten, bei denen ist Cannabis wirksamer als alles andere", sagt Gerhard Müller-Schwefe über den Einsatz von Cannabis-Produkten in der Medizin. Er ist Tagungsleiter des "Deutschen Schmerztags", der am 15. März in Frankfurt beginnt.

Die Nutzer sind chronische Schmerzpatienten, die auf Grund ihrer Krebserkrankung permanent erbrechen müssen, und Multiple-Sklerose-Patienten. Aber auch bei Epileptikern, Spastikern oder Menschen mit Psychosen habe man "durchweg gute Erfahrungen gemacht", sagt Müller-Schwefe.

Die deutsche Bundesregierung steht dem Einsatz von Cannabis in der Medizin grundsätzlich positiv gegenüber: "In Deutschland steht dem kontrollierten Einsatz als Arzneimittel nichts mehr im Wege", sagt die Drogenbeauftragte Marion Caspers-Merk.

Die Möglichkeiten

Wer seine Schmerzen mit den seit Alters her bekannten Wirkstoffen der Hanfpflanze lindern will, hat drei Möglichkeiten: Illegal die Droge beschaffen und



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rauchen, legal synthetische Nachahmer-Produkte aus dem Ausland bestellen - oder die Dienste einer kleinen Firma in Frankfurt nutzen.

THC Pharm spielt die Verbote, Verordnungen und Verfahren um den Schmerz stillenden Hanf gegeneinander aus. Die Firma arbeitet mit Faserhanf, der nur geringe Anteile des Schmerz stillenden Wirkstoffs enthält und daher nicht dem Betäubungsmittelgesetz unterliegt. Aus ihm gewinnen die Chemiker den Wirkstoff THC oder Dronabinol, der seit 1998 "verkehrsfähig" ist und damit vom Arzt verschrieben werden darf.

Endprodukt aus der Apotheke

THC Pharm liefert diese Grundsubstanz an rund 100 Apotheken in Deutschland - zu einem Viertel des Preises, den die Importprodukte kosten. Dort erst entsteht das Endprodukt: Kapseln zum Schlucken oder Tropfen zum Inhalieren.

"Das Verfahren ist völlig legal, solange die Abgabe-Menge nicht 100 Packungen pro Tag überschreitet", erläutert THC-Pharm-Chef Christian Steup seine nach eigenen Angaben deutschlandweit einmalige Geschäftsidee. Sie war aus der Not geboren: Ein querschnittsgelähmter Freund bat den studierten Apotheker Steup um Hilfe bei der möglichst legalen Cannabis-Beschaffung. Seither gehört das Arzneimittelgesetz zu Steups Lieblingslektüre.

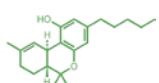
(2002) "Cannabinoide: Tetrahydrocannabinol zur Therapie chronischer Schmerzen?" Medizinische Monatsschrift für Pharmazeuten **25** (3): 97.

Cannabis wurde bereits im 19. Jahrhundert auch zur Therapie der Migräne oder von neuropathischen Schmerzen eingesetzt. In den USA ist schon seit längerem Dronabinol (synthetisch hergestelltes Δ-9-Tetrahydrocannabinol) im Handel, in Deutschland ist es als Rezepturstoffsubstanz verfügbar. Einsatzgebiete sind die Behandlung von Übelkeit und Appetitlosigkeit bei Chemotherapie.

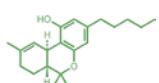
(2003) "Synthetics Cannabis hilft bei Neuropathien." Deutsche Medizinische Wochenschrift **128** (45): 2350.

(2003) "Cannabis-based medicines--GW pharmaceuticals: high CBD, high THC, medicinal cannabis--GW Pharmaceuticals. THC:CBD." Drugs in R & D **4** (5): 306-309.

GW Pharmaceuticals is undertaking a major research programme in the UK to develop and market distinct cannabis-based prescription medicines [THC:CBD, High THC, High CBD] in a range of medical conditions. The cannabis for this programme is grown in a secret location in the UK. It is expected that the product will be marketed in the US in late 2003. GW's cannabis-based products include selected phytocannabinoids from cannabis plants, including Δ-9 tetrahydrocannabinol (THC) and cannabidiol (CBD). The company is investigating their use in three delivery systems, including sublingual spray, sublingual tablet and inhaled (but not smoked) dosage forms. The technology is protected by patent applications. Four different formulations are currently being investigated, including High THC, THC:CBD (narrow ratio), THC:CBD (broad ratio) and High CBD. GW is also developing a specialist security technology that will be incorporated in all its drug delivery systems. This technology allows for the recording and remote monitoring of patient usage to prevent any potential abuse of its cannabis-based medicines.



GW plans to enter into agreements with other companies following phase III development, to secure the best commercialisation terms for its cannabis-based medicines. In June 2003, GW announced that exclusive commercialisation rights for the drug in the UK had been licensed to Bayer AG. The drug will be marketed under the Sativex brand name. This agreement also provides Bayer with an option to expand their license to include the European Union and certain world markets. GW was granted a clinical trial exemption certificate by the Medicines Control Agency to conduct clinical studies with cannabis-based medicines in the UK. The exemption includes investigations in the relief of pain of neurological origin and defects of neurological function in the following indications: multiple sclerosis (MS), spinal cord injury, peripheral nerve injury, central nervous system damage, neuroinvasive cancer, dystonias, cerebral vascular accident and spina bifida, as well as for the relief of pain and inflammation in rheumatoid arthritis and also pain relief in brachial plexus injury. The UK Government stated that it would be willing to amend the Misuse of Drugs Act 1971 to permit the introduction of a cannabis-based medicine. GW stated in its 2002 Annual Report that it was currently conducting five phase III trials of its cannabis derivatives, including a double-blind, placebo-controlled trial with a sublingual spray containing High THC in more than 100 patients with cancer pain in the UK. Also included is a phase III trial of THC:CBD (narrow ratio) being conducted in patients with severe pain due to brachial plexus injury, as are two more phase III trials of THC:CBD (narrow ratio) targeting spasticity and bladder dysfunction in multiple sclerosis patients. Another phase III trial of THC:CBD (narrow ratio) in patients with spinal cord injury is also being conducted. Results from the trials are expected during 2003. Three additional trials are also in the early stages of planning. These trials include a phase I trial of THC:CBD (broad ratio) in patients with inflammatory bowel disease, a phase I trial of High CBD in patients with psychotic disorders such as schizophrenia, and a preclinical trial of High CBD in various CNS disorders (including epilepsy, stroke and head injury). GW Pharmaceuticals submitted an application for approval of cannabis-based medicines to UK regulatory authorities in March 2003. Originally GW hoped to market cannabis-based prescription medicines by 2004, but is now planning for a launch in the UK towards the end of 2003. Several trials for GW's cannabis derivatives have also been completed, including four randomised, double-blind, placebo-controlled phase III clinical trials conducted in the UK. The trials were initiated by GW in April 2002, to investigate the use of a sublingual spray containing THC:CBD (narrow ratio) in the following medical conditions: pain in spinal cord injury, pain and sleep in MS and spinal cord injury, neuropathic pain in MS and general neuropathic pain (presented as allodynia). Results from these trials show that THC:CBD (narrow ratio) caused statistically significant reductions in neuropathic pain in patients with MS and other conditions. In addition, improvements in other MS symptoms were observed as well. Phase II studies of THC:CBD (narrow ratio) have also been completed in patients with MS, spinal cord injury, neuropathic pain and a small number of patients with peripheral neuropathy secondary to diabetes mellitus or AIDS. A phase II trial of THC:CBD (broad ratio) has also been completed in a small number of patients with rheumatoid arthritis, as has a trial of High CBD in patients with neurogenic symptoms. A phase II trial has also been evaluated with High THC



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in small numbers of patients for the treatment of perioperative pain. The phase II trials provided positive results and confirmed an excellent safety profile for cannabis-based medicines. GW Pharmaceuticals received an IND approval to commence phase II clinical trials in Canada in patients with chronic pain, multiple sclerosis and spinal cord injury in 2002. Following meetings with the US FDA, Drug Enforcement Agency (DEA), the Office for National Drug Control Policy, and National Institute for Drug Abuse, GW was granted an import license from the DEA and has imported its first cannabis extracts into the US. Preclinical research with these extracts in the US is ongoing.

(2005) "Von der „Einstiegsdroge“ zum Arzneimittel – GC/MS: Das ungewöhnliche Produkt eines ungewöhnlichen Unternehmens." Shimadzu News 1/2005: 15-17.

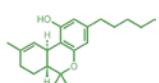
Das Unternehmen THC Pharm ist europaweit der erste Hersteller von Dronabinol (THC) und Cannabidiol (CBD), den krampflösenden und schmerzstillenden Hauptwirkstoffen der Cannabispflanze (Hanf). Diese Wirkstoffe sind auf Betäubungsmittelrezept erhältlich und werden immer häufiger bei der Bekämpfung von Spastiken, Schmerzen, Übelkeit oder Appetitlosigkeit eingesetzt. Die Reinheits- und Qualitätskontrolle der Produkte erfolgt auf GC/MS-Systemen von Shimadzu.

1996 wurde das Frankfurter Unternehmen THC Pharm gegründet. Es entstand aus einer Patienteninitiative von vier befreundeten Gesellschaftern. Sie wollte Patienten, die teilweise schon gute therapeutische Erfahrungen mit illegal konsumiertem Cannabis gemacht hatten, den Wirkstoff legal, gut dosierbar und in pharmazeutisch besserer Qualität zugänglich machen. Ein Unterfangen, das zunächst im Umfeld einer polemisch geführten Drogendebatte enorme Widerstände seitens Staatsanwaltschaft und Behörden hervorrief, obwohl schon damals ein vergleichbares, wenn auch sehr teures Produkt auf Cannabinoid-Basis in den USA existierte. Dass sämtliche Hindernisse nach und nach überwunden wurden, lag nicht zuletzt an der besonderen Motivation der Gesellschafter, zu denen Dr. Joachim Hartinger gehört, nach einem Autounfall querschnittgelähmt.

Geschichte des Cannabis

Der Hanf ist als Kultur- bzw. Nutzpflanze schon seit vielen Jahrhunderten bekannt. Bereits im 4. Jahrhundert v. Chr. wurde Hanf in China kultiviert, weil sich die faserige Pflanze hervorragend zur Herstellung von Papier, Textilien und Seilen eignet. In dieser Funktion erlebte die Pflanze auch eine Hochzeit in Europa – u.a. als Hauptlieferant für die bei der Schifffahrt benötigten Seile und Segel. Nicht nur die alte Chinesische Medizin, sondern auch die Ägypter, Assyrer und Inder wussten um die medizinische Wirksamkeit des Hanfs. Er wurde vorwiegend als Schmerz- und Entspannungsmittel, aber auch bei Appetitlosigkeit und Unterleibsbeschwerden verabreicht. Bis heute spielt der Hanf nicht zuletzt auf Grund seiner vielfältigen therapeutischen Anwendungsmöglichkeiten eine wichtige Rolle in der Ayurvedischen Medizin. Dagegen wurde der medizinische Nutzen des Hanfs in Europa erst im 19. Jh. bekannt. Bald erschien eine Reihe von Schmerztabletten auf Hanfbasis. Nach dem Zweiten Weltkrieg wurde die bekannte Heilpflanze allmählich von neuen patentrechtlich geschützten Schmerzmitteln vom Markt verdrängt. Heutzutage ist die Verwendung der Pflanze oder deren Bestandteile zur Selbstmedikation oder zu Genusszwecken verboten.

In den letzten Jahren erleben jedoch medizinische Forschungsprojekte mit



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Cannabinoiden auf Grund ihrer guten Verträglichkeit und ihres geringen Suchtpotenzials eine weltweite Renaissance. Dabei spielt sicher eine Rolle, dass die Diskussion über den medizinischen Nutzen von Cannabis inzwischen auf einer streng sachlichen Ebene geführt wird. Allerdings ist man noch nicht soweit wie bei den Opiaten, bei denen wohl kaum Assoziationen von Opiumpfeifen oder Heroinspritzen geweckt werden.

Wirkung und Einsatzgebiete für Dronabinol

Gut belegt sind die muskelrelaxierende, appetitanregende, übelkeitshemmende und schmerzstillende Wirkung von Cannabisprodukten. Hinzu kommen beruhigende, stimmungsaufhellende, Bronchien erweiternde und Augeninnendruck senkende Effekte, die in weiteren Studien untersucht werden. In den meisten Einsatzbereichen kommen mehrere dieser Wirkungen zugleich zum Tragen.

Seit 1985 ist in den USA ein Cannabis-Präparat unter dem Handelsnamen Marinol zugelassen. Es wird zur Behandlung von Patienten eingesetzt, die unter chemotherapiebedingter Übelkeit und Erbrechen leiden und die auf eine Standardtherapie nicht ansprechen. Vor einigen Jahren kam als weitere erlaubte Indikation die Behandlung von Appetitlosigkeit bei AIDS-Patienten hinzu. Der Import des vollsynthetischen Marinols aus den USA benötigt jedoch Zeit und ist teuer. Zudem ist das Medikament nur als Tablette verfügbar – ein gravierendes Hindernis für schwerkranke Patienten, die oft unter Übelkeit und Erbrechen oder massiven Schluckbeschwerden leiden.

Standardisierung des Wirkstoffanteils

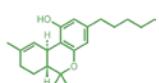
Für die Gründer von THC Pharm war zunächst die schmerzlindernde und krampflösende Wirkung des Dronabinols bedeutend, da sie dem querschnittsgelähmten Dr. Hartinger erlaubt, ein „normales“ Leben zu führen und seine wissenschaftlichen Forschungen weiter zu betreiben. Zudem profitieren austherapierte Schmerzpatienten, Patienten mit Multipler Sklerose und querschnittsgelähmte Patienten von der Substanz, die bei vielen eine signifikante Besserung der Lebensqualität und Mobilität bewirkte – eine Erfahrung, die viele Patienten auch schon mit dem illegalen Cannabis gemacht hatten. So schätzen Experten, dass sich etwa jeder dritte schwerkranke MS- und Querschnittspatient in der Rehabilitation mit illegalen Cannabisprodukten therapiert.

Allerdings ist dieser Weg durch das Verbot von Cannabis sehr erschwert und die Patienten, die auf die Selbstmedikation angewiesen waren, mussten sich die Hanfprodukte auf dem Schwarzmarkt „besorgen“.

Das Hauptproblem mit Produkten vom Schwarzmarkt liegt nicht nur in der Illegalität, sondern auch in der schlechten Dosierbarkeit, da der Wirkstoffanteil des illegal gehandelten Krauts sehr unterschiedlich ist. Für eine sinnvolle Medikation muss der Wirkstoffanteil standardisiert werden können. Es versteht sich von selbst, dass der Schwarzmarkt auch kaum die pharmazeutisch wesentlichen Kriterien, wie Schadstofffreiheit, Stabilität und garantierte gleich bleibende Qualität erfüllen kann.

GC/MS identifiziert Einzelkomponenten

Nach der Unternehmensgründung 1996 entwickelte THC Pharm ein Verfahren, um aus Faserhanf halbsynthetisches THC (Dronabinol) zu gewinnen. Der Anbau von Faserhanf ist gesetzlich gesehen unproblematisch, da diese Hanfart nur eine geringe Menge des psychoaktiven THC und eine bis zu zehnfach höhere Konzentration des kaum psychoaktiven Cannabidiols



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enthält. Dieses Cannabidiol lässt sich chemisch in 99 % reines THC umwandeln.

Die Reinheitskontrollen für die ersten Versuche wurden zunächst auf einem Gas-Chromatographen mit FID durchgeführt. Dabei stellte sich das Problem, dass es keine Standards zur Identifizierung der einzelnen Komponenten des Reaktionsgemisches gab. So wurde ein gebrauchtes GCMS-QP-5000 (Gas-Chromatograph/Massenspektrometer) von Shimadzu angeschafft, mit dessen Hilfe anhand von Massenspektraten die einzelnen Komponenten des Reaktionsgemisches sicher identifiziert werden konnten. Dieses Gerät ist noch immer in der Qualitätskontrolle tätig.

Juli 2000: Genehmigung und Zulassung

Somit stand das Synthese- und QS-Verfahren. Doch ein Antrag auf Erlaubnis zur Herstellung eines Cannabisextraktes wurde 1997 abgelehnt. Anfang 1998 wurde Dronabinol in Deutschland als Betäubungsmittel verschreibungsfähig. Da es Apotheken erlaubt ist, in begrenztem Umfang Arzneimittel selber herzustellen, zog der Pharmazeut und Mediziner Christian Steup mit seinen Apparaturen zu einem befreundeten Apotheker in die Frankfurter Bock-Apotheke, um dort nach seinem Verfahren Dronabinol herzustellen und gegen BTM-Rezept auszugeben.

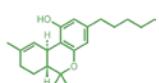
Im Juli 2000 bekam THC Pharm die Genehmigung nach Betäubungsmittelgesetz, den Wirkstoff Dronabinol bundesweit an Apotheken sowie auch an Apotheken in Österreich und in der Schweiz zu vertreiben. Inzwischen besitzt THC Pharm nicht nur eine Genehmigung für die Herstellung eines standardisierten Cannabisextraktes, sondern plant auch die Zulassung eines Fertigarzneimittels auf Cannabis-Basis.

Das anfangs geringe Interesse der pharmazeutischen Industrie an der Entwicklung von cannabishaltigen Handelspräparaten hat sich nachhaltig gewandelt. Neben dem Erscheinen von „Me too“-Produkten haben die Wiedereinführung von Cannabispräparaten durch THC Pharm und aktuelle Forschungsergebnisse des Münchener Max-Planck-Instituts zu dem körpereigenen und mit Cannabis verwandten Anandamidsystem eine ganz neue Wirkstoffklasse in den Fokus der Mediziner gerückt. Das pharmakologische Potenzial dieser Wirkstoffklasse ist bei weitem noch nicht abschätzbar.

(2005) "THC Pharm GmbH erhält Patent für Dronabinol-Herstellung / Herstellung von synthetischen Cannabinoiden für 2005 geplant." MedKolleg 2005-03-10.

Die THC Pharm GmbH hat den Erhalt des Patentes für die Herstellung von halbsynthetischem Dronabinol, dem medizinischen Hauptwirkstoff der Cannabispflanze, am Rande des Deutschen Schmerztages bekannt gegeben. Damit sichert sich die aus einer Patienteninitiative hervorgegangene Firma ihren Qualitätsvorsprung im Markt. Seit 1998 produziert und vertreibt die in Frankfurt am Main ansässige Firma Dronabinol als Rezeptursubstanz in Deutschland. Eingesetzt werden die vom Apotheker herzustellenden Tropfen und Kapseln als nebenwirkungsarme Alternative zur Bekämpfung von Spastiken, Schmerzen, Übelkeit oder Appetitlosigkeit. Weitere Cannabinoide befinden sich derzeit in der Testphase.

Das patentierte Herstellungsverfahren erlaubt nun, Dronabinol aus Faserhanf in bisher einzigartiger Qualität und Reinheit herzustellen. "Im Gegensatz zu den geforderten 95 Prozent Wirkstoffgehalt, können wir nun 99 prozentiges



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Dronabinol herstellen, ein deutliches Plus an Sicherheit für Ärzte, Apotheker und Patienten", so Christian Steup, Laborleiter der auch in andere EU Länder exportierenden Firma.

Zusätzlich plant die seit 1996 bestehende Firma die Herstellung von vollsynthetischem Dronabinol, um der zu erwartenden Nachfrage besonders aus dem Ausland nachkommen zu können. Noch in diesem Jahr wird die Zulassung von Medikamenten auf Cannabisbasis gegen Multiple Sklerose in Kanada durch einen britischen Mitbewerber erwartet. Dadurch verspricht sich das als Vorreiter der Cannabismedizin geltende Unternehmen auch positive Effekte für den deutschen Markt. "Mit der Zulassung von cannabishaltigen Medikamenten im Ausland, wird sich voraussichtlich auch in Deutschland die Verschreibungssituation verbessern", so Holger Rönitz, Geschäftsführer der THC-Pharm GmbH. Derzeit besteht noch keine einheitliche Regelung über die Kostenerstattung durch die gesetzliche Krankenkasse.

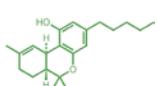
Unter www.thc-pharm.de steht alles Wissenswerte über Indikationen, Anwendungshinweise und Verschreibungsmöglichkeiten des Hauptwirkstoffes der Cannabispflanze. Die betäubungsmittelrechtlich relevanten Seiten sind über DocCheck Passwort-geschützt.

(2007) "Hier wird das THC gemacht." HanfBlatt 102.

Im beschaulichen Frankfurter Stadtteil Oberrad am Main, wo Gartenbaubetriebe die Kräuter für "Grüne Soße" sprießen lassen, feiert ein außergewöhnliches mittelständisches Unternehmen sein 10jähriges Bestehen: Die THC-Pharm (The Health Concept) GmbH. Fünf befreundete Gesellschafter hatten das Unternehmen 1996 aus einer Patienteninitiative heraus gegründet um Schwerkranken, insbesondere als austherapiert geltenden Schmerzpatienten Δ-9-Tetrahydrocannabinol (THC) auf legale Weise verfügbar zu machen. Durch die Änderung des Betäubungsmittelgesetzes (BtmG) im Jahre 1998 wurde es Ärzten möglich Δ-9-THC als Medikament zu verschreiben. Im gleichen Jahr konnte Christian Steup, der Hauschemiker von THC-Pharm, erstmals in einer Apotheke Δ-9-THC als Rezeptursubstanz herstellen. Dank anhaltendem Engagement und guter Öffentlichkeitsarbeit, der Geschäftsführer Holger Rönitz arbeitete einst als Sprecher für Greenpeace, hat THC-Pharm heute 17 MitarbeiterInnen, macht einen Umsatz im Millionenbereich und versorgt durch den Großhandel über etwa 2000 Apotheken mehrere Tausend Patienten mit Medikamenten auf Hanfbasis.

Das mittlerweile zu bemerkenswerten 99,5% reine Δ-9-THC, das hier in Oberrad im Labor teilsynthetisch hergestellt wird, wird unter dem Namen "Dronabinol" als Rezeptursubstanz vertrieben. Als Ausgangsmaterial für die Synthese wird in Hessen biologisch angebauter Hanf zugelassener Faserhanfsorten verwendet. Die getrockneten Blütenstände inklusive Samen und Stengeln werden mit einem lipophilen Lösungsmittel extrahiert. Aus diesem Extrakt wird als weiße kristallinische Substanz Cannabidiol (CBD) abgeschieden. Die Ausbeute liegt dabei bezogen auf das allerdings relativ kostengünstige Ausgangsmaterial im Promillebereich. Das CBD wird nun auf chemischem Wege mittels Isomerisierung in das bei Zimmertemperatur feste und im Idealfall wasserklare Δ-9-THC umgewandelt.

Es muss vor Zersetzung im Kontakt mit der Luft geschützt werden. Deshalb wird es im erwärmteten Zustand auf Spritzen aufgezogen und zur Sicherheit im



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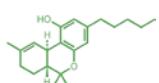
dunklen Kühlschrank aufbewahrt. So ist es relativ lange haltbar. Durch Luftkontakt verfärbt es sich an der Kontaktfläche erst rosaviolett, dann hin zu braun. Bei der Zersetzung entsteht das in reinem Zustand als weiße Kristalle dem CBD optisch ähnliche Cannabinol (CBN). CBN weist keine nennenswerte mit dem Δ -9-THC vergleichbare Psychoaktivität mehr auf, wurde aber in Zusammenhang mit leicht unangenehmen Nebenwirkungen wie Kopfschmerzen gebracht. Interessanterweise ist das Δ -9-THC auch in äthanolischer Lösung luftabgeschlossen aufbewahrt ohne allzu große Verluste lange haltbar. Wird es jedoch in Ölen gelöst, beschränkt sich die Haltbarkeit auf einige Monate bei schließlich vollständiger Zersetzung.

Man mag sich fragen, warum THC-Pharm diesen kompliziert anmutenden Weg zur Gewinnung des nach allen bisherigen Kenntnissen mit Abstand bedeutenden Hanfwerkstoffes, dem Δ -9-THC, geht. Dieses erklärt sich aus der komplizierten Rechtslage unter den Bedingungen des real existierenden BtmGs. Das gestattet den Anbau THC-reichen Hanfes nämlich allenfalls für wissenschaftliche Zwecke, nicht jedoch zur Herstellung pharmazeutischer Präparate. Nebenbei bemerkt, wäre die Gewinnung reinen Δ -9-THCs aus an diesem reichen Hanf, wie er beispielsweise für pharmazeutische Zwecke staatlich kontrolliert in den Niederlanden angebaut wird, bei der dortigen Preislage gegenwärtig nicht wesentlich günstiger. In der Schweiz ist gar nur die Verwendung vollsynthetischen Δ -9-THC's (wie im US-Präparat "Marinol") gestattet.

Immer wieder wird kritisch ins Feld geführt, warum man nicht einfach einen standardisierten Extrakt aus psychoaktivem Δ -9-THC-reichem Hanf mit dem gesamten Spektrum der Inhaltsstoffe herstellt. Dies hat neben den erwähnten rechtlichen Gründen noch den, dass die meisten wissenschaftlichen Studien im medizinischen Bereich mit der Reinsubstanz erfolgt sind. Diese wird auch für das Gros der erwünschten Wirkungen verantwortlich gemacht. Die Dronabinol-Patienten legen in erster Linie Wert auf ein legal verschriebenes Präparat zur Linderung ihres Leids und sind nicht unbedingt genussmittelerfahren und so vielleicht auf Hanf fixiert. In Zukunft wäre sicherlich ein breiteres Spektrum an Präparaten wünschenswert.

Ein weiterer die Vermarktung erschwerender Punkt ist, dass nur den Apothekern die Weiterverarbeitung des Δ -9-THCs zu pharmazeutischen Präparaten für den Endverbraucher gestattet ist. Aus diesem Grunde verschickt THC-Pharm seit 2003 Dronabinol-Sets an die Apotheker, die diesen erlauben, den Wirkstoff mit Kakaobutter zu verschmelzen und in Kapseln zu füllen, ihn in Öle (wie Sesamöl) einzubringen oder aufgelöst in 97%igem Alkohol zu einem Inhalat zu verarbeiten. Das bringt zwar den Apotheker im klassischen Sinne wieder auf Trab und gewährt ein frisches Präparat, erhöht aber die Kosten für die Endabgabe erheblich.

Für den Patienten ist der Weg zum Dronabinol immer noch kompliziert. Leider ist es THC-Pharm auf Grund des BtmGs nämlich nicht gestattet, potentielle Patienten über das medizinische Potential von Δ -9-THC direkt zu informieren. Wer meint, sein Leiden könne eventuell durch Δ -9-THC gelindert werden, sollte sich deshalb an den Arzt seines Vertrauens wenden, denn nur Ärzte und Apotheker können entsprechendes Material anfordern. Sie sollten sich nicht scheuen, von dieser Möglichkeit Gebrauch zu machen, zumal THC-Pharm über ein umfangreiches gut sortiertes Archiv verfügt und obendrein seine Homepage laufend mit Daten wissenschaftlicher Studien aktualisiert.



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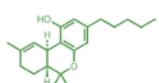
Die Hauptindikationen, bei denen Δ-9-THC auf Grund seiner entspannenden, entkrampfenden, schmerzlindernden, appetitanregenden, übelkeitvertreibenden etc. Wirkungen zur Anwendung gelangt, sind schwerwiegende Krankheitsbilder, wie Spastiken, Querschnittslähmung, neuropathische Schmerzen und Tumorkachexie. Weitere Indikationsfelder sind der Einsatz als Anti-Emetikum bei der Tumortherapie (hier nur über wenige Tage), bei therapieresistenten Schmerzen, auch in Co-Medikation mit Opoiden, bei MS, bei Dystonien und Tourette-Syndrom. Unter anderem bei ALS, COPD, Parkinson und Alzheimer scheint es Potentiale zu geben. Durch die Entdeckung des körpereigenen Cannabinoid-Systems haben sich hier ganz neue wissenschaftliche Perspektiven eröffnet.

Bei regelmäßiger Medikation muss ein Patient, der Dronabinol-Zubereitungen über seinen Arzt per Btm-Rezept verschrieben und von seinem Apotheker zubereitet bekommt, mit monatlichen Kosten von 200-500 Euro rechnen. Theoretisch sollten die Krankenkassen diese Kosten im Einzelfall in den erwähnten schweren Krankheitsfällen übernehmen. Hierfür gibt es aber leider immer noch keine verbindliche Regelung, so dass in der Praxis immer noch mehr als die Hälfte der Patienten die Kosten selbst tragen müssen. Generell würden die Kosten deutlich sinken, wenn sich die in vielen Fällen sinnvolle Anwendung von Δ-9-THC als wertvolles Medikament auf breiterer Ebene durchsetzen würde und auch Fertigpräparate ausgeliefert werden könnten. Dann ist allerdings zu vermuten, dass sich auch größere weniger enthusiastische Unternehmen für diesen Markt interessieren werden.

Dronabinol ist zweifellos das wichtigste Produkt von THC-Pharm. Gelegentlich bestellen Apotheker auch CBD, um es allein oder in Kombination mit Dronabinol einzusetzen. Selbst kaum psychoaktiv, soll es das Wirkspektrum von Δ-9-THC variieren können. Eine medizinisch hochinteressante Substanz ist das im Kolben glasartig erstarrte vollsynthetisch hergestellte Propyl-Δ-9-THC (THCV), das mir der Chemiker zeigt. Es wurde verschiedentlich aus Rauschhanfproben isoliert und stand einst fälschlich im Ruf eines Super-THCs. Jetzt hat man herausgefunden, dass es als starker Antagonist für das körpereigene Cannabinoid Anandamid (nicht aber für THC!) wirkt. Ein anderes für die Forschung attraktives synthetisches Cannabinoid ist das Heptyl-Δ-9-THC. Eine einzige Dosis soll bis zu einer Woche lang wirken können.

Ein Standbein jüngeren Datums in der Firmengeschichte ist die Synthese von möglichst reinen Researchchemikalien für wissenschaftliche Forschungsarbeiten und als Referenzsubstanzen für die Analysen der Landeskriminalämter. Bei den Btm-Substanzen sind extrem hohe Auflagen der Bundesopiumstelle zu erfüllen. Dementsprechend ist der dick gepanzerte Tresorraum des Labors von THC-Pharm a la Fort Knox mit Bewegungsmeldern und einem direktem Draht zur lokalen Polizei gesichert. Hier glitzern hinter Türen, die sich für den neugierigen Journalisten wie einst "Sesam" öffnen, in Erlenmeyerkolben fluffig rosig Lysergid-Kriställchen und schimmern schneeweisse DMT- und gräulich-weiße Psilocybin-Kristalle in kleinen Glasphiolen. Allein der Anblick hat schon was. Einen sinnvollen Einsatz dieser Steinchen der Weisen bei einer entspannteren Gesetzgebung kann man sich da für die Zukunft nur wünschen.

(2011) "Neuropathischer Schmerz: Gerauchtes Cannabis bessert Schmerz und Schlaf." Neuro-Depesche 14 (1/2): 17.



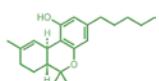
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Abrams, D.I., Ch. Jay, K. Petersen, S. Shade, H. Vizoso, H. Reda, N. Benowitz, and Rowbotham, (2003) "The effects of smoked cannabis in painful peripheral neuropathy and cancer pain refractory to opioids." IACM 2nd Conference on Cannabinoids in Medicine, 12-13 September 2003, Cologne.

Introduction: There is significant evidence that cannabinoids may be involved in the modulation of pain, especially of neuropathic origin. There is also theoretical rationale to suggest that cannabinoids may provide synergistic analgesia with opioids while possibly reducing opioid-related side effects. No information is available on potential pharmacokinetic interactions between cannabinoids and opioids. Methods: We are currently conducting two clinical trials of smoked marijuana in two populations of patients with pain: HIV patients with painful peripheral neuropathy and cancer patients with persistent pain despite an opioid analgesic. Both studies are designed to begin with a 16 patient open-label pilot proof-of-concept phase. If effectiveness is demonstrated in the pilot, the magnitude of the effect allows us to calculate a follow-on randomized, double-blind controlled trial of smoked marijuana vs smoked placebo. In addition to the effect of smoked marijuana on the subjects' chronic clinical pain, we are also evaluating the impact on an experimental heat/capsaicin pain model. Here we report experience with the open label phase of the neuropathy study. Results: Sixteen subjects (14 men, 2 women, mean age 43 years) completed the HIV neuropathy pilot trial. Patients had an average of 6 years of neuropathic pain. In 3 cases the pain was felt to be secondary to HIV alone, in 8 secondary to dideoxynucleoside antiretrovirals and to both in 5. Excellent correlation was seen between the response to smoking in the effect on both the chronic neuropathic and the acute experimental pain model over a six-hour period. Overall 10 of the 16 participants experienced a greater than 30% reduction in their neuropathic pain after seven days. This allowed us to proceed with our currently enrolling randomized placebo-controlled trial with a target sample size of 50 subjects. Additional controlled trials of smoked marijuana for HIV peripheral neuropathy are being conducted by other University of California Center for Medicinal Cannabis Research investigators. Conclusion: Preliminary results from a small, uncontrolled trial of smoked marijuana in HIV peripheral neuropathy are encouraging. The ongoing randomized trials will better elucidate the role of cannabinoids in this condition. A heat/capsaicin experimental pain model appears to be a good predictor of response to chronic pain. The potential of a beneficial clinical interaction between cannabinoids and opioids requires further study.

Aggarwal, S. K., G.T. Carter, M D. Sullivan, C. ZumBrunnen, R. Morrill and J.D. Mayer (2009) "Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington State." *Journal of Opioid Management* 5 (5): 257-286.

Objectives: This study was conducted to better understand the characteristics of chronic pain patients seeking treatment with medicinal cannabis (MC). Design: Retrospective chart reviews of 139 patients (87 males, median age 47 years; 52 females, median age 48 years); all were legally qualified for MC use in Washington State. Setting: Regional pain clinic staffed by university faculty. Participants: Inclusion criteria: age 18 years and older; having legally



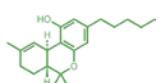
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accessed MC treatment, with valid documentation in their medical records. All data were de-identified. Main Outcome Measures: Records were scored for multiple indicators, including time since initial MC authorization, qualifying condition(s), McGill Pain score, functional status, use of other analgesic modalities, including opioids, and patterns of use over time. Results: Of 139 patients, 15 (11 percent) had prior authorizations for MC before seeking care in this clinic. The sample contained 236.4 patient-years of authorized MC use. Time of authorized use ranged from 11 days to 8.31 years (median of 1.12 years). Most patients were male (63 percent) yet female patients averaged 0.18 years longer authorized use. There were no other gender-specific trends or factors. Most patients ($n = 123$, 88 percent) had more than one pain syndrome present. Myofascial pain syndrome was the most common diagnosis ($n = 114$, 82 percent), followed by neuropathic pain ($n = 89$, 64 percent), discogenic back pain ($n = 72$, 51.7 percent), and osteoarthritis ($n = 37$, 26.6 percent). Other diagnoses included diabetic neuropathy, central pain syndrome, phantom pain, spinal cord injury, fibromyalgia, rheumatoid arthritis, HIV neuropathy, visceral pain, and malignant pain. In 51 (37 percent) patients, there were documented instances of major hurdles related to accessing MC, including prior physicians unwilling to authorize use, legal problems related to MC use, and difficulties in finding an affordable and consistent supply of MC. Conclusions: Data indicate that males and females access MC at approximately the same rate, with similar median authorization times. Although the majority of patient records documented significant symptom alleviation with MC, major treatment access and delivery barriers remain.

Aggarwal, S. K., G.T. Carter, M.D. Sullivan, C. ZumBrunnen, R. Morrill and J.D. Mayer (2009) "Medicinal use of cannabis in the United States: historical perspectives, current trends, and future directions." *Journal of Opioid Management* 5 (3): 153-168.

Cannabis (marijuana) has been used for medicinal purposes for millennia, said to be first noted by the Chinese in c. 2737 BCE. Medicinal cannabis arrived in the United States much later, burdened with a remarkably checkered, yet colorful, history. Despite early robust use, after the advent of opioids and aspirin, medicinal cannabis use faded. Cannabis was criminalized in the United States in 1937, against the advice of the American Medical Association submitted on record to Congress. The past few decades have seen renewed interest in medicinal cannabis, with the National Institutes of Health, the Institute of Medicine, and the American College of Physicians, all issuing statements of support for further research and development. The recently discovered endocannabinoid system has greatly increased our understanding of the actions of exogenous cannabis. Endocannabinoids appear to control pain, muscle tone, mood state, appetite, and inflammation, among other effects. Cannabis contains more than 100 different cannabinoids and has the capacity for analgesia through neuromodulation in ascending and descending pain pathways, neuroprotection, and anti-inflammatory mechanisms. This article reviews the current and emerging research on the physiological mechanisms of cannabinoids and their applications in managing chronic pain, muscle spasticity, cachexia, and other debilitating problems.

Albrecht, H. (2000) Cannabis – Stoff geben. *Die Zeit* 47.



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Die Wissenschaft entdeckt Hanf als Heilmittel. Doch der Durchbruch in Deutschland lässt auf sich warten – weil alle nur ans Kiffen denken. Im Frankfurter Stadtteil Oberrad, wo die Bewohner im Volksmund "Krautäsch" heißen, weil sie leidenschaftlich gern Gemüse anbauen, steht in einem Hinterhof ein schmales Haus. Eine Holzstiege führt von außen zum ersten Stock, die Dachschiefer sind von Efeu überwuchert. Die im Internet annoncierte Postadresse des Hexenhauses stimmt nicht mit der wahren Adresse überein. "Muss ja nicht jeder gleich direkt hierher finden", erklärt Christian Steup das konspirative Verwirrspiel -und lächelt milde. Pakete nimmt seine Mama am anderen Ende der Stadt entgegen.

Der ausgebildete Arzt und Apotheker steht im Untergeschoss der lieblichen Laube, um ihn herum rotieren Glaskolben in Heizschalen, blubbert die Hochvakuumdestillation, wirft ein Massenspektrograf bunte Linien auf einen Computermonitor. In dem High-Tech-Labor mit dem Charme einer Land-WG betreibt Steup mit seinen fünf Mitstreitern die Pharma-Firma THC Pharm The Health Concept, das einzige deutsche Unternehmen, welches aus Cannabis Substanzen für Arzneimittel herstellt.

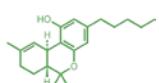
Die Existenz des Kleinstlabors belegt, dass nach jahrzehntelanger Verteufelung die Wissenschaft nun Wirkungen, aber auch Nebenwirkungen des Uraltherapeutikums neu erkundet. In den USA, Großbritannien, Kanada und jüngst auch in Australien haben die Regierungen von Forschern den Nutzen von Cannabis für die Medizin bewerten lassen und sind zu einem eindeutigen Votum gekommen: Der zentrale Wirkstoff des Gewächses, Δ-9-Tetrahydrocannabinol (THC), der bei Kiftern auch das Wohlgefühl erzeugt, ist für die Medizin nützlich. Noch aber ist das verfemte Hippie-Kraut nicht völlig rehabilitiert.

Als Joint geraucht, in Tee gelöst oder unter die Backmischung gemixt, ist Cannabis seit langem als illegale sanfte Droge beliebt. Mit der Dröhnung für Kiffer, die ein Substanzgemisch enthält, hat das Produkt aus dem Frankfurter Hinterhof nur noch entfernt Ähnlichkeit: In der Arznei steckt einzig halb synthetisches THC. Seit Juli hilft es ganz legal Kranken mit Querschnittslähmung oder Multipler Sklerose (MS), Aids- und Krebspatienten. Am Main profitieren rund 100 Menschen schon seit drei Jahren vom Engagement der THC-Pharmazeuten. Denen ist es gelungen, die Droge erst zu synthetisieren und dann durch geschickte Interpretation des Betäubungsmittelgesetzes als Dronabinol in die Apotheken zu bringen. Den Weg wies ein Passus im Arzneimittelgesetz, der Apothekern erlaubt, in geringem Umfang eigene Betäubungsmittel herzustellen.

Zentralküche für die Drogenzubereitung war zunächst die Frankfurter Bock-Apotheke. Schon bald pilgerten Patienten aus über 100 Kilometer Entfernung in die Offizin. Vor allem unter gut organisierten chronisch Kranken, die stets über alle Therapiemöglichkeiten informiert sind, ist schon lange bekannt, dass in Joints Linderung steckt. Ausgemergelte Aids- und Krebspatienten fanden ihren Appetit wieder, und MS-Kranken löste der Stoff die verkrampten Muskeln. Es gibt kaum ein Leiden, bei dem Betroffene den Eigenversuch mit illegalem Marihuana scheut.

Das Telefon wurde abgehört, der Zoll schlich ums Gebäude

Die krampflösende Wirkung war es auch, die Christian Steup auf die Cannabis-Spur brachte. Vor fünf Jahren fragte ein querschnittsgelähmter Biologe beim chemiekundigen Freund an, ob in Deutschland ein THC-



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Medikament gegen die verspannten Muskeln produziert würde. Steup musste verneinen. Kurzerhand nahmen die beiden die Synthese selbst in die Hand. Vorsorglich informierten sie den Frankfurter Oberstaatsanwalt, schnornten bei Pharmaunternehmen abgeschriebene Gerätschaften und entwickelten ein Verfahren, das auf raffinierte Weise mit dem Gesetz vereinbar ist.

Das Betäubungsmittelgesetz verbietet den Anbau von Cannabis sativa, das mehr als 0,3 Prozent der psychoaktiven Substanz THC enthält. Erlaubt ist hingegen der Anbau von THC-armem Faserhanf, aus dem Seile, Hemden, Papier und andere Öko-Utensilien hergestellt werden. In dem politisch und juristisch korrekten Gewächs steckt wenig THC, dafür umso mehr Cannabidiol (CBD), eine natürliche Vorstufe des THC, die aber keinen Rausch beschert. THC Pharm bezieht den Faserhanf von deutschen Bauern, extrahiert das CBD mittels Feuerzeugbenzin und überführt das weiße Pulver dann chemisch in das THC. Dieses wird gereinigt und zu einem blassgelben Harz konzentriert – pures Dronabinol.

Obwohl die THC-Pharmazeuten mit offenen Karten spielten, blieb manchen Behörden die Produktion suspekt. Das Telefon wurde abgehört, der Zoll schlief um das Gebäude.

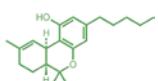
"Zeitweise dachten die, wir würden hier ein Designerdrogenlabor betreiben", sagt Steup und grinst. Die Bundesopiumstelle zierte sich, doch die Sache war legal. Erst im April dieses Jahres erhielt die Firma THC Pharm für das Qualitätsprodukt die Handelsgenehmigung für Europa. Seither darf Steup Dronabinol auch bundesweit über Apotheken vertreiben. Dort wird der Stoff in Kapseln gepresst oder als Tropfen aufbereitet und gegen Betäubungsmittelrezept vom Hausarzt an Patienten abgegeben: 25 Kapseln zu 5 Milligramm für 354,10 Mark.

Das Cannabis-Dilemma schien sanft gelöst, die Versorgung der Kranken gesichert. Aber Pillen, die potenziell euphorisierend sind, müssen in Deutschland offenbar besonders bitter schmecken. Im Fall der Cannabis-Arznei verhindern hohe Kosten zuverlässig die Verbreitung. Bis zu 3000 Mark im Monat bezahlen Patienten aus eigener Tasche für das Hanfprodukt.

Während die Krankenkassen Morphine und Valium bereitwillig bezahlen, erstatten sie Dronabinol nur in ausgewählten Fällen – in der Regel für Anwendungen, für die auch das US-Konkurrenzprodukt Marinol in den USA zugelassen ist. MS-Kranke, welche die Frankfurter Substanz aus der Apotheke beziehen, müssen selbst zahlen – erstattungspflichtig sind nur vom Bundesinstitut für Arzneimittel zugelassene Fertigarzneimittel.

Kranke fürchten, als Kriminelle abgestempelt zu werden

Nicht nur die hohen Kosten verleiden vielen Betroffenen den **THC-Einsatz**. Sie fürchten die vielleicht **bedeutendste Nebenwirkung des Konsums: die Kriminalisierung**. Vor sechs Jahren bekam der 56-jährige MS-Patient Dietmar B. aus Dortmund von einem Freund den Tipp, die nächtlichen Muskelkrämpfe mit Cannabis zu bekämpfen. "Erst wollte ich gar nichts davon wissen", sagte der Patient, "ich treib mich doch nicht auf dem Bahnhof rum und besorge mir das Zeug." Doch er fürchtete die Alternative. Das zugelassene krampflösende Lioresal hatte gravierende Nebenwirkungen wie völlig erschlaffende Muskeln, Verwirrtheit und Blutdruckabfall. Also ließ B. sich etwas Marihuana mitbringen und inhalierte. "Zuerst war die Dosis viel zu hoch." Der gehschwache Rollstuhlfahrer stand auf, kicherte vor sich hin und fühlte sich auch sonst "ziemlich gelöst". Obwohl die Empfindungen angenehm waren, wollte der



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Frührentner "nicht riskieren, abhängig zu werden". Inzwischen hat er die richtige Dosis ermittelt und raucht ab und an mit großem Erfolg vor dem Schlafengehen ein Wasserpfeifchen.

Die Zulassungsbehörden oder verschreibungswilligen Ärzte aber interessiert einzig und allein, ob Dietmar B. die Besserung seines Leidens einem spezifischen pharmakologischen Effekt verdankt. Ärzte würden sich nur auf die neuen Substanzen einlassen, sagt Franjo Grotenhermen, Vorstandsvorsitzender der Internationalen Arbeitsgemeinschaft Cannabis als Medizin (ACM) in Köln, wenn ausreichend wissenschaftliche Erkenntnisse vorlägen.

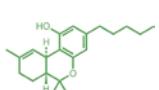
Früher mührte sich die Cannabis-Forschung zumeist, die vermeintliche Einstiegsdroge zu diskreditieren. Einziger Beleg für die Wirkungen der Pflanze waren die Anekdoten experimentierfreudiger Laien. Seit 1996 in dem US-Staat Kalifornien der Marihuana-Konsum zu medizinischen Zwecken im Prinzip erlaubt worden ist – nach einem Dauerzwist mit den Bundesbehörden in Washington –, rauchten sich schätzungsweise 315 000 Patienten ihre Gebresten vom Leib. Nicht weniger als 250 verschiedene Indikationen fand der amerikanische Cannabis-Arzt Tod Mikuriya in einer Umfrage: unter anderem gegen Bluthochdruck, Diabetes, Stottern, Farbenblindheit, Knorpelschäden, nächtliches Zähneknirschen.

Ob Cannabis ein Megaplacebo ist oder die pharmakologischen Wirkungen Problemlöser gewesen waren, blieb noch ungeklärt. Wenn Cannabis-Produkte es zum ernsthaften Arzneimittel bringen wollen, brauchen sie einen wissenschaftlich soliden Beipackzettel: Welche Nebenwirkung muss ein unbedarfter Patient in Kauf nehmen? Welche Dosierungen helfen bei welchen Erkrankungen? Wem sollte abgeraten werden? Ist reines THC während der Schwangerschaft unbedenklich? Ohne wissenschaftliche Abklärung solcher Fragen lässt das deutsche Bundesamt für Arzneimittel den Stoff nicht als Fertigarzneimittel zu.

Immerhin, die Datenlage bessert sich wöchentlich, die 400 Substanzen in der Pflanze geben ihr Geheimnis preis. Seit im Jahre 1992 der israelische Pharmakologe Raphael Mechoulam die Anandamide, eine Art körpereigenes Cannabis, entdeckt hatte, entschlüsselten weltweit Forscher, auf welche Weise die Droge im Körper ihre Wirkung entfaltet. Zwei Cannabinoidrezeptoren wurden gefunden und im Körper und Immunsystem nachgewiesen. Anfang November veröffentlichten beispielsweise neapolitanische Forscher im Fachblatt *Nature*, warum die körpereigenen Anandamide die Bronchien öffnen, und erklärten, auf welchem Wege THC Asthmatikern hilft. Inzwischen sind die biochemischen Zusammenhänge geklärt. Immer mehr Anwendungen sind denkbar: bei Schizophrenie, Hirntumoren, Rheuma, Husten, Brustkrebs, Bluthochdruck und Schlaganfall. Aber auch mehr Nebenwirkungen werden diskutiert: Unfruchtbarkeit und die Entstehung von Krebs durch Hemmung des Immunsystems, Herzinfarkt nach Marihuana-Konsum und bedrohlicher Blutdruckabfall bei Herzkranken.

Dass Lungen- und MS-Patienten völlig ohne gängige Pharmazeutika wie Cortison auskommen, glaubt ohnehin niemand. Aber Cannabis könnte helfen, nebenwirkungsreiche Substanzen einzusparen. Und schließlich: An einem "goldenen Joint", das müssen auch die Skeptiker zugeben, ist noch keiner gestorben. Menschen vertragen extrem hohe Dosen THC.

Bislang war die klinische Abklärung der Fragen in Deutschland kaum möglich,



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weil der Anbau von Drogenhanf nach Betäubungsmittelgesetz strikt untersagt ist. Im letzten Jahr hat sich die Lage etwas entspannt. In Berlin vergleicht das private Institut für onkologische und immunologische Forschung die Wirkung eines Cannabis-Extraktes mit der eines synthetischen THC-Präparates. Allein für die Importgenehmigung der Cannabis-Produkte aus der Schweiz gingen fünf Jahre ins Land. Jetzt testen die Berliner, ob der naturnahe Extrakt so gut oder womöglich besser verträglich ist als reines THC.

Die akribische Beweisführung in Sachen Cannabis zerstreut die Befürchtung, dass ein paar Kranke Rauschorgien auf Rezept abhalten könnten. "Am Anfang hatten wir Probleme, Patienten für unsere Studie zu gewinnen", sagt Martin Schnelle, Versuchsleiter im Berliner Institut. Man brauchte 445 Patienten, aber bis zum Sommer fanden sich nur 40 zum Drogenexperiment ein. Aufgerufen waren Krebskranke mit fortgeschrittener Erkrankung, die drastisch an Gewicht verloren hatten. Die Cannabis-Arzneien sollten den Appetit wieder anregen.

Obgleich genau diese Wirkung in den USA umstritten ist, weiß die wissenschaftliche Gemeinde hierzulande offiziell nichts davon. Also werden die beiden Cannabis-Präparate nicht gegeneinander getestet, sondern jedes für sich gegen ein Placebo. "In einem Krankheitsstadium, in dem es den Patienten sehr schlecht geht", sagt Martin Schnelle, "sind diese kaum bereit, drei Monate möglicherweise ein Placebo zu schlucken."

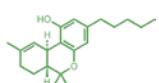
Darf der Staat den Cannabis-Anbau genehmigen?

Das Versuchsprotokoll wurde inzwischen angepasst, die Teilnehmer erhalten sechs Wochen lang das Placebo oder das Original und danach garantiert den wahren Stoff. Seitdem hat sich die Kooperationsbereitschaft gebessert, und Schnelle kann hoffen, dass er die für die Statistik notwendige Patientenzahl in spätestens eineinhalb Jahren beisammen hat. Wenn die Daten überzeugend sind – und daran zweifelt niemand –, ist ein weiterer Schritt auf dem Weg zum erstattungsfähigen Fertigarzneimittel getan, zumindest für die Indikation Appetitsteigerung. Gerüchte kursieren, ein deutsches Unternehmen bereite das millionenteure Zulassungsverfahren bereits vor.

Die MS-Kranken aber haben das Nachsehen. Kein Institut hat die notwendige Forschung für die Anwendung bei MS betrieben. Dabei wäre den Forschern die Unterstützung des Bundesministeriums für Gesundheit (BMG) gewiss. "Wir wollen Cannabis-Arzneimittel", sagt Horst Möller, im BMG zuständig für Drogenfragen, und ergänzt schnell: "aber ordentliche Cannabis-Arzneimittel." Das Arzneimittelgesetz habe nun mal bestimmte Anforderungen, und die müssten erfüllt werden. "Einen Joint für die Gesundheit rauchen ist eine Absurdität an sich", sagt Möller, "ein Joint enthält meines Wissens zehnmal so viel Krebs erregende Stoffe wie eine Zigarette."

Bis die Patienten wirklich ein Fertigarzneimittel mit ordentlichem Beipackzettel in Händen halten, werden Jahre vergehen. In der Zwischenzeit, sagt Franjo Grotenhermen vom Arbeitskreis Cannabis in der Medizin, gäbe es doch vielleicht "verschiedene Modelle, die eine schnelle Erleichterung brächten". So könnten, wie in einigen Staaten der USA, Patienten Ausnahmegenehmigungen für den Cannabis-Selbstanbau erhalten oder das Rauchkraut vom Staat beziehen.

Vor die Wahl gestellt, 50-mal mehr für ein synthetisches Präparat zu bezahlen als für die Rauchware vom Dealer, entscheiden sich viele für den illegalen Weg. Dietmar B. machte bei einem Kuraufenthalt die Erfahrung, dass er nicht



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allein ist. Noch immer hat sich der ehemalige Energietechniker nicht ganz daran gewöhnt, eine im Prinzip strafbare Handlung zu begehen. Als er einen anderen Patienten fragte, was er gegen die Muskelkrämpfe einnehme, zog dieser nur eine Dose mit Marihuana aus der Tasche. Inzwischen weiß B., dass viele sich mit Joints behelfen.

Was aber den kleinen Kräutergarten zum Eigenverzehr angeht, bleibt das BMG hart. "Sie wissen nicht, wie viel Wirkstoff darin ist, was für Schwermetalle oder Insektizide", sagt Horst Möller. Aber ein Zugeständnis macht Möller doch: "Wenn sich das Cannabis-Extrakt als wirksam erweist, dann spricht nichts gegen eine Zulassung des Anbaus von Drogenhanf unter Kontrolle." Zwei Bauern haben schon die Genehmigung beantragt – einer will in einem ehemaligen Luftschutzbunker Pflanzen gedeihen lassen. Am vergangenen Wochenende ließ der Frankfurter Oberstaatsanwalt Harald Körner, Leiter der Zentralstelle für die Betäubungsmittelkriminalität, in einem Gutachten durchblicken, dass auch er die Versorgung von Patienten mit Cannabis für statthaft hält. Möglicher Versorger: Das Stadtgesundheitsamt.

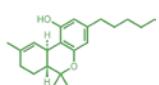
In Großbritannien ist man schon so weit. In einem geheimen Gewächshaus in Südengland baut die britische Firma GW Pharmaceuticals unter strenger Bewachung Drogenhanf bester Qualität an. Kurz vor Anbruch des neuen Millenniums wurde die erste Marihuana-Ernte eingefahren: 5000 Pflanzen, jede 2,5 Meter hoch. Ab Frühjahr erhielten 2000 Patienten Extrakte aus dem Drogenhanf. Geoffrey Guy, Leiter des Pharmaunternehmens, glaubt an den Erfolg: "Möglicherweise werden wir sogar eine spezielle Sorte für Multiple Sklerose oder Epilepsie züchten."

Alsasua del Valle, A. (2006) "Implication of cannabinoids in neurological diseases." Cellular and Molecular Neurobiology **26** (4-6): 579-591.

1. Preparations from Cannabis sativa (marijuana) have been used for many centuries both medicinally and recreationally. 2. Recent advances in the knowledge of its pharmacological and chemical properties in the organism, mainly due to Δ-9-tetrahydrocannabinol, and the physiological roles played by the endocannabinoids have opened up new strategies in the treatment of neurological and psychiatric diseases. 3. Potential therapeutic uses of cannabinoid receptor agonists include the management of spasticity and tremor in multiple sclerosis/spinal cord injury, pain, inflammatory disorders, glaucoma, bronchial asthma, cancer, and vasodilation that accompanies advanced cirrhosis. CB(1) receptor antagonists have therapeutic potential in Parkinson's disease. 4. Dr. Julius Axelrod also contributed in studies on the neuroprotective actions of cannabinoids.

Amtmann, D., P. Weydt, K.L. Johnson, M.P. Jensen, and G.T. Carter (2004) "Survey of cannabis use in patients with amyotrophic lateral sclerosis." American Journal of Hospice and Palliative Care **21** (2): 95-104.

Cannabis (marijuana) has been proposed as treatment for a widening spectrum of medical conditions and has many properties that may be applicable to the management of amyotrophic lateral sclerosis (ALS). This study is the first, anonymous survey of persons with ALS regarding the use of cannabis. There were 131 respondents, 13 of whom reported using cannabis in the last 12 months. Although the small number of people with ALS that reported using cannabis limits the interpretation of the survey findings, the



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results indicate that cannabis may be moderately effective at reducing symptoms of appetite loss, depression, pain, spasticity, and drooling. Cannabis was reported ineffective in reducing difficulties with speech and swallowing, and sexual dysfunction. The longest relief was reported for depression (approximately two to three hours).

Aragona, M., E. Onesti, V. Tomassini, A. Conte, S. Gupta, F. Gilio, P. Pantano, C. Pozzilli, and M. Inghilleri (2009) "Psychopathological and cognitive effects of therapeutic cannabinoids in Multiple Sclerosis: a double-blind, placebo controlled, crossover study." *Clinical Neuropharmacology* 32 (1): 41-47.

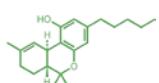
Objectives: To study possible psychopathological symptoms and cognitive deficits, abuse induction, as well as general tolerability and effects on quality of life, fatigue and motor function in cannabis-naïve patients with multiple sclerosis (MS) treated with a free-dose cannabis plant extract (Sativex).

METHODS: In an 8-week, randomized, double-blind, placebo-controlled, parallel group crossover trial, 17 cannabis-naïve patients with MS were assessed at baseline and at the end of the cannabis and placebo phases of the trial (each of 3 weeks) by means of Symptom Checklist-90 Revised, Self-rating Anxiety Scale, Multiple Sclerosis Functional Composite (of which 1 dimension is the Paced Auditory Serial Additional Test that was used to evaluate cognition), Visual Analogue Scale on health-related quality of life, Multiple Sclerosis Impact Scale-29, and Fatigue Severity Scale. Results:

Postplacebo versus postcannabinoid scores showed that no significant differences could be detected on all the variables under study. A significant positive correlation was found between Δ-9-tetrahydrocannabinol blood levels and scores at the General Symptomatic Index and at the "Interpersonal sensitivity," "aggressive behaviour," and "paranoiac tendencies" subscales of the Symptom Checklist-90 Revised. No serious adverse events, abuse tendencies, or direct withdrawal symptoms were reported. Increased desire for Sativex with secondary depression was reported in 1 subject. Conclusions: Cannabinoid treatment did not induce psychopathology and did not impair cognition in cannabis-naïve patients with MS. However, the positive correlation between blood levels of Δ-9-tetrahydrocannabinol and psychopathological scores suggests that at dosages higher than those used in therapeutic settings, interpersonal sensitivity, aggressiveness, and paranoiac features might arise, although greater statistical power would be necessary to confirm this finding.

Ashton, C. H. (1999) "Biomedical benefits of cannabinoids?" *Addiction Biology* 4 (2): 111-126.

Cannabinoids appear to be of therapeutic value as antiemetics, antispasmodics, analgesics and appetite stimulants and may have potential uses in epilepsy, glaucoma and asthma. Scientific evidence for any of these indications, except for antiemetic effects, is extremely sparse and claims for clinical utility are largely based on anecdotal reports. Furthermore, the mechanisms of action of any of the therapeutic effects are unknown. This paper reviews the clinical trials which have been carried out with cannabinoids including Δ-9-tetra-hydrocannabinol (THC) and synthetic cannabinoids such as nabilone and levonantradol, and discusses the advantages and adverse effects of cannabinoids in clinical use. The place of cannabinoids in modern



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medicine remains to be properly evaluated, but present evidence suggests that they could be valuable, particularly as adjuvants, for symptom control in a range of conditions for which standard drugs are not fully satisfactory.

Ashton, H. (2002) "Cannabis or health?" *Current Opinion in Psychiatry* **15** (3): 247-253.

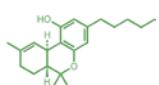
Prevalence of recreational cannabis use has risen in many countries. Users are starting younger, continuing for longer and preferring more potent plant preparations. Such use is likely to increase cannabis-associated risks, which, on present evidence, include vehicle and other accidents, dependence, exacerbation of psychosis, impairment of adolescent development and school performance, respiratory disease and perhaps progression to other illicit drugs. Devising effective control policies is difficult, but perhaps greater efforts should be directed towards reducing prevalence and providing treatment for dependent users. Increased knowledge of the way in which plant cannabinoids interact with endogenous cannabinoid systems has helped to explain some of the adverse effects of cannabis and has also opened the way to therapeutic uses. Pure plant cannabinoids and synthetic analogues have a potential role in the treatment of pain conditions, spastic disorders and in palliative care, and give promise of future benefits in a range of illnesses.

Ashton, J. C. and E.D. Milligan (2008) "Cannabinoids for the treatment of neuropathic pain: clinical evidence." *Current Opinion in Investigational Drugs* **9** (1): 65-75.

Neuropathic pain is a worldwide epidemic that occurs in 3 to 8% of individuals in industrialized countries and is often refractory to existing treatments. Drugs currently available to target neuropathic pain are, at best, moderately effective and include antidepressants, gabapentin, NMDA receptor antagonists, as well as other anticonvulsants, all of which are limited by their adverse-effect profiles. Cannabinoid drugs are emerging as a promising class of drugs to treat neuropathic pain and have been tested for analgesic effects in a range of chronic pain conditions. Data show that cannabinoids are often effective in individuals with refractory pain receiving concomitant analgesic drugs. Clinical studies on cannabinoids for the treatment of neuropathic pain are reviewed, focusing on clinical trials published within the last five years. Data from large, well-controlled studies show that cannabinoids are moderately effective in reducing chronic pain and that side effects are comparable to existing treatments, suggesting that cannabinoids can play a useful role in the management of chronic pain. Like other drugs for neuropathic pain, cannabinoids have a dose titration that is limited by psychoactive side effects. The development of cannabinoid drugs to target neuropathic pain with improved therapeutic ratios will depend upon the development of cannabinoid treatments with reduced psychoactivity.

Azad, S.C. and G. Rammes (2005) "Cannabinoids in anaesthesia and pain therapy." *Current Opinion in Anaesthesiology* **18** (4): 424-427.

Purpose of Review: Cannabinoids have been known for their analgesic, anxiolytic, antiemetic and antispasmodic properties for many centuries. Since an endogenous cannabinoid system has been identified in the past two decades, cannabinoids have also become the focus of interest in western medicine. This review summarizes preclinical and clinical studies on the role of the



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endocannabinoid system and exogenous cannabinoids in anaesthesia and pain management. Recent Findings: It has recently been shown that the endocannabinoid system is involved in the effects of the widely used anaesthetic drug propofol. In terms of nociception, preclinical data suggest that the endocannabinoid system plays an important role in the control of synaptic transmission and synaptic plasticity in pain pathways. In patients, the treatment of acute pain often requires relatively high doses of cannabinoids, which are associated with considerable side-effects such as dizziness and sedation. In contrast, preclinical and clinical data suggest that lower doses of cannabinoids may be effective for the treatment of allodynia and hyperalgesia in neuropathic pain. In multiple sclerosis, cannabinoids have been shown to have beneficial effects on spasticity, pain, tremor and bladder dysfunction.

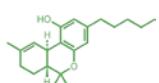
SUMMARY: In general, the results of the very few well-conducted clinical trials often diverge from the highly interesting and promising findings of preclinical studies. Taken together, the most recent preclinical and clinical data suggest that cannabinoids should be applied as low-dose co-analgesics to inhibit neuroplasticity and central sensitization rather than as analgesics in acute pain.

Baker, D., S.J. Jackson and G. Pryce (2007) "Cannabinoid control of neuroinflammation related to multiple sclerosis." *British Journal of Pharmacology* **152** (5): 649-654.

The cannabis plant (*Cannabis sativa*) has been known by many names but the question remains 'Can we call it medicine?' There has been renewed interest in the value of cannabis for the control of neuroinflammatory conditions such as multiple sclerosis, where it has been shown to have some effect on spasticity and pain both experimentally and in clinical trials in humans. However, in addition to symptom control potential, the question remains whether cannabinoids can modify the neuroinflammatory element which drives relapsing neurological attacks and the accumulation of progressive disability. In experimental studies it has been recently shown that synthetic cannabinoids can affect the immune response both indirectly via CB1 receptor-mediated signalling nerve centres controlling the systemic release of immunosuppressive molecules and directly by CB2 receptor-mediated inhibition of lymphocyte and macrophage/microglial cell function. However, these immunosuppressive possibilities that would limit the frequency of relapsing attacks will probably not be realized clinically, following use of medical cannabis, due to dose constraints. However, cannabinoids may still affect the glial response within the damaged central nervous system, which facilitate the slow, neurodegenerative processes that account for progressive neurodegeneration, and therefore may have utility in addition to value of cannabis-related drugs for symptom control.

Baker, D. and G. Pryce (2008) "The endocannabinoid system and multiple sclerosis." *Current Pharmaceutical Design* **14** (23): 2326-2336.

Multiple sclerosis (MS) is a neurodegenerative disease that is characterised by repeated inflammatory/demyelinating events within the central nervous system (CNS). In addition to relapsing-remitting neurological insults, leading to loss of function, patients are often left with residual, troublesome symptoms such as spasticity and pain. These greatly diminish "quality of life" and have



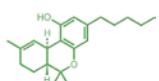
prompted some patients to self-medicate with and perceive benefit from cannabis. Recent advances in cannabinoid biology are beginning to support these anecdotal observations, notably the demonstration that spasticity is tonically regulated by the endogenous cannabinoid system. Recent clinical trials may indeed suggest that cannabis has some potential to relieve, pain, spasms and spasticity in MS. However, because the CB(1) cannabinoid receptor mediates both the positive and adverse effects of cannabis, therapy will invariably be associated with some unwanted, psychoactive effects. In an experimental model of MS, and in MS tissue, there are local perturbations of the endocannabinoid system in lesional areas. Stimulation of endocannabinoid activity in these areas either through increase of synthesis or inhibition of endocannabinoid degradation offers the positive therapeutic potential of the cannabinoid system whilst limiting adverse events by locally targeting the lesion. In addition, CB(1) and CB(2) cannabinoid receptor stimulation may also have anti-inflammatory and neuroprotective potential as the endocannabinoid system controls the level of neurodegeneration that occurs as a result of the inflammatory insults. Therefore cannabinoids may not only offer symptom control but may also slow the neurodegenerative disease progression that ultimately leads to the accumulation of disability.

Baker, D., G. Pryce, G. Giovannoni and A.J. Thompson (2003) "The therapeutic potential of cannabis" *Lancet Neurology* **2** (5): 291-298.

Research of the cannabinoid system has many similarities with that of the opioid system. In both instances, studies into drug-producing plants led to the discovery of an endogenous control system with a central role in neurobiology. Few compounds have had as much positive press from patients as those of the cannabinoid system. While these claims are investigated in disorders such as multiple sclerosis spasticity and pain, basic research is discovering interesting members of this family of compounds that have previously unknown qualities, the most notable of which is the capacity for neuroprotection. Large randomised clinical trials of the better known compounds are in progress. Even if the results of these studies are not as positive as many expect them to be, that we are only just beginning to appreciate the huge therapeutic potential of this family of compounds is clear.

Baker, D., G. Pryce, J.L. Croxford, P. Brown, R.G. Pertwee, J.W. Huffman and L. Layward (2000) "Cannabinoids control spasticity and tremor in a multiple sclerosis model." *Nature* **404** (6773): 84-87.

Chronic relapsing experimental allergic encephalomyelitis (CREAE) is an autoimmune model of multiple sclerosis. Although both these diseases are typified by relapsing-remitting paralytic episodes, after CREAE induction by sensitization to myelin antigens Biozzi ABH mice also develop spasticity and tremor. These symptoms also occur during multiple sclerosis and are difficult to control. This has prompted some patients to find alternative medicines, and to perceive benefit from cannabis use. Although this benefit has been backed up by small clinical studies, mainly with non-quantifiable outcomes, the value of cannabis use in multiple sclerosis remains anecdotal. Here we show that cannabinoid (CB) receptor agonism using R(+)-WIN 55,212, Δ-9-tetrahydrocannabinol, methanandamide and JWH-133 quantitatively ameliorated both tremor and spasticity in diseased mice. The exacerbation of



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these signs after antagonism of the CB1 and CB2 receptors, notably the CB1 receptor, using SR141716A and SR144528 indicate that the endogenous cannabinoid system may be tonically active in the control of tremor and spasticity. This provides a rationale for patients' indications of the therapeutic potential of cannabis in the control of the symptoms of multiple sclerosis, and provides a means of evaluating more selective cannabinoids in the future.

Baker, D., G. Pryce, J.L. Croxford, P. Brown, R.G. Pertwee, A. Makryannis, A. Khanolkar, L. Layward, F. Fezza, T. Bisogno, and V. Di Marzo (2001) "Endocannabinoids control spasticity in a multiple sclerosis model." *FASEB Journal* 15 (2): 300-302.

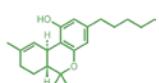
Spasticity is a complicating sign in multiple sclerosis that also develops in a model of chronic relapsing experimental autoimmune encephalomyelitis (CREAE) in mice. In areas associated with nerve damage, increased levels of the endocannabinoids, anandamide (arachidonylethanolamide, AEA) and 2-arachidonoyl glycerol (2-AG), and of the AEA congener, palmitoylethanolamide (PEA), were detected here, whereas comparable levels of these compounds were found in normal and non-spastic CREAE mice. While exogenously administered endocannabinoids and PEA ameliorate spasticity, selective inhibitors of endocannabinoid re-uptake and hydrolysis—probably through the enhancement of endogenous levels of AEA, and, possibly, 2-arachidonoyl glycerol—significantly ameliorated spasticity to an extent comparable with that observed previously with potent cannabinoid receptor agonists. These studies provide definitive evidence for the tonic control of spasticity by the endocannabinoid system and open new horizons to therapy of multiple sclerosis, and other neuromuscular diseases, based on agents modulating endocannabinoid levels and action, which exhibit little psychotropic activity.

Baker, D., G. Pryce, G. Giovannoni and A.J. Thompson (2003) "The therapeutic potential of cannabis." *Lancet Neurology* 2 (5): 291-298.

Research of the cannabinoid system has many similarities with that of the opioid system. In both instances, studies into drug-producing plants led to the discovery of an endogenous control system with a central role in neurobiology. Few compounds have had as much positive press from patients as those of the cannabinoid system. While these claims are investigated in disorders such as multiple sclerosis spasticity and pain, basic research is discovering interesting members of this family of compounds that have previously unknown qualities, the most notable of which is the capacity for neuroprotection. Large randomised clinical trials of the better known compounds are in progress. Even if the results of these studies are not as positive as many expect them to be, that we are only just beginning to appreciate the huge therapeutic potential of this family of compounds is clear.

Baker, D., G. Pryce, S.J. Jackson, C. Bolton and G. Giovannoni (2012) "The biology that underpins the therapeutic potential of cannabis-based medicines for the control of spasticity in multiple sclerosis." *Multiple Sclerosis and Related Disorders* 1 (2): 64-75.

Cannabis-based medicines have recently been approved for the treatment of pain and spasticity in multiple sclerosis (MS). This supports the original



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perceptions of people with MS, who were using illegal street cannabis for symptom control and pre-clinical testing in animal models of MS. This activity is supported both by the biology of the disease and the biology of the cannabis plant and the endocannabinoid system. MS results from disease that impairs neurotransmission and this is controlled by cannabinoid receptors and endogenous cannabinoid ligands. This can limit spasticity and may also influence the processes that drive the accumulation of progressive disability.

Barnes, M.P. (2006) "Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain." Expert Opinion on Pharmacotherapy **7** (5): 607-615.

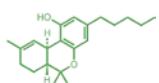
Sativex is one of the first cannabis-based medicines to undergo conventional clinical development and to be approved as a prescription medicine. It is an oromucosal spray that allows flexible, individualised dosing. Patients self titrate their overall dose and pattern of dosing according to their response to and tolerance of the medicine. This usually results in the administration of approximately 8-12 sprays/day. Each spray delivers tetrahydrocannabinol 2.7 mg and cannabidiol 2.5 mg, giving an approximate average dose of tetrahydrocannabinol 22-32 mg/day and cannabidiol 20-30 mg/day.

Development has concentrated on the treatment of symptoms of multiple sclerosis, notably spasticity and neuropathic pain, as well as the treatment of neuropathic pain of other aetiologies. Positive results in placebo-controlled trials of the use of Sativex as an add-on therapy in these indications demonstrate that Sativex is efficacious and well tolerated in the treatment of these symptoms. Sativex has been approved for use in neuropathic pain due to multiple sclerosis in Canada. If ongoing studies replicate the results already observed, further approvals for the treatment of spasticity in multiple sclerosis and for neuropathic pain are likely.

Beaconsfield, P., J. Ginsburg and R. Rainsbury (1973) "Therapeutic potential of marihuana." New England Journal of Medicine **289**: 1315.

Ben Amar, M. (2006) "Cannabinoids in medicine: A review of their therapeutic potential." Journal of Ethnopharmacology **105** (1-2): 1-25.

In order to assess the current knowledge on the therapeutic potential of cannabinoids, a meta-analysis was performed through Medline and PubMed up to July 1, 2005. The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human. The research also included the reports and reviews published in English, French and Spanish. For the final selection, only properly controlled clinical trials were retained, thus open-label studies were excluded. Seventy-two controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Cannabinoids present an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, and in the treatment of



multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy and glaucoma.

Berman, J., T. Bosworth, G. Guy and C. Stott (2007) "Sativex® in the Treatment of Central Neuropathic Pain due to Spinal Cord Injury: A Randomised Controlled Study." British Pain Society, Annual Scientific Meeting, April 2007.

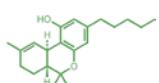
Sativex® in the Treatment of Central Neuropathic Pain due to Spinal Cord Injury: A Randomised Controlled Study

Background Little is known of the efficacy and safety of cannabinoids (including Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)) in the treatment of central neuropathic pain (CNP) due to spinal cord injury (SCI).

Aim: To assess the efficacy and safety of Sativex in the relief of neuropathic pain due to spinal cord injury. Methods Sativex® (THC:CBD), an endocannabinoid system modulator, was investigated as an-add on treatment in a 3-week, multi-centre, randomised, double-blind, placebo-controlled trial of 117 SCI patients with CNP, who did not have an adequate response to existing medications. Subjects had CNP, of at least six months duration, associated with SCI. Subjects also had a mean CNP severity score of at least 4 on an 11-point Numeric Rating Scale (0-10 NRS) during their last 7 days in the baseline period. Each Sativex oromucosal spray (100l), delivered 2.7mg THC and 2.5mg CBD. Patients self-titrated their dosage up to a daily maximum of 48 sprays per day. The primary endpoint was the mean difference in the change from baseline mean Numerical Rating Scale (NRS) pain scores. Secondary endpoints included Brief Pain Inventory (BPI),

Patient's Global Impression of Change (PGIC), sleep disturbance, escape analgesic usage, Short Orientation-Memory-Concentration test (SOMC), Caregiver Strain Index (CSI) and Spitzer Quality of Life Index (Spitzer QLI).

Results Of the 117 randomised (n=57 Sativex, n=60 placebo), 11 patients withdrew during the study, with the remaining 106 completing treatment. The mean number of sprays per day of study treatment was 9.5 sprays for Sativex and 19.2 sprays for placebo. Sativex and placebo produced similar reductions in mean NRS pain score from baseline but this treatment difference was not statistically significant (NRS pain score: Sativex: -1.08, placebo: -1.00; p=0.708) either in the ITT analysis (p = 0.708) or the Per Protocol analysis (p=0.878). Statistically significant treatment differences in pain relief in favour of Sativex was detected using the BPI. (Total BPI Score (1.93 points, p=0.032), Mean BPI (0.46 points, p=0.040) and Least Pain in the last 24 hours (0.79 points, p=0.007)). The analysis of the PGIC was also statistically in favour of Sativex: 54.5% of patients reported that their condition had 'improved' compared to those who had "not improved" (20.7%) was (p<0.001) with an odds ratio of 3.40 (p=0.001). Outcomes for other secondary endpoints were not significant. Sativex was generally well tolerated. Most adverse events (AEs) were reported as mild or moderate. The most common treatment related AE was dizziness (Sativex: 24.6%; placebo: 6.7%). Conclusion In this study, although Sativex produced a reduction from baseline in NRS pain score, the difference from placebo was not statistically significant. Some secondary pain-related endpoints did provide statistically significant evidence of analgesic effect and the study medication was generally well tolerated.



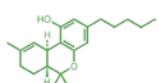
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Berman, J.S., C. Symonds, and R. Birch (2004) "Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial." *Pain* **112** (3): 299-306.

The objective was to investigate the effectiveness of cannabis-based medicines for treatment of chronic pain associated with brachial plexus root avulsion. This condition is an excellent human model of central neuropathic pain as it represents an unusually homogenous group in terms of anatomical location of injury, pain descriptions and patient demographics. Forty-eight patients with at least one avulsed root and baseline pain score of four or more on an 11-point ordinate scale participated in a randomised, double-blind, placebo-controlled, three period crossover study. All patients had intractable symptoms regardless of current analgesic therapy. Patients entered a baseline period of 2 weeks, followed by three, 2-week treatment periods during each of which they received one of three oromucosal spray preparations. These were placebo and two whole plant extracts of Cannabis sativa L.: GW-1000-02 (Sativex), containing Δ -9-tetrahydrocannabinol (THC):cannabidiol (CBD) in an approximate 1:1 ratio and GW-2000-02, containing primarily THC. The primary outcome measure was the mean pain severity score during the last 7 days of treatment. Secondary outcome measures included pain related quality of life assessments. The primary outcome measure failed to fall by the two points defined in our hypothesis. However, both this measure and measures of sleep showed statistically significant improvements. The study medications were generally well tolerated with the majority of adverse events, including intoxication type reactions, being mild to moderate in severity and resolving spontaneously. Studies of longer duration in neuropathic pain are required to confirm a clinically relevant, improvement in the treatment of this condition.

Berman, J.S., C. Symonds, R. Birch (2004) "Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial." *Pain* **112** (3): 299-306.

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Bertsche, T. and M. Schulz (2003) "Multiple Sklerose: Cannabis kann Spastik lindern." Pharmazeutische Zeitung 05/2003.

Interferone und Glatirameracetat haben die therapeutischen Möglichkeiten bei einer Multiple-Sklerose-Erkrankung (MS) deutlich verbessert. Sehr begrenzt sind die Optionen dagegen bei der MS-bedingten Spastik. Cannabis kann die Beschwerden bei einzelnen Patienten erleichtern.

Bingensis, Hildegardis " Physica Heilkraft der Natur – Das Buch von dem inneren Wesen der verschiedenen Naturen der Geschöpfe." (1150-1160, Ausgabe 1991)
Basler Hildegard-Gesellschaft (eds.) Pattloch, Augsburg.

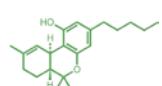
Brady, C.M., R. DasGupta, O.J. Wiseman, K.J. Berkley and C.J. Fowler (2001)
"Acute and chronic effects of cannabis based medicinal extract on refractory lower urinary tract dysfunction in patients with advanced multiple sclerosis – early results." 2001 Congress on Cannabis and the Cannabinoids, International Association for Cannabis as Medicine, Köln: 9.

The primary aim of this open label pilot study is to evaluate the safety, tolerability and efficacy of 2 sublingual preparations of cannabis based medicinal extract (CBME) in patients with advanced multiple sclerosis (MS; Kurtzke > 6.5) and refractory lower urinary tract symptoms (LUTS) in whom indwelling catheterisation is being considered.

Inclusion criteria are troublesome LUTS and detrusor hyperreflexia demonstrated by cystometry. Patients with an indwelling catheter or mini-mental state examination score < 27 are excluded. Data are collected using cystometry, frequency volume charts and pad testing. For the first 8 weeks of treatment patients receive CBME containing equal amounts of cannabidiol (CBD) and tetrahydrocannabinol (THC), whereas THC-only is prescribed for weeks 9-16. At the first treatment visit patients take up to 4 sprays of CBME as tolerated, under supervision (equivalent to 10 mgs of THC and 10 mgs of CBD).

17 patients have so far been recruited. We present the early results of 10 evaluable patients (2M:8F, 31-63yr), 8 of whom have now completed 16 weeks of CBME. Mean maximum cystometric capacity (MCC) was 278mls at baseline. After 8 weeks of treatment this increased to 344 mls (without CBME use for the previous 24 hrs) and to 435 mls following administration of the maximum tolerated dose of THC:CBD:1:1. This suggests both a chronic and acute effect. At the 16-week visit the MCC decreased from a mean of 405 mls before, to 392 mls after, the maximum tolerated dose of THC-only extract. These early results indicate that CBME may have a role in the management of patients with advanced MS and refractory LUTS.

Briseño, C (2012) "Umstrittene Therapie: Mykayla, 7, kämpft gegen den Krebs - mit Cannabis." SpiegelOnline, 06.12., 15:49 Uhr;



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<http://www.spiegel.de/gesundheit/diagnose/cannabis-krebs-der-7-jaehrigen-mykayla-soll-mit-drogen-therapiert-werden-a-871095.html>

Mykayla ist sieben Jahre alt, hat Blutkrebs, macht eine Chemotherapie - und schluckt zweimal täglich eine Cannabis-Kapsel. Im US-Bundesstaat Oregon ist das gesetzlich erlaubt, die Eltern stehen hinter der Therapie. Doch der Fall hat in den USA eine stürmische Debatte ausgelöst..

Mykayla Comstock sitzt auf dem braunen Sofa im Wohnzimmer. Sie trägt einen lilafarbenen Kapuzenpulli, die türkis-violette Strickmütze hängt ihr tief in das mit Sommersprossen gesprenkelte Gesicht. Mykayla wirkt verunsichert und lehnt den Kopf an die schützende Schulter ihrer Mutter. Schüchtern spricht die Siebenjährige in die Kamera: "Ich bin die tapfere Mykayla", sagt sie.

"Wie wurde aus dir die tapfere Mykayla?", fragt eine Reporterin hinter der Kamera. "Warum bist du nicht einfach nur Mykayla?" "Hm", sagt das Mädchen und zieht beide Schultern nach oben. Dann denkt es nach, atmet tief aus und sagt mit fester Stimme: "Ich war schon immer die tapfere Mykayla." Wieder fragt die Reporterin nach: "Wie kam es dazu, dass du tapfer sein musstest?" Mykaylas Antwort ist kurz: "Ich habe Krebs."

Das Video mit der Siebenjährigen, aufgenommen von Reportern der US-Zeitung "The Oregonian", hat in den USA eine stürmische Debatte ausgelöst - und Mykayla innerhalb von wenigen Tagen zu einem der berühmtesten krebskranken Kindern des Landes gemacht. Mykayla leidet an der Akuten Lymphatischen Leukämie (ALL), einer aggressiven Form von Blutkrebs, die 80 Prozent aller an Blutkrebs erkrankten Kinder betrifft. Mykaylas Behandlung besteht im Wesentlichen aus zwei Teilen: Chemotherapie und Cannabis.

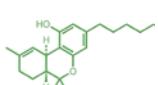
Mykayla ist eines von 52 Kindern im US-Bundesstaat Oregon, die am "Medical Marijuana Program" teilnehmen. Insgesamt haben etwa 2200 Krebspatienten in dem Staat die offizielle Erlaubnis, Marihuana als Medizin zu nutzen. Diese wird von einem Arzt erteilt, sofern dafür eine medizinische Notwendigkeit und bei Kindern das elterliche Einverständnis bestehen. Die Höhe der Dosis sowie die Häufigkeit der Einnahme bleibt den Betroffenen oder ihren Eltern überlassen. So sieht es das Gesetz in Oregon vor.

"Es macht mich lustig"

Jeden Morgen und Nachmittag schluckt Mykayla eine Kapsel mit Cannabisöl, insgesamt ein Gramm. Der Extrakt enthält den berauschenenden Wirkstoff Tetrahydrocannabinol, bekannt als THC, in einer viel höheren Dosis, als er in einem Joint vorkommt. "Es macht mich lustig", sagt Mykayla. Ihre Mutter kichert, Mykayla auch. "Und glücklich."

Das THC hilft dem Mädchen vor allem, die Nebenwirkungen der Chemotherapie zu umgehen. "Wegen ihr kann ich nur schlecht essen. Und mir wird übel", erzählt die Siebenjährige von der Behandlung. "Ohne Cannabis fühle ich mich müder. Mit Cannabis habe ich mehr Energie zum Spielen." Keine Schmerzen mehr, keine Übelkeit, der Appetit ist zurückgekehrt - und der Krebs scheint sich zurückzubilden.

Seit dem Bericht im "The Oregonian" hat Mykaylas Familie, die in einfachen Verhältnissen in einem Ort namens Gladstone lebt, kaum Ruhe. Journalisten belagern sie, alle wollen ein Interview mit dem kleinen Mädchen oder ihren Eltern führen. Die Eltern, das sind für Mykayla ihre leibliche Mutter Erin Purchase und deren Freund Brandon Krenzler. Beide sind noch jung, Purchase bekam ihre Tochter im Alter von 17 Jahren. Von Mykaylas



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leiblichem Vater Jesse Comstock trennte sie sich früh. Comstock zahlt Unterhalt für die Siebenjährige und ihre Krankenversicherung. Beschimpfungen und Verständnis zugleich Als Comstock eines Tages im August zu Besuch kam, fand er seine Tochter, so erzählt er es, "vollkommen stoned" vor. Jetzt macht er sich Sorgen, seine Tochter könnte abhängig werden. "Sie ist nicht todkrank", sagt Comstock. Den Krebs werde sie besiegen. Aber mit dem "ganzen Hasch werden sie ihr Gehirnwachstum behindern". Ähnlich entsetzt äußern sich viele Leser in den Kommentaren zum "The Oregonian"-Artikel, sie beschimpfen Mykaylas Eltern wüst. Von Verantwortungslosigkeit ist die Rede und von möglichen schrecklichen Nebenwirkungen - besonders bei einem Kind.

Etliche andere aber verstehen die Aufregung nicht: "Sie geben dem Kind Gift (Chemo), um Krebszellen zu töten, und dann macht man sich Sorgen über das Hasch?", schreibt einer. Eine andere Frau glaubt im Forum gar zu wissen, dass es dem Cannabisöl zu verdanken sei, dass der Krebs zurückgeht.

Nicht nur viele Artikel, die den Fall aufgegriffen haben, titeln in die gleiche Richtung: "Siebenjährige besiegt mit Cannabis den Krebs", heißt es etwa. Auch Mykaylas Familie ist überzeugt, dass dem Mittel der Erfolg zu verdanken ist. Auf etlichen Fotos in ihrem Facebook-Profil posiert das kleine, fast kahlköpfige Mädchen mit den niedlichen Sommersprossen lächelnd mit einem Stück Karton. Auf dem steht: "Cannabis ist meine Medizin, und es hat meinen Krebs geheilt."

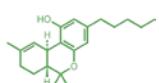
Ist Cannabis eine Hoffnung für Krebskranke?

Es ist eine Hoffnung, die das Mädchen und ihre Eltern mit vielen Krebskranken teilen - die Studienlage dazu ist bisher allerdings noch dünn. Zwar gibt es Untersuchungen, denen zufolge Cannabinoide, also die Wirkstoffe der Hanfpflanze, bei der Behandlung bestimmter Krebsarten helfen könnten. Immer wieder beobachten Forscher, dass sie die Ausbreitung von Tumorzellen blockieren oder zum Tod von Krebszellen führen können.

Allerdings wurde der Effekt bisher nur in Zellkulturen oder bei Mäusen nachgewiesen, Studien mit Menschen fehlen noch.

Ebenso unklar ist, welchen Einfluss eine längerfristige Cannabis-Einnahme bei Kindern und Jugendlichen haben könnte. Zumaldest der Entwicklung der geistigen Fähigkeiten scheint Cannabis zu schaden: Erst im August erschien eine Langzeitstudie, die Hinweise darauf liefert, dass langjähriges Rauchen von Marihuana den IQ eines Menschen senkt, besonders bei Jugendlichen. Gut dokumentiert ist dagegen die Wirksamkeit von Cannabis gegen Übelkeit, Erbrechen und starke oder chronische Schmerzen. Deshalb dürfen seit Mai 2011 auch in Deutschland cannabishaltige Arzneimittel hergestellt und nach klinischer Prüfung in bestimmten Fällen verschrieben werden.

Grundsätzlich spricht viel dafür, dass das Cannabis die Nebenwirkungen der Chemotherapie zwar reduzieren kann. Dass Cannabis Mykaylas Erkrankung geheilt haben soll, lässt sich aber nicht nachweisen. Wahrscheinlicher ist, dass die Chemotherapie dem Mädchen half. Laut der Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) können heutzutage mit Hilfe von Kombinations-Chemotherapien fast 80 Prozent der betroffenen Kinder dauerhaft von ALL geheilt werden. In manchen Fällen ist eine Bestrahlung oder eine Stammzelltransplantation notwendig. Beides blieb Mykayla erspart. Erin Purchase und ihr Freund mussten nicht lange überlegen. Sie entschieden sich sofort für eine Chemotherapie - und beantragten nur wenige Tage nach



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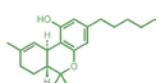
dem ersten Behandlungszyklus den Cannabis-Schein für ihre Tochter. Beide sind von der heilenden Kraft von Cannabis überzeugt und kennen sich bestens damit aus: Auch Purchase war bereits Teilnehmerin des "Oregon Medical Marijuana Program". In einer US-Sendung erzählte sie, sie habe wegen Stoffwechselproblemen teilgenommen. Und Cannabis habe ihr gegen die Übelkeit bei der Schwangerschaft ihres zweiten Kindes geholfen. Für Mykaylas Eltern steht fest: Trotz aller Kritik, sie würden jederzeit wieder so handeln.

Bostwick, J.M. (2012) "Blurred Boundaries: The Therapeutics and Politics of Medical Marijuana." *Mayo Clinic Proceedings* **87** (2): 172-186.

For 5 millennia, Cannabis sativa has been used throughout the world medically, recreationally, and spiritually. From the mid-19th century to the 1930s, American physicians prescribed it for a plethora of indications, until the federal government started imposing restrictions on its use, culminating in 1970 with the US Congress classifying it as a Schedule I substance, illegal, and without medical value. Simultaneous with this prohibition, marijuana became the United States' most widely used illicit recreational drug, a substance generally regarded as pleasurable and relaxing without the addictive dangers of opioids or stimulants. Meanwhile, cannabis never lost its cachet in alternative medicine circles, going mainstream in 1995 when California became the first of 16 states to date to legalize its medical use, despite the federal ban. Little about cannabis is straightforward. Its main active ingredient, δ -9-tetrahydrocannabinol, was not isolated until 1964, and not until the 1990s were the far-reaching modulatory activities of the endocannabinoid system in the human body appreciated. This system's elucidation raises the possibility of many promising pharmaceutical applications, even as draconian federal restrictions that hamstring research show no signs of softening. Recreational use continues unabated, despite growing evidence of marijuana's addictive potential, particularly in the young, and its propensity for inducing and exacerbating psychotic illness in the susceptible. Public approval drives medical marijuana legalization efforts without the scientific data normally required to justify a new medication's introduction. This article explores each of these controversies, with the intent of educating physicians to decide for themselves whether marijuana is panacea, scourge, or both. PubMed searches were conducted using the following keywords: medical marijuana, medical cannabis, endocannabinoid system, CB1 receptors, CB2 receptors, THC, cannabidiol, nabilone, dronabinol, nabiximols, rimonabant, marijuana legislation, marijuana abuse, marijuana dependence, and marijuana and schizophrenia. Bibliographies were hand searched for additional references relevant to clarifying the relationships between medical and recreational marijuana use and abuse.

Brady, C.M., R. DasGupta, C. Dalton, O.J. Wiseman, K.J. Berkley and C.J. Fowler (2004) "An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis." *Multiple Sclerosis Journal* **10** (4): 425-433.

The majority of patients with multiple sclerosis (MS) develop troublesome lower urinary tract symptoms (LUTS). Anecdotal reports suggest that cannabis may alleviate LUTS, and cannabinoid receptors in the bladder and nervous system are potential pharmacological targets. In an open trial we evaluated



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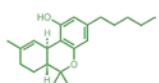
the safety, tolerability, dose range, and efficacy of two whole-plant extracts of Cannabis sativa in patients with advanced MS and refractory LUTS. Patients took extracts containing Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD; 2.5 mg of each per spray) for eight weeks followed by THC-only (2.5 mg THC per spray) for a further eight weeks, and then into a long-term extension. Assessments included urinary frequency and volume charts, incontinence pad weights, cystometry and visual analogue scales for secondary troublesome symptoms. Twenty-one patients were recruited and data from 15 were evaluated. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia all decreased significantly following treatment ($P < 0.05$, Wilcoxon's signed rank test). However, daily total voided, catheterized and urinary incontinence pad weights also decreased significantly on both extracts. Patient self-assessment of pain, spasticity and quality of sleep improved significantly ($P < 0.05$, Wilcoxon's signed rank test) with pain improvement continuing up to median of 35 weeks. There were few troublesome side effects, suggesting that cannabis-based medicinal extracts are a safe and effective treatment for urinary and other problems in patients with advanced MS.

Brenneisen, R., A. Egli, M.A. Elsohly, V. Henn and Y. Spiess (1996) "The effect of orally and rectally administered Δ-9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients." International Journal of Clinical Pharmacology Therapy and Toxicology **34** (10): 446-452.

Multiple doses of Δ-9-tetrahydrocannabinol (THC) capsules (Marinol) and THC hemisuccinate suppositories were administered in 24-hour intervals to 2 patients with organically caused spasticity. After oral doses of 10-15 mg THC, peak plasma levels from 2.1 to 16.9 ng/ml THC and 74.5 to 244.0 ng/ml 11-nor-9-carboxy- Δ-9-tetrahydrocannabinol (THC-COOH, major THC metabolite) were measured by GC/MS within 1-8 h and 2-8 h, respectively. After rectal doses of 2.5-5 mg THC, peak plasma levels from 1.1 to 4.1 ng/ml THC and 6.1 to 42.0 ng/ml THC-COOH were measured within 2-8 h and 1-8 h, respectively. The bioavailability resulting from the oral formulation was 45-53% relative to the rectal route of administration, due to a lower absorption and higher first-pass metabolism. The effect of THC on spasticity, rigidity, and pain was estimated by objective neurological tests (Ashworth scale, walking ability) and patient self-rating protocols. Oral and rectal THC reduced at a progressive stage of illness the spasticity, rigidity, and pain, resulting in improved active and passive mobility. The relative effectiveness of the oral vs. the rectal formulation was 25-50%. Physiological and psychological parameters were used to monitor psychotropic and somatic side-effects of THC. No differences in the concentration ability, mood, and function of the cardiovascular system could be observed after administration of THC.

Brooks, J. W., G. Pryce, T. Bisogno, S.I. Jaggar, D.J.R. Hankey, P. Brown, D. Bridges, C. Ledent, M. Bifulco, A.S.C. Rice, V. Di Marzo and D. Baker (2002) "Arvanil-induced inhibition of spasticity and persistent pain: Evidence for therapeutic sites of action different from the vanilloid VR1 receptor and cannabinoid CB1/CB2 receptors." European Journal of Pharmacology **439** (1-3): 83-92.

Activation of cannabinoid receptors causes inhibition of spasticity, in a mouse model of multiple sclerosis, and of persistent pain, in the rat formalin test. The



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endocannabinoid anandamide inhibits spasticity and persistent pain. It not only binds to cannabinoid receptors but is also a full agonist at vanilloid receptors of type 1 (VR1). We found here that vanilloid VR1 receptor agonists (capsaicin and N-N'-(3-methoxy-4-aminoethoxy-benzyl)-(4-tert-butyl- benzyl)-urea (SDZ-249-665)) exhibit a small, albeit significant, inhibition of spasticity that can be attenuated by the vanilloid VR1 receptor antagonist, capsazepine. Arvanil, a structural "hybrid" between capsaicin and anandamide, was a potent inhibitor of spasticity at doses (e.g. 0.01 mg/kg i.v.) where capsaicin and cannabinoid CB_{(sub)1} receptor agonists were ineffective. The anti-spastic effect of arvanil was unchanged in cannabinoid CB_{(sub)1} receptor gene-deficient mice or in wildtype mice in the presence of both cannabinoid and vanilloid receptor antagonists. Likewise, arvanil (0.1-0.25 mg/kg) exhibited a potent analgesic effect in the formalin test, which was not reversed by cannabinoid and vanilloid receptor antagonists. These findings suggest that activation by arvanil of sites of action different from cannabinoid CB_{(sub)1}/CB_{(sub)2} receptors and vanilloid VR1 receptors leads to anti-spastic/ analgesic effects that might be exploited therapeutically.

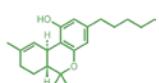
Bühring, P. (2012) "Medizinischer Einsatz von Cannabis: Kein Geld für Cannabis." **Deutsches Ärzteblatt** **109** (21): A-1074.

Die Grünen fordern in einem Antrag an die Bundesregierung einen besseren Zugang zu Cannabismedikamenten. Ärzte und Patienten unterstützen die Forderungen weitestgehend. Die Krankenkassen sind dagegen.

Die Bundestagsfraktion Bündnis 90/Die Grünen setzt sich in einem Antrag (Drucksache 17/6127) für einen besseren Zugang von Patienten zu medizinischem Cannabis ein. Denn: „Die Versorgung von bedürftigen Patienten ist nach wie vor unzureichend.“ Dabei sei wissenschaftlich belegt, dass Cannabis bei HIV, multipler Sklerose, chronischen Schmerzen, Epilepsie oder Krebs Linderung bewirken könne. Unterstützung erhielten die Grünen bei einer öffentlichen Anhörung ihres Antrags im Gesundheitsausschuss von Ärzten und Patienten. Der GKV-Spitzenverband hingegen lehnte Vorschläge zur leichteren Kostenerstattung von Cannabismedikamenten ab.

Die Grünen fordern in dem Antrag einen Gesetzentwurf, durch den ein betäubungsmittelrechtliches Strafverfahren ausgeschlossen wird, wenn Patienten Cannabis aufgrund einer ärztlichen Empfehlung besitzen, anbauen oder sich verschaffen. Gleichzeitig schlagen die Abgeordneten eine Liste von Indikationen vor, nach denen eine solche ärztliche Empfehlung ausgestellt werden kann.

Weiter fordern die Grünen, eine Expertengruppe nach § 32 c Absatz 1 Sozialgesetzbuch V (off-label use) einzuberufen, um eine zulassungsüberschreitende Anwendung von Cannabismedikamenten durch Beschluss des Gemeinsamen Bundesausschusses (G-BA) auch schwerstkranken, jedoch nicht an einer regelmäßig tödlich verlaufende Erkrankung leidenden Patienten zu ermöglichen. Bei todkranken Patienten ist die Kostenübernahme der gesetzlichen Krankenkassen im Off-label-Gebrauch bereits möglich. Als einziges Fertigarzneimittel steht in Deutschland seit Mai 2011 ein Extrakt aus Cannabis sativa (Sativex) zur Verfügung, zugelassen zur zusätzlichen Symptomverbesserung bei Multiple-Sklerose-Patienten mit schwerer Spastik, die nicht auf eine andere Therapie ansprechen. Der G-BA wird allerdings erst Mitte dieses Jahres über den Zusatznutzen dieses



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Medikaments entscheiden. Weiter gibt es die Cannabinoide Dronabinol und Nabilon, die Ärzte im Rahmen eines individuellen Heilversuchs auf Betäubungsmittelrezept verordnen können. Medikamente mit den Wirkstoffen sind in den USA und in Großbritannien zugelassen; in Deutschland übernehmen die Krankenkassen die Kosten (300 bis 600 Euro pro Monat) in der Regel nicht. Außerdem können Patienten eine Ausnahmeerlaubnis nach § 3 Absatz 2 Betäubungsmittelgesetz (BtMG) zum therapeutischen Einsatz von Cannabisextrakt oder -blüten durch das Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) beantragen. Die Kosten betragen bis zu 1 500 Euro monatlich. Das BfArM hat diese Ausnahmegenehmigungen seit 2007 bisher in etwa 60 Fällen erteilt.

In Konflikt mit dem Betäubungsmittelgesetz

„Selbst die Schwerstkranken, die eine Ausnahmegenehmigung erhalten haben, können sich die Therapie meist nicht leisten“, sagte Gabriele Gebhardt von der Patientenvereinigung Selbsthilfenetzwerk Cannabis als Medizin (SCM) in der Anhörung. Cannabis werde dann selbst angebaut oder auf dem Schwarzmarkt bezogen. Da die Patienten somit unweigerlich mit dem BtMG in Konflikt geraten, forderte Gebhardt strafrechtliche Ausnahmen für die schwer kranken Patienten.

Die Ärzte waren sich einig, dass eine Selbstmedikation mit nichtstandardisiertem Cannabis nicht empfohlen werden kann. „Der Wirkstoffgehalt variiert stark. Außerdem können Kontaminationen die kranken Patienten gefährden“, sagte Prof. Dr. med. Lukas Radbruch, Bonn, der die Bundesärztekammer (BÄK) und die Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) vertrat. Die Behandlung müsse unter ärztlicher Aufsicht erfolgen. Eine Aufhebung der Strafverfolgung, wie von den Grünen vorgeschlagen, lehnte Radbruch deshalb ab. Eine Therapie mit Cannabismedikamenten könne aber für einige Patienten sinnvoll sein, bei denen eine Standardtherapie nicht wirksam ist. „Es gibt ein sehr enges therapeutisches Fenster.“

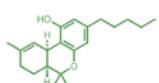
Hausärzte müssen die Therapie beenden

Grundsätzlich sei die Zulassung von cannabinoiden Fertigarzneimitteln auch für andere Indikationen „sinnvoll und wünschenswert“, erklärte Radbruch. BÄK und AkdÄ befürworten deshalb die Forderung der Grünen, eine Expertengruppe zu berufen, die Empfehlungen zum Off-label-Gebrauch erstellt. Radbruch sieht häufig das Problem, dass Patienten, zum Beispiel in Schmerzzentren, auf Cannabismedikamente eingestellt werden, die Hausärzte die Therapie aber beenden müssen, weil die Kosten nicht übernommen werden.

Der GKV-Spitzenverband blieb bei seinem Standpunkt: Der Vorschlag der Grünen zur zulassungsüberschreitenden Anwendung von Cannabismedikamenten stelle einen Missbrauch der Ausnahmeregelung zum off-label use dar und sei deshalb abzulehnen.

Cabranes, A., G. Pryce, D. Baker and J. Fernández-Ruiz (2006) "Changes in CB1 receptors in motor-related brain structures of chronic relapsing experimental allergic encephalomyelitis mice." *Brain Research* **1107** (1): 199-205.

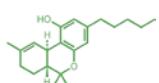
Recent studies have examined the changes in the activity of cannabinoid signalling system in multiple sclerosis (MS), as a way to explain the efficacy of cannabinoid compounds to alleviate spasticity, pain, tremor and other signs of



this autoimmune disease. In the present study, we have further explored this issue by examining density, mRNA expression and activation of GTP-binding proteins for the cannabinoid CB1 receptor subtype in several brain structures of mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), a chronic model of MS that reproduces many of the pathological hallmarks of the human disease. CREAE animals were used at different phases in the progression of the disease (acute, remission and chronic) and compared to control mice. We observed several changes in the status of CB1 receptors that were region-specific and mainly circumscribed to motor-related regions, which is compatible with the symptomatology described for these animals that is preferentially of motor nature. We found a moderate decrease in the density of CB1 receptors in the caudate-putamen during the acute phase of CREAE. These reductions disappeared during the remission phase, but they were again observed, to a more marked extent, in the chronic phase. The same pattern for CB1 receptor density was observed in the cerebellum which, in this case, was accompanied by a progressive decrease in the capability of these receptors to activate GTP-binding proteins that was maximal in the chronic phase. The decrease in the density of CB1 receptors in the acute phase was also found in the globus pallidus but, in this case, the reduction was maintained during the further phases. No changes were observed in CB1 receptor-mRNA levels in any of the different regions examined. Finally, by contrast with the observations in motor structures, the status of CB1 receptors remained unaltered in cognition-related regions, such as the cerebral cortex and the hippocampus, during the different phases of CREAE. In summary, CB1 receptors were affected by the development of CREAE in mice exhibiting always down-regulatory responses that were circumscribed to motor-related regions and that were generally more marked during the acute and chronic phases. These observations may explain the efficacy of cannabinoid agonists to improve motor symptoms (spasticity, tremor, ataxia) typical of MS in both humans and animal models.

Cabranes, A., K. Venderova, E. de Lago, F. Fezza, A. Sánchez, L. Mestre, M. Valenti, A. García-Merino, J.A. Ramos, V. Di Marzo and J. Fernández-Ruiz (2005) "Decreased endocannabinoid levels in the brain and beneficial effects of agents activating cannabinoid and/or vanilloid receptors in a rat model of multiple sclerosis." *Neurobiology of Disease* **20** (2): 207-217.

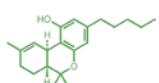
Recent studies have addressed the changes in endocannabinoid ligands and receptors that occur in multiple sclerosis, as a way to explain the efficacy of cannabinoid compounds to alleviate spasticity, pain, tremor, and other signs of this autoimmune disease. Using Lewis rats with experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis, we recently found a decrease in cannabinoid CB1 receptors mainly circumscribed to the basal ganglia, which could be related to the motor disturbances characteristic of these rats. In the present study, using the same model, we explored the potential changes in several neurotransmitters in the basal ganglia that might be associated with the motor disturbances described in these rats, but we only found a small increase in glutamate contents in the globus pallidus. We also examined whether the motor disturbances and the changes of CB1 receptors found in the basal ganglia of EAE rats disappear after the treatment with rolipram, an inhibitor of type IV phosphodiesterase able to suppress EAE in



different species. Rolipram attenuated clinical decline, reduced motor inhibition, and normalized CB1 receptor gene expression in the basal ganglia. As a third objective, we examined whether EAE rats also exhibited changes in endocannabinoid levels as shown for CB1 receptors. Anandamide and 2-arachidonoylglycerol levels decreased in motor related regions (striatum, midbrain) but also in other brain regions, although the pattern of changes for each endocannabinoid was different. Finally, we hypothesized that the elevation of the endocannabinoid activity, following inhibition of endocannabinoid uptake, might be beneficial in EAE rats. AM404, arvanil, and OMDM2 were effective to reduce the magnitude of the neurological impairment in EAE rats, whereas VDM11 did not produce any effect. The beneficial effects of AM404 were reversed by blocking TRPV1 receptors with capsazepine, but not by blocking CB1 receptors with SR141716, thus indicating the involvement of endovanilloid mechanisms in these effects. However, a role for CB1 receptors is supported by additional data showing that CP55,940 delayed EAE progression. In summary, our data suggest that reduction of endocannabinoid signalling is associated with the development of EAE in rats. We have also proved that the reduction of CB1 receptors observed in these rats is corrected following treatment with a compound used in EAE such as rolipram. In addition, the direct or indirect activation of vanilloid or cannabinoid receptors may reduce the neurological impairment experienced by EAE rats, although the efficacy of the different compounds examined seems to be determined by their particular pharmacodynamic and pharmacokinetic characteristics.

Campbell, F.A., M.R. Tramèr, D. Carroll, D.J.M. Reynolds, R.A. Moore and H.J. McQuay (2001) "Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review." British Medical Journal **323** (7303): 13-16.

Objective: To establish whether cannabis is an effective and safe treatment option in the management of pain. Design: Systematic review of randomised controlled trials. Data sources: Electronic databases Medline, Embase, Oxford Pain Database, and Cochrane Library; references from identified papers; hand searches. Study selection: Trials of cannabis given by any route of administration (experimental intervention) with any analgesic or placebo (control intervention) in patients with acute, chronic non-malignant or cancer pain. Outcomes examined were pain intensity scores, pain relief scores, and adverse effects. Validity of trials was assessed independently with the Oxford score. Data extraction: Independent data extraction; discrepancies resolved by consensus. Data synthesis: 20 randomised controlled trials were identified, 11 of which were excluded. Of the 9 included trials (222 patients), 5 trials related to cancer pain, 2 to chronic non-malignant pain, and 2 to acute postoperative pain. No randomised controlled trials evaluated cannabis; all tested active substances were cannabinoids. Oral Δ -9-tetrahydrocannabinol (THC) 5-20 mg, an oral synthetic nitrogen analogue of THC 1 mg, and intramuscular levonantradol 1.5-3 mg were about as effective as codeine 50-120 mg, and oral benzopyranoperidine 2-4 mg was less effective than codeine 60-120 mg and no better than placebo. Adverse effects, most often psychotropic, were common. Conclusion: Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system



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that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used. Before cannabinoids can be considered for treating spasticity and neuropathic pain, further valid randomised controlled studies are needed.

Check, W.A. (1979) "Marijuana may lessen spasticity of MS." Journal of the American Medical Association **241** (23): 2476.

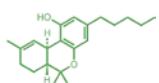
Chong, M.S., K. Wolff, K. Wise, C. Tanton, A. Winstock, and E. Silber (2006) "Cannabis use in patients with multiple sclerosis." Multiple Sclerosis Journal **12** (5): 646-651

Introduction: Little is known about the extent and patterns of cannabis use in people with multiple sclerosis (MS). Methods: MS patients attending neurology outpatient clinics at two hospitals in London and one in Kent, UK completed a questionnaire. RESULTS: Questionnaires were completed by 254/337 (75%) MS patients. Forty-three per cent had used cannabis at some stage (ever users). Of these, 68% (75/110) had used cannabis to alleviate symptoms of MS (MS-related cannabis use). Forty-six (18%) had used cannabis in the last month (current users), of whom 12% (31/254) had used it for symptom relief. Being married or having a long-term partner, tobacco smokers and increasing disability were independent risk factors for MS-related cannabis use.

Compared to patients who could walk unaided, cannabis use was more likely in those who were chair-bound (adjusted OR 2.47; 1.10-5.56) or only able to walk with an aid (adjusted OR 1.56; 0.90-3.60). Pain and spasms were common reasons for cannabis use. Seventy-one per cent of individuals who had never used cannabis said they would try the drug if it were available on prescription. Conclusion: A large proportion of MS patients had tried cannabis for symptom control, however current use was small. A subgroup with greater disability appears to derive some symptomatic benefit.

Clermont-Gnamien, S., S. Atlani, N. Attal, F. Le Mercier, F. Guirimand, and L. Brasseur (2002) "[The therapeutic use of Δ-9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain]." Presse Medicale **31** (39 Pt 1): 1840-1845.

Introduction: Despite the recent discovery of the potential mechanisms underlying the analgesic effects of cannabis, few clinical studies have so far assessed its analgesic effects, notably in the treatment of chronic non-malignant pain. All the studies used administration of cannabis alone. The aim of this open, pilot, study was to assess the efficacy and side effect profile of oral dronabinol (tetrahydrocannabinol - THC) in the treatment of refractory neuropathic pain. Methods: Seven patients (3 women/4 men), aged 60 +/- 14 years, suffering from chronic refractory neuropathic pain, received oral THC titrated to the maximum dose of 25 mg/day (mean dose: 15 +/- 6 mg), during an average of 55,4 days (range: 13-128). Various components of pain (continuous, paroxysmal and brush-induced allodynia) were assessed using VAS scores. Health-related Quality of Life (HRQL) was evaluated using the Brief Pain Inventory, and the Hospital Anxiety and Depression scale was used to measure depression and anxiety. Results: THC did not induce significant effect on the various pain, HRQL and anxiety and depression scores. Numerous side effects (notably sedation and asthenia) were observed in 5 patients out of 7, requiring premature discontinuation of the drug in 3 patients.



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Conclusion: The present study did not reveal any significant efficacy of THC in a small cohort of patients with chronic refractory neuropathic pain, but underlined the unfavorable side effect profile of the drug. These results may partly relate to the fact that oral dronabinol exhibits a poor therapeutic ratio (efficacy at the price of side effects). The development of new and better tolerated cannabinoids is warranted.

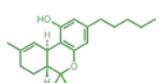
Cohen, S. (1977). "Therapeutic aspects." NIDA Research Monograph Series 14: 194-225.

Collen, M. (2012) "Prescribing cannabis for harm reduction." Harm Reduction Journal 9 (1): 1.

Neuropathic pain affects between 5% and 10% of the US population and can be refractory to treatment. Opioids may be recommended as a second-line pharmacotherapy but have risks including overdose and death. Cannabis has been shown to be effective for treating nerve pain without the risk of fatal poisoning. The author suggests that physicians who treat neuropathic pain with opioids should evaluate their patients for a trial of cannabis and prescribe it when appropriate prior to using opioids. This harm reduction strategy may reduce the morbidity and mortality rates associated with prescription pain medications.

Collin C, Z. Ambler, R. Kent and R. McCalla (2006) "A randomised controlled study of Sativex® in patients with symptoms of spasticity due to multiple sclerosis." 22nd Congress of the ECTRIMS, 27-30 September 2006, Madrid, Spain.

Muscle spasticity is a common clinical problem in about 60% of patients with multiple sclerosis (MS) often leading to considerable distress. Methods: A 15 week, multi-centre, double blind, randomized, placebo controlled parallel group study was undertaken to evaluate the efficacy of standardised whole plant cannabis medicine (Sativex®) in patients with MS. After a 7 day baseline period, 337 subjects were randomised to receive either Sativex or placebo. The endpoints included change in mean spasticity NRS score, spasticity NRS at clinic visits, Modified Ashworth Scale, timed 10 metre walk, Barthel activities of daily living, carer global impression of change (CGIC), quality of life questionnaires, EQ-5D and MSQoL-54, sleep quality, review of pain, tremor and fatigue, spasm severity and bladder symptoms. Results: For the primary endpoint, the mean NRS spasticity scores showed a statistically significant treatment difference of -0.46 points in favour of Sativex in the per protocol (PP) population ($p=0.035$; 95% CI: -0.88, -0.03). The intention to treat (ITT) population showed a trend in favour of Sativex with a treatment difference of -0.23 points ($p=0.219$; 95%CI: -0.59, 0.14). In the PP population 36% of patients achieved at least a 30% improvement in spasticity NRS with an odds ratio of 1.74 (95% CI: 0.005, 0.266). This trend was also observed in the ITT population with an odds ratio of 1.34 in favour of Sativex. These findings were supported by the CGIC assessment which was strongly in favour of Sativex (Odds ratio 1.25, $p=0.270$; 95% CI: 0.84, 1.85). The following secondary endpoints showed trends in favour of Sativex: spasticity and sleep assessments at clinic visits, Modified Ashworth Scale; timed 10-metre walk, quality of life questionnaire EQ-5D, sleep quality, review of pain, tremor, spasm severity and bladder symptoms. When the data from this and a



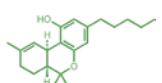
previous study were pooled, a statistically significant difference in spasticity in favour of Sativex was seen in the ITT population (-0.34, 95% CI: -0.64, -0.04, p=0.027). Conclusions: The patients randomized in this study exhibited severe levels of spasticity despite ongoing treatment with the best available anti-spasticity treatments. In the PP population the reduction in symptoms of spasticity in the Sativex-treated group was statistically significant. This did not extend to the ITT populations but in this, and other secondary endpoints, the outcomes were in favour of Sativex.

Collin, C., P. Davies, I.K. Mutiboko and S. Ratcliffe (2007) "Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis." European Journal of Neurology **14** (3): 290-296.

Symptoms relating to spasticity are common in multiple sclerosis (MS) and can be difficult to treat. We have investigated the efficacy, safety and tolerability of a standardized oromucosal whole plant cannabis-based medicine (CBM) containing Δ-9 tetrahydrocannabinol (THC) and cannabidiol (CBD), upon spasticity in MS. A total of 189 subjects with definite MS and spasticity were randomized to receive daily doses of active preparation (n = 124) or placebo (n = 65) in a double blind study over 6 weeks. The primary endpoint was the change in a daily subject-recorded Numerical Rating Scale of spasticity. Secondary endpoints included a measure of spasticity (Ashworth Score) and a subjective measure of spasm. The primary efficacy analysis on the intention to treat (ITT) population (n = 184) showed the active preparation to be significantly superior (P = 0.048). Secondary efficacy measures were all in favour of active preparation but did not achieve statistical significance. The responder analysis favoured active preparation, 40% of subjects achieved >30% benefit (P = 0.014). Eight withdrawals were attributed to adverse events (AEs); six were on active preparation and two on placebo. We conclude that this CBM may represent a useful new agent for treatment of the symptomatic relief of spasticity in MS.

Collin, C., E. Ehler, G. Waberzinek, Z. Alsindi, P. Davies, K. Powell, W. Notcutt, C. O'Leary, S. Ratcliffe, I. Novakova, O. Zapletalova, J. Pikova and Z. Ambler (2010) "A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis." Neurological Research **32** (5): 451-459.

Background: Muscle spasticity is common in multiple sclerosis (MS), occurring in more than 60% of patients. Objective: To compare Sativex with placebo in relieving symptoms of spasticity due to MS. Methods: A 15-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group study in 337 subjects with MS spasticity not fully relieved with current anti-spasticity therapy. Results: The primary endpoint was a spasticity 0-10 numeric rating scale (NRS). Intention-to-treat (ITT) analysis showed a non-significant improvement in NRS score, in favor of Sativex. The per protocol (PP) population (79% of subjects) change in NRS score and responder analyses (> or =30% improvement from baseline) were both significantly superior for Sativex, compared with placebo: -1.3 versus -0.8 points (change from baseline, p=0.035); and 36% versus 24% (responders, p=0.040). These were supported by the time to response (ITT: p=0.068; PP: p=0.025) analyses, carer global impression of change assessment (p=0.013) and timed 10-meter



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walk ($p=0.042$). Among the subjects who achieved a > or =30% response in spasticity with Sativex, 98, 94 and 73% reported improvements of 10, 20 and 30%, respectively, at least once during the first 4 weeks of treatment. Sativex was generally well tolerated, with most adverse events reported being mild-to-moderate in severity. Discussion and Conclusions: The 0-10 NRS and responder PP analyses demonstrated that Sativex treatment resulted in a significant reduction in treatment-resistant spasticity, in subjects with advanced MS and severe spasticity. The response observed within the first 4 weeks of treatment appears to be a useful aid to prediction of responder/non-responder status.

Consroe, P. (1998) "Brain cannabinoid systems as targets for the therapy of neurological disorders." Neurobiology of Disease **5** (6 Pt B): 534-551.

Unprecedented developments in cannabinoid research within the past decade include discovery of a brain (CB1) and peripheral (CB2) receptor; endogenous ligands, anandamide, and 2-arachidonoylglycerol; cannabinoid drug-induced partial and inverse agonism at CB1 receptors, antagonism of NMDA receptors and glutamate, and antioxidant activity; and preferential CB1 receptor localization in areas subserving spasticity, pain, abnormal involuntary movements, seizures, and amnesia. These endogenous structures and chemicals and mechanisms are potentially new pathophysiologic substrates, and targets for novel cannabinoid treatments, of several neurological disorders.

Consroe, P., R. Musty, J. Rein, W. Tillary and R. Pertwee (1997) "The perceived effects of smoked cannabis on patients with multiple sclerosis." European Neurology **38** (1): 44-48.

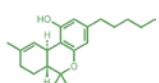
Fifty-three UK and 59 USA people with multiple sclerosis (MS) answered anonymously the first questionnaire on cannabis use and MS. From 97 to 30% of the subjects reported cannabis improved (in descending rank order): spasticity, chronic pain of extremities, acute paroxysmal phenomenon, tremor, emotional dysfunction, anorexia/weight loss, fatigue states, double vision, sexual dysfunction, bowel and bladder dysfunctions, vision dimness, dysfunctions of walking and balance, and memory loss. The MS subjects surveyed have specific therapeutic reasons for smoking cannabis. The survey findings will aid in the design of a clinical trial of cannabis or cannabinoid administration to MS patients or to other patients with similar signs or symptoms.

Constantinescu, C., B. Hoggart, M. Serpell and N. Sarantis (2006) "Long term open label treatment with Sativex[®] in patients with Multiple Sclerosis and neuropathic pain." European Journal of Pain **10** (Suppl. 1): S117-S118.

Randomised placebo-controlled trials have shown Sativex to be effective in the treatment of neuropathic pain (NP) and spasticity and other symptoms associated with Multiple Sclerosis (MS). On completion of acute trials, patients could enter a long-term open-label safety study.

Methods: Sativex was administered as an oromucosal spray and was self-titrated by patients. The endpoints were the incidence of adverse events (AEs) and serious adverse events (SAEs).

Results: A total of 662 patients entered the study for a mean duration of 409



days. 158 patients received more than 2 years treatment. The mean number of sprays of Sativex taken per day was 7.9 (± 6.2). In the long-term studies 93.2% of patients experienced at least one treatment-emergent AE, of which 83.8% were treatment-related. A total of 16.8% of patients withdrew from the study due to AEs. In randomised studies, 86.5% of Sativex and 70.4% of placebo patients experienced treatment-emergent AEs. The most common AEs were dizziness (27.6%), nausea (12.8%), diarrhoea (9.8%), fatigue (9.2%), dry mouth (8.0%) and dysgeusia (8.0%). The majority of AEs were mild or moderate in severity, occurring at levels lower than 3%. SAEs were experienced by 15% of patients only 3.6% of which were considered treatment-related. There were neither out of range values nor notable trends in biochemistry, haematology and urinalysis measures.

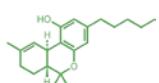
Conclusions: Sativex was well tolerated in this long-term study. The AEs were generally mild to moderate and did not commonly lead to withdrawal from the study.

Corey, S. (2005) "Recent developments in the therapeutic potential of cannabinoids." Puerto Rico Health Sciences Journal **24** (1): 19-26.

Objective: To examine the recent evidence that marijuana and other cannabinoids have therapeutic potential. Methods: Literature published since 1997 was searched using the following terms: cannabinoid, marijuana, THC, analgesia, cachexia, glaucoma, movement, multiple sclerosis, neurological, pain, Parkinson, trial, vomiting. Qualifying clinical studies were randomized, double-blind, and placebo-controlled. Selected open-label studies and surveys are also discussed. Results: A total of 15 independent, qualifying clinical trials were identified, of which only three had more than 100 patients each. Two large trials found that cannabinoids were significantly better than placebo in managing spasticity in multiple sclerosis. Patients self-reported greater sense of motor improvement in multiple sclerosis than could be confirmed objectively. In smaller qualifying trials, cannabinoids produced significant objective improvement of tics in Tourette's disease, and neuropathic pain. A new, non-psychotropic cannabinoid also has analgesic activity in neuropathic pain. No significant improvement was found in levodopa-induced dyskinesia in Parkinson's Disease or post-operative pain. No difference from active placebo was found for management of cachexia in a large trial. Some immune system parameters changed in HIV-1 and multiple sclerosis patients treated with cannabinoids, but the clinical significance is unknown. Quality of life assessments were made in only three of 15 qualifying clinical trials.

Conclusion: Cannabinoids may be useful for conditions that currently lack effective treatment, such as spasticity, tics and neuropathic pain. New delivery systems for cannabinoids and cannabis-based medicinal extracts, as well as new cannabinoid derivatives expand the options for cannabinoid therapy. More well-controlled, large clinical trials are needed, especially with active placebo.

Corey-Bloom, J. T. Wolfson, A. Gamst, S. Jin, T.D. Marcotte, H. Bentley and B. Gouaux (2012) "Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial." Canadian Medical Association Journal – CMAJ **184** (10): 1143-1150.



Cannabis, Dronabinol und die Behandlung schwerer Erkrankungen

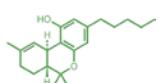
Background: Spasticity is a common and poorly controlled symptom of multiple sclerosis. Our objective was to determine the short-term effect of smoked cannabis on this symptom. Methods: We conducted a placebo-controlled, crossover trial involving adult patients with multiple sclerosis and spasticity. We recruited participants from a regional clinic or by referral from specialists. We randomly assigned participants to either the intervention (smoked cannabis, once daily for three days) or control (identical placebo cigarettes, once daily for three days). Each participant was assessed daily before and after treatment. After a washout interval of 11 days, participants crossed over to the opposite group. Our primary outcome was change in spasticity as measured by patient score on the modified Ashworth scale. Our secondary outcomes included patients' perception of pain (as measured using a visual analogue scale), a timed walk and changes in cognitive function (as measured by patient performance on the Paced Auditory Serial Addition Test), in addition to ratings of fatigue. Results: Thirty-seven participants were randomized at the start of the study, 30 of whom completed the trial. Treatment with smoked cannabis resulted in a reduction in patient scores on the modified Ashworth scale by an average of 2.74 points more than placebo ($p < 0.0001$). In addition, treatment reduced pain scores on a visual analogue scale by an average of 5.28 points more than placebo ($p = 0.008$). Scores for the timed walk did not differ significantly between treatment and placebo ($p = 0.2$). Scores on the Paced Auditory Serial Addition Test decreased by 8.67 points more with treatment than with placebo ($p = 0.003$). No serious adverse events occurred during the trial. Interpretation: Smoked cannabis was superior to placebo in symptom and pain reduction in participants with treatment-resistant spasticity. Future studies should examine whether different doses can result in similar beneficial effects with less cognitive impact.

Cravatt, B.F. and A.H. Lichtman (2003) "Fatty acid amide hydrolase: an emerging therapeutic target in the endocannabinoid system." Current Opinion in Chemical Biology 7 (4): 469-475.

The medicinal properties of exogenous cannabinoids have been recognized for centuries and can largely be attributed to the activation in the nervous system of a single G-protein-coupled receptor, CB1. However, the beneficial properties of cannabinoids, which include relief of pain and spasticity, are counterbalanced by adverse effects such as cognitive and motor dysfunction. The recent discoveries of anandamide, a natural lipid ligand for CB1, and an enzyme, fatty acid amide hydrolase (FAAH), that terminates anandamide signalling have inspired pharmacological strategies to augment endogenous cannabinoid ('endocannabinoid') activity with FAAH inhibitors, which might exhibit superior selectivity in their elicited behavioral effects compared with direct CB1 agonists.

Croxford, J. L. (2003) "Therapeutic potential of cannabinoids in CNS disease." CNS Drugs 17 (3): 179-202.

The major psychoactive constituent of Cannabis sativa, Δ -9-tetrahydrocannabinol (Δ -9-THC), and endogenous cannabinoid ligands, such as anandamide, signal through G-protein-coupled cannabinoid receptors localised to regions of the brain associated with important neurological processes. Signalling is mostly inhibitory and suggests a role for cannabinoids

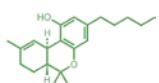


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as therapeutic agents in CNS disease where inhibition of neurotransmitter release would be beneficial. Anecdotal evidence suggests that patients with disorders such as multiple sclerosis smoke cannabis to relieve disease-related symptoms. Cannabinoids can alleviate tremor and spasticity in animal models of multiple sclerosis, and clinical trials of the use of these compounds for these symptoms are in progress. The cannabinoid nabilone is currently licensed for use as an antiemetic agent in chemotherapy-induced emesis. Evidence suggests that cannabinoids may prove useful in Parkinson's disease by inhibiting the excitotoxic neurotransmitter glutamate and counteracting oxidative damage to dopaminergic neurons. The inhibitory effect of cannabinoids on reactive oxygen species, glutamate and tumour necrosis factor suggests that they may be potent neuroprotective agents. Dexanabinol (HU-211), a synthetic cannabinoid, is currently being assessed in clinical trials for traumatic brain injury and stroke. Animal models of mechanical, thermal and noxious pain suggest that cannabinoids may be effective analgesics. Indeed, in clinical trials of postoperative and cancer pain and pain associated with spinal cord injury, cannabinoids have proven more effective than placebo but may be less effective than existing therapies. Dronabinol, a commercially available form of Δ-9-THC, has been used successfully for increasing appetite in patients with HIV wasting disease, and cannabinoid receptor antagonists may reduce obesity. Acute adverse effects following cannabis usage include sedation and anxiety. These effects are usually transient and may be less severe than those that occur with existing therapeutic agents. The use of nonpsychoactive cannabinoids such as cannabidiol and dexanabinol may allow the dissociation of unwanted psychoactive effects from potential therapeutic benefits. The existence of other cannabinoid receptors may provide novel therapeutic targets that are independent of CB(1) receptors (at which most currently available cannabinoids act) and the development of compounds that are not associated with CB(1) receptor-mediated adverse effects. Further understanding of the most appropriate route of delivery and the pharmacokinetics of agents that act via the endocannabinoid system may also reduce adverse effects and increase the efficacy of cannabinoid treatment. This review highlights recent advances in understanding of the endocannabinoid system and indicates CNS disorders that may benefit from the therapeutic effects of cannabinoid treatment. Where applicable, reference is made to ongoing clinical trials of cannabinoids to alleviate symptoms of these disorders.

Croxford, J.L. and S.D. Miller (2004) "Towards cannabis and cannabinoid treatment of multiple sclerosis." *Drugs Today (Barcelona)* **40** (8): 663-676.

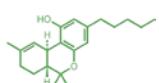
Multiple sclerosis is a common human demyelinating disease of the central nervous system (CNS), and it is thought to involve autoimmune responses to CNS myelin antigens. Current symptomatic therapies for multiple sclerosis are in some cases ineffective and may have a high risk of serious side effects. This has led some multiple sclerosis patients to self-medicate with cannabis, which anecdotal evidence suggests may be beneficial in controlling symptoms such as spasticity, pain, tremor and bladder dysfunction. In support of these claims, results from experimental studies have suggested that cannabinoid-based treatments may be beneficial in a wide number of diseases. Furthermore, recent research in animal models of multiple sclerosis has



demonstrated the efficacy of cannabinoids in controlling disease-induced symptoms such as spasticity and tremor, as well as in ameliorating the severity of clinical disease. However, these initially promising results have not yet been fully translated into the clinic. Although cannabinoid treatment of multiple sclerosis symptoms has been shown to be both well tolerated and effective in a number of subjective tests in several small-scale clinical trials, objective measures demonstrating the efficacy of cannabinoids are still lacking. Currently, a number of large-scale phase III clinical trials are under way to further elucidate the use of cannabinoids in the symptomatic treatment of multiple sclerosis. This review highlights the recent advances in our understanding of the endocannabinoid system, discusses both the experimental and clinical evidence for the use of cannabinoids to treat multiple sclerosis and explores possible future strategies of cannabinoid therapy in multiple sclerosis.

Curtis, A., C. E. Clarke, et al. (2009) "Cannabinoids for Tourette's Syndrome." Cochrane Database of Systematic Reviews (4): CD006565.

Background: Gilles de la Tourette Syndrome (GTS) is a developmental neuropsychiatric disorder characterised by the presence of chronic motor and phonic tics. Drugs currently used in the treatment of GTS either lack efficacy or are associated with intolerable side effects. There is some anecdotal and experimental evidence that cannabinoids may be effective in treating tics and compulsive behaviour in patients with GTS. There are currently no systematic Cochrane reviews of treatments used in GTS. There is one other Cochrane review being undertaken at present, on the use of fluoxetine for tics in GTS.
Objectives: To evaluate the efficacy and safety of cannabinoids as compared to placebo or other drugs in treating tics, premonitory urges and obsessive compulsive symptoms (OCS), in patients with GTS.
Search Strategy: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (in The Cochrane Library Issue 4 2008), MEDLINE (January 1996 to date), EMBASE (January 1974 to date), PsycINFO (January 1887 to date), CINAHL (January 1982 to date), AMED (January 1985 to date), British Nursing Index (January 1994 to date) and DH DATA (January 1994 to date). We also searched the reference lists of located trials and review articles for further information.
Selection Criteria: We included randomised controlled trials (RCTs) comparing any cannabinoid preparation with placebo or other drugs used in the treatment of tics and OCS in patients with GTS.
Data Collection and Analysis: Two authors abstracted data independently and settled any differences by discussion.
Main Results: Only two trials were found that met the inclusion criteria. Both compared a cannabinoid, Δ-9-Tetrahydrocannabinol (Δ-9-THC), either as monotherapy or as adjuvant therapy, with placebo. One was a double blind, single dose crossover trial and the other was a double blind, parallel group study. A total of 28 different patients were studied. Although both trials reported a positive effect from Δ-9-THC, the improvements in tic frequency and severity were small and were only detected by some of the outcome measures.
Authors' Conclusions: Not enough evidence to support the use of cannabinoids in treating tics and obsessive compulsive behaviour in people with Tourette's syndrome.



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Czajka, S. (2001) "Mit Cannabis vergessen Nerven den Schmerz." Pharmazeutische Zeitung **146** (42): 38.

Ist Cannabis ein brauchbares Medikament gegen Schmerzen? Diese Frage wird derzeit von Ärzten und Grundlagenforschern intensiv untersucht. So wie für Opioide, gibt es auch für Cannabinoide Rezeptoren und dazugehörige körpereigene Liganden, die Endocannabinoide. Mit den molekularen und zellulären Mechanismen dieser endogenen Botenstoffe beschäftigte sich ein Symposium auf dem Deutschen Schmerzkongress in Berlin.

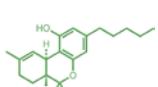
Derzeit sind zwei Rezeptoren für Cannabinoide bekannt, CB1 und CB2. Diese Rezeptorsubtypen gleichen sich in etwa 40 Prozent ihrer Bausteine. Bisher wurden die CB2-Rezeptoren nur in Verbindung mit peripherem Nerven- und Immunsystem gefunden. Auf Neuronen des Zentralnervensystems wurden bisher ausschließlich CB1-Rezeptoren gefunden. Diese CB1-Rezeptoren sitzen dabei vorwiegend auf Interneuronen in Regionen, die für Motorik, Schmerzempfinden und Lernen zuständig sind. Sie werden durch die beiden derzeit bekannten Endocannabinoide Anandamid (Arachidonylethanolamid) und 1-Arachidonylglycerol aktiviert.

Diese Liganden ähneln in ihrer chemischen Struktur Arachidonsäure-Derivate wie Prostaglandinen oder Leukotrienen. Sie vermitteln aber Signale ähnlich Neurotransmittern. "Es handelt sich hier um einen neuartigen retrograden synaptischen Kontrollmechanismus durch Lipid-Neurotransmitter", erklärte Professor Dr. Walter Zieglgänsberger vom Max Planck-Institut für Psychiatrie in München. Denn im Unterschied zu den meisten Neurotransmittern oder Endorphinen haben Endocannabinoide keine Peptid-Grundstruktur und werden nicht aus Vesikeln sondern aus der Zellmembran freigesetzt. Das Signal wird auf den depolarisierenden Stimulus hin nicht vom prä- zum post-synaptischen Nervenende gesendet, sondern umgekehrt. Funktionell wirken Endocannabinoide ähnlich dämpfend auf die Reizweiterleitung wie Endorphine.

Aktionspotentiale in der Peripherie

Ein Schmerzreiz löst in dünnen Nervenfasern (Nozizeptoren) in der Peripherie Aktionspotentiale aus. Diese kurzen elektrischen Impulse setzen an ihrer ersten Schaltstelle im Hinterhorn des Rückenmarks erregende Neurotransmitter frei. Aus präsynaptischen Endigungen werden unter anderen Transmitter wie L-Glutamat und Substanz P in den synaptischen Spalt freigesetzt. Diese erregenden Neurotransmitter diffundieren über den synaptischen Spalt zur postsynaptischen Membran und depolarisieren sie, der Reiz wird weitergeleitet. Diese Depolarisation führt auch zur Synthese von Endocannabinoiden. Diese werden gegen die Richtung des Schmerzreizes in den synaptischen Spalt abgegeben und können dann durch die Aktivierung von präsynaptischen CB1-Rezeptoren wirken (retrogrades Signal). Die Aktivierung dieser Rezeptoren bremst die präsynaptische Freisetzung weiterer Transmitter. Der synaptische Übertragungsvorgang und damit der Reizeinstrom werden abgeschwächt. Nach Aktivierung des Rezeptors und des angekoppelten G-Proteins werden Adenylatzyklase und Proteinkinase gehemmt, die Aktivitäten von Kalium- und Calcium-Kanälen ändern sich. So wird die Freisetzung von erregenden und hemmenden Neurotransmittern wie L-Glutamat und g-Aminobuttersäure (GABA) kontrolliert.

CB1-Rezeptoren wurden bisher insbesondere auf Interneuronen gefunden. Interneurone sind Nervenzellen mit kurzen Axonen, die meist die Erregbarkeit



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derjenigen Nervenzellen regulierend beeinflussen, deren Axone längere Bahnen bilden. Wie Zieglänsberger erklärte, werden meist mehrere erregende und hemmende Interneurone parallel aktiviert. Diese untereinander vernetzten Interneurone unterdrücken während eines einlaufenden Schmerzreizes vermutlich kurzzeitig ihre hemmende Wirkung auf Nervenzellen und ermöglichen so die rasche Weiterleitung des Reizes. Ihre meist hemmende Wirkung auf die Weiterleitung von Schmerzreizen setzt aber rasch wieder ein und verhindert so, dass diese Reize zu einer langandauernden Erregbarkeitssteigerung führen (wind up).

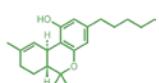
Cannabinoid gegen Teufelskreis

Werden Nervenzellen wiederholt synaptisch durch Schmerzreize gereizt, so verstärkt sich die Reizübertragung an den dafür verantwortlichen Synapsen. Der Schmerz bahnt sich seinen Weg. Das kann so weit gehen, dass der Prozess sich verselbständigt und Nervenzellen aus dem Rückenmark auch ohne Reiz von außen Signale an das Gehirn senden. Für normale Lernprozesse ist es hilfreich, wenn Reize schneller übertragen und verarbeitet werden, beim Schmerz kann es so zu einem quälenden Teufelskreis kommen. Endocannabinoide sind an diesen Regulationsmechanismen beteiligt. Es ist daher auch davon auszugehen, dass ein therapeutisch eingesetztes Cannabinoid dieses Aufschaukeln der neuronalen Aktivität unterdrücken kann, und so das Gleichgewicht der neuronalen Erregung wieder hergestellt wird. Versuche an Mäusen bekräftigen diese Vermutung. In-vitro-Versuche zeigen, dass transgene Mäuse ohne den CB1-Rezeptor (CB1-Knock-out-Mäuse) gegenüber Wildtypieren eine deutliche verstärkte Langzeitpotenzierung in bestimmten Gehirnarealen aufweisen, also eine Veränderung der neuronalen Netze, die eng mit Lernen und Gedächtnis assoziiert sind, berichtete Frau Dr. Shahnaz Christina Azad, Max-Planck-Institut für Psychiatrie, München. Die wiederholte Applikation von Schmerzreizen in diesen transgenen Tieren senkte im Gegensatz zu den Wildtypieren die Schmerzschwelle. Auch emotional gekoppelte Lernprozesse wie die Angst konditionierung, die bei der Chronifizierung von Schmerz nach neuesten Erkenntnissen eine wichtige Rolle spielen, scheinen eng mit dem Endocannabinoidsystem verbunden zu sein.

"Es ist daher zu erwarten", sagte Azad, "dass der Aktivierung des endogenen Cannabinoid-Systems durch exogen zugeführte Cannabinoide, insbesondere auch im Hinblick auf die dazu beitragenden emotionalen Komponenten, eine bedeutende Rolle zukommt."

de Ridder, D., C.S. Constantinescu, C. Fowler, R. Kavia, and N. Sarantis (2006) "Randomised controlled study of cannabis-based medicine (Sativex®) in patients suffering from multiple sclerosis associated detrusor overactivity." 22nd Congress of the ECTRIMS, 27-30 September 2006, Madrid, Spain.

Bladder problems are a common feature of Multiple Sclerosis (MS), with up to 80% of MS subjects experiencing voiding dysfunction. Methods: A 10 week double blind, randomized, placebo controlled parallel group trial was conducted. After a 2 week baseline period, 135 subjects with MS and detrusor overactivity were randomized to receive either Sativex (a standardised whole plant cannabis medicine), or placebo. The primary end point was a reduction in the daily number of episodes of urgency incontinence. Other end points included incidence of nocturia and urgency, overall bladder condition



(measured on an 11-point numerical rating scale), daytime frequency, quality of life, patient's global impression of change (PGIC) and volume voided.

Results: For the primary endpoint, the decrease from baseline in incontinence episode frequency per day was in favour of the Sativex treated group but was not statistically significant (-1.08, p=0.57). Of the secondary/tertiary end points, 10 of the 11 were in favour of Sativex. In 4 out of 7 secondary end points there was statistical significance in favour of Sativex. These were reduction in nocturia episodes (-0.28, p=0.010); highly statistically significant improvement in patient's opinion of bladder symptom severity (-1.16 points, p=0.001); reduction in the number of voids per day (-0.85, p=0.007) and PGIC where 83.6% of subjects receiving Sativex compared with 58.2% receiving placebo considered the status of their bladder condition had improved (odds ratio 2.56, p=0.005). The decrease in number of urgency episodes in Sativex treated subjects just failed to reach statistical significance (-0.76, p=0.071). Of the tertiary end points, the number of daytime voids was statistically significantly in favour of Sativex (-0.57, p=0.044). There was a trend in favour of improvement in Quality of Life but which did not reach statistical significance. Conclusions: Sativex treatment had a positive impact on the symptoms of overactive bladder in multiple sclerosis patients. It provides qualitative and quantitative symptomatic improvement and a normalisation of the symptoms of urinary frequency for many subjects with MS and further research is warranted.

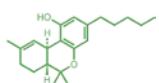
Deadwyler, S., J. Vivian, I. Meng, J.M. Walker, D. Simone and K. Hargreaves (1997) "Marijuana & Analgesia" Symposium: ,Functional Role of Cannabinoid Receptors' in New Orleans by the Society of Neuroscience USA.

New research shows that substances similar to or derived from marijuana, known as cannabinoids, could benefit the more than 97 million Americans who experience some form of pain each year.

In the past, the majority of evidence suggesting that cannabinoids could crush pain without causing a loss of touch was anecdotal. Some animal studies did show that cannabinoids decreased pain sensitivity in animals, but they also induced a wide variety of additional behavioral effects, such as changes in attention, deficits in movement, and cognitive impairment. It was unclear whether the animals showed a decrease in pain sensitivity because of these other behavioral effects or if the cannabinoids directly targeted the pain system.

Now careful studies are showing that the substances have a direct affect on pain signals in the central nervous system and peripheral tissues. The cannabinoids not only act as an analgesic, but also prevent the condition hyperalgesia, or an enhanced sensitivity to pain, which often accompanies tissue injury and inflammation. In addition, the new research reveals similarities and differences between cannabinoids and a group of pain killers that are used today called opioids or morphine-like drugs. Opioids are very effective but also cause many unwanted side effects. The most severe is physical dependence. The studies show that cannabinoids could be manipulated to form a new type of pain reliever.

In one new study scientists show that the active ingredient in marijuana, Δ-9-THC, and another synthetic cannabinoid, WIN 55212, exhibit analgesic characteristics in monkeys. In addition, the pain relief occurs through a system that is different from opioids, according to the researchers from the University



of Michigan Medical School.

In the study, the researchers measured the compounds analgesic characteristics in three rhesus monkeys with a technique that involved a warm-water bath. Monkeys will keep their tails in water kept at 50 degrees Celsius for a longer time than normal if they have received drugs with analgesic properties. "As the dose of the cannabinoids or the opioids increased, the monkeys were slower to remove their tails from the warm-water bath, revealing an analgesic action for these compounds," says Jeffrey Vivian. "It is important to note, however, that many cannabinoids produce a very rapid tolerance necessitating the use of higher doses and they aren't better at reducing pain than traditional analgesics such as opioids. "In general, opioids had a greater analgesic effect than cannabinoids.

In other findings, the scientists discovered that the administration of a drug that incapacitates the cannabinoids will block the cannabinoid effects but not the opioid effects. And a drug that solely knocks the opioids out of commission will block the opioid effects but not the cannabinoid effects. "This demonstrates the independence of the cannabinoid and opioid systems to cause pain relief," says Vivian.

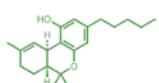
Another group of researchers also found that cannabinoids and opioids relieve pain through different mechanisms. They found, however, that cannabinoids and opioids both target the same pain-modulating nerve cells or neurons.

"The results suggest that marijuana-like drugs may be useful as an adjuvant in combination with other therapies for treating certain types of pain," says Ian Meng of the University of California at San Francisco.

Meng and his co-workers studied anaesthetised rats with electrophysiology, a technique that allowed the researchers to measure the electrical impulses, known as action potentials, of single brain cells in a region of the brain that modulates pain. They found that following administration of the synthetic cannabinoid, WIN55 212-2, the rats no longer moved their tails away from a heat source. This shows a sign of reduced pain. In addition, the effect of the cannabinoid was not reversed by a drug that prevents the action of the opioid, morphine, nor was the effect of morphine reversed by a drug that prevents the action of cannabinoids. "While this shows that the drugs reduce pain through different mechanisms, we also have shown that both cannabinoids and opioids produce similar changes in the activity of specific neurons that help reduce pain," says Meng.

These neurons are in the rostral ventromedial medulla, a pain-modulating center of the brain. Scientists recently discovered that under certain circumstances pain signals can be modulated by certain brain areas. These pain-modulating centers can increase or decrease the amount of pain a person feels by influencing the number of pain signals that are allowed to pass through the spinal cord. "For example, people injured in war often do not feel pain for a long time after the injury because pain-modulating centers prevent pain information from reaching parts of the brain that are important for the conscious perception of pain," says Meng.

In the rostral ventromedial medulla region, there are two types of neurons that control pain transmission through the spinal cord. The "off-cell" neurons can inhibit the pain signals passing through the spinal cord. The "on-cell" neurons may actually increase the amount of pain signals. Previous studies have shown that morphine increases the activity of off-cell neurons and decreases



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the activity of on-cell neurons. "Our study shows that cannabinoids can produce the same effect as morphine on off-cell and on-cell activity in the brain," says Meng.

Other researchers studied the spinal cord and also have discovered that cannabinoids play a crucial role in pain processing. "Specifically we found that cannabinoids depress the reactions of spinal neurons that transmit pain messages back to the brain," says J. Michael Walker of Brown University. "The responses of neurons that transmit messages about non-painful stimuli, however, are unaltered."

In addition, the researchers found that cannabinoids target the brain region, nucleus A5, which is near the rostral ventromedial region and like that area, acts in the front of the pain processing loop, by sending painful messages to the spinal cord.

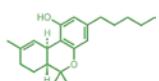
In the study, the scientists injected the cannabinoid WIN55 212-2 into the nucleus A5 in rats. "Injections of less than a tenth of a millionth of an ounce of the cannabinoid cause a profound loss of pain sensitivity," says Walker. This brain area appears to contribute to pain processing by using norepinephrine - a brain neurotransmitter - to send messages. The messages can block the transmission of information about painful events. Past research has shown that injections of drugs that block the action of norepinephrine also inhibit the analgesic effects of cannabinoids. "Our new research isolates the particular source of norepinephrine and makes a direct link to pain pathways in the brain," says Walker.

The findings also provides insight on the brain's natural cannabinoid, anandamide, derived from the Sanskrit word meaning "internal bliss," according to the researchers. The marijuana-like substance was discovered by the cannabinoid researchers William Devane and Raphael Mechoulam, in 1992. It produces its effects on the brain through the same chemical mechanism that is used by the main psychoactive constituent of the marijuana plant. "The new research provides insight into the functions of this newly discovered neuro-chemical system by demonstrating that the synthetic cannabinoids act on known pathways that function naturally to control the entry of pain messages into the spinal cord," says Walker.

The cannabinoids ability to target the body's natural pain system also can prevent the development of an enhanced sensitivity to pain, or hyperalgesia, according to a new study by researchers at the University of Minnesota. Pain and hyperalgesia often accompany tissue injury and inflammation. Severe hyperalgesia, which can be debilitating and often difficult to treat, also is associated with many chronic painful syndromes such as nerve disease, chronic inflammation and spinal cord injury. The condition can be so intense that warming the skin or gently touching the skin is perceived as painful.

In the new work, the researchers infused the cannabinoid WIN55 212-2 intravenously into the rats. Next, they initiated a model of hyperalgesia by injecting the rat's hind paw with capsaicin, the pungent ingredient in hot chile peppers. "The pain and hyperalgesia from capsaicin was shown to be due in part to the activation and hyperactivity of pain neurons in the spinal cord to touching or gently warming the skin," says Donald Simone. "In these studies, we determined that cannabinoids would block the pain as well as the hyperactivity of spinal neurons."

Animals that received 10 micrograms per kilogram or higher of the



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cannabinoid exhibited a dramatic decrease in the amount of time that they spent guarding their hind paws after the capsaicin injections, say the researchers. Pre-treatment with the cannabinoid also decreased the amount of sensitivity observed to warmth and touch. And animals that received 100 micrograms per kilogram of the cannabinoid did not display any hyperalgesia at all. "In fact, their withdrawal responses to noxious heating were normal," says Simone. "This demonstrates that the cannabinoid did not impair the animals' capability to withdraw from the stimulus."

Another group studied a different rat model of hyperalgesia, the carrageenan model. This model of inflammation has previously been shown to be predictive of drugs which relieve pain due to arthritis. The researchers discovered that the natural cannabinoid, anandamide, produced pain relief when it was injected in the skin at the site of the perceived injury. While cannabinoids can interact with receptors or receiving areas on pain sensitive cells in the spinal cord and brain to reduce pain, they also have an opportunity to initiate side effects such as disorientation, say the researchers. "These results suggest that local administration of the cannabinoid to the site of injury may be able to both prevent pain from occurring and reduce pain which has already occurred without producing side effects," says Kenneth Hargreaves of the University of Texas who conducted the research when he was at the University of Minnesota. The researchers believe side effects are limited because the cannabinoid acts locally and does not reach the spinal cord or brain.

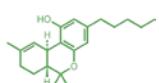
Hargreaves found that the cannabinoid works immediately in the peripheral tissues by reducing the amount of leakiness in nearby blood vessels and preventing the flow of pain-enhancing substances. Hyperalgesia is known to occur when blood vessels become leaky and allow compounds, some of which activate pain receptors, to flow into the injured tissue. The administration of anandamide to isolated skin could prevent the release of the pain-enhancing substances following a painful stimulus, according the researchers.

"Collectively the research shows that the cannabinoid administered at the site of injury works locally to produce analgesia with limited side effects, says Hargreaves.

Dehnel, T. (2011) "Cannabis, a new option for chronic cancer pain?" *Lancet* **12** (11): 995.

Derkinderen, P., E. Valjent, Darcel, F., Damier, P. and J. A. Girault (2004) "[Cannabis and cannabinoid receptors: from pathophysiology to therapeutic options]" *Revue Neurologique (Paris)* **160** (6-7): 639-649.

Although cannabis has been used as a medicine for several centuries, the therapeutic properties of cannabis preparations (essentially haschich and marijuana) make them far most popular as a recreational drugs. State of the art Scientific studies on the effects of cannabis were advanced considerably by the identification in 1964 of cannabinoid Δ-9-tetrahydrocannabinol (THC), recognized as the major active constituent of cannabis. Cloning of the centrally located CB1 receptor in 1990 and the identification of the first endogenous ligand of the CB1 receptor, anandamide, in 1992 further advanced our knowledge. Perspective and conclusions Progress has incited further research on the biochemistry and pharmacology of the cannabinoids in



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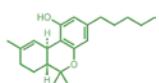
numerous diseases of the central nervous system. In the laboratory animal, cannabinoids have demonstrated potential in motion disorders, demyelinating disease, epilepsy, and as anti-tumor and neuroprotector agents. Several clinical studies are currently in progress, but therapeutic use of cannabinoids in humans could be hindered by undesirable effects, particularly psychotropic effects. CB1 receptor antagonists also have interesting therapeutic potential.

Deutsch, S.I., R.B. Rosse, J.M. Connor, J.A. Burkett, M.E. Murphy, and F.J. Fox (2008) "Current status of cannabis treatment of multiple sclerosis with an illustrative case presentation of a patient with MS, complex vocal tics, paroxysmal dystonia, and marijuana dependence treated with dronabinol." *CNS Spectrums* **13** (5): 393-403.

Pain, spasticity, tremor, spasms, poor sleep quality, and bladder and bowel dysfunction, among other symptoms, contribute significantly to the disability and impaired quality of life of many patients with multiple sclerosis (MS). Motor symptoms referable to the basal ganglia, especially paroxysmal dystonia, occur rarely and contribute to the experience of distress. A substantial percentage of patients with MS report subjective benefit from what is often illicit abuse of extracts of the Cannabis sativa plant; the main cannabinoids include Δ-9-tetrahydrocannabinol (Δ-9-THC) and cannabidiol. Clinical trials of cannabis plant extracts and synthetic Δ-9-THC provide support for therapeutic benefit on at least some patient self-report measures. An illustrative case is presented of a 52-year-old woman with MS, paroxysmal dystonia, complex vocal tics, and marijuana dependence. The patient was started on an empirical trial of dronabinol, an encapsulated form of synthetic Δ-9-THC that is usually prescribed as an adjunctive medication for patients undergoing cancer chemotherapy. The patient reported a dramatic reduction of craving and illicit use; she did not experience the "high" on the prescribed medication. She also reported an improvement in the quality of her sleep with diminished awakenings during the night, decreased vocalizations, and the tension associated with their emission, decreased anxiety and a decreased frequency of paroxysmal dystonia.

Di Marzo, V. and L. De Petrocellis (1997) "The Endogenous Cannabinoid Signalling System: Chemistry, Biochemistry and Physiology." **1**. <http://www.netsci-journal.com/97v1/97007/index.htm>

The cloning of central and peripheral cannabinoid receptor subtypes and the finding, in animal tissues, of endogenous metabolites capable of selectively binding them, opened a new age in cannabinoid research. In this article, starting from the pharmacology and chemistry of Indian hemp-derived as well as synthetic cannabinoids, and ending with the most recent findings on the biochemistry of *endocannabinoids*, we review the current state of the art of cannabinoid research, and explore the possible physiological roles of a newly discovered chemical regulatory apparatus: the *endogenous cannabinoid system*. Contents: Introduction – Pharmacological properties of plant and synthetic cannabinoids – Chemical signalling through cannabinoid receptors – The discovery of the 'endocannabinoids' – Metabolic aspects of the 'endocannabinoids': biosynthesis, uptake and degradation – Possible physiological roles of the endogenous cannabinoid system – Concluding remarks – Acknowledgements – References.



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Domino, L. (1997) "Medicinal marijuana?" New England Journal of Medicine **336** (16): 1185.

Dunn, M. and R. Davis (1974) "The perceived effects of marijuana on spinal cord injured males." Paraplegia **12** (3).

A recent, informal, confidential survey was taken on a Spinal Cord Injury ward concerning the effects of marijuana on pain and spasticity in spinal cord injured males. Ten patients who admitted that they had used marijuana after they had been injured were asked how the drug affected burning, phantom pain, muscle spasms, bladder spasms, urinary retention, headache pain and pleasant sensations. A table indicates the number of patients in each category with the column labelled 'Distract' indicating that the drug did not decrease the pain but helped the patient pay less attention to it and the column labelled 'Not applicable' indicating that the patient did not experience the sensation in the non drug state. The perceived decrease in pain and spasticity shown by this survey, even though replies may be biased, indicates that better controlled studies would be worthwhile.

DuPont, R.L., P.D. Kanof, W.A. Hensel, L. Domino, R.M. Dorizzi, A. Taub, M.E. Deutsch, D. Grant, J.E. Copple, J.A. Tilelli, G.A. Johnson, R. Mays, D.P. Tashkin, Duran, M., J.R. Laporte and D. Capella (2004) "[News about therapeutic use of Cannabis and endocannabinoid system]." Medicina Clinica (Barcelona) **122** (10): 390-398.

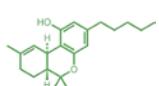
Growing basic research in recent years led to the discovery of the endocannabinoid system with a central role in neurobiology. New evidence suggests a therapeutic potential of cannabinoids in cancer chemotherapy-induced nausea and vomiting as well as in pain, spasticity and other symptoms in multiple sclerosis and movement disorders. Results of large randomized clinical trials of oral and sublingual Cannabis extracts will be known soon and there will be definitive answers to whether Cannabis has any therapeutic potential. Although the immediate future may lie in plant-based medicines, new targets for cannabinoid therapy focuses on the development of endocannabinoid degradation inhibitors which may offer site selectivity not afforded by cannabinoid receptor agonists.

EMCDDA – ELDD Comparative Study May 2002 "Medicinal cannabis and derivatives" 15 Pages:

http://eldd.emcdda.org/databases/eldd_comparative_analyses.cfm

Eppinger, U. (2013) "Cannabis in der Therapie: Geregelter Einsatz möglich?" MedScape Deutschland: <http://praxis.medscapemedizin.de/artikel/4900822>

Keine Frage – Cannabis polarisiert. Wie sehr dies der Fall ist, war jetzt im New England Journal of Medicine zu lesen. Der Fall: Marylin, 68 Jahre alt mit Brustkrebs-Metastasen in Lunge, Brustraum und Lendenwirbelsäule. Die Chemo mit Doxorubicin raubt ihr Kraft und Appetit, verursacht Brechreiz. Ondansetron und Prochlorperazine helfen mäßig bis gar nicht, Acetaminophen (in Deutschland Paracetamol) – alle 8 Stunden 1000 mg – und Oxycodon lindern kaum die Schmerzen. Marylin will einen Versuch mit Marihuana starten. Zwei Ärzte wurden in dem Bericht nach ihrer Meinung befragt:



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Dr. J. Michael Bostwick vom Department of Psychiatry and Psychology der Mayo Clinic in Rochester, USA, meint: „Ein gutes Arzt-Patienten-Verhältnis vorausgesetzt, würde ich die Verordnung von medizinischem Cannabis für Patienten in ähnlichen Situationen wie Marylins befürworten.“ Eine wachsende Zahl von Berichten unterstützt dessen Effektivität, speziell bei Schmerzen und Übelkeit, wenn Patienten auf herkömmliche Mittel nicht ansprechen.

Dr. Gary M. Reisfield vom Institute for Behavior and Health, Rockville, MD und Dr. Robert L. DuPont von der Georgetown University School of Medicine in Washington, DC, warnen hingegen davor, einen Patienten mit unkontrollierten Symptomen bei Brustkrebs einfach mit einer Erlaubnis zum Cannabisrauchen nach Hause zu entlassen. Gerauchtes Marihuana sei eine nicht medizinische, nicht spezifische und potenziell riskante Methode der Behandlung. Als verschreibungspflichtige Mittel stünden sowohl Dronabinol und Nabilon zur Therapie von Übelkeit und Erbrechen zur Verfügung.

Das BfArM muss Ausnahmen bestätigen

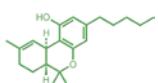
Auch hierzulande verstößt ein schwerstkranker Patient, der zur Schmerzlinderung Marihuana konsumiert, gegen das Betäubungsmittelgesetz. Seit einem Urteil des Bundesverwaltungsgerichtes vom 19. Mai 2005 sind Ausnahmen vom Cannabis-Verbot aber in Einzelfällen möglich. Wie Maik Pommer, Sprecher des Bundesinstituts für Arzneimittel und Medizinprodukte (BfArM) in Bonn erklärt, gibt es für Patienten nur einen legalen Weg, an cannabishaltige Medikamente zu kommen: über eine Ausnahmegenehmigung des BfArM. „Unsere Experten prüfen dann, ob Cannabis schmerztherapeutisch sinnvoll ist. Ist das so, etwa weil es keine vernünftigen alternativen Therapien gibt, wird die Genehmigung erteilt.“ Diese befugt die Patienten, via Rezept über ihre Apotheke Cannabis-Therapeutika wie Dronabinol oder Sativex® zu beziehen.

278 Patientinnen und Patienten haben seit 2005 beim BfArM Anträge auf Erteilung einer entsprechenden Ausnahmeverlaubnis gestellt, 140 Patienten erhielten sie. Momentan gibt es 119 Genehmigungen, da zwischenzeitlich 21 Patienten ihre Erlaubnis an das BfArM zurückgegeben haben oder verstorben sind. Von diesen 119 Fällen wurde 100 Mal der Erwerb von Cannabis-Blüten und 19 Mal der Erwerb von Cannabis-Extrakt genehmigt.

Bezahlen muss der Patient das Mittel allerdings aus eigener Tasche – und genau hier liegt für viele das Problem. So kann zwar das vor 2 Jahren für Spastiken bei MS zugelassene Sativex® von den Krankenkassen zur Schmerztherapie übernommen werden. Bei dem hierzulande nicht zugelassenen Dronabinol hingegen fallen schnell Kosten von mehreren 100 Euro im Monat an. Leisten kann sich das längst nicht jeder Schwerkranke. Reagiert die Kasse dann nicht kulant, sehen viele nur einen Weg: Marihuana illegal anzubauen.

Kassen zahlen in der Regel nicht

Denn in vielen Köpfen scheint noch das Bild des „Kiffers auf Staatskosten“ herumzugeistern. Dr. Peter Cremer-Schaeffer, Leiter der Bundesopiumstelle am BfArM, bringt es so auf den Punkt: „Cannabis sollte raus aus der Schmuddelecke.“ Die Bundesregierung im Rahmen einer Kleinen Anfrage schreibt: „Die gesetzlichen Rahmenbedingungen bieten einen gewissen Ermessensspielraum, eine Kostenübernahme von Rezepturarzneimitteln mit nicht zugelassenen Wirkstoffen [...] in besonderen Einzelfällen zu gewähren, [...] wenn für die Behandlung einer lebensbedrohlichen bzw. schwerwiegenden



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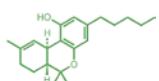
Erkrankung keine andere Therapie zur Verfügung steht.“ Das zu beurteilen obliege den Experten des Medizinischen Dienstes im Auftrag der jeweiligen Krankenkasse.

Ann Marini, Sprecherin des GKV-Spitzenverbandes, erklärt hierzu: “Die regelmäßige Anfertigung von Rezepturen in größerem Umfang ist nach unserer Auffassung ein Unterlaufen der arzneimittelrechtlichen Zulassung.“ Davon unabhängig seien Rezepturen nach § 135 SGB V (Neue Untersuchungs- und Behandlungsmethoden) zu bewerten. Aufgrund der unzureichenden Datenlage zu Cannabinoiden sei das bislang nicht erfolgt. Ein Urteil des Bundessozialgerichts vom 27.3.2007 (Az.: B1 KR 30/06 R) verneine die Erstattungsfähigkeit von Dronabinol-Rezepturen. Marini: „Es gibt keine Kostenübernahme - auch nicht im Ausnahmefall - von Dronabinol-Rezepturen durch die GKV.“

Der schwarze Peter bleibt also bei den schwerkranken Patienten und ihren behandelnden Ärzten.

Farrar, J.T., A.B. Troxel, C. Stott, P. Duncombe, and M.P. Jensen (2008) "Validity, reliability, and clinical importance of change in a 0-10 numeric rating scale measure of spasticity: a post hoc analysis of a randomized, double-blind, placebo-controlled trial." *Clinical Therapeutics* **30** (5): 974-985.

Background: The measurement of spasticity as a symptom of neurologic disease is an area of growing interest. Clinician-rated measures of spasticity purport to be objective but do not measure the patient's experience and may not be sensitive to changes that are meaningful to the patient. In a patient with clinical spasticity, the best judge of the perceived severity of the symptom is the patient. **Objectives:** The aim of this study was to assess the validity and reliability, and determine the clinical importance, of change on a 0-10 numeric rating scale (NRS) as a patient-rated measure of the perceived severity of spasticity. **Methods:** Using data from a large, randomized, doubleblind, placebo-controlled study of an endocannabinoid system modulator in patients with multiple sclerosis-related spasticity, we evaluated the test-retest reliability and comparison-based validity of a patient-reported 0-10 NRS measure of spasticity severity with the Ashworth Scale and Spasm Frequency Scale. We estimated the level of change from baseline on the 0-10 NRS spasticity scale that constituted a clinically important difference (CID) and a minimal CID (MCID) as anchored to the patient's global impression of change (PGIC). **Results:** Data from a total of 189 patients were included in this assessment (114 women, 75 men; mean age, 49.1 years). The test-retest reliability analysis found an interclass correlation coefficient of 0.83 ($P < 0.001$) between 2 measures of the 0-10 NRS spasticity scores recorded over a 7- to 14-day period before randomization. A significant correlation was found between change on 0-10 NRS and change in the Spasm Frequency Scale ($r = 0.63$; $P < 0.001$), and a moderate correlation was found between the change on 0-10 NRS and the PGIC ($r = 0.47$; $P < 0.001$). A reduction of approximately 30% in the spasticity 0-10 NRS score best represented the CID and a change of 18% the MCID. **Conclusions:** The measurement of the symptom of spasticity using a patient-rated 0-10 NRS was found to be both reliable and valid. The definitions of CID and MCID will facilitate the use of appropriate responder analyses and help clinicians interpret the significance of future results.



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Fassing, P. (2012) "Cannabis auf Rezept - Besuch bei THC Pharm." Intro 200 (3): 68-71.

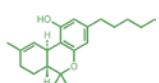
Im Januar forderte die Partei Die Linke eine Legalisierung des geregelten Cannabis-Anbaus für den Eigenbedarf. Während sie dabei vor allem ein hedonistisch motiviertes Klientel im Blick gehabt haben dürfte, haben kranke Konsumenten ganz andere Probleme. Das Unternehmen THC-Pharm hat den Wirkstoff der umstrittenen Pflanze in Deutschland erstmals für diese zugänglich gemacht und hilft so gegen Depressionen, Übelkeit und Appetitlosigkeit. Ganz legal, aber unter strengen Auflagen. Philip Fassing reiste nach Frankfurt am Main, um sich ein Bild vom Laboralltag der THC-Farm in Deutschland zu machen.

Ein skeptischer Blick in meine Notizen bestätigt meine Annahme: Hier soll tatsächlich die Avantgarde der medizinischen Cannabis-Forschung ihren Sitz haben. Ich stehe an der Offenbacher Landstraße in Frankfurt, die mit ihren rauen Pflastersteinen eher einer größeren Altstadt-Gasse gleicht, und suche nach Anhaltspunkten für die medizinische Pionier-Arbeit, die hier geleistet wird. Statt Fertigungshallen, Laborkomplexen oder Passierkontrollen umgibt einen aber lediglich das unaufgeregte Vorort-Ambiente des südöstlich gelegenen Stadtteils Oberrad. Über einen Hinterhof gelange ich schließlich in den Bürokomplex von THC-Pharm, wo mich Mitbegründer Holger Rönitz freundlich empfängt. Gewöhnlich komme er legerer zur Arbeit, heute trägt er aber, unserem Termin geschuldet, Nadelstreifen. Ohne Krawatte allerdings. Der langjährige Greenpeace-International-Sprecher ist mittlerweile seit zwölf Jahren bei THC-Pharm tätig und neugierige Journalisten gewohnt. Zuletzt stand das hessische Unternehmen im Mittelpunkt, als seine Chemiker vor etwa drei Jahren den Wirkstoff der Modedroge Spice identifizierten – die Presse-Resonanz war enorm und reichte vom Spiegel bis zur FAZ. Bekannt ist das Unternehmen aber vor allem für seine Rezeptur-Substanz Dronabinol, dem synthetisierten und nahezu reinen Wirkstoff der Cannabis-Pflanze.

Cannabis als Statussymbol

Medizinisches Cannabis fristet in Deutschland ein Schattendasein. Die meisten Menschen ahnen, dass es so etwas gibt – assoziieren die Praxis aber eher mit popkulturellen Mythen angloamerikanischer Prägung. Nach denen wird gegen Vorzeichen der sogenannten Medical Card – längst Statussymbol unter US-amerikanischen Rap-Stars – ein prall gefüllter Beutel »Purple Haze«-Cannabis über die Drugstore-Theke geschoben. Die deutsche Realität sieht um einiges bürokratischer aus: »Es gibt in Deutschland etwa 50 bis 70 Menschen, die eine Einfuhr-Erlaubnis für medizinisches Marihuana aus Holland besitzen«, hatte mir Gabriele Gebhardt, Sprecherin des »Selbsthilfenetzwerk Cannabis als Medizin«, einige Tage zuvor erklärt. »Vorher muss der Patient alles andere probiert haben, was für das entsprechende Krankheitsbild in Frage kommt. Ungeachtet der möglichen Nebenwirkungen. Außerdem braucht man einen engagierten Arzt und eine Apotheke, die den Antrag beim Bundesinstitut für Arzneimittel und Medizinprodukte stellt«, fasst Gebhardt die schwierige Lage zusammen. Ich male mir aus, wie Snoop Dogg mit aufgesetzter Lesebrille komplizierte Anträge wälzen muss, bevor er sein geliebtes »Kush« (eine Klassiker-Hanfsorte) bekommt. Er würde wahrscheinlich nach fünf Minuten kapitulieren und den Jungs im Stadtpark einen Besuch abstatten.

Cannabis aus dem Labor



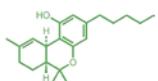
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Holger Rönitz und ich erreichen nach einigen Minuten zu Fuß den Laborkomplex des Unternehmens, der wie die Verwaltung im Frankfurter Stadtteil Oberrad liegt. Wobei »Laborkomplex« auf den ersten Blick etwas übertrieben klingt. Der unscheinbare quaderförmige Bau im Hinterhof eines Mehrfamilienhauses ähnelt vielmehr einer Hausmeister-Unterkunft oder einem zu groß geratenen Stromhäuschen. Rönitz bittet darum, auf Außenaufnahmen zu verzichten – man wolle keine unnötige Aufmerksamkeit auf die Einrichtung lenken. Wir werden mit Schutzbrillen und Kitteln ausgestattet und betreten das Labor, in dem das synthetische THC gereinigt wird, bevor es unter dem Namen Dronabinol in den Apotheken landet. Reaktions-Gefäße in allen Formen und Größen, verworrne Schlauchkonstruktionen und ausladende Stative dominieren den kleinen Raum. So unscheinbar die Einrichtung von außen wirkt, so beeindruckend kommt die Innenausstattung daher.

»Der Reinigungsprozess läuft hier komplett automatisiert«, erklärt mir die Herstellungsleiterin Dr. Vera Mikat und fügt hinzu: »Der Vorgang muss lediglich überwacht werden.« Sie löst einen großen Rundkolben aus einer rotierenden Fassung und hält ihn prüfend gegen das Licht. Das Gefäß enthält etwa 1000 Gramm Dronabinol, eine Menge, mit der ungefähr 1200 Patienten über drei Monate versorgt werden könnten. Der noch leicht rötliche Inhalt wird so lange gereinigt, bis er einen exorbitanten THC-Gehalt von 98% aufweist. Rönitz veranschaulicht die Potenz des Stoffes an einem Beispiel: »Die Einstiegsdosierung liegt in der Palliativmedizin bei gerade mal 2x3 Tropfen am Tag, was etwa 5 Milligramm der Substanz entspricht.« In den USA sind bei der Behandlung mit natürlichem Cannabis bis zu 2 Gramm täglich nicht unüblich. Dieses enthält zwar je nach Qualität zwischen 100 und 400 Mg THC, von dem allerdings ein großer Teil beim Konsum schlicht weg verdampft.

Cannabis gegen die Spastik

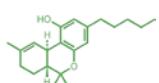
»Ein ausschlaggebender Grund für die Firmengründung war, dass Joachim Hartinger, einer unserer Mitgesellschafter, am eigenen Leib erfuhr, dass Cannabis gegen seine Spastik hilft«, führt Holger Rönitz aus und merkt an: »Solange er aber in einem wissenschaftlichen Beruf tätig war, brauchte er etwas, das verlässlich zu dosieren ist, um einen klaren Kopf zu behalten.« So entwickelte Hartinger in der Gartenlaube, die hinter dem Hauptkomplex heute als Reinigungsraum fungiert, als Erster eine Methode, mit der sich aus dem THC-armen Nutzhanf eine hochpotente Substanz extrahieren lässt. Denn die Einfuhr und der Anbau der wirkstoffreichen weiblichen Cannabis-Pflanze ist hierzulande bis heute lediglich zu wissenschaftlichen Zwecken erlaubt. Ich werfe neugierige Blicke durch die Fenster der Gartenlaube. Im Inneren arbeiten in Weiß gehüllte und hygienisch verummumpte Menschen hochkonzentriert an der letzten Reinigungsstufe von Dronabinol und registrieren nur beiläufig unsere Blicke. Betreten dürfen wir den Raum ohne eine spezielle Schulung nicht. So routiniert wie in der High-Tech-Gartenlaube konnten die Mitarbeiter von THC-Pharm allerdings nicht immer ihrer Arbeit nachgehen. »Es hat sich mittlerweile wahnsinnig viel geändert. Es gab Zeiten, in denen die Staatsanwaltschaft auch schon mal die Wohnungen unserer Mitarbeiter auf den Kopf gestellt hat«, erinnert sich Rönitz und stellt fest: »Aber das ist halt das Leid des Pioniers.« Gegenwind kam jedoch nicht immer nur aus der Politik. Im starren und profitorientierten System der pharmazeutischen Industrie ist man auch heute noch Außenseiter. Da Dronabinol eine Rezeptur-Substanz für Apotheker und kein Fertig-Arzneimittel



ist, lässt sich das Medikament patentrechtlich nicht schützen. Diese Lücke macht den Stoff trotz medizinisch hohen Potenzials für größere Pharma-Konzerne uninteressant, da die Gewinnmargen weit unter den Vorstellungen der Großunternehmen liegen. »Es wird nicht immer unbedingt das bestmögliche Medikament entwickelt, sondern im Zweifel auch mal das, wofür man den besten Patentschutz erhält«, kritisiert Rönnitz. Die Aussage, dass ausschließlich Fertig-Arzneimittel die größtmögliche Sicherheit für den Endanwender gewähren, hält er für eine Schutzbehauptung der Industrie. Rönnitz selbst lässt sich nicht zu einer pathetischen Verklärung des Unternehmensanfangs hinreißen. Das macht ihn sympathisch, genauso wie der allgegenwärtig spürbare Idealismus des Unterfangens.

Als wir am späteren Nachmittag in das gutbürgerliche Restaurant Borussia einkehren, neigt sich die Sonne bereits tief über die Frankfurter Skyline. Während sich draußen die glänzenden Wolkenkratzer im Main spiegeln, herrscht im Inneren ein traditionelles Ambiente. Dr. Ingmar Hornke stößt zu uns und bestellt Backen vom irischen Salzwiesen-Bullen mit Kartoffelpüree. Der Anästhesiologe leitet ein ambulantes Palliativ-Team, das Patienten betreut, die nur noch eine begrenzte Lebenserwartung haben und die die verbleibende Zeit lieber in den eigenen vier Wänden verbringen möchten. »Es geht nicht darum, dem Leben mehr Tage zu geben, sondern den Tagen mehr Leben.« Bereits zum zweiten Mal höre ich an diesem Tag das Zitat von Cicely Saunders, die als Begründerin der modernen Hospizbewegung und Palliativ-Medizin gilt.

Hornke hat gute Erfahrungen mit Dronabinol gemacht und bei seinen Patienten in vielen Fällen eine deutliche Steigerung der Lebensqualität beobachten können. Trotzdem kommt das Cannabinoid seiner Meinung nach viel zu selten zum Einsatz: »Die Krankenkassen sind in vielen Fällen nicht dazu bereit, die Kosten zu übernehmen, obwohl es sich die Patienten oder Angehörigen selbst häufig gar nicht leisten können«, stellt Hornke fest. 500 Milligramm Dronabinol kosten den Apotheker etwa 200 Euro, für den Patienten verdoppelt sich der Preis durch die relativ aufwendige Weiterverarbeitung in der Apotheke. Einen tolerierten Eigenanbau als kostengünstige Alternative hält der Intensivmediziner trotzdem für den falschen Weg. Er könne sich zwar vorstellen, dass es Patienten gäbe, die vom Rauchen der Blüten mehr profitieren als von Dronabinol, aber aus medizinischer Perspektive fehle es an konkreten Belegen und zielgerichteten Anwendungsmöglichkeiten. Saatgut, Wachstumsbedingungen und die schwierige Dosierung seien ebenfalls problematische Faktoren. »Die Idee hat einen gewissen anarchistischen Charme vor dem Hintergrund einer sicher nicht immer patientenorientiert agierenden Pharma-Industrie«, wirft Rönnitz ein und bestellt Espresso. Das Borussia hat sich inzwischen sichtlich geleert. Ich frage Rönnitz zum Abschluss, wie es bei einem solch ungewöhnlichen Job denn so mit den Vorurteilen im Alltag aussehe. »Rumgewitzelt wird natürlich immer mal, aber das stört mich nicht weiter. Wenn ich Damenunterwäsche oder so was produzieren würde, wäre das ja auch nicht anders«, antwortet er. Und ergänzt, dass er andererseits auch immer wieder auf großen Respekt dafür stoße, dass man sich als kleine Patienteninitiative überhaupt in dieses Haifischbecken aus Gesetzesgebern, Pharma-Lobbyisten und Kassen-Vereinigungen gewagt habe.



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Felter, H.W. and J.U. Lloyd (1898) "Cannabis Indica (U.S.P.) — Indian Cannabis." King's American Dispensatory

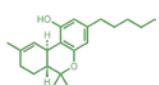
Specific Indications and Uses.—Great nervous depression; irritation of the genito-urinary tract; painful micturition, with tenesmus; ardor urinae, scalding, burning, frequent micturition; low mental conditions; wakefulness; insomnia, with unpleasant dreams during momentary sleep; spasmodic and painful conditions, with nervous depression; mental illusions; menstrual headache; palpitation of the heart, with sharp stitching pains in the heart; hallucinations; cerebral anemia, from spasm of cerebral vessels.

Fernandez-Ruiz, J. (2012) "[Cannabinoid drugs for neurological diseases: what is behind?]" *Revista de Neurologia* 54 (10): 613-628.

In recent years progress has been made in the development of pharmaceuticals based on the plant Cannabis sativa or on synthetic molecules with a similar action. Some of these pharmaceuticals, such as the mouth spray Sativex, have recently been approved for the treatment of spasticity in multiple sclerosis, but they are not the first and others, such as Marinol or Cesamet for the treatment of vomiting and nausea, and anorexia-cachexia syndrome, had already been approved. This incipient clinical use of cannabinoid drugs confirms something that was already known from fairly ancient times up to practically the last century, which is the potential use of this plant for medicinal applications - something which was brought to a standstill by the abusive use of preparations of the plant for recreational purposes. In any case, this incipient clinical use of cannabinoid drugs is not backed just by the anecdote of the medicinal use of cannabis since ancient times, but instead the boost it has been given by scientific research, which has made it possible to identify the target molecules that are activated or inhibited by these substances. These targets are part of a new system of intercellular communication that is especially active in the central nervous system, which is called the 'endogenous cannabinoid system' and, like many other systems, can be manipulated pharmacologically. The aim of this review is to probe further into the scientific knowledge about this system generated in the last few years, as a necessary step to justify the development of pharmaceuticals based on its activation or inhibition and which can be useful in different neurological diseases.

Flemming, T., R. Muntendam, C. Steup and O. Kayser, (2007) "Chemistry and Biological Activity of Tetrahydrocannabinol and its Derivatives." *Topics in Heterocyclic Chemistry* 10/2007: 1-42.

Cannabinoids and in particular the main psychoactive Δ-9-THC are promising substances for the development of new drugs and are of high importance in biomedicine and pharmacy. This review gives an overview of the chemical properties of Δ-9-THC, its synthesis on industrial scale, and the synthesis of important metabolites. The biosynthesis of cannabinoids in Cannabis sativa is extensively described in addition to strategies for optimization of this plant for cannabinoid employment in medicine. The metabolism of Δ-9-THC in humans is shown and, based on this, analytical procedures for cannabinoids and their metabolites in human forensic samples as well as in C. sativa will be discussed. Furthermore, some aspects of medicinal indications for Δ-9-THC



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and its ways of administration are described. Finally, some synthetic cannabinoids and their importance in research and medicine are delineated.

Finnerup, N.B., S.H. Sindrup and T.S Jensen (2010) "The evidence for pharmacological treatment of neuropathic pain." *Pain* **150** (3): 573-581.

Randomized, double-blind, placebo-controlled trials on neuropathic pain treatment are accumulating, so an updated review of the available evidence is needed. Studies were identified using MEDLINE and EMBASE searches. Numbers needed to treat (NNT) and numbers needed to harm (NNH) values were used to compare the efficacy and safety of different treatments for a number of neuropathic pain conditions. One hundred and seventy-four studies were included, representing a 66% increase in published randomized, placebo-controlled trials in the last 5 years. Painful poly-neuropathy (most often due to diabetes) was examined in 69 studies, postherpetic neuralgia in 23, while peripheral nerve injury, central pain, HIV neuropathy, and trigeminal neuralgia were less often studied. Tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors, the anticonvulsants gabapentin and pregabalin, and opioids are the drug classes for which there is the best evidence for a clinical relevant effect. Despite a 66% increase in published trials only a limited improvement of neuropathic pain treatment has been obtained. A large proportion of neuropathic pain patients are left with insufficient pain relief. This fact calls for other treatment options to target chronic neuropathic pain. Large-scale drug trials that aim to identify possible subgroups of patients who are likely to respond to specific drugs are needed to test the hypothesis that a mechanism-based classification may help improve treatment of the individual patients.

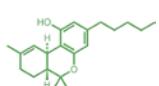
Formukong, E. A., A.T. Evans and F.J. Evans (1989) "The medicinal uses of cannabis and its constituents." *Phytotherapy Research* **3** (6): 219-231.

Recent work contributing towards an understanding of the mechanism of action of cannabis and its constituents is described and the known therapeutic and pharmacological activities of these substances reviewed, together with synthetic drugs derived from tetrahydrocannabinol (Δ -sup(1)-THC). The medical uses discussed include the actions of cannabinoids in the treatment of glaucoma, asthma, emesis, hyperthermia, convulsion, muscle spasticity, anxiety, hypertension, pain and inflammation.

Fox, R. and G. Watling (2001) "Anaesthesia for patients with chronic spinal cord injury." *Current Anaesthesia and Critical Care* **12** (3): 154-158.

Patients with chronic spinal cord injury are surviving longer, therefore the possibility of presentation with the need for incidental surgery outside a spinal injury unit is increasing. With an understanding of the complex pathophysiology consequent to a cord injury, particularly the cardiovascular and respiratory changes, and the relevance of spasticity, appropriate and safe anaesthetic management can be undertaken.

Francisco, G.E. and C.B. Ivanhoe (1997) "Pharmacologic management of spasticity in adults with brain injury." *Physical Medicine and Rehabilitation Clinics of North America* **8** (4): 707-731.



Spasticity is one of the most devastating musculoskeletal sequelae of brain injury because it leads to functional impairments that augment disability. In spite of recent therapeutic advances, spasticity remains one of the most challenging impairments encountered by physiatrists. When treating brain-injured patients, drug side effects become a crucial consideration in determining appropriate treatment because many of the individuals cannot afford the known sedative and adverse cognitive effects of many spasmolytic medications. For this and several other reasons, spasticity management in brain injury is complex and requires certain considerations to increase the likelihood of therapeutic success.

Frazetto, G. (1996) "Does marijuana have a future in pharmacopoeia?" EMBO Reports 4 (7): 651–653.

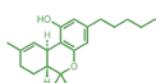
Summary: Although recent research backs the therapeutic benefits of cannabis, its adverse effects and the risk of addiction push against the legalization of the drug for medical use

Its Latin name in botanical classification is Cannabis sativa L. but most people know it as marijuana, grass, pot, dope or weed, mainly when referring to its recreational use. Recently, this green plant, which grows up to five metres, has acquired a new name: 'the aspirin of the new century', reflecting hopes that cannabis could be used to treat a variety of ailments, ranging from migraine to cancer (Baker et al., 2003). By discovering how the active ingredients of the plant exert their effect on the human metabolism, scientists think that cannabis could have great potential for the development of new drugs. But whether or not the beneficial effects of marijuana are further supported by biomedical research, those counting on them will nevertheless have to face the legal aspects of using the drug in their countries. Indeed, the negative aspects of the plant, mainly the risk of addiction, are the reasons why most countries have outlawed the growth, possession and consumption of cannabis. The debate about the health benefits of cannabis is thus lost in a bitter clash between authorities that enforce strict laws against its use and proponents pushing for its legalization.

The many beneficial aspects of cannabis are not a new discovery—the plant has a long tradition in medicine that originated in oriental and Middle Eastern countries. The Chinese documented its medicinal value more than 4,000 years ago, using seeds, leaves and sap as sedatives or painkillers and to treat fevers, nausea and ulcers. Ancient herbalists made unguents for burns and other wounds from its roots. Galen, and other physicians of the classical and Hellenistic eras, also noted cannabis as a remedy, and the Arabs started using the plant as early as the mid-1200s. Although there is evidence of cannabis use in Europe from the thirteenth century, after Marco Polo returned from his journey to the east in 1297, its medical use became more popular in the nineteenth century, when the British physician William B. O'Shaugnessy brought back an account of the remarkable effects of this plant from India. Even Queen Victoria is said to have sipped marijuana tea prescribed by her court physician to treat menstrual cramps.

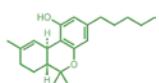
The debate about the health benefits of cannabis is thus lost in a bitter clash between authorities that enforce strict laws against its use and proponents pushing for its legalization

Such anecdotal claims of the healing properties of cannabis are now



supported by modern research on the metabolism of cannabinoids—the active components of the plant—and their potential use in medicine. The plant contains more than 60 active compounds, of which the most psychoactive ingredient is Δ9-tetrahydrocannabinol (THC), which was first identified in the 1940s and first synthesized in 1965. THC mainly recognizes a receptor of the central nervous system called CB1, the cannabinoid receptor, which is involved in the regulation of synaptic transmission of excitatory and inhibitory neural circuits. Dronabinol, a synthetic form of THC, was approved by the US Food and Drug Administration to stimulate the appetite of AIDS patients and to treat their anorexia and associated weight loss. The same drug has been indicated for the treatment of nausea and vomiting associated with cancer chemotherapy. Cannabis also helps in the treatment of patients suffering from glaucoma, one of the most common causes of blindness, by reducing fluid pressure in the eye. Injections of synthetic THC eradicated malignant brain tumours in rats, suggesting that cannabinoids may even protect against the development of certain types of tumours (Galve-Roperh et al., 2000). Also of great interest is the ability of cannabis to mitigate symptoms of multiple sclerosis (MS), such as muscle spasms and spasticity.

But to claim that smoking marijuana solves many of your health problems is certainly not true, thinks Daniele Piomelli, Professor of Pharmacology at the University of California, Irvine, USA. "Although I am not against the compassionate use of cannabis in certain conditions, such as cancer anorexia or MS, where there is a great deal of evidence for its effectiveness," he said, "if you want a selective and safe medication, in most cases cannabis is not for you." Indeed, cannabis smoke can induce unpleasant effects such as panic and paranoia, hallucinations, increase in heart rate and lowering of blood pressure, and it leads to amotivational syndrome. Chronic marijuana smoking adversely affects short-term memory and cognitive abilities. Young adults who smoke cannabis have a slightly higher risk of developing psychosis and the frequent use of marijuana may promote a recurrence of schizophrenia in people who are vulnerable to this condition. In animal tests, THC also lowered testosterone production and reduced sperm production, motility and viability. Although most of the current clinical use of cannabis concentrates on symptom management, researchers have increasingly become interested in the metabolic and neurological processes triggered by cannabinoids. "The greatest potential offered by cannabis lies in the glimpse it offers to a signalling system, the endocannabinoid system, which can be modulated pharmacologically in various selective ways and which may well open up a new generation of endocannabinoid-based therapeutic drugs," Piomelli said. The biology of the cannabinoids suggests that there might be other benefits in the treatment of neurological disorders, especially in slowing the progression of neurodegenerative diseases. For example, sustained receptor stimulation by cannabinoids can make up for the gradual loss of the CB1 receptor, which is associated with the onset of Huntington's disease. Through understanding and exploiting the biology of cannabinoids, researchers may in fact be able to bypass the main problem with the use of cannabis as a medicine: the impossibility of dissociating the potential therapeutic activities from the adverse effects. Researchers are now trying to design drugs that might work as agonists or antagonists of the endogenous cannabinoid system without the side-effects, with some evidence emerging in the treatment of anxiety.



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But major difficulties in using cannabis as a medicine are dosage and route of administration. At present, dronabinol, the commercial form of THC, is administered orally. But this is not the most effective route as cannabinoids are readily soluble in fats and are subject to considerable metabolism in the liver, leading to quick degradation. Smoking marijuana has a more rapid effect, but it is difficult to dose and can cause smoking-related diseases, and probably lung cancer, to the same degree that cigarettes do. "I am not a strong believer of inhaled cannabis as a drug," Piomelli said, "it contains too many unknown and potentially toxic compounds and smoking, the most effective mode of administration, is dangerous and unacceptable to many people."

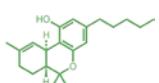
The biggest concern about the consumption of cannabis is the possibility of it constituting a 'gateway' to harder drugs. A recent study by Australian scientists provides new arguments for those who call for a ban on the use of cannabis, whether recreational or medical. The researchers from the Queensland Institute of Medical Research in Brisbane investigated the drug habits of 311 pairs of same-sex twins, including 136 identical twins, and found that the early marijuana smokers were up to five times more likely to move on to harder drugs than their twins (Lynskey et al., 2003). This provides further arguments for those who seek a complete ban on the growth, trade and consumption of cannabis, among them the current US administration, who recently escalated their war on pot.

Indeed, the USA already has some of the harshest laws on cannabis, which date back more than half a century. The first official ban on marijuana was the 1937 Cannabis Tax Act, the culmination of a campaign by Harry Anslinger, head of the Federal Bureau of Narcotics. Anslinger, a prohibitionist, made the public believe that marijuana was addictive and caused violent crimes, psychosis and mental deterioration. In 1970, the Controlled Substances Act put marijuana into the Schedule I category, together with heroin, LSD and other hallucinogenic amphetamines, as a drug of high potential for abuse and no medicinal use. Nowadays, growing a single plant of marijuana or possession of a single joint is illegal by US federal law and the number of marijuana arrests each year approaches 750,000.

However, in a 1996 state-wide referendum, California adopted a new law, known as Proposition 215, which legalizes the growth and consumption of marijuana for medicinal purposes. California was soon followed by Alaska, Arizona, Colorado, Hawaii, Maine, Nevada, Oregon and Washington.

Particularly in California, where the climate is better suited for growing marijuana than in, say, Maine, under the patronage of the state or city councils, people started growing plants and selling marijuana to seriously ill people.

One of them was Ed Rosenthal from Oakland (CA, USA), author of more of a dozen books on marijuana cultivation. But earlier this year, Rosenthal found himself in the middle of a serious juridical clash between the State of California and the federal administration in Washington. In cracking down on illegal drug trafficking, federal agents seized and destroyed marijuana fields all over California. Rosenthal was arrested on charges of marijuana cultivation and conspiracy by federal laws and now faces a lawsuit that could bring him a life sentence. He claims that "laws controlling the use of marijuana are more harmful to society than what they intend to regulate. Those who think that



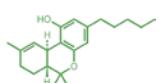
marijuana is not a medicine and that those advocating its medical use have only the legalization of the drug on their agenda are either liars or ignorant. The medical potential of cannabis is enormous and it is well documented." Rosenthal is not the only one. Fearing prosecution in their country, an increasing number of Americans convicted for drug use and claiming to be seriously ill moved to Canada and applied for political asylum. Marijuana is illegal in both countries, but Canada has legalized possession of the drug for chronically ill people and has just introduced a bill that will decriminalize possession of up to 15 g of marijuana.

In Europe too, the growth, possession and consumption of cannabis is not legal, with the exception of The Netherlands. But many countries, including Germany, Denmark, Belgium, Finland, Spain and Italy, have shown during the past ten years a clear tendency to ease drug policy and decriminalize personal possession and use (see the European Monitoring Centre for Drugs and Drug Addiction website: www.emcdda.org). The UK, which probably has the harshest drug law enforcement in Europe—and the highest level of drug use and addiction—may also soon make a big step towards the legalization of cannabis as a therapeutic drug. Cannabis was first outlawed and declared to be of no medical benefit in the UK in 1971 with the Misuse of Drugs Act, but patients continued to purchase cannabis on the black market for self-medication. This 'patient-led investigation' showed various benefits for sufferers of many disorders and, after having assessed all the evidence, the House of Lords regarded the therapeutic potential of cannabis for MS as the best-supported case and warranting further investigation. Funded by the Medical Research Council, and co-ordinated among others by Alan Thompson from University College London and John Zajicek from the Derriford Hospital in Plymouth, UK, the largest trial on MS since 2001, with 660 patients, has now been conducted, and the results are expected later this summer. Should these show an acceptable level of benefit from cannabis, the UK government is likely to rethink legalization, but only for medical use.

Be it in the USA, the UK or elsewhere, the study of the potential medical use of cannabis is still very contradictory. Although some evidence exists, proponents still need more valid and unequivocal clarification, without which it is going to be hard to convince governments to lift restrictions. The main problem in this inconclusive and controversial debate—whether presented by conservative politicians or ex-hippie activists looking for legalization of the drug—is that there are more opinions than facts. "An unfortunate consequence of this polarization of opinion has been the absence of any consensus on what health information the medical profession should give to patients who are users or potential users of cannabis," commented Wayne Hall and Nadia Solowij, from the University of New South Wales in Australia, in *The Lancet* (1998).

Freeman, R.M., O. Adekanmi, M.R. Waterfield, A.E. Waterfield, D. Wright, and J. Zajicek (2006) "The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS)." *International Urogynecology Journal - and Pelvic Floor Dysfunction* **17** (6): 636-641.

Objective: To test whether cannabinoids reduce urge incontinence episodes without affecting voiding in patients with multiple sclerosis. This was part of the multicentre trial of the Cannabinoids in Multiple Sclerosis (CAMS) study.



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Subjects and Methods: The CAMS study randomised 630 patients to receive oral administration of cannabis extract, Δ-9-tetrahydrocannabinol (THC) or matched placebo. For this substudy subjects completed incontinence diaries. **Results:** All three groups showed a significant reduction, $p<0.01$, in adjusted episode rate (i.e. correcting for baseline imbalance) from baseline to the end of treatment: cannabis extract, 38%; THC, 33%; and placebo, 18%. Both active treatments showed significant effects over placebo (cannabis extract, $p=0.005$; THC, $p=0.039$). **Conclusion:** The findings are suggestive of a clinical effect of cannabis on incontinence episodes in patients with MS. This is in contrast to the negative finding of the CAMS study, where no difference was seen in the primary outcome of spasticity.

Frink, K. (2010) "Cannabis als Medikament – Grünes Licht von der Bundesregierung?." In: Gesundheit! vom Bayerischen Rundfunk, Sendedatum: 14.09.2010.

Noch immer löst die Droge Cannabis heftige Debatten aus – auch im Einsatz als Medikament. Dabei ist unbestritten, dass viele schwerkranke Menschen positiv darauf reagieren. Die schwarz-gelbe Koalition plant deshalb, den Zugang zu cannabishaltigen Medikamenten zu erleichtern. Der richtige Schritt?

Hanf zählt zu den ältesten Nutz- und Zierpflanzen der Welt. Aus verschiedenen Hanfsorten wird auch Rauschmittel gewonnen, Cannabis genannt. In den Niederlanden legal, in Deutschland eine illegale Droge. Umso verwirrender waren die Schlagzeilen im August: "Cannabis bald aus der Apotheke" oder "Koalition erlaubt Cannabis auf Rezept". Klar ist, die Bundesregierung möchte das Betäubungsmittelgesetz ändern. Schwerkranke Menschen sollen leichter an cannabishaltige Medikamente kommen. Doch was bedeutet das und wem hilft es?

Cannabis für Schwerkranke

Immer noch wird der Einsatz von Cannabis in der Medizin diskutiert. Einzelfallbeschreibungen begründen die klinische Effizienz, es fehlen jedoch noch umfangreichere klinische Studien. Dennoch gibt es einige gut dokumentierte Anwendungsgebiete. Cannabis kann Übelkeit vermindern sowie den Appetit anregen. Somit hilft es häufig Krebspatienten, die eine Chemotherapie bekommen oder auch HIV-Erkrankten. Außerdem wird Cannabis in der Schmerztherapie eingesetzt. Es wird von schmerzlindernden sowie schmerzhemmenden Effekten gesprochen. Zudem soll Cannabis bei spastischen Lähmungen und Multipler Sklerose helfen.

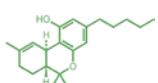
Cannabis hat allerdings einen schlechten Ruf. Damit soll endlich Schluss sein, fordert die Deutsche Gesellschaft für Schmerztherapie. Dr. Gerhard H.H. Müller-Schwefe, Präsident der Deutschen Gesellschaft für Schmerztherapie: "Wir denken, dass die Behandlung mit Cannabis-Derivaten ganz normale Medizin ist, so wie die Therapie mit Entzündungshemmern oder Morphin-Derivaten. Es ist dringend notwendig, dass Cannabis aus dieser Schmutzdecke rauskommt."

Die Ausgangslage

Schon jetzt gibt es Therapiemöglichkeiten mit Cannabis beziehungsweise einzelnen Cannabinoiden.

Möglichkeit 1: Dronabinol

Jeder Arzt in Deutschland kann Dronabinol verschreiben, allerdings nur mittels



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eines Betäubungsmittelrezept. Arzneimittelrechtlich ist es nicht zugelassen, das heißt, es gibt kein Fertigarzneimittel. Der Apotheker stellt eine Rezeptur her, in Form von öligen oder alkoholischen Tropfenlösungen oder Kapseln. Dronabinol wird aus THC-armem Nutzhanf gewonnen und in ihm steckt nur ein Cannabinoid. Zum Vergleich: In Cannabisblüten stecken rund 60 verschiedene Cannabinoide. Die Gewinnung von Dronabinol ist sehr teuer, daher auch der hohe Preis.

Nach Einschätzungen der Arbeitsgemeinschaft Cannabis als Medizin werden zu wenige Patienten in Deutschland mit Dronabinol behandelt. Der Grund hierfür ist auch, dass die gesetzlichen Krankenkassen die Kosten nur in Ausnahmefällen zahlen. Denn da Dronabinol kein Fertigarzneimittel ist, sind die Krankenkassen zur Kostenübernahme nicht verpflichtet. Das Argument: Es fehlt die Anerkennung des therapeutischen Nutzens sowie der Notwendigkeit.

Die monatlichen Behandlungskosten belaufen sich auf etwa 250 bis 400 Euro, ein Problem, da viele Schwererkrankte nicht erwerbstätig sind und sich Dronabinol nicht leisten können.

Birgit Eilbacher erkrankte vor einigen Jahren an Knochenkrebs. Sie hatte sehr starke Schmerzen. Das Morphinpflaster vertrug sie nicht. Daraufhin bekam sie von ihrer Ärztin Dronabinol verschrieben. Sie probierte es aus, war begeistert und nahm es zweieinhalb Jahre.

"Ich habe es mit gutem Erfolg ausprobiert, meine Stimmung war besser, der Schmerz wurde weniger und ich konnte das mit anderen Schmerzmitteln kombinieren. Ich hatte wieder Appetit, ich hatte sehr abgenommen damals, und mein Befinden war einfach besser. Das hat mir sehr gut getan."

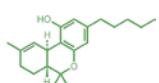
Die Allgemeinmedizinerin Dr. Sylvia Mieke hat Birgit Eilbacher das Dronabinol verschrieben. Sie sagt, dass Dronabinol nicht für jeden geeignet sei, es hilft nicht jedem. Viele kommen auch mit anderen Medikamenten zurecht, doch wer zum Beispiel Opiate nicht verträgt, bei dem ist es sinnvoll, Dronabinol auszuprobieren. Oftmals wird Dronabinol aber auch in Kombination mit anderen Medikamenten verwendet, so auch bei Birgit Eilbacher. Dronabinol kann Opiate in ihren schmerzhemmenden Eigenschaften ergänzen, gleichzeitig aber die Übelkeit, die durch Opiate hervorgerufen wird, lindern. Macht Dronabinol süchtig?

Dronabinol besitzt ein Suchtpotential. Unter medizinischer Kontrolle ist es aber nicht relevant. Die Entzugssymptome sind gering oder aber es gibt gar keine, so wie bei Birgit Eilbacher: "Ich finde die Kritik nicht berechtigt, da ja viele Menschen Schmerzpflaster nehmen und da stellt sich ja auch nicht die Frage, ob sie abhängig machen oder nicht. Ich hatte gar keine Probleme, Dronabinol abzusetzen. So etwas wie Entzugserscheinungen gab es bei mir nicht."

Dr. Sylvia Mieke setzt Dronabinol nur in bestimmten Dosen ein, es wird ein- und ausgeschlichen. Sie kennt bisher keine Patienten, die Probleme mit dem Absetzen hatten.

Risiken und Nebenwirkungen von Dronabinol

In der Regel sind die Nebenwirkungen gering. Wichtig ist, dass Dronabinol nicht zu schnell aufdosiert wird. Durch die Einnahme kann es aber zu Blutdruckabfall, Mundtrockenheit, Schwindel oder Sehstörungen kommen. Außerdem gibt es auch Kontraindikationen: Für Patienten mit Psychosen oder einem hohen Abhängigkeitspotential sowie Patienten mit Herz-Problemen ist Dronabinol nicht geeignet.



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Was bringt der Vorstoß der Bundesregierung?

Eine Änderung des Betäubungsmittelgesetzes wird Patienten, die Dronabinol brauchen, vorerst nichts bringen. Ein deutsches Pharmaunternehmen arbeitet zwar an einer Zulassung, aber solange Dronabinol nur eine Rezeptur ist, werden die meisten gesetzlichen Kassen nicht zahlen und so haben nur wenige Patienten die Chance, Dronabinol zu nehmen.

Die Ausgangssituation

Therapiemöglichkeit 2: Die Ausnahmegenehmigung

Frank Clemens ist einer von rund 40 Patienten in Deutschland, die Cannabis legal in der Apotheke kaufen dürfen. Mit 17 Jahren hatte er einen Badeunfall, seitdem ist er querschnittsgelähmt. Mit 36 erkrankte er an Krebs und verlor dadurch mehrere Rippen- und Muskelteile. Seitdem kämpft er nicht nur mit seiner Spastik, sondern auch mit extremen Schmerzen. Er behandelt sich mit Cannabis, raucht oder inhaliert die Cannabisblüten. 20 g bekommt er pro Monat legal in seiner Apotheke. Rund 290 EUR zahlt er dafür monatlich. Das ist das Drei- bis Vierfache von dem, was er auf dem Schwarzmarkt zahlen würde. Lange hat er mit seinem Arzt dafür gekämpft - bis er die Ausnahmegenehmigung von der Bundesopiumstelle des Bundesinstituts für Arzneimittel und Medizinprodukte bekommen hat.

"Ich habe ein chronisches Schmerzsyndrom, das mit Cannabis super zu behandeln ist. Die Alternative wären Opiate, die ich aber nicht vertrage. Die Nebenwirkungen sind enorm, unter anderem: Wortfindungsstörungen, Benommenheit und starke Verstopfung. Ich habe eh schon Probleme durch meinen Querschnitt, Blase und Darm sind gelähmt."

Nur wer wirklich schwerkrank ist und bei dem alle anderen Therapien versagt haben, hat eine Chance, die Ausnahmegenehmigung zu bekommen. Dabei wird es trotz des Vorstoßes der Bundesregierung bleiben. Auch die Kosten werden die 40 Patienten vorerst weiterhin selbst übernehmen müssen.

Fazit: Eine Gesetzesänderung durch die Bundesregierung wird den meisten Schwererkrankten vorerst wenig helfen, trotzdem begrüßt die Deutsche Gesellschaft für Schmerztherapie e.V. den Vorstoß von Koalitionsfraktion.

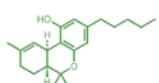
Dr. Gerhard H.H. Müller-Schwefe, Präsident der Deutschen Gesellschaft für Schmerztherapie: "Kurzfristig wird sich nichts ändern für die Patienten.

Langfristig aber werden wir Fertigarzneimittel, die cannabishaltig sind, in der Apotheke zur Verfügung haben. Das heißt, sie werden billiger werden, sie werden verfügbar werden und wir gehen davon aus, dass auch die Erstattungssituation anders wird."

Eine kleinere Patientengruppe kann sich schon freuen. 2011 wird die Zulassung vom Cannabisextrakt „Sativex“ erwartet, zur Behandlung von Multiple Sklerose. Hier wird die Kasse die Kosten dann wohl übernehmen.

Frohman, T.C., W. Castro, A. Shah, A. Courtney, J. Ortstadt, S.L. Davis, D. Logan, T. Abraham, J. Abraham, G. Remington, K. Treadaway, D. Graves, J. Hart, O. Stuve, G. Lemack, B. Greenberg and E.M. Frohman (2011) "Symptomatic therapy in multiple sclerosis." *Therapeutic Advances in Neurological Disorders* 4 (2): 83–98.

Multiple sclerosis is the most common disabling neurological disease of young adults. The ability to impact the quality of life of patients with multiple sclerosis should not only incorporate therapies that are disease modifying, but should also include a course of action for the global multidisciplinary management focused on quality of life and functional capabilities.



Gambi, F., D. De Berardis, G. Sepede, R. Quartesan, E. Calcagni, R.M. Salerno, C.M. Conti, and F.M. Ferro (2005) "Cannabinoid receptors and their relationships with neuropsychiatric disorders." International Journal of Immunopathology and Pharmacology **18** (1): 15-19.

Cannabinoids are the constituents of the marijuana plants. The central effects of exogenous cannabinoids are implicated in enhancing mood, altering emotional states, and interfering in the formation of short-term memory. Cannabinoid receptors are G protein-coupled receptors with seven transmembrane domains that are expressed on the cell surface with their binding domain exposed to the extracellular space. To date, two cannabinoid receptors have been cloned, CB1 and CB2. Recent evidence suggests that a third CB3 receptor is out there, waiting to be cloned. The endocannabinoids may represent the first members of a new classes of neuromodulators, that are not stored in cell vesicles, but rather synthesised by the cell on demand. The endogenous cannabinoid system could play a central role in several neuropsychiatric disorders and is also involved in other conditions such as pain, spasticity and neuroprotection. Implication of cannabinoid system in the pathogenesis and development of schizophrenia is also discussed.

Gieringer, D. (1996) "Review of Human Studies on Medical Use of Marijuana." by California NORML, San Francisco.

http://norml.org/pdf_files/ReviewofHumanStudies.pdf

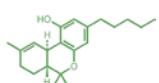
There have been hundreds of studies on the medical uses of cannabis since its introduction to western medicine in the early nineteenth century. A review of the literature reveals over 65 human studies, most of them in the 1970s and early '80s.

The best established medical use of smoked marijuana is as an anti-nauseant for cancer chemotherapy. Marijuana's efficacy was demonstrated in studies by half a dozen states, involving hundreds of subjects. Most research has found smoked marijuana superior to oral THC (Marinol).

Many oncologists are currently recommending marijuana to their patients. Marijuana is widely used to treat nausea and appetite loss associated with AIDS, but the government has blocked research in this area. Studies have shown that marijuana helps improve appetite, and Marinol has been FDA approved for treatment of AIDS wasting syndrome. Nearly 10,000 PWAs were reported to be using marijuana through the San Francisco Cannabis Buyers' Club. However, the government has blocked efforts by Dr. Donald Abrams of the University of California at San Francisco to proceed with an FDA-approved study of marijuana and AIDS wasting syndrome, by refusing to grant him access to research marijuana. Research is badly needed on the relative merits of smoked and oral marijuana versus Marinol.

There is much evidence, largely anecdotal, that marijuana is useful as an anti-convulsant for spinal injuries, multiple sclerosis, epilepsy, and other diseases. Similar evidence suggests marijuana may be useful as an analgesic for chronic pain from cancer and migraine as well as for rheumatism and a variety of auto-immune diseases. There is a conspicuous lack of controlled studies in this area; further research is needed.

Cannabidiol, a constituent of natural marijuana not found in Marinol, appears to have distinctive therapeutic value as an anti-convulsant and hypnotic, and



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to counteract acute anxiety reactions caused by THC. It has been established that marijuana reduces intra-ocular pressure, the primary object of glaucoma therapy. Due to its psychoactivity, however, marijuana has not gained widespread acceptance in this application. Many patients report using marijuana as a substitute for more addictive and harmful psychoactive drugs, including prescription painkillers, opiates, and alcohol. Marijuana and Marinol have also been found useful as a treatment for depression and mood disorders in Alzheimer's and other patients. More research is needed.

Goodin, D. (2004) "Marijuana and multiple sclerosis." *Lancet Neurology* **3** (2): 79-80.

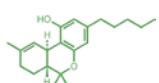
Gottschling, S (2011) "Cannabinoids in children. [Cannabinoide bei Kindern.]" *Angewandte Schmerztherapie und Palliativmedizin* **1**: 55-57.

According to case reports of the Centre for Palliative Medicine and Paediatric Pain Therapy of the University of the Saarland (Germany) THC (dronabinol) is an effective and well-tolerated medicinal drug in the treatment of different severe illnesses in children. A scientist of a university reported of experiences from the treatment of 13 children with severe disabilities and spasticity aged 7 months to 17 years as well as of about 50 cancer patients aged three months and older.

All children received a slowly increased dose. Mean dronabinol dose was 0.2 mg/kg bodyweight in children with spasticity and pain after finishing dose finding. In all children a reduction in pain, which was considerable in some of them, was observed within 48 hours after start of treatment. Efficacy with regard to spasticity set in within one to two weeks. In some patients opioid treatment could be reduced. Most cancer patients profited from an increase in appetite and weight, reduction of nausea and vomiting, as well as improved sleep and reduced anxiety. Even with long-term treatment no relevant side-effects were noted.

Gracies, J.M., E. Elovic, J. McGuire and D. Simpson (1997) "Traditional pharmacological treatment for spasticity: Part II. General and regional treatments." *Muscle and Nerve* **0** (Suppl. 6): S92-S120.

Systemic pharmacologic treatments may be indicated in conditions in which the distribution of muscle overactivity is diffuse. Antispastic drugs act in the CNS either by suppression of excitation (glutamate), enhancement of inhibition (GABA, glycine), or a combination of the two. Only four drugs are currently approved by the US FDA as antispastic agents: baclofen, diazepam, dantrolene sodium, and tizanidine. However, there are a number of other drugs available with proven antispastic action. This chapter reviews the pharmacology, physiology of action, dosage, and results from controlled clinical trials on side effects, efficacy, and indications for 21 drugs in several categories. Categories reviewed include agents acting through the GABAergic system (baclofen, benzodiazepines, piracetam, progabide); drugs affecting ion flux (dantrolene sodium, lamotrigine, riluzole); drugs acting on monoamines (tizanidine, clonidine, thymoxamine, beta blockers, and cyproheptadine); drugs acting on excitatory amino acids (orphenadrine citrate); cannabinoids; inhibitory neuromediators; and other miscellaneous agents. The technique, advantages, and limitations of intrathecal administration of baclofen,



morphine, and midazolam are reviewed. Two consistent limitations appear throughout the controlled studies reviewed: the lack of quantitative and sensitive functional assessment and the lack of comparative trials between different agents. In the majority of trials in which meaningful functional assessment was included, the study drug failed to improve function, even though the antispastic action was significant. Placebo-controlled trials of virtually all major centrally acting antispastic agents have shown that sedation, reduction of global performance, and muscle weakness are frequent side effects. It appears preferable to use centrally acting drugs such as bactofen, tizanidine, and diazepam in spasticity of spinal origin (spinal cord injury and multiple sclerosis), whereas dantrolene sodium, due to its primarily peripheral mechanism of action, may be preferable in spasticity of cerebral origin (stroke and traumatic brain injury) where sensitivity to sedating effects is generally higher. Intrathecal administration of antispastic drugs has been used mainly in cases of muscle overactivity occurring primarily in the lower limbs in nonambulatory, severely disabled patients, but new indications may emerge in spasticity of cerebral origin. Intrathecal therapy is an invasive procedure involving long-term implantation of a foreign device, and the potential disadvantages must be weighed against the level of disability in each patient and the resistance to other forms of antispastic therapy in all forms of treatment of muscle overactivity, one must distinguish between two different goals of therapy: improvement of active function and improvement of hygiene and comfort. The risk of global performance reduction associated with general or regional administration of antispastic drugs may be more acceptable when the primary goal of therapy is hygiene and comfort than when active function is a priority.

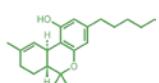
Grant, D. (1997) "Medicinal marijuana?" New England Journal of Medicine **336** (16): 1185.

Grant, B. (2012) "Medical Marijuana: Smoke, Fire, and Science." In: "Alternative Medicines" The Scientist **26** (7).

Facts about the benefits of medical marijuana are sparse, hampered by the politics and regulatory difficulties of doing such research.

Marijuana (Cannabis sp.) has been used as a medicine for more than 4,000 years. But in the eyes of the US federal government, cannabis is an illegal drug that has no place in the clinic. Biomedical researchers who would like to study cannabis in a medical setting are frustrated by the challenges of obtaining government clearance and funding. But some data pointing to medical benefits of smoking marijuana do exist.

In 1970, the US Congress voted to classify cannabis under Schedule I of the Controlled Substances Act. Marijuana joined heroin, LSD, and peyote on Schedule I, and according to the Act, it—along with all other Schedule I drugs—has a high potential for abuse, lacks safety, and has “no currently accepted medical use in treatment in the United States.” Since then, 16 US states and the District of Columbia have legalized the use of medicinal cannabis for a variety of indications, from chronic pain to cancer- and HIV-related appetite and weight loss, nausea, and vomiting. But despite the recent wave of state-level legalization, and the enactment of similar laws in Canada and elsewhere around the globe, the US federal government still classifies



marijuana as a Schedule I drug, a designation that makes studying the medical effects of the drug in the U.S. extremely difficult (requiring approval from the Drug Enforcement Administration in addition to the Department of Health and Human Services (HHS)). Therefore, it has been far more common (and easier) to get funding and clearance to study the negative impacts of marijuana as a substance of abuse than to investigate its positive effects as a therapeutic agent.

Nonetheless, some researchers have braved the bureaucratic obstacles to conduct a handful of randomized, placebo-controlled trials that point to benefits of smoking cannabis, though they acknowledge that smoking the plant comes with its own risks and drawbacks. A more extensive body of literature involves molecular components, extracts, or synthetic forms of marijuana, simply because studying these non-Schedule I substances is less fraught with regulatory obstacles than is studying the whole plant.

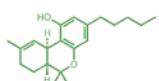
The strongest evidence of smoked marijuana's benefit exists in patients who experience chronic pain. With funding from the University of California Center for Medicinal Cannabis Research (CMCR), researchers published studies in 2007, 2008, and 2009 that all suggested smoked cannabis possessed analgesic properties. A study published in 2007, for example, noted that HIV patients experiencing neurological pain, or neuropathy—a general name for burning pain, hypersensitivity to light touch, and other uncomfortable symptoms—experienced a dulling of that pain when they smoked a cannabis cigarette three times a day for 5 days.

Psychiatrist Igor Grant, director of the center and an HIV/AIDS researcher at the University of California, San Diego, says that patients suffering from neuropathy in particular seem to find relief in cannabis. "We don't have terrific agents to treat it. There are agents [such as antiepileptics and antidepressants] and they are modestly effective in many people," Grant says. "The bottom line is that [cannabis] seems to work, and the effects are comparable in strength to traditional agents."

Other studies from the CMCR have probed new conditions the plant might be used to treat. For example, UC San Diego researchers reported in 2008 that smoked marijuana has the potential to reduce muscle spasticity in multiple sclerosis (MS) patients. That finding was bolstered by a randomized, double-blind, placebo-controlled study published last year on the liquid marijuana extract Sativex, which is approved for use in some European countries, Canada, and New Zealand. The results of that trial, conducted by European researchers, indicated that a 4-week course of Sativex, an oral spray that contains the cannabinoids cannabidiol (CBD) and Δ-9 tetrahydrocannabinol (THC), was safe and effective at reducing spasticity in many MS patients.

US researchers are completing Phase III trials of Sativex for the treatment of pain associated with cancer, and Otsuka Pharmaceutical, the US licensing partner of UK drugmaker GW Pharmaceuticals, hopes to gain FDA approval soon.

Aside from the relative logistical ease of studying constituents, extracts, or synthetics due to the fact that they do not run afoul of the Controlled Substances Act, these compounds stimulate the endocannabinoid system, the body's homegrown constellation of receptors that interact with the active components of cannabis in a more tractable way than does smoked cannabis. "Harnessing that system with medications is a potentially new avenue for



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therapeutics," says Mark Ware, McGill University neurologist and pain physician.

For example, Marinol is a synthetic THC drug that is used by chemotherapy patients experiencing nausea and vomiting or AIDS patients who are rapidly losing weight. It is the only FDA-approved synthetic cannabinoid, and offers an alternative to conventional therapies for these patients, though results have been mixed when comparing its effects to those of smoked cannabis, with the herbal version usually outperforming the synthetic.

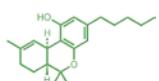
This highlights one problem with going the synthetic route in the eyes of some cannabis researchers. "We shouldn't forget that the herbal product contains multiple other constituents which may add to the effects of any one single agent," says Ware. Also problematic are isolated cannabinoids' tendency to be rapidly broken down in the liver and the difficulty in determining optimal doses. As the political and social storm around medical cannabis continues to brew, most researchers who have seriously tested the drug's therapeutic properties lament their inability to freely study it in a medical context. "The [cannabis] laws date to a time when what we knew about marijuana was voodoo," says Mayo Clinic psychiatrist Michael Bostwick. "[The drug] can't be applied to humans and to therapeutics because the laws don't permit it to be done. The whole attitude towards medical marijuana is just irrational."

For its part, the NIH claims that studying smoked marijuana is fair game. "Research projects seeking to determine the therapeutic potential of smoked marijuana are considered under the same criteria as any other project submitted for NIH funding," the agency wrote in an e-mail to *The Scientist*. "Investigator-initiated applications for NIH funding are evaluated by peer-review groups composed of scientists from outside the NIH. The peer-review group evaluates the scientific and technical merit of the proposed research." That said, the NIH's Research Portfolio online Reporting Tools (RePORT) database lists many more active projects focusing on molecular components of cannabis or marijuana as a harmful drug than it does projects seeking to probe the potential medical benefits of smoking cannabis. Still, officials at the HHS also claim that the US government is game to fund studies of medical marijuana. "We're very open to people submitting applications and trying to make [evaluating medical marijuana study proposals] a transparent and efficient process," says Sarah Wattenberg, senior advisor for substance abuse policy at HHS. "In order for us to move this forward at all, we have to take the politics and stigma away, deal with it as a therapeutic class, and give people what science there is," says Ware.

Particularly vexing to Ware is that so many people all over the world are using marijuana either recreationally or for the treatment of some ailment, legally or more often illegally, while science is forced to sit idly by and miss out on all that potential data. "We have so many people who are already doing the drug in one form or another in some sort of legal framework, but they're not being involved in any type of research," he says. "There's kind of a huge natural experiment going on right now, and we're not learning from it."

Grant, I., J.H. Atkinson, B. Gouaux, and B. Wilsey (2012) "Medical marijuana: clearing away the smoke." *The Open Neurology Journal* 6: 18-25.

Recent advances in understanding of the mode of action of tetrahydrocannabinol and related cannabinoid ingredients of marijuana, plus



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the accumulating anecdotal reports on potential medical benefits have spurred increasing re-search into possible medicinal uses of cannabis. Recent clinical trials with smoked and vaporized marijuana, as well as other botanical extracts indicate the likelihood that the cannabinoids can be useful in the management of neuropathic pain, spasticity due to multiple sclerosis, and possibly other indications. As with all medications, benefits and risks need to be weighed in recommending cannabis to patients. We present an algorithm that may be useful to physicians in determining whether cannabis might be recommended as a treatment in jurisdictions where such use is permitted.

Grant, I. and B.R. Cahn (2005) "Cannabis and endocannabinoid modulators: Therapeutic promises and challenges." Clinical Neuroscience Research **5** (2-4): 185-199.

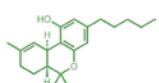
The discovery that botanical cannabinoids such as Δ-9 tetrahydrocannabinol exert some of their effect through binding specific cannabinoid receptor sites has led to the discovery of an endocannabinoid signalling system, which in turn has spurred research into the mechanisms of action and addiction potential of cannabis on the one hand, while opening the possibility of developing novel therapeutic agents on the other. This paper reviews current understanding of CB1, CB2, and other possible cannabinoid receptors, their arachidonic acid derived ligands (e.g. anandamide; 2 arachidonoyl glycerol), and their possible physiological roles. CB1 is heavily represented in the central nervous system, but is found in other tissues as well; CB2 tends to be localized to immune cells. Activation of the endocannabinoid system can result in enhanced or dampened activity in various neural circuits depending on their own state of activation. This suggests that one function of the endocannabinoid system may be to maintain steady state. The therapeutic action of botanical cannabis or of synthetic molecules that are agonists, antagonists, or which may otherwise modify endocannabinoid metabolism and activity indicates they may have promise as neuroprotectants, and may be of value in the treatment of certain types of pain, epilepsy, spasticity, eating disorders, inflammation, and possibly blood pressure control.

Gray, C. (1998) "Legalize use of marijuana for medical purposes, MDs and patients plead." Canadian Medical Association Journal – CMAJ **158** (3): 375.

As debate about the legalization of marijuana continues in Canada, physicians are joining the fray. Ottawa family physician Don Kilby is working hard to make it easier for ill patients to use the marijuana that alleviates their symptoms. A recent case in Toronto indicates that the courts are starting to share these views.

Greenberg, H.S., S.A.S. Werness, J.E. Pugh, R.O. Andrus, D.J. Anderson, and E.F. Domino (1994) "Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers." Clinical Pharmacology and Therapeutics **55** (3): 324-328.

A double-blind randomized placebo-controlled study of inhaled marijuana smoke on postural responses was performed in 10 adult patients with spastic multiple sclerosis (MS) and 10 normal volunteers matched as closely as possible for age, sex, and weight. A computer-controlled dynamic posturographic platform with a video line scan camera measured shoulder



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displacement in response to pseudorandom platform movements. Premarijuana smoking patient tracking was inferior to that of the normal volunteers as indicated by the higher noise variance of the former. Smoking one marijuana cigarette containing 1.54% Δ-9-tetrahydrocannabinol increased postural tracking error in both the patients and normal control subjects with both eyes open and closed; this untoward effect was greatest for the patients. The tracking error was also accompanied by a decrease in response speed for the patients with their eyes closed. Marijuana smoking further impairs posture and balance in patients with spastic MS.

Grinspoon, L. and J.B. Bakalar (1994) "Marijuana, the forbidden medicine. [Marijuana, die verbotene Medizin. Mit einer Kurzstudie zur rechtlichen und medizinischen Situation.]" Zweitausendeins Verlag, Frankfurt am Main.

Grotenhermen, F. (1999) "[Hemp (cannabis) as a medicinal drug]." Zeitschrift für Phytotherapie **20** (2): 70-71.

Grotenhermen, F. (1999) "Cannabis als Medizin – Die Wiederentdeckung einer verfemten Alltagsdroge als Heilmittel." Dr. med. Mabuse **24** (118): 189 Seiten. AT Verlag Frankfurt am Main.

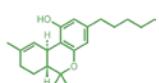
Franjo Grotenhermen über das therapeutische Potential, mögliche Nebenwirkungen und die Anwendungspraxis von Cannabis.
Die Hanfpflanze erlebt heute eine Renaissance. In den vergangenen Jahren wurden wichtige neue wissenschaftliche Erkenntnisse über ihren medizinischen Nutzen gewonnen. Mit Inkrafttreten der 10. Betäubungsmittelrechts-Änderungsverordnung im Februar 1998 wurde der pharmakologisch wichtigste Inhaltsstoff der Hanfpflanze in Deutschland rezeptierfähig. Seither darf der Cannabiswirkstoff Dronabinol (THC) - z.B. das in den USA zugelassene THC-Präparat Marinol - auch ärztlich verschrieben werden; demnächst soll ein Cannabisextrakt zur Verfügung stehen. Auch im öffentlichen Bewußtsein und in der Haltung von Politik und Justiz zeigt sich eine zunehmende Öffnung hin zur Akzeptanz von Cannabis zu medizinischen Zwecken.

Die Verwendung natürlicher Cannabisprodukte bleibt weiterhin ausnahmslos verboten. Aus verschiedenen Gründen spielt die illegale Selbstmedikation mit natürlichen Cannabisprodukten dennoch weiterhin die größere Rolle. Cannabis und Cannabisprodukte lassen sich oft erfolgreich bei schweren Erkrankungen einsetzen. Anwendungsgebiete sind heute vor allem chronische Schmerzen, chronische Entzündungen, neurologische Erkrankungen wie multiple Sklerose und Querschnittslähmung, Appetitlosigkeit und Abmagerung bei Aids und Krebs, Hemmung der Übelkeit bei Krebs-Chemotherapie.

Zahlreiche Patienten erleben Cannabis als das beste Medikament, das sie je versucht haben und das zudem völlig nebenwirkungsfrei ist.

Das Buch beschreibt ausführlich:

- Chancen und Risiken der Behandlung mit Cannabis und seinen Inhaltsstoffen.
- Wirkungsweise der Cannabinoide, Anwendungsgebiete, Nebenwirkungen, Dosierungen und mögliche Wechselwirkungen.
- Wissenschaftliche Forschungsergebnisse und Erfahrungsberichte von Patienten



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Grotenhermen, F. (1996) "Two new clinical trials with THC and Cannabis in Europe." Journal of the International Hemp Association **3** (2): 71-72.

The Swiss and German governments have permitted controlled clinical tests to investigate the benefits of oral Cannabis extracts and synthetic THC (tetrahydrocannabinol) for the treatment of spasticity, anorexia and cachexia. In a Swiss trial, synthetic Δ-9-TCH was shown to decrease pain, spasticity and ataxia in 2 patients with severe spasticity. Other trials have shown that Δ-9-TCH and a TCH-standardized extract of Cannabis have applications in treating anorexia and cachexia. Further trials in Germany, Austria, Switzerland and the Netherlands are planned.

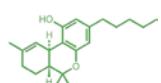
Grotenhermen, F. (2002) "[Treatment of severe chronic pain with cannabis preparations]." Ärztliche Praxis Neurologie Psychiatrie **5**: 28-30.

Grotenhermen, F. (2005) "Cannabinoids." Current Drug Targets - CNS & Neurological Disorders **4** (5): 507-530.

Since the discovery of an endogenous cannabinoid system, research into the pharmacology and therapeutic potential of cannabinoids has steadily increased. Two subtypes of G-protein coupled cannabinoid receptors, CB(1) and CB(2), have been cloned and several putative endogenous ligands (endocannabinoids) have been detected during the past 15 years. The main endocannabinoids are arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), derivatives of arachidonic acid, that are produced "on demand" by cleavage of membrane lipid precursors. Besides phytocannabinoids of the cannabis plant, modulators of the cannabinoid system comprise synthetic agonists and antagonists at the CB receptors and inhibitors of endocannabinoid degradation. Cannabinoid receptors are distributed in the central nervous system and many peripheral tissues, including immune system, reproductive and gastrointestinal tracts, sympathetic ganglia, endocrine glands, arteries, lung and heart. There is evidence for some non-receptor dependent mechanisms of cannabinoids and for endocannabinoid effects mediated by vanilloid receptors. Properties of CB receptor agonists that are of therapeutic interest include analgesia, muscle relaxation, immunosuppression, anti-inflammation, antiallergic effects, improvement of mood, stimulation of appetite, antiemesis, lowering of intraocular pressure, bronchodilation, neuroprotection and antineoplastic effects. The current main focus of clinical research is their efficacy in chronic pain and neurological disorders. CB receptor antagonists are under investigation for medical use in obesity and nicotine addiction. Additional potential was proposed for the treatment of alcohol and heroine dependency, schizophrenia, conditions with lowered blood pressure, Parkinson's disease and memory impairment in Alzheimer's disease.

Grotenhermen, F. and B. Reckendrees (2012) "Die Behandlung mit Cannabis und THC" Nachtschatten Verlag, Solothurn.

Grotenhermen, F. and K. Müller-Vahl (2012) "Das therapeutische Potenzial von Cannabis und Cannabinoiden." Deutsches Ärzteblatt International **109** (29-30): 495-501.

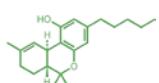


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Hintergrund: Seit der Entdeckung des endogenen Cannabinoid-Rezeptorsystems vor etwa 20 Jahren werden Medikamente auf Cannabisbasis intensiv erforscht. Im Jahr 2011 wurde in Deutschland erstmals ein Cannabisextrakt arzneimittelrechtlich zugelassen. Methode: Selektive Literaturrecherche Ergebnisse: Die klinischen Wirkungen von Cannabismedikamenten sind in der Mehrzahl auf eine Aktivierung von endogenen Cannabinoid-CB1- und CB2-Rezeptoren zurückzuführen. Seit 1975 wurden mehr als 100 kontrollierte klinische Studien mit Cannabinoiden oder Ganzpflanzenzubereitungen bei unterschiedlichen Indikationen durchgeführt. Die Ergebnisse dieser Studien führten in zahlreichen Ländern zur Zulassung von Medikamenten auf Cannabisbasis (Dronabinol, Nabilon und einem Cannabisextrakt [THC : CBD = 1 : 1]). In Deutschland ist dieser Cannabisextrakt seit 2011 für die Behandlung der mittelschweren oder schweren therapieresistenten Spastik bei multipler Sklerose zugelassen. Eine „off-label“-Behandlung erfolgt derzeit am häufigsten bei Appetitlosigkeit, Übelkeit und neuropathischen Schmerzen. Alternativ können Patienten bei der Bundesopiumstelle eine Ausnahmeerlaubnis zum Erwerb von Medizinal-Cannabisblüten im Rahmen einer ärztlich überwachten Selbsttherapie beantragen. Die häufigsten Nebenwirkungen von Cannabinoiden sind Müdigkeit und Schwindel (> 1/10), psychische Effekte und Mundtrockenheit. Gegenüber diesen Nebenwirkungen entwickelt sich fast immer innerhalb kurzer Zeit eine Toleranz. Entzugssymptome stellen im therapeutischen Kontext kaum jemals ein Problem dar. Schlussfolgerungen: Es gilt heute als erwiesen, dass Cannabinoide bei verschiedenen Erkrankungen einen therapeutischen Nutzen besitzen.

Hagenbach, U., N. Ghafoor, R. Brenneisen, S. Luz, and M. Mäder (2001) "Clinical investigation of delta-9-tetrahydrocannabinol (THC) as an alternative therapy for overactive bladders in spinal cord injury (SCI) patients." 2001 Congress on Cannabis and the Cannabinoids, International Association for Cannabis as Medicine, Köln: 10.

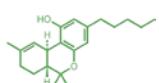
We are presenting the preliminary results of a pilot study. THC was administered over a period of 6 weeks. In 15 patients with spastic spinal cord injury the effect of THC on the overactive bladder has been investigated. The effect of THC was compared with urodynamic and clinical parameters, first without any bladder medication and after 6 weeks medication with THC. There are no data of invasive investigation in literature up till now. Patients and methods: THC was administered for 6 weeks in two different groups orally as Dronabinol (Marinol®) in 9 patients and rectally as THC-Hemisuccinate suppositories (THC-HS-supp) in 6 patients in several individual dosages per day. An urodynamic investigation, urine analysis and urine bacteriology was performed at the beginning of the study (without any bladder medication and without any spasmolytic therapy) and in the end after 6 weeks treatment. On the last day of medication all patients have been administered either 10 mg Dronabinol or 10 mg THC-HS-supp 2 h before the urodynamic investigation (relating to the group they were in). Investigated parameters: first desire to void (FDV), maximum cystometric capacity (MCC), intravesical pressure (IVP), bladder compliance (CPL), post void residual urine volume (RV), volume at first detrusor contraction (VFC). Results: The dronabinol group showed an increase of the CPL from mean 34.3 ml/cm H₂O (9 – 100) to mean 52.2 ml/cm H₂O (11 – 200). All other parameters have not been changed essentially. The



THC-HS-sup group showed a trend with increase of MCC from mean 227 ml (143 – 323) to mean 278 ml (121 – 322) (*p* value = 0.075), and an increase of the VFC from mean 191.3 ml (121 – 322) to mean 224.6 ml (96 – 407), CPL increased from mean 21.3 ml/cm H₂O (6 – 60) to mean 40 ml/cm H₂O (10 – 120) significantly (*p* value = 0.028). All other parameters have not been changed essentially. Conclusion: These preliminary results indicate a reduction of the overactivity of the detrusor of the bladder especially in the THC-HS-sup group with potential therapeutic consequences. The different results between oral and rectal application may demonstrate their different bioavailability.

Hagenbach, U.; S. Luz, R. Brenneisen, M. Mäder (2003) "The treatment of spasticity with Δ-9-tetrahydrocannabinol (Δ-9-THC) in patients with spinal cord injury:" Spinal Cord **45** (8): 551-562.

Introduction: Spasticity is a common complaint after traumatic SCI. Δ-9-THC the main psychoactive cannabinoid of cannabis has been shown to have beneficial effects in the treatment of spasticity of different origin. The aim of the study was to assess the effectiveness and safety of Δ-THC (Dronabinol, Marinol® capsules) and THC-hemisuccinate suppositories (THC-HS) for the treatment of spasticity in patients with SCI as a homogeneous population of patients. We are presenting the results of spasticity as partial results of a finished study with a wide spectrum of other investigations. Methods: Phase 1: open trial, six weeks treatment of 22 patients with Dronabinol (7 drop outs) Phase 2: open trial, six weeks treatment of 8 patients with THC-HS (1 drop out) Phase 3: randomized, double-blind, placebo controlled clinical trial with 13 patients (Marinol®/placebo) 25 patients mean age 42.3 years with spasticity due to SCI (11 para- and 14 tetraplegics) were included. Mean time since injury was 13.4 years. Inclusion criteria for spasticity were minimum of 3 points on the Ashworth scale without therapy, negative urine drug screening, age > 18 years. Spasticity was investigated using the modified Ashworth scale (MAS) after administration of 10 mg Dronabinol (Marinol®) or 10 mg THC-HS at day one and after one and six weeks treatment with an individual dose. Self-rating of spasticity was performed every day using a seven point scale from absent to unbearable. Results: Phase 1: Dronabinol (Marinol®) significantly decreased the mean spasticity sum score (± SD) (summed Ashworth scores divided by four) in 15 patients after a single dose of 10 mg (day 1) from 16.72 ± 7.60 to 7.75 ± 7.00 points (*p*<0.001) and after 6 weeks of treatment with an individual symptom oriented mean dose of 30 mg Dronabinol to 8.92 ± 7.14 points (*p*<0.05). Phase 2: THC-HS significantly decreased the mean spasticity sum score (± SD) in 7 patients after a single dose of 10 mg (day 1) from 22.71 ± 11.68 to 9.86 ± 8.15 points (*p*<0.05) and after 6 weeks of treatment with an individual symptom oriented mean dose of 43 mg THC-HS to 9.21 ± 9.25 points (*p*<0.05). The comparison of oral and rectal application in five patients showed no difference. Phase 3: summed spasticity scores for the Dronabinol group (7.21 points) differed significantly from summed scores of the placebo group (12.10 points) as a treatment effect of Dronabinol during the entire 6 weeks (*p*=0.001). Conclusion: The results demonstrate a significant therapeutic effect of Δ9-THC (Dronabinol, Marinol®) as well as THC-HS in patients with SCI. However the antispastic efficacy is significant the treatment often is limited by side effects.



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Hagenbach, U., S. Luz, N. Ghafoor, J.M. Berger, F. Grotenhermen, R. Brenneisen and M. Mader (2007) "The treatment of spasticity with Δ-9-tetrahydrocannabinol in persons with spinal cord injury." *Spinal Cord* **45** (8): 551-562.

Study Design: Open label study to determine drug dose for a randomized double-blind placebo-controlled parallel study. **Objectives:** To assess the efficacy and side effects of oral Δ-9-tetrahydrocannabinol (THC) and rectal THC-hemisuccinate (THC-HS) in SCI patients. **Setting:** REHAB Basel, Switzerland. **Method:** Twenty-five patients with SCI were included in this three-phase study with individual dose adjustment, each consisting of 6 weeks. Twenty-two participants received oral THC open label starting with a single dose of 10 mg (Phase 1, completed by 15 patients). Eight subjects received rectal THC-HS (Phase 2, completed by seven patients). In Phase 3, six patients were treated with oral THC and seven with placebo. Major outcome parameters were the spasticity sum score (SSS) using the Modified Ashworth Scale (MAS) and self-ratings of spasticity. **Results:** Mean daily doses were 31 mg with THC and 43 mg with THC-HS. Mean SSS for THC decreased significantly from 16.72 (+/-7.60) at baseline to 8.92 (+/-7.14) on day 43. Similar improvement was seen with THC-HS. We observed a significant improvement of SSS with active drug ($P=0.001$) in the seven subjects who received oral THC in Phase 1 and placebo in Phase 3. Major reasons for drop out were increase of pain and psychological side effects. **Conclusion:** THC is an effective and safe drug in the treatment of spasticity. At least 15-20 mg per day were needed to achieve a therapeutic effect.

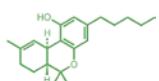
Haller, R., I. Dittrich, W.W. Fleischhacker (2004) "Expertenpapier der Österreichischen Gesellschaft für Psychiatrie und Psychotherapie (ÖGPP) zum Thema "Cannabis".

Einleitung

Cannabis, dessen medizinische Anwendung im Jahr 2737 v. Chr. in China erstmals beschrieben wurde, hat seit den 60er-Jahren weltweite Verbreitung erfahren und ist heute in vielen Industrieländern die am weitesten verbreitete illegale Droge.

Zubereitung und Gebrauch des Cannabis haben sich in den letzten Jahren in den meisten Ländern stark verändert. So ist in den USA von einer „neuen Marihuana-Epidemie“ die Rede welche nach der Inkubationsphase nun in jene der Expansion übergehe.

Nach der amerikanischen Jugendumfrage „Monitoring the Future“ hat sich der Cannabisgebrauch unter den 14- bis 16-Jährigen von 1992 bis 1997 verdoppelt, bis 2001 haben sich die Prävalenzzahlen auf einem konstant hohen Niveau eingependelt. Die europäischen Länder verzeichnen in den letzten zehn Jahren einen so deutlichen Anstieg in den Lebenszeitprävalenzen des Cannabisgebrauchs, dass manche Autoren von einem „Quantensprung“ sprechen. Von den 21 Ländern, die am Europäischen Schulsurvey-Projekt über Alkohol und andere Drogen (ESPAD) von 1995 bis 1999 durchgängig teilnahmen, ist bei 14 ein Anstieg der Lebenszeitprävalenzen des Cannabiskonsums zu konstatieren, während nur in drei Ländern eine Abnahme zu verzeichnen ist. Die Europäische Beobachtungsstelle für Drogen und Drogensucht (EBDD) in Lissabon berichtet, dass jeder fünfte Europäer im Alter zwischen 15 und 64 Jahren – das sind 50 Millionen Menschen – Cannabis wenigstens einmal probiert hat.



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Kraus et al. gehen in Deutschland bei 18- bis 59-Jährigen von einer Lebenszeitprävalenz für Cannabiserfahrung von 21,4% aus, was mit österreichischen Schätzungen übereinstimmt. Eine in Österreich im Jahr 2000 durchgeführte Studie des Ludwig Boltzmann-Instituts an 200 14- bis 24jährigen verschiedener jugendlicher Teilkulturen ergab eine starke Verbreitung von Cannabiserfahrung nicht nur bei Ravern und Funsportlern, sondern auch bei jener Population, die in früheren Untersuchungen traditionell eher nur geringe Tendenzen erkennen ließ, mit illegalen Drogen zu experimentieren. Nach wie vor steigt die Zahl der Cannabiskonsumenten, was durch gegenwärtige Trends hinsichtlich Konsum, Verfügbarkeit, Preis und sozialer Toleranz begünstigt wird. Schweizer Studien, die für die Gruppe der 15- bis 19-Jährigen eine Probiererfahrung von fast 50% annehmen, kommen zum Schluss, dass Cannabiskonsum für einen nicht zu vernachlässigenden Teil der Bevölkerung zu einer Gewohnheit geworden ist und sich das bei den Konsumenten früher vorherrschende Streben nach Berauschungen zu einem Freizeitverhalten, einem Konsum aus Genussgründen gewandelt habe. Daraus wird auf eine zunehmende Normalisierung im Sinne von weniger Devianz bzw stärkerer Akzeptanz in der Bevölkerung geschlossen, sodass Cannabis zu einer Alltagsdroge geworden ist und ähnlich wie Tabak und Alkohol konsumiert wird. Cannabis wird vorwiegend in Form von Zigaretten, sogenannten Joints, oder mit Hilfe von Wasserpfeifen geraucht. Seltener ist die Verarbeitung in Essgerichten oder Tees.

Zur weiten Verbreitung des Cannabis kommt, dass der THC-Gehalt der Hanfpflanzen durch ausgeklügelte Kultivation in den letzten Jahren erheblich angestiegen ist. In den 60er- und 70er Jahren des letzten Jahrtausends enthielt ein Joint durchschnittlich 10 mg THC, heute sind es 150-200 mg.

In Anbetracht der hohen Verbreitung von Cannabis, der kontrovers diskutierten gesundheitlichen Gefahren dieser Substanz und der anhaltenden gesellschaftlichen Diskussion über den Umgang mit Cannabis und Cannabiskonsumenten sieht sich die Österreichische Gesellschaft für Psychiatrie und Psychotherapie (ÖGPP) verpflichtet, eine grundsätzliche Stellungnahme zur psychiatrischen Relevanz des Cannabis, zu dessen medizinischer Bedeutung und zur Cannabisgesetzgebung abzugeben.

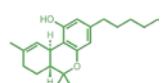
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Schlussfolgerungen und Empfehlungen

Die zunehmende Verbreitung des Cannabiskonsums in unserer Gesellschaft, der zum Teil dramatische Anstieg der Prävalenzraten von Cannabiserfahrungen, die deutliche Erhöhung des THC-Gehaltes von Cannabiszubereitungen und die nach wie vor mangelhaften Kenntnisse über das genaue Schädigungsmuster der Cannabinoide haben die Diskussion über die Risiken des Konsums und über den besten gesetzlichen Status polarisiert. Anzustreben ist eine Versachlichung der Meinungsbildung, welche einerseits eine wissenschaftsgestützte, nicht ideologisierte Diskussion über günstige und ungünstige Effekte des Cannabis und andererseits eine möglichst hilfreiche, gesetzliche Handhabung zulässt. Die Debatte über die Prohibitions- bzw Liberalisierungs- und Legalisierungspolitik darf nicht jene über die gesundheitlichen Auswirkungen des Cannabisgebrauchs oder jene über die möglichen therapeutischen Effekte von Cannabinoiden überschatten oder gar behindern.

Aus Sicht der Österreichischen Gesellschaft für Psychiatrie und Psychotherapie (ÖGPP) scheint es wichtig, über die Effekte des Cannabiskonsums in folgenden Punkten einen Konsens zu erzielen:

1. Die wichtigsten Gesundheitsrisiken des Cannabisgebrauchs sind, mit Ausnahme



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der üblichen Risiken einer Berauschtung durch psychotrope Substanzen, Folge eines regelmäßigen, intensiven (d.h., täglichen oder fast täglichen) Cannabisgebrauchs. Der gelegentliche Cannabisgebrauch beeinflusst allerdings auch Aufmerksamkeit und Reaktionsvermögen. Bis heute gibt es keine Hinweise für tödliche Intoxikationen durch Cannabis.

2. Wissenschaftlich belegt ist das erhöhte Risiko des Auftretens folgender negativer Auswirkungen:

- ◆ Ängstlichkeit und Panik, vor allem bei unerfahrenen Benutzern.
- ◆ Verschlechterte Aufmerksamkeit, Erinnerungsvermögen und psychomotorische Leistungsfähigkeit während der Intoxikation.
- ◆ Möglicherweise ein erhöhtes Unfallrisiko, wenn eine Person ein Fahrzeug lenkt, während sie mit Cannabis berauscht ist, vor allem, wenn Cannabis gleichzeitig mit Alkohol konsumiert wird.
- ◆ Erhöhtes Risiko psychotischer Symptome bei jenen, die aufgrund ihrer persönlichen oder familiären Krankheitsgeschichte vulnerabel sind.

3. Folgende negative Folgeerscheinungen treten nicht gesichert, jedoch höchst wahrscheinlich auf:

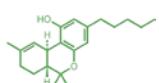
◆ Chronische Bronchitis und histopathologische Veränderungen, die Vorläufer für die Entwicklung maligner Krankheiten sein können.

- ◆ Ein psychiatrisches Cannabisabhängigkeitssyndrom, das charakterisiert wird durch die Unfähigkeit, sich des Cannabisgebrauchs zu enthalten oder ihn zu kontrollieren.

Es muss in einer auf wissenschaftlichen Kriterien gestützten, fachlichen Diskussion möglich sein, diese Erkenntnisse zu erörtern, durch weitere Untersuchungen abzustützen und sowohl in die Gesundheitsberatung als auch in die Therapie und die Gesetzgebung einfließen zu lassen.

Des weiteren vertritt die Österreichische Gesellschaft für Psychiatrie und Psychotherapie (ÖGPP) die Meinung, dass Cannabiszubereitungen im Rahmen der Bedingungen der gesetzlichen Zulassungsverfahren als Medikamente geprüft werden sollen. Wenngleich die vorliegenden Untersuchungen die Überlegenheit von Cannabinoiden in verschiedenen Imitationen gegenüber zugelassenen Präparaten nicht eindeutig belegen können, sollte eine begleitende Behandlung von Schmerzen, Spastik, Dystonie, Brechreiz, Anorexie, Appetitlosigkeit, Glaukom und Bronchospasmen mit Cannabinoiden möglich sein. Das Argument der Gefahr von Gewöhnung und Abhängigkeit hat in diesem Diskussionspunkt keinen Bestand, da die entsprechenden Effekte beim Cannabis nicht sehr stark ausgeprägt sind und zudem Substanzen mit wesentlich höherer Suchtpotenz in der Medizin enorme Bedeutung haben und selbstverständlich zur Anwendung kommen. Doppelblind durchgeföhrte Zulassungsstudien, wie sie bei synthetischen Pharmaka durchgeführt werden, werden klarerweise auch auf psychiatrischem Gebiet gefordert.

Die ÖGPP ist der Meinung, dass justizielle Reaktionen die Situation von drogengefährdeten oder -abhängigen Menschen nicht zusätzlich erschweren sollen und dem Prinzip „Therapie statt Strafe“ absoluter Vorrang einzuräumen ist. Gesetzestechisch flexible Lösungen, die weder eine undifferenzierte Gleichstellung des Cannabis mit anderen Drogen noch eine völlige Freigabe des gesamten Cannabishandels beinhalten, sind anzustreben. Zu denken ist etwa an eine moderate Abstufung der Strafandrohungen gegenüber Cannabiskonsumenten, welche unter Anlehnung an die von Kreuzer



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vorgeschlagenen Überlegungen folgende Punkte berücksichtigen sollte:

- ◆ die inzwischen weite Verbreitung des Cannabis bzw. die hohen Prävalenzzahlen von Cannabisprobier- und Gelegenheitskonsumenten, insbesondere in den jüngeren Altersstufen;
- ◆ die wachsende Akzeptanz dieser Droge in vielen Teilen der Bevölkerung;
- ◆ die vergleichsweise geringen Gesundheitsrisiken des Cannabiskonsums im Vergleich zu jenen von Heroin oder Alkohol;
- ◆ die Erkenntnis, dass bei Klein- und Gelegenheitskonsumenten häufig weder Strafe noch Therapie angezeigt sind;
- ◆ die zumindest faktisch weitgehende „Entkriminalisierung“ des Cannabiskonsumenten in der tatsächlichen Strafverfolgung;
- ◆ die Widersprüchlichkeit eines Strafsystems, welches einerseits selbstschädigendes Verhalten grundsätzlich straffrei lässt, andererseits den Drogenkonsum als ebensolches mittelbar unter Strafe stellt;
- ◆ Erfahrungen über negative Wirkungen übermäßig repressiven, strafenden Vorgehens gegen Einmal- und Gelegenheitskonsumenten;
- ◆ die Notwendigkeit, einen internationalen Kompromiss zwischen jenen Ländern, die eine teilweise oder völlige Freigabe und jenen, welche nach wie vor an der Prohibition festhalten, zu erzielen.

Vorgeschlagen wird konkret, dass unter voller Ausnutzung der Möglichkeiten des Suchtmittelgesetzes bzw. unter Neuformulierung mancher Bestimmungen bei Erstauffälligkeiten wegen des Konsums bzw. Besitzes geringer Mengen von Cannabis das Verfahren durch die Staatsanwaltschaft eingestellt bzw. ein Opportunitätsprinzip nach dem holländischen Modell verwirklicht wird.

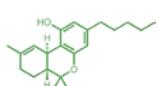
Cannabiskonsum und -handel könnten bis zu bestimmten Grenzen zudem aus dem Strafrecht herausgenommen und als Ordnungswidrigkeiten, die nach Verwaltungsermessen durch Verwarnungs- oder (bedingte) Geldstrafen zu ahnden wären, abgestuft werden. Durch solche Lösungen ließe sich das Signal, das mit einer generellen Drogenfreigabe verbunden wäre, ebenso vermeiden wie die Gefahr von Übermaßreaktion mit desozialisierenden Wirkungen.

In allen wissenschaftlichen Untersuchungen wird die Notwendigkeit von intensivierter Forschung im Cannabispark betont. Für entsprechende Projekte, welche sich mit dem Zusammenhang zwischen Drogenmissbrauch und psychischen Folgen sowie der Effizienz von Beratungs- und Therapiemaßnahmen befassen, sollten daher auch in Österreich genügend finanzielle Mittel zur Verfügung gestellt werden.

In Anbetracht der neuen Risiken, die sich aus der Verbreitung hochkonzentrierter Cannabiszubereitungen ergeben, ist eine Intensivierung der Aufklärungsmaßnahmen erforderlich. Die ÖGPP empfiehlt deshalb eine Verstärkung der primär- und sekundärpräventiven Bemühungen, in welche die relevanten Fachgesellschaften miteinbezogen werden sollten.

Hanigan, W.C., R. Destree, and X.T. Truong, (1986) "The Effect of Delta-9-Tetrahydrocannabinol on Human Spasticity." Clinical Pharmacology and Therapeutics **39** (2): 198.

Five patients with traumatic paraplegia were given oral Δ -9-THC at 35 mg/day in a double blind, 20-day crossover trial. Separate investigators graded muscle resistance and deep tendon reflexes while patients and nursing staff evaluated spasticity using a visual analog scale. Mean scores for each trial period were



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compared using unpaired t-tests.

In two patients significant reductions in stretch resistance and reflex activity were demonstrated during the Δ-9-THC period. Both patients identified the active drug with reduction in spasticity scores. No change in stretch resistance or reflex activity was demonstrated in a third patient although both nursing staff and patient evaluation agreed on a reduction in the spasticity score. No significant changes were seen in the fourth patient. One patient withdrew from the study because of negative emotional side effects. In summary, Δ-9-THC proved clinically beneficial in two of five patients with intractable spasticity. Two patients showed no objective effects while negative psychological side effects limited its use in the remaining patient.

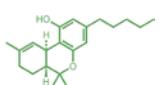
Haroutiunian, S., G. Rosen, R. Shouval, and E. Davidson, (2008) "Open-label, add-on study of tetrahydrocannabinol for chronic nonmalignant pain." Journal of Pain & Palliative Care Pharmacotherapy **22** (3): 213-217.

Cannabinoids have been used for pain relief for centuries and recent studies have investigated their analgesic and anti-inflammatory mechanisms, as well as clinical efficacy, in treating chronic pain. We report an open-label study addressed to evaluate the effect and adverse events of orally administered Δ-9-tetrahydrocannabinol (Δ-9-THC) in 13 patients with chronic nonmalignant pain (CNMP) unresponsive to conventional pharmacotherapy. The effect of the treatment was assessed on an eight-item HRQoL questionnaire. Five out of 13 patients reported adequate response to the treatment while eight patients reported inadequate or no response. Seven patients did not experience any adverse events (AEs), six patients reported AEs, two of which discontinued the treatment. We conclude that oral THC may be a valuable therapeutic option for selected patients with CNMP that are unresponsive to previous treatments, though further research is warranted to characterize those patients.

Hartinger, J. (1995) "Haschisch als Medikament für Querschnittspatienten." Hanf! **10/95:** 26.

Hazekamp, A., R. Ruhaak, L. Zuurman, J. van Gerven, and R. Verpoorte (2001) "Evaluation of a vaporizing device (Volcano®) for the pulmonary administration of tetrahydrocannabinol." Journal of Pharmaceutical Sciences **95** (6): 1308–1317.

What is currently needed for optimal use of medicinal cannabinoids is a feasible, nonsmoked, rapid-onset delivery system. Cannabis "vaporization" is a technique aimed at suppressing irritating respiratory toxins by heating cannabis to a temperature where active cannabinoid vapors form, but below the point of combustion where smoke and associated toxins are produced. The goal of this study was to evaluate the performance of the Volcano vaporizer in terms of reproducible delivery of the bioactive cannabinoid tetrahydrocannabinol (THC) by using pure cannabinoid preparations, so that it could be used in a clinical trial. By changing parameters such as temperature setting, type of evaporation sample and balloon volume, the vaporization of THC was systematically improved to its maximum, while preventing the formation of breakdown products of THC, such as cannabinol or Δ-8-THC. Inter- and intra-device variability was tested as well as relationship between loaded- and delivered dose. It was found that an average of about 54% of



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loaded THC was delivered into the balloon of the vaporizer, in a reproducible manner. When the vaporizer was used for clinical administration of inhaled THC, it was found that on average 35% of inhaled THC was directly exhaled again. Our results show that with the Volcano a safe and effective cannabinoid delivery system seems to be available to patients. The final pulmonal uptake of THC is comparable to the smoking of cannabis, while avoiding the respiratory disadvantages of smoking.

Hecht, B. (1991) "The case for medicinal marijuana." New Republic July 15 & 22, 1991.

Last week the Public Health Service announced that it will phase out its program of allowing seriously ill patients to smoke marijuana. The reason seems to have little to do with the effectiveness of pot in relieving various medical symptoms and a lot to do with the politics of the "drug war." With the recent attention pot has received as an appetite enhancer in AIDS cases, the government correctly anticipated a flood of applications from AIDS patients for "compassionate" approval of the drug. AIDS activists, who have had much success in liberalizing the prescription drug approval process, may have met their match.

The debate over the medical use of marijuana started two decades ago and has hinged on its effectiveness in treating glaucoma, spasticity, and chemotherapy-induced nausea. Pot, like heroin, is classified by the Drug Enforcement Administration as a Schedule I drug, which means it has a high potential for abuse, induces

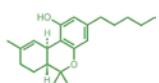
harmful side effects, and has "no currently accepted medical use in treatment in the United States." Pot advocates argue that marijuana should be moved to the category of Schedule II drugs, which also have a high potential for abuse and can have bad side effects, but are considered to be useful medically and thus can be prescribed by physicians. Interestingly, cocaine -- the drug war's No. 1 bogey -- is a Schedule II drug.

In 1985 the government did recognize that the principal active ingredient in marijuana - Δ -9-tetrahydrocannabinol, or THC-has medical use. A synthetic drug containing THC is now available by prescription under the name Marinol, manufactured by Unimed Pharmaceuticals.

Why does the government allow THC pills but not marijuana joints? THC has been put through a level of testing acceptable to the Food and Drug Administration. Because of the expense, this typically requires a pharmaceutical-industry corporate sponsor, which pot -- a plant that grows like a weed and requires no processing -- is unlikely to attract.

Nevertheless, in response to a 1972 petition for rescheduling filed by NORML and other pot advocacy groups, in 1988 DEA administrative law judge Francis L. Young ruled that the ban on prescription pot is "unreasonable, arbitrary, and capricious."

The DEA chose to ignore his recommendation for rescheduling, calling the medical use of marijuana a "cruel and dangerous hoax." Then this April the U.S. Court of Appeals in D.C. ordered the DEA to change three of its eight criteria for reclassification. Under those three criteria, a drug can be removed from Schedule I only if it is generally (i.e., legally available and used in the medical community; by definition, the court noted, these are conditions that an illegal drug can never meet. The decision might appear to be a big victory for



the medical rise of marijuana. But the court did approve five of the DEA criteria, and pot advocates, who think the DEA will have no trouble reshaping the other three to satisfy the court, see this judicial path to rescheduling as effectively closed.

The only other path (short of congressional action) is through the FDA, which has the authority to tell the DEA that a drug has "currently accepted medical use" and that it should be rescheduled. The hope among pot and AIDS activists had been that the onslaught of "compassionate" approval applications by AIDS patients and their doctors -- which began last year when two AIDS patients, Barbara and Kenny Jenkins, were arrested for growing marijuana to treat themselves -- would force the FDA to recognize marijuana's medical use. Instead, the Public Health Service, which oversees the FDA, has supported its decision with the same argument the DEA has been using for years: evidence of the medical value of marijuana is purely anecdotal and the drug has not been rendered safe.

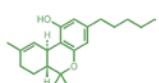
Pot advocates acknowledge that although there is copious research on marijuana, they are short on the kinds of institutionally sponsored studies that would typically satisfy the FDA. And since marijuana treatment of appetite loss in AIDS patients is very new, there are no formal studies. Nevertheless, there is plenty of evidence to suggest that the medical benefits of using marijuana outweigh the risks. The debate can be boiled down to three questions

1. Is the drug safe?
2. Does it work? and
3. How does it compare with other available drugs?

The DEA argues that marijuana contains more than 400 chemicals, which appear in widely varying proportions and whose chemical properties are not completely known. Marijuana's side effects, it claims, are intensive, though not fully understood. Pot causes acute changes in heart and circulation rates, has "produced genetic and non-genetic birth defects in many animal species," can reduce sperm count, and "may also have a toxic effect on the human brain." Lately the government, especially Herbert Kleber of the Office of National Drug Control Policy, has been pointing out the irony of using marijuana -- which itself suppresses the immune system -- in treating Acquired Immune Deficiency Syndrome.

Although pot advocates dispute the extent of marijuana's side effects, they point out that all drugs have side effects, and that in the case of pot, as with other drugs, such reactions (even immune suppression) need to be weighed against the benefits. They note that government-approved THC also suppresses the immune system (it gets you high too.) They add that common anti-emetic (anti-vomiting) drugs such as Compazine and Decadron can have side effects far worse than those of marijuana, such as liver damage and death. Dr. Ivan Silverberg, an oncologist who has spoken with hundreds of cancer patients who use marijuana, testified in 1988 that "the only side effect I've seen would bill be sedation," which he characterized as "mild." A study conducted by the state of New Mexico found adverse effects in only three of 250 patients tested.

And if we may venture into the realm of "anecdotal" evidence, it is worth noting that tens of millions of Americans -- including U.S. senators, prospective Supreme Court judges, and maybe even First Ladies -- have smoked pot without suffering noticeable damage. No one has ever died of a marijuana



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overdose; the lethal dosage is so high that no human could ever smoke enough pot to kill himself.

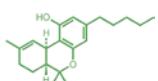
So is pot effective? The DEA, argues that its use in treating nausea, glaucoma, and spasticity has not been sufficiently proved by double-blind studies.

And the evidence for AIDS treatment, it claims, is nonexistent. Yet in 1973, Dr. Leo E. Hollister of the Veterans Administration Hospital in Palo Alto proved scientifically what anyone who has ever smoked pot will tell you: marijuana gives you the munchies. Dr. Ernest Abel of Berkeley confirmed Hollister's results later that year. In a now famous 1975 study, Drs. Steven Sallan and Norman Zinberg at Boston's Sidney Farber Cancer Research Center also confirmed that pot is effective as an anti-emetic. And a 1979 double-blind and placebo-controlled study by Dr. Alfred Chang of the National Cancer Institute confirmed the 1975 results. Several states, including New Mexico, Michigan, and New York, in independent studies over the last twenty years, have also proved pot's effectiveness as an anti-emetic. And besides, notes Dr. John Morgan of CUNY Medical School, there is no rule that saves a drug must be the best at what it does to warrant approval. If it is effective in even a small number of cases, it deserves serious attention as a therapeutic product.

The new Health and Human Services policy directive says that patients applying for medicinal marijuana must first try Marinol. But pot advocates point out that marijuana is more effective than Marinol. In a 1988 study by Dr. Vincent Vinciguerra published in the New York State Journal of Medicine, 29 percent of those who did not respond to oral THC did respond to smoked marijuana. The NCI/Chang study found that smoke from marijuana, absorbed through the lungs, acts on the brain almost immediately, while orally ingested pills can leave a nauseous cancer patient to suffer for several hours. Besides, notes CUNY's Morgan, "It is absurd that we only have an oral tablet" to treat vomiting. It's like treating diarrhea with a suppository.

But if the government is truly looking to satisfy its "currently accepted medical use" criteria, officials should turn to a just-published study in the Journal of Clinical Oncology, conducted by Richard Doblin and Mark A. R. Kleiman of Harvard's Kennedy School. Forty-eight percent of oncologists responding said they would prescribe marijuana to some of their patients if it were legal. Fifty-four percent said they thought smoked marijuana should be available by prescription, and 44 percent said they had recommended pot to a patient, even though it is illegal.

In justifying the new decision, PHS Chief James O. Mason told me: "It puts the government in sort of a tenuous situation to be passing out marijuana cigarettes that can be used by a person that can cloud their judgment if they choose to use an automobile or get out in the street or in the context of sexual behavior. I think it sends a signal that's not the best signal." Mason's rationale was uncannily prophesied by Judge Young in his 1988 decision: "There are those who, in all sincerity, argue that the transfer of marijuana to Schedule II will 'send a signal' that marijuana is, 'ok' generally for recreational use. This argument is specious. . . . If marijuana should be placed in Schedule II, in obedience to the law, then that is where marijuana should be placed, regardless of misinterpretation of the placement by some." The fact that AIDS has been added to the list of conditions treatable by pot should have helped, not hindered, efforts at reclassification.



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Marijuana, it seems, does indeed cloud the mind. But in this instance, the clouded minds are in government buildings, not in doctors' offices or patients' sick rooms.

Heim, M.E. (1982) "[Cannabis and cannabinoids. Possibilities of their therapeutic use]." MMW Fortschritte der Medizin **100** (9): 343-346.

Newer aspects of therapeutic potentials of cannabis and cannabinoids are reviewed. The major active constituent of cannabis sativa, Δ-9-tetrahydrocannabinol and synthetic cannabinoids are evaluated in several clinical trials on their antiemetic efficacy in cancer chemotherapy induced vomiting. 80% of patients refractory to standard antiemetic treatment could be improved with the synthetic cannabinoid levonantradol. Other therapeutic effects, which are presently investigated in clinical trials are analgesia, antispasticity, anticonvulsion and the reduction of intraocular pressure in glaucoma. The future goal of cannabinoid research is the separation between specific pharmacologic activities and undesirable psychotropic effects.

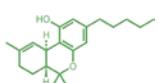
Helferich, P.S., Krüger, A., Pavlovic, N. und Schilling, M. (2005) Cannabis auf Rezept – Warum immer mehr Kranke auf das Kifferkraut vertrauen. cebeef Forum Konkret, **02/2005**: 5–6.

Es ist ein grauer Mittwochnachmittag. Die Cafeteria in der Orthopädie der Uniklinik Frankfurt ist gut gefüllt: Joachim Hartinger gibt mit der rechten Hand Milch und Zucker in seinen Kaffee. Die Linke ruht in seinem Schoß, sie ist taub. «Bei einer Spastik ist die Muskulatur ständig angespannt, die hemmenden Nervenbahnen sind zerstört. Deshalb kann ich meine Hand nicht gut kontrollieren», erklärt uns der Neurobiologe geduldig, während er den Löffel in die Tasse steckt und umröhrt. Bei einem Autounfall 1994 zog er sich schwere Verletzungen an der Halswirbelsäule zu. Von da an ist der 39-Jährige inkomplett querschnittsgelähmt.

«Natürlich bekam ich Medikamente gegen die Schmerzen, aber ich hatte das Gefühl, dass sie einfach nicht helfen», berichtet Hartinger und nimmt einen großen Schluck Kaffee. Nach und nach ließ er die verordneten Tabletten weg. Dass er schon an den Nebenwirkungen der Medikamente litt, wurde ihm dadurch erst bewusst. «Ich war total schockiert, als mein Nachbar zu mir kam und sagte, Mensch Joachim, du lallst ja gar nicht mehr.» Über einen Mitpatienten kam er auf die Idee, sein Leiden mit Cannabis zu therapieren. Der rauchte jeden Morgen einen Joint, um überhaupt auf die Beine zu kommen. «Die Ärzte haben das stillschweigend geduldet», grinst Hartinger und spielt mit dem Henkel der Tasse.

Auf die Wirkung der Cannabispflanze setzen auch viele Krebspatienten. So etwa der Mann von Barbara Lohmann. Er ist vor zwei Jahren an Krebs gestorben. «Einen Tag vor seinem Tod rauchte er einen Joint und sagte mir noch, wie schön es ist, mal keine Schmerzen zu haben», erzählt die Witwe mit gedämpfter aber fester Stimme. Ihr Sohn hatte die verbotene Pflanze teilweise selbst angebaut. Ein Freund, der an Hodenkrebs litt, griff ebenfalls während seiner Chemotherapie gerne auf diesen privaten Vorrat zurück.

Diese Art der Selbsthilfe ist in Deutschland allerdings gesetzlich verboten. Anders dagegen das Medikament «Dronabinol». Es enthält den Wirkstoff der Cannabispflanze und kann ganz legal von einem Arzt über ein Betäubungsmittelrezept verschrieben werden. Die Krankenkasse übernimmt



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die Kosten, aber nur für Austherapierte, wie etwa Joachim Hartinger. Dieser ist allerdings weit mehr als nur einer unter 1000 Patienten, die derzeit mit Dronabinol kuriert werden. Er ist Mitbegründer der Firma THC Pharm, die bis Anfang des Jahres 2002 der bundesweit einzige Hersteller von cannabishaltigen Medikamenten war.

Alles begann 1995 mit der Suche nach einem legalen Weg der Cannabisnutzung als Arzneimittel. «Wir waren sogar schon fest entschlossen zu klagen. Dann teilte uns das Bundesgesundheitsministerium aber mit, dass es das Betäubungsmittelgesetz umstufen werde», berichtet Hartinger und bestellt einen weiteren Kaffee. Cannabis-Arzneimittel wurden von der so genannten Anlage II in die Anlage III umgestuft und wurden 1996 tatsächlich verschreibungsfähig. Der Weg schien geebnet. Doch leider wagte niemand ein solches Medikament auf den Markt zu bringen.

In der Öffentlichkeit hatte das «Kifferkraut» immer noch den Ruf der Einstiegsdroge anhaften. «Da beschlossen wir, das Ganze einfach selbst in die Hand zu nehmen.»

Gesagt, getan: Joachim Hartinger, Martin Fröhlich, Andreas Königsdorfer, Christian Steup und Holger Rönitz gründeten am 1. April 1996 die Firma THC Pharm in einem Gartenhäuschen in Oberrad.

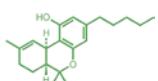
Anfangs mussten die frischgebackenen Unternehmer noch mit Geldproblemen und harten Auflagen kämpfen. Es durfte nur so genannter Faserhanf angebaut werden, der allerdings nur zwei bis drei Prozent Cannabidiol enthält.

Außerdem musste die Herkunft des Krauts immer belegt werden können. «Die haben sogar unsere Wohnungen durchsucht. Aber gefunden haben sie nichts», der Spott ist deutlich in Hartingers Augen zu sehen.

Heute ist die Firma kräftig im Aufwind und auf vielen wichtigen Schmerz- und Krebskongressen präsent. Rund 450 Apotheken in Deutschland und Österreich verarbeiten auf Betäubungsmittelrezept die Substanz zum Endprodukt, das entweder aus Tropfen oder Kapseln bestehen kann. Der Umsatz hat sich im Vergleich zum letzten Jahr mehr als verdoppelt. «Die Akzeptanz von Dronabinol wächst bisher kontinuierlich», versichert uns der Pressesprecher Holger Rönitz auf unsere Anfrage.

Siegessicher strebt das Unternehmen demnächst sogar den Europaweiten Vertrieb an. Der mächtige Erfolgskurs wird auch von anderen Pharma-Firmen beobachtet. Seit Anfang 2002 verarbeitet ein zweites deutsches Unternehmen, die Δ-9Pharma aus Neumarkt, den Cannabiswirkstoff. Vieles spricht für das teilweise synthetisch hergestellte Medikament. «Dronabinol kann ich ganz genau dosieren», preist Hartinger die Vorteile des Präparats an. Bei dem Cannabis, das man auf der Straße kaufen kann, schwankt der Wirkstoffanteil zwischen 3 und 20 Prozent. «Wenn ich am Abend meine Dosis nehme, weiß ich, dass ich am nächsten Morgen klar bin», erklärt er weiter. Im Blut ist der Wirkstoff allerdings auch dann noch nachzuweisen. Falls ihn die Polizei so mit seinem Auto anhält, müsste er erstmal belegen, dass er den «Stoff» auf Rezept genommen hat.

So bleiben doch unter dem Strich noch einige Probleme. Natürlich hat Dronabinol auch Nebenwirkung. Diese scheinen aber im Gegensatz zu denen anderer Mittel lächerlich. «Ich habe oft einen trockenen Mund», beschreibt Hartinger seine Erlebnisse. «Außerdem kann es vorkommen, dass sich der Herzschlag etwas erhöht und man unruhig wird». Konkurrent zum Straßenhandel würde Dronabinol aber selbst dann nicht werden, wenn es frei



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in den Apotheken erhältlich wäre. Heute kostet ein Gramm Cannabis beim Dealer des Vertrauens um die 3,50 Euro. Ein Gramm Dronabinol ist knapp zehnmal so teuer. Dennoch gibt es Hoffnung, für alle; die diesen stolzen Preis nicht aus der eigenen Tasche bezahlen können. «Wenn der Aufwärtstrend weiter anhält, können wir Dronabinol schon bald günstiger anbieten», prognostiziert Christian Steup, der Geschäftsführer von THC Pharm.

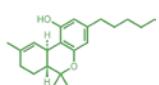
Hensel, W.A. (1997) "Medicinal marijuana?" New England Journal of Medicine **336** (16): 1184-1185.

Heutink, M. M.W. Post, M.M. Wollaars, and F.W. van Asbeck (2011) "Chronic spinal cord injury pain: pharmacological and non-pharmacological treatments and treatment effectiveness." Disability and Rehabilitation **33** (5): 433-440.

Purpose: To describe pharmacological and non-pharmacological pain treatments used for chronic spinal cord injury pain (CSCIP) and current treatment effectiveness in a large Dutch population with a spinal cord injury (SCI). Method: Postal survey among 575 persons with SCI. The main outcome measures were the pain intensity score of the Chronic Pain Grade questionnaire, past and current pain treatments, and perceived effectiveness of current pain treatments. Results: Response rate was 49% (279 persons) and 215 respondents (77.1%) had CSCIP. Most respondents with CSCIP (62.8%) reported more than one pain type, of which neuropathic pain was most frequently reported (69.3%). Of this group with CSCIP, 63.8% was currently involved in some kind of treatment, but nevertheless high levels of pain (mean 52.8 on a 0-100 scale) were reported. Massage (therapy)/relaxation (training), anticonvulsants, and non-steroidal anti-inflammatory drugs (NSAIDs) were the most often used treatments. The current treatments that were most often perceived as effective were acupuncture/magnetising, cannabis/alcohol, physiotherapy and exercise, and massage (therapy)/relaxation (training). TENS/ultrasound and antidepressants were least often perceived as effective. Conclusions: Many SCI pain treatments have been tried. Acupuncture/magnetising, cannabis/alcohol, and physiotherapy and exercise were considered most effective. Further research is needed to establish effective SCI pain treatments.

Holdcroft, A. and P. Patel (2001) "Cannabinoids and Pain Relief." Expert Revue of Neurotherapeutics **1**(1): 92-99.

Understanding of the structure and function of the endocannabinoid system is rapidly evolving. Physiological and pharmacological manipulations based on cannabinoid receptors, ligands and endocannabinoids have explained some medicinal attributes of cannabinoids as used across the world for thousands of years. Plant-derived and synthetic cannabinoids are available for therapeutic use. Small clinical trials have demonstrated analgesic potential in acute and chronic pain. Regulatory and pharmacological limitations of these agents have hindered pain research in humans. Selective agonists, antagonists and metabolic targets to enhance endogenous cannabinoid activity are in development. Government reports in Europe and North America have encouraged research into the use of cannabinoids for pain relief and endorsed the clinical trials in acute and chronic pain. The results of large clinical trials into cannabinoid use for acute pain is expected to be the catalyst for wider



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studies and possible changes in legislation. Long-term effects of psychoactive cannabinoids require close monitoring and international cooperation to define their role, if any, in CNS disorders.

Hollister, L.E. (2000) "An approach to the medical marijuana controversy." Drug and Alcohol Dependence **58** (1-2): 3-7.

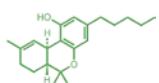
The use of smoked marijuana as a therapeutic agent is presently a matter of considerable debate in the United States. Many people suffering from a variety of disorders maintain that it is necessary for their adequate treatment. Yet, the evidence to support claims is insufficient for FDA approval. An interim solution is proposed which would allow patients referred by their physicians to participate in a 6-month program of legal marijuana availability, similar to the 'compassionate IND' program of a number of years ago. A technique similar to that used for post-marketing surveillance is proposed for obtaining quantitative data for a limited number of potential indications. These are: (1) nausea and vomiting associated with cancer chemotherapy or other causes, (2) weight loss associated with debilitating illnesses, (3) spasticity secondary to neurological diseases, and (4) chronic pain syndromes.

Hollister, L.E. (2001) "Marijuana (Cannabis) as Medicine." Journal of Cannabis Therapeutics **1** (1): 5-28.

The modern published literature on the therapeutic potentials of cannabis has been reviewed. A pure preparation of the major active component, Δ-9-tetrahydrocannabinol (THC), Marinol® or dronabinol, is available for treating nausea and vomiting associated with cancer chemotherapy and as an adjunct to weight loss in patients with wasting syndrome associated with AIDS. Although such approval currently applies only to orally administered THC, for practical purposes smoked marijuana should also be expected to be equally effective. Promising leads, although often fragile, suggest possible uses for treating chronic pain syndromes, neurological disease with spasticity and other causes of weight loss. These possible indications require more study.

Hosking, R.D. and J.P. Zajicek (2006) "Therapeutic potential of cannabis in pain medicine." British Journal of Anaesthesia **101** (1): 59-68.

Advances in cannabis research have paralleled developments in opioid pharmacology whereby a psychoactive plant extract has elucidated novel endogenous signalling systems with therapeutic significance. Cannabinoids (CBs) are chemical compounds derived from cannabis. The major psychotropic CB Δ-9-tetrahydrocannabinol (Δ-9-THC) was isolated in 1964 and the first CB receptor (CB(1)R) was cloned in 1990. CB signalling occurs via G-protein-coupled receptors distributed throughout the body. Endocannabinoids are derivatives of arachidonic acid that function in diverse physiological systems. Neuronal CB(1)Rs modulate synaptic transmission and mediate psychoactivity. Immune-cell CB(2) receptors (CB(2)R) may down-regulate neuroinflammation and influence cyclooxygenase-dependent pathways. Animal models demonstrate that CBRs play a fundamental role in peripheral, spinal, and supraspinal nociception and that CBs are effective analgesics. Clinical trials of CBs in multiple sclerosis have suggested a benefit in neuropathic pain. However, human studies of CB-mediated analgesia have been limited by study size, heterogeneous patient populations, and subjective



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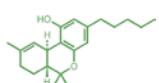
outcome measures. Furthermore, CBs have variable pharmacokinetics and can manifest psychotropism. They are currently licensed as antiemetics in chemotherapy and can be prescribed on a named-patient basis for neuropathic pain. Future selective peripheral CB(1)R and CB(2)R agonists will minimize central psychoactivity and may synergize opioid anti-nociception. This review discusses the basic science and clinical aspects of CB pharmacology with a focus on pain medicine.

Husseini, L., V.I. Leussink, C. Warnke, H.P. Hartung, and B.C. Kieseier, (2012) "Cannabinoids for symptomatic therapy of multiple sclerosis [Cannabinoide zur symptomatischen Therapie der Multiplen Sklerose]." *Der Nervenarzt* **83** (6): 695-702.

Spasticity represents a common troublesome symptom in patients with multiple sclerosis (MS). Treatment of spasticity remains difficult, which has prompted some patients to self-medicate with and perceive benefits from cannabis. Advances in the understanding of cannabinoid biology support these anecdotal observations. Various clinical reports as well as randomized, double-blind, placebo-controlled studies have now demonstrated clinical efficacy of cannabinoids for the treatment of spasticity in MS patients. Sativex is a 1:1 mix of Δ -9-tetrahydocannabinol and cannabidiol extracted from cloned Cannabis sativa chemovars, which recently received a label for treating MS-related spasticity in Germany. The present article reviews the current understanding of cannabinoid biology and the value of cannabinoids as a symptomatic treatment option in MS.

Irving, G., V. Goli, and E. Dunteman (2004) "Novel pharmacologic options in the treatment of neuropathic pain." *CNS Spectrums* **9** (10, Suppl.10): 1-11.

Neuropathic pain is highly prevalent in the United States, occurring in up to 4 million people. Many changes affecting the ascending facilitatory system and the descending inhibitory system occur within the central nervous system as a result of neuropathy, making successful treatment difficult. The physiological changes are more complicated in humans than in animals, and medications which have been shown to be successful in animal models are often determined to be failures in phase II or III studies in humans. The concepts of peripheral and central sensitization help to elucidate the pathophysiology of neuropathic pain, and functional magnetic resonance imaging (fMRI) shows promise in further informing us about the brain's processing of different pains. Neuropathic pain is commonly treated with anticonvulsant medications. There are several potential new treatments being evaluated for neuropathic pain, including N-methyl-D-aspartate antagonists, cannabinoids, immunomodulatory medications, and some antidepressants. Given the complexity of neuropathic pain, a multidisciplinary approach to treatment is preferable to pharmacologic treatment alone. Treatment goals should target improving pain and physical function, and reducing psychological stress. This involves use of behavioral treatments such as cognitive-behavioral therapy, operant conditioning, and biofeedback; alternative therapies such as hypnosis and acupuncture; and in some patients, controversial treatments such as opioids and herbal medicines, in addition to standard pharmacologic treatment.



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Iskedjian, M., B. Bereza, A. Gordon, C. Piwko, and T.R. Einarson (2007) "Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain." Current Medical Research and Opinion **23** (1) 17-24.

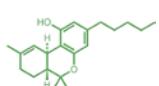
Objective: Debilitating pain, occurring in 50-70% of multiple sclerosis (MS) patients, is poorly understood and infrequently studied. We summarized efficacy and safety data of cannabinoid-based drugs for neuropathic pain.

Data Sources: Studies were identified from Medline, Embase, and Cochrane databases; Bayer Healthcare provided additional trials. Study Selection: Accepted were randomized, double-blinded placebo-controlled trials of cannabinoid-based treatments for MS-related/neuropathic pain in adults > or = 18 years of age. Data Extraction: Two reviewers identified studies and extracted data; a third adjudicated disagreements. Data included baseline and endpoint pain scores on visual analog or 11-point ordinal scales. Data Synthesis: Of 18 articles and three randomized controlled trial (RCT) reports identified, 12 articles and two reports were rejected (9 = inappropriate disease or outcome, 1 = duplicate, 1 = review, and 1 = abstract); six accepted articles and one RCT-report involved 298 patients (222 treated, 76 placebo); four examined Sativex (a cannabidiol/ Δ -9-tetrahydrocannabinol (THC) buccal spray) (observations = 196), five cannabidiol (n = 41), and three dronabinol (n = 91). Homogeneity chi(2) values were non-significant, allowing data combination. Analyses focused on baseline-endpoint score differences. The cannabidiol/THC buccal spray decreased pain 1.7 +/- 0.7 points (p = 0.018), cannabidiol 1.5 +/- 0.7 (p = 0.044), dronabinol 1.5 +/- 0.6 (p = 0.013), and all cannabinoids pooled together 1.6 +/- 0.4 (p < 0.001). Placebo baseline-endpoint scores did not differ (0.8 +/- 0.4 points, p = 0.023). At endpoint, cannabinoids were superior to placebo by 0.8 +/- 0.3 points (p = 0.029). Dizziness was the most commonly observed adverse event in the cannabidiol/THC buccal spray arms (39 +/- 16%), across all cannabinoid treatments (32.5 +/- 16%) as well as in the placebo arms (10 +/- 4%). Conclusion: Cannabinoids including the cannabidiol/THC buccal spray are effective in treating neuropathic pain in MS. Limitations: This review was based on a small number of trials and patients. Pain related to MS was assumed to be similar to neuropathic pain.

Iskedjian, M., O. Desjardins, C. Piwko, B. Bereza, B. Jaszewski, and T.R. Einarson (2009) "Willingness to pay for a treatment for pain in multiple sclerosis."

PharmacoEconomics **27** (2): 149-158.

Background: Multiple sclerosis (MS) is a chronic neurological disease that affects 240 per 100 000 Canadians. Of these patients, 10-80% (average 70%) experience pain. Sativex is a cannabis-based drug recently approved for neuropathic pain. Objectives: In this study, we determine individuals' preferences between two treatment options as well as the willingness to pay (WTP) for Sativex, expressed as the amount they would pay in insurance premiums to have access to that treatment. Methods: The WTP instrument comprised a decision board as a visual aid, and a questionnaire. A decision board helps clinicians standardize the presentation of treatment information. In this study, the decision board described two treatment options: a three-drug combination (gabapentin, amitriptyline, acetaminophen [paracetamol] {i.e. pills}) and the three-drug combination plus Sativex (i.e. 'pills and oral spray'). Information on efficacy and adverse effects was taken from trial data; wording



was guided by a panel of neurologists and tested for clarity on lay people. The instrument was administered to 500 participants from Canada's general population using the bidding game approach. Descriptive statistics were calculated. Results: Mean (SD) age of participants was 39 (13) years, with a female : male distribution of 56 : 44. The decision board was presented in both English (85%) and French (15%). Of 500 interviewees, 253 (50.6%) chose the 'pills and oral spray'. **Mean monthly** WTP for the **insurance** premium for those who chose the 'pills and oral spray' was **Can dollars 8** (SD +/- 15, median 4, range 0-200). Conclusions: Assuming that 51% of the general population are willing to pay additional premiums as reported in this study, the premiums collected would cover the cost of Sativex for all Canadian MS patients experiencing pain, with a surplus.

Iversen, L.L. (1993) "Medical uses of marijuana?" Nature **365** (6441): 12-13.

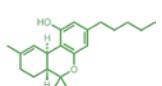
Kalsi, V. and C.J. Fowler C.J. (2005) "Therapy Insight: Bladder Dysfunction Associated with Multiple Sclerosis." Nature Clinical Practice Urology **2** (10): 492-501.

Bladder dysfunction is a common problem for patients with multiple sclerosis. The severity of symptoms often correlate with the degree of spinal cord involvement and, hence, the patient's general level of disability. The emphasis of management is now mainly medical and is increasingly offered by nonurologists. Treatments can be highly effective, relieving patients of what are otherwise very troublesome symptoms that would compound their neurological disability. This article gives an overview of the neural control of the bladder, followed by an explanation of the pathophysiology of detrusor overactivity secondary to neurological disease. A review of methods available for treating bladder dysfunction in multiple sclerosis then follows. The treatment options for this disorder are largely medical and include established first-line measures such as anticholinergics, clean intermittent self-catheterization and the use of desmopressin, as well as potential second-line agents, such as cannabinoids, intravesical vanilloids and intradetrusor botulinum neurotoxin type A. The diminishing role of surgical intervention is also discussed.

Kanof, P.D. (1997) "Medicinal marijuana?" New England Journal of Medicine **336** (16): 1184.

Karst, M. and M. Bernateck (2008) "[Pain relief with cannabinoids – the importance of endocannabinoids and cannabinoids for pain therapy]" Anästhesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie **43** (7-8): 522-528.

The endocannabinoid system reduces sensitization processes. Low doses of cannabinoids may enhance the potency of opioid-drugs and reduce the risk of tolerance to opioids. So far no cannabinoid has been approved for the treatment of acute pain due to lack of consistent data. In contrast, a Cannabis Based Medicine spray consisting of Δ-9-tetrahydrocannabinol and cannabidiol has been approved for the treatment of neuropathic pain in patients with multiple sclerosis. The adjunct of cannabidiol and the oromucosal formulation increase the therapeutic index of Δ-9-tetrahydrocannabinol. The differentiation of analgetic effects and cannabimimetic effects may be increased while compounds--such as ajulemic acid--are used which preferentially act on



peripheral cannabinoid receptors and exert receptor independent effects. A further approach in this direction is the use of enzymes which metabolize endocannabinoids.

Kassirer, J.P. (1997) "Federal Foolishness and Marijuana" New England Journal of Medicine **336** (5): 366-367.

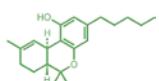
The advanced stages of many illnesses and their treatments are often accompanied by intractable nausea, vomiting, or pain. Thousands of patients with cancer, AIDS, and other diseases report they have obtained striking relief from these devastating symptoms by smoking marijuana. The alleviation of distress can be so striking that some patients and their families have been willing to risk a jail term to obtain or grow the marijuana.

Despite the desperation of these patients, within weeks after voters in Arizona and California approved propositions allowing physicians in their states to prescribe marijuana for medical indications, federal officials, including the President, the secretary of Health and Human Services, and the attorney general sprang into action. At a news conference, Secretary Donna E.

Shalala gave an organ recital of the parts of the body that she asserted could be harmed by marijuana and warned of the evils of its spreading use.

Attorney General Janet Reno announced that physicians in any state who prescribed the drug could lose the privilege of writing prescriptions, be excluded from Medicare and Medicaid reimbursement, and even be prosecuted for a federal crime. General Barry R. McCaffrey, director of the Office of National Drug Control Policy, reiterated his agency's position that marijuana is a dangerous drug and implied that voters in Arizona and California had been duped into voting for these propositions. He indicated that it is always possible to study the effects of any drug, including marijuana, but that the use of marijuana by seriously ill patients would require, at the least, scientifically valid research.

I believe that a federal policy that prohibits physicians from alleviating suffering by prescribing marijuana for seriously ill patients is misguided, heavy-handed, and inhumane. Marijuana may have long-term adverse effects and its use may presage serious addictions, but neither long-term side effects nor addiction is a relevant issue in such patients. It is also hypocritical to forbid physicians to prescribe marijuana while permitting them to use morphine and meperidine to relieve extreme dyspnea and pain. With both these drugs the difference between the dose that relieves symptoms and the dose that hastens death is very narrow; by contrast, there is no risk of death from smoking marijuana. To demand evidence of therapeutic efficacy is equally hypocritical. The noxious sensations that patients experience are extremely difficult to quantify in controlled experiments. What really counts for a therapy with this kind of safety margin is whether a seriously ill patient feels relief as a result of the intervention, not whether a controlled trial "proves" its efficacy. Paradoxically, dronabinol, a drug that contains one of the active ingredients in marijuana (tetrahydrocannabinol), has been available by prescription for more than a decade. But it is difficult to titrate the therapeutic dose of this drug, and it is not widely prescribed. By contrast, smoking marijuana produces a rapid increase in the blood level of the active ingredients and is thus more likely to be therapeutic. Needless to say, new drugs such as those that inhibit the nausea associated with chemotherapy may well be more beneficial than



smoking marijuana, but their comparative efficacy has never been studied. Whatever their reasons, federal officials are out of step with the public. Dozens of states have passed laws that ease restrictions on the prescribing of marijuana by physicians, and polls consistently show that the public favors the use of marijuana for such purposes. Federal authorities should rescind their prohibition of the medicinal use of marijuana for seriously ill patients and allow physicians to decide which patients to treat. The government should change marijuana's status from that of a Schedule 1 drug (considered to be potentially addictive and with no current medical use) to that of a Schedule 2 drug (potentially addictive but with some accepted medical use) and regulate it accordingly. To ensure its proper distribution and use, the government could declare itself the only agency sanctioned to provide the marijuana. I believe that such a change in policy would have no adverse effects. The argument that it would be a signal to the young that "marijuana is OK" is, I believe, specious.

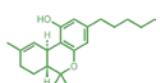
This proposal is not new. In 1986, after years of legal wrangling, the Drug Enforcement Administration (DEA) held extensive hearings on the transfer of marijuana to Schedule 2. In 1988, the DEA's own administrative-law judge concluded, "It would be unreasonable, arbitrary, and capricious for DEA to continue to stand between those sufferers and the benefits of this substance in light of the evidence in this record." Nonetheless, the DEA overruled the judge's order to transfer marijuana to Schedule 2, and in 1992 it issued a final rejection of all requests for reclassification.

Some physicians will have the courage to challenge the continued proscription of marijuana for the sick. Eventually, their actions will force the courts to adjudicate between the rights of those at death's door and the absolute power of bureaucrats whose decisions are based more on reflexive ideology and political correctness than on compassion.

Anmerkung: Schedule 1 entspricht ungefähr der Anlage 1 BtmG während Schedule 2 mit Anlage 3 BtmG vergleichbar ist. Negative Kommentare dazu konnte ich im NEJM (der ältesten, meistgelesenen und sehr gut angesehenen medizinischen Fachzeitschrift in den USA, vgl. Scientific Citation Index) nicht finden.

Kavia, R., D. De Ridder, N. Sarantis, C. Constantinescu and C. Fowler, (2000) "Randomised controlled trial of cannabis based medicine (CBM, Stativex[®]) to treat detrusor overactivity in multiple sclerosis." Neurology and Urodynamics **25**: 106.

Hypothesis / aims of study The overactive bladder (OAB) is a common and difficult problem to manage in patients suffering from multiple sclerosis (MS). Treatment at present is limited to anticholinergics with or without intermittent self catheterisation and most recently, intradetrusor injections of botulinum toxins. However patients using 'street cannabis' reported up to a 64% improvement in one of the symptoms of OAB and an improvement was also seen in an open labelled study of patient with severe MS. More recently a subset analysis of a double blind RCT (CAMS) with oral cannabis reported improvement in urgency incontinence (1). The scientific rationale for the use of cannabis is the finding of CB1 cannabinoid receptor on the rodent bladder and immunohistochemical endocannabinoid production in the human detrusor. This study aims to report the preliminary results of a randomised double blind parallel group placebo-controlled of the use of oromucosal



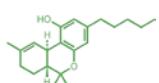
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cannabis based medicinal extract with constituents of tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 mixture (2.7mg of THC and 2.5mg CBD per spray). Study design, materials and methods 135 patients were randomised to receive either CBM or placebo (PLO) in a double blind parallel group study for eight weeks, with a two week baseline period. The study was powered to detect a difference between treatments of 0.5 episodes of incontinence per 24 hours. Ethical approved and written informed consent was obtained for all patients. 37 Male and 98 females were recruited from 3 EUROPean countries (UK, Belgium and Romania). The primary end point for this study was the reduction in urgency incontinence episodes as evaluated by voiding diary. Secondary end points included urgency, day frequency, nocturia, bladder symptom severity score, quality of life and Patients Global Impression of Change. Intention to treat analysis and Per-Protocol analysis was utilised, as well as subgroup analysis using recognised statistical tests.

Results The primary end point i.e. reduction in numbers of daily incontinence at the end of treatment, did not reach significance . CBM was superior to placebo for nocturia (CBM -0.52 PLO – 0.24, p=0.01). This was present at all levels of severity of nocturia and the size of effect was greater for more severe disease. Substantial numbers of patients became nocturia free on the active treatment. The patient's opinion of bladder symptom severity (0 – 10 NRS) showed a significant difference in favour of CBM at the end of treatment (CBM -2.21 PLO -1.05, p=0.001). Patients on CBM were three times more likely to report an improvement of more than 30% compared with those on placebo (P = 0.006). The reduction in the number of daytime voids also reached significance (P = 0.044) and the total number of voids per 24 hours was also significantly reduced (P = 0.001). There was no difference in the volume of urine produced between the CBM and placebo groups. Patient's global impression of change (i.e. how much better the patient felt on medication as compared to baseline) which was highly significant in favour of CBM (p = 0.001) There was a trend in favour of improvement in Quality of Life in the treated group but this did not reach statistical significance. CBM was well tolerated. The most common adverse events were dizziness, UTI and headache and (18% vs 7%, 6% vs 10% and 8% vs 7% for CBM and placebo respectively). Interpretation of results This randomised placebo controlled trial demonstrates that CBM has a major impact on bladder symptoms in patients with MS and severe urinary symptoms particularly on the nocturia and frequency. The difference that patients reported in the PGIC and bladder symptom severity scores provides strong evidence of the positive impact of CBM on their condition for the patients. None of the difference in treatment effect was due to urine volumes, as these were comparable between the two groups. Concluding message Our results show a beneficial effect in a double blind randomised placebo controlled trial of (Sativex®) on the symptoms of overactive bladder in multiple sclerosis.

Keizer, D., M. van Wijhe, W.J. Post, D.R. Uges and J.M. Wierda (2007) "Assessment of the clinical relevance of quantitative sensory testing with Von Frey monofilaments in patients with allodynia and neuropathic pain. A pilot study" European Journal of Anaesthesiology **24** (8): 658-663.

Background: Allodynia is a common and disabling symptom in many patients with neuropathic pain. Whereas quantification of pain mostly depends on



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subjective pain reports, allodynia can also be measured objectively with quantitative sensory testing. In this pilot study, we investigated the clinical relevance of quantitative sensory testing with Von Frey monofilaments in patients with allodynia as a consequence of a neuropathic pain syndrome, by means of correlating subjective pain scores with pain thresholds obtained with quantitative sensory testing. Methods: During a 4-week trial, we administered a cannabis extract to 17 patients with allodynia. We quantified the severity of the allodynia with Von Frey monofilaments before, during and after the patients finished the trial. We also asked the patients to rate their pain on a numeric rating scale at these three moments. Results: We found that most of the effect of the cannabis occurred in the last 2 weeks of the trial. In this phase, we observed that the pain thresholds, as measured with Von Frey monofilaments, were inversely correlated with a decrease of the perceived pain intensity. Conclusion: These preliminary findings indicate clinical relevance of quantitative sensory testing with Von Frey monofilaments in the quantification of allodynia in patients with neuropathic pain, although confirmation of our data is still required in further studies to position this method of quantitative sensory testing as a valuable tool, for example, in the evaluation of therapeutic interventions for neuropathic pain.

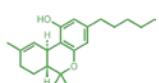
Kesselring, J. and A.J. Thompson (1997) "Spasticity, ataxia and fatigue in multiple sclerosis." Bailliere's Clinical Neurology **6** (3): 429-445.

Multiple sclerosis frequently results in a wide range of symptoms which often coexist, creating a complex pattern of disability. Chief among these symptoms, both in relation to their frequency and their impact on the patient, are spasticity, ataxia and fatigue. This chapter discusses the pathological basis and current treatment of these symptoms and stresses the importance of a multidisciplinary approach to their management, producing a comprehensive care plan which incorporates these and any other coexisting problems.

Kezar, L.B. and T.J. Ness (2001) "Systemic Medications." Topics in Spinal Cord Injury Rehabilitation **7** (2): 57-72.

Spinal cord injury (SCI) pain has a mixture of nociceptive and neuropathic etiologies. There are few controlled studies to guide medical therapy specifically for SCI pain, and so an extrapolation must be made from other painful conditions. This article attempts to establish a rational basis for the trial of pharmacologic agents as treatments for SCI pain. Pain localized to sites above the level of SCI should be approached and treated in an identical fashion to pain in patients without SCIs, with the recognition that some processes are common in SCI populations. Pain localized at or below the level of SCI is more complex, and treatment is more empiric with the use of nociceptive pain medications (anti-inflammatories and opioids) and neuropathic pain medications (e.g., antidepressants, anticonvulsants) directed by features suggestive of those types of pain. Relevant literature related to the treatment of nociceptive and neuropathic pains, in general, and SCI pain, in particular, is reviewed.

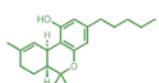
Klinkhammer, G. (2012) "Betäubungsmittelgesetz: Schmerzfreiheit rund um die Uhr." Deutsches Ärzteblatt **107** (34): A-1655.



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Nur selten stoßen geplante Gesetzesänderungen der Bundesregierung auf fast einhellig positive Resonanz. Doch genau das ist jetzt der Fall. Die Koalitionsfraktionen haben sich nämlich am 17. August darauf geeinigt, dass künftig auch in Einrichtungen der spezialisierten ambulanten Palliativversorgung (SAPV) und in stationären Hospizen ärztlich verschriebene und nicht mehr benötigte betäubungsmittelhaltige Schmerzmittel für andere Patientinnen und Patienten weiterverwendet werden dürfen. Gleichzeitig wird auch die rechtliche Möglichkeit geschaffen, Notfallvorräte von Betäubungsmitteln in stationären Hospizen und in der SAPV vorzuhalten. Damit wird erlaubt, was seit langem gängige Praxis ist. „Der behandelnde Arzt stand allerdings bereits mit einem Bein im Knast“, sagte dazu Dr. med. Matthias Thöns, Vorstandsmitglied im Palliativnetz Bochum. Jetzt werden diese Strafvorschriften erfreulicherweise entschärft, denn, so brachte es Thomas Sitte von der Deutschen Palliativstiftung treffend auf den Punkt: „Schmerzen halten sich nicht an Öffnungszeiten der Apotheken.“ Diese Aussage wird durch eine im Juli veröffentlichte Umfrage unter Palliativmedizinern gestützt (Schmerz 2010;24: 367–72). Danach fanden es 99 Prozent von 208 Befragten wichtig, dass ambulant tätige Palliativmediziner jederzeit auf einen gewissen Pool an Betäubungsmitteln zugreifen können. 86,3 Prozent der Befragten hielten die Versorgung durch öffentliche Apotheken für unzureichend. Teilweise wurde sogar über eklatante Missstände berichtet. Besonders in ländlichen Gebieten sind die Anfahrten zu lang, die notwendigen Medikamente oft nicht vorrätig und gerade am Wochenende nicht verfügbar. Die Weitergabe von Betäubungsmitteln in Hospizen und Pflegeheimen mittels Neuausstellung eines Betäubungsmittelrezepts hielten 89 Prozent der Palliativmediziner für praxisuntauglich.

Das dürfte sich künftig erfreulicherweise ändern. Schwerstkranke Patientinnen und Patienten könnten durch die Verbesserung im Bereich der Palliativmedizin zu jeder Tages- und Nachtzeit sowie in Notfallsituationen betäubungsmittelhaltige Schmerzmittel erhalten, um ihre oft unerträglichen Schmerzen zu lindern. Außerdem sollen auch cannabishaltige Fertigarzneimittel künftig unter den strengen Voraussetzungen des Arzneimittelgesetzes zugelassen und auf Betäubungsmittelrezept verschrieben werden dürfen. Diese Entscheidung, „Cannabis aus der Schmuddelecke“ zu holen, wie es der Präsident der Deutschen Gesellschaft für Schmerztherapie, Dr. med. H. H. Gerhard Müller-Schwefe, ausdrückte, ist ebenfalls überfällig. Denn mit dem teilsynthetisch produzierten Cannabinoid Dronabinol, das aus natürlichen Cannabinoiden gewonnen wird, haben die Schmerztherapeuten nach eigenen Angaben bisher gute Erfahrungen gemacht. Zum Einsatz kommt die Substanz beispielsweise bei Schmerzen nach Polioerkrankungen oder Schmerzformen wie Fibromyalgie, die durch eine mangelhafte körpereigene Schmerzkontrolle verursacht werden. Spastische Schmerzen bei multipler Sklerose können mit dem Hanfwirkstoff besser behandelt werden als mit anderen Medikamenten. Wenn Cannabinoide also aufgrund der Gesetzesänderung generell leichter erforscht, zugelassen und verordnet werden, kann dies neue Therapieoptionen eröffnen. Der Handel und die Verwendung von Cannabis zu Rauschzwecken bleiben übrigens weiterhin verboten.



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Killestein, J., P.M. Bet, A.C. van Loenen and C.H. Polman (2004) "[Medicinal cannabis for diseases of the nervous system: no convincing evidence of effectiveness]." *Nederlands Tijdschrift Voor Geneeskunde* **148** (48): 2374-2378.

In 1996, the Netherlands Health Council issued a negative recommendation regarding the use of medication on the basis of cannabis (marijuana). However, interest in medicinal cannabis has certainly not waned since. The neurological diseases for which cannabis could presently be used therapeutically are: multiple sclerosis, chronic (neuropathic) pain and the syndrome of Gilles de la Tourette. Since September 2003, the Dutch Ministry of Health, Welfare and Sport delivers medicinal cannabis to Dutch pharmacies, so that now for the first time, medicinal cannabis can be given to patients on a prescription basis within the framework of the Opium Law. The result of this is that doctors and patients now assume that this is a medication for which the efficacy and safety have been established. The question arises whether new scientific data have become available since 1996 that provide scientific support for the current Governmental policy. In a recent clinical trial that has aroused much discussion, patients with multiple sclerosis and problematic spasticity were treated with oral cannabis or a placebo. There was no significant effect of treatment on the primary outcome measure, i.e. objectively determined spasticity. Nevertheless, it was concluded that the mobility was improved and that the pain was subjectively decreased.

[Persönliche Anmerkung: wenn das nicht für den Nutzen spricht, was dann?] Until now, convincing scientific evidence that cannabinoids are effective in neurological conditions is still lacking. However, it is also not possible to conclude definitely that cannabinoids are ineffective; still, this is no basis for official stimulation of their use.

Killestein, J., E.L. Hoogervorst, M. Reif, N.F. Kalkers, A.C. Van Loenen, P.G. Staats, R.W. Gorter, B.M. Uitdehaag and C.H. Polman (2002) "Safety, tolerability, and efficacy of orally administered cannabinoids in MS." *Neurology* **58**: 1404-1407.

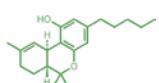
The authors conducted a randomized, double-blind, placebo-controlled, twofold crossover study in 16 patients with MS who presented with severe spasticity to investigate safety, tolerability, and efficacy of oral Δ -9-Tetrahydrocannabinol (THC) and Cannabis sativa plant extract. Both drugs were safe, but adverse events were more common with plant-extract treatment. Compared with placebo, neither THC nor plant-extract treatment reduced spasticity. Both THC and plant-extract treatment worsened the participant's global impression.

Comments:

Neurology. 2002 May 14; **58** (9): 1323.

Klein, T.W. (2005) "Cannabinoid-based drugs as anti-inflammatory therapeutics." *Nature Reviews Immunology* **5** (5): 400-411.

In the nineteenth century, marijuana was prescribed by physicians for maladies ranging from eating disorders to rabies. However, as newer, more effective drugs were discovered and as the potential for abuse of marijuana was recognized, its use as a therapeutic became restricted, and only recently has its therapeutic potential been re-evaluated. Recent studies in animal models and in humans have produced promising results for the treatment of various disorders - such as obesity, cancer, and spasticity and tremor due to



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neuropathology - with drugs based on marijuana-derived cannabinoids. Moreover, as I discuss here, a wealth of information also indicates that these drugs have immunosuppressive and anti-inflammatory properties; therefore, on the basis of this mode of action, the therapeutic usefulness of these drugs in chronic inflammatory diseases is now being reassessed.

Koblenz, A. (2002) Einfluß einer Einminalgabe von Delta-9-Tetrahydrocannabinol auf kognitive Funktionen und Befindlichkeit bei Patienten mit Gilles de la Tourette-Syndrom : eine doppel-blinde placebokontrollierte Cross-over-Studie. Hannover, Medizinische Hochschule. PhD: 103 Seiten.

Kogel, R.W., P.B. Johnson, R. Chintam, C.J. Robinson and B.A. Nemchausky (1995) "Treatment of Spasticity in Spinal Cord Injury with Dronabinol, a Tetrahydrocannabinol Derivative." American Journal of Therapeutics **2** (10): 799-805.

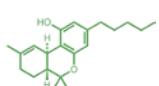
Spinal-cord-injured patients and the medical literature have increasingly reported anecdotes regarding tetrahydrocannabinol (THC)-induced spasmolysis. These reports motivated this trial of dronabinol, a THC derivative, for the treatment of spasticity in the spinal-cord-injured population. Five male quadriplegic patients were given oral dronabinol in escalating doses from 5 mg BID to 20 mg TID in addition to their current, but ineffective, spasmolytic regime. The pendulum drop test was used to quantify spasticity (stiffness) in the knees. The Weschler Memory Scale (WMS), Profile of Mood States (POMS), and personal interviews were administered by the clinical psychologist to evaluate any changes in the subjects' cognition and/or emotional states. Spasticity was markedly improved in two of the five subjects, unchanged in a third, fluctuated in a fourth and made progressively worse in a fifth. The WMS revealed improvement in memory skills of two subjects and no change in the other. Psychological interviews and the POMS indicated decreased vigor in all subjects, but otherwise demonstrated highly individualized emotional changes as indicated by increases and/or decreases in the dysphoric mood scales.

Köppelle, W. (2010) "Editorial Yes we can: Amerikaner legalisieren Marihuana!" Laborjournal online: 442.

Was ist nur mit den Amis los? Erst wählen sie einen Präsidenten, der mindestens so cool rüberkommt wie ein jüngerer Bruder von Denzel Washington, und jetzt erlauben sie auch noch den professionellen Hanfanbau. Zumindest in Oakland, Kalifornien, erlauben sie ihn, und zumindest vorläufig – denn was deutsche Medien verschwiegen: Das Votum des zuständigen Stadtrats-Ausschusses muss in einer zweiten, endgültigen Abstimmung erst noch bestätigt werden („the preliminary ordinance must still be approved on a second, final vote“).

Ohnehin sollten sich eingefleischte Pot-Fans nicht zu früh freuen: Der großflächige Anbau der THC-haltigen Hanf-Pflänzlein (*Cannabis sativa* bzw. *C. indica*) diene ausschließlich medizinischen Zwecken, berichtete ABC-News, und spricht weiter von Plänen „to license four large-scale marijuana factories“. Mit „factory“ meint die Nachrichtenagentur voluminöse Gewächshäuser in Fußballfeld-Größe samt angegliederten Verarbeitungs- und Verpackungsstätten.

Umstrittenes Arzneimittel Cannabis



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Für die Wirkung von Cannabis und der daraus gewonnenen Produkte (Haschisch, Marihuana, etc.) sind die Komponenten Tetrahydrocannabinol (THC, psychoaktive Effekte), Cannabinol (CBN, krampflösend) sowie Cannabidiol (CBD, wirkt THC entgegen) verantwortlich; sie binden an Rezeptoren des Endocannabinoid-Systems im zentralen Nervensystem. Besonders THC-reich sind die unbefruchteten weiblichen Blütenstände der Pflanze sowie die Blätter nahe der Blüte.

Gerade in konservativ regierten Ländern wird der angebliche oder tatsächliche medizinische Wert von Cannabis immer wieder heiß diskutiert. Zumindest unter Wissenschaftlern umstritten, da ausreichend dokumentiert, ist die Wirkung der genannten Inhaltsstoffe unter anderem bei Schmerzen, Krankheiten des Stütz- und Bewegungsapparates, Spastiken, Arthritis und Depression. In Ländern wie Österreich, Deutschland, den Niederlanden, Spanien sowie in einigen Bundesstaaten der USA sind bestimmte Cannabis-basierende Arzneimittel erlaubt, wenn auch meist nur in Einzelfällen.

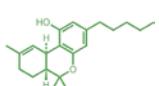
In Deutschland beispielsweise darf das halbsynthetische THC-Mittel Dronabinol für die individuelle Therapie von chronischer Appetitlosigkeit bei AIDS-Patienten und zur Behandlung von durch Zytostatika verursachter Übelkeit und Erbrechen bei Krebspatienten als Rezepturarzneimittel verordnet (beziehungsweise als Einzelimport aus den USA bezogen) werden. Diese Behandlung, die bis zu 800 Euro im Monat kosten kann, wird von den gesetzlichen Krankenkassen nur fallweise übernommen, obwohl sie von Ärzten gerne als „letzte Möglichkeit für solche Patienten“ bezeichnet wird. Andere Mediziner relativieren die therapeutische Bedeutsamkeit derzeit erhältlicher Cannabis-basierter Fertigarzneimittel: Es gebe längst Alternativen mit besserem Nutzen-Risiko-Verhältnis, zumal sei die Zahl möglicher Anwendungsgebiete gering. Allerdings plädieren zahlreiche Wissenschaftler dafür, die bisher verpönte oder gar verbotene Forschung an Cannabis-basierten Mitteln zu steigern.

Probleme mit Schlamper-Gärtnern

Zurück nach Kalifornien. Als wichtigen Grund für den Entschluss der Stadtväter Oaklands, künftig professionell arbeitende, fabrikähnliche Cannabis-Betriebe genehmigen zu wollen, nennt ABC-News fortwährende Probleme mit den bereits existierenden, semiprofessionell agierenden „mittelgroßen“ Cannabis-Anbauern. Diese würden ihre Pflänzchen oftmals vorsintflutlich im Hinterzimmer ihrer Wohnung in feucht-schwüler Umgebung kultivieren, die beispielsweise elektrische Kurzschlüsse und dadurch Brände provoziere. Zudem würde Gewaltkriminalität gefördert. Bei von Gemeindeseite kontrollierter Massenproduktion in weniger, dafür größeren Betrieben träten diese Probleme nicht oder nur vermindert auf, hoffen die Stadträte (wie sie zu dieser Ansicht kommen, sagte ABC allerdings nicht).

Wie auch immer: Den „hunderten“ mittelgroßen „medizinischen“ Anbaubetrieben, die es anscheinend allein in Oakland gibt und die nach Schätzungen einen Jahresumsatz von insgesamt 28 Millionen Dollar erzielen, würde die Geschäftstätigkeit mit der neuen Regelung künftig untersagt sein. Schlamper-Gärtner will man dort nicht mehr haben. Der Privatanbau für persönliche Zwecke hingegen werde in der Stadt – sofern der Anbauer ein ärztliches Rezept vorweisen kann – weiterhin erlaubt (oder besser: geduldet, denn nach den Bundesgesetzen ist Marihuana nach wie vor illegal).

Stadt will sich finanziell sanieren



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Ein Gegner der Produktionsfreigabe unkte, Oakland würde mit der Produktionserlaubnis zu einem „Silicon Valley of Cannabis“. Die Befürworter der Anbau-Freigabe hingegen führen, neben bereits genannten Gründen, schlicht finanzielle Argumente ins Feld: es würden Arbeitsplätze geschaffen und die Firmen künftig eine Menge Steuern zahlen. ABC-News nennt unter anderem eine Firma namens iGrow, die bereits Interesse bekundet habe, und zitiert einen Sprecher einer Firma namens Agramed, der die Stadtväter mit knapp 400 Jobs und 1,5 Millionen Dollar an zu erwartenden Gewerbesteuereinnahmen lockt. Er wolle 26 Kilogramm Marihuana täglich herstellen, kündigte er weiter an, und zudem Gebüren zahlen, mit denen der Unterhalt für ein städtisches Aufsichtsamt bestimmt würde.

Die Stadt Oakland ist, wie auch der Staat Kalifornien, faktisch pleite. Die Stadt sei mit „severe budget deficits“ konfrontiert und habe beispielsweise, so ABC-News, unlängst „80 police officer positions“ abgebaut.

Den Bundesbehörden ist das alles wurstegal

Ärger mit den Bundesbehörden in Washington ist vorprogrammiert. Die Verantwortlichen bei der amerikanischen Drogenbekämpfungsbehörde DEA kümmern sich selten um regionale Spezialfälle und -regelungen; sie pochen aufs Bundesgesetz und in dem steht: Der Besitz von Marihuana ist illegal. Dabei ist es den Fahndern bisher ziemlich egal, ob die betreffende Person eine Ausnahmegenehmigung vom Hausarzt oder vom örtlichen Sheriff besitzt: der Besitzer/Anbauer wird verhaftet und alles, was auch nur ansatzweise THC-haltig ist, plattgemacht.

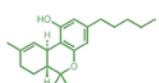
Auch in Kalifornien ist das bisher so. Im November allerdings wird über die Legalisierung von Marihuana (und zwar nicht nur für medizinische Zwecke) im Staate Arnold Schwarzeneggers abgestimmt.

Lack, M. (2007) "BSG-Urteil vom März bestätigt: Marinol und Dronabinol sind keine Kassenleistung" Berliner Budget-Bulletin 02.

In einer Sitzung am 27. 3. 2007 entschied das Bundessozialgericht, dass sowohl cannabinoidhaltige Fertig- als auch Rezepturarzneimittel keine Kassenleistung sind. Für cannabinoidhaltige Fertigarzneimittel gibt es zur Zeit weder in Deutschland noch EU-weit eine arzneimittelrechtliche Zulassung. Importe aus anderen Staaten, wie zum Beispiel das Präparat Marinol aus den USA, sind – wie berichtet – bereits seit dem BSG-Urteil vom 18. 5. 2004 von der GKV-Versorgung ausgeschlossen.

Auch cannabinoidhaltige Rezepturen, wie die bereits seit längerem in Deutschland angebotenen Dronabinolrezepturen, können nicht zu Kassenlasten verordnet werden. Da für Wirkstoffe, die nur als Rezeptursubstanz erhältlich sind, kein amtlich bestätigter Wirksamkeits- bzw. Unbedenklichkeitsnachweis in Form einer arzneimittelrechtlichen Zulassung existiert, bedarf es für eine Verordnung auf Kassenrezept der positiven Bewertung durch den Gemeinsamen Bundesausschuss (G-BA) gem. § 135 Abs. 1 SGB V. Eine derartige Bewertung liegt für Dronabinol jedoch nicht vor.

Persönliche Anmerkung: Damit sind gesetzlich gegenüber privat versicherten Patient/inn/en grundsätzlich und in einem wesentlichen, nämlich ihre Gesundheit und deren Versorgung erheblich betreffenden Punkt, massiv schlechter gestellt (siehe auch Lauterbach, 2006 und Kassirer, 1997) und sind letztlich auf illegale und möglicherweise gesundheitsschädliche Produkte ohne ärztliche Aufsicht für behandlungsbedürftige Symptome angewiesen.



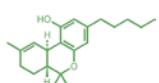
Cannabis, Dronabinol und die Behandlung schwerer Erkrankungen

Lakhan, S.E. and M. Rowland (2009) "Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review." BioMed Central Neurology **9**: 59.

Background: Cannabis therapy has been considered an effective treatment for spasticity, although clinical reports of symptom reduction in multiple sclerosis (MS) describe mixed outcomes. Recently introduced therapies of combined Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) extracts have potential for symptom relief with the possibility of reducing intoxication and other side effects. Although several past reviews have suggested that cannabinoid therapy provides a therapeutic benefit for symptoms of MS, none have presented a methodical investigation of newer cannabinoid treatments in MS-related spasticity. The purpose of the present review was to systematically evaluate the effectiveness of combined THC and CBD extracts on MS-related spasticity in order to increase understanding of the treatment's potential effectiveness, safety and limitations. **Methods:** We reviewed MEDLINE/PubMed, Ovid, and CENTRAL electronic databases for relevant studies using randomized controlled trials. Studies were included only if a combination of THC and CBD extracts was used, and if pre- and post-treatment assessments of spasticity were reported. **Results:** Six studies were systematically reviewed for treatment dosage and duration, objective and subjective measures of spasticity, and reports of adverse events. Although there was variation in the outcome measures reported in these studies, a trend of reduced spasticity in treated patients was noted. Adverse events were reported in each study, however combined TCH and CBD extracts were generally considered to be well-tolerated. **Conclusion:** We found evidence that combined THC and CBD extracts may provide therapeutic benefit for MS spasticity symptoms. Although some objective measures of spasticity noted improvement trends, there were no changes found to be significant in post-treatment assessments. However, subjective assessment of symptom relief did often show significant improvement post-treatment. Differences in assessment measures, reports of adverse events, and dosage levels are discussed.

Lamarine, R.J. (2012) "Marijuana: modern medical chimaera." Journal of Drug Education **42** (1): 1-11.

Marijuana has been used medically since antiquity. In recent years there has been a resurgence of interest in medical applications of various cannabis preparations. These drugs have been cited in the medical literature as potential secondary treatment agents for severe pain, muscle spasticity, anorexia, nausea, sleep disturbances, and numerous other uses. This article reviews the research literature related to medical applications of various forms of cannabis. Benefits related to medical use of cannabinoids are examined and a number of potential risks associated with cannabis use, both medical and recreational, are considered. There is a clearly identified need for further research to isolate significant benefits from the medical application of cannabinoids and to establish dosage levels, appropriate delivery mechanisms and formulations, and to determine what role, if any, cannabinoids might play in legitimate medical applications. It is also imperative to determine if reported dangers pose a significant health risks to users.



Lauterbach, G. (2006) "Richtig kämpfen für sein Medikament." in: Ratgeber Recht, WDR; Köln. Sendung in der ARD vom 19.08.2006.

Das deutsche Gesundheitssystem ist an die Grenze seiner finanziellen Leistungsfähigkeit gekommen. Die gesetzlichen Krankenkassen sind hoch verschuldet und müssen sparen. Auf den ersten Blick scheint es deshalb konsequent, dass die Krankenkassen heute sehr genau hinschauen, wenn es um die Kostenerstattung von Medikamenten und Therapien geht. Doch es gibt Grenzfälle: Dazu gehören Schmerzpatienten und Schwerstkranke, die zum Beispiel an Krebs, Multipler Sklerose, HIV oder Polio leiden und denen herkömmliche Medikamente nicht mehr helfen können. Patienten, die nach Ansicht der Schulmedizin austherapiert sind.

Der Fall Ute Köhler

Ute Köhler aus Thüringen ist heute 52 Jahre alt. Vor zwanzig Jahren stellen Ärzte bei ihr Unterleibskrebs fest. Die Bestrahlungen des Tumors verursachen schwere Verletzungen der inneren Organe. Dann wird Frau Köhler bei einer Operation durch eine mit Hepatitis B verseuchten Blutkonserve geschädigt. Ihre Leber erkrankt. Seither verträgt sie kein herkömmliches

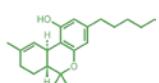
Schmerzmedikament mehr. Die damals noch junge Mutter leidet Tag und Nacht an unerträglichen Schmerzen. Sie wird von einer Rehabilitationsklinik in das nächste Schmerzzentrum überwiesen. Alle üblichen, schulmedizinisch anerkannten Schmerzmittel und Therapien werden ausprobiert, doch nichts hilft. Ute Köhler erzählt uns im Interview, was ein Leben mit ständigen Schmerzen bedeutet: "Ich lag nur noch. Ich habe nicht mehr gegessen, nicht mehr getrunken, ich war apathisch. Bei mir war es so, dass ich nachts, wenn ich nicht mehr schlafen konnte und die Schmerzen nicht aufgehört haben, Selbstmordgedanken hatte. Ich war wirklich an dem Punkt: ich konnte nicht mehr und man will auch nicht mehr."

Patientenorganisationen schätzen, dass sich jährlich etwa fünftausend Schmerzpatienten das Leben nehmen, weil sie ihr Leiden physisch und psychisch nicht mehr ertragen.

Ute Köhler hat die Hoffnung beinahe schon aufgegeben, als nach vierzehn Jahren ein Arzt endlich das erlösende Medikament für sie findet: Dronabinol. Der Wirkstoff dieser Arznei wird aus der Cannabispflanze gewonnen.

Dronabinol hilft nicht allen, aber vielen Schmerzpatienten. Das Medikament hat kaum Nebenwirkungen und die Gefahr, davon abhängig zu werden, ist acht Mal geringer als zum Beispiel durch das gängige Schmerzmittel Morphin.

Für Ute Köhler ist Dronabinol die Rettung. Nach nur wenigen Wochen ist sie völlig schmerzfrei. Zweimal täglich nimmt sie die Tropfen. Allerdings kann die Therapie mit Dronabinol gerade am Anfang, wenn das Medikament hochdosiert verabreicht wird, sehr teuer sein. Im Fall von Ute Köhler zahlte die AOK Krankenkasse für das Medikament etwa 1.200 Euro im Monat. Doch nach eineinhalb Jahren ist Schluss: Die AOK Thüringen weigert sich, die Kosten für das Dronabinol weiterhin zu übernehmen. Begründet wird dies durch die Stellungnahme einer Ärztin vom Medizinischen Dienst der AOK: Sie ist der Meinung, dass noch nicht alle herkömmlichen Therapiemöglichkeiten ausgeschöpft sind. Die AOK empfiehlt Frau Köhler daraufhin eine Psychotherapie. Ute Köhler fragt sich, wie eine Psychotherapie die Schmerzen lindern soll, die von den verletzten inneren Organen verursacht



werden.

Ute Köhler legt gegen den Bescheid der AOK Widerspruch ein und schickt der Krankenkasse mehrere fachärztliche Gutachten und Stellungnahmen. Diese belegen, dass sie austherapiert ist, dass alle herkömmlichen Therapien nichts gebracht haben, dass nur Dronabinol ihr hilft und dass die Behandlung mit diesem Medikament sogar "ökonomisch äußerst zu empfehlen" ist. Doch die AOK Thüringen lehnt die Kostenerstattung weiterhin ab.

Ute Köhler klagt vor dem Sozialgericht - und verliert. Die Richter geben der Krankenkasse recht.

Ute Köhler gibt nicht auf. Sie weiß, dass Tausende Schmerzpatienten illegal Cannabis konsumieren, weil Cannabis den gleichen Wirkstoff enthält wie die Arznei Dronabinol. Sie kommt auf eine merkwürdige, aber wirkungsvolle Idee: Ute Köhler besorgt sich Hanfsamen und züchtet die Pflanzen auf ihrem Balkon. Das ist illegal. Sie nimmt die Pflanzen und zeigt sich damit bei der Polizei selbst an. Ute Köhler erhält einen Strafbefehl über 537 Euro wegen illegalem Drogenbesitz, den sie absichtlich nicht bezahlt. Sie will es auf einen Prozess ankommen lassen. Die Aktion wird von der örtlichen Presse begleitet. Der Richter erkennt ihre ausweglose Situation und reduziert die Strafe auf 200 Euro zur Bewährung. Ute Köhler macht immer wieder deutlich, dass es ihr nicht um eine generelle Legalisierung von Cannabis geht. Sie fordert nur, dass die Krankenkasse ihr das Dronabinol bezahlt, weil sie keine medizinische Alternative hat. Aber bis heute bleibt die AOK Thüringen dabei: keine Kostenerstattung für Dronabinol im Fall Köhler.

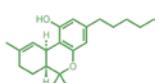
Der ARD Ratgeber Recht hat bei der Krankenkasse in Thüringen nachgefragt, warum sie die Kosten für das Dronabinol im Fall Köhler nicht erstattet? Die AOK antwortet: "Für Dronabinol liegt weder eine arzneimittelrechtliche Zulassung noch eine positive Bewertung durch den Gemeinsamen Bundesausschuss vor."

Ute Köhler weiß, dass viele private Krankenkassen das Medikament zahlen. Doch mit ihrer Krankengeschichte will keine private Krankenkasse sie versichern. Ute Köhler vermutet, dass selbst die AOK in anderen Bundesländern Dronabinol erstattet. Daraufhin recherchiert der ARD Ratgeber Recht und findet Belege dafür, dass die AOK in einigen Bundesländern tatsächlich die Kosten übernimmt.

Wir fragen den Bundesverband der AOK, wie es sein kann, dass die AOK in einigen Bundesländern zahlt und andere eine Kostenerstattung generell verweigern. Die Antwort: "Die Tatsache, dass einzelnen Versicherten das Rezepturarzneimittel Dronabinol erstattet wird und anderen nicht, kann eine Einzelfallentscheidung auf der Grundlage einer gerichtlichen Entscheidung und / oder eines medizinischen Gutachtens sein. Darin wird individuell geprüft, ob die jeweiligen medizinischen Indikationen bei dem betreffenden Patienten oder der betreffenden Patientin vorliegen oder nicht." Der Bundesverband der AOK bestätigt demnach, dass Dronabinol von den gesetzlichen Krankenkassen im Einzelfall erstattet werden kann.

Bundesverfassungsgericht stärkt Patientenrechte

Ute Köhler hat jetzt erneut einen Antrag auf Kostenerstattung für Dronabinol bei der AOK Thüringen gestellt. Lehnt ihre Krankenkasse wieder ab, wird Ute Köhler zum zweiten Mal vor dem Sozialgericht klagen. Jetzt allerdings mit besseren Chancen. Das Bundesverfassungsgericht hat am 6. Dezember 2005 (AZ: 1 BvR 347/98) ein wegweisendes Urteil gesprochen: Das höchste



Deutsche Gericht hat das Recht auf Kostenerstattung von alternativen Therapien und arzneimittelrechtlich nicht zugelassenen Medikamenten für schwerstkranken Patienten verbessert. Die gesetzlichen Krankenkassen müssen im Einzelfall auch die Kosten für arzneimittelrechtlich nicht zugelassene Medikamente erstatten, wenn folgende Voraussetzungen gegeben sind:

- Der Patient muss an einer lebensbedrohlichen oder zum Tode führenden Erkrankung leiden.
- Die herkömmlichen anerkannten medizinischen Behandlungsmethoden müssen ausgeschöpft sein. Das heißt: Der Patient muss nachweislich austherapiert sein.
- Die Behandlung muss einen nicht ganz entfernt liegenden Heilungserfolg oder eine spürbare positive Einwirkung auf den Krankheitsverlauf haben.

Diese Voraussetzungen hat jetzt auch das Bundessozialgericht in einem Urteil (AZ: B 1 KR 7/05 R) übernommen. Das ist wichtig, denn an die Entscheidungen des Bundessozialgerichts sind die untergeordneten Sozialgerichte, bei denen Patienten ihre Klage einreichen, gebunden. Seither haben schwerstkranken Patienten auch vor den Sozialgerichten bessere Chancen, wenn sie ihre Krankenkasse auf Kostenerstattung verklagen. So hat erst kürzlich das Hamburger Sozialgericht in einem Fall entschieden, dass die Krankenkasse die Kosten für Dronabinol vorläufig erstatten muss.

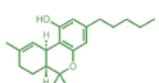
Der ARD Ratgeber Recht sprach mit dem Präsidenten der Deutschen Gesellschaft für Medizinrecht, Prof. Christian Dierks, darüber, wie sich das Urteil des Bundesverfassungsgerichts konkret bei den Sozialgerichtsverfahren auswirken wird. Dierks: "Das Gesetz und die Arzneimittelrichtlinien sind restriktiv und müssen auch restriktiv sein, aber es gibt Grenzfälle. In diesen Grenzfällen ist nun nach der Rechtsprechung des Bundesverfassungsgerichts zu Gunsten des Patienten zu entscheiden. Das heißt konkret, dass ein Sozialgericht jetzt prüfen muss, ob es sich um eine lebensbedrohliche oder sogar tödlich verlaufende Erkrankung handelt und ob die Therapie als letzte Therapiemöglichkeit für diesen Patienten eine nicht ganz entfernt liegende Aussicht auf Behandlungserfolg verspricht."

Klärung einer widersprüchlichen Rechtslage

Bis vor wenigen Monaten hatten Patienten wie Ute Köhler noch schlechte Karten, wenn sie die Krankenkasse auf Kostenerstattung vor einem Sozialgericht verklagen wollten. Der Grund dafür liegt in einer widersprüchlichen Rechtsauffassung: einerseits verbietet das V. Sozialgesetzbuch den gesetzlichen Krankenkassen die Kostenerstattung für arzneimittelrechtlich nicht zugelassener Medikamente bzw. nicht anerkannter Therapien und Heilmethoden. Andererseits haben die Patienten einen im Grundgesetz garantierten Anspruch auf körperliche Unversehrtheit. Das Bundesverfassungsgericht führt dazu aus:

"Übernimmt der Staat mit dem System der gesetzlichen Krankenversicherung Verantwortung für Leben und körperliche Unversehrtheit der Versicherten, so gehört die Vorsorge in Fällen einer lebensbedrohlichen oder regelmäßig tödlichen Erkrankung unter den genannten Voraussetzungen zum Kernbereich der Leistungspflicht und der von Art. 2 Abs. 2 Satz 1 GG geforderten Mindestversorgung."

Das heißt: Bisher war nicht klar, welche konkreten Rechte schwerstkranken Patienten aus dem Grundgesetz ableiten können. Deshalb haben sich die



meisten Sozialgerichte ausschließlich auf die Regeln im V. Sozialgesetzbuch verlassen und damit die Klagen der Patienten auf Kostenerstattung abgelehnt. Das Urteil des Bundesverfassungsgerichts hebt die widersprüchliche Rechtslage zwar nicht auf, aber es stellt klar: Patienten haben unter den im Urteil formulierten Voraussetzungen einen über die gesetzlichen Bestimmungen des V. Sozialgesetzbuches hinausgehenden Anspruch auf Kostenerstattung durch die gesetzlichen Krankenkassen.

Für die Sozialgerichte bedeutet das: Sie können jetzt nicht mehr jede Klage auf Kostenerstattung für arzneimittelrechtlich nicht zugelassener Medikamente und Behandlungen mit dem Hinweis auf das V. Sozialgesetzbuch ablehnen. Vor einer Entscheidung müssen die Sozialgerichte erst prüfen, ob der Patient die Voraussetzungen des Bundesverfassungsgerichts erfüllt.

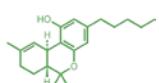
Was tun, wenn die Krankenkasse die Kostenübernahme ablehnt?

1. fristgerecht schriftlichen Widerspruch gegen den Bescheid einlegen.
2. Ärztliche Gutachten und Stellungnahmen dem Widerspruchschreiben beifügen, die belegen, dass alle herkömmlich anerkannten Therapien ausgeschöpft sind und dass nur durch ein bestimmtes Medikament eine nicht ganz entfernt liegende Aussicht auf Behandlungserfolg besteht oder das Medikament zumindest eine positive Einwirkung auf den Krankheitsverlauf hat.
3. Lehnt die Krankenkasse weiterhin die Kostenübernahme ab, sollte beim Sozialgericht ein Antrag auf eine einstweilige Anordnung gestellt werden.

Viele Patienten sind in einer Notlage und brauchen dringend ein bestimmtes Medikament oder eine Therapie. Zwar bleibt auch diesen Patienten der Weg über eine Klage nicht erspart, aber sie können über das Rechtsmittel der Einstweiligen Anordnung beim Sozialgericht möglicherweise schneller an ihr Medikament kommen. Prof. Christian Dierks: "Sozialgerichtsverfahren können ohne Zweifel sehr lange dauern.

Dafür gibt es den einstweiligen Rechtsschutz beim Sozialgericht, zum Beispiel in Form der einstweiligen Anordnung. Das kann man machen, wenn der ablehnende Bescheid der Krankenkasse offensichtlich rechtswidrig ist. Beispielsweise, wenn der Patient auf eine therapeutische Alternative verwiesen wird, von der man schon weiß, dass sie ihm nicht hilft. Zweitens muss dem Patienten nicht zuzumuten sein, den Ausgang des Verfahrens abzuwarten, weil beispielsweise irreversible Schäden drohen." Mit der einstweiligen Anordnung kann der Richter innerhalb kurzer Zeit eine Vorabentscheidung treffen und die Krankenkasse dazu verpflichten, ab sofort die Kosten für das Medikament zu übernehmen. Diese Entscheidung ist jedoch nur vorläufig, bis die Klage in der Hauptverhandlung entschieden wird. Oft prüfen die Richter bereits im Vorverfahren anhand der medizinischen Gutachten sehr genau, ob der Patient einen Anspruch auf das Medikament hat. Immerhin wissen auch die Richter, dass die Krankenkassen die vorab erstatteten Kosten für das Medikament vom Patienten zurückverlangen können. Jedoch ist bisher kein einziger Fall bekannt, bei dem eine Krankenkasse die Kosten zurückfordert hat. Auch sie wüssten, dass eine solche Rückforderung für schwerstkranke Patienten den finanziellen Ruin bedeutet, betont Prof. Dierks.

Dennoch besteht das Risiko. Deshalb ist es sinnvoll, eine solche Klage nur gemeinsam mit einem Anwalt einzureichen, auch, wenn im Sozialgerichtsverfahren die Vertretung durch einen Anwalt nicht



vorgeschrieben ist. Für eine aussichtsreiche Klage ist es sinnvoll, wenn die behandelnden Ärzte und der Anwalt zusammenarbeiten. Die Ärzte sollten aus medizinischer und der Anwalt aus juristischer Sicht vor Einreichung der Klage prüfen, ob der Patient die Voraussetzungen des Bundesverfassungsgerichts erfüllt.

Um welche Medikamente geht es?

Medikamente werden von der Pharma industrie in aufwändigen und teuren klinischen Studien entwickelt und hergestellt. Bevor ein neues Medikament jedoch auf den Markt kommt, findet eine Sicherheitsprüfung, in Deutschland durch das Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), statt. Diese Bundesbehörde erteilt auch die arzneimittelrechtliche Zulassung, ohne die ein Medikament theoretisch nicht eingesetzt werden darf. Außerdem ist eine gesetzliche Verkehrs- und Verordnungsfähigkeit vorgeschrieben, damit der Arzt das Medikament verschreiben und die Krankenkasse die Kosten dafür erstatten kann.

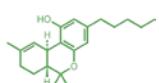
Trotz der strengen gesetzlichen Regelungen werden in der Medizin täglich tausende Fertigarzneimittel verabreicht, die zwar vom Arzt verordnet werden dürfen, aber keine arzneimittelrechtliche Zulassung haben. Diese

Fertigarzneien sind so genannte "Off-Label-Use"-Medikamente. In der Kinderheilkunde werden beinahe ausschließlich solche Medikamente verwendet. Dabei handelt es sich zum Beispiel um Arzneien, die zwar für Erwachsene klinisch getestet sind, aber nicht für Kinder. Streng genommen müssten die Pharmaunternehmen die Wirksamkeit und die Risiken auch für die Behandlung von Kindern mit klinischen Studien belegen. Doch hier sieht der Gesetzgeber großzüig über seine eigenen strengen Bestimmungen hinweg und die Krankenkassen erstatten diese Medikamente anstandslos.

Eine Besonderheit unter den Medikamenten sind die so genannten Rezepturarzneien. Bei diesen Arzneimitteln produziert ein Pharmaunternehmen den Wirkstoff und liefert diesen, mit der Rezeptur zur Herstellung der Arznei, an eine Apotheke. Diese stellt das Medikament zum Beispiel in Form von Tropfen, Kapseln oder Salben her.

Dronabinol ist solch eine Rezepturarznei. Der Wirkstoff in Dronabinol ist ein THC Molekül, das aus der Cannabispflanze gewonnen wird. Die Arznei wird vor allem bei Patienten eingesetzt, die herkömmliche Opiate, wie zum Beispiel Morphium, nicht vertragen.

Bis Anfang des 20. Jahrhunderts war Cannabis eine ganz legale Medizin. Nach dem zweiten Weltkrieg wurden Cannabis und auch die cannabishaltigen Arzneien in Deutschland verboten. Erst seit 1998 ist der Wirkstoff Dronabinol wieder verordnungsfähig. Verordnungsfähig heißt, dass Ärzte dieses Medikament verschreiben dürfen – mit der Erstattungsfähigkeit durch die Krankenkassen hat das nichts zu tun. Dronabinol kann aber problemlos über Privatrezept verschrieben werden. Auch die gesetzlichen Krankenkassen könnten die Kosten für Dronabinol erstatten, wenn sie einen Antrag beim Gemeinsamen Bundesausschuss (G-BA) stellen würden. Der G-BA kann bei Medikamenten, die keine arzneimittelrechtliche Zulassung haben, eine Empfehlung aussprechen; dann dürfen die gesetzlichen Krankenkassen auch solche Rezepturarzneien bezahlen. Auch die Kassenärztliche Bundesvereinigung kann diesen Antrag stellen. Darauf warten tausende von Schmerzpatienten seit Jahren vergebens, doch bisher ist nichts passiert.



Persönliche Anmerkung: Natürlich hat Frau Köhler bis heute die Kosten-erstattung nicht genehmigt bekommen. Selbst der Sachverständigenrat des Gesundheitsausschusses hat sich bereits im Herbst 2005 für eine Übernahme der Kosten durch die Krankenkassen ausgesprochen. Auch ein amtlich bestätigter Wirksamkeits- bzw. Unbedenklichkeitsnachweis (siehe Lack, 2007), wie er bei europäischen Zulassungsverfahren von Sativex® (hat eine Zulassung zur Behandlung von Spastik und neuropathischen Schmerzen) zwingend vorgelegt werden musste, ist heute offensichtlich nicht mehr ausreichend. Mittlerweile ist eine weitere neue Bundesbehörde dafür federführend. Kennen Sie Franz Kafka? (siehe auch Lack, 2007 und Kassirer, 1997)

Lenk, R. and R. Likar (2008) "[Cannabinoids in medicine]. Wiener Medizinische Wochenschrift **158** (23-24): 668-673.

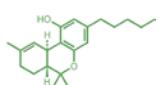
Cannabinoids have been known for many centuries because of their various effects in healthcare. They are primarily effective in reducing nausea, vomiting, pain, anorexia, spasticity and depression. Some other effects are known, all seem to be mediated by cannabinoid receptors in the central nervous system. In the past years, medical use has been proven in several studies. Today, the therapeutical use of cannabinoids in medicine is increasing, and access was made easier. Especially in pain-management and palliative care, they seem to be a valuable therapeutic option.

Leung, L. (2011) "Cannabis and its derivatives: review of medical use." Journal of the American Board of Family Medicine **24** (4): 452-462.

Background: Use of cannabis is often an under-reported activity in our society. Despite legal restriction, cannabis is often used to relieve chronic and neuropathic pain, and it carries psychotropic and physical adverse effects with a propensity for addiction. This article aims to update the current knowledge and evidence of using cannabis and its derivatives with a view to the sociolegal context and perspectives for future research. Methods: Cannabis use can be traced back to ancient cultures and still continues in our present society despite legal curtailment. The active ingredient, Δ-9-tetrahydrocannabinol, accounts for both the physical and psychotropic effects of cannabis. Though clinical trials demonstrate benefits in alleviating chronic and neuropathic pain, there is also significant potential physical and psychotropic side-effects of cannabis. Recent laboratory data highlight synergistic interactions between cannabinoid and opioid receptors, with potential reduction of drug-seeking behavior and opiate sparing effects. Legal rulings also have changed in certain American states, which may lead to wider use of cannabis among eligible persons. Conclusions: Family physicians need to be cognizant of such changing landscapes with a practical knowledge on the pros and cons of medical marijuana, the legal implications of its use, and possible developments in the future.

Case 1 Scenario

You are a family physician in Ontario, Canada. A 54-year-old man suffering from multiple sclerosis came to your office asking for a prescription for medical marijuana to control his pain. He was taking continuous-release morphine, gabapentin, and lamotrigine, but this combination was still insufficient. He visited Florida a few times, where he smoked cannabis, which helped tremendously to reduce the neuropathic pain and detach his mind from it. He



would like to continue using cannabis but is worried about the legal implications and the purity of sample he may obtain on the street.

Suggested Management

The evidence of various forms of cannabis (smoked, oral, and oromucosal spray) for treating neuropathic pain caused by multiple sclerosis should be discussed against the known harms and challenges of usage. Sativex (legally available form of cannabis in Canada; GW Pharmaceuticals, Salisbury, Wiltshire, UK) could be recommended as a first-line treatment. If the patient still decided to pursue a smoked or oral extract of cannabis, referral should be made to recognized specialists in Quebec for a full assessment of eligibility of patient's use and possession of medical marijuana. Close monitoring of the patient would be necessary.

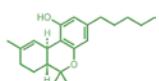
Case 2 Scenario

You are a family physician in the state of California. A 65-year-old male veteran came to your office as a new patient. He had a history of chronic leg pain caused by a shrapnel injury he suffered during the Vietnam War in 1968. Since the 1970s, he has been treated at the local veterans hospital under a pain management program, but control has been unsatisfactory. When asked if he used any recreational drugs, including marijuana, he evaded your question and said he needed to stay on the pain program. You suspected he was using marijuana for his chronic pain.

Suggested Management

The patient should be informed of the new directive from the Veterans Health Administration regarding veterans' use of marijuana and be reassured that he would not be denied his pain management services at the veterans hospital on that basis. He also should be encouraged to discuss his marijuana use with you so that you can monitor his progress. Liaising with an addiction medicine specialist can be helpful to ensure the best follow-up of this patient.

Cannabis, also known as marijuana, refers to the preparation 53 from the plant belonging to the family Cannabaceae, the genus Cannabis, and the species Cannabis sativa, which possess psychoactive effects. The flowering tops, leaves, and stalks of the mature female plant are commonly used as the herbal form of cannabis, but sometimes the resinous extract of compressed herb is also used and is called "hash." Archaeologists have identified fibers from cannabis stems in specimens dating back to 4000 BC, and its incorporation into textiles and paper was found in the tombs of the Chinese Han dynasty (~100 BC). The first record of cannabis as a medicine can be found in the oldest Chinese pharmacopeia, Shen Nong Ben Cao Jing, written in the Eastern Han Dynasty (AD 25 to AD 220), which was indicated for rheumatic pain, malaria, constipation, and disorders of the female reproductive system. Though the cannabis leaf and stem is rarely used nowadays in Chinese herbal medicine, cannabis seeds, which contain very few psychoactive ingredients, are still commonly prescribed for their laxative effects. Smoking cannabis is often an under-reported behavior in our society, with a reported prevalence from the World Health Organization of 3.9% among the global population aged 15 to 64 years. There are more than 70 psychoactive compounds called "cannabinoids" that have been identified in cannabis, among which Δ -9-tetrahydrocannabinol (THC) accounts for most of the psychological and physical effects, and its content is often used as a measure of sample potency. We now know that THC acts on 2 types of



cannabinoid receptors: CB1 and CB2. CB1 receptors are mainly found in the brain, peripheral nerves, and autonomic nervous system, whereas CB2 receptors are found both in the neurons and immune cells. THC exerts its effects primarily via CB1 receptors.

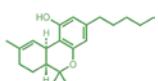
The Laws Regarding Cannabis

In the United States, cannabis is an illicit drug either to possess or trade. Since the inception of the Controlled Substance Act in 1970, the US Federal Law penalizes any act of possessing, dispensing, and prescribing marijuana. Enforcement of prohibition carries an annual price tag of up to \$7.7 billion in the United States alone. However, since 1996 the situation has been changing rapidly—14 states (California, Alaska, Oregon, Washington, Maine, Hawaii, Colorado, Nevada, Vermont, Montana, Rhode Island, New Mexico, Michigan, and New Jersey) already have amended their state laws to allow the use of marijuana by persons with debilitating medical conditions as certified by licensed physicians. The impact has been significant: a recent study in Washington estimated that per annum, up to 2000 licensed physicians have prescribed medical cannabis; in California, more than 350,000 patients already possess a physician's recommendation to use cannabis.

Nevertheless, among these 14 states, there is substantial variation in the regulation of the quality control, prescription limit, patient registry, and dispensing outlets. For example, in Oregon and Washington, it is legal to possess up to 24 ounces of marijuana, but in Nevada, Montana, and Alaska, the legal limit is only 1 ounce. Cannabis is currently schedule I; additional research would be facilitated if the drug were reclassified to schedule II. From a public health standpoint, there is some evidence that decriminalization of cannabis could free up law enforcement resources to curtail other trafficking activities without leading to increased cannabis abuses. Overall, however, the US Federal law remains unchanged regarding the penal stance toward marijuana, creating various ambiguities and difficulties. For those veterans who are permitted to use medical marijuana by law of their state, these difficulties have been lessened. This has posed an administrative dilemma for those veterans who are allowed to use; the Department of Veterans Affairs issued a directive in July 2010 that permits veterans to continue their use of medical marijuana in states where it is legal without losing their medical benefits from Veterans Affairs.

Recent news from USA Today reports that the US federal government has issued warning letters to several states that have approved the use of medical marijuana with an implication that anyone involved in the growth, operation, or legal regulation of medical marijuana will be subjected to prosecution. These states include Washington, California, Montana, and Rhode Island. This was coupled by recent large-scale raids at marijuana growing operations in Montana. Despite reassurance from Eric Holder, US Attorney General, that the penal policy is directed at those who violate both deferral and state laws, this unexpected siren from the federal government has been heard loud and clear, leading Governor Chris Gregoire, of the state of Washington, to abort a proposal to create licensed marijuana dispensaries and Governor Chris Christie, of the state of New Jersey, to postpone plans for marijuana operators.

In Canada, it is also illegal to trade or possess 104 marijuana according to provincial and government laws. However, access to marijuana for medical



use is possible under Health Canada's Marijuana Medical Access Regulations, which came into force on July 30, 2001. The regulations clearly outline 2 categories of persons who can apply to possess for an authorization to possess marijuana for medical purposes. Category 1 refers to people with end-of-life care; seizures from epilepsy; severe pain and/or persistent muscle spasms caused by multiple sclerosis, spinal cord diseases, or spinal cord injury; severe pain; cachexia; anorexia; weight loss and/or severe nausea from cancer or HIV/AIDS infection. A medical declaration from a licensed medical practitioner is required. Category 2 refers to people who have debilitating symptom(s) of medical condition(s), other than those described in category 1, which have failed conventional medical treatment. An assessment by a designated specialist is necessary along with a medical declaration from a licensed medical practitioner.

Under the regulations, the maximum amount of marijuana that can be possessed by any authorized user is a 30-day total of daily requirement. Health Canada sources its supply of dried marijuana and seeds from Prairie Plant Systems Incorporated (Saskatoon, Saskatchewan, Canada), a company that specializes in the growing, harvesting, and processing of plants for pharmaceutical products and research. Alternatively, authorized marijuana users can apply for a permit to produce and grow their own supply provided they meet specific and detailed criteria.

The Harms of Cannabis

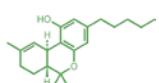
Physical and Psychiatric Effects

Among naive users, cannabis smoking often leads to adverse effects. Physical symptoms include increased heart rate and fluctuations in blood pressure; psychomotor sequelae include euphoria, anxiety, psychomotor retardation, and impairment of cognition and memory. The estimated lethal dose for humans is between 15 g and 70 g. When compared with cigarette smoke, cannabis contains a similar array of detrimental and carcinogenic compounds, some of which are present even at higher concentrations. Among chronic users, population studies have associated cannabis use with decreased pulmonary function, chronic obstructive airway diseases, and pulmonary infections, although data may be confounded by concomitant tobacco smoking and other social factors. In vitro and in vivo animal studies have demonstrated mutagenic effects of cannabis smoke, and precancerous pulmonary pathology as seen in tobacco smokers has been described in cannabis users.

Nevertheless, there is still inconsistency from the published literature regarding an increased risk for upper respiratory tract cancer caused by cannabis smoking. Various reports have associated cannabis with cardiac arrhythmias, coronary insufficiency and myocardial infarction. A retrospective cross-sectional study revealed a 4.8-times increased risk of developing myocardial infarction within the first hour after smoking cannabis. Earlier data from population studies and meta-analysis have associated cannabis smoking with low birth weight, which is maybe confounded by cigarette smoking and socioeconomic status and is not supported by more recent studies. Finally, the controversial link of cannabis use and psychosis has found more support in recent publications.

Dependence and Abuse

Cannabis is recognized as a substance with a high potential for dependence, which occurs in 1 out of 10 people who have ever used cannabis. It leads to



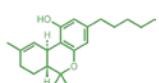
behaviors of preoccupation, compulsion, reinforcement, and withdrawal after chronic use. An Australian survey found that symptoms of cannabis withdrawal satisfied the diagnostic criteria of both International Classification of Diseases 10 and Diagnostic and Statistical Manual of Mental Disorders IV for substance dependence, which included sleep disturbance, anorexia, irritability, dysphoria, lethargy, and cravings. In the United States, cannabis is now ranked among alcohol and tobacco as one of the most common substances of among adolescents. There is also ample evidence indicating that regular use of cannabis predicts subsequent psychosocial problems and abuse behavior of other addictive substances. A review of cohort studies by McLaren et al. supported a causal link between cannabis use and psychosis. A recent 10-year follow-up study of adolescents in Australia who used cannabis occasionally were found to be at higher risks of drug abuse and educational problems. However, several issues have been identified in the published literature about cannabis, which have limited our understanding on the adverse effects of cannabis: (1) lack of consensus on the definition and classification of different types of cannabis users (heavy, regular, occasional, and nonusers); (2) variable quality of studies regarding design, effect sizes, and control of confounding factors; and (3) the polarization of the approach to either studying nonusers versus light/infrequent users or, infrequent/light/nondependent users versus frequent/heavy/dependent users.

New Kids on the Block

Recently, synthetic analogues of marijuana, known generically as "spice" or "K2," have gained rapid popularity among youths in the United States and Europe. Marketed as an incense or herbal blend, the exact constituents of spice has been a myth, and its place of origin is often unclear. Despite sharing similar psychotropic effects as genuine cannabis, spice cannot be reliably tested by drug screens and poses a technical problem for the law enforcement; hence it is capable of evading legal scrutiny among most states in America. A report from the Drug Enforcement Administration of the US Department of Justice in June 2010 had divulged the possible constituents of spice (or K2), which included HU-210, JWH-018, JWH-073 and CP-47,497, all of which were synthetic cannabinoids legally endorsed for scientific research. This was echoed by a recent research publication that identified a synthetic cannabinoid in commercially obtained spice, JWH-018, which activated CB1.

Analgesic Potential and Synergism With Opioids

Despite legal curtailment, cannabis is still used by 10% to 15% of patients with multiple sclerosis and noncancer types of chronic pain for both analgesia and psychological detachment. Various well-designed, randomized, placebo-controlled trials have shown that smoked cannabis can relieve peripheral, posttraumatic, and HIV-induced neuropathic pain. Evidence has been accumulating from molecular and cell-signaling studies that suggest that the opioids and cannabinoid systems can interact synergistically to enhance analgesic effects. Animal studies have shown that topical cannabinoid enhances the action of topical morphine, an effect that is preserved in a morphine-tolerant state. Moreover, cannabinoids are increasingly being recognized in animal models for their potential sparing effects with opioids of neuropathic pain and arthritic pain. Although similar effects have not been translated to human studies, Robert et al. found a synergistic affective analgesia between Δ-9-THC and morphine in experimentally induced pain in



human volunteers.

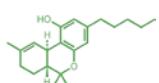
Evidence From Clinical Studies

To review the latest evidence of cannabis use and its derivatives, a literature search was conducted from the MEDLINE, EMBASE, PsycINFO, and Cochrane Database of Systematic Reviews from their inception dates to 30 November 2010, using the following keywords: "cannabis," "marijuana," " $\Delta 9$ -tetrahydrocannabinol," "clinical trial," "benefits," and "side effects." Relevant articles were selected and their quality of evidence was rated according to the Strength of Recommendations Taxonomy (SORT), with recommendations rated as A, B, or C. The results are summarized in Table 1. In brief, the efficacy of smoked cannabis has been studied for Gilles de la Tourette syndrome, glaucoma, and pain, with good evidence for clinical benefits in HIV-induced neuropathic pain. Oral extract of cannabis has better evidence of relieving self-reported symptoms of spasticity caused by multiple sclerosis. Finally, the oromucosal form of cannabis extract (Sativex, GW Pharmaceuticals) is efficacious for peripheral and central neuropathic pain, especially that caused by multiple sclerosis.

The Challenges of using Cannabis

Despite the evidence of benefits in certain conditions, the use of medical marijuana within a legal jurisdiction still faces a number of challenges: Method of Delivery and Quality Control. Smoking raw cannabis remains the most common and easiest route of delivery, but the actual amount of cannabinoids deliverable to the alveolar space varies considerably depending on the individual's techniques of inhalation/exhalation, the percentage of aeroingestion, and the individual's functional lung capacity. Without prior training, it could be difficult for a family physician in daily practice to advise an eligible patient on the proper techniques of administration and quality control of prescription regarding medical marijuana. The content of THC in cannabis may vary remarkably according by geographic origin, the parts of plant being used (buds versus stem and seeds), the methods of storage, and the techniques of cultivation. There are 2 main strains used in medical marijuana: the Sativa and the Indica. The Sativa plant is usually taller with longer leaves that grow better outdoors, whereas the Indica plant is more bushy with shorter leaves that thrive better indoors. Although both strains exist in pure forms, various combinations of the 2 strains are packaged as medical marijuana, which may result in variable therapeutic and side effects. Health Canada's policy of adopting a centralized source of medical marijuana from an approved plantation is a good way to assure quality; however, it is still technically difficult to endorse it globally for all licensed users and growers. As a prescription, standardization and titration of dose efficacy remain a challenge for medical marijuana.

Adequate Monitoring and Prevention of Addiction. As with other substances of abuse, cannabis may lead to varying adverse effects and addiction potential among different individuals. Before facilitating an eligible person to receive medical marijuana, family physicians should possess the knowledge and skills to screen for addiction potential. During the course of treatment, close surveillance of the patient to prevent addiction and adverse effects, in collaboration with a specialist when necessary, remains a top priority. In Canada and in those American states where it is legal to use medical marijuana, more training and educational resources should be made available



for the practicing family physician to enhance their competence in approaching cannabis.

Contaminants in Cannabis. Studies have reported an alarming level of biological contaminants in cannabis, which include Aspergillus fungus and bacteria, potentially leading to fulminant pneumonia, especially among the immunosuppressed. Nonbiological contaminants also have been found, which include heavy metals from soil like aluminum and cadmium, the latter of which seems to be absorbed by the cannabis plant in particularly high concentrations. Organophosphate pesticides are other nonbiological contaminants that are found less in cannabis cultivated outdoors than indoors. Finally, tiny glass beads or sand have been found in street samples of cannabis, which were added for weight to boost profits and can cause damage to the oral mucosa and lungs.

Contamination by Cannabis. Secondary inhalation of cannabis fumes released by primary smokers is a theoretical but negligible threat, as shown by a study of airborne particulates in urban Spain and another study of passive exposure to cannabis smoke in a Netherlands coffee shop. More research in this area is warranted from the perspective of public health.

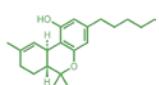
The Controversy Remains

In 1969, an article published in the New England Journal of Medicine quoted from the Wootton Report that cannabis is "a potent drug, having as wide a capacity as alcohol to alter mood, judgment, and functional ability, and admitted that it is a dangerous drug in that sense, but in terms of physical harmfulness much less dangerous than opiates, amphetamines, and barbiturates and also less dangerous than alcohol." Since then, scientific and clinical data have helped us understand the mechanisms of actions of cannabis and its derived compounds for treating chronic and neuropathic pain, highlighting the potential analgesic synergism with opioids and the potential of an opiate sparing effect in clinical settings. In particular, animal studies have recently shown that cannabidiol (CBD), a nonpsychoactive constituent of marijuana, is capable of decreasing self-administration and drug-seeking behavior caused by heroin, in addition to other anti-inflammatory antipsychotic and neuroprotective effects. Another observational study of the ratio of CBD:THC from street cannabis samples suggests that a higher CBD content reduced reinforcing behavior and attention bias to marijuana. Further directions of research include a better understanding of the mechanisms of action of CBD and its interplay with THC, plus bioengineering a safer marijuana strain that contains the appropriate composition of CBD and THC for optimal therapeutic effects with the least adverse profile and addictive potential. Thus, important issues of dosage standardization, quality control, adverse effects profiling, and prevention of addiction could be resolved. Until then, family physicians in North America and Canada continue to face the under-reported use of cannabis in our society and its risks of abuse.

Ley, W. (1844) "The Medicinal Properties of Indian Hemp." Lancet **43** (1078): 153.

Lorenz, R. (2004) "On the application of cannabis in paediatrics and epileptology." NeuroEndocrinology Letters **25** (1-2): 40-44.

An initial report on the therapeutic application of Δ-9-THC (THC) (Dronabinol, Marinol) in 8 children resp. adolescents suffering from the following conditions,



is given: neurodegenerative disease, mitochondriopathy, posthypoxic state, epilepsy, posttraumatic reaction. THC effected reduced spasticity, improved dystonia, increased initiative (with low dose), increased interest in the surroundings, and anticonvulsive action. The doses ranged from 0.04 to 0.12 mg/kg body weight a day. The medication was given as an oily solution orally in 7 patients, via percutaneous gastroenterostomy tube in one patient. At higher doses disinhibition and increased restlessness were observed. In several cases treatment was discontinued and in none of them discontinuing resulted in any problems. The possibility that THC-induced effects on ion channels and transmitters may explain its therapeutic activity seen in epileptic patients is discussed.

Losseff, N. and A.J. Thompson (1995) "The medical management of increased tone." Physiotherapy **81** (8): 480-484.

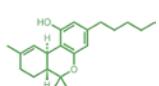
Spasticity does not need treatment in its own right. Aims of intervention are to improve function, prevent complications and relieve pain. Types of pharmacological treatment and available drugs are reviewed.

Mahoney, J.S., J.C. Engebretson, F. Cook, Karon, A. Hart, Karen, S. Robinson-Whele, and A.M. Sherwood (2007) "Spasticity Experience Domains in Persons with Spinal Cord Injury." Archives of Physical Medicine and Rehabilitation **88** (3): 287-294.

Spasticity experience domains in persons with spinal cord injury. Objective To understand the everyday life experiences of persons who have spasticity associated with spinal cord injury (SCI). Design Applied ethnographic design. Setting Patients' homes and rehabilitation clinics. Participants Twenty-four people with SCI who experience spasticity. Interventions Not applicable. Main Outcome Measures Domains identified through qualitative analysis of in-depth open-ended interviews. Results Domain analysis revealed 7 domains: physical, activity, emotional, economic, interpersonal, management, and cognitive. Descriptive subcategories within each domain were identified. Patients personalized the meaning of spasticity and expressed their understandings of the condition in ways that may not be consistent with clinical definitions. Some patients suggested that being able to control spasticity was preferable to total suppression. Conclusions Spasticity-related interventions need to be aimed at what matters most to the patient. It is critical for clinicians to understand patients' experiences to make accurate assessments, effectively evaluate treatment interventions, and select appropriate management strategies. When providers reconfigure patients' descriptions to fit neatly with a biomedical understanding of spasticity without carefully assessing the descriptions in terms of what matters most to patients, a potential risk for misappropriating interventions may arise.

Mai, L. (2005) "Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion : results of a randomised controlled trial." Douleurs: Evaluation – Diagnostic – Traitement **6** (3): 180.

Malec, J., R.F. Harvey and J. Cayner (1981) "Cannabis Use and Reported Changes in Spasticity Among Spinal Cord Injured Persons." Archives of Physical Medicine and Rehabilitation **62** (10): 116-118.



Malec, J., R.F. Harvey and J. Cayner (1982) "Cannabis effect on spasticity in spinal cord injury." Archives of Physical Medicine and Rehabilitation **63** (3): 198.

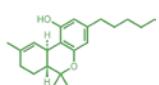
A study was done to examine the perceived effects of cannabis on spasticity of spinal cord injured persons. Data compiled from 43 questionnaires of spinal cord injured persons suggested the following: 1) spinal cord injured persons reported decreased spasticity with marijuana use; 2) present use of marijuana correlated positively with past use; and 3) the person's reference or peer group contributed significantly to current use. The study suggests the need to examine the relationship between measurable and reported changes in spasticity.

Malfitano, A. M., G. Matarese and M. Bifulco (2005) "From cannabis to endocannabinoids in multiple sclerosis: a paradigm of central nervous system autoimmune diseases." Current Drug Targets - CNS & Neurological Disorders **4** (6): 667-675.

An increasing body of evidence suggests that cannabinoids have beneficial effects on the symptoms of multiple sclerosis, including spasticity and pain. Endogenous molecules with cannabinoid-like activity, such as the "endocannabinoids", have been shown to mimic the anti-inflammatory properties of cannabinoids through the cannabinoid receptors. Several studies suggest that cannabinoids and endocannabinoids may have a key role in the pathogenesis and therapy of multiple sclerosis. Indeed, they can down regulate the production of pathogenic T helper 1-associated cytokines enhancing the production of T helper 2-associated protective cytokines. A shift towards T helper 2 has been associated with therapeutic benefit in multiple sclerosis. In addition, cannabinoids exert a neuromodulatory effect on neurotransmitters and hormones involved in the neurodegenerative phase of the disease. In vivo studies using mice with experimental allergic encephalomyelitis, an animal model of multiple sclerosis, suggest that the increase of the circulating levels of endocannabinoids might have a therapeutic effect, and that agonists of endocannabinoids with low psychoactive effects could open new strategies for the treatment of multiple sclerosis.

Malfitano, A.M., M.C. Proto and M. Bifulco (2008) "Cannabinoids in the management of spasticity associated with multiple sclerosis." Journal of Neuropsychiatric Disease and Treatment **4** (5): 847-853.

The endocannabinoid system and cannabinoid-based treatments have been involved in a wide number of diseases. In particular, several studies suggest that cannabinoids and endocannabinoids may have a key role in the pathogenesis and therapy of multiple sclerosis (MS). In this study we highlight the main findings reported in literature about the relevance of cannabinoid drugs in the management and treatment of MS. An increasing body of evidence suggests that cannabinoids have beneficial effects on the symptoms of MS, including spasticity and pain. In this report we focus on the effects of cannabinoids in the relief of spasticity describing the main findings in vivo, in the mouse experimental allergic encephalomyelitis model of MS. We report on the current treatments used to control MS symptoms and the most recent clinical studies based on cannabinoid treatments, although long-term studies



are required to establish whether cannabinoids may have a role beyond symptom amelioration in MS.

Health Canada Federal Department responsible for helping Canadians maintain and improve their health – Marihuana Medical Access Division (2008) "Fact Sheet - Medical Access to Marihuana"

The Marihuana Medical Access Regulations came into force on July 30, 2001. The regulations establish a framework to allow access to marihuana by individuals suffering from grave or debilitating illnesses, where conventional treatments are inappropriate or are not providing adequate relief.

The Regulations clearly define the circumstances and the manner in which access to marihuana for medical purposes is permitted. Following is an overview of the Regulations and a look at how they work.

Patient Eligibility

The Regulations outline two categories of people who can apply to possess marihuana for medical purposes.

Category 1: This category is comprised of any symptoms treated within the context of providing compassionate end-of-life care; or the symptoms associated with the specified medical conditions listed in the schedule to the Regulations, namely:

- Severe pain and/or persistent muscle spasms from multiple sclerosis;
- Severe pain and/or persistent muscle spasms from a spinal cord injury;
- Severe pain and/or persistent muscle spasms from spinal cord disease;
- Severe pain, cachexia, anorexia, weight loss, and/or severe nausea from cancer;
- Severe pain, cachexia, anorexia, weight loss, and/or severe nausea from HIV/AIDS infection;
- Severe pain from severe forms of arthritis; or
- Seizures from epilepsy.

Applicants must provide a declaration from a medical practitioner to support their application.

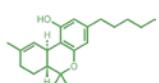
Category 2: This category is for applicants who have debilitating symptom(s) of medical condition(s), other than those described in Category 1. Under Category 2, persons with debilitating symptoms can apply to obtain an Authorization to Possess dried marihuana for medical purposes, if a specialist confirms the diagnosis and that conventional treatments have failed or judged inappropriate to relieve symptoms of the medical condition. While an assessment of the applicant's case by a specialist is required, the treating physician, whether or not a specialist, can sign the medical declaration.

The Application Process

Patients can obtain a guide and application form online or by calling Health Canada's Marihuana Medical Access Division toll-free, at: 1-866-337-7705.

The guide also explains the application process to access the dried marihuana grown under contract with Health Canada; or to obtain a licence to produce for those individuals who want to grow their own supply of marihuana for medical purposes; or for those who have chosen a designated person to grow the marihuana for them.

Applicants must provide information about themselves, their medical condition, and indicate if they plan to access the government supply of dried marihuana, grow their own supply of marihuana or have someone grow it for them.



A physician must complete and sign a medical declaration indicating the nature of the symptom for which marihuana would be used. Specific guidelines for applicants in categories 1 or 2 must be followed. Applicants require the signature of a medical practitioner to support the application. The application form must be accompanied by two passport-sized photographs, with one signed by the medical practitioner, to be used on an identification card issued to applicants authorized to possess. The card can be shown to a police officer as evidence that the person is authorized to possess marihuana.

Applications from patients with terminal conditions are given priority for processing. Processing time for the application varies depending on whether all of the necessary information has been received.

Applicants who are approved are notified in writing. If Health Canada is unable to process the application, usually because the application is incomplete, the applicant will be contacted by Health Canada in writing or by phone to explain why the application cannot be approved. Health Canada will try to work with the applicant to obtain the information required for a complete application.

Obtaining Marihuana

Holders of an authorization to possess can currently obtain marihuana for medical purposes from three possible sources:

- They can apply for access to purchase dried marihuana from Health Canada;
- They can grow their own supply; or
- They can designate someone else to grow it for them.

Possessing Marihuana

Holders of an authorization to possess may possess a maximum 30-day treatment supply of marihuana at any given time. For example, a patient whose daily amount is 3 grams will be allowed to possess no more than 90 grams (3 grams x 30 day treatment) at a given time. See table below for more examples.

Table 1 - Possessing Marihuana Amount
(grams/day)

Possession
(grams/month)

1	30
2	60
3	90
4	120
5	150

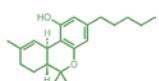
Health Canada's Marihuana Supply

Health Canada obtains dried marihuana and seeds for medical use from Prairie Plant Systems Incorporated, a company specializing in the growing, harvesting and processing of plants for pharmaceutical products and research. The production of this specific strain of marihuana is highly standardized and secure. Patients have the option of purchasing dried marihuana and/or seeds in order to grow their own.

For patients seeking access to marihuana for medical access, please refer to the pages "How to Apply". To learn more about Health Canada's supply of medical marihuana, refer to the pages "Marihuana Supply"

Growing Marihuana

Holders of an authorization to possess can also hold a licence to produce and grow their own marihuana, or they can choose to have a designated person



grow the marihuana for them. Applicants are asked to indicate their preference on the application form.

A designated person, or grower, must be 18 years of age or older, and ordinarily a resident of Canada. A grower will be issued a production licence and an identification card. A production licence is required to grow marihuana for medical purposes.

Plants can be grown indoors or outdoors, providing specific criteria are met. Growers must take the necessary precautions to protect plants and the dried marihuana from loss or theft. The amount of marihuana that can be grown and stored at any time depends on the daily amount that has been approved, and whether plants are grown indoors or outdoors.

Martens, D.(2011) "Zwischen illegaler Droge und wirksamer Arznei." Tagesspiegel vom 3. Februar 2011.

Cannabis soll Nervenschmerzen und Multiple Sklerose lindern. Doch die Hanfpflanze ist illegal. Ihre Wirkstoffe könnten aber bald als Medikament zugelassen werden.

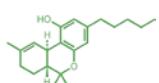
Weiches Fell streift über gerötete, geschwollene Haut: Die Katze Lola berührt Hans-Jürgen Scholz' Fingergelenke mit ihrer Schwanzspitze. Scholz sitzt auf einem Stuhl, sein rechter Arm hängt schlaff herunter, die Hand ist zu einer Kralle verzerrt. Die Berührung des Tieres spürt er nicht. Der Hauptnervenstrang des Arms wurde bei einem Unfall aus dem Rückenmark gerissen, ein Autofahrer hatte ihn vor 34 Jahren angefahren, 18 war er damals. Seitdem ist der Arm gelähmt. Ein Jahr nach dem Unfall begannen plötzlich die Schmerzen: "Stellen Sie sich vor, Sie hätten einen starken Sonnenbrand auf dem Arm, und dann würde jemand ihn wie ein Handtuch auswringen." Neuropathische Schmerzen nennt man das, sie entstehen, weil die Nerven beschädigt sind.

"Mein Gehirn bildet sich ein, Schmerz produzieren zu müssen", sagt Scholz. Der Schmerz sei immer da, 24 Stunden am Tag. Und dann sind da noch die "Attacken", in denen die Schmerzen fast doppelt so schlimm werden – 100 bis 200 Mal pro Tag: "Manchmal kommt die nächste Attacke nach einer Minute, manchmal nach einer Stunde." Und es gebe Tage, an denen sie so heftig und häufig sind, dass er nicht mehr sprechen könne. Lange hat er den Schmerz irgendwie ertragen, sogar ganz normal gearbeitet. "Ich habe gelernt, ihn nicht als Feind zu sehen. Aber es wurde immer schwieriger, damit zu leben."

Gesundheit

Vor etwa acht Jahren begann er eine Schmerztherapie. Seitdem hat er viele Medikamente durchprobiert. Zurzeit nimmt er Morphin-Tabletten, die sich langsam in seinem Magen auflösen, so dass sie das Betäubungsmittel kontinuierlich abgeben. Wie die meisten Schmerzmittel, die er versucht hat, fallen sie unter das Betäubungsmittelgesetz. Er hat einen Ausweis, in dem steht, dass ein Arzt es ihm legal verschrieben hat. Aber nur ein halbes Jahr lang habe das Morphin ein bisschen geholfen. Jetzt sei alles wieder wie vor Beginn der Therapie. Er nehme es nur noch, weil er sonst Entzugserscheinungen bekomme und die Schmerzen wohl noch schlimmer würden.

Jetzt allerdings meint Scholz, er habe einen Weg gefunden, wirklich vor den Schmerzen zu fliehen: Er hat einen Joint geraucht. Und plötzlich waren sie weg. "Aber ich habe mich so benommen gefühlt, bekifft, das war furchtbar



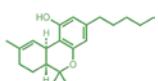
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unangenehm." Und er sei "ein gesetzestreuer Bürger", der keine illegalen Drogen nehmen will. Also ließ er sich von seinem Arzt den Hauptwirkstoff im Cannabis verschreiben: Dronabinol besteht aus Δ-9-Tetrahydrocannabinol, das man unter dem Kürzel THC kennt. Man könnte es mit Scholz' Morphindosis kombinieren, er müsste dann wesentlich weniger davon nehmen. Doch eine Behandlung mit dem Wirkstoff, der in Apotheken eigens mit einem Öl zusammengemischt werden muss, kostet bis zu 400 Euro pro Monat. Und Scholz' Krankenkasse zahlt das nicht, anders als das Morphin. Deswegen hat er Klage beim Landessozialgericht eingereicht. Damit ist er Teil eines Problems, das zurzeit diskutiert wird: Die Linkspartei hat der Regierung vorgeworfen, sie tue nichts dafür, die Situation von Menschen zu verbessern, die zwar eine Ausnahmegenehmigung für den Gebrauch von Cannabis als Medikament bekommen, aber die Behandlung nicht selbst zahlen können. Ist Cannabis als Schmerzmittel denn überhaupt medizinisch eine geeignete Alternative zum Morphin? "Ja, aber mit Einschränkungen", sagt Hans Rommelspacher, klinischer Neurobiologe an der Charité in Berlin. Außer Dronabinol gebe es auch noch ein Cannabis-Extrakt und das Kraut in Apotheken. Seit 2005 können Patienten bei der Bundesopiumstelle eine Therapie mit Cannabis beantragen. Doch das tun nur sehr wenige. Denn weder Dronabinol noch das Extrakt sind als Medikament zugelassen – die Apotheken stellen es erst vor Ort her. Deshalb müssen die Kassen die Kosten nicht übernehmen. Cannabis könne bei neuropathischen Schmerzen wirksamer sein als Morphin, gerade nach Unfällen, sagt Rommelspacher. Seine Wirkung sei aber noch kaum erforscht – anders als die von Morphin. "Davon wird man zwar körperlich abhängig, aber nicht psychisch süchtig. Beim Cannabis weiß man das noch nicht genau." Auch ob es mehr sediere als Morphin, sei schwer zu sagen. Patienten hätten ihm außerdem berichtet, dass Dronabinol nicht so wirksam sei wie Cannabis, das man als Joint raucht. Das liege wohl daran, dass dem Dronabinol andere Inhaltsstoffe aus dem Cannabis fehlten, die die Wirkung verstärkten. Doch wenn man Cannabis als Joint rauche, könne man das THC nicht richtig dosieren. Das ist generell schwierig.

Auch der Extrakt ist schwer zu dosieren, wie Multiple-Sklerose-Patienten feststellten, die 2009 an einer britischen Studie teilnahmen. Einige brachen die Behandlung schon zu Beginn wegen der Nebenwirkungen ab – während ihre persönliche Dosis ermittelt wurde. "Cannabis kann Schwindel hervorrufen und den Blutdruck zu sehr senken", sagt Hans Rommelspacher. "Außerdem könnte es schwierig werden, geistig anspruchsvolle Aufgaben damit auszuüben. Wer mit Multipler Sklerose wieder ins Berufsleben eingegliedert werden will, sollte es nicht unbedingt nehmen."

Insgesamt kam die Studie dennoch zu positiven Ergebnissen. 30 Prozent der Teilnehmer fühlten sich besser in Bezug auf Muskelsteifheit, Schmerzen, Spastik und Schlafstörungen, wie das Berliner Institut für klinische Forschung (IkF) mitteilt, das die Studie durchgeführt hat. Ziel war die Zulassung des Extrakts als Arzneimittel. Das ist noch nicht geschehen.

Andere Hersteller könnten jedoch noch in diesem Jahr in England die Zulassung für ein Cannabis-Extrakt bekommen, das den Namen Sativex bekommen soll und auch bald in Deutschland zugelassen werden könnte. Dann müssen die Kassen die Kosten übernehmen. **Persönliche Anmerkung: Genau das müssen die gesetzlichen Krankenkassen jetzt leider nicht.**



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Martin Fontelles, M.I. and C. Goicoechea Garcia (2008) "Role of cannabinoids in the management of neuropathic pain." *CNS Drugs* **22** (8): 645-653.

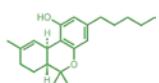
The treatment of pain, particularly neuropathic pain, is one of the therapeutic applications of cannabis and cannabinoids that is currently under investigation and that stimulates interest among clinicians and basic researchers. Animal pain models, including models of acute, antinociceptive, inflammatory and neuropathic pain, have demonstrated the antinociceptive efficacy of cannabinoids without causing serious alterations in animal behaviour. These data, together with the historic and current empiric use of cannabinoids, support the interest in the analysis of their effectiveness in treating neuropathic pain. The evaluation of controlled trials that focus on the effect of cannabinoids on neuropathic pain reveals that this class of drugs is able to significantly reduce pain perception. Nevertheless, this effect is generally weak and clinical relevance remains under evaluation. Moreover, there is a lack of controlled trials and, in particular, comparisons with other drugs generally used in the treatment of neuropathic pain. Despite the fact that further research is required to achieve a definitive assessment, current data obtained from basic research and from analysis of the available controlled trials indicate that cannabinoids can be accepted as a useful option in the treatment of neuropathic pain.

Martin, W.J. (1999) "Basic Mechanisms of Cannabinoid-Induced Analgesia." Technical Corner of the International Association for the Study of Pain® Newsletter Summer 1999.

The identification of cannabinoid receptors and the discovery of endogenous cannabinoids ushered in a new era of research on the biological effects of cannabis-like compounds. These advances, coupled with the ever-present need for safe, reliable pain-relieving compounds, have re-ignited interest in the cannabinoid receptor system as it relates to the transmission and modulation of pain. There is now unequivocal evidence that cannabinoids are antinociceptive in animal models of acute pain. Recent studies suggest that endogenous cannabinoids come into play under conditions of injury and contribute to the control of pain.

Historical Notes on Cannabis and Pain

Cannabis has been used for recreational and medicinal purposes throughout the world for many centuries. The co-evolution of these two uses forms the basis for the current debates on the benefits of "marijuana as medicine." At the center of these debates is the notion that analgesia is a possible indication for cannabinoids, as recently reviewed in a report by the Institute of Medicine. In 1839, W.B. O'Shaughnessy introduced cannabis to the Western medical establishment in a detailed article on its medicinal applications. After extensive investigations of this drug in both humans and animals, he concluded that it was effective in relieving several clinical conditions including, but not limited to, pain. Some 50 years later, this sentiment was echoed by an American professor of medicine, Hobart Hare, who wrote in his textbook that "cannabis is very valuable for the relief of pain, particularly that depending on nerve disturbances" (Hare and Chrystie 1892). Horatio Wood, a contemporary of Hare, wrote in his *Treatise on Therapeutics* that "cannabis is used chiefly for the relief of pain; especially of neuralgic character, although it will palliate even



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pain of organic origin" (Wood 1886). Perhaps one of the most revealing testimonials on the clinical attributes of cannabis came from a British physician to the Queen, J. Russell Reynolds, who made note of its unique pain-relieving properties by saying: "In almost all of painful maladies I have found Indian hemp by far the most useful of drugs" (Reynolds 1890).

Martínez-Rodríguez, J.E., E. Munteis, M. Carreño, Y. Blanco, J. Roquer, S. Abanades, F. Graus, and A. Saiz (2008) "Cannabis use in Spanish patients with multiple sclerosis: Fulfilment of patients' expectations?" Journal of the Neurological Sciences **273** (1-2): 103-107.

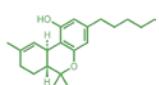
Objective Medicinal use of cannabis in chronic neurological diseases is a controversial topic of medical research and the subject of intense public debate. The aim of the study was to evaluate the prevalence of cannabis use, related factors, and degree of satisfaction in Spanish patients with multiple sclerosis (MS) prior to the establishment of medically supervised use. Methods Cross-sectional, questionnaire-based survey provided during routine medical visits to consecutive patients in two university-based neurology clinics. Results The questionnaire was returned by 175 MS patients (94.1% response rate). The prevalence of ever-use and medicinal cannabis use were 43% and 17.1%, respectively. At the time of the survey, cannabis was being used by 12.5% (5/45) of recreational and 56.7% (17/30) of medical users ($p < 0.001$). First cannabis consumption was after MS onset in 15 (50%) medicinal users. Clinical improvement was reported by 14 (46.7%) medicinal users. Smoking use, awareness of cannabis potential benefits, pain, higher disability, and lower age were independently associated with the medicinal use of cannabis. Most patients would support a future legalisation of cannabis for the control of their symptoms and were willing to receive cannabis under medical control once legalised (83.4% of never-users, 94.5% of ever-users, $p < 0.05$). Conclusion Almost half of our MS patients had tried cannabis at some time. However, medicinal use was low and clinical improvement after cannabis use was only reported by a subset of patients. Overall, MS patients were highly motivated for a future medically controlled use.

Maurer, M., V. Henn, A. Dittrich and A. Hofmann (1990) "Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial." European Archives of Psychiatry and Clinical Neuroscience **240** (1): 1-4.

A double-blind study was performed comparing 5 mg Δ-9-tetrahydrocannabinol (THC) p.o., 50 mg codeine p.o., and placebo in a patient with spasticity and pain due to spinal cord injury. The three conditions were applied 18 times each in a randomized and balanced order. Δ-9-THC and codeine both had an analgesic effect in comparison with placebo. Only Δ-9-THC showed a significant beneficial effect on spasticity. In the dosage of THC used no altered consciousness occurred.

Mbvundula, E.C., K.D. Rainsford and R.A. Bunning (2004) "Cannabinoids in pain and inflammation." Inflammopharmacology **12** (2): 99-114.

Cannabinoids exhibit medicinal properties including analgesic, anti-inflammatory and immunosuppressive properties. This paper reviews some of the recent findings in the study of cannabinoids in pain and inflammation.



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Some of the effects of cannabinoids are receptor mediated and others are receptor independent. Endocannabinoids naturally reduce pain and are cerebroprotective. Natural and synthetic cannabinoids have the potential to reduce nociception, reverse the development of allodynia and hyperalgesia, reduce inflammation and inflammatory pain and protect from secondary tissue damage in traumatic head injury.

McQuay, H.J. (2010) "More evidence cannabis can help in neuropathic pain." Canadian Medical Association Journal – CMAJ **182** (14): 1494-1495.

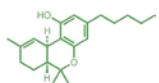
Meinck, H.M., P.W. Schonle and B. Conrad (1989) "Effect of cannabinoids on spasticity and ataxia in multiple sclerosis." Journal of Neurology **236** (2): 120-122.

The chronic motor handicaps of a 30-year-old multiple sclerosis patient acutely improved while he smoked a marihuana cigarette. This effect was quantitatively assessed by means of clinical rating, electromyographic investigation of the leg flexor reflexes and electromagnetic recording of the hand action tremor. It is concluded that cannabinoids may have powerful beneficial effects on both spasticity and ataxia that warrant further evaluation.

Mechoulam, R. (2012) "Cannabis - A Valuable Drug That Deserves Better Treatment." Mayo Clinic Proceedings **87** (2): 107–109.

About 150 years ago, a French psychiatrist, J. J. Moreau, conducted a novel clinical experiment in which he administered hashish to humans. His volunteers, including Moreau himself, experienced "occurrences of delirium or of actual madness. ..." He concluded that "There is not a single, elementary manifestation of mental illness that cannot be found in the mental changes caused by hashish. ..." In contrast, most marijuana users today will presumably state that their senses appear enhanced, concomitant with an increase in relaxation and euphoria; while forgetfulness is enhanced, their focus on their surroundings is augmented. These surprisingly contrasting experiences are due to the ingestion or smoking of products of the same plant, and neither is inaccurate if one considers the difference in doses presumably taken, the presence in cannabis (a term that includes both marijuana and hashish preparations) of at least 2 compounds with opposite effects— δ -9-tetrahydrocannabinol (THC), the psychoactive component, and cannabidiol (CBD), a nonpsychoactive constituent—and the different users' susceptibilities to the effects of the drug. It is also well known that the activity of THC is biphasic in many assays—low and high doses may cause opposite effects. Presumably the Moreau volunteers consumed (orally) huge amounts of North African hashish, which has a very high concentration of THC. However, North Americans and Europeans today generally smoke cannabis and can titrate (ie, finely adjust) the level of the psychotropic effects and thus do not typically reach the high psychotic state.

Cannabidiol modifies the effects of THC. Thus, CBD blocks anxiety provoked by THC; cannabis with high CBD content is associated with fewer psychotic experiences than cannabis with low CBD content,⁵ and CBD attenuates the memory-impairing effects produced by THC. Cannabidiol is also a potent anti-inflammatory compound and has an anti-autoimmune diabetes effect (in a mouse model). However, most users are not aware of the amounts of THC and CBD in the cannabis they use. Most of the marijuana sold illegally today in



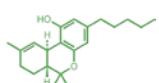
the United States actually contains no CBD, or very low amounts of it, and the THC levels in marijuana may vary from about 3% to 25%. These large variations of THC levels are due mainly to the different sources of the drug, but even samples from the same source may vary, depending on the portion of the plant and the plant's age. Hence, much of the statistics based on "street users" is quite useless. Modern medical practice is based on the administration of defined levels of drugs. Most physicians are not comfortable prescribing a plant product with varying concentrations of active pharmacological compounds, and certainly no other prescribed drug is administered by smoking. However, from a medical point of view, marijuana is a valuable drug. It lowers certain types of pain; has antianxiety, anti-inflammatory, and antispastic effects; and enhances appetite. Its adverse effects are also well known. It can precipitate anxiety attacks or even schizophrenia in susceptible individuals, although, surprisingly, the extent of schizophrenia in the general population does not seem to have increased in parallel with the very wide use of marijuana for recreational purposes. The United Nations Office on Drugs and Crime has estimated that in 2006 cannabis was used (presumably mostly for recreation) by 166 million adults. Dependence to cannabis has been noted in about 9% of heavy users.

Recent research has shown that many of the therapeutic effects of cannabinoids are not due solely to the cannabinoid CB1 receptors, whose stimulation causes the cannabis psychoactivity, but also to CB2 receptor activation, which causes no psychoactivity but attenuates inflammation, decreases injury, and accelerates regeneration in many disease states. However, essentially all the published research on specific CB2 stimulation has been done in animals.

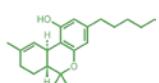
The current issue of Mayo Clinic Proceedings has 2 articles on cannabis. One of them, by Simonetto et al, deals with the rather uncommon severe vomiting seen in some "street marijuana" users.¹⁰ The other, by Bostwick, is a general review on the therapeutic effects of cannabis and the politics of medical use of marijuana.

Hyperemesis is not an acute effect of cannabis smoking. In the case series reported by Simonetto et al, hyperemesis appeared in most patients after more than 2 years of smoking at least once a week. Surprisingly, most patients (83%) had lost weight (median loss, 12 kg), and 23% had diarrhea. These are not effects expected in cannabis users. On the contrary, THC is known to block vomiting, enhance appetite, and cause constipation. The authors do not discuss these observations, but it is tempting to speculate that an endogenous CB1 receptor antagonist-like compound is produced as a result of prolonged THC use, perhaps involving some form of a novel "cannabinoid immune-type reaction." If this speculation is correct, such an endogenous CB1 receptor antagonist would be expected to block some physiologic processes affected by THC. Indeed, synthetic CB1 receptor blockers are known to cause weight loss induce nausea, and increase defecation. Other mechanisms of the hyperemesis are also conceivable.

Simonetto et al suggest that "the central effects of long-term cannabis use on the hypothalamic-pituitary-adrenal axis might play a major role in the development of [cannabinoid hyperemesis]." While these suggestions have a certain intellectual appeal, we should not forget that the quality of the material used by these patients is unknown and that we know nothing about the



presence (or levels) of additional cannabis constituents or foreign substances (most commonly pesticides) with unknown pharmacological effects that may have been included in the street marijuana consumed. Hence, although the direct connection between hyperemesis and cannabis seems reasonable, full proof is lacking. Nevertheless, the authors' viewpoint is of clinical importance: "Given the prevalence of cannabis use worldwide, the very recent recognition of [cannabinoid hyperemesis], and the paucity of [cannabinoid hyperemesis] literature, it is likely that this disease is underrecognized and underdiagnosed." The article by Bostwick deals with the therapeutics and politics of medical use of marijuana. He has critically and very well presented both aspects. In most countries, including the United States, marijuana is a Schedule I controlled substance (high potential for abuse; no currently accepted medical use). Like individuals, countries can also be hypocritical. In contrast to marijuana, THC, also called dronabinol, is a Schedule III drug (has potential for abuse less than that of substances in Schedules I or II). Dronabinol is an approved drug in the United States and numerous other countries for several medical conditions, mostly as an antiemetic during cancer chemotherapy and to improve appetite in patients with human immunodeficiency virus. Nabilone, marketed as Cesamet, a synthetic analogue of THC, is actually a Schedule II drug (high potential for abuse) and is prescribed for similar indications. It parallels the effects of THC, although it is more potent and its activity persists longer than that of THC. A 50:50 THC:CBD mixture of cannabis plant origin (named Sativex) is in medical use as an oral spray in many European countries, as well as in Canada. There is also a plethora of articles on the therapeutic effects of marijuana. For example, Abrams et al. recently showed that "vaporized cannabis augments analgesia in individuals with chronic pain on a treatment regimen of stable doses of sustained-release morphine or oxycodone, and that the mechanism of augmentation is not explained by elevation of plasma opioid concentrations or inhibition of opioid metabolism." Aren't all the aforementioned evidence of "currently accepted medical use"? In his article, Bostwick points out that "[a]s the mysteries of the endocannabinoid system were unraveled ... , a rationale for both its recreational and sweeping medical effects has emerged," and he therefore recommends that marijuana should be rescheduled as something other than Schedule I. This rescheduling, Bostwick argues, would facilitate future research on marijuana. Whether intended by him or not, it also would make marijuana available by prescription. The presence of 2 active compounds in cannabis may open the possibility of individualized treatment. By modifying the ratio of THC:CBD, it should be possible to establish a personal dose for specific patients, depending on the diagnosis and the individual susceptibility. However, to make such treatment possible, we should demand that medical marijuana be supplied with an analysis of at least its 2 major constituents and that a variety of mixtures should be available. Various types of marijuana preparations for oral administration should also be attainable. Research on specific CB2 receptor agonists promises to lead to novel drugs, which may, in part at least, diminish the need for medical marijuana. Nevertheless, I believe that medical marijuana as a therapeutic entity is here to stay. It is being used in numerous medical conditions, at times with considerable success. Are we entitled to neglect a valuable drug?



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Mestre, L., F. Correa, A. Arevalo-Martin, E. Molina-Holgado, M. Valenti, G. Ortar, V. Di Marzo and C. Guaza (2005) "Pharmacological modulation of the endocannabinoid system in a viral model of multiple sclerosis." *Journal of Neurochemistry* **92** (6): 1327-1339.

Theiler's virus infection of the central nervous system (CNS) induces an immune-mediated demyelinating disease in susceptible mouse strains and serves as a relevant infection model for human multiple sclerosis (MS). Cannabinoids have been shown to exert beneficial effects on animal models of MS and evidence suggests that the endocannabinoid system plays a role in the tonic control of spasticity. In this study we show that OMDM1 [(R)-N-oleoyl-(1'-hydroxybenzyl)-2'-ethanolamine] and OMDM2 [(S)-N-oleoyl-(1'-hydroxybenzyl)-2'-ethanolamine], two selective inhibitors of the putative endocannabinoid transporter and hence of endocannabinoid inactivation, provide an effective therapy for Theiler murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD). Treatment of TMEV-infected mice with OMDM1 and OMDM2 enhanced anandamide levels in the spinal cord and ameliorated motor symptoms. This was associated with a down-regulation of inflammatory responses in the spinal cord. In addition we show that OMDM1 and OMDM2 down-regulate macrophage function by (i) decreasing the surface expression of major histocompatibility complex (MHC) class II molecules, (ii) inhibiting nitric oxide synthase-2 (NOS-2) expression and (iii) reducing the production of the pro-inflammatory cytokines interleukin-1beta (IL-1beta) and interleukin-12 (IL-12p40). Taken together, these results point to the manipulation of the endocannabinoid system as a possible strategy to develop future MS therapeutic drugs.

Metz, L. and S. Page (2003) "Oral cannabinoids for spasticity in multiple sclerosis: will attitude continue to limit use?" *Lancet* **362** (9395): 1513.

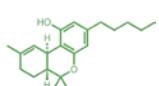
Mikuriya, T. (2002) "Uses of Medical Marijuana" Source: Dale Gieringer, "Medical Use of Cannabis in California," in Franjo Grotenhermen, M.D. & Ethan Russo, M.D., ed., *Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential* Haworth Press. <http://www.canorml.org/prop/MMJIndications.htm>

California's Proposition 215 allows medical marijuana to be used for ANY serious condition for which marijuana provides relief. Cannabis has a remarkably wide spectrum of medical uses, ranging from chronic pain, muscle spasticity, nausea and appetite loss to psychiatric conditions such as post-traumatic stress disorder, anxiety and depression.

Following is a survey of conditions reported by medical cannabis specialist Dr. Tod Mikuriya. Altogether, Dr. Mikuriya has recorded over 250 indications for medical cannabis, as classified by the International Classification of Diseases (ICD-9). Following is a compilation of diseases reported by 2,480 of Dr.

Mikuriya's 9,000 patients, according to the primary indication for which the patients were diagnosed. In practice, many patients report more than one indication. One of the most important uses of cannabis is as a substitute for other, more dangerous or costly pharmaceutical drugs. Many patients report substantial reductions in use of narcotics, non-steroidal anti-inflammatories, anti-depressants, tranquilizers, sleeping pills and other drugs. This usage is not reported below, because it does not count as a "primary indication."

Because of government restrictions on research, very few of marijuana's



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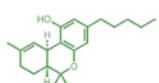
medical indications have been clinically studied. For a survey of recent medical marijuana research, see www.cannabis-med.org, International Assoc. for Cannabis Medicine) "Recent Research on Medical Marijuana," (NORML, 2006), and "Human Studies on Medical Use of Marijuana" (Cal NORML, 1996).

Moalem, G. and D.J. Tracey (2006) "Immune and inflammatory mechanisms in neuropathic pain." *Brain Research Reviews* **51** (2): 240-264.

Tissue damage, inflammation or injury of the nervous system may result in chronic neuropathic pain characterised by increased sensitivity to painful stimuli (hyperalgesia), the perception of innocuous stimuli as painful (allodynia) and spontaneous pain. Neuropathic pain has been described in about 1% of the US population, is often severely debilitating and largely resistant to treatment. Animal models of peripheral neuropathic pain are now available in which the mechanisms underlying hyperalgesia and allodynia due to nerve injury or nerve inflammation can be analysed. Recently, it has become clear that inflammatory and immune mechanisms both in the periphery and the central nervous system play an important role in neuropathic pain. Infiltration of inflammatory cells, as well as activation of resident immune cells in response to nervous system damage, leads to subsequent production and secretion of various inflammatory mediators. These mediators promote neuroimmune activation and can sensitise primary afferent neurones and contribute to pain hypersensitivity. Inflammatory cells such as mast cells, neutrophils, macrophages and T lymphocytes have all been implicated, as have immune-like glial cells such as microglia and astrocytes. In addition, the immune response plays an important role in demyelinating neuropathies such as multiple sclerosis (MS), in which pain is a common symptom, and an animal model of MS-related pain has recently been demonstrated. Here, we will briefly review some of the milestones in research that have led to an increased awareness of the contribution of immune and inflammatory systems to neuropathic pain and then review in more detail the role of immune cells and inflammatory mediators.

Moussoultas, M. (2004) "Cannabis use and cerebrovascular disease." *Neurologist* **10** (1): 47-53.

Background: Cannabis is the most commonly abused illicit drug and is often considered innocuous. However, cases of acute onset neurologic dysfunction occurring in relation to cannabis use have been described and corresponding cerebral imaging studies have documented focal ischemic changes and vessel abnormalities. **Review Summary:** This article reviews all reported cases of presumed cannabis related cerebral ischemic events in the medical literature, as well as pertinent human and animal experimental studies on the cardiovascular and cerebrovascular effects of cannabis. **Conclusions:** Cannabis use seems to have been causally related to several instances of cerebral ischemia and infarction. Proposed etiologic mechanisms have included cerebral vasospasm, cardioembolization, and systemic hypotension with impaired cerebral autoregulation, but most of the available data points to a vasospastic process. The exact relation of cannabis to cerebrovascular disease remains to be determined.



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Müller-Vahl, K. R., H. Kolbe, et al. (1997) "[Gilles de la Tourette syndrome. Influence of nicotine, alcohol, and marijuana on the clinical symptom]."Der Nervenarzt **68** (12): 985-989.

Das Gilles de la Tourette-Syndrom ist eine komplexe neuropsychiatrische Erkrankung ungeklärter Ätiologie. Während verschiedene Studien Hinweise ergaben, dass Nikotin zu einer Symptoreduktion führen kann, liegen nur Einzelbeschreibungen zum Einfluss von Alkohol und Marihuana vor. Mittels eines strukturierten Interviews befragten wir eine grosse in unserer Ambulanz betreute Patientengruppe mit Tourette-Syndrom zu Gewohnheiten und subjektiven Erfahrungen. Von 47 befragten erwachsenen Patienten berichteten lediglich 2 von 28 rauchenden Patienten (7%) über eine Tic-Reduktion während des Rauchens, hingegen verspürten 24 von 35 Patienten (69%), die gelegentlich oder regelmässig Alkohol trinken, eine deutliche Symptomreduktion. Von 13 Patienten mit gelegentlichem oder regelmässigem Marihuanagebrauch schilderten 11 (85%) eine deutliche Symptomreduktion während des Konsums. Unsere Ergebnisse belegen, dass Alkohol und (mehr noch) Marihuana zu einer sehr viel ausgeprägteren Symptomverbesserung führen als Nikotin. Marihuana könnte durch Bindung an spezielle, vermutlich mit Dopamin-D1- und -D2-Rezeptoren interagierende, Cannabinoid-Rezeptoren zu einer Beeinflussung des motorischen Systems führen.

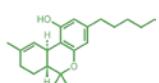
Müller-Vahl, K. R., H. Kolbe, Schneider, U. and Emrich, H.M. (1998) "Cannabinoids: possible role in patho-physiology and therapy of Gilles de la Tourette syndrome."Acta Psychiatrica Scandinavica **98** (6): 502-506.

High densities of cannabinoid receptors were found in the basal ganglia and hippocampus, indicating a putative functional role of cannabinoids in movement and behaviour. Anecdotal reports suggested beneficial effects of marijuana in Tourette's syndrome (TS). We therefore interviewed 64 TS patients with regard to use of marijuana and its influence on TS symptomatology. Of 17 patients (27%) who reported prior use of marijuana, 14 subjects (82%) experienced a reduction or complete remission of motor and vocal tics and an amelioration of premonitory urges and obsessive-compulsive symptoms. Our results provide more evidence that marijuana improves tics and behavioural disorders in TS. It can be speculated that cannabinoids might act through specific receptors, and that the cannabinoid system might play a major role in TS pathology.

Müller-Vahl, K. R., U. Schneider, et al. (1999) "Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol."American Journal of Psychiatry **156** (3): 495.

Müller-Vahl, K. R., A. Koblenz, Kolbe, H. and Emrich, H.M. (2001) "Influence of treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta-9-THC) on neuropsychological performance."Pharmacopsychiatry **34**(1): 19-24.

Previous studies have suggested that marijuana (*cannabis sativa*) and Δ -9-tetrahydrocannabinol (Δ -9-THC), the major psychoactive ingredient of marijuana, are effective in the therapy of tics and associated behavioral disorders in Tourette Syndrome (TS). Because there is also evidence that *cannabis sativa* may cause cognitive impairment in healthy users, we performed a randomized double-blind placebo-controlled crossover trial for Δ -9-THC in 12 adult TS patients to investigate whether treatment of TS with a



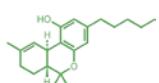
single dose of Δ-9-THC at 5.0 to 10.0 mg causes significant side effects on neuropsychological performance. Using a variety of neuropsychological tests, we found no significant differences after treatment with Δ-9-THC compared to placebo treatment in verbal and visual memory, reaction time, intelligence, sustained attention, divided attention, vigilance, or mood. Only when using the Symptom Checklist 90-R (SCL-90-R) did our data provide evidence for a deterioration of obsessive-compulsive behavior (OCB) and a trend towards an increase in phobic anxiety. However, these results should be interpreted with caution as SCL-90-R has known limitations on measuring OCB. We suggest that the increase in phobic anxiety is mainly due to the fact that a single-dose treatment rules out the possibility of administering the dosage slowly. In contrast to results obtained from healthy marijuana users, a single-dose treatment with Δ-9-THC in patients suffering from TS does not cause cognitive impairment. We therefore suggest that further investigations should concentrate on the effects of a longer-term therapy of TS with Δ-9-THC.

Müller-Vahl, K.R., U. Schneider and Emrich, H.M. (2002) "Combined treatment of Tourette syndrome with Delta-9-THC and dopamine receptor antagonists." Journal of Cannabis Therapeutics **2** (3-4): 145-154.

Animal studies suggest that cannabinoid receptor agonists might enhance the effect of dopamine receptor antagonists (neuroleptics, NL) in hyperkinetic movement disorders. In Tourette syndrome, NL are the most effective drugs for the treatment of tics. Recent clinical trials demonstrated that Δ-9-tetrahydrocannabinol (Δ-9-THC) also produces a tic-suppressing effect. In this single case study in a 24 years old female suffering from TS with extreme tics, it is suggested for the first time that Δ-9-THC may be useful in augmenting the pharmacological response to atypical NL such as amisulpride and risperidone in TS patients. No serious adverse reactions occurred. Controlled studies are necessary to confirm this initial report.

Müller-Vahl, K.R., U. Schneider, Koblenz, A., Joebes, M., Kolbe, H., Daldrup, T. and Emrich, H. M. (2002) "Treatment of Tourette's syndrome with Delta-9-tetrahydrocannabinol (THC): A randomized crossover trial." Pharmacopsychiatry **35** (2): 57-61.

Anecdotal reports in Tourette's syndrome (TS) have suggested that marijuana (*cannabis sativa*) and Δ-9-tetrahydrocannabinol (Δ-9-THC), the major psychoactive ingredient of marijuana, reduce tics and associated behavioral disorders. We performed a randomized double-blind placebo-controlled crossover single-dose trial of Δ-9-THC (5.0, 7.5 or 10.0 mg) in 12 adult TS patients. Tic severity was assessed using a self-rating scale (Tourette's syndrome Symptom List, TSSL) and examiner ratings (Shapiro Tourette's syndrome Severity Scale, Yale Global Tic Severity Scale, Tourette's syndrome Global Scale). Using the TSSL, patients also rated the severity of associated behavioral disorders. Clinical changes were correlated to maximum plasma levels of THC and its metabolites 11-hydroxy-Δ-9-tetrahydrocannabinol (11-OHTHC) and 11-nor-Δ-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH). Using the TSSL, there was a significant improvement of tics ($p = 0.015$) and obsessive-compulsive behavior (OCB) ($p = 0.041$) after treatment with Δ-9-THC compared to placebo. Examiner ratings demonstrated a significant difference for the subscore "complex motor tics" ($p = 0.015$) and a



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trend towards a significant improvement for the subscores "motor tics" ($p = 0.065$), "simple motor tics" ($p = 0.093$), and "vocal tics" ($p = 0.093$). No serious adverse reactions occurred. Five patients experienced mild, transient side effects. There was a significant correlation between tic improvement and maximum 11-OH-THC plasma concentration. Results obtained from this pilot study suggest that a single-dose treatment with Δ -9-THC is effective and safe in treating tics and OCB in TS. It can be speculated that clinical effects may be caused by 11-OH-THC. A more long-term study is required to confirm these results.

Müller-Vahl, K.R. (2009) "Tourette's syndrome" Current Topics in Behavioral Neurosciences 1: 397-410.

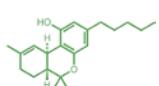
Tourette's syndrome (TS) is a chronic disorder characterized by motor and vocal tics and a variety of associated behaviour disorders. Because current therapy is often unsatisfactory, there is expanding interest in new therapeutic strategies that are more effective, cause less side effects and ameliorate not only tics but also behavioural problems. From anecdotal reports and preliminary controlled studies it is suggested that - at least in a subgroup of patients - cannabinoids are effective in the treatment of TS. While most patients report beneficial effects when smoking marijuana (Cannabis sativa L.), available clinical trials have been performed using oral Δ -9-tetrahydrocannabinol (THC). In otherwise treatment-resistant TS patients, therefore, therapy with THC should not be left unattempted. To date, it is unknown whether other drugs that interact with the endocannabinoid receptor system might be more effective in the treatment of TS than smoked marijuana or pure THC. Since it has been suggested that abnormalities within the endocannabinoid receptor system might underlie TS pathophysiology, it would be of interest to investigate the effect of substances that for example bind more selectively to the central cannabinoid receptor or inhibit the uptake or the degradation of different endocannabinoids.

Nahas, G., K. Sutin, and W.M. Bennett (2000) "Review of Marihuana and Medicine." New England Journal of Medicine 343 (7): 514-515.

Nance, P.W. (2001) "Alpha adrenergic and serotonergic agents in the treatment of spastic hypertonia." Physical Medicine and Rehabilitation Clinics of North America 12 (4): 889-905.

In the treatment of patients with problematic spasticity, it is important to consider the following steps: 1. Establish the functional impact of the spasticity. 2. Identify the functional goal to be achieved by treatment. 3. Eliminate any remediable spasticity aggravating factors. 4. Evaluate the effects of previous antispasticity treatments. 5. Consider nonpharmacologic and pharmacologic treatments. 6. Initiate therapy with a low dosage, and titrate judiciously. 7. Stop the titration when functional goal is achieved. 8. If goal is not achieved or if side effects are intolerable, consider a second medication.

Nau, J.Y. (2002) "Some truths concerning the consumption of cannabis" Medecine et Hygiene 60 (2384): 601.



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Nauck, F. and E. Klaschik (2005) "Dronabinol (Δ -9-Tetrahydrocannabinol) in der Langzeittherapie. Symptomkontrolle bei multipier Sklerose mit Spastik, neuropathischen Schmerzen, Appetitlosigkeit und Kachexie." Der Schmerz 18 (Suppl. 2): 26.

Nedelmann, C. (2000) "Drogenpolitik: Das Verbot von Cannabis ist ein „kollektiver Irrweg.“" Deutsches Ärzteblatt 97 (43): A-2833 / B-2429 / C-2257

Der Autor vertritt die These, dass der Konsum von Cannabis keinen ernsthaften Schaden nach sich zieht – weder körperlich noch seelisch, weder akut noch chronisch. Das Cannabis-Verbot könnte daher nicht durch medizinische Argumente gestützt werden.

Das Bundesverfassungsgericht hat 1994 die Ansicht vertreten, dass die Strafvorschriften des Betäubungsmittelgesetzes geeignet sind, die von Cannabis ausgehenden Gefahren zu verringern und die Verbreitung der Droge zu beschränken. Diese Ansicht wird von der Realität widerlegt: Die von Cannabis ausgehenden Gefahren sind geringer als die der legalen Drogen Alkohol und Nikotin. Die Verbreitung der Droge wird durch das Verbot nicht beschränkt, sondern sogar gefördert. Der Rechtsphilosoph Michael Köhler kam zu der Einschätzung, dass das Cannabis-Verbot ein „kollektiver Irrweg“ ist, der „nicht guten Gewissens weitergegangen werden kann“.

Holland: Zahl der Drogentoten gesunken

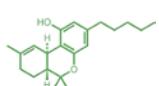
Das Beispiel Holland zeigt, was passiert, wenn nicht nur der unmittelbare Konsum, sondern auch der Handel von Cannabis freigegeben wird: Dort gibt es Coffeeshops, wo der Verkauf kleiner Mengen geduldet wird. Die Zahl der Cannabis-Konsumenten ist dadurch nicht – wie vielfach befürchtet – gestiegen, sondern sogar zurückgegangen. Obwohl

Anmerkung: nein, mittel- bis langfristig gerade weil die Märkte für weiche und harte Drogen weitgehend getrennt sind, ist auch die Zahl der Konsumenten harter Drogen zurückgegangen. Die Zahl der Drogentoten ist gesunken.

Zurück nach Deutschland: 1971 hat der Gesetzgeber Cannabis dem Betäubungsmittelgesetz mit dem Argument unterstellt, „es wäre nicht zu verantworten, die Droge jetzt frei zu geben“; man erwartete jedoch aufgrund medizinischer Forschung, „dass man in etwa fünf Jahren zu konkreteren Ergebnissen gelangen wird.“ 1994 hielt das Bundesverfassungsgericht daran fest, das Cannabis-Verbot vor dem Grundgesetz mit medizinischen Argumenten zu verteidigen, und schrieb in der Begründung: „Obwohl sich ... die von Cannabisprodukten ausgehenden Gesundheitsgefahren aus heutiger Sicht als geringer darstellen, als der Gesetzgeber bei Erlass des Gesetzes angenommen hat, verbleiben dennoch auch nach dem jetzigen Erkenntnisstand nicht unbeträchtliche Gefahren und Risiken.“

Die im Betäubungsmittelgesetz hergestellte Nähe zu den Opiaten konnte jedoch keine Glaubwürdigkeit mehr finden. Das Bundesverfassungsgericht entschloss sich daher, Cannabis zur besseren Einschätzung mit Alkohol zu vergleichen. Da Alkohol ein Genuss- und Suchtmittel ist, fordert der Vergleich zum einen Antworten auf die Fragen nach Sucht und Abhängigkeit generell. Die Fragen reichen vom akuten Rausch bis zu den Folgen des chronischen und des exzessiven Gebrauchs.

Zum andern fordert der Vergleich mit Alkohol Antworten auf die Fragen nach dem Genuss. Was ist Cannabis als Genussmittel? Hält es auf primitiver Stufe



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fest? Ist es sublimierungsfähig, also ein Rauschmittel, das sich unserer Kultur angeleichen kann?

Schließlich ist zu fragen, ob der Meinungsstreit über Cannabis nicht auf dem Missverständnis beruht, dass die Medizin über Legalität oder Illegalität entscheiden müsste. Das ist nicht ihre Aufgabe; die Medizin ist verantwortlich für die erhobenen Befunde und welches Ausmaß sie haben.

Vier umfangreiche Publikationen gewähren einen Überblick, wie er bisher nicht möglich war. Die erste ist eine im Auftrag des Bundesgesundheitsministeriums erstellte Expertise, die die Forschungsliteratur zu pharmakologischen und toxikologischen Wirkungen sowie zu psychosozialen Konsequenzen des Cannabis-Konsums untersucht. Die zweite Publikation, gefördert vom Bundesgesundheitsministerium, präsentiert die Ergebnisse einer empirischen Forschung, der eine umfangreiche Befragung von 1.458 cannabisfahrenden Personen zugrunde liegt. Die dritte Veröffentlichung ist dem Spezialproblem Cannabis im Straßenverkehr gewidmet. Es ist ein Sammelband, in dem grundlegende medizinische, psychologische und juristische Aspekte abgehandelt werden. Die vierte Publikation ist ein Handbuch zur Suchtmedizin.

Unterschiedliches Konsumverhalten

Cannabis wird in der Erwartung konsumiert, Verstimmungen zu beheben, Spannungen zu lindern, Genüsse des Hörens, Sehens, Fühlens und Spürens zu intensivieren oder eine andere Art des Denkens zu genießen. Zu unterscheiden ist der vernünftige Gebrauch, in dem das rechte Maß eingehalten wird, vom unvernünftigen Gebrauch, der bis zur akuten Intoxikation oder bis zum chronischen Exzess führt. Zu unterscheiden ist außerdem zwischen Anfängern, die ausprobieren, und erfahrenen Konsumenten, die präzise Erwartungen haben.

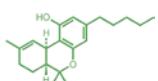
Anfänger empfinden Cannabis-Konsum als Abenteuer und Wagnis. Sie wissen nicht, worauf sie achten müssen. Sie kennen die feinen Zeichen des Rausches nicht und nehmen häufig zu viel. Der Konsum hat ihnen keine Lust gebracht, manchen sogar quälende Unlust. Dies erklärt, weshalb zwei Drittel derer, die Cannabis probieren, es bald wieder aufgeben.

Problematisch sind die gewohnheitsmäßigen Dauer-Konsumenten. Sie haben mit 23,5 Jahren nicht nur das niedrigste Durchschnittsalter, sondern auch am frühesten mit dem Konsum von Cannabis begonnen (Mittel: 15,9 Jahre). Sie konsumieren Cannabis bis zu viermal pro Tag, meist um sich vorübergehend aus Angst und Lebensnot befreit zu fühlen. Wer vor schädlichen Folgen des Cannabis-Konsums warnt, bezieht sich auf die Gruppe dieser exzessiven Konsumenten.

Erfahrene Cannabis-Konsumenten sorgen für hinreichend gute äußere Umstände und werden von den Wirkungen der Droge nicht überrascht. Wie es Alkohol-Genießer gibt, so gibt es Cannabis-Genießer. Die Forschungsergebnisse lassen es zu, auf einem vergleichbaren Niveau des Genusses den Cannabis-Rausch zu beschreiben.

Der Rausch ist nach vier Stunden verflogen

Cannabis wird in den allermeisten Fällen inhalirt und zielt unmittelbar auf den Genuss des Rausches, der sofort oder nach wenigen Minuten eintritt. Seine Tiefe kann daher in der Einnahmephase kontrolliert werden. Nach einer Stunde lässt die Wirkung nach, hält sich noch eine weitere Stunde und verschwindet dann allmählich. Nach drei, höchstens vier Stunden ist sie



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verflogen. Das macht den Cannabis-Rausch besser kontrollierbar und kalkulierbar als den Alkohol-Rausch.

Ein entscheidendes Charakteristikum des Cannabis-Rausches ist die veränderte Wahrnehmung. Äußere und innere Anforderungen sorgen bei Nüchternheit für gezielte Aufmerksamkeit. Unter dem Einfluss des Cannabis-Rausches intensiviert und erweitert sich die Wahrnehmung. Die gezielte Aufmerksamkeit lässt nach, sonst wenig Bemerktes kann in die Wahrnehmung einfließen.

Ungestörtes Eingehen auf sonst weniger zugängliche Realien, Fantasien und Stimmungen und auf freieres Denken wird durch zwei Eigenschaften des Cannabis-Rausches gefördert. Zum einen wird die Zeit anders erlebt. Sie erscheint gedeihnt. Bei angespannter, verantwortungsvoller Berufstätigkeit, bei Sorgen oder bei Kummer, aber auch um der puren Lust willen kann das Gefühl, vorübergehend auf einer Insel der Zeitlosigkeit zu leben, zu den besonderen Erwartungen gehören, die Cannabis zum Genuss machen. Zum anderen bleibt im Cannabis-Rausch das Bewusstsein des Rausches erhalten. Es ist jederzeit möglich, die vollständige Kontrolle über das eigene Verhalten herzustellen.

Folgen

Im Rahmen des gelegentlichen oder regelmäßigen Freizeitkonsums, selbst wenn er die Frequenz von zweimal pro drei Tagen erreicht, entsteht durch Cannabis keine Sucht und keine Abhängigkeit und ist mit gesundheitlichen Schäden nicht zu rechnen. Dieses Fazit der Wissenschaft steht fest.

Wird Cannabis exzessiv konsumiert, entstehen außer Toleranz-Erscheinungen keine Zeichen einer Sucht. Entsteht eine Abhängigkeit, kann sie leichter überwunden werden als beim Alkohol; denn die Entzugssymptome sind flüchtig und klingen innerhalb von Stunden, höchstens von Tagen ab. Es gibt keine somatischen Befunde von Belang.

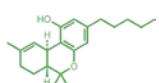
Die psychischen Befunde, die bisher in der medizinischen und dann auch in der juristischen Cannabis-Diskussion die Hauptrolle gespielt haben, sind widerlegt oder so sehr relativiert worden, dass sie als Gesundheitsgefahren, die der Gesetzgeber respektieren müsste, nicht in Frage kommen.

Löst Cannabis Psychosen aus? Neuere Studien fanden keine Hinweise für eine charakteristische Psychopathologie bei Cannabis-Konsumenten, die die Diagnose einer eigenständigen „Cannabis-Psychose“ rechtfertigen würden. Kann Cannabis-Konsum Stunden, Tage oder Monate später einen Flash-Back (Echo-Rausch) auslösen? Eine solche Kausalität lässt sich wissenschaftlich nicht belegen, spielt aber praktisch eine immense Rolle, wenn auch nicht mehr im Strafrecht und Strafgericht, so doch im Verwaltungsrecht und in Verwaltungsmaßnahmen.

Macht Cannabis abhängig? Nach den strengen Kriterien der medizinischen Definition der Abhängigkeit macht Cannabis-Konsum ohne den gleichzeitigen Konsum anderer Rauschmittel zwei Prozent der Konsumenten abhängig.

Jedoch spricht in diesen Fällen viel dafür, dass nicht Cannabis die Abhängigkeit bewirkt, sondern dass ungünstige Lebensumstände und -einstellungen dafür verantwortlich sind. In dieser Sichtweise erscheint die Abhängigkeit von Cannabis als ein Symptom, dessen Ursache nicht in einer substanzimmanen Gefahr, sondern in psychischen Problemen liegt.

Ist Cannabis eine Einstiegsdroge? Diesem Argument liegt ein Fehlschluss zugrunde. Aus dem Befund, dass Heroin-Süchtige zuvor Cannabis konsumiert



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hatten, war geschlossen worden, dass Cannabis den Weg bahnt. In der epidemiologischen und in der klinischen Forschung gibt es für diesen Umkehrschluss keinen Beleg.

Führt Cannabis zu einem amotivationalen Syndrom? Auch bei Störungsbildern, die durch Passivität und Leistungsverweigerung gekennzeichnet sind, stellt sich die Frage nach Ursache und Wirkung. In genügend kontrollierten Studien erscheint Cannabis nicht als Risikofaktor für Demotivationserscheinungen.

Verkehrssicherheit

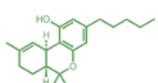
In der ersten Stunde nach Rauschbeginn sind deutliche Leistungsdefizite festzustellen. Es ist aber wenig wahrscheinlich, dass in dieser Zeit Auto gefahren wird. Die Erklärung liegt in der Kalkulierbarkeit des Rausches. Der Beginn ist bestimmbar. Will der Konsument den beabsichtigten Rausch auch auskosten, wird eine Teilnahme am Straßenverkehr während dieser Zeit eher unwahrscheinlich. Dies wird durch Befragung zur Fahrbereitschaft bestätigt. Schon in der zweiten Stunde nach Rauschbeginn bessern sich die Leistungsdefizite. In der vierten Stunde zeigen sich keine signifikanten Verschlechterungen mehr. Es gibt Resultate, die andeuten, dass häufige Cannabis-Konsumenten schneller zu ihrer Ausgangsleistung zurückfinden als seltene Konsumenten.

Die Verkehrsmedizin hat experimentell bestätigt, dass durch Cannabis bedingte Leistungsdefizite, wie sie für das Autofahren relevant sind, durch Kontrollfunktionen, durch Anstrengungen in anderen Bereichen, so gut ausgeglichen werden, dass das Unfallrisiko durch Cannabis-Einfluss verringert wird, also nicht zu-, sondern abnimmt.

In einer Feldstudie von 1994 fuhren 0,5 Prozent der Fahrer mit Alkohol ab 0,8 Promille BAK. Ebenso viele fuhren mit Cannabis-Konzentrationen, die auch von wochenlang zurückliegendem Konsum stammen konnten. Die Alkoholiker waren an 11,2 Prozent aller Unfälle mit schwerem Sach- oder Personenschaden beteiligt. Die Cannabis-Fahrer lagen nach Unfallhäufigkeit und -schwere unter oder höchstens im Normbereich. Die Praxis des Verwaltungsrechts jedoch, die für die Fahrerlaubnis zuständig ist, hat Cannabis, als wäre Cannabis mit LSD vergleichbar, den Halluzinogenen unterstellt und damit der Hypothese vom Flash-Back zu neuer Wirksamkeit verholfen. Zwar ist in der neuesten Auflage des Gutachters „Krankheit im Kraftverkehr“, dessen Leitlinien die Praxis bestimmen, der spezielle Hinweis auf die Flash-Back-Gefahren gestrichen worden, aber die Behauptung ist erhalten geblieben, indem von einem „besonderen Wirkungsverlauf“ die Rede ist, der „jederzeit unvorhersehbar und plötzlich“ die Leistungsfähigkeit beeinträchtigen kann. Mit dieser Behauptung kann die Eignung zum Führen eines Kraftfahrzeuges verneint werden, wenn eine regelmäßige Einnahme von Cannabis vorliegt.

Was ist regelmäßiger Konsum? Da Fahren unter Cannabis kein vermehrtes Unfallrisiko auslöst, macht es im Hinblick auf die Verkehrssicherheit keinen Sinn, eine Grenze zwischen gelegentlichem und regelmäßigm Konsum festzulegen.

Die Führung in der Cannabis-Verfolgung haben das Verwaltungsrecht und die Toxikologie übernommen. Die Verwaltung droht mit Führerschein-Entzug, die Toxikologie liefert die Nachweise. Das Zusammenspiel der Fächer ist inzwischen so weit gediehen, dass zu einer einjährigen Abstinenz, unwürdige



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Unterwerfung darin eingeschlossen, gezwungen werden kann, wer auffällig geworden war und nun den Führerschein wieder begehrt. Den Konsum-Gewohnheiten nach trifft es hauptsächlich Jugendliche und junge Erwachsene. Die Verbürgung der Verhältnismäßigkeit der Mittel wird verletzt und Glaubwürdigkeitspotenziale werden aufs Spiel gesetzt.

Da Cannabis-Einflüsse die Sicherheit des Straßenverkehrs nicht gefährden, gibt es eigentlich keinen Strafgrund, noch nicht einmal durch Fahren im akuten Rausch. Da aber die selektive Wahrnehmung, die für sicheres Autofahren unerlässlich ist, durch den Rausch geschwächt wird, lässt sich insoweit medizinisch ein Strafgrund vertreten.

Resümee

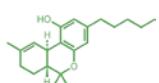
Die medizinischen Argumente, die zur Aufrechterhaltung des Cannabis-Verbotes verwendet worden sind, stammen aus Befunden schwerer Pathologie. Dabei ist allerdings zu beachten, dass Schäden, die Alkohol anrichtet, schwer, häufig und anhaltend sind; Schäden, die Cannabis anrichtet, sind leicht, selten und flüchtig. Aus medizinischer Sicht wird kein Schaden angerichtet, wenn Cannabis vom Verbot befreit wird. Das Cannabis-Verbot kann durch medizinische Argumente nicht gestützt werden.

Nelemans, J.K.E.S.A. (1997) "Therapeutic applications and biomedical effects of cannabinoids; a pharmacological basis." Nederlands Tijdschrift Voor Geneeskunde **141** (35): 1689-1693.

The Authors review the pharmacology, effects and side-effects of cannabinoids, notably Δ -9-tetrahydrocannabinol (THC), cannabidiol, nabilon or dronabinol, with reference to their positive effects on multiple sclerosis, bone marrow disorders, cerebrovascular accident, head injuries, Parkinson's disease, Huntington's chorea, Tourette's syndrome, epilepsy, migraine, trigeminal neuralgia, arthritis, post-operative, menstrual and phantom pain, glaucoma, nausea and vomiting after chemotherapy and loss of appetite in AIDS and cancer patients, in some cases compared to conventional therapy with metoclopramide, prochlorperazine, haloperidol, ondansetron, diltiazem or verapamil. Side-effects include exacerbation of respiratory disorders or schizophrenia and possible teratogenic effects.

Neuhaus, O., B.C. Kieseier, A. Klimke, W. Gaebel, R. Hohlfeld and H.P. Hartung (2004) "[Cannabinoids in multiple sclerosis. Opportunity or hazard?]." Nervenarzt **75** (10): 1022-1026.

Based on patient reports, animal data, and in vitro experiments, evidence has emerged indicating a positive effect of cannabinoids as symptomatic treatment of spasticity and pain in multiple sclerosis. The recently published CAMS study was the first multicenter, randomized, placebo-controlled phase III trial to examine the efficacy of cannabinoids on symptoms related to MS. There was no treatment effect of cannabinoids on the primary outcome measure, a difference in the reduction of spasticity as assessed by the so-called Ashworth score. In contrast, significant effects on patient-reported spasticity and pain were documented. A major problem of the study was a high degree of patient unmasking in the active treatment group. In this review, the results of the CAMS study are discussed in the context of previous trials, the putative mechanism of action of cannabinoids and their adverse event profile.



Cannabis, Dronabinol und die Behandlung schwerer Erkrankungen

Nickolaus, B. (2002) "Cannabis verhindert Schmerz und Spastik" Deutsches Ärzteblatt **99** (43): A 2880.

Etwa acht Millionen Menschen in Deutschland gelten als chronisch schmerzkrank; zwei Millionen ist mit den bekannten Therapieregimen nicht ausreichend zu helfen. Dazu zählen Patienten mit fortgeschrittenen onkologischen Erkrankungen, multipler Sklerose (MS) und Aids. Die schmerzlindernde Wirkung von Cannabinoiden und Opioiden, zum Beispiel Dronabinol, kann in diesen Fällen eine therapeutische Perspektive bieten.

Dronabinol ist der internationale Name für Δ -9-trans-Tetrahydrocannabinol (Δ -9-THC), dem medizinisch wirksamen Bestandteil der Hanfpflanze. Dronabinol wirkt antiphlogistisch, analgetisch, anxiolytisch, antiemetisch, muskelrelaxierend, sedierend und appetitanregend. Anders als Opiate oder Kokain sind das Suchtpotenzial und die Gesamttoxizität sehr gering.

Prof. Michael Popp (Bionorica) verwies darauf, dass Dronabinol in den USA seit Jahren als Fertigarzneimittel zur Verfügung stehe, das aus Kostengründen in Deutschland selten eingesetzt werde. Mit Dronabinol als Rezeptur-Arzneimittel wolle man hierzulande ein kostengünstiges Mittel anbieten, das Apotheker nach Vorlage des gelben Btm-Rezepts von Δ -9 Pharma als Herstellungs-Set beziehen können.

Die analgetische Wirkung beim Akutschmerz wurde am Tiermodell geprüft. Hier zeigte sich beim – von vielen Schmerzmitteln schlecht beeinflussbaren – neuropathischen Schmerz eine besondere Wirkung. Bestimmte Interaktionen zwischen Cannabinoiden und Opioiden sind belegbar, so erfolgt zum Beispiel eine Vermittlung der Wirkungsweise von Dronabinol zum Teil über Opioid-Rezeptoren.

Ernst hielt daher die Komedikation von Opioiden und niedrig dosierten Cannabinoiden für eine durchaus sinnvolle Strategie.

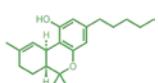
Auch antispastische Wirkungen bei MS oder Rückenmarkverletzungen und bei opioid-resistenten zentralen Schmerzen sind belegbar, ebenso wie Palliativeffekte, wie zum Beispiel Stimmungsaufhellung, antiemetische Wirkung oder Appetitanregung.

An unerwünschten Wirkungen zeigten sich Tachykardie und orthostatische Hypotonie sowie eine erhöhte Rate an Ischämien, sodass die Medikation bei Patienten mit koronarer Herzkrankung kontraindiziert ist.

Dr. Dietrich Jungck vom Schmerzzentrum Hamburg betonte, die Dronabinolbehandlung sei keine Monotherapie, sondern immer ein (additiver) Baustein im Gesamtgefüge der Behandlung chronischer, multimorbider Schmerzkranker. Schmerzlinderung und Erhöhung der Lebensqualität durch das Verdrängen der Schmerzen aus dem Wahrnehmungszentrum und Besetzung dieses Zentrums mit anderen Lebensinhalten seien anzustreben. Eine totale Schmerzbeseitigung zu erhoffen sei in vielen Fällen unrealistisch und sollte nicht zum erklärten Ziel der Behandlung gemacht werden.

Vielfältige Einsatzgebiete

Die Einsatzgebiete von Dronabinol sind vielfältig: Von Spastiken bei MS oder Schlaganfall über neuropathische Schmerzen bei Polyneuropathie, Rückenmarktrauma, Gürtelrose oder bei Phantomschmerzen, Arthrose- oder Osteoporose-Schmerzen oder Fibrose, zum Beispiel nach Radiotherapie. Die Dosierung sollte nach Aussage von Jungck einschleichend mit 2,5 mg im acht- bis zwölfstündigen Intervall einsetzen und vorsichtig bis zur erwünschten Wirkung erhöht werden.



Cannabis, Dronabinol und die Behandlung schwerer Erkrankungen

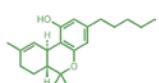
Dr. Claude Vaney (Montana/ Schweiz) berichtete über die Ergebnisse der ersten schweizerischen, im Doppelblindversuch durchgeföhrten, placebokontrollierten Cannabis-Studie, in die 57 Patienten mit nicht befriedigend therapierbaren schmerhaften Muskelspasmen und nachweisbaren Entzündungsherden eingeschlossen waren. Die Studie ergab, dass erste Effekte einer Abnahme der Spastik bei einer Dosierung von circa 7,5 mg einsetzen. Die individuelle Dosierung von THC-Extrakt lag zwischen 5 und 30 mg/die. Bei neun Patienten kam es zu minimalen psychoaktiven Effekten, bei acht trat eine Besserung des Tremors auf. Vaney wies auf eine laufende Studie in Großbritannien mit 660 Teilnehmern hin, deren Ergebnis mit Interesse erwartet wird.

Notcutt, W.G. (2012) "A questionnaire survey of patients and carers of patients prescribed Sativex as an unlicensed medicine." Primary Health Care Research & Development 2012 Jul 12. 1-8:

Aim To identify the areas of daily function most affected by the introduction of Sativex, a cannabis-based medicine, and the impact on caregivers and people with multiple sclerosis (MS). Background: Cannabinoid medicines have recently become available on prescription in several parts of the world, principally for the treatment of spasticity in people with MS. Their efficacy and safety have been demonstrated in the setting of randomised controlled clinical trials. Results of such studies may not always reflect the wider effectiveness that a medicine shows when used in clinical practice. Methods: A short questionnaire survey consisting mostly of multiple-choice questions, along with some free-text questions aimed at the patient and primary caregiver (ie, partner, mother, nurse or outside carer). The questionnaire was developed in consultation with a patient representative organisation, field tested, ethics approval gained, then distributed to prescribers in the United Kingdom, with the request that they in turn forward it to any patients who had received repeat prescriptions for Sativex within the previous 16 weeks. Patients were seen in both a primary care (general practice) and a secondary care (hospital) setting. There was no control group in this study. Most patients had MS, and the primary reasons for using Sativex were spasticity and pain. Findings The response rate was 57%, with 124 questionnaires returned. The majority of respondents and their caregivers reported improvements across a range of daily functional activities, alongside a reduction in the use of concomitant anti-spasticity medication and in the use of other healthcare resources.

Notcutt, W., R. Langford, P. Davies, S. Ratcliffe, and R. Potts (2012) "A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex® (nabiximols)". Multiple Sclerosis 18 (2): 219-228.

Background: Open-label studies are not ideal for providing robust evidence for long-term maintenance of efficacy of medicines, especially where medicines provide symptom relief and where long-term use of a placebo may be problematic and not ethical. Objective: To evaluate the maintenance of efficacy of Sativex in subjects who have gained long-term symptomatic relief of spasticity in multiple sclerosis (MS), and to assess the impact of sudden medicine withdrawal. Methods: An enriched enrolment randomized withdrawal study design was used. Eligible subjects with ongoing benefit from Sativex for



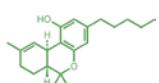
at least 12 weeks entered this 5-week placebo-controlled, parallel-group, randomized withdrawal study. Each subjects' previous effective and tolerated dose was continued. Results: A total of 18 subjects per group were enrolled. Demographics showed a mean duration of MS of 16.4 years, spasticity 12.7 years, mean duration of Sativex use of 3.6 years (median 3.4 years) and a mean daily dose of 8.25 sprays. Primary outcome of time to treatment failure was significantly in favour of Sativex ($p = 0.013$). Secondary endpoints showed significant changes in the Carer and Subject's Global Impression of Change scales in favour of Sativex. Conclusions: Maintenance of Sativex efficacy in long-term symptomatic improvement of spasticity to a group of subjects with MS has been confirmed using this study design.

Notcutt, W., M. Price, R. Miller, S. Newport, C. Phillips, S. Simmons and C. Sansom (2004) "Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies." *Anaesthesia* **59** (5): 440-452.

Three Cannabis Based Medicinal Extracts (CBMEs) for sublingual use became available in 2000. A total of 34 'N of 1' studies were undertaken using this novel therapy for patients with chronic, mainly neuropathic, pain and associated symptoms to explore efficacy, tolerability, safety and dosages. Three CBMEs (Δ -9 Tetrahydrocannabinol (THC), Cannabidiol (CBD) and a 1:1 mixture of them both) were given over a 12-week period. After an initial open-label period, the CBMEs were used in a randomised, double-blind, placebo controlled, crossover trial. Extracts which contained THC proved most effective in symptom control. Regimens for the use of the sublingual spray emerged and a wide range of dosing requirements was observed. Side-effects were common, reflecting a learning curve for both patient and study team. These were generally acceptable and little different to those seen when other psycho-active agents are used for chronic pain. These initial experiences with CBME open the way to more detailed and extensive studies.

Novotna, A., J. Mares, S. Ratcliffe, I. Novakova, M. Vachova, O. Zapletalova, C. Gasperini, C. Pozzilli, L. Cefaro, G. Comi, P. Rossi, Z. Ambler, Z. Stelmasiak, A. Erdmann, X. Montalban, A. Klimek, and P. Davies (2011) "A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex[®]), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis." *European Journal of Neurology* **18** (9): 1122-1131.

Background: Spasticity is a disabling complication of multiple sclerosis, affecting many patients with the condition. We report the first Phase 3 placebo-controlled study of an oral antispasticity agent to use an enriched study design. Methods: A 19-week follow-up, multicentre, double-blind, randomized, placebo-controlled, parallel-group study in subjects with multiple sclerosis spasticity not fully relieved with current antispasticity therapy. Subjects were treated with nabiximols, as add-on therapy, in a single-blind manner for 4 weeks, after which those achieving an improvement in spasticity of $>/=20\%$ progressed to a 12-week randomized, placebo-controlled phase. Results: Of the 572 subjects enrolled, 272 achieved a $>/=20\%$ improvement after 4 weeks of single-blind treatment, and 241 were randomized. The primary end-point was the difference between treatments in the mean spasticity Numeric Rating Scale (NRS) in the randomized, controlled phase of the study. Intention-to-treat (ITT) analysis showed a highly significant



difference in favour of nabiximols ($P = 0.0002$). Secondary end-points of responder analysis, Spasm Frequency Score, Sleep Disturbance NRS Patient, Carer and Clinician Global Impression of Change were all significant in favour of nabiximols. Conclusions: The enriched study design provides a method of determining the efficacy and safety of nabiximols in a way that more closely reflects proposed clinical practice, by limiting exposure to those patients who are likely to benefit from it. Hence, the difference between active and placebo should be a reflection of efficacy and safety in the population intended for treatment.

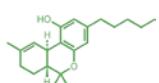
Nurmikko, T.J., M.G. Serpell, B. Hoggart, P.J. Toomey, B.J. Morlion and D. Haines (2007) "Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial." *Pain* **133** (1-3): 210-220.

Cannabinoids are known to have analgesic properties. We evaluated the effect of oro-mucosal sativex, (THC: CBD), an endocannabinoid system modulator, on pain and allodynia, in 125 patients with neuropathic pain of peripheral origin in a five-week, randomised, double-blind, placebo-controlled, parallel design trial. Patients remained on their existing stable analgesia. A self-titrating regimen was used to optimise drug administration. Sixty-three patients were randomised to receive sativex and 62 placebo. The mean reduction in pain intensity scores (primary outcome measure) was greater in patients receiving sativex than placebo (mean adjusted scores -1.48 points vs. -0.52 points on a 0-10 Numerical Rating Scale ($p=0.004$; 95% CI: -1.59, -0.32). Improvements in Neuropathic Pain Scale composite score ($p=0.007$), sleep NRS ($p=0.001$), dynamic allodynia ($p=0.042$), punctate allodynia ($p=0.021$), Pain Disability Index ($p=0.003$) and Patient's Global Impression of Change ($p<0.001$) were similarly greater on sativex vs. placebo. Sedative and gastrointestinal side effects were reported more commonly by patients on active medication. Of all participants, 18% on sativex and 3% on placebo withdrew during the study. An open-label extension study showed that the initial pain relief was maintained without dose escalation or toxicity for 52 weeks.

Nurmikko, T.J., M.G. Serpell, B. Hoggart, P.J. Toomey, B.J. Morlion, D. Haines and N. Sarantis (2006) "A Randomised Controlled Study of Sativex, a Cannabis Based Medicine, in Neuropathic Pain Characterized by Allodynia" *European Journal of Pain* **10** (Suppl. 1): S125.

Oreja-Guevara, C. (2012) "Clinical efficacy and effectiveness of Sativex, a combined cannabinoid medicine, in multiple sclerosis-related spasticity:" *Expert Review of Neurotherapeutics* **12** (4, Suppl.): 3-8.

Multiple sclerosis (MS) is associated with a wide range of disease symptoms and amongst these, spasticity is one of the most disabling and has the greatest impact on patient well-being and quality of life. Until now, available drug therapies for spasticity appear to have limited benefit and are often associated with poor tolerability. In a recent Spanish survey it was noted that multidrug therapy and a low control rate were common features for a large proportion of patients with MS-related spasticity, suggesting that currently available monotherapies lack significant activity. Sativex is a 1:1 mixture of Δ -9-tetrahydrocannabinol and cannabidiol derived from Cannabis sativa



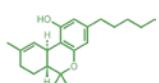
chemovars, which is available as an oromucosal spray. Clinical experience with Sativex in patients with MS-related spasticity is steadily accumulating. Results from randomized, controlled trials have reported a reduction in the severity of symptoms associated with spasticity, leading to a better ability to perform daily activities and an improved perception of patients and their carers regarding functional status. These are highly encouraging findings that provide some much needed optimism for the treatment of this disabling and often painful symptom of MS.

Otto, M., F.W. Bach, T.S. Jensen, and S.H. Sindrup, (2007) "Health-related quality of life and its predictive role for analgesic effect in patients with painful polyneuropathy." *European Journal of Pain* **11** (5): 572-578.

Painful polyneuropathy is a common neuropathic pain condition. The present study describes health-related quality of life (HRQL) in a sample of patients with painful polyneuropathy of different origin and the possible predictive role of HRQL for analgesic effect. Ninety-three patients with a diagnosis of painful polyneuropathy were included in the analysis. Data were obtained from three randomised, placebo-controlled cross-over studies testing the effect of different drugs on polyneuropathic pain (St. John's wort, venlafaxine/imipramine and valproic acid). Patients completed a HRQL questionnaire (SF-36) after a drug-free baseline period and at the end of each treatment period. At baseline, all eight SF-36 scores were lower than in the normal population. No significant differences were found between SF-36 scales during placebo and treatment with valproic acid and St. John's wort. Those two drugs had not shown a pain relieving effect in former analysis. The SF-36 scale of bodily pain (BP) was improved by venlafaxine treatment ($p = 0.023$). General health (GH) and vitality (VT) were improved under treatment with imipramine (GH: $p = 0.006$, VT: $p = 0.015$). In a multivariate logistic regression analysis, baseline SF-36 scores predicted subsequent response to pharmacological treatment. Results show an impaired HRQL in painful polyneuropathy and suggest that HRQL may predict response to analgesic treatment.

Overney, L.S., S. Arzy and O. Blanke (2009) "Deficient mental own-body imagery in a neurological patient with out-of-body experiences due to cannabis use." *Cortex* **45** (2): 228-235.

In the present work, we report repeated out-of-body experiences (OBEs) in a patient with tetraplegia and severe somatosensory loss due to multiple sclerosis and predominant involvement of the cervical spinal cord. OBEs were experienced on a daily basis and induced by cannabis treatment that was started for severe spasticity with painful cramps and cloni. In order to investigate the link between OBEs and mental own-body imagery, the patient was asked to imagine himself in the position and visual perspective that is generally reported during OBEs, using front- and back-facing schematic human stimuli. Performance was measured before and after cannabis consumption. First, our data reveal that the patient was less accurate for back-facing than front-facing stimuli. This was found before and after cannabis consumption and is the opposite pattern to what is generally observed in healthy participants and in our control subjects (who did not use cannabis). We refer to this as lesion effect and argue that this relative facilitation for



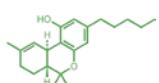
stimuli reflecting the position and visual perspective that is generally reported during OBEs might be due to recurrent and spontaneous own-body transformations during the patient's frequent OBEs. Secondly, we found a cannabis effect, namely a performance improvement in the back-facing condition while performance in the front-facing condition remained unchanged, after cannabis administration. We argue that cannabis administration may interfere with own-body imagery when reflecting the actual body position and only when associated with brain damage. Based on these data we propose an extended neurological model for own-body illusions including multisensory and sensorimotor mechanisms, cannabis consumption, and cortical and subcortical processing.

Page, S.A., M.J. Verhoef, R.A. Stebbins, L.M. Metz and J.C. Levy (2003) "Cannabis use as described by people with multiple sclerosis." Canadian Journal of Neurological Sciences **30** (3): 201-205.

Background: Multiple sclerosis (MS) is one of the most common neurological diseases affecting young adults. The prevalence of MS in Alberta has been described as among the highest reported in the world, estimated at 217 per 100,000. Numerous anecdotal reports, and a few small empirical investigations have suggested that cannabis use may relieve the symptom experience of those with MS. The present study was undertaken to describe cannabis use by this patient group. Information on peoples' beliefs, practices and experiences related to use were investigated. **Methods:** A questionnaire was mailed to a sample of 780 adults with MS in southern Alberta, Canada. **RESULTS:** Completed questionnaires were returned by 420/673 eligible subjects (response rate 62%). Mean sample age was 48 years and 75% were women. Respondents ranged from mildly to severely impaired. The majority of respondents (96%) was aware cannabis was potentially therapeutically useful for MS and most (72%) supported legalization for medicinal purposes. Forty-three percent had tried cannabis at some point in their lives, 16% for medicinal purposes. Symptoms reported to be ameliorated included anxiety/depression, spasticity and chronic pain. Reasons given for not trying cannabis were the fact that it is an illegal substance, concern about side effects and lack of knowledge on how to obtain it. **Conclusions:** Subjective improvements in symptom experience were reported by the majority of people with MS who currently use cannabis. Further evaluation of this substance is warranted.

Page, S.A. and M.J. Verhoef (2006) "Medicinal marijuana use: experiences of people with multiple sclerosis." Canadian Family Physician **52**: 64-65.

Objective: To describe medical marijuana use from the perspectives of patients with multiple sclerosis. **Design:** A qualitative, descriptive design was used. Participants discussed their medicinal marijuana use in one-to-one, semistructured interviews. **Setting:** Interviews were conducted at a time and place convenient to participants. **Participants:** Six men and eight women with multiple sclerosis participated. **Method:** Potential participants identified themselves to the researcher after receiving an invitation in a mailed survey. Eligibility was confirmed, and purposive sampling was used to recruit subjects. A range of issues emerged from the interviews. Interviews and data analysis continued until saturation occurred. **Main Findings:** Descriptions fell into three broad areas: patterns of use, legal or social concerns, and perceived effects.



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Consumption patterns ranged from very infrequent to very regular and were influenced by symptoms, social factors, and supply. Legal concerns expressed by most respondents were negligible. Social concerns centred on to whom use was revealed. The perceived benefits of use were consistent with previous reports in the literature: reduction in pain, spasms, tremors, nausea, numbness, sleep problems, bladder and bowel problems, and fatigue and improved mood, ability to eat and drink, ability to write, and sexual functioning. Adverse effects included problems with cognition, balance, and fatigue and the feeling of being high. Although participants described risks associated with using marijuana, the benefits they derived made the risks acceptable.

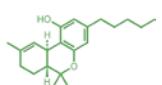
Conclusion: Further research is needed to clarify the safety and efficacy of marijuana use by patients with multiple sclerosis. If evidence of benefit is seen, medicinal marijuana should be made available to patients who could benefit from it. Until then, discussing medicinal marijuana use with patients will be awkward for health professionals.

Perez, J. (2006) "Combined cannabinoid therapy via an oromucosal spray." *Drugs Today (Barcelona)* **42** (8): 495-503.

Extensive basic science research has identified the potential therapeutic benefits of active compounds extracted from the Cannabis sativa L. plant (the cannabinoids). It is recognized that a significant proportion of patients suffering with the debilitating symptoms of pain and spasticity in multiple sclerosis or other conditions smoke cannabis despite the legal implications and stigma associated with this controlled substance. GW Pharmaceuticals have developed Sativex (GW- 1,000-02), a combined cannabinoid medicine that delivers and maintains therapeutic levels of two principal cannabinoids, Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), via an oromucosal pump spray, that aims to minimize psychotropic side effects. Sativex has proved to be well tolerated and successfully self-administered and self-titrated in both healthy volunteers and patient cohorts. Clinical assessment of this combined cannabinoid medicine has demonstrated efficacy in patients with intractable pain (chronic neuropathic pain, pain due to brachial plexus nerve injury, allodynic peripheral neuropathic pain and advanced cancer pain), rheumatoid arthritis and multiple sclerosis (bladder problems, spasticity and central pain), with no significant intoxication-like symptoms, tolerance or withdrawal syndrome.

Perez, J. and M.V. Ribera (2008) "Managing neuropathic pain with Sativex: a review of its pros and cons." *Expert Opinion on Pharmacotherapy* **9** (7): 1189-1195.

Background: Although not new, the use of cannabis-based drugs for treating chronic pain patients is becoming a hot topic for pain physicians and other specialists due to the constant flow of medical information regarding this pharmacological therapy. Its indication is becoming more clearly targeted towards pain syndromes arising from nerve damage. The number of cases reported, clinical trials and reviews published on this subject exponentially increase year by year. A possible explanation for this may be the fact that neuropathic pain is a highly disabling symptom and, consequently, there is a demand from patients and health professionals for a definitive remedy to treat this pain. Methods: Parallel to the number of articles on the effectiveness, recent articles describing the tolerability of cannabis-based drugs along with a



more accurate characterisation of its side-effect profile and/or lack of effectiveness have been published, and they are placing a cautious stop for a more precise prescription of these medications. Conclusion: This article reviews the current knowledge on the use of Sativex for treating neuropathic pains of different origin, and analyses the balance between the advantages and drawbacks of this therapy.

Perras, C. (2005) "Sativex for the management of multiple sclerosis symptoms." Issues in Emerging Health Technologies **72**: 1-4.

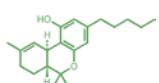
Sativex® is a cannabis-based pharmaceutical product containing Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio, delivered in an oromucosal (mouth) spray. It has been approved as adjunctive treatment for neuropathic pain in patients with multiple sclerosis (MS). It is being investigated for the management of other MS symptoms, such as spasticity. THC:CBD spray is regulated as a narcotic. Five randomized controlled trials (RCTs) compared the benefits and harms of THC:CBD spray with placebo. A total of 368 patients with various neurological conditions (including MS) were recruited. In some trials, THC:CBD spray significantly reduced neuropathic pain, spasticity, muscle spasms and sleep disturbances. The most common adverse events (AEs) reported in trials were dizziness, sleepiness, fatigue, feeling of intoxication and a bad taste. Long-term safety and the potential for dependence, abuse, misuse and diversion are unknown.

Pertwee, R.G. (1997) "Cannabis and cannabinoids: Pharmacology and rationale for clinical use." Pharmaceutical Sciences **3** (11): 539-545.

There are two types of cannabinoid receptor, CB sub(1) and CB sub(2), both coupled to G(i/o) proteins. CB sub(1) receptors are present on certain central and peripheral neurons whereas CB sub(2) receptors have been found mainly in immune cells. Endogenous agonists for cannabinoid receptors have also been identified. These recent discoveries have prompted the development of selective CB sub(1) and CB sub(2) receptor ligands. They have also stimulated renewed interest in the clinical potential of these ligands. Two cannabinoids, Δ-9-tetrahydrocannabinol and nabilone, are already prescribed in the UK or USA as anti-emetics or to stimulate appetite. Other possible uses for cannabinoid receptor agonists include pain relief, suppression of muscle spasticity (and pain) associated with multiple sclerosis or spinal injury, management of glaucoma, bronchial asthma and inflammatory disorders, and modulation of immune function. Cannabinoid receptor antagonists may also have clinical applications, for example in reducing memory deficits associated with ageing or neurological diseases. It is important that further preclinical and clinical investigations are carried out so that the therapeutic potential of cannabinoids can be exploited to the full.

Pertwee, R.G. (1997) "The therapeutic potential of cannabis and cannabinoids for multiple sclerosis and spinal injury." Journal of the International Hemp Association **4** (1): 4-8.

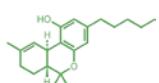
There is growing preclinical, anecdotal and clinical evidence that cannabis (*Cannabis sativa*) and individual cannabinoids are effective in suppressing some of the more troublesome symptoms of multiple sclerosis (MS) or the collateral effects of spinal injury, particularly spasticity and pain. The



preclinical evidence suggests that activation of central cannabinoid CB1 receptors provokes marked changes in motor function and reduces pain perception. It has also been found in experiments with rats and guineapigs that cannabinoids can decrease the intensity of behavioural and histological signs of experimental autoimmune encephalomyelitis, a putative animal model of MS. The anecdotal evidence is to be found in newspaper reports and also in response to a recent questionnaire by 112 MS patients who self-medicate with cannabis. The clinical evidence comes from 7 clinical trials, albeit each with rather small numbers of patients. These indicate that cannabis, Δ-9-tetrahydrocannabinol or nabilone can reduce spasticity, pain, tremor and nocturia in patients with MS or spinal injury. Taken together, the available data provide sufficient grounds for conducting further clinical trials that will test the efficacy of cannabis or individual cannabinoids against the signs and symptoms of MS or spinal injury, both objectively and conclusively.

Pertwee, R.G. (1999) "[Cannabis and Cannabinoids: Pharmacology and rationale for clinical use]." *Forschende Komplementärmedizin* **6** (Suppl. 3): 12-15.

It is now known that there are at least two types of cannabinoid receptors. These are CB sub(1) receptors, present mainly on central and peripheral neurones, and CB sub(2) receptors, present mainly on immune cells, Endogenous cannabinoid receptor agonists ('endocannabinoids') have also been identified. The discovery of this 'endogenous cannabinoid system' has led to the development of selective CB sub(1) and CB sub(2) receptor ligands and fuelled renewed interest in the clinical potential of cannabinoids. Two cannabinoid CB sub(1) receptor agonists are already used clinically, as antiemetics or as appetite stimulants. These are Δ-9-tetrahydrocannabinol (THC) and nabilone. Other possible uses for CB sub(1) receptor agonists include the suppression of muscle spasm/ spasticity associated with multiple sclerosis or spinal cord injury, the relief of chronic pain and the management of glaucoma and bronchial asthma. CB sub(1) receptor antagonists may also have clinical applications, e. g. as appetite suppressants and in the management of schizophrenia or disorders of cognition and memory. So too may CB sub(2) receptor ligands and drugs that activate cannabinoid receptors indirectly by augmenting endocannabinoid levels at cannabinoid receptors. When taken orally, THC seems to undergo variable absorption and to have a narrow 'therapeutic window' (dose range in which it is effective without producing significant unwanted effects). This makes it difficult to predict an oral dose that will be both effective and tolerable to a patient and indicates a need for better cannabinoid formulations and modes of administration. For the therapeutic potential of cannabis or CB sub (1) receptor agonists to be fully exploited, it will be important to establish objectively and conclusively (a) whether these agents have efficacy against selected symptoms that is of clinical significance and, if so, whether the benefits outweigh the risks, (b) whether cannabis has therapeutic advantages over individual cannabinoids, (c) whether there is a need for additional drug treatments to manage any of the disorders against which cannabinoids are effective, and (d) whether it will be possible to develop drugs that have reduced psychotropic activity and yet retain the ability to act through CB sub(1) receptors to produce their sought-after effects.



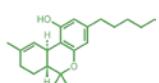
Cannabis, Dronabinol und die Behandlung schwerer Erkrankungen

Pertwee, R.G. (1999) "Pharmacology of cannabinoid receptor ligands." Current Medicinal Chemistry **6** (8): 635-664.

Mammalian tissues contain at least two types of cannabinoid receptor, CB1 and CB2, both coupled to G proteins. CB1 receptors are expressed mainly by neurones of the central and peripheral nervous system whereas CB2 receptors occur in certain non-neuronal tissues, particularly in immune cells. The existence of endogenous ligands for cannabinoid receptors has also been demonstrated. The discovery of this endogenous cannabinoid system has been paralleled by a renewed interest in possible therapeutic applications of cannabinoids, for example in the management of pain and in the suppression of muscle spasticity/spasm associated with multiple sclerosis or spinal cord injury. It has also prompted the development of a range of novel cannabinoid receptor ligands, including several that show marked selectivity for CB1 or CB2 receptors. This review summarizes current knowledge about the in vitro pharmacological properties of important CB1 and CB2 receptor ligands. Particular attention is paid to the binding properties of these ligands, to the efficacies of cannabinoid receptor agonists, as determined using cyclic AMP or [35S]GTPgammaS binding assays, and to selected examples of how these pharmacological properties can be influenced by chemical structure. The in vitro pharmacological properties of ligands that can potently and selectively oppose the actions of CB1 or CB2 receptor agonists are also described. When administered by themselves, some of these ligands produce effects in certain tissue preparations that are opposite in direction to those produced by cannabinoid receptor agonists and the possibility that the ligands producing such inverse cannabimimetic effects are inverse agonists rather than pure antagonists is discussed.

Pertwee, R.G. (1999) "Prescribing cannabinoids for multiple sclerosis: Current issues." CNS Drugs **11** (5): 327-334.

Anecdotal evidence and preclinical and clinical data indicate that cannabis and individual cannabinoids can suppress muscle spasticity/ spasm and pain associated with multiple sclerosis (MS). Anecdotal data come from the responses to a questionnaire by 112 patients with MS who self-medicated with cannabis. The preclinical data come from animal experiments showing that cannabinoid receptor agonists are antinociceptive and can depress motor function, reduce the severity of primary generalised dystonia, and decrease inflammation and the intensity of behavioural signs of experimental autoimmune encephalomyelitis. The clinical data derive from 7 clinical trials, albeit involving small numbers of patients, which indicate that cannabis itself, the cannabinoid Δ-9-tetrahydrocannabinol (Δ-9-THC) and the synthetic analogue of Δ-9-THC nabilone can reduce the intensity of several symptoms in patients with MS or spinal cord injury, including spasticity, pain, tremor and nocturia. These data provide sufficient evidence to warrant a large scale clinical trial to attempt to provide an objective and conclusive answer to the questions of whether cannabis and cannabinoids are effective in MS and, if they are, whether these effects are achievable at dose levels that do not provoke unacceptable adverse effects. Likely drug candidates for a clinical trial include Δ-9-THC and nabilone, both of which are already licensed medicines. When taken orally, Δ-9-THC seems to undergo variable absorption and to have a narrow 'therapeutic window'. This makes it difficult to predict an



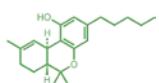
oral dose that will be both effective and tolerable, so prompting a need for better cannabinoid formulations, cannabinoid vehicles and modes of administration. There is also a need to establish whether cannabis has any therapeutic advantages over individual cannabinoids such as Δ-9-THC and, if so, to investigate the basis for this. In addition, it will be worth seeking out a way of separating the therapeutic properties of cannabinoids from their unwanted effects, particularly their psychotropic effects, and several strategies for achieving this goal are described. To succeed, any clinical study with cannabinoids will require sufficient funding, the use of adequate outcome measures, and the committed involvement of scientists and physicians who have appropriate cannabinoid and clinical expertise.

Pertwee, R.G. and R.A. Ross (2002) "Cannabinoid receptors and their ligands." Prostaglandins, Leukotrienes, and Essential Fatty Acids **66** (2-3): 101-121.

There are at least two types of cannabinoid receptors, CB(1) and CB(2), both coupled to G proteins. CB(1) receptors exist primarily on central and peripheral neurons, one of their functions being to modulate neurotransmitter release. CB(2) receptors are present mainly on immune cells. Their roles are proving more difficult to establish but seem to include the modulation of cytokine release. Endogenous agonists for cannabinoid receptors (endocannabinoids) have also been discovered, the most important being arachidonoyl ethanamide (anandamide), 2-arachidonoyl glycerol and 2-arachidonoyl glyceryl ether. Other endocannabinoids and cannabinoid receptor types may also exist. Although anandamide can act through CB(1) and CB(2) receptors, it is also a vanilloid receptor agonist and some of its metabolites may possess yet other important modes of action. The discovery of the system of cannabinoid receptors and endocannabinoids that constitutes the 'endocannabinoid system' has prompted the development of CB(1)- and CB(2)-selective agonists and antagonists/inverse agonists. CB(1)/CB(2) agonists are already used clinically, as anti-emetics or to stimulate appetite. Potential therapeutic uses of cannabinoid receptor agonists include the management of multiple sclerosis/spinal cord injury, pain, inflammatory disorders, glaucoma, bronchial asthma, vasodilation that accompanies advanced cirrhosis, and cancer. Following their release onto cannabinoid receptors, endocannabinoids are removed from the extracellular space by membrane transport and then degraded by intracellular enzymic hydrolysis. Inhibitors of both these processes have been developed. Such inhibitors have therapeutic potential as animal data suggest that released endocannabinoids mediate reductions both in inflammatory pain and in the spasticity and tremor of multiple sclerosis. So too have CB(1) receptor antagonists, for example for the suppression of appetite and the management of cognitive dysfunction or schizophrenia.

Pertwee, R.G. (2002) "Cannabinoids and multiple sclerosis." Pharmacology and Therapeutics **95** (2): 165.

There is a growing amount of evidence to suggest that cannabis and individual cannabinoids may be effective in suppressing certain symptoms of multiple sclerosis and spinal cord injury, including spasticity and pain. Anecdotal evidence is to be found in newspaper reports and also in responses to questionnaires. Clinical evidence comes from trials, albeit with rather small



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numbers of patients. These trials have shown that cannabis, Δ-9-tetrahydrocannabinol, and nabilone can produce objective and/or subjective relief from spasticity, pain, tremor, and nocturia in patients with multiple sclerosis (8 trials) or spinal cord injury (1 trial). The clinical evidence is supported by results from experiments with animal models of multiple sclerosis. Some of these experiments, performed with mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), have provided strong evidence that cannabinoid-induced reductions in tremor and spasticity are mediated by cannabinoid receptors, both CB(1) and CB(2). Endocannabinoid concentrations are elevated in the brains and spinal cords of CREAE mice with spasticity, and in line with this observation, spasticity exhibited by CREAE mice can be ameliorated by inhibitors of endocannabinoid membrane transport or enzymic hydrolysis. Research is now needed to establish whether increased endocannabinoid production occurs in multiple sclerosis. Future research should also be directed at obtaining more conclusive evidence about the efficacy of cannabis or individual cannabinoids against the signs and symptoms of these disorders, at devising better modes of administration for cannabinoids and at exploring strategies that maximize separation between the sought-after therapeutic effects and the unwanted effects of these drugs.

Petro, D.J. (1981) "Marijuana as a therapeutic agent for muscle spasm or spasticity." *Psychosomatics* 21 (1): 81-85.

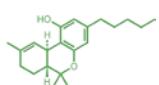
The first of the two case reports:

Die injuries in an automobile accident in 1970, including fractures of the pelvis, right patella, L-5 vertebra, and multiple ribs. Her recovery was complicated by persistent, severe pain and muscle spasms of the neck and low back, which were treated using medication including meperidine, pentazocine, and diazepam. When we first saw her in consultation in 1974, her neurologic examination was normal except for bilateral tenderness of the paraspinal muscles in the neck and a subtle sensory loss to light touch over the C-5 dermatome on the left. She complained that the medication caused excessive sedation, interfering with her work. In addition, the long-term consequences of combination drug use concerned her. We discussed alternative therapy with conventional drugs. Since the occurrence of the automobile accident, the woman had abstained from cannabis use.

Over a period of three months, the woman eliminated use of medication for pain and muscle spasm and substituted cannabis when symptoms occurred. She reported that the cannabis produced both analgesic and muscle-relaxant effects without the drug side-effects that had disturbed her. Nor did it produce drowsiness. In four years of intermittent use, she claims her cannabis pattern has not changed; she uses up to one cannabis cigarette every second or third evening.

Petro, D.J. (2002) "Cannabis in multiple sclerosis: Women's health concerns." *Journal of Cannabis Therapeutics* 2 (3-4): 161-175.

Women's health has received greater attention with the recognition of significant differences in disease expression and drug action in men and women. Multiple sclerosis is a neurological disorder with important gender differences. MS patients have employed cannabis to treat a number of



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symptoms associated with the disease including spasticity, pain, tremor, fatigue, and autonomic dysfunction. The scientific literature includes supportive case reports, single-patient (N-of-1) trials and randomized clinical trials. Large-scale clinical trials are underway to answer questions concerning the efficacy and safety of cannabis in patients with MS. While these studies will answer important questions concerning the actions of cannabinoids on the nervous system, additional studies in female MS patients will be needed to address issues such as gender-specific actions on symptoms such as pain and autonomic dysfunction along with studies in menopausal and post-menopausal women. Since the drug-drug interactions have been reported with cannabinoids, the effects of cannabis on the actions of other centrally-acting drugs should be explored.

Petro, D.J. and C. Ellenberger, Jr. (1981) "Treatment of human spasticity with delta 9-tetrahydrocannabinol." Journal of Clinical Pharmacology **21** (8-9 Suppl.).

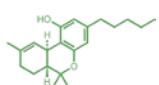
Spasticity is a common neurologic condition in patients with multiple sclerosis, stroke, cerebral palsy or an injured spinal cord. Animal studies suggest that THC has an inhibitory effect on polysynaptic reflexes. Some spastic patients claim improvement after inhaling cannabis. We tested muscle tone, reflexes, strength and performed EMGs before and after double-blinded oral administration of either 10 or 5 mg THC or placebo. The blinded examiner correctly identified the trials in which the patients received THC in seven of nine cases. For the group, 10 mg THC significantly reduced spasticity by clinical measurement (P less than 0.01). Quadriceps EMG interference pattern was reduced in those four patients with primarily extensor spasticity. THC was administered to eight other patients with spasticity and other CNS lesions. Responses varied, but benefit was seen in three of three patients with "tonic spasms." No benefit was noted in patients with cerebellar disease.

Poliwoda, S. (2012) "Kiffen gegen die Schmerzen." Die Zeit **16**.

Kalifornien ist mal wieder weiter als andere: Dort dürfen Menschen Marihuana konsumieren, wenn es ihrer Gesundheit dient. Ein Vorbild auch für Deutschland?

Vor der Tür stehen drei Sicherheitsleute mit Sonnenbrille und Waffe. Noch mal zwei direkt an der Tür. Dann ein Metalldetektor, an dem sich die Kunden mit einer Patient Identification Card ausweisen müssen. Hinter dem Metalldetektor schließlich öffnet sich die lichte Verkaufshalle mit bodentiefen Fenstern und 20 Überwachungskameras an den Decken. Eine Mischung aus H&M und Club-Lounge, mit hellen Bastteppichen ausgelegt. Dazwischen braune Läufer, die zu einem der neun gläsernen Verkaufstresen führen. Unter den blank polierten Glasscheiben das Sortiment: 36 verschiedene Marihuana-Sorten, in Schälchen aufgereiht. Darüber 38 Edelsteindöschen mit braunen Haschisch-Krümeln, das Stück ab 35 Dollar. Außerdem Marihuana-Seife, Shampoos, sieben Sorten Cannabis-Schokolade, fertig gedrehte Joints, Karamellbonbons. Willkommen im Harborside Health Center, der größten Marihuana-Apotheke in der Region San Francisco.

Zwar ist der Gebrauch von Marihuana nach nationalem US-Recht illegal und damit strafbar, aber Kalifornien und 15 weitere US-Bundesstaaten erlauben es seit 1996 für medizinische Zwecke. In Deutschland ist so etwas momentan noch undenkbar. Doch glaubt man vielen Forschern und Ärzten, die sich mit



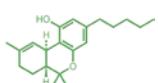
dem Thema beschäftigen, sollte, nein, müsste sich das ändern. Und zwar sehr bald. Denn Marihuana soll diverse Krankheiten lindern können, von Herz- über Nervenleiden bis zu Krebs.

Außerdem lässt sich viel Geld mit dem Stoff verdienen – in Kalifornien auf legale Art und Weise. Das für die Steuererhebung zuständige Board of Equalization schätzt, dass in dem Bundesstaat knapp 18 Milliarden Dollar jährlich mit Marihuana umgesetzt werden. Davon fallen etwa 1,4 Milliarden Dollar an Steuern ab. So wäre es doch sinnvoll, sagen viele US-Bürger, Cannabis ganz zu legalisieren und den neuen Wirtschaftszweig weiter auszubauen: Kiffen gegen die Staatskrise.

Doch es gibt Widerstände. 2010 stimmten die Bürger über die komplette Freigabe von Marihuana ab: 53,5 Prozent waren dagegen, darunter vor allem Republikaner, die Bierbrauergewerkschaft und die Pharmalobby – die wohl nicht ganz uneigennützige Interessen hatten. 46,5 Prozent waren für die Freigabe: Demokraten, Forscher oder auch Polizisten. Letztere sicher mit dem Kalkül, dass es dann weniger Drogendelikte geben würde.

Doch die Abstimmung war nicht das Ende der Debatte, der Kampf geht weiter. Kalifornien ringt mit Washington, Legalisierer streiten mit Politikern, Züchter kämpfen gegen die nationale Drogenbehörde, Ärzte gegen Ignoranz. Und Patienten gegen ihre Leiden. »Hier herrscht Krieg«, sagt Richard Lee, Kopf der Legalisierungsbefürworter, »der Krieg um das Kraut.« Lee leitet die Oaksterdam University, die ihren Sitz im Stadtzentrum von Oakland hat, 20 Autominuten von San Francisco entfernt. Ein weißer Steinklotz mit fünf Stockwerken, verspiegelter Fensterfront und einem Graffito über der kompletten Seitenwand. Seit Lee die Universität 2007 gegründet hat, haben über 15.000 Studenten hier alles über Anbau und Hege, Ernte und Verkauf von Cannabis gelernt. Um dann als lizenzierte Anbauer selbst zu züchten oder eine Cannabis-Apotheke zu betreiben.

Der Red Diesel steht in voller Blüte. Zärtlich streicht Mike Parker über die Blätter. Er hat acht Kinder »und 129 Babys«: 129 Cannabis-Pflanzen flattern im warmen Wind, verteilt auf fünf Räume, unter viel Licht und ständig ventilirt. Big Mike, wie ihn alle hier nennen, ist ein Hüne mit Rauschekinnbart. Er leitet das Labor an der Oaksterdam-Universität. »Die weibliche sexuelle Frustration ist an allem schuld«, sagt er. Denn nur die weiblichen Pflanzen bilden die Blüten, die geerntet werden. Sie wollen mit männlichen Pollen bestäubt werden, deshalb treiben sie immer mehr Blüten aus. Aber männliche Pflanzen gibt es in der Cannabis-Zucht nicht. Eine sieben Meter hohe Pflanze in freier Natur kann aus lauter Frust schon mal vier Kilogramm Blüten tragen. Die werden abgeschnitten und getrocknet – fertig ist das Marihuana. Das gepresste Harz der Pflanze, das eigentliche Haschisch, nennt sich auch Shit. Dessen süßlicher Duft aus öffentlicher Toilette, getragenen Strümpfen und frisch geschnittenem Rasen hängt im gesamten Gebäude der Universität. Der zentrale Hörsaal liegt im zweiten Stock. 76 Studenten lauschen dort dem Anwalt James Clark. »Die Rechnung ist einfach«, sagt er: »Für den Besitz von 100 Pflanzen kriegen Sie laut US-Bundesrecht ein Jahr, für 1000 Pflanzen zehn Jahre Gefängnis. Minimum.« Einige der Zuhörer schütteln verständnislos den Kopf. Gut zwei Drittel sind Männer, viele entsprechen dem Klischee des Marihuana-Fans mit ihren Caps, Rastazöpfen oder kahl rasierten Köpfen. Aber auch übergewichtige Familienväter mit Handy am Gürtel sitzen da, sowie Surftypen und ältere Herren mit Jaguar-Cabrio vor der Tür. Ein Querschnitt



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der Gesellschaft.

Die Studenten erfahren in den Vorlesungen und Seminaren alles über THC und CBD. Das sind die magischen Buchstaben. Δ-9-Tetrahydrocannabinol (THC) ist der eine Wirkstoff im Cannabis, Cannabidiol (CBD) der andere. THC wirkt stark psychoaktiv, CBD dagegen, das Cannabidiol, hat kaum einen Einfluss auf die Psyche. Hinzu kommen etwa 600 weitere Inhaltsstoffe, deren Zusammenspiel bis heute noch nicht wirklich erforscht ist. Bekannt dagegen sind die umfassend schmerzlindernden, entzündungshemmenden und nervenschützenden Kräfte von THC und CBD.

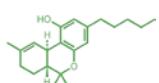
Vor allem das Cannabidiol rückt immer stärker in den Fokus der Forscher, sowohl in der Krebsforschung, etwa bei der Behandlung von Hirntumoren oder Brustkrebs, als auch in der Kardiologie. Eine Studie des amerikanischen staatlichen National Institute of Health (NIH) hat gezeigt, dass CBD bei der diabetischen Kardiomyopathie – einer Herzkrankheit, die in Verbindung mit der Zuckerkrankheit auftritt und Tausende Menschen auch in Deutschland betrifft – ein »großes Behandlungspotenzial besitzt, indem es oxidativen Stress reduziert«. Belegt ist auch, dass Cannabis bei der multiplen Sklerose Schmerzen und Spasmen nimmt; dass es bei Aids die Schluckbeschwerden und die Appetitlosigkeit lindert; dass es bei Depressionen die Stimmung aufhellt oder beim Glaukom den Augeninnendruck verringert. Für 30 weitere Krankheiten, darunter Parkinson, Schlaganfall oder Anämie, ist dokumentiert, dass Cannabis zumindest die Symptome bessert.

Uni-Gründer Lee kennt die medizinischen Vorteile aus eigener Erfahrung. Seit einem Arbeitsunfall Mitte der achtziger Jahre sitzt er im Rollstuhl, er raucht Cannabis gegen den Phantomschmerz in den Beinen. Seine Rolle in der Diskussion um die Freigabe von Marihuana spielt er allerdings herunter: »Ich bin nur ein kleiner Krieger in einem großen Krieg. Aber mittlerweile haben wir eine große Armee.«

Das Harborside Health Center ist ein wichtiger Stützpunkt dieser Armee. Die Marihuana-Apotheke versucht, bei den Politikern nicht aufzufallen und in aller Ruhe ihren Geschäften nachzugehen. Drei Sicherheitsschleusen nach der Verkaufshalle ruht hinter einer silbernen Tresortür Stoff im Wert von mehreren Millionen Dollar. Der teuerste lagert hier nochmals im Safe verschlossen, daneben ist Marihuana säckeweise gestapelt, in acht deckenhohen Regalen auf beiden Seiten.

»Alles für die Patienten«, beteuert Steve DeAngelo, der Direktor, mit sanfter Stimme. Zeitungsartikel über seine Apotheke bedecken die Wand hinter ihm. 20 Millionen Dollar nimmt DeAngelo pro Jahr ein, »über 50000 Dollar am Tag«. Er ist einer der zehn größten Steuerzahler in Oakland, beschäftigt 80 Angestellte hier und 40 in einer zweiten Apotheke in San José. Sein Marihuana sei »absolut sauber«, sagt Richard Lee. »Harbourside hat als erste Apotheke Marihuana in Labors testen lassen.«

Das kann man etwa bei Pure Analytics in Santa Rosa tun, zwei Stunden nördlich von San Francisco. Samantha Miller fixiert dort mit dem Okular eine Blüte auf dem Objektträger des Mikroskops. »Fungus«, Pilzbefall, sagt sie nach einem kurzen Blick. Miller testet in ihrem Labor Cannabis auf Reinheit, THC- und CBD-Gehalt, auf Pestizide und Pilze. Sie prüft für rund 60 Züchter und Apotheken. Bis zu 800 Proben untersucht sie pro Monat. »Das ist Dienst am Patienten«, sagt sie. »Kalifornien hat dadurch das sauberste Marihuana.« In Deutschland hingegen gibt es laut Hanfverband auf dem Schwarzmarkt so



gut wie kein Marihuana, das nicht gestreckt ist – mit Sand, Haarspray oder Glas.

Es ist auch die Qualität des kalifornischen Mariuanas, die Richard Lee zu der Prognose veranlasst, es sei nur noch eine Frage der Zeit, »bis die Freigabe kommt«. Davor aber stehen so mächtige Institutionen wie die Drug Enforcement Administration, die nationale Drogenbehörde der USA. Ihre Polizisten werden nicht müde, mit Maschinenpistole und kugelsicherer Weste willkürlich Marihuana-Apotheken auch in Kalifornien zu schließen oder Züchtern die Plantagen umzupflügen. Denn es steht immer noch Bundes- gegen Staatenrecht, und Bundesrecht siegt.

»Es ist alles so absurd, was da passiert«, sagt Yvonne White, 58. Sie sitzt seit 1988 im Rollstuhl, Hüfte und Sprunggelenke sind festgeschnallt, der rechte Arm ist gelähmt. 1979 hat man bei ihr multiple Sklerose festgestellt. »Ich hatte sieben gute Jahre seit dem Ausbruch. Das war's.« Ihre blauen Augen funkeln in ihrem dunklen Gesicht. »Mit Cannabis kann ich die meisten von den vielen Tabletten einfach weglassen.« Sie braucht kein Valium mehr, kein Vicodin, ein Morphinderivat, »und das ganze andere Zeugs auch nicht. Wenn ich das alles nehme, bin ich groggy, schlafe nur, hab keinen Willen mehr, nichts.« Stattdessen raucht sie acht Joints pro Tag. »Jetzt kann ich wieder jeden Sonntag in die Kirche gehen.« Dann zieht sie sich die Lippen nach. Und lächelt.

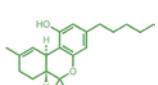
Marjorie Gardiner, 74, ist das Lächeln vergangen. »Das ist alles so schlimm«, sagt sie, während sie im Hauptaum der Berkeley Patients Group an einer Plastikdose mit Sour Diesel riecht. »Schizophren ist das hier in Kalifornien. Dabei will ich bloß meine blöden Schmerzen loswerden.«

Gardiners arthritisch verkrüppelte Hände können die Dose kaum halten. Sie ist klapperdürr, trägt Kopftuch und Paisleybluse. Sie hat eine künstliche Hüfte und zwei künstliche Kniegelenke. »Marihuana ist immer noch billiger als die ganzen Tabletten, die ich sonst schlucken müsste. Die machen mich dämlich, die Dinger. Das bin dann nicht mehr ich.« Sie stopft sich ihre Glaspfeife.

»Mein Doktor sagt, er sei froh, dass ich nicht saufe gegen die Schmerzen.« Amanda Reiman, eine Ärztin mit einem Tattoo vom Knöchel bis zum Knie leitet die Verteilungsstelle der Berkeley Patients Group: »Wir fragen nicht, ob jemand das Marihuana wirklich braucht. Auch ein Apotheker sagt ja nicht: Sie sehen aber nicht wie jemand aus, der ein Anti-Depressivum braucht!« Das Durchschnittsalter der Patienten hier beträgt 39 Jahre. Sie sitzen auf hellen Stühlen, stopfen sich ihre Pfeife und schauen aus der verglasten Rotunde auf die San Pablo Avenue.

Der wohl entscheidende Schlüssel für die Wirkung von Cannabis ist das sogenannte Endocannabinoid-System – ein körpereigenes Botenstoffsystem, das ähnliche Angriffspunkte hat wie Cannabis. Die Endocannabinoide, vor allem das sogenannte Anandamid, aktivieren zwei Rezeptoren, die vor allem im Gehirn sitzen. Sie regeln dort etwa das Hungergefühl, schützen aber auch vor zu großer neuronaler Aktivität. Fällt das Endocannabinoid-System aus oder funktioniert es nicht richtig, kann man Ängste kaum steuern oder negative Ereignisse nicht richtig löschen. In Tierversuchen zeigte sich zudem, dass ein Mangel an einem der Rezeptoren zu Depressionen führt, ein überaktives System mit zu vielen Rezeptoren dagegen zu Fettleibigkeit.

Im übrigen Körper haben die Endocannabinoide stark schmerzlindernde und entzündungshemmende Wirkung. Sie seien »an vielen Orten im Körper



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protektiv wirksam«, sagt Beat Lutz vom Institut für Physiologische Chemie der Universität Mainz. Er erforscht das Cannabinoid-System und seine Rolle für das Gedächtnis. »Das Endocannabinoid-System zu verstehen wird exponentiell komplizierter, je weiter es vom Gehirn weggeht«, sagt Lutz. »Es gibt noch viel zu entdecken.«

Studien legen zum Beispiel die Vermutung nahe, dass es auch eine Unterfunktion des Endocannabinoid-Systems geben kann, die zu schweren chronischen Krankheiten führen kann. »Generell können wir vom System viel mehr Gutes als Schlechtes sagen«, so Lutz.

Beat Lutz warnt allerdings auch vor einer allgemeinen Freigabe von Cannabis: »Wenn Cannabis in der Jugend geraucht wird, gibt es irreversible Schädigungen. Die Gehirnentwicklung von Jugendlichen reicht bis in die späte Pubertät. Die Hirnsynapsen werden dann nicht mehr verknüpft, was zu kognitiven Defiziten und zu einem vermehrten Auftreten von Depressionen und Epilepsie führt. Bei Jugendlichen muss man die Behandlung mit Cannabis sehr gut abwägen.«

Wichtig ist auch, wie Cannabis den Körper erreicht. Wird es geraucht, überschwemmen die Cannabinoide den Körper – die Wirkung lässt sich dann nur sehr schwer steuern. Und das kann Probleme machen, denn THC wirkt »in geringen Mengen gegen Ängste, in hohen Konzentration aber erzeugt es sie«, sagt Lutz.

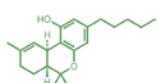
Donald Abrams sitzt in einem Zimmer des General Hospital, des Lehrkrankenhauses der University of California San Francisco. Zehn Auszeichnungen für seine Forschungen hängen an der Wand. Der Arzt war einer der Ersten, der Aids-Patienten Cannabis gab. Und der dabei nachwies, dass es signifikant Schmerzen reduzierte, Schlaflosigkeit, Depressionen und Übelkeit besserte. »Krebstherapeutika kann man nicht mit Cannabis ersetzen«, sagt er. »Aber man kann sie unterstützen. Eigentlich müssten wir Cannabis als eine Heilpflanze beurteilen.«

Brad Ramsey, 49, ein Patient von Abrams, ist seit 1982 HIV-infiziert, 1992 kamen die ersten Symptome. Er nimmt an einer Aids-Studie mit Cannabis teil. »Das Zeug ist das Einzige, was gegen die Übelkeit hilft. Auf das gängige Medikament reagiere ich allergisch. Jetzt habe ich sogar zugenommen.« Er streckt seinen dünnen Bauch in die Sonne.

Für Patienten wie Ramsey forscht Mike Parker. Er beschallt seine Pflanzen mit Musik. Während der Wachstumsphase mit Mozart oder Chopin, während der Ernte mit Lynyrd Skynyrd oder Iron Maiden. Jeden Morgen begrüßt er seine Pflanzen. »Die spüren genau, wenn du schlecht drauf bist, wenn du Probleme hast. Das sind lebende Geschöpfe.«

Pollmann, W. and W. Feneberg (2008) "Current management of pain associated with multiple sclerosis." CNS Drugs **22** (4): 291-324.

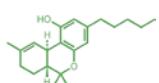
While pain is a common problem in patients with multiple sclerosis (MS), it is not frequently mentioned by patients and a more direct approach is required in order to obtain information about pain from patients. Many patients with MS experience more than one pain syndrome; combinations of dysaesthesia, headaches and/or back or muscle and joint pain are frequent. For each pain syndrome a clear diagnosis and therapeutic concept needs to be established. Pain in MS can be classified into four diagnostically and therapeutically relevant categories: (i) neuropathic pain due to MS (pain directly related to



MS); (ii) pain indirectly related to MS; (iii) MS treatment-related pain; and (iv) pain unrelated to MS. Painful paroxysmal symptoms such as trigeminal neuralgia (TN), or painful tonic spasms are treated with antiepileptics as first choice, e.g. carbamazepine, oxcarbazepine, lamotrigine, gabapentin, pregabalin, etc. Painful 'burning' dysaesthesia, the most frequent chronic pain syndrome, are treated with TCAs such as amitriptyline, or antiepileptics such as gabapentin, pregabalin, lamotrigine, etc. Combinations of drugs with different modes of action can be particularly useful for reducing adverse effects. While escalation therapy may require opioids, there are encouraging results from studies regarding cannabinoids, but their future role in the treatment of MS-related pain has still to be determined. Pain related to spasticity often improves with adequate physiotherapy. Drug treatment includes antispastic agents such as baclofen or tizanidine and in patients with phasic spasticity, gabapentin or levetiracetam are administered. In patients with severe spasticity, botulinum toxin injections or intrathecal baclofen merit consideration. While physiotherapy may ameliorate malposition-induced joint and muscle pain, additional drug treatment with paracetamol (acetaminophen) or NSAIDs may be useful. Moreover, painful pressure lesions should be avoided by using optimally adjusted aids. Treatment-related pain associated with MS can occur with subcutaneous injections of interferon-beta or glatiramer acetate, and may be reduced by optimizing the injection technique and by local cooling. Systemic (particularly 'flu-like') adverse effects of interferons, e.g. myalgias, can be reduced by administering paracetamol, ibuprofen or naproxen. A potential increase in the frequency of pre-existing headaches after starting treatment with interferons may require optimization of headache attack therapy or even prophylactic treatment. Pain unrelated to MS, such as back pain or headache, is common in patients with MS and may deteriorate as a result of the disease. In summary, a careful analysis of each pain syndrome will allow the design of the appropriate treatment plan using various medical and nonmedical options (multimodal therapy), and will thus help to improve the quality of life (QOL) of the patients.

Pollmann, W., W. Feneberg, A. Steinbrecher, M.R. Haupts and T. Henze (2005) "[Therapy of pain syndromes in multiple sclerosis -- an overview with evidence-based recommendations]." *Fortschritte der Neurologie • Psychiatrie* **73** (5): 268-285.

While pain is a common problem in multiple sclerosis (MS) patients, it is frequently overlooked and has to be asked for actively. Pain can be classified into 4 diagnostically and therapeutically relevant categories. 1. Pain Directly Related to MS: Painful paroxysmal symptoms like trigeminal neuralgia or painful tonic spasms are treated with carbamazepine as first choice, or lamotrigine, gabapentin, oxcarbazepine and other anticonvulsants. Painful "burning" dysaesthesia, the most frequent chronic pain syndrome, are treated with tricyclic antidepressants or carbamazepine, further options include gabapentin or lamotrigine. While escalation therapy may require opioids, the role of cannabinoids in the treatment of pain still has to be determined. 2. Pain Indirectly Related to MS: Pain related to spasticity often improves with adequate physiotherapy. Drug treatment includes antispastic agents like baclofen or tizanidine, alternatively gabapentin. In severe cases botulinum toxin injections or intrathecal baclofen merit consideration. Physiotherapy and physical therapy may ameliorate malposition-induced joint and muscle pain.



Moreover, painful pressure lesions should be avoided using optimally adjusted aids. 3. Treatment-related pain can occur with subcutaneous injections of beta interferons or glatiramer acetate and may be reduced by optimizing the injection technique and by local cooling. Systemic side effects of interferons like myalgias can be reduced by paracetamol or ibuprofen. 4. Pain unrelated to MS such as back pain or headache are frequent in MS patients and may be worsened by the disease. Treatment should follow established guidelines. In summary, a careful analysis of the pain syndrome will allow the design of the appropriate treatment plan using various medical and non-medical options and thus will help to ameliorate the patients' quality of life.

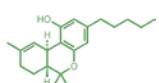
Pryce, G. and D. Baker (2007) "Control of spasticity in a multiple sclerosis model is mediated by CB1, not CB2, cannabinoid receptors." British Journal of Pharmacology **150** (4): 519-525.

Background and Purpose: There is increasing evidence to suggest that cannabis can ameliorate muscle-spasticity in multiple sclerosis, as was objectively shown in experimental autoimmune encephalomyelitis models. The purpose of this study was to investigate further the involvement of CB1 and CB2)cannabinoid receptors in the control of experimental spasticity.

Experimental Approach: Spasticity was induced in wildtype and CB1-deficient mice following the development of relapsing, experimental autoimmune encephalomyelitis. Spastic-hindlimb stiffness was measured by the resistance to flexion against a strain gauge following the administration of CB1 and CB2 agonists. **Key Results:** As previously suggested, some CB2-selective agonists (RWJ400065) could inhibit spasticity. Importantly, however, the anti-spastic activity of RWJ400065 and the therapeutic effect of non-selective CB1/CB2 agonists (R(+))WIN55,212-2 and CP55, 940) was lost in spastic, CB1-deficit mice. **Conclusions and Implications:** The CB1 receptor controls spasticity and cross-reactivity to this receptor appears to account for the therapeutic action of some CB2 agonists. As cannabinoid-induced psychoactivity is also mediated by the CB1 receptor, it will be difficult to truly dissociate the therapeutic effects from the well-known, adverse effects of cannabinoids when using cannabis as a medicine. The lack of knowledge on the true diversity of the cannabinoid system coupled with the lack of total specificity of current cannabinoid reagents makes interpretation of in vivo results difficult, if using a purely pharmacological approach. Gene knockout technology provides an important tool in target validation and indicates that the CB1 receptor is the main cannabinoid target for an anti-spastic effect.

Pryce, G. and D. Baker (2012) "Potential control of multiple sclerosis by cannabis and the endocannabinoid system." CNS & Neurological Disorders Drug Targets **11** (5): 624-641

For many years, multiple sclerosis (MS) patients have been self-medicating with illegal street cannabis to alleviate symptoms associated with MS. Data from animal models of MS and clinical studies have supported the anecdotal data that cannabis can improve symptoms such as limb spasticity, which are commonly associated with progressive MS, by the modulation of excessive neuronal signalling. This has led to cannabis-based medicines being approved for the treatment of pain and spasticity in MS for the first time. Experimental studies into the biology of the endocannabinoid system have



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revealed that cannabinoids have activity, not only in symptom relief but also potentially in neuroprotective strategies which may slow disease progression and thus delay the onset of symptoms such as spasticity. This review appraises the current knowledge of cannabinoid biology particularly as it pertains to MS and outlines potential future therapeutic strategies for the treatment of disease progression in MS.

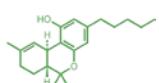
Quensel, S., B. Kolte und F. Nolte (1996) "Zur Cannabis-Situation in der Bundesrepublik Deutschland." In: Peter Cohen & Arjan Sas (Eds) "Cannabisbeleid in Duitsland, Frankrijk en de Verenigde Staten." Amsterdam, Centrum voor Drugsonderzoek, Universiteit van Amsterdam: 17-78. <http://www.cedro-uva.org/lib/quensel.cannabis.pdf>

Radbruch, L. and F. Elsner (2005) "[Palliative pain therapy, cannabinoids]." *Internist (Berlin)* **46** (10): 1105-1114.

Cancer pain treatment should follow the recommendations of the World Health Organisation. Treatment should be with oral application, regular application times and following the analgesic step-ladder. Non-opioids such as dipyrone or non-steroids are used for slight to moderate pain, step-2 opioids such as tramadol or tilidine/naloxone for moderate pain and step-3 opioids such as morphine, oxycodone or hydromorphone for severe pain. Transdermal application of fentanyl or buprenorphine offer a non-invasive parenteral alternative for patients with stable pain syndromes. Cannabinoids such as tetrahydrocannabinol offer a valuable add-on option for cancer patients with refractory pain, spasticity, nausea or appetite loss.

Rahn, E.J. and A.G. Hohmann (2009) "Cannabinoids as Pharmacotherapies for Neuropathic Pain: From the Bench to the Bedside." *Neurotherapeutics* **6** (4): 713-737.

Neuropathic pain is a debilitating form of chronic pain resulting from nerve injury, disease states, or toxic insults. Neuropathic pain is often refractory to conventional pharmacotherapies, necessitating validation of novel analgesics. Cannabinoids, drugs that share the same target as Δ -9-tetrahydrocannabinol (Δ -9-THC), the psychoactive ingredient in cannabis, have the potential to address this unmet need. Here, we review studies evaluating cannabinoids for neuropathic pain management in the clinical and preclinical literature. Neuropathic pain associated with nerve injury, diabetes, chemotherapeutic treatment, human immunodeficiency virus, multiple sclerosis, and herpes zoster infection is considered. In animals, cannabinoids attenuate neuropathic nociception produced by traumatic nerve injury, disease, and toxic insults. Effects of mixed cannabinoid CB(1)/CB(2) agonists, CB(2) selective agonists, and modulators of the endocannabinoid system (i.e., inhibitors of transport or degradation) are compared. Effects of genetic disruption of cannabinoid receptors or enzymes controlling endocannabinoid degradation on neuropathic nociception are described. Specific forms of allodynia and hyperalgesia modulated by cannabinoids are also considered. In humans, effects of smoked marijuana, synthetic Δ -9-THC analogs (e.g., Marinol[®], Cesamet[®]) and medicinal cannabis preparations containing both Δ -9-THC and cannabidiol (e.g., Sativex[®], Cannador[®]) in neuropathic pain states are reviewed. Clinical studies largely affirm that neuropathic pain patients derive



benefits from cannabinoid treatment. Subjective (i.e., rating scales) and objective (i.e., stimulus-evoked) measures of pain and quality of life are considered. Finally, limitations of cannabinoid pharmacotherapies are discussed together with directions for future research.

Recktor, B. und M. Schnelle (2000) "Cannabis – eine alte Heilpflanze." Dr. med. Mabuse **25** (128), AT Verlag Frankfurt am Main.

Reichbach, G.L. (2012) "A Judge's Plea for Pot." New York Times May 17, p. A27.

Three and a half years ago, on my 62nd birthday, doctors discovered a mass on my pancreas. It turned out to be Stage 3 pancreatic cancer. I was told I would be dead in four to six months. Today I am in that rare coterie of people who have survived this long with the disease. But I did not foresee that after having dedicated myself for 40 years to a life of the law, including more than two decades as a New York State judge, my quest for ameliorative and palliative care would lead me to marijuana.

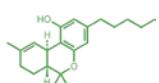
Nausea and pain are constant companions. One struggles to eat enough to stave off the dramatic weight loss that is part of this disease. Eating, one of the great pleasures of life, has now become a daily battle, with each forkful a small victory. Every drug prescribed to treat one problem leads to one or two more drugs to offset its side effects. Pain medication leads to loss of appetite and constipation. Anti-nausea medication raises glucose levels, a serious problem for me with my pancreas so compromised. Sleep, which might bring respite from the miseries of the day, becomes increasingly elusive.

Inhaled marijuana is the only medicine that gives me some relief from nausea, stimulates my appetite, and makes it easier to fall asleep. The oral synthetic substitute, Marinol, prescribed by my doctors, was useless. Rather than watch the agony of my suffering, friends have chosen, at some personal risk, to provide the substance. I find a few puffs of marijuana before dinner gives me ammunition in the battle to eat. A few more puffs at bedtime permits desperately needed sleep.

This is not a law-and-order issue; it is a medical and a human rights issue. Being treated at Memorial Sloan Kettering Cancer Center, I am receiving the absolute gold standard of medical care. But doctors cannot be expected to do what the law prohibits, even when they know it is in the best interests of their patients. When palliative care is understood as a fundamental human and medical right, marijuana for medical use should be beyond controversy.

Sixteen states already permit the legitimate clinical use of marijuana, including our neighbor New Jersey, and Connecticut is on the cusp of becoming No. 17. The New York State Legislature is now debating a bill to recognize marijuana as an effective and legitimate medicinal substance and establish a lawful framework for its use. The Assembly has passed such bills before, but they went nowhere in the State Senate. This year I hope that the outcome will be different. Cancer is a nonpartisan disease, so ubiquitous that it's impossible to imagine that there are legislators whose families have not also been touched by this scourge. It is to help all who have been affected by cancer, and those who will come after, that I now speak.

Given my position as a sitting judge still hearing cases, well-meaning friends question the wisdom of my coming out on this issue. But I recognize that fellow cancer sufferers may be unable, for a host of reasons, to give voice to



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our plight. It is another heartbreaking aporia in the world of cancer that the one drug that gives relief without deleterious side effects remains classified as a narcotic with no medicinal value.

Because criminalizing an effective medical technique affects the fair administration of justice, I feel obliged to speak out as both a judge and a cancer patient suffering with a fatal disease. I implore the governor and the Legislature of New York, always considered a leader among states, to join the forward and humane thinking of 16 other states and pass the medical marijuana bill this year. Medical science has not yet found a cure, but it is barbaric to deny us access to one substance that has proved to ameliorate our suffering.

Gustin L. Reichbach is a justice of the State Supreme Court in Brooklyn.

Re "A Judge's Plea for Pot" (Op-Ed, May 18):

To the Editor:

I salute Justice Gustin L. Reichbach for his courageous act of civil disobedience and his willingness to admit publicly his use of marijuana for medical purposes.

Anyone who has personally suffered or has seen a friend or family member suffer from debilitating pain that traditional remedies do not sufficiently help knows that it does not permit a person to function productively. It is hard to engage in the everyday activities, like eating, sleeping, playing with children, and enjoying the company of friends and family, that make life worthwhile. One's life becomes entirely focused on the pain.

The judge's plea to legalize marijuana for medical purposes comes from both his head and his heart. Legally, it does not make sense to criminalize a treatment when the decision should best be left to the discretion of a patient and his doctor.

Why should a person be punished for seeking relief using a drug that is known to alleviate suffering, while causing no side effects and no harm to others?

Why should his friends be exposed to arrest for their altruistic response? It seems cruel for a civilized society to withhold available help.

I hope that the New York State Legislature acts, as many other states have already done, to change the law. No more unnecessary suffering. Let's make a person's final days as comfortable as possible.

Barbara Swartz

Brooklyn, May 17, 2012

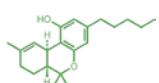
The writer is a professor at Touro Law School.

To the Editor:

I am a cancer survivor, and my heart goes out to Justice Gustin L. Reichbach and his family.

Although Justice Reichbach reports that marijuana had a benefit for him, anecdotal reports are not reliable scientific evidence because the claimed benefits are not independently verified and do not reflect double-blind controls. Anecdotal reports may also be inaccurate because of the emotional expectations of the person using marijuana and the placebo effect. In some cases, there may be deliberate exaggeration for ideological reasons.

Public health must be protected by standards based on unbiased science and



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objective clinical testing, not on politics, emotion and anecdotal accounts. The Food and Drug Administration did a comprehensive study of smoked marijuana as medicine and found that there are "no sound scientific studies" supporting the medical use of marijuana. The F.D.A.'s modern, sophisticated drug approval process is our best defense against marketing unsafe and ineffective drugs.

It is true compassion to make sure that medicines are safe and effective and that the claims about them are true.

David G. Evans
Executive Director

Drug Free Schools Coalition Belvidere, N.J., May 18, 2012

To the Editor:

Like Justice Gustin L. Reichbach, I, too, suffered the depredations of cancer treatment and obtained no relief from synthetic marijuana substitutes. Though I lived in Washington, a state in which medical marijuana "possession" was legal, it was difficult to legally obtain it.

So, like Justice Reichbach, I was provided the real thing by friends. The relief was immediate, requiring no more than one or two puffs, making my treatment-racked body immeasurably more comfortable.

Because marijuana is illegal under federal law, state dispensing of the substance is a rat's nest of conflicting laws and ordinances, rife with potential for abuse. That marijuana remains a Schedule I drug, along with heroin and LSD, is beyond absurd.

It's time for the medical community to demand action on patients' behalf.

Jesse Allen

Santa Fe, N.M., May 17, 2012

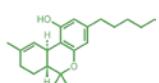
The writer is co-author of "Breast Cancer — Getting Through It as a Couple."

Reisfield, G.M. (2010) "Medical cannabis and chronic opioid therapy." Journal of Pain & Palliative Care Pharmacotherapy 24 (4): 356-361.

Fourteen states and the District of Columbia have legalized the use of cannabis for medical purposes. A small, high-quality literature supports the efficacy of medical cannabis for the treatment of neuropathic pain.

Rice, A.S.C. (2001) "Cannabinoids and pain." Current Opinion in Investigational Drugs 2 (3): 399-414.

Recent advances have dramatically increased our understanding of cannabinoid pharmacology: The psychoactive constituents of Cannabis sativa have been isolated, synthetic cannabinoids described and an endocannabinoid system identified, together with its component receptors, ligands and their biochemistry. Strong laboratory evidence now underwrites anecdotal claims of cannabinoid analgesia in inflammatory and neuropathic pain. Sites of analgesic action have been identified in brain, spinal cord and the periphery, with the latter two presenting attractive targets for divorcing the analgesic and psychotropic effects of cannabinoids. Clinical trials are now required, but are hindered by a paucity of cannabinoids of suitable bioavailability and therapeutic ratio.



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Rintala, D.H., R.N.Fiess, G. Tan, S.A.Holmes and B.M. Bruel (2010) "Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study." American Journal of Physical Medicine & Rehabilitation **89** (10): 840-848.

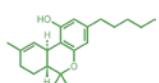
Objective: To test the efficacy and safety of a cannabinoid, dronabinol, compared with an active control, diphenhydramine, in relieving neuropathic pain in persons with spinal cord injury. Design: A randomized, controlled, double-blind, crossover pilot study. Results: Seven adults with spinal cord injury and neuropathic pain below the level of injury participated. Two participants withdrew while receiving dronabinol, their first medication. For the remaining five participants, change in pain on a scale of 0-10 from baseline to the end of the maintenance phase did not differ significantly between the two medications (mean change, dronabinol: 0.20 +/- 0.837, range = -1.00 to 1.00; diphenhydramine: -1.80 +/- 2.490, range = -6.00 to 0; Wilcoxon Z = 1.63, P = 0.102). Similar results were found when the average of the two ratings during the maintenance phase was used (dronabinol: -0.20 +/- 0.671, range = -0.50 to 1.00; diphenhydramine: -1.40 +/- 1.245, range = -3.50 to -0.50; Wilcoxon Z = 1.60, P = 0.109). The most common side effects were dry mouth, constipation, fatigue, and drowsiness for both medications. Conclusions: On average, dronabinol was no more effective than diphenhydramine for relieving chronic neuropathic pain below the level of injury.

Robson, P. (2011) "Abuse potential and psychoactive effects of delta-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine." Expert Opinion on Drug Safety **10** (5): 675-685.

Introduction: There is a growing consensus that cannabis dependence is a substantial and underappreciated problem. The key component responsible for the euphoric effects of cannabis and its dependence potential is Δ-9-tetrahydrocannabinol (THC). THC-containing cannabinoid medicines theoretically pose a risk of abuse and dependence. Areas covered: In order to evaluate the potential of Sativex to cause cannabis-like psychoactivity, abuse or dependence relevant data from all published papers have been reviewed along with the integrated safety analysis for Sativex use in multiple sclerosis (MS) patients on file at GW Pharmaceuticals. Expert opinion: In clinical trials, intoxication scores have been low and euphoria reported by only 2.2% of patients. Tolerance has not occurred, abrupt withdrawal has not resulted in a formal withdrawal syndrome, and no cases of abuse or diversion have been reported to date. A formal abuse liability study of Sativex in experienced cannabis smokers showed some abuse potential in comparison with placebo at higher doses, but scores were consistently lower than equivalent doses of THC. Evidence to date suggests that abuse or dependence on Sativex is likely to occur in only a very small proportion of recipients.

Robson P, D. Wade, P. Makela, H. House and C. Bateman (2005) "Cannabis-based medicinal extract (Sativex) produced significant improvements in a subjective measure of spasticity which were maintained on long-term treatment with no evidence of tolerance." IACM 3rd Conference on Cannabinoids in Medicine, September 9-10, 2005, Leiden.

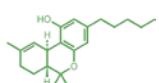
Introduction: Patients with multiple sclerosis (MS) usually experience a range of impairments, of which muscle spasticity is often prominent and disabling. Following completion of a double-blind, placebo-controlled trial of a cannabis-



based medicinal extract (CBME) in the symptomatic treatment of MS, patients were given the option to enter a long-term follow-up trial to determine whether benefits seen following CBME might be maintained over many months of treatment. Methods: Acute study: a randomised, placebo-controlled, double-blind parallel group study over six weeks of treatment at three centres in the UK. Eligible patients were experiencing significant problems from at least one of the following: spasticity, spasms, bladder problems, tremor or pain. CBME (Sativex) containing equal amounts of Δ -9-tetrahydrocannabinol (THC) and cannabidiol (CBD), and placebo was delivered by oro-mucosal spray in a self-titrated dose up to a maximum of 48 sprays (120mg of THC and CBD) daily in divided doses. Primary symptoms were measured by 100 mm visual analogue scale (VAS). Long-term study: Patients completing the acute study were eligible for inclusion in this open label study. Participating patients attended the clinic at eight-weekly intervals, completed a weekly symptom and intoxication diary using VAS, and recorded daily CBME doses. Results: 160 patients completed the acute study, with daily doses following self-titration averaging 15 sprays of CBME (37.5mg of THC and CBD) and 26 for placebo. In the 39 patients with spasticity as their primary symptom VAS spasticity scores fell by 31.2mm following CBME and by 8.4mm following placebo (95% CI for difference -35.52, -10.07; SE 6.26; $p = 0.001$). Diary scores produced a similar result ($p = 0.009$). 137 patients entered the long-term study and were followed for an average of 434 days (range 21-814), and 58 (42.3%) withdrew for the following reasons: lack of efficacy 24; adverse events 17; withdrawn consent 6; lost to follow-up 3; other 8. Sixty-six patients with spasticity completed 82 weeks CBME treatment. At entry to the acute study this group had a mean VAS spasticity score of 69.5, which had reduced to 34.2 on entry into the long-term study. After 82 weeks, the mean score was 31.8 and average daily dose had reduced marginally from 12 sprays on entry to 10 sprays at the last assessment. Similar reductions were seen in VAS measures of bladder-related problems, muscle spasm and pain in the long-term patients. Sudden interruption of CBME for two weeks in a sub-group of 25 patients did not result in a consistent withdrawal syndrome. Commonest unwanted effects were oral irritation from the ethanolic spray, dizziness, diarrhoea and nausea but these were generally mild to moderate in intensity and well tolerated. Conclusion: Beneficial effects of CBME (Sativex) on spasticity (and other symptoms) in MS seem to be maintained over long-term treatment, with no evidence of tolerance.

Rog, D.J. (2010) "Cannabis-based medicines in multiple sclerosis - A review of clinical studies." *Immunobiology* **215** (8): 658-672.

For some years a mixture of anecdotal report and data from animal models have implied a potential role for cannabis-based medicines in ameliorating a variety of symptoms of multiple sclerosis. Only recently however have large randomised controlled trials (RCTs) examined these potential effects rigorously. At present the results of RCTs have lacked a coherent message to the prescribing clinician and reasons for such heterogeneity in cannabinoid trials are discussed.



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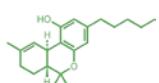
Rog, D.J., T.J. Nurmikko, T. Friede, and C.A. Young (2005) "Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis." *Neurology* **65** (6): 812-819.

Background: Central pain in multiple sclerosis (MS) is common and often refractory to treatment. Methods: We conducted a single-center, 5-week (1-week run-in, 4-week treatment), randomized, double-blind, placebo-controlled, parallel-group trial in 66 patients with MS and central pain states (59 dysesthetic, seven painful spasms) of a whole-plant cannabis-based medicine (CBM), containing Δ -9-tetrahydrocannabinol:cannabidiol (THC:CBD) delivered via an oromucosal spray, as adjunctive analgesic treatment. Each spray delivered 2.7 mg of THC and 2.5 mg of CBD, and patients could gradually self-titrate to a maximum of 48 sprays in 24 hours. Results: Sixty-four patients (97%) completed the trial, 34 received CBM. In week 4, the mean number of daily sprays taken of CBM ($n = 32$) was 9.6 (range 2 to 25, SD = 6.0) and of placebo ($n = 31$) was 19.1 (range 1 to 47, SD = 12.9). Pain and sleep disturbance were recorded daily on an 11-point numerical rating scale. CBM was superior to placebo in reducing the mean intensity of pain (CBM mean change -2.7, 95% CI: -3.4 to -2.0, placebo -1.4 95% CI: -2.0 to -0.8, comparison between groups, $p = 0.005$) and sleep disturbance (CBM mean change -2.5, 95% CI: -3.4 to -1.7, placebo -0.8, 95% CI: -1.5 to -0.1, comparison between groups, $p = 0.003$). CBM was generally well tolerated, although more patients on CBM than placebo reported dizziness, dry mouth, and somnolence. Cognitive side effects were limited to long-term memory storage. Conclusions: Cannabis-based medicine is effective in reducing pain and sleep disturbance in patients with multiple sclerosis related central neuropathic pain and is mostly well tolerated.

Rog, D.J., T.J. Nurmikko, N.S. Sarantis, and C.A. Young (2007) "Long-term use of sativex in multiple sclerosis central pain; dosing and changes in concomitant analgesia." *European Journal of Pain* **11** (1, Suppl. 1): 136.

Rog, D.J., T.J. Nurmikko, and C.A. Young, (2007) "Oromucosal [Delta]9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: An uncontrolled, open-label, 2-year extension trial." *Clinical Therapeutics* **29** (9): 2068-2079.

Background: Central neuropathic pain (CNP), pain initiated or caused by a primary lesion or dysfunction of the central nervous system, occurs in ~28% of patients with multiple sclerosis (MS). Δ -9-Tetrahydrocannabinol/cannabidiol (THC/CBD), an endocannabinoid system modulator, has demonstrated efficacy for up to 4 weeks in randomized controlled trials in the treatment of CNP in patients with MS. Objective: The purpose of this extension was to establish long-term tolerability and effectiveness profiles for THC/CBD (Sativex[®], GW Pharmaceuticals plc, Salisbury, United Kingdom) oromucosal spray in CNP associated with MS. Methods: This uncontrolled, open-label trial was an indefinite-duration extension of a previously reported 5-week randomized study in patients with MS and CNP. In the initial trial, patients were randomized to placebo or THC/CBD. Patients were only required to maintain their existing analgesia in the randomized study. In the open-label trial they could vary their other analgesia as required. All patients (placebo and THC/CBD) who completed the randomized trial commenced the open-label

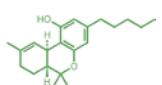


follow-up on THC/CBD (27 mg/mL: 25 mg/mL). Patients titrated their dosage, maintaining their existing analgesia. The primary end point of the trial was the number, frequency, and type of adverse events (AEs) reported by patients. Secondary end points included changes from baseline in 11-point numerical rating scale (NRS-11) neuropathic pain score, hematology and clinical chemistry test results, vital signs, trial drug usage, and intoxication visual analogue scale scores. Results: Sixty-six patients were enrolled in the randomized trial; 64 (97%) completed the randomized trial and 63 (95%) entered the open-label extension (race, white, 100%; sex, male, 14 [22%]; mean [SD] age, 49 [8.4] years [range, 27-71 years]). The mean (SD) duration of open-label treatment was 463 (378) days (median, 638 days; range, 3-917 days), with 34 (54%) patients completing >1 year of treatment with THC/CBD and 28 (44%) patients completing the open-label trial with a mean (SD) duration of treatment of 839 (42) days (median, 845 days; range, 701-917 days). Mean NRS-11 pain scores in the final week of the randomized trial were 3.8 in the treatment group and 5.0 in the placebo group. In the 28 (44%) patients who completed the 2-year follow up, the mean (SD) NRS-11 pain score in the final week of treatment was 2.9 (2.0) (range, 0-8.0). Fifty-eight (92%) patients experienced >=1 treatment-related AE. These AEs were rated by the investigator as mild in 47 (75%) patients, moderate in 49 (78%), and severe in 32 (51%). The most commonly reported AEs were dizziness (27%), nausea (18 %), and feeling intoxicated (11%). Two treatmentrelated serious AEs (ventricular bigeminy and circulatory collapse) were judged to be treatment-related. Both serious AEs occurred in the same patient and resolved completely following a period of discontinuation. Eleven (17%) patients experienced oral discomfort, 4 persistently. Regular oral examinations revealed that 7 (11%) patients developed white buccal mucosal patches and 2 (3%) developed red buccal mucosal patches; all cases were deemed mild and resolved. Seventeen (25%) patients withdrew due to AEs. The mean number of sprays and patients experiencing intoxication remained stable throughout the follow-up trial. Conclusions: THC/CBD was effective, with no evidence of tolerance, in these select patients with CNP and MS who completed ~2 years of treatment ($n = 28$). Ninety-two percent of patients experienced an AE, the most common of which were dizziness and nausea. The majority of AEs were deemed to be of mild to moderate severity by the investigators.

Rönitz, H. (2002) Cannabis als Medizin – "Von der Patienteninitiative zum Pharmaunternehmen." Deutsche Zeitschrift für Klinische Forschung 7/8 2002: 68-70.

Rosenthal, M.S. and H.D. Kleber (1999) "Making sense of medical marijuana." Proceedings of the Association of American Physicians 111 (2): 159-165.

The case for marijuana's medical use is primarily from anecdotal clinical reports, human studies of Δ-9-tetrahydrocannabinol, and animal studies on constituent compounds. The authors believe that while a key policy issue is to keep marijuana out of the hands of children, its use for medicinal purposes should be resolved by scientific research and Food and Drug Administration (FDA) review. Weighed against possible benefits are increased risks such as cancer, pulmonary problems, damage to the immune system, and unacceptable psychological effects. More study is needed to determine the efficacy of marijuana as an antiemetic for cancer patients, as an appetite



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stimulant for AIDS and cancer patients, as a treatment for neuropathic pain, and as an antispasmodic for multiple sclerosis patients. If this new research shows marijuana to have important medical uses, FDA approval could be sought. However, the better response is accelerated development of delivery systems other than smoking for key ingredients, as well as the identification of targeted molecules that deliver beneficial effects without intoxicating effects. If the National Institutes of Health conducts research on marijuana, we would propose parallel trials on those indications under careful controls making marijuana available to appropriate patients who fail to benefit from standard existing treatments. This effort would begin after efficacy trials and sunset no later than 5 years. If this open-trial mechanism is adopted, the compassion that Americans feel for seriously ill individuals would have an appropriate medical/scientific outlet and not need to rely on referenda that can confuse adolescents by disseminating misleading information about marijuana effects.

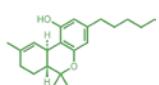
Roth, M.D., S.M. Dubinett, and J.P. Kassirer (1997) "Medicinal marijuana?" New England Journal of Medicine **336** (16): 1184.

Rudich, Z., J. Stinson, M. Jeavons, and S.C. Brown (2003) "Treatment of chronic intractable neuropathic pain with dronabinol: case report of two adolescents." Pain Research Management **8** (4): 221-224.

Objective: To evaluate the effectiveness of dronabinol for the treatment of neuropathic pain refractory to previous treatment. Methods: We studied the response (reduction of pain intensity and functional improvement) to dronabinol (5 mg/day to 25 mg/day) in two adolescents with neuropathic pain and depression refractory to previous treatments over two and five years, respectively. Results: Reduction in pain intensity (45%) was achieved in patient 2 and was unchanged in patient 1. Functional improvement was markedly increased in terms of academic performance, mood and sleep in both patients over four to five months, without major adverse effects. While these improvements dissipated over time, the patients were more reconnected with rehabilitation and focused less on the intrusiveness of their pain problem in their every day lives. Conclusions: Dronabinol appeared to be effective in improving pain affect and psychosocial functioning in the treatment of refractory neuropathic pain and may be considered as an adjuvant medication in the rehabilitation process. Well-controlled placebo studies are required for further evaluation.

Ruggieri, M.R., Sr. (2011) "Cannabinoids: potential targets for bladder dysfunction." Handbook of Experimental Pharmacology 202: 425-451.

Cannabinoids are the active chemical components of Cannabis sativa (marijuana). The medical use of cannabis goes back over 5,000 years. Cannabinoids produce a very wide array of central and peripheral effects, some of which may have beneficial clinical applications. The discovery of cannabinoid receptors has spawned great interest within the pharmaceutical industry with the hopes of capitalizing on the beneficial effects of cannabis without the unwanted psychotropic effects on the central and peripheral nervous system. This chapter presents an overview of the pharmacology of cannabinoids and their derivatives. It reviews the current literature on central and peripheral cannabinoid receptors as related to effects on the lower urinary



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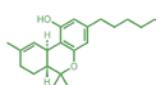
tract and the role of these receptors in normal and abnormal urinary tract function. An objective evaluation of the published results of clinical trials of cannabis extracts for the treatment of bladder dysfunction resulting from multiple sclerosis is also presented. It is clear that cannabinoid receptors are present in the lower urinary tract as well as spinal and higher centers involved in lower urinary tract control. Systemic cannabinoids have effects on the lower urinary tract that may be able to become clinically useful; however, a much greater understanding of the mechanisms of cannabinoid receptors in control of the human lower urinary tract is necessary to facilitate development of novel cannabinoid drugs for treatment of pelvic disorders.

Russo, E.B. (2008) "Cannabinoids in the management of difficult to treat pain." Therapeutics and Clinical Risk Management **4** (1): 245-259.

This article reviews recent research on cannabinoid analgesia via the endocannabinoid system and non-receptor mechanisms, as well as randomized clinical trials employing cannabinoids in pain treatment. Tetrahydrocannabinol (THC, Marinol®) and nabilone (Cesamet®) are currently approved in the United States and other countries, but not for pain indications. Other synthetic cannabinoids, such as ajulemic acid, are in development. Crude herbal cannabis remains illegal in most jurisdictions but is also under investigation. Sativex®, a cannabis derived oromucosal spray containing equal proportions of THC (partial CB(1) receptor agonist) and cannabidiol (CBD, a non-euphoriant, anti-inflammatory analgesic with CB(1) receptor antagonist and endocannabinoid modulating effects) was approved in Canada in 2005 for treatment of central neuropathic pain in multiple sclerosis, and in 2007 for intractable cancer pain. Numerous randomized clinical trials have demonstrated safety and efficacy for Sativex in central and peripheral neuropathic pain, rheumatoid arthritis and cancer pain. An Investigational New Drug application to conduct advanced clinical trials for cancer pain was approved by the US FDA in January 2006. Cannabinoid analgesics have generally been well tolerated in clinical trials with acceptable adverse event profiles. Their adjunctive addition to the pharmacological armamentarium for treatment of pain shows great promise.

Russo, E.B. (2003) "Cannabis and Cannabis Based Medicine Extracts: Additional Results." Journal of Cannabis Therapeutics **3/4**: 153-161.

This study reviews results in recent human clinical trials with cannabis based medicine extract (CBME), THC or cannabis. In a study performed at Queen's Square, London, both High THC and THC:CBD fixed ratio sublingual CBME demonstrated significant benefits on mean maximum cystometric capacity, mean daytime frequency of urination, frequency of nocturia, and mean daily episodes of incontinence in 11 multiple sclerosis patients with intractable lower urinary tract symptoms. A Phase II clinical study in Oxford, England with 24 MS and intractable pain patients was performed as a consecutive series of double-blind, randomized, placebo-controlled single patient cross-over trials with sublingual CBME. Pain scores on visual analogue scales were significantly improved over placebo with both High THC and High CBD CBME. Subjectively, spasm was significantly improved with High THC and THC:CBD fixed ratio extracts. Spasticity was also subjectively improved with the High THC CBME. All three extracts significantly improved objective measures of



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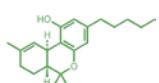
spasticity, while the High THC and THC:CBD fixed ratio CBME significantly improved objective measures of spasm. In 34 intractable pain patients in Great Yarmouth, England, seven experienced substantial improvement over best available conventional treatment with CBME, 13 moderate, and eight some benefit. Many extended the range of their activities of daily living with acceptable levels of adverse effects. Preliminary results of four Phase III clinical trials of CBME by GW Pharmaceuticals have revealed highly significant benefits in neuropathic pain in MS, pain and sleep disturbance in MS and other neurological diseases, multiple symptoms in MS, and neuropathic pain in brachial plexus injury, respectively. Most patients attained good symptomatic control with minimal side effects. In Germany, a recent Phase II clinical trial has demonstrated significant benefit of oral THC in treatment of the tics of Tourette syndrome.

Russo, E.B. (2003) "Future of Cannabis and Cannabinoids in Therapeutics." Journal of Cannabis Therapeutics **3/4**: 163-174.

This study reviews human clinical experience to date with several synthetic cannabinoids, including nabilone, levonantradol, ajulemic acid (CT3), Dexanabinol (HU-211), HU-308, and SR141716 (Rimonabant®). Additionally, the concept of "clinical endogenous cannabinoid deficiency" is explored as a possible factor in migraine, idiopathic bowel disease, fibromyalgia and other clinical pain states. The concept of analgesic synergy of cannabinoids and opioids is addressed. A cannabinoid-mediated improvement in night vision at the retinal level is discussed, as well as its potential application to treatment of retinitis pigmentosa and other conditions. Additionally noted is the role of cannabinoid treatment in neuroprotection and its application to closed head injury, cerebrovascular accidents, and CNS degenerative diseases including Alzheimer, Huntington, Parkinson diseases and ALS. Excellent clinical results employing cannabis based medicine extracts (CBME) in spasticity and spasms of MS suggests extension of such treatment to other spastic and dystonic conditions. Finally, controversial areas of cannabinoid treatment in obstetrics, gynecology and pediatrics are addressed along with a rationale for such interventions.

Russo, E.B. and G.W. Guy (2006) "A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol." Medical Hypotheses **66** (2): 234-246.

This study examines the current knowledge of physiological and clinical effects of tetrahydrocannabinol (THC) and cannabidiol (CBD) and presents a rationale for their combination in pharmaceutical preparations. Cannabinoid and vanilloid receptor effects as well as non-receptor mechanisms are explored, such as the capability of THC and CBD to act as anti-inflammatory substances independent of cyclo-oxygenase (COX) inhibition. CBD is demonstrated to antagonise some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties in its own right. In modern clinical trials, this has permitted the administration of higher doses of THC, providing evidence for clinical efficacy and safety for cannabis based extracts in treatment of spasticity, central pain and lower urinary tract symptoms in multiple sclerosis, as well as sleep disturbances, peripheral neuropathic pain,



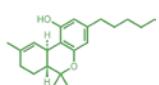
brachial plexus avulsion symptoms, rheumatoid arthritis and intractable cancer pain. Prospects for future application of whole cannabis extracts in neuroprotection, drug dependency, and neoplastic disorders are further examined. The hypothesis that the combination of THC and CBD increases clinical efficacy while reducing adverse events is supported.

Russo, E.B., G.W. Guy, and P.J. Robson (2007) "Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine." Chemistry & Biodiversity 4 (8): 1729-1743.

Cannabis sativa L. has been utilized for treatment of pain and sleep disorders since ancient times. This review examines modern studies on effects of Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) on sleep. It goes on to report new information on the effects on sleep in the context of medical treatment of neuropathic pain and symptoms of multiple sclerosis, employing standardized oromucosal cannabis-based medicines containing primarily THC, CBD, or a 1 : 1 combination of the two (Sativex). Sleep-laboratory results indicate a mild activating effect of CBD, and slight residual sedation with THC-predominant extracts. Experience to date with Sativex in numerous Phase I-III studies in 2000 subjects with 1000 patient years of exposure demonstrate marked improvement in subjective sleep parameters in patients with a wide variety of pain conditions including multiple sclerosis, peripheral neuropathic pain, intractable cancer pain, and rheumatoid arthritis, with an acceptable adverse event profile. No tolerance to the benefit of Sativex on pain or sleep, nor need for dosage increases have been noted in safety extension studies of up to four years, wherein 40-50% of subjects attained good or very good sleep quality, a key source of disability in chronic pain syndromes that may contribute to patients' quality of life.

Russo, E.B., G.W. Guy, and P.J. Robson (2007) "Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine." Chemistry & Biodiversity 4 (8):

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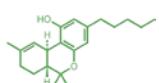
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Russo, E. and G.W. Guy (2006) "A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol." Medical Hypotheses **66** (2): 234-246.

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Russo, E., M.L. Mathre, A. Byrne, R. Velin, P.J. Bach, J. Sanchez-Ramos and K.A. Kirlin (2002) "Chronic Cannabis Use in the Compassionate Investigational New Drug Program: An Examination of Benefits and Adverse Effects of Legal Clinical Cannabis." Journal of Cannabis Therapeutics **2** (1): 3-57.

The Missoula Chronic Clinical Cannabis Use Study was proposed to investigate the therapeutic benefits and adverse effects of prolonged use of "medical marijuana" in a cohort of seriously ill patients. Use of cannabis was approved through the Compassionate Investigational New Drug (IND) program of the Food and Drug Administration (FDA). Cannabis is obtained from the National Institute on Drug Abuse (NIDA), and is utilized under the supervision of a study physician. The aim of this study is to examine the overall health status of 4 of the 7 surviving patients in the program. This project provides the first opportunity to scrutinize the long term effects of cannabis on patients who have used a known dosage of a standardized, heat sterilized quality controlled supply of low grade marijuana for 11 to 27 years. Results demonstrate clinical effectiveness in these patients in treating glaucoma, chronic musculoskeletal pain, spasm and nausea, and spasticity of multiple sclerosis. All 4 patients are stable with respect to their chronic conditions, and are taking many fewer standard pharmaceuticals than previously. Mild changes in pulmonary function were observed in 2 patients, while no functionally significant attributable sequelae were noted in any other physiological system examined in the study, which included: MRI scans of the brain, pulmonary function tests, chest Xray, neuropsychological tests, hormone and immunological assays, electroencephalography, P300 testing, history, and neurological clinical examination. These results would support the provision of clinical cannabis to a greater number of patients in need. We believe that cannabis can be a safe and effective medicine with various suggested improvements in the existing Compassionate IND program.



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Russo, E.B. (2007) "History of cannabis and its preparations in saga, science, and sobriquet." Chemistry & Biodiversity **4** (8): 1614-1648.

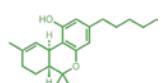
Cannabis sativa L. is possibly one of the oldest plants cultivated by man, but has remained a source of controversy throughout its history. Whether pariah or panacea, this most versatile botanical has provided a mirror to medicine and has pointed the way in the last two decades toward a host of medical challenges from analgesia to weight loss through the discovery of its myriad biochemical attributes and the endocannabinoid system wherein many of its components operate. This study surveys the history of cannabis, its genetics and preparations. A review of cannabis usage in Ancient Egypt will serve as an archetype, while examining first mentions from various Old World cultures and their pertinence for contemporary scientific investigation. Cannabis historians of the past have provided promising clues to potential treatments for a wide array of currently puzzling medical syndromes including chronic pain, spasticity, cancer, seizure disorders, nausea, anorexia, and infectious disease that remain challenges for 21st century medicine. Information gleaned from the history of cannabis administration in its various forms may provide useful points of departure for research into novel delivery techniques and standardization of cannabis-based medicines that will allow their prescription for treatment of these intractable medical conditions.

Sandyk, R. and G. Awerbuch (1988) "Marijuana and Tourette's syndrome." Journal of Clinical Psychopharmacology **8** (6): 444-445.

Sanz Ortiz, J. and C. Cara Terribas (2002) "[Cannabis and their synthetics derivates. Could they be useful in medicine?]" Medicina Paliativa **9** (3): 120-128.

Cannabinoids have a long history of consumption for recreational and medical reasons. The primary active constituent of the hemp plant cannabis sativa is Δ-9-tetrahydrocannabinol (Δ-9-THC). The discovery of cannabinoid CB(1) receptors and CB(2) receptors and endogenous agonists for these receptors has renewed the scientific community's interest. Cannabinoids have been suggested to have therapeutic value as analgesics and in various conditions, including migraine headaches, nausea and vomiting, wasting syndrome and appetite stimulation in HIV-infected patients, muscle spasticity due to multiple sclerosis or spinal cord injury, movement disorders such as Parkinson's disease, epilepsy, and glaucoma. When new therapeutic indications are suggested, two major factors should be taken into account: what are the adverse effects of the treatment and how does its effectiveness compare with that of existing alternatives? However, the current information is that the adverse effects of cannabinoids outweigh their effectiveness. This review can help us to keep on research about potential benefit of cannabinoids. Recently nabilone has been approved by FDA and Healthy Authorities in Spain to treat emesis post chemotherapy. Would it be possible to research this compound as pain killer in oncology? Future research may provide us with better cannabinoid compounds with potential new therapeutic applications.

Sastre-Garriga, J., C. Vila, S. Clissold, and X. Montalban, (2011) "THC and CBD oromucosal spray (Sativex®) in the management of spasticity associated with multiple sclerosis." Expert Review of Neurotherapeutics **11** (5): 627-637.



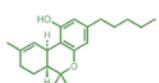
People with multiple sclerosis may present with a wide range of disease symptoms during the evolution of the disease; among these, spasticity can have a marked impact on their well-being and quality of life. Symptom control, including spasticity, remains a key management strategy to improve the patient's well-being and functional status. However, available drug therapies for spasticity sometimes have limited benefit and they are often associated with poor tolerability. Sativex is a 1:1 mix of 9- Δ -tetrahydrocannabinol and cannabidiol extracted from cloned Cannabis sativa chemovars, which is available as an oromucosal spray. Clinical experience with Sativex in patients with multiple sclerosis is accumulating steadily. Results from randomized, controlled trials have reported a reduction in the severity of symptoms associated with spasticity, leading to a better ability to perform daily activities and an improved perception of patients and their carers regarding functional status when Sativex was added to the current treatment regimen. Adverse events such as dizziness, diarrhea, fatigue, nausea, headache and somnolence occur quite frequently with Sativex, but they are generally of mild-to-moderate intensity and their incidence can be markedly reduced by gradual 'uptitration'. In summary, initial well-controlled studies with Sativex oromucosal spray administered as an add-on to usual therapy have produced promising results and highlight encouraging avenues for future research.

Schaeffer, J., T. Andrysiak and J.T. Ungerleider (1981) "Cognition and long-term use of ganja (Cannabis)." Science **213** (4506): 465-466.

Neuropsychological variables and urine cannabinoid metabolites were evaluated in ten subjects born, raised, and educated in the United States and having histories of heavy or prolonged use of cannabis. No impairment of cognitive function was found. Cannabinoid metabolites in excess of 50 nanograms per milliliter were present in the ten urine samples. The tetrahydrocannabinol content of cannabis exceeded 8.0%.

Schapiro, R.T. (1994) "Symptom management in multiple sclerosis." Annals of Neurology **36**: S123-S129.

Presently, the course of multiple sclerosis (MS) can be altered little, if at all. Appropriate symptom management, however, can change the course of lives and allow for more comfortable, healthier living despite significant disease. Symptoms in MS are divided into three broad categories. Those that result from actual demyelination include decreased vision, weakness, spasticity, bladder problems, ataxia, numbness, and decreased cognition. Secondary symptoms spring from the primary; these symptoms include contractures, urinary tract infections, megacolon, decubiti, decreased bony calcification, and muscle atrophy. Tertiary symptoms are the unavoidable psychological, vocational, and social problems that occur with chronic disease. This article reviews standard therapies, but the emphasis is on newer management solutions that may not have reached their full potential, though they add to the development of an appropriate life-management plan for persons with MS. The pharmacological approach to symptom management is emphasized, while understanding that rehabilitation and medications cannot be separated in the real life alleviation of MS symptoms.



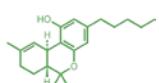
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Schapiro, R.T. (2001) "Management of spasticity, pain, and paroxysmal phenomena in multiple sclerosis." *Current Neurology and Neuroscience Reports* 1 (3): 299-302.

Multiple sclerosis (MS) is a disease with tremendous variability and innumerable symptoms. Among the more common symptoms is spasticity. Despite a lack of full knowledge of the physiology causing this phenomenon, successful treatments have been developed. Many of these have had a recent introduction. Pain and paroxysmal phenomena are surprisingly common in MS, but have not had the recognition their frequency deserves. It is not unusual to hear that they are rare in MS, but surprisingly they are all too common. Their management is changing as newer treatments are developed.

Schnelle, M., F. Grotenhermen, M. Reif and R.W. Gorter (1999) "Results of a standardized survey on the medical use of Cannabis products in the German-speaking area." *Forschende Komplementärmedizin* 6 (Suppl. 3): 28-36.

The plant Cannabis sativa has a long history of medical use in the treatment of pain and spasms, the promotion of sleep, and the suppression of nausea and vomiting. However, in the early 70s cannabis was classified in the Narcotic Acts in countries all over the world as having no therapeutic benefit; therefore, it cannot be prescribed by physicians or dispensed by pharmacists. In the light of this contradictory situation an increasing number of patients practices a self-prescription with cannabis products for relieving a variety of symptoms. An anonymous standardized survey of the medical use of cannabis and cannabis products of patients in Germany, Austria and Switzerland was conducted by the Association for Cannabis as Medicine (Cologne, Germany). During about one year 170 subjects participated in this survey; questionnaires of 128 patients could be included into the evaluation. 68% of these participants were males, 32% females, with a total mean age of 37.5 (+-9.6) years. The most frequently mentioned indications for medicinal cannabis use were depression (12.0%), multiple sclerosis (10.8%), HIV- infection (9.0%), migraine (6.6%), asthma (6.0%), back pain (5. 4%), hepatitis C (4.8%), sleeping disorders (4.8%), epilepsy (3.6%), spasticity (3.6%), headache (3.6%), alcoholism (3.0%), glaucoma (3.0%), nausea (3.0%), disk prolapse (2.4%), and spinal cord injury (2.4%). The majority of patients used natural cannabis products such as marihuana, hashish and an alcoholic tincture; in just 5 cases dronabinol (Marinol[®]) was taken by prescription. About half of the 128 participants of the survey (52. 4%) had used cannabis as a recreational drug before the onset of their illness. To date 14.3% took cannabis orally, 49.2% by inhalation and in 36.5% of cases both application modes were used. 72.2% of the patients stated the symptoms of their illness to have 'much improved' after cannabis ingestion, 23.4% stated to have 'slightly improved' 4.8% experienced 'no change' and 1.6% described that their symptoms got 'worse'. Being asked for the satisfaction with their therapeutic use of cannabis 60.8% stated to be 'very satisfied', 24.0% 'satisfied', 11.2% 'partly satisfied' and 4.0% were 'not satisfied'. 70.8% experienced no side effects, 26.4% described 'moderate' and 3.3% 'strong' side effects. 84.1% of patients have not felt any need for dose escalation during the last 3 months, 11.0% had to increase their cannabis dose 'moderately' and 4.8% 'strongly' in order to maintain the therapeutic effects. Thus, this survey demonstrates a successful use of cannabis products for the treatment of a multitude of various illnesses and symptoms. This use was usually accompanied only by slight and in general acceptable side



effects. Because the patient group responding to this survey is presumably highly selected, no conclusions can be drawn about the quantity of wanted and unwanted effects of the medicinal use of the hemp plant for particular indications.

Die Arbeitsgemeinschaft Cannabis als Medizin (Köln) führte in Zusammenarbeit mit dem Europäischen Institut für onkologische und immunologische Forschung (Berlin) eine anonyme, standardisierte Umfrage zur medizinischen Verwendung von Cannabisprodukten in Deutschland, der Schweiz und Österreich durch. Daran nahmen zwischen April 1998 und April 1999 170 Personen teil. 128 Fragebögen gingen in die Auswertung ein.

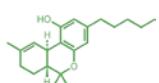
Schulz, V. (2009) "Cannabis-Inhalation gegen neuropathische Schmerzen. Randomisierte Doppelblindstudie zur Nutzen-Risiko-Abwägung." Zeitschrift für Phytotherapie **30** (2): 75.

Schwarz, S., H. Leweling and H.M. Meinck (2005) "[Alternative and complementary therapies in multiple sclerosis]." Fortschritte der Neurologie Psychiatrie **73** (8): 451-462.

Most MS patients use unconventional therapies, usually as complementary measures in addition to the conventional treatment. Only a few adequate clinical trials exist in this field. By definition, the efficacy of these therapies is unproven. Moreover, the possible risks are also largely unknown. Some therapies rely on rational pathophysiological considerations, others must be regarded as potentially harmful. The influence of diet on MS is unproven. Possibly, unsaturated fatty acids are beneficial. However, a few randomized trials yielded inconclusive results. Long-term supplementation of Vitamin D is associated with a decreased MS incidence. There is, however, insufficient evidence for an influence of Vitamin D on the course of the disease. Because of the high prevalence of osteoporosis in MS patients, prophylaxis with Vitamin D and Calcium is widely accepted. The effects of various minerals, selenium, antioxidant compounds, fish oil or vitamins remain speculative. Many patients use cannabis to alleviate spasticity and pain. Small series indicated positive effects, but randomized trials were negative for spasticity. However, many patients report subjective improvement under cannabis even if their objective parameters remain unchanged. Hyperbaric oxygenation was the subject of several small studies with heterogeneous results which, overall, do not support its use. Generally, physical therapies are perceived as an established therapy for MS. Short-term effects are probable, whereas the possible favourable long-term effects are unclear.

Schwenkreis, P. and M. Tegenthoff (2003) "[Therapeutic use of cannabinoids in neurology]." Schmerz **17** (5): 367-373.

This review gives insight into the potential therapeutical role of cannabinoids in neurology. Preclinical data are presented which could give a rationale for the clinical use of cannabinoids in the fields of multiple sclerosis, spasticity, epilepsy, movement disorders, and neuroprotection after traumatic head injury or ischemic stroke. Besides, clinical data (case reports, open-label and randomised controlled studies) dealing with the therapeutical use of cannabinoids in these fields are reported and discussed. At present, clinical data are insufficient to recommend the use of cannabinoids in any



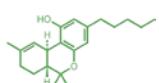
neurological disease as standard therapy. Several questions still have to be answered (which cannabinoid? which way of administration? stimulation of endogenous cannabinoids? separation between desired and undesired effects?), and controlled studies are still needed to clarify the potential therapeutical role of cannabinoids in neurology.

Serpell, M.G., W. Notcutt and C. Collin (2012) "Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis." Journal of Neurology: Epub ahead of print.

Sativex is an endocannabinoid system modulator principally containing Δ -9-tetrahydrocannabinol (THC) and cannabidiol (CBD). During a 6-week randomised controlled trial, Sativex had a clinically relevant effect on spasticity associated with multiple sclerosis (MS). Patients self-titrated oromucosal Sativex to symptom relief or maximum tolerated dose (maximum of 130 mg THC and 120 mg CBD daily). The primary objective was to evaluate the safety and tolerability of long-term treatment by recording the incidence and severity of adverse events (AEs). Secondary outcomes were to determine evidence of developing tolerance and to assess the long-term dosing profile of Sativex. A validated 11-point Numerical Rating Scale of spasticity severity was used to assess efficacy. A total of 146 patients elected to enter this open-label follow-up safety trial. Mean treatment exposure was 334 days (standard deviation, SD = 209 days), and patients administered on average 7.3 (SD = 4.42) actuations per day. Fifty-two (36 %) patients withdrew from the study in the first year, 14 % due to AEs and 9 % due to lack of efficacy. Most AEs were mild/moderate in severity. Common (>10 %) treatment-related AEs were dizziness (24.7 %) and fatigue (12.3 %). Serious AEs occurred in five patients (3.4 %), with two psychiatric events reported by one patient. No psychoses, psychiatric AE trends, or withdrawal symptoms occurred following abrupt cessation of treatment. Baseline symptoms including spasticity did not deteriorate but were maintained to study completion in those patients who did not withdraw. No new safety concerns were identified with chronic Sativex treatment, and serious AEs were uncommon. There was no evidence of tolerance developing, and patients who remained in the study reported continued benefit.

Smith, P.F. (2007) "Symptomatic treatment of Multiple Sclerosis using cannabinoids: recent advances." Expert Review of Neurotherapeutics 7 (9): 1157-1763.

Recent years have seen a dramatic increase in the number of clinical trials investigating the potential efficacy of medicinal cannabinoids for the symptomatic treatment of chronic pain and spasticity in multiple sclerosis (MS). A number of different cannabinoids have been used, including: Δ -9-tetrahydrocannabinol (THC) itself; the synthetic Δ -9-THC, dronabinol; a 1:1 ratio of Δ -9-THC:cannabidiol (Sativex); and the synthetic Δ -9-THC metabolites CT-3 and nabilone. Other Cannabis extracts have also been tested. While 2-3 years ago there was little consensus in the literature, now the majority of studies are beginning to suggest that cannabinoids are useful in the treatment of MS in at least a subset of individuals. Their adverse side-effect profile has generally been mild compared with other drugs used for pain and spasticity; nonetheless, there is still concern about potential long-term side effects, particularly psychiatric side effects and effects on fetal development.



Cannabis, Dronabinol und die Behandlung schwerer Erkrankungen

Svendsen, K.B., T.S. Jensen, and F.W. Bach (200) "[Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis.]" Ugeskrift For Laeger 167 (25-31): 2772-2774.

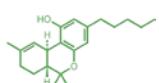
Cannabinoids reduce allodynia/hyperalgesia in animal pain models, but few clinical studies evaluated the analgesic action in humans. We aimed to evaluate the effect of Δ-9-tetrahydrocannabinol (dronabinol) on central pain in MS patients. Twenty-four MS patients participated in a double-blind placebo-controlled crossover trial. Dronabinol reduced the spontaneous pain intensity significantly compared with placebo (4.0 (2.3-6.0) vs. 5.0 (4.0-6.4), median (25th-75th percentiles), $p = 0.02$). Though dronabinol's analgesic effect is modest, its use should be evaluated considering the general difficulty in treating central pain.

Svendsen, K.B., T.S. Jensen, and F.W. Bach (2004) "Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial." British Medical Journal 329 (7460): 253.

Objective: To evaluate the effect of the oral synthetic Δ-9-tetrahydrocannabinol dronabinol on central neuropathic pain in patients with multiple sclerosis. Design: Randomised double blind placebo controlled crossover trial. Setting: Outpatient clinic, University Hospital of Aarhus, Denmark. Participants: 24 patients aged between 23 and 55 years with multiple sclerosis and central pain. Intervention: Orally administered dronabinol at a maximum dose of 10 mg daily or corresponding placebo for three weeks (15-21 days), separated by a three week washout period. Main Outcome Measure: Median spontaneous pain intensity (numerical rating scale) in the last week of treatment. Results: Median spontaneous pain intensity was significantly lower during dronabinol treatment than during placebo treatment (4.0 (25th to 75th centiles 2.3 to 6.0) v 5.0 (4.0 to 6.4), $P = 0.02$), and median pain relief score (numerical rating scale) was higher (3.0 (0 to 6.7) v > 0 (0 to 2.3), $P = 0.035$). The number needed to treat for 50% pain relief was 3.5 (95% confidence interval 1.9 to 24.8). On the SF-36 quality of life scale, the two items bodily pain and mental health indicated benefits from active treatment compared with placebo. The number of patients with adverse events was higher during active treatment, especially in the first week of treatment. The functional ability of the multiple sclerosis patients did not change. Conclusions: Dronabinol has a modest but clinically relevant analgesic effect on central pain in patients with multiple sclerosis. Adverse events, including dizziness, were more frequent with dronabinol than with placebo during the first week of treatment.

Seamon, M.J., J.A. Fass, M. Maniscalco-Feichtl and N.A. Abu-Shraie (2007) "Medical marijuana and the developing role of the pharmacist." American Journal of Health-System Pharmacy 64 (10): 1037-1044.

Purpose: The pharmacology, therapeutic uses, safety, drug-drug interactions, and drug-disease interactions of medical marijuana are reviewed, and the legal issues related to its use and the implications of medical marijuana for the pharmacist are presented. SUMMARY: Marijuana contains more than 460 active chemicals and over 60 unique cannabinoids. The legal landscape surrounding marijuana is surprisingly complex and unsettled. In the United



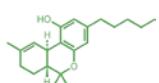
States, 11 states and several municipalities have legalized medical marijuana. Another state provides legislation that allows patients to claim a defense of medical necessity. Nevertheless, patients using medical marijuana may never interact with a pharmacist. Marijuana is a Schedule I controlled substance and its use is illegal under federal law. Marijuana has a number of purported therapeutic uses with a broad range of supporting evidence. There are five general indications for medical marijuana: (1) severe nausea and vomiting associated with cancer chemotherapy or other causes, (2) weight loss associated with debilitating illnesses, including HIV infection and cancer, (3) spasticity secondary to neurologic diseases, such as multiple sclerosis, (4) pain syndromes, and (5) other uses, such as for glaucoma. Marijuana is associated with adverse psychiatric, cardiovascular, respiratory, and immunologic events. Moreover, marijuana may interact with a number of prescription drugs and concomitant disease states. CONCLUSION: Several states have legalized the use of marijuana for chronic and debilitating medication conditions. Pharmacists need to understand the complex legal framework surrounding this issue so that they can protect themselves and better serve their patients.

Slof, J. and A. Gras (2012) "Sativex® in multiple sclerosis spasticity: a cost-effectiveness model" Expert Review of Pharmacoeconomics & Outcomes Research: Epub ahead of print.

Background: Multiple sclerosis (MS) is a chronic, progressive disease that carries a high socioeconomic burden. Spasticity (rigidity and spasms) is common in MS and a key contributor to MS-related disability. Objectives: This study evaluated the cost-effectiveness of Sativex®, a Δ-9-tetrahydrocannabinol/cannabidiol-based oromucosal spray that acts as an endocannabinoid system modulator. Sativex was recently approved for the management of resistant MS spasticity as add-on medication. Methods: A Markov model-based analysis was performed over a 5-year horizon from a German and Spanish healthcare payer perspective. The incremental cost of Sativex was low compared with current spasticity treatments, and provided a quality-adjusted life-year gain over the current standard of care. Results: The base-case incremental cost-effectiveness ratio for Sativex was estimated at euro11,214/quality-adjusted life-year in Germany, while the drug was the dominant option in Spain, providing savings of euro3496/patient over a 5-year period (year of costing: 2010). This was seen because the lower severity of spasticity in patients who had improved led to reduced resource consumption (e.g., physiotherapy and medications). Conclusion: Despite having a relatively high acquisition cost, Sativex was shown to be a cost-effective treatment option for patients with MS-related spasticity.

Smith, P.F. (2002) "Cannabinoids in the treatment of pain and spasticity in multiple sclerosis." Current Opinion in Investigational Drugs 3 (6): 859-864.

There is a large amount of evidence to support the view that the psychoactive ingredient in cannabis, Δ-9-tetrahydrocannabinol (Δ-9-THC), and cannabinoids in general, can reduce muscle spasticity and pain under some circumstances. Cannabinoid (CB1) receptors in the CNS appear to mediate both of these effects and endogenous cannabinoids may fulfill these functions to some extent under normal circumstances. However, in the context of



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multiple sclerosis (MS), it is still questionable whether cannabinoids are superior to existing, conventional medications for the treatment of spasticity and pain. In the case of spasticity, there are too few controlled clinical trials to draw any reliable conclusion at this stage. In the case of pain, most of the available trials suggest that cannabinoids are not superior to existing treatments; however, few trials have examined chronic pain syndromes that are relevant to MS. Whether or not cannabinoids do have therapeutic potential in the treatment of MS, a further issue will be whether synthetic cannabinoids should be used in preference to cannabis itself. Smoking cannabis is associated with significant risks of lung cancer and other respiratory dysfunction. Furthermore, Δ -9-THC, as a broad-spectrum cannabinoid receptor agonist, will activate both CB1 and CB2 receptors. Synthetic cannabinoids, which target specific cannabinoid receptor subtypes in specific parts of the CNS, are likely to be of more therapeutic use than Δ -9-THC itself. If rapid absorption is necessary, such synthetic drugs could be delivered via aerosol formulations.

Smith, P.F. (2004) "Medicinal cannabis extracts for the treatment of multiple sclerosis." Current Opinion in Investigational Drugs 5 (7): 727-730.

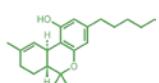
Prior to 2002, few clinical data were available to indicate whether cannabis extracts may be beneficial. However, in the last two years, results of several placebo-controlled clinical trials of orally administered compounds have been published, and these cast doubt on the efficacy of Δ -9-tetrahydrocannabinol (Δ -9-THC) in objectively reducing spasticity in MS. By contrast, it has been claimed that sublingually administered cannabis extracts that contain approximately equal concentrations of Δ -9-THC and cannabidiol, a natural cannabinoid that does not act on the CB1 receptor, can produce a statistically and clinically significant reduction in spasticity, although this claim has yet to be thoroughly validated. Nonetheless, results of preclinical trials also lend support to the hypothesis that the endogenous cannabinoid system may be involved in the regulation of spasticity and pain. A better indication of the clinical potential of the different cannabis extracts will have to await the publication of the most recent clinical trial data. This review critically evaluates the most recent evidence available on the potential use of medicinal extracts of cannabis to relieve pain and spasticity in multiple sclerosis.

Smith, P.F. (2004) "GW-1000. GW Pharmaceuticals." Current Opinion in Investigational Drugs 5 (7): 748-754.

GW Pharmaceuticals is developing GW-1000 (Sativex), a narrow ratio Δ -9-tetrahydrocannabinol-cannabidiol product for the potential treatment of multiple sclerosis, spinal cord injury, neurogenic pain and peripheral neuropathy. In March 2003, the company filed for approval for the treatment of MS with the UK Medicines Control Agency, and in May 2004, filed for new drug submission with Health Canada.

Smith, P.F. (2005) "The safety of cannabinoids for the treatment of multiple sclerosis." Expert Opinion on Drug Safety 4 (3): 443-456.

The evidence for the therapeutic efficacy of cannabinoids in the treatment of multiple sclerosis (MS) is increasing but is not as yet convincing. Although several trials have reported no significant effect, the majority of the evidence



which supports a beneficial effect on spasticity and pain is based on subjective measurements in trials where unblinding was likely to be a problem. The available clinical trial data suggest that the adverse side effects associated with using cannabis-based medicinal extracts (CBMEs) are generally mild, such as dry mouth, dizziness, somnolence, nausea and intoxication, and in no case did toxicity develop. However, most of these trials were run over a period of months and it is possible that other adverse side effects, not seen in these short-term studies, could develop with long-term use. Despite the evidence that cannabinoids can disrupt cognitive function and promote depression, on the basis of current data, such adverse effects seem unlikely to be associated with the use of CBMEs. Likewise, there is no evidence to suggest that their effects on balance and motor control, or immune function, may be clinically significant. There is, however, reason to be concerned about the use of therapeutic cannabinoids by people predisposed to psychosis and by pregnant women, given the increasing evidence of their adverse effects on the fetus. In conclusion, given the modest therapeutic effects of cannabinoids demonstrated so far, and the risk of long-term adverse side effects, there is reason to be cautious about their use in the treatment of MS.

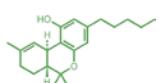
Smith, P.F. (2007) "Symptomatic treatment of multiple sclerosis using cannabinoids: recent advances." *Expert Review of Neurotherapeutics* 7 (9): 1157-1163.

Recent years have seen a dramatic increase in the number of clinical trials investigating the potential efficacy of medicinal cannabinoids for the symptomatic treatment of chronic pain and spasticity in multiple sclerosis (MS). A number of different cannabinoids have been used, including: Δ-9-tetrahydrocannabinol (THC) itself; the synthetic Δ-9-THC, dronabinol; a 1:1 ratio of Δ-9-THC:cannabidiol (Sativex); and the synthetic Δ-9-THC metabolites CT-3 and nabilone. Other Cannabis extracts have also been tested. While 2-3 years ago there was little consensus in the literature, now the majority of studies are beginning to suggest that cannabinoids are useful in the treatment of MS in at least a subset of individuals. Their adverse side-effect profile has generally been mild compared with other drugs used for pain and spasticity; nonetheless, there is still concern about potential long-term side effects, particularly psychiatric side effects and effects on fetal development.

Steup, C. (2001) "Zitrone gegen Vitamin C, Cannabis gegen Dronabinol - Versuch einer Versachlichung der Debatte um Cannabis in der medizinischen Therapie." Zur Cannabusiness 2001. *Hanf! 13/2001*: 45.

Cannabis gehört zu den traditionellen Arzneimitteln und kommt schon seit über 3.000 Jahren zur Anwendung. In der Folge des Aufbaus einer hochprofitablen chemischen und pharmazeutischen Industrie nach dem zweiten Weltkrieg geriet allerdings die Verwendung dieses nicht sehr gewinnträchtigen natürlichen Rohstoffes in Vergessenheit. Während die medizinische Cannabisforschung um die Jahrhundertwende noch recht aktiv war, ließ das Interesse ab den 30er Jahren aufgrund fehlender standardisierter Präparate und ab den 60er Jahren aufgrund der Stigmatisierung von Hanfprodukten stark nach.

Die Vollsynthese des Cannabiswirkstoffes und Umbenennung von THC zu Dronabinol entkoppelte in den 80er Jahren den Wirkstoff von der Pflanze und ermöglichte so die Zulassung von Marinol durch Unimed. Nach der Änderung



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des Betäubungsmittelgesetzes im Februar 1998 wurde es möglich, den Cannabiswirkstoff auch in Deutschland zu verschreiben.

Die 1996 von Betroffenen gegründete THC-Pharm entwickelte daraufhin ein Verfahren, den Hauptwirkstoff Dronabinol aus Faserhanf herzustellen, da die Verwendung von THC-reichem Hanf weiterhin verboten bleibt.

zu Christian Steup & THC-Pharm GmbH

Der verheiratete Vater von zwei Söhnen begann nach dem Abschluss des Medizinstudiums mit dem Pharmaziestudium, das er 1995 als Apotheker abschloss. Seine wissenschaftliche Neugier drängte ihn, ein eigenes Labor aufzubauen, das sich auf die Synthese komplexer Wirk- und Heilstoffe spezialisierte.

Positive Erfahrungen eines befreundeten querschnittgelähmten Biochemikers, der Cannabis zur Linderung auftretender Spasmen einsetzte, führten zu der Idee, Dronabinol zu synthetisieren und als Rezeptur auf den Markt zu bringen. Dazu wurde 1996 gemeinsam mit zwei unabhängigen Beratern aus dem Umwelt- und dem Finanzbereich die THC-Pharm GmbH gegründet. Ziel der Gesellschaft ist die legale Erforschung und Bereitstellung von dringend benötigten Medikamenten aus Cannabis und anderen nachwachsenden Rohstoffen für eine Vielzahl von medizinischen Indikationen. Hierbei soll besonders auch auf den Gebieten geforscht werden, die aufgrund einer zu kleinen Patientenzahl oder fehlender Patentierbarkeit für die pharmazeutischen Konzerne als unattraktiv gelten (so genannte "Orphan Drugs").

Christian Steup ist seit 1996 Geschäftsführender Gesellschafter der THC-Pharm GmbH.

Steup, C. and J. Hartinger (2001) "Informationen zu Betäubungsmitteln für Apotheker und Ärzte: Dronabinol." Frankfurt/Main, Informationsbroschüre der THC Pharm GmbH The Health Concept: 1-6. [<http://www.thc-pharm.de/aerzte.html>; DocCheck-Passwort nötig]

Seit dem 1. Februar 1998 ist Dronabinol, der psychotrope Hauptwirkstoff der Cannabispflanze (auch bekannt als THC oder Tetrahydrocannabinol), in Deutschland als Betäubungsmittel verschreibungsfähig.

Patienten, die bisher wegen ihres Gebrauchs von Cannabispräparationen (Marihuana und Haschisch) zu medizinischen Zwecken Probleme mit dem Strafrecht hatten, können nun mit dem Wirkstoff versorgt werden. Damit wurde ein medizinisch akzeptabler Handlungsrahmen für den Umgang mit den betroffenen Patienten geschaffen.

Dronabinol – (6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

Molekulargewicht: 314,468

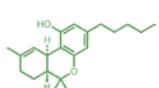
Summenformel: C₂₁H₃₀O₂

pK_s-Wert: 10,6

Steup, C. (2008) "Therapie mit Cannabinoiden – Die Rezepturstanz Dronabinol. Informationen für Fachpersonal." 2. Auflage. THC Pharm GmbH, Frankfurt.

Cannabis als Medizin Wirkstoff – Pharmazeutische Informationen – Indikationen – Studienlage – Verordnung – Dosierung – Fallbeispiele – Weitere Informationen

Cannabis ist ein traditionelles Heilmittel, das seit Jahrtausenden verwendet



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wird. Bis in das 20. Jahrhundert hinein wurde Cannabis bei den verschiedensten Beschwerden, von Asthma bis zu Migräne, eingesetzt. Gute Erfolge wurden traditionell bei der Linderung von Krämpfen und Schmerzen erzielt. Seine Zuverlässigkeit war jedoch aufgrund der unklaren Wirkkomponenten und ihrer stark schwankenden Konzentration und Bioverfügbarkeit eingeschränkt.

Steup, C. (2008) "Untersuchung des Handelsproduktes ‚Spice‘." Pressemitteilung der Fa. THC Pharm GmbH The Health Concept Frankfurt/Main

Einleitung

Seit einiger Zeit ist ein, als Räuchermischung beworbenes, angeblich nur aus Kräutern bestehendes Produkt unter dem Namen "Spice" erhältlich. Obwohl das Produkt als Räuchermischung bezeichnet wird, ist der allgemeine Gebrauch das Rauchen, insbesondere auch wegen der angenehmen psychotropen Effekte, die im Wesentlichen mit denen von Cannabis übereinstimmen. Da sich die Wirkung nicht aus der Zusammensetzung der Kräuter erklären lässt, wurde schon wiederholt die Vermutung geäußert, dass außer den gelisteten Stoffen, nicht aufgeführte Beimengungen die eigentliche Wirkung verursachen. Erste Untersuchungen einer Spice Probe auf Cannabinoide vor etwa einem Jahr zeigten jedoch nur ihre Abwesenheit. Beauftragt durch das Drogenreferat Frankfurt widmete sich die THC Pharm der Identifizierung der aktiven Ingredienzien.

Cannabinoide

Unter Cannabinoiden versteht man einerseits bestimmte Substanzen aus der Cannabis Pflanze, von denen nur das THC die typische Cannabiswirkung besitzt. Zum anderen bezeichnet man damit Stoffe, unabhängig von ihrer chemischen Struktur, die wie THC am Cannabinoid Rezeptor (CB-Rezeptor) binden. In der Arzneimittelforschung wurden seit der Entdeckung des CB-Rezeptors hunderte bis tausende von sogenannten CB-Agonisten synthetisiert. Die überwiegende Mehrzahl wurde nie am Menschen getestet, es ist jedoch offensichtlich, dass die meisten davon auch beim Menschen Cannabiseffekte hervorrufen.

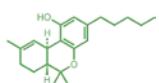
Untersuchung

Zunächst wurden zwei Proben untersucht: Yukatan Fire und Arctic Synergy. HPLC

Beide Proben zeigen ein fast identisches Muster. Es werden zwei Hauptpeaks gefunden. Der erste Peak (7,88 min) zeigt ein ähnliches UV-Spektrum wie Indometacin (ein Schmerzmittel aus der Klasse der NSAID). Der zweite Peak (19,08 min) zeigt ein ähnliches UV-Spektrum wie Cannabinoide.

Beurteilung der HPLC-Daten Der erste Peak mit Ähnlichkeit zum Indometacin weist in eine Richtung von Verbindungen, welche aus Pravadol (einem Indometacin Analog der Firma Winthrop), entwickelt wurden. Berühmtester Vertreter ist das WIN 55,212-2, ein hochpotentes Cannabinoid, welches heute einen Standard in der Arzneimittelforschung darstellt. Der zweite Peak stellt höchstwahrscheinlich eine Aromakomponente dar. GC-MS Die GC-MS Spektren zeigen wiederum eine starke Übereinstimmung beider Proben. Hier finden sich mehrere unbekannte Stoffe, neben Vitamin E.

Typische Cannabinoide (Benzochromenone) wurden nicht gefunden. WIN 55,212 ist nicht nachweisbar. Ein Peak (10,9 min) zeigt Übereinstimmung mit einem Abkömmling des WIN 55,212-2, der Substanz JWH-018 entwickelt an



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der Universität Clemson (Gruppe J. W. Huffman).

Beurteilung

Die gefundene Substanz JWH-018 ist ein CB Rezeptor Agonist mit THC Wirkung und erklärt vollständig die durch Spice hervorgerufenen Effekte. JWH-018 wurde entwickelt in dem Versuch, die Struktur des WIN55,212-2 zu vereinfachen.

Es besitzt eine ähnliche Stärke wie THC (im unteren Milligramm Bereich).

Es ist nicht wasserlöslich.

Die Applikation durch Rauchen ist möglich.

Rechtliche Lage

Nach Arzneimittelgesetz (AMG) stellen Stoffe (Zubereitungen), die das Bewusstsein verändern sollen, Arzneimittel dar. Arzneimittel dürfen ohne Zulassung weder verkauft, noch bereitgestellt werden. Verstöße sind nach AMG strafbewehrt.

Die Herstellung von Arzneimitteln unterliegt strengen Regeln (GMP, Pharmazeutische Herstellerlaubnis).

Die Nichtdeklaration des Wirkstoffes ist hierbei besonders bedenklich.

Bestimmung des Gehaltes an JWH018 in verschiedenen Spice Proben

Seit der Identifizierung der Verunreinigung konnten zwischenzeitlich weitere Proben untersucht werden. Diese wurden auf das Vorhandensein von JWH-018 geprüft, sowie eine ungefähre Quantifizierung vorgenommen.

Probe 1 über das Drogenreferat erhalten. Herkunft unbekannt, Aufschrift "Spice" war negativ (kein Wirkstoff nachweisbar). Probe 2 bis 7 über Internet, jeweils Doppelproben der Sorten "Spice Gold", "Yucatan Fire" und "Arctic Synergy", von denen alle JWH-018 in unterschiedlichen Konzentrationen enthalten.

Stevens, A. (2002) "[Cannabis and cannabinoids as therapeutic drugs.]" Sucht **48** (5): 329-335.

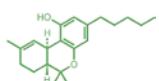
Aims: The essay gives a critical overview of the clinical use of cannabinoids.

Methods: Controlled double-blind studies since 1970 are reviewed. Results:

The analgesic and antiemetic properties of cannabinoids are well documented. However, there seems insufficient knowledge about the pharmacokinetics, dosage and interactions to warrant a safe and efficient therapeutic use of cannabinoids. Also with regard to adverse events, standard drugs are clearly preferable in antiemetic and analgesic therapy. For other, theoretical, uses, as in anorexia, spasticity, glaucoma, asthma, anxiolysis and epilepsy there is a dearth of controlled studies demonstrating the efficacy of cannabinoids. However, the system of cannabinoid receptors promises new paths of treatment for a variety of disorders. Conclusion: At present, the evidence for medical use of cannabinoid-based drugs is unfavorable. Future developments of cannabinoid derivatives or cannabinoid receptor agonists endowed with specific activities may change this judgment.

Svizenska, I., P. Dubovy and A. Sulcová (2008) "Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures – a short review." Pharmacology Biochemistry and Behavior **90** (4): 501-511.

In the last 25 years data has grown exponentially dealing with the discovery of the endocannabinoid system consisting of specific cannabinoid receptors,



their endogenous ligands, and enzymatic systems of their biosynthesis and degradation. Progress is being made in the development of novel agonists and antagonists with receptor subtype selectivity which should help in providing a greater understanding of the physiological role of the endocannabinoid system and perhaps also in a broad number of pathologies. This could lead to advances with important therapeutic potential of drugs modulating activity of endocannabinoid system as hypnotics, analgesics, antiemetics, antiasthmatics, antihypertensives, immunomodulatory drugs, antiphlogistics, neuroprotective agents, antiepileptics, agents influencing glaucoma, spasticity and other "movement disorders", eating disorders, alcohol withdrawal, hepatic fibrosis, bone growth, and atherosclerosis. The aim of this review is to highlight distribution of the CB1 and CB2 receptor subtypes in the nervous system and functional involvement of their specific ligands.

Szendrei, K. (2004) "[A novel analgesics made from Cannabis]." Ideggyogy Szemle **57** (1-2): 36-40.

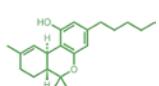
Bayer AG has recently announced that it acquired exclusive rights for the marketing of GW Pharmaceuticals' new medicine Sativex in Europe and in other regions. Sativex is a sublingual spray on Cannabis extract basis, and is equipped with an electronic tool to facilitate accurate dosing and to prevent misuses. It is standardized for the THC and CBD. The new analgesic is proposed for the treatment of muscle spasticity and pains accompanying multiple sclerosis and as an efficient analgetic for neurogenic pain not responding well to opioids and to other therapies available. The entirely new mechanism of action through the recently discovered cannabinoid receptor system may offer a real therapeutic potential to the drug. Although the Government of Netherlands has authorized the sale of pharmaceutical grade Cannabis herb by pharmacies in the Netherlands, the availability on the pharmaceutical market of the registered preparation may render requests for the authorization of the smoking of Cannabis herb (marijuana) by individuals suffering of multiple sclerosis, neurogenic pain, AIDS wasting syndrome unnecessary. Nevertheless, the "old chameleon" plant Cannabis appears to gradually regain its previous status in mainstream therapy and pharmacy. As long as the plant Cannabis and its products continue to be classified as narcotic drugs, medical use of the new preparation will need close supervision.

Tashkin, D.P., M.D. Roth, and S.M. Dubinett (1997) "Medicinal marijuana?" New England Journal of Medicine **336** (16): 1186.

Taylor, H.G. (1998) "Analysis of the medical use of marijuana and its societal implications." Journal of the American Pharmaceutical Association (Washington) **38** (2): 220-227.

Objective: To review the pharmacology, therapeutics, adverse effects, and societal implications of the medical use of marijuana. Data Sources: MEDLINE and manual searches of English-language marijuana literature, supplemented with interviews of scientists currently conducting cannabinoid research.

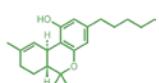
Search terms included pain OR palliative care AND cannabis or ALL marijuana; cachexia OR appetite OR appetite stimulants; muscle spasticity



OR spasm; immune system and cannabis; nausea and vomiting and cancer and cannabis. MEDLINE search terms: cannabis OR marijuana smoking OR marijuana abuse; all glaucoma; multiple sclerosis AND cannabis OR marijuana smoking OR marijuana abuse. Study Selection: Studies on pharmacology, risks, and medical potential of marijuana. Data Extraction: Not applicable. Data Synthesis: The most prominent effects of marijuana are mediated by receptors in the brain. Acute intoxication is characterized by euphoria, loss of short-term memory, stimulation of the senses, and impaired linear thinking. Depersonalization and panic attacks are adverse effects. Increased heart rate and reddened conjunctivae are common physical effects. Chronic, high doses may cause subtle impairment of cognitive abilities that appear to be long-term, but of unknown duration. Marijuana may be a risk factor for individuals with underlying mental illness. It causes dependence, but compared with cocaine, alcohol, heroin, and nicotine, marijuana has little addictive power and produces only mild withdrawal symptoms. Marijuana shows clinical promise for glaucoma, nausea and vomiting, analgesia, spasticity, multiple sclerosis, and AIDS wasting syndrome. Conclusion: As a recreational drug, marijuana poses dangers, particularly to social and emotional development during adolescence and young adulthood. As a medical drug, marijuana should be available for patients who do not adequately respond to currently available therapies.

Thaera, G.M., K.E. Wellik, J.L. Carter, B.M. Demaerschalk, and D.M. Wingerchuk (2009) "Do cannabinoids reduce multiple sclerosis-related spasticity?" *Neurologist* **15** (6): 369-371.

Background: The plant Cannabis sativa contains numerous cannabinoids, which are aromatic hydrocarbons that have central nervous system effects mediated through specific cannabinoid receptors. Some patients with multiple sclerosis (MS) report symptomatic relief from spasticity, pain, and other symptoms when using smoked cannabis, and small trials have suggested some symptomatic benefit. Objective: Do cannabinoids improve spasticity in patients with MS? Methods: We addressed the question through the development of a structured, critically appraised topic. Participants included consultant and resident neurologists, clinical epidemiologists, medical librarian, and clinical content experts in the field of MS. Participants started with a clinical scenario and a structured question, devised search strategies, located and compiled the best evidence, performed a critical appraisal, synthesized the results, summarized the evidence, provided commentary, and declared bottom-line conclusions. Results: The largest randomized, placebo-controlled trial of oral cannabinoid therapy detected no improvement for MS-related spasticity as measured by the Ashworth scale. However, subjective participant reports indicated improvement in spasticity ($P = 0.01$), spasms ($P = 0.038$), sleep quality ($P = 0.025$), and pain ($P = 0.002$) without detriment to depression, fatigue, irritability, or walk time. A second randomized controlled trial, which used subjective participant report as the primary outcome, revealed the same discrepancy between subjective and objective spasticity outcome measures. Conclusion: Randomized controlled trials have failed to confirm objective evidence for a beneficial effect of cannabinoids on MS-related spasticity. However, improvement in subjective assessments of spasticity and other related symptoms have been consistently noted, raising



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questions about the sensitivity and validity of current objective outcome instruments. Further research is warranted with regards to both outcome instrument development and the effects of cannabinoids on MS-related spasticity.

Thaler, A., A. Gupta, and S.P. Cohen (2011) "Cannabinoids for Pain Management." Advances in Psychosomatic Medicine **30**: 125-138.

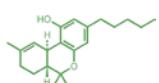
Cannabinoids have been used for thousands of years to provide relief from suffering, but only recently have they been critically evaluated in clinical trials. This review provides an in-depth examination of the evidence supporting cannabinoids in various pain states, along with an overview of potential adverse effects. In summary, there is strong evidence for a moderate analgesic effect in peripheral neuropathic and central pain conditions, and conflicting evidence for their use in nociceptive pain. For spasticity, most controlled studies demonstrate significant improvement. Adverse effects are not uncommon with cannabinoids, though most are not serious and self-limiting. In view of the limited effect size and low but not inconsequential risk of serious adverse events, cannabinoids should be employed as analgesics only when safer and more effective medication trials have failed, or as part of a multimodal treatment regimen.

Thompson, A.J. (2005) "Neurorehabilitation in multiple sclerosis: foundations, facts and fiction." Current Opinion in Neurology **18** (3): 267-271.

Purpose of Review: This review of recent work in the area of neurorehabilitation of multiple sclerosis patients surveys progress and underscores the need for further work to evaluate the effectiveness of treatments. Recent Findings: Several recent review documents have summarized the current position regarding neurorehabilitation and symptomatic management in multiple sclerosis. They have highlighted the paucity of evidence underpinning current practice, thereby identifying the need for more scientifically sound studies in both neurorehabilitation and symptomatic treatment. However, as will be apparent from this review, there has been a welcome increase in studies evaluating both aspects of neurorehabilitation and specific areas such as the role of cannabinoids in spasticity and pain and new treatments for cognitive impairment. Summary: Overall, there is an encouraging trend both in questioning our current practice and in designing more scientifically sound trials incorporating new and more appropriate outcome measures. There is, however, much more to be done before we are in a position to provide the expert, comprehensive, joined-up, care that is required to meet the complex, ever-changing needs of patients with multiple sclerosis.

Thompson, A.J., A.T. Toosy and O. Ciccarelli (2010) "Pharmacological management of symptoms in multiple sclerosis: current approaches and future directions." Lancet Neurology **9** (12): 1182-1199.

Management of symptoms in multiple sclerosis (MS) has received little attention compared with disease-modifying treatments. However, the effect of these symptoms on quality of life can be profound. Clinical trials of pharmacological drugs to treat symptoms of MS have often been underpowered and have used inappropriate measures of outcome. Many



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currently used symptomatic drugs were introduced decades ago, when study quality was considerably below current standards. Therefore, the evidence base on which to make clinical decisions is less than adequate. Interest in pharmacological treatment of symptoms in MS has increased in recent years, and several large randomised controlled trials have been reported.

Pharmacological strategies are a core component of the treatment of these symptoms, but it is imperative to remember that a multidisciplinary rehabilitation approach is needed for effective management.

Thyssen (2006) "Cannabis in der Medizin – Einstellungen der Deutschen – Ergebnis einer Allensbacher Repäsentativbefragung", Institut für Demoskopie Allensbach, 31 Seiten. <http://www.cannabis-med.org/german/nav/home-archive.htm>

Fazit: Nach diesen Befunden lässt sich von einer breiten Unterstützung in der Bevölkerung ausgehen, wenn es um die Verwendung natürlicher Cannabisprodukte in der Medizin bei Schwerkranken geht, und auch in der Frage der Kostenübernahme bei Dronabinol-Behandlung durch die Krankenkassen.

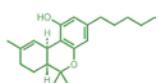
Tolmein, O. (2010) " Cannabis auf Rezept? Pläne der Bundesregierung helfen Schmerzpatienten nicht." Dr. med. Mabuse **35** (187): 55 Seiten, AT Verlag Frankfurt am Main.

Trebst, C. and M. Stangel (2005) "[Cannabinoids in multiple sclerosis – therapeutically reasonable?]." Fortschritte der Neurologie, Psychiatrie **73** (8): 463-469.

For centuries extracts from the Cannabis sativa plant have been used for recreational use and as remedies. Anecdotal reports from patients with multiple sclerosis (MS) experiencing relief of their spasticity and pain after smoking marihuana have prompted discussions about a potential therapeutic application of cannabis preparations in MS. Only recently the first large, multicenter, double-blind, placebo controlled study was conducted evaluating the use of cannabinoids for treatment of spasticity and other symptoms related to MS. Based on this trial and previous uncontrolled observations together with insights from basic research and animal experiments there is reasonable evidence for the therapeutical employment of cannabinoids in the treatment of MS related symptoms. Furthermore, data are arising that cannabinoids have immunomodulatory and neuroprotective properties. However, results from clinical trials do not allow the recommendation for the general use of cannabinoids in MS. This article summarizes the present knowledge of clinical and experimental research regarding the therapeutic potential of cannabinoids for the treatment of MS.

Turcotte, D., J.A. Le Dorze, F. Esfahani, E .Frost, A. Gomori, and M. Namaka (2010) "Examining the roles of cannabinoids in pain and other therapeutic indications: a review." Expert Opinion on Pharmacotherapy **11** (1): 17-31.

Importance of the field: In recent times, our knowledge of cannabinoids and the endocannabinoid system has greatly advanced. With expanding knowledge, synthetic cannabinoids - including nabilone, dronabinol and a combination of synthetic Δ -THC and cannabidiol - have been developed and tested for benefit in a variety of therapeutic indications. Areas covered in this



review: The aim of this article is to provide a summative review of the vast amount of clinical trial data now available on these agents. What the reader will gain: To locate clinical trials for review, a literature search was performed using PubMed between the dates of 25 May and 30 June 2009. Search parameters were set to isolate only human randomized controlled trials (RCTs) published between 1990 and 2009. Keywords consistently used for each search include: cannabinoids, marijuana, THC, nabilone and dronabinol. Preferential selection was given to the best-designed trials, focusing on placebo-controlled, double-blind RCTs with the largest patient populations, if available. Take home message: As efficacy and tolerability of these agents remain questionable, it is important that cannabinoids not be considered 'first-line' therapies for conditions for which there are more supported and better-tolerated agents. Instead, these agents could be considered in a situation of treatment failure with standard therapies or as adjunctive agents where appropriate.

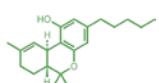
Uhlenbrock, S. and C. Langebrake (2002) "Cannabis Sativa: Von der Hippie-Droge zum Medikament für Schwerkranke." Pharmazeutische Zeitung 147 (21): 36-44.

Cannabis sativa hat als Heilmittel Tradition. Als Monographie Tinctura Cannabis indicae war Haschisch vor sechzig Jahren im Ergänzungsbuch zum Deutschen Arzneibuch zu finden. Zahlreiche Forschungsarbeiten auf dem Gebiet der Cannabinoide scheinen nun ein Comeback als Arzneimittel zu ermöglichen. Der Apotheker in der Rezeptur ist gefordert.

Δ-9-Tetrahydrocannabinol (THC, Dronabinol) ist der wichtigste psychotrope Inhaltsstoff von Cannabis sativa L. Er wird zur Linderung von Zytostatika-induziertem Erbrechen und zur Behandlung von Anorexie mit Gewichtsverlust bei AIDS-Patienten eingesetzt. Allerdings stehen Fertigpräparate mit cannabinoiden Inhaltsstoffen in Deutschland derzeit nur als Importarzneimittel zur Verfügung. Seit Juli 2000 können Apotheken jedoch Dronabinol als Rezeptursubstanz in pharmazeutischer Qualität erwerben und zu Arzneimitteln verarbeiten. In der Apotheke des Universitätsklinikums Münster stellen wir seit einem Jahr Dronabinol-haltige Kapseln und eine peroral anwendbare Lösung her.

Dronabinol ist ein peroral und parenteral aktives Cannabinoid mit komplexen zentralen Wirkungen einschließlich sympathomimetischen Effekten auf das Zentralnervensystem (ZNS). Als Wirkort wurden Anfang der neunziger Jahre Cannabinoidrezeptoren (CB-Rezeptoren) im ZNS (vornehmlich CB1) nachgewiesen, die den intrazellulären cAMP- und Ca²⁺-Spiegel modulieren. Im peripheren Nerven- und Immunsystem befinden sich insbesondere Rezeptoren vom Subtyp CB2. Als körpereigene Liganden (Endocannabinoide) wurden kurze Zeit später die Anandamide (Sanskrit: ananda, Glückseligkeit) identifiziert.

Dronabinol induziert sympathomimetische kardiovaskuläre Effekte wie Tachykardien und individuell unterschiedliche Blutdruckveränderungen, die sich durch orthostatische Dysregulationen bis hin zu Synkopen äußern können, sowie Konjunktivitiden. Dosisabhängig und reversibel regt Dronabinol den Appetit an, hebt die Stimmung und verändert (Zeit-) Wahrnehmung, Erinnerung und Kognition. Diese Effekte sind von Patient zu Patient unterschiedlich stark ausgeprägt. Es wirkt sedierend und kann Hyperthermie induzieren. In seltenen Fällen treten Übelkeit und Erbrechen, Verwirrtheit,



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Euphorie, Halluzinationen, paranoide Reaktionen oder Schläfrigkeit auf (1, 3). Seit 1985 ist Dronabinol in den USA unter dem Handelsnamen Marinol® (Roxane Laboratories, Inc.) zugelassen als Fertigarzneimittel für die Behandlung von Chemotherapie-bedingter Übelkeit und Erbrechen (chemotherapy-induced emesis, CIE) bei Patienten, die auf eine antiemetische Standardtherapie nicht ansprechen. 1992 kam als weitere Indikation "Anorexie mit Gewichtsverlust bei Aids-Patienten" hinzu.

Dronabinol in Deutschland

Da der Import von Marinol gemäß § 73 Absatz 3 Arzneimittelgesetz (AMG) aus den USA bis zu zwei Wochen dauert und teuer ist (Marinol 2,5 mg 25 Kapseln kosteten im März 2001 225 Euro), spart die Eigenherstellung Dronabinol-haltiger Arzneimittel Zeit und ist kostengünstiger. Das in Deutschland erhältliche Dronabinol der Firma THC-Pharm GmbH wird halbsynthetisch durch Umwandlung von nativem Cannabidiol aus Faserhanf zu THC gewonnen. Apotheken können es in Mengen von 0,5 g und 1,0 g (zu 400 Euro und 600 Euro; Stand Februar 2002) beziehen und zu genau dosierbaren Rezepturen verarbeiten. Die gesetzlich vorgeschriebene Identitätsprüfung der Rezeptursubstanz ist gemäß der Monographie des Deutschen Arzneimittel-Codex (DAC) im Rahmen des üblichen Apothekenbetriebs mit Dünnschichtchromatographie und Farbreaktionen möglich.

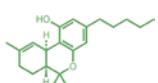
Momentan dürfen Ärzte gemäß Betäubungsmittel-Verschreibungsverordnung (BtMVV § 2) maximal 500 mg Dronabinol pro Patient innerhalb von dreißig Tagen verschreiben. Ist in begründeten Einzelfällen eine Überschreitung der festgesetzten Höchstmenge erforderlich, muss dies auf dem Betäubungsmittelrezept durch den Buchstaben "A" gekennzeichnet sein (BtMVV § 2 (2)). Eine Meldung an die zuständige Überwachungsbehörde ist seit Inkrafttreten der 10. Betäubungsmittelrechts-Änderungsverordnung (BtMÄndV) am 1. Februar 1998 nicht mehr notwendig.

Vom Harz zu Kapseln und Tropfen

THC-Pharm schlägt für die Verarbeitung des lipophilen und bei Raumtemperatur festen Harzes Dronabinol jeweils eine Rezeptur für Kapseln oder ölige Tropfen zur peroralen Applikation sowie für alkoholische Tropfen zur Inhalation vor. Die Wirkung tritt nach Angaben des Unternehmens bei inhalativer Anwendung mit Hilfe spezieller Inhalatoren gegenüber der peroralen Applikation schneller und bei geringeren Dosen ein. Damit könne man die Therapiekosten erheblich senken. Da die Wirkstoffresorption nicht mehr von der Nahrungsaufnahme abhängig sei, ließe sich die Wirkung besser steuern.

In der Apotheke des Universitätsklinikums Münster stellen wir seit März 2001 in Anlehnung an die in der Bock-Apotheke, Frankfurt, entwickelten Arbeitsanweisungen Dronabinol-haltige Kapseln und Lösungen her. Vorteil der Lösung ist eine individuelle Dosierung; außerdem ist diese Arzneiform für Patienten mit Schluckbeschwerden besser geeignet.

Für die Herstellung von 400 Dronabinol-Kapseln à 2,5 mg wird 1,0 g Substanz verwendet und die Masse mit Kakaobutter auf 90,0 g ergänzt. Die Mischung wird auf dem Wasserbad bei 35 bis 38 °C geschmolzen und so lange gerührt, bis sich der Wirkstoff vollständig in der Fettschmelze gelöst hat. Anschließend gibt man mit Hilfe einer Kolbenhubpipette (Eppendorf Reference 1000) jeweils 250 µl der Lösung in die Kapselböden von Gelatine-Steckkapseln Größe 2



und verschließt diese nach dem Erstarren der Fettschmelze fest mit den Kapselkappen. Jeweils 25 Kapseln werden in Kruken aus Polypropylen mit Originalitäts-Schnappverschluss aus Polyethylen abgepackt.

Die Herstellung der Lösung von Dronabinol in Kakaobutter erfolgt gewichtsbezogen, wobei eine Dichte der zu verarbeitenden Fettschmelze von 0,9 g/cm³ zu Grunde gelegt wird. Die anschließende Befüllung der Leerkapseln erfolgt volumendosiert. Mit dieser Methode ist eine Ausbeute von 94 Prozent (15 mal 25 Kapseln) erreichbar. Die Massen der befüllten Kapseln aus einem Herstellungsprozess lagen innerhalb der Grenzen von 92 und 109 Prozent der Durchschnittsmasse.

Für die Herstellung von 200 ml Dronabinol-Lösung 0,5 Prozent (m/V) wird 1,0 g Substanz in einem Messkolben mit Sesamöl auf ein Volumen von etwa 180 ml ergänzt. Anschließend erwärmt man die Flüssigkeit im Wasserbad zügig auf etwa 60 °C. Nachdem sich der Wirkstoff unter häufigem Umschwenken in dem fetten Öl vollständig gelöst hat und die Flüssigkeit auf Raumtemperatur abgekühlt ist, wird das Volumen mit Sesamöl auf 200,0 ml ergänzt. Jeweils 10,5 ml werden mit einer 20 ml-Einmalspritze und einer Kanüle in 10 ml ISO-Injektionsflaschen aus Braunglas abgefüllt (Entnahmeverum 10 ml). Die Flaschen werden mit Chlorbutylstopfen und Flipp-off-Bördelkappen verschlossen. Das Pflegepersonal kann das verordnete Volumen mit Hilfe einer Einwegspritze und einer Kanüle entnehmen. Mit dieser Methode können 18 Flaschen à 10 ml Dronabinol-Lösung (Ausbeute 90 Prozent) hergestellt werden.

Die gaschromatographische Gehaltsbestimmung einer Stichprobe der Kapseln und der Lösung ergab sowohl unmittelbar nach der Herstellung als auch nach sechsmonatiger Lagerung bei Raumtemperatur Wirkstoffgehalte innerhalb der Grenzen von 90 bis 110 Prozent des deklarierten Gehalts.

Standardisierte Vorschriften im NRF

Mit der 18. Ergänzungslieferung des Neuen Rezeptur-Formulariums (NRF) im Dezember 2001 stehen nun zwei standardisierte Rezepturen zur Verfügung. Als Füllstoff für "Dronabinol-Kapseln 2,5, 5 oder 10 mg (NRF 22.7.)" schreibt das NRF an Stelle von Kakaobutter allerdings ein Hartfett, zum Beispiel

Softisan

□ 378, vor, da dieses

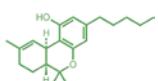
Vergleich zu Kakaobutter keinen prooxidativen Effekt auf das oxidationsempfindliche THC ausübt.

Angesichts des konstanten Fassungsvermögens der Kapselböden (Größe 1:0,5 ml) und bei bekannter Dichte des Hartfetts wird der geforderte THC-Gehalt pro Kapsel - in Anlehnung an das Gießverfahren bei der Herstellung von Suppositorien - durch vollständige Befüllung der Kapselböden mit einer 1 ml-Einmalspritze und einer Kanüle gewährleistet. Bei ausreichender Dosiergenauigkeit ist diese Methode apothekengerechter als die Herstellung mit Hilfe einer Dosierpipette. Die Produktion einer größeren Zahl von Kapseln ist mit einer Dosierpipette allerdings komfortabler.

Als flüssige Darreichungsform schlägt das NRF ölige Dronabinol-Tropfen 2,5 Prozent (m/m) vor, wobei an Stelle des oxidationsempfindlichen Sesamöls mittelkettige Triglyceride (MKT) als Grundlage verwendet werden.

Für die Abgabe an Patienten sind "Dronabinol-Tropfen 2,5 Prozent (NRF 22.8.)" besser geeignet als Dronabinol-Lösung, die nur mit Hilfe von Einmalspritze und Kanüle aus der Stechampulle entnommen werden kann.

Nach dem allgemein anerkannten Stand der pharmazeutischen



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Wissenschaften sowie den Grundsätzen der guten pharmazeutischen Praxis muss die verwendete Tropfflasche - ebenso wie das Behältnis für die Dronabinol-Kapseln - bei Abgabe an den Endverbraucher mit einem kindergesicherten Verschluss versehen sein (8). Die Tropfflasche muss ferner über einen Senkrechttropfer für ölige Lösungen verfügen, der eine ausreichende Dosiergenauigkeit (30 Tropfen entsprechen 1 g) gewährleistet. Bei der Herstellung der von uns vorgeschlagenen Dronabinol-Lösung 0,5 Prozent (m/V) in einem Messkolben kann die Trägersubstanz Sesamöl ebenfalls gegen MKT ausgetauscht werden, um einen prooxidativen Effekt auf den Wirkstoff zu vermeiden.

Hinweise bei der Abgabe

Nach peroraler Applikation setzt die Wirkung von Dronabinol innerhalb von 30 bis 60 Minuten ein; das Wirkungsmaximum wird nach zwei bis vier Stunden erreicht. Psychotrope Effekte dauern vier bis sechs Stunden an, während der Appetit stimulierende Effekt bis zu 24 Stunden und länger anhalten kann. In der Beratung sollte man die Patienten darauf hinweisen, dass Stimmungsschwankungen und -verstärkungen sowie Verhaltensänderungen auftreten können. Daher sollte bei der ersten Einnahme von Dronabinol und einer darauffolgenden Dosiseinstellung eine verantwortliche erwachsene Person anwesend sein. Die meisten kardiovaskulären und subjektiven unerwünschten Effekte verschwinden nach wenigen Tagen regelmäßigen Gebrauchs auf Grund von Toleranzentwicklung oder Tachyphylaxie, während andere Wirkungen wie die Anregung des Appetits keinen Toleranzeffekten unterliegen.

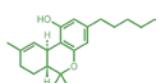
Zur Appetitstimulation nehmen die Patienten 2,5 bis 20 mg pro Tag ein; zur Antiemese erhalten sie 5 mg/m² bis zu sechsmal täglich. Eine Dosisescalation ist bis zu 15 mg/m² pro Einzelpille möglich.

Eine deutliche Wirkung auf das ZNS wird nach peroraler Gabe von 0,4 mg/kg Körpergewicht beobachtet. Allerdings kann auch bei geringeren Dosierungen das Reaktionsvermögen so weit verändert werden, dass die Fähigkeit zur aktiven Teilnahme am Straßenverkehr oder zum Bedienen von Maschinen beeinträchtigt wird. Höhere Dosen sollen einschleichend verabreicht werden. Besonders ältere Menschen können empfindlicher auf die psychoaktiven Effekte von Dronabinol reagieren. In Pilotstudien wurde festgestellt, dass die Gabe als Appetitstimulans am frühen Morgen häufiger mit unerwünschten Wirkungen verbunden ist als die zweimal tägliche Applikation jeweils eine Stunde vor dem Mittag- und Abendessen.

Dronabinol ist plazentagängig. Epidemiologische Untersuchungen über Fruchtschädigungen bei Schwangeren liegen bisher nicht vor. Da der Wirkstoff in der Muttermilch konzentriert wird, ist er auch in der Stillperiode kontraindiziert. Auf Grund der möglichen Tachykardie und Beeinflussung des Blutdrucks müssen Nutzen und Risiko bei herzkranken Patienten sorgfältig abgewogen werden; dies gilt auch für die gleichzeitige Applikation von Psychopharmaka, da Wechselwirkungen mit Dronabinol auftreten können. Die zentral dämpfenden Wirkungen von alkoholischen Getränken und Dronabinol können sich bei gleichzeitiger Einnahme addieren (1, 3). Bei Probanden wurden nach Ethanolkonsum und anschließendem Rauchen von Marihuana sogar erhöhte THC-Blutspiegel beobachtet.

Ein Weg in die Abhängigkeit?

Nach längerer hochdosierter Einnahme von Dronabinol wurde bei Gesunden



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sowohl eine psychische als auch eine physische Abhängigkeit beobachtet. Es gibt Berichte, dass Probanden nach dem abrupten Absetzen hoher Dosierungen (täglich 210 mg an 12 bis 16 aufeinander folgenden Tagen) ein Abstinenzsyndrom mit Reizbarkeit, Schlaflosigkeit, Unruhe, Hitzewallungen, Schwitzen, Rhinorrhö, Schluckauf und Anorexie erleben. Eine Dronabinol-Sucht ist nach Aussage von Roxane Laboratories in therapeutischen Dosierungen jedoch ungewöhnlich. Bei Aids-Patienten gab es nach bis zu fünfmonatiger Anwendung von Dronabinol keine Hinweise auf eine missbräuchliche Anwendung, sowie Persönlichkeits- oder Verhaltensveränderungen, obwohl Patienten mit Drogenabusus in der Anamnese in die Studie eingeschlossen worden waren.

Nach abschließender Bewertung der amerikanischen Regulierungsbehörde DEA (Drug Enforcement Administration) ist das Abhängigkeitspotenzial von Dronabinol eher mit dem von Codein als dem von Morphin vergleichbar. Im Experiment an Affen entsprach das Potenzial für den Missbrauch von THC allerdings etwa dem von Kokain. Bei Untersuchungen am Rattenhirn stieg die extrazelluläre Konzentration von Dopamin in der Hülle des Nucleus accumbens, einem Zielgebiet des mesolimbischen Systems, nach der Applikation von THC oder Heroin an. Es gibt Hinweise dafür, dass auch andere missbräuchlich verwendete Substanzen ihre berauschenden und Sucht erzeugenden Wirkungen durch Aktivierung dopaminerger mesolimbischer Neuronen auslösen. Weitere Untersuchungen am Rattenhirn deuten darauf hin, dass die chronische Anwendung von Cannabinoiden die Funktion des Corticotropin-Releasing Factors (CRF) im limbischen System in ähnlicher Weise wie andere Suchtstoffe, zum Beispiel Ethanol, Kokain oder Opiate, verändert und dass neuroadaptive Prozesse angestoßen werden, die möglicherweise zu einer späteren Anfälligkeit für Drogensucht führen.

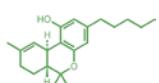
Neue Optionen für Dronabinol

Nach einer Metaanalyse randomisierter kontrollierter Studien sind peroral appliziertes Dronabinol und andere Cannabinoide bei mäßig emetogener Chemotherapie effektiver als herkömmliche Antiemetika wie Metoclopramid. Trotz vermehrter unerwünschter Wirkungen bevorzugten Patienten Cannabinoide für weitere Chemotherapie-Zyklen. Für bestimmte Patienten, zum Beispiel durch chronische Schmerzen deprimierte Menschen oder Patienten im Finalstadium einer malignen Erkrankung, scheinen Cannabinoide als stimmungsaufhellende Adjuvantien zur Behandlung von CIE geeignet zu sein.

Bislang fehlen vergleichende Studien mit 5-HT3-Antagonisten, den wirksamsten Antiemetika bei stark emetogenen Chemotherapien. Die inhalative Anwendung von Marihuana zeigte im Vergleich zu Ondansetron allerdings eine mäßige antiemetische Wirksamkeit bei Probanden nach der Einnahme von Ipecacuanha-Sirup. Der emetogene Effekt der Ipecacuanha-Alkaloide beruht ebenso wie der von Cisplatin auf der Freisetzung von Serotonin (5-HT) im Gastrointestinaltrakt. Er kann daher durch einen 5-HT3-Antagonisten erfolgreich verhindert werden.

Der Wirkungsmechanismus des antiemetischen Effekts von THC ist bisher nicht bekannt. Die Wirksamkeit gegen Übelkeit und Erbrechen, die durch D2-Agonisten, histaminerge oder cholinerge Systeme ausgelöst werden, ist bisher nicht untersucht worden.

Die analgetischen Effekte von Cannabinoiden und Opiaten scheinen zwar in



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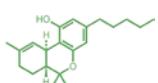
der selben Hirnregion angesiedelt, aber unabhängig voneinander geregelt zu sein. Im Tierversuch verminderte die gleichzeitige Applikation des Opiat-Antagonisten Naloxon die Wirksamkeit eines Cannabinoid-Agonisten nicht. Cannabinoide sind demnach offenbar zentral wirksame Analgetika mit einem neuen Wirkungsmechanismus, die die Schmerztherapie um eine weitere Substanzgruppe mit moderaten und zum Teil erwünschten Nebenwirkungen ergänzen könnten. Der analgetische Effekt der Cannabinoide war in randomisierten, kontrollierten Studien jedoch nicht größer als der von Codein, und die unerwünschten Wirkungen auf das ZNS limitieren deren Einsatz in höherer Dosierung.

Vielversprechender erscheint die Behandlung neuropathischer Schmerzen und spastischer Zustände bei Multipler Sklerose (MS). So konnte gezeigt werden, dass CB-Agonisten Tremor und Spastiken bei Mäusen, die an einem Autoimmunmodell für MS erkrankt sind, quantitativ lindern.

Ferner könnten Cannabinoide eine neue Option bei bestimmten Hirntumoren darstellen. Bei intratumoraler Applikation von THC oder einem synthetischen CB-Agonisten wurde eine erhebliche Regression maligner Gliome im Tierexperiment beschrieben. Die induzierte Apoptose löste unter Versuchsbedingungen keine anhaltenden neurotoxischen Effekte aus. Cannabidiol (CBD) gilt als wichtigster nicht psychotroper Inhaltsstoff der Hanfpflanze und unterliegt nicht dem Betäubungsmittelgesetz (BtMG). Nach Angaben des Herstellers THC-Pharm wird CBD in klinischen Studien auf seine Wirksamkeit bei psychischen Erkrankungen untersucht. Es hat antiepileptische Wirkungen und wirkt sedierend, bakterizid und viruzid. Ferner konnten ausgeprägte analgetische und antiinflammatorische Effekte bei Mäusen nachgewiesen werden. In vitro wirkt CBD als Cyclooxygenase- und Lipoxygenase-Inhibitor, während nach peroraler Gabe im Tierexperiment die Lipoxygenase-hemmenden Eigenschaften überwiegen. CBD könnte daher auch eine Basis für die Entwicklung cannabinoider Analgetika ohne psychoaktive Eigenschaften darstellen.

Cannabisextrakt besser verträglich

Verschiedene Firmen bereiten gemeinsam mit dem DAC Untersuchungen zur Herstellung eines standardisierten Cannabisextrakts vor, da natürliche Gemische möglicherweise wirksamer und nebenwirkungsärmer sind als isolierte Wirkstoffe. So konnte an Probanden gezeigt werden, dass die gleichzeitige Gabe von CBD durch THC ausgelöste Angstreaktionen vermindert. Dies spricht für eine bessere Verträglichkeit des Extraks im Vergleich zu reinem Dronabinol. Cannabis und Cannabisharz sind bisher allerdings Bestandteile der Anlage I des BtMG und damit nicht verkehrsfähig. Die Bundesopiumstelle hat der THC-Pharm die Erlaubnis zum Verkehr mit medizinischem Cannabisextrakt zu wissenschaftlichen Zwecken (BtMG § 3) erteilt. Das Unternehmen will hierfür Pflanzenmaterial aus Zentralasien verwenden, das im Gegensatz zu europäischen Produkten weder geklonnt noch radioaktiv bestrahlt und zudem kostengünstiger sein soll. Wenn der wissenschaftliche Nachweis für reproduzierbare Qualität, Wirksamkeit und Unbedenklichkeit von standardisiertem Cannabisextrakt erbracht worden ist, könnte dieser von Anlage I in Anlage III des BtMG übernommen und auf ärztliche Verschreibung von Apothekern zu Arzneimitteln verarbeitet werden. Derzeit wird eine Änderung des BtMG vorbereitet, die nach Angaben von THC-Pharm eventuell noch in diesem Jahr zu erwarten ist.



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Bereits 1999 startete eine doppelblinde klinische Multicenterstudie, die vom Europäischen Institut für onkologische und immunologische Forschung Berlin koordiniert wird. Darin soll die Wirksamkeit von Cannabisextrakt zur Appetitanregung bei Krebspatienten verglichen werden mit den Effekten eines Präparats mit isoliertem Dronabinol. Die Endauswertung wird 2003 erwartet. Die Zulassung von Fertigarzneimitteln mit standardisiertem Cannabisextrakt ist erst möglich, wenn der Pflanzenauszug als verkehrs- und verschreibungsfähiges Betäubungsmittel akzeptiert ist. Zudem ist die Erstzulassung von Fertigarzneimitteln mit sehr hohen Kosten verbunden (etwa 3,5 Millionen Euro pro Indikation). Da weder Cannabisextrakt noch Dronabinol patentrechtlich geschützt sind, zeigte die pharmazeutische Industrie bisher wenig Interesse an der Entwicklung von Handelspräparaten. Das britische Unternehmen GW Pharmaceuticals erforscht jedoch die Anwendung THC- und CBD-haltiger Arzneimittel bei einer Vielzahl von Indikationen. In klinischer Prüfung befindet sich derzeit ein Cannabis-haltiges Sublingualspray. Dank intensiver Forschung könnte das alte Heilmittel aus dem Arzneibuch von 1941 nun eine Renaissance zum Medikament für schwer kranke Menschen erfahren.

Ungerleider, J.T. and T. Andrysiak (1985) "Therapeutic issues of marijuana and THC (tetrahydrocannabinol)." *International Journal of the Addictions* **20** (5): 691-699.

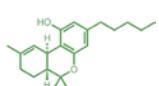
This article summarizes current knowledge about the medicinal value of cannabis and its principal psychoactive ingredient, Δ-9-tetrahydrocannabinol (THC), particularly in the control of nausea and vomiting, in glaucoma, and in reduction of spasticity in multiple sclerosis. The major issues in the controversy about marijuana and medicine, primarily moral and ethical, are discussed.

Ungerleider, J.T., T. Andrysiak, L. Fairbanks, G.W. Ellison and L.W. Myers (1987) "Delta-9-THC in the treatment of spasticity associated with multiple sclerosis." *Advances in Alcohol and Substance Abuse* **7** (1): 39-50.

Marijuana is reported to decrease spasticity in patients with multiple sclerosis. This is a double blind, placebo controlled, crossover clinical trial of Δ-9-THC in 13 subjects with clinical multiple sclerosis and spasticity. Subjects received escalating doses of THC in the range of 2.5-15 mg., five days of THC and five days of placebo in randomized order, divided by a two-day washout period. Subjective ratings of spasticity and side effects were completed and semiquantitative neurological examinations were performed. At doses greater than 7.5 mg there was significant improvement in patient ratings of spasticity compared to placebo. These positive findings in a treatment failure population suggest a role for THC in the treatment of spasticity in multiple sclerosis.

Usdin, M., V. Mesnage, et al. (2005) "Maladie de Gilles de la Tourette. Un auto-questionnaire." *Revue Neurologique* **161** (8-9): 795-803.

An association of patients with Gilles de la Tourette syndrome enabled us to gather a large body of information regarding the disease manifestations, and patient-perceived consequences. Method 350 questionnaires were sent to patients belonging to the AFSGT (French Association of Patients Suffering from Gilles de la Tourette Syndrome). 187 responses were received (53 percent). The patients were divided into four groups: those with motor tics,

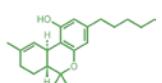


vocal tics, complex tics and complex tics with coprolalia. This last group corresponds to the DSM IV definition of "Tourette Disorder". The questions were grouped in five sections: simple manifestations, complex manifestations, family study, treatment and psycho-affective perception (social and in the context of schooling). The study of the simple manifestations of the disorder revealed the homogeneity of the four groups with an age of onset at on average 7 years and a male-to-female ratio of 3.5. The first signs of the disorder are motor tics of the face and neck, and the disorder shows a variable and fluctuating course characterized by periods of decreased or absent symptoms. Familial cases (58 percent) are found in all four groups. The complex signs included in part of behaviors corresponding to the definition of tics: sudden, brusque, repetitive, varied, escape despite efforts to repress them and reappearance more intensely after a period of conscious control. The complex signs also consisted of accompanying factors such as agitation, need to organize, classify or count. Treatments have been of limited success and a significant number of patients have abandoned treatment entirely. Our study demonstrates that this condition seriously affects the daily life of patients, including family and social relations, schooling and occupational life. No patients suffering from transient tics responded to our survey, but such tics were reported in family members. Overall, the condition is considered to be single family of disorders, despite the broad phenotypic spectrum, from transitory cases by children to very severe forms. Escape despite efforts to repress tics and the rebound after control tics is characteristic of the Georges Gilles de la Tourette syndrome.

Van Dam, N.T. and M. Earleywine, (2010) "Pulmonary function in cannabis users: Support for a clinical trial of the vaporizer." *International Journal of Drug Policy* **21** (6): 511-513.

Background: Debates about cannabis policy often mention respiratory symptoms as a negative consequence of use. The cannabis vaporizer, a machine that heats the plant to release cannabinoids in a mist without smoke and other respiratory irritants, appears to have the potential to minimize respiratory complaints. **Methods:** Twenty frequent cannabis users (uninterested in treatment) reporting at least two respiratory symptoms completed subjective ratings of respiratory symptoms and spirometry measures prior to and following 1 month's use of a cannabis vaporizer in a pre/post-design. **Outcome measures** included self-reported severity of nine respiratory symptoms as well as spirometry measures, including the maximum amount of air exhaled in 1 s (forced expiratory volume; FEV1) and maximum total lung volume (forced vital capacity; FVC). **Results:** The 12 participants who did not develop a respiratory illness during the trial significantly improved respiratory symptoms ($t(11) = 6.22$, $p = 0.000065$, $d = 3.75$) and FVC, $t(11) = 2.90$, $p = 0.007$, $d = 1.75$. FEV1 improved but not significantly $t(11) = 1.77$, $p = 0.053$, $d = 1.07$. **Conclusions:** These preliminary data reveal meaningful improvements in respiratory function, suggesting that a randomized clinical trial of the cannabis vaporizer is warranted. The vaporizer has potential for the administration of medical cannabis and as a harm reduction technique.

Vaney, C., M. Heinzel-Gutenbrunner, P. Jobin, F. Tschopp, B. Gattlen, U. Hagen, M. Schnelle and M. Reif (2004) "Efficacy, safety and tolerability of an orally administered



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cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study." Multiple Sclerosis Journal **10** (4): 417-424.

Objective: Cannabis may alleviate some symptoms associated with multiple sclerosis (MS). This study investigated the effect of an orally administered standardized Cannabis sativa plant extract in MS patients with poorly controlled spasticity. Methods: During their inpatient rehabilitation programme, 57 patients were enrolled in a prospective, randomized, double-blind, placebo-controlled crossover study of cannabis-extract capsules standardized to 2.5 mg tetrahydrocannabinol (THC) and 0.9 mg cannabidiol (CBD) each. Patients in group A started with a drug escalation phase from 15 to maximally 30 mg THC by 5 mg per day if well tolerated, being on active medication for 14 days before starting placebo. Patients in group B started with placebo for seven days, crossed to the active period (14 days) and closed with a three-day placebo period (active drug dose escalation and placebo sham escalation as in group A). Measures used included daily self-report of spasm frequency and symptoms, Ashworth Scale, Rivermead Mobility Index, 10-m timed walk, nine-hole peg test, paced auditory serial addition test (PASAT), and the digit span test. RESULTS: In the 50 patients included into the intention-to-treat analysis set, there were no statistically significant differences associated with active treatment compared to placebo, but trends in favour of active treatment were seen for spasm frequency, mobility and getting to sleep. In the 37 patients (per-protocol set) who received at least 90% of their prescribed dose, improvements in spasm frequency ($P = 0.013$) and mobility after excluding a patient who fell and stopped walking were seen ($P = 0.01$). Minor adverse events were slightly more frequent and severe during active treatment, and toxicity symptoms, which were generally mild, were more pronounced in the active phase. Conclusion: A standardized Cannabis sativa plant extract might lower spasm frequency and increase mobility with tolerable side effects in MS patients with persistent spasticity not responding to other drugs.

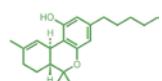
Vaney, C. (2004) " Multiple Sklerose, Spastik und Cannabis. Muskelpasmen – manchmal sehr schmerzhafte – beeinträchtigen die Lebensqualität bei Multipler Sklerose. Können die Spasmen mit Cannabis gelindert werden? Wie wird Cannabis verabreicht, und welches sind die rechtlichen Grundlagen?" Swiss Medical Forum **4** (28): 732.

Vaney, C. and A. Pillai (2005) "Cannabis ist gefährlich, Medizin ist er trotzdem." Swiss Medical Forum **5** (10): 287.

Vetschera, T. and A. Pillai (1979) "The use of hemp and opium in India." Ethnomedizin. Zeitschrift für interdisziplinäre Forschung **5** (1/2): 11-23.

Vicente-Valor, M.I.P., Garcia-Llopis, L., Mejia Andujar, G., Antonino de la Camara, N., García Del Busto, M., Lopez Tinoco, B., Quintana Vergara. C., Peiro Vilaplana, J.A., Dominguez Moran, A. and Sánchez Alcaraz, A. (2013) "Cannabis derivatives therapy for a seronegative stiff-person syndrome: a case report." Journal of Clinical Pharmacy and Therapeutics **38** (1):71-73.

What is known and Objective: Stiff-person syndrome (SPS) is an uncommon and disabling disorder characterized by progressive rigidity and episodic



painful spasms involving axial and limb musculature. SPS treatment is mostly based on benzodiazepines, baclofen, immunosuppressants and intravenous immunoglobulin. Cannabis derivatives [tetrahydrocannabinol (THC) and cannabidiol (CBD)] are available as an oromucosal spray (Sativex®), indicated as add-on treatment, for symptom improvement in patients with moderate to severe spasticity because of multiple sclerosis (MS). Our objective is to report a case of seronegative SPS successfully treated with THC-CBD oromucosal spray.

Case Summary: We report a case of a 40-year-old man presenting with progressive muscle stiffness and intermittent spasms for 6-years. The diagnosis of stiff-person syndrome was based on the clinical features and neuroelectrophysiologic findings of continuous motor unit activity. Glutamic acid decarboxylase autoantibodies was absent in our patient, in both serum and cerebrospinal fluid (CSF). Cannabis derivatives oromucosal spray was introduced after a series of unsatisfactory traditional medical treatments. After 14 months treated with THC-CBD oromucosal spray, improvement was verified in the eight dimensions of the scale of SF-36 quality of life questionnaire.

What is new and Conclusion: Clinical experience with cannabis derivatives in patients with multiple sclerosis is accumulating steadily, but there is no current literature about its efficacy for SPS. Because MS and SPS share some neurological symptoms such as spasticity and rigidity, it is thought that THC-CBC can be an option for SPS patient. Our case report suggests that THC-CBD oromucosal spray is an alternative treatment for patients with refractory SPS, and further validation is appropriate.

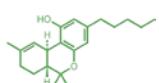
Volk, R.-B. (2006) "Hanf als Medizin. Therapie mit Cannabis und Co."

Pharmazeutische Zeitung 5/2009.

Über lange Zeit nicht verfügbar, sind Cannabis- und Cannabinoid-haltige Fertigarzneimittel seit den 1980er-Jahren unter anderem in den USA und Kanada wieder auf dem Markt. In Deutschland kommt Dronabinol als Rezeptursubstanz in DAC-Qualität zum Einsatz.

Cannabis- oder synthetische Δ-9-Tetrahydrocannabinol-, sprich: Dronabinol-haltige Fertigarzneimittel sind in der Bundesrepublik Deutschland bisher nicht zugelassen. Zwei neuerliche Anträge zur erleichterten medizinischen Verwendung von Cannabis sowie der Vorschlag der Freigabe eines Cannabis-Anbaus wurden am 3. Dezember 2008 vom Gesundheitsausschuss des Bundestags abgelehnt.

Aus den USA kann jedoch das Präparat Marinol® mit Dronabinol-haltigen Weichgelatinekapseln in den Dosierungen 2,5, 5,0 und 10 mg gemäß § 73 Abs. 3 AMG importiert werden. Es ist in den Vereinigten Staaten zur Therapie von Anorexie mit Gewichtsverlust bei Aids sowie zur Behandlung von Übelkeit und Erbrechen bei Chemotherapie in der Krebsbehandlung zugelassen. In Kanada ist ein auf Δ-9-Tetrahydrocannabinol-/Cannabidiol standardisiertes Sublingualspray (Sativex®) zur begleitenden Behandlung von neuropathischen Schmerzen bei Multipler Sklerose und zur Schmerzbehandlung von Krebspatienten, bei denen eine Opioidtherapie nicht anschlägt, verfügbar. In niederländischen Apotheken sind unter anderem mit Bedrocan® unter standardisierten Bedingungen kultivierte Hanfblüten für medizinische Zwecke in Apotheken auf Rezept erhältlich.



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Das synthetische Cannabinoid Nabilon (Cesamet[®]), ebenfalls zugelassen zur Therapie von Anorexie und Kachexie bei Aids sowie als Antiemetikum bei Übelkeit und Erbrechen unter Zytostatikagabe beziehungsweise Bestrahlung im Rahmen einer Krebstherapie, ist als Betäubungsmittel in der Anlage III des deutschen Betäubungsmittelgesetzes aufgeführt. Es ist somit in Deutschland verkehrsfähig, muss jedoch auf BTM-Rezepten verordnet werden. In Deutschland wird zudem Dronabinol als Rezeptursubstanz in DAC-Qualität angeboten und kann seit fünf Jahren auf BTM-Rezept in deutschen Apotheken zur Herstellung von Kapseln oder ölichen Tropfen für medizinische Zwecke nach NRF-Vorschrift (NRF 22.7. und 22.8.) eingesetzt werden. Der Sachverständigenrat des Gesundheitsausschusses sprach sich bereits im Herbst letzten Jahres für eine Übernahme der Kosten durch die Krankenkassen aus.

Lange Geschichte und Tradition

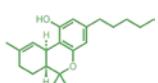
Es gibt eine Vielzahl potenzieller Wirkungen und Indikationsgebiete für Cannabis und Cannabinoide. Die Datenlage ist allerdings sehr uneinheitlich. Erkenntnisse zum Einsatz von Cannabis und Cannabinoiden beruhen oftmals auf Erfahrungswerten betroffener Patienten, die diese ohne Verordnung und inoffiziell anwandten und dabei eine Besserung ihrer Symptomatik beobachteten. In der Folge durchgeföhrte klinische Studien unterscheiden sich stark in ihrem Design und ihrer Aussagekraft.

Doch zunächst einige Sätze zur Geschichte: Cannabis als Pflanzengattung in der Familie der Hanfgewächse begleitet die Menschen bereits seit Jahrtausenden nicht nur als Arznei-, sondern auch als Nutz- und Rauschpflanze. Archäologische Funde in China weisen auf eine Verwendung als Kulturpflanze zur Fasergewinnung bereits 8000 Jahre vor Christus, also lange vor Entwicklung der Schrift hin. Als erste Beschreibung des medizinischen Einsatzes gilt heute das Kompendium der chinesischen Heilkräuter des chinesischen Kaisers Shen Nung aus dem Jahr 2737 vor Christus.

Von China gelangte die Hanf-Pflanze nach Indien und in den arabischen Raum, wo ihre Extrakte nicht zuletzt aufgrund ihrer berauschenden Wirkung zunächst Verwendung bei religiösen und schamanischen Ritualen, dann, tausend Jahre vor Christus, auch in der Medizin gefunden habe. Auch den Griechen und Römern der Antike war Cannabis sativa nicht nur als Faserlieferant, sondern ebenso als vielfältiges Arzneimittel ein Begriff. Insbesondere die Hanf-Samen wurden in Europa bis in das Mittelalter und darüber hinaus volksmedizinisch als Heilmittel genutzt.

Basierend auf umfangreichen, 1839 veröffentlichten Berichten des in Kalkutta stationierten irischen Arztes Dr. William Brooke O'Shaughnessy fand der indische Hanf Cannabis indica Eingang in die europäische Schulmedizin. O'Shaughnessy beobachtete analgetische, antikonvulsive und muskelrelaxierende Wirkungen und propagierte die Anwendung von Cannabis beispielsweise bei Rheuma, Cholera, Tetanus oder Delirium tremens. Cannabis fand rasch Aufnahme in verschiedene westliche Arzneibücher, in denen es teilweise bis in die 1930er- (England) und 1940er-Jahre (USA) verblieb.

Das wahrscheinlich populärste Cannabismedikament jener Zeit war das Schlafmittel Bromidia[®], das 1886 als Präparat in Kombination mit Chloralhydrat, Bromkalium und Bilsenkraut eingeführt wurde. Während



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Cannabispräparate um die Jahrhundertwende zur Therapie verschiedener Krankheitsbilder medizinisch noch rege genutzt wurden, verschwanden sie gegen Mitte des 20. Jahrhunderts aufgrund Einführung anderer und besserer Therapeutika vollständig vom Markt. Als Folge des zunehmenden Missbrauchs von Cannabis und Cannabiszubereitungen als Rauschdrogen wurden diese zunächst der Betäubungsmittelpflicht unterworfen und letztlich ganz verboten.

Mit der Isolierung, Identifizierung und Strukturaufklärung von Δ-9-Tetrahydrocannabinol (Δ-9-THC) 1964 nahm das wissenschaftliche Interesse an Cannabis wieder deutlich zu. Wenig später gelang es, Δ-9-THC und verschiedene strukturanehme Verbindungen zu synthetisieren. Beim Studium des pharmakologischen Profils der ausschließlich in der Hanfpflanze gefundenen Wirkstoffe in den 1970er und 1980er Jahren wurde unter anderem die am C3 gebundene Seitenkette als Schlüsselpharmakophor beschrieben. In der Folge wurden 70 verschiedene Phytocannabinoide identifiziert. Das nach dem psychotropen Δ-9-THC mengenmäßig dominierende Phytocannabinoid ist das Cannabidiol, das psychotrop nicht aktiv ist und sogar die psychotropen Effekte von Δ-9-THC abschwächen kann.

Körpereigene Endocannabinoide

Die Erforschung der Phytocannabinoide führte zur Entdeckung des körpereigenen Endocannabinoid-Systems gegen Ende der 1980er- und zu Beginn der 1990er-Jahre. Dieses umfasst die körpereigenen Cannabinoid-, sprich CB1- und CB2-Rezeptoren, endogene Liganden sowie am Auf- und Abbau der Endocannabinoide beteiligte Enzyme.

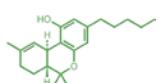
Die CB1-Rezeptoren gehören zu den häufigsten Rezeptoren im ZNS von Säugetieren und Menschen und sind in verschiedenen Hirnarealen und im Rückenmark, aber auch in peripheren Geweben, beispielsweise in peripheren Nervenfasern, im Gastrointestinaltrakt, in der Leber, dem Fettgewebe, Uterus und der Plazenta lokalisiert. Die CB2-Rezeptoren werden vor allem von peripheren Immun-Zellen und -Geweben wie T- und B-Lymphozyten, natürlichen Killerzellen (NK-Zellen) oder Makrophagen exprimiert. Sie sind ferner in Milz, Mandel, Lunge, Uterus und Fettgewebe gefunden worden.

Beide Cannabinoid-Rezeptortypen zeigen zu 44 Prozent Übereinstimmung in ihrer Aminosäure-Sequenz (3). Sie gehören zur Gruppe der siebenfach membrangängigen G-Protein-gekoppelten Rezeptoren.

Nach Aktivierung der Cannabinoid-Rezeptoren werden zahlreiche komplexe Zellprozesse moduliert, in deren Folge körpereigene Transkriptionsfaktoren in ihrer Funktion einerseits eingeschränkt, andererseits gesteigert werden. Die Proteinsyntheseleistung der Zellen und folglich auch die Produktion verschiedener Mediatoren kann somit in verschiedener Weise beeinflusst werden. Dies ist eine Erklärung für die Beobachtung, dass Cannabis und Cannabinoide zum Teil paradoxe Effekte auslösen.

1992 wurde mit Anandamid als Kondensationsprodukt von Arachidonsäure und Ethanolamin der erste endogene Ligand an Cannabinoid-Rezeptoren identifiziert. Der Name des Liganden leitet sich vom indisch-hinduistischen Sanskrit-Wort »ananda« für »inneres Glück« oder »Glückseligkeit« ab. In den Folgejahren wurden weitere endogene Cannabinoide identifiziert, die zumeist agonistisch an den Rezeptoren wirken und wie Anandamid Derivate der Arachidonsäure sind.

Die Endocannabinoide unterscheiden sich hinsichtlich ihrer Rezeptor-



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Affinitäten. So bindet Anandamid stärker an CB1-, 2-Arachidonylglycerol hingegen stärker an CB2-Rezeptoren. Letzteres hat daher einen deutlich ausgeprägteren Einfluss auf das Immunsystem. Interessanterweise wirkt das 2002 identifizierte Endocannabinoid Virodhamin antagonistisch an CB1-, jedoch agonistisch an CB2-Rezeptoren. Endocannabinoide sind keineswegs ausschließlich Liganden der Cannabinoid-Rezeptoren. Sie können unter anderem auch an Vanilloid-Rezeptoren binden und über diese die Schmerzwahrnehmung modulieren.

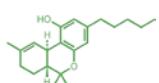
Komplexe und paradoxe Effekte

Endocannabinoide besitzen auch im Nervensystem eine besondere modulierende Funktion: Nach Freisetzung durch Stimulierung postsynaptischer Zellen können sie an präsynaptisch lokalisierte CB1-Rezeptoren binden. Hierdurch kommt es unter anderem zur Herabsetzung der Aktivität zelleinwärts gerichteter und im präsynaptischen Axonende lokalisierter Calciumkanäle und somit zur reduzierten synaptischen Neurotransmitterfreisetzung. CB1-Rezeptor-agonistische Endocannabinoide zeigen eine retrograde Hemmung der Transmitterfreisetzung. Die postsynaptische Signalübertragung wird moduliert. Endocannabinoide sind zur Feinregulation der synaptischen Erregungsübertragung und Transmitterfreisetzung insbesondere an GABA-, Noradrenalin-, Acetylcholin-, Serotonin- oder Dopamin-Rezeptoren fähig. Ihre modulierende Wirkung an den Synapsen gilt als weiteres Beispiel für die Komplexität der zum Teil gegensätzlichen und paradoxen Effekte, die Phyto- und Endocannabinoide erzielen können.

Wie der unkontrollierte Cannabis-Konsum kann auch der medikamentöse Einsatz von Cannabis und Cannabinoiden mit erheblichen negativen Wirkungen auf die Gesundheit einhergehen. Diese können akut oder chronisch sein. Unter den akuten Effekten dominiert insbesondere die Rauschwirkung mit gravierenden Einflüssen auf Psyche und Wahrnehmung mit Euphorie, »High«-Gefühl und Entspannung sowie Intensivierung der sensorischen Wahrnehmung zum Beispiel von Farben und Geräuschen, alles Effekte, die zum weitverbreiteten Gebrauch von Cannabis als Rauschdroge geführt haben. Weitere akute Effekte und potenzielle Nebenwirkungen sind Müdigkeit und Konzentrationsstörungen, reduziertes Reaktionsvermögen, Beeinträchtigung des Kurzzeitgedächtnisses, Sprachstörungen, Störungen der motorischen Koordination mit verlangsamten Reaktionszeiten, verringerte Muskelkraft und Ataxie, Dysphorie und Depression sowie Angst- und Panikanfälle.

Cannabis-Konsum kann eine akute Psychose mit Delirium, Verwirrtheit, Desorientiertheit, Realitätsverlust sowie optischen und akustischen Halluzinationen auslösen. Er verursacht eine Steigerung der Herzfrequenz und des Blutdrucks. Bei Vorschädigung des Herzens steigt daher die Gefahr eines Herzinfarktes. Cannabis kann andererseits aber auch zu einer Vasodilatation peripherer Gefäße und in Folge zu einem Blutdruckabfall führen.

Beim wiederholten Gebrauch bildet sich innerhalb von Tagen bis Wochen eine Toleranz gegenüber vielen Wirkungen der Cannabinoide aus. Dies ist sowohl für die psychotropen Wirkungen als auch für die kognitiven und psychomotorischen Einschränkungen, aber auch für die Einflüsse auf das kardiovaskuläre System beschrieben.



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Die regelmäßige inhalative Anwendung von Cannabis geht oftmals mit chronischen Erkrankungen der Atemwege durch Irritation der Bronchien mit Ausbildung von Bronchitis und Emphysemen einher. Einzelne Fallberichte geben Hinweise auf eine kanzerogene Aktivität mit erhöhter Inzidenz von Tumoren im Rachen, an der Zunge und am Kehlkopf. Bei chronischem Cannabis-Konsum kann es zur Ausbildung eines Amotivationssyndroms mit Passivität, Lethargie, Antriebsmangel, verflachter Affektivität, Interesselosigkeit und kognitiven Defiziten kommen. Das Absetzen der Droge geht zumeist mit starken Entzugssyndromen einher. Ähnlich wie beim Entzug von Opioiden oder Alkohol werden Unruhe, Angst, Dysphorie, Erregbarkeit, Reizbarkeit, Schlaflosigkeit, Muskelzittern und verstärkte Reflexe beschrieben (**die Aussagen dieses Absatzes finden, vor allem bei den empfohlenen Dosierungen den medizinischen Gebrauch betreffend, keine experimentelle oder klinische Unterstützung in der aktuellen Literatur**).

Mittel der zweiten Wahl

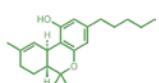
Auch wenn mit Marinol®, Cesamet® oder Sativex® Cannabinoid-haltige Fertigarzneimittel beziehungsweise standardisierte Extrakte auf dem Markt sind, so wird der Stellenwert dieser Präparate nicht sehr hoch eingeschätzt. Dies liegt nicht nur an der geringen Zahl der Indikationsgebiete, für die die Präparate zugelassen sind, sondern auch an der Tatsache, dass auf diesen Indikationsgebieten andere, zumeist effektivere Therapeutika verfügbar sind. Nichtsdestotrotz gelten Cannabis- und Cannabinoid-Präparate als vielversprechende therapeutische Optionen bei Patienten, die nur ungenügend auf die jeweiligen Standardtherapien ansprechen und sich daher oftmals in einer ausweglosen Situation befinden.

Auch und gerade bei der Therapie von Übelkeit und Erbrechen infolge Zytostatikagabe und -applikation können Cannabis- und Cannabinoid-Präparate eine bedeutende Rolle spielen. Insbesondere den synthetischen Cannabinoiden Dronabinol und Nabilon wird eine antiemetische Potenz zugeschrieben. In den 1970er- und 1980er-Jahren wurde in zahlreichen Studien die Wirksamkeit beider Verbindungen mit der Effektivität der damals gängigen Antiemetika Prochlorperazin und Metoclopramid verglichen. Beide Cannabinoide zeigten bei oraler Gabe eine vergleichbare Effektivität. Die Kombination von Dronabinol und Prochlorperazin erwies sich wirksamer als die Monotherapie mit Prochlorperazin. Durch diese Kombination wurden auch die Cannabinoid-induzierten Nebenwirkungen reduziert.

Die damaligen positiven Studienergebnisse waren Grundlage für die Zulassung der Cannabinoide Dronabinol und Nabilon als Antiemetika zur Behandlung des Chemotherapie-induzierten Erbrechens in den USA und Kanada. Häufigkeit und Stärke von Nebenwirkungen wie Konzentrationsstörungen, »High«-Gefühl, Müdigkeit, Euphorie, Blutdruckabfall, Dysphorie und Depression, Halluzinationen und Paranoia sprachen und sprechen allerdings gegen den Einsatz dieser Wirkstoffe als Mittel der ersten Wahl. Die Markteinführung der noch effektiveren und verträglicheren 5-HT3-Antagonisten und Setrone drängte die Cannabinoide weiter auf die hinteren Ränge. Bei Patienten, die mit den herkömmlichen Antiemetika nicht ausreichend behandelt werden können, sind sie jedoch eine wertvolle Ergänzung der antiemetischen Therapie.

Anorexie, Kachexie und MS

1992 wurde in den USA die Zulassung von Dronabinol (Marinol®) um die



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Indikation Wasting-Syndrom erweitert. Das Wasting-Syndrom mit Anorexie, also Appetitlosigkeit, und Kachexie, also schweren Formen der Abmagerung infolge eines gesteigerten Stoffwechsels, einer verringerten Nahrungsaufnahme, Entzündungen von Rachen oder Speiseröhre, Durchfall oder einer gestörten Verwertung der aufgenommenen Nahrung, zählt zum Aids related complex, ist also häufige Begleiterscheinung der fortgeschrittenen Aids-Erkrankung. Das Syndrom geht mit einer deutlichen Erhöhung der Aids-Morbidität und -Mortalität einher.

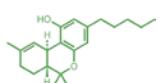
Berichte, dass Cannabis-Konsum den Hunger und den Appetit anregt, sind sehr alt. Mittlerweile weiß man, dass das zentrale Cannabinoidsystem bei der Appetitregulation eine wichtige Rolle spielt. CB1-Agonisten stimulieren den Appetit beziehungsweise das Fressverhalten bei Tieren, während Rezeptor-Antagonisten wie SR141716A, also Rimonabant, das Fressverhalten beziehungsweise das Hungergefühl dämpfen. In verschiedenen placebokontrollierten Studien an Aids-Patienten, die zumeist oral Dronabinol erhielten, wurde ein positiver Effekt auf Appetit und Gewichtszunahme der Patienten belegt. Allerdings traten bei bis zu 38 Prozent der Patienten Nebenwirkungen wie Angstzustände, Verwirrung, Euphorie, Müdigkeit und Denkstörungen auf.

In der Therapie des Wasting-Syndroms kommen unter anderem Kortikosteroide, Progestagene, Gastrokinetika wie Metoclopramid, anabole Steroide oder Wachstumshormone zum Einsatz. Die derzeit vorliegenden Studien weisen darauf hin, dass Dronabinol in begründeten Fällen das therapeutische Spektrum als Mittel der zweiten Wahl auch hier bereichern kann.

Sativex® ist in Kanada seit 2005 zur begleitenden Behandlung von neuropathischen Schmerzen bei Multipler Sklerose zugelassen. Das Mittel enthält Extrakte aus zwei speziellen Cannabis-Züchtungen und wird unter die Zunge gesprüht. Es ist auf definierte Mengen an Δ-9-THC und Cannabidiol (2,7 und 2,5 mg pro Sprühstoß) eingestellt. Studien belegen eine Linderung von neuropathischen Schmerzen sowie eine Verbesserung von spastischen Lähmungen, Muskelspasmen und Blasenschwäche ohne Toleranzentwicklung bei lediglich moderaten Nebenwirkungen. Schlaf, Wohlbefinden und Lebensqualität werden erhöht. Die Applikation auf die Mundschleimhaut ermöglicht offenbar eine bessere Dosis-Titration, bedingt durch die höhere Bioverfügbarkeit. Es fehlen allerdings vergleichende Untersuchungen mit Präparaten, die für die Behandlung der beschriebenen Symptome etabliert sind. Welchen Stellenwert das Mittel in der Therapie haben wird, muss die Zukunft zeigen.

Die Datenlage aus Studien zur Wirksamkeit anderer Cannabis- oder Cannabinoid-haltiger Produkte in der symptomatischen Behandlung der Multiplen Sklerose ist im Vergleich zu Sativex sehr uneinheitlich.

Zu den neurologischen Bewegungsstörungen zählt das Tourette-Syndrom als hyperkinetische Bewegungsstörung mit plötzlichen ticartigen Zuckungen im Gesicht (Augenzwinkern, Mundverzerrungen und Zungenschnalzen) sowie am Hals und der Schultern mit ruckartigen Kopfdrehungen. Einer standardisierten Befragung von 47 Betroffenen gemäß kann das Syndrom durch den gelegentlichen oder regelmäßigen Cannabis-Konsum deutlich reduziert werden. Einige placebokontrollierte Studien mit allerdings niedrigen Probandenzahlen oder kurzem Studienzeitraum belegten eine signifikante



Verbesserung der motorischen und verbalen Tics durch die orale Applikation von Dronabinol. Danach werden kognitive Funktionen nicht negativ beeinflusst. Diese Daten deuten darauf hin, dass die Substanz beim Tourette-Syndrom effektiv ist und gut toleriert wird. Zur Abklärung sind allerdings weitere Studien nötig. Studien mit Parkinson- oder Huntington-Patienten waren hingegen nicht so erfolgreich. Nach derzeitigem Kenntnisstand haben Cannabis und Cannabinoide keinen positiven Einfluss auf die Symptomatik dieser beiden Erkrankungen.

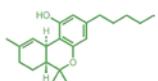
Schmerz und Migräne

Die Verwendung von Cannabiszubereitungen als Schmerzmittel hat eine mehrere Jahrtausende lange Historie. Untersuchungen mit den ab der 2. Hälfte des 20. Jahrhunderts in isolierter Form zur Verfügung stehenden Phyto- und synthetischen Cannabinoiden bestätigten ihr analgetisches Potenzial. Allerdings liegen derzeit nur wenige gut designete klinische Studien vor. Auch deren Ergebnisse sind sehr unterschiedlich. Neben anekdotischen Berichten werden auch viele Fallbeispiele beschrieben (38, 39), bei denen ansonsten therapieresistente Schmerz-Patienten erfolgreich unter anderem mit Dronabinol behandelt wurden. Dabei zeigten sich jedoch neben einer bis zu 50-prozentigen Nonresponder-Rate auch ausgeprägte Nebenwirkungen. Dieses wird auf die für die therapeutischen Effekte notwendigen hohen Dosen von 10 bis 20 mg Δ-9-THC zurückgeführt. Psychotrope Effekte können bereits ab Dosierungen von 5 bis 10 mg auftreten.

2007 wurde in Kanada die Zulassung von Sativex® um die Schmerzbehandlung von Krebspatienten erweitert, bei denen eine Opioidtherapie nicht anslägt. Als weiteres Präparat mit einem standardisierten Cannabis-Extrakt sind derzeit Cannador-Kapseln mit 2,5 mg Δ-9-THC, 1,25 mg Cannabidiol und maximal 5 Prozent weiteren Cannabinoiden pro Kapsel in der klinischen Prüfung.

Ebenfalls auf eine lange Tradition kann Cannabis in der Therapie von Migräne verweisen. Es sind allerdings nur anekdotische und ethnobotanische Berichte, die von einer positiven Wirkung bei Migräne zeugen (**ich schließe mich diesen Berichten, bezüglich geclusterter Kopfschmerzen, an**). Auch bei Befragungen von Personen, die Cannabis zu therapeutischen Zwecken rauchten, wird sehr häufig Migräne als Grund genannt. Wie die Resorption über die Mundschleimhaut geht auch die Inhalation mit einer besseren Bioverfügbarkeit einher. Für Inhalation spricht ferner die Tatsache, dass die gastrointestinale Absorption bei Migräne gestört sein kann. Auch die antiemetischen Effekte der Cannabinoide können bei Migräne durchaus von Vorteil sein. Allerdings dürfen die bereits beschriebenen, bei Inhalation verstärkten Nebenwirkungen von Cannabis durch Irritation des respiratorischen Systems nicht außer Acht gelassen werden. Bislang mangelt es an kontrollierten Studien, die die Effektivität von Cannabis und Cannabinoiden bei Migräne belegen. Der therapeutische Nutzen ist daher nach momentanem Kenntnisstand als fraglich anzusehen.

Positive Fallberichte liegen auch über die Effektivität von Cannabis bei Glaukom als chronische Augenerkrankung mit erhöhtem Augeninnendruck und der Gefahr der Erblindung vor. In zwei, in den 1980er-Jahren durchgeführten kontrollierten Studien wurde eine Reduktion des Augeninnendrucks sowohl bei inhalativer Applikation als auch bei Applikation in Form Δ-9-THC-haltiger Augentropfen konstatiert. Vor allem wegen der nur



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kurz anhaltenden Wirkung, aber auch wegen der Häufigkeit von Nebenwirkungen muss der Nutzen von Cannabis bei Glaukom nach momentanem Kenntnisstand als begrenzt angesehen werden, zumal es effektivere und nebenwirkungsärmere Arzneistoffe gibt.

Außer den bereits genannten Indikationen werden derzeit noch weitere Anwendungsgebiete für Cannabis und Cannabinoide wie beispielsweise Epilepsie, Depressionen oder Allergien diskutiert. Das therapeutische Potenzial entsprechender Mittel muss sich allerdings erst noch in weiteren Studien erweisen.

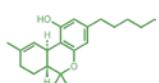
Cannabis in der Apotheke

Seit 2003 werden Hanfblüten (Bedrobinol[®], Bedrocan[®]) in niederländischen Apotheken für medizinische Zwecke auf Rezept abgegeben. Zwar ist auch in den Niederlanden der Anbau von Cannabis verboten. Die Firma Bedrocan, Groningen, darf Cannabis jedoch legal unter standardisierten Bedingungen kultivieren. Die nach 15 Wochen geernteten und getrockneten Blüten der weiblichen Pflanzen enthalten besonders hohe Konzentrationen an Δ-9-THC. Bedrocan enthält circa 18 Prozent Δ-9-THC und weniger als 1 Prozent Cannabidiol, Bedrobinol hingegen nur circa 13 Prozent Δ-9-THC und ebenfalls weniger als 1 Prozent Cannabidiol. 2007 kam zudem Bediol[®]-Granulat mit einem deutlich niedrigeren Δ-9-THC-Gehalt von circa fünf Prozent, jedoch einem deutlich höheren Cannabidiol-Gehalt von circa sechs Prozent auf den Markt in der Hoffnung, dass dieses Präparat weniger psychotrope Nebenwirkungen zeigt.

Deutsche Patienten können in niederländischen Apotheken zwar mit einem Rezept ebenfalls Cannabis beziehen, aber sie dürfen es offiziell nicht nach Deutschland einführen. Nach einem Urteil des Bundesverwaltungsgerichtes aus dem Jahr 2005 (Az. 3C 17.04) besteht gemäß § 3 Abs. 2 BtMG auch in Deutschland die Möglichkeit, in begründeten Ausnahmefällen Cannabis zu therapeutischen Zwecken legal über Apotheken zu beziehen. Die erste einer solchen, stets individuell zu beurteilenden Ausnahmegenehmigung wurde 2007 vom Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) für eine MS-Patientin erteilt.

Voscopoulos, C. and M. Lema (2010) "When does acute pain become chronic?" *British Journal of Anaesthesia* **105** (Suppl. 1): i69-85.

The transition from acute to chronic pain appears to occur in discrete pathophysiological and histopathological steps. Stimuli initiating a nociceptive response vary, but receptors and endogenous defence mechanisms in the periphery interact in a similar manner regardless of the insult. Chemical, mechanical, and thermal receptors, along with leucocytes and macrophages, determine the intensity, location, and duration of noxious events. Noxious stimuli are transduced to the dorsal horn of the spinal cord, where amino acid and peptide transmitters activate second-order neurones. Spinal neurones then transmit signals to the brain. The resultant actions by the individual involve sensory-discriminative, motivational-affective, and modulatory processes in an attempt to limit or stop the painful process. Under normal conditions, noxious stimuli diminish as healing progresses and pain sensation lessens until minimal or no pain is detected. Persistent, intense pain, however, activates secondary mechanisms both at the periphery and within the central nervous system that cause allodynia, hyperalgesia, and hyperpathia that can



diminish normal functioning. These changes begin in the periphery with upregulation of cyclo-oxygenase-2 and interleukin-1beta-sensitizing first-order neurones, which eventually sensitize second-order spinal neurones by activating N-methyl-d-aspartic acid channels and signalling microglia to alter neuronal cytoarchitecture. Throughout these processes, prostaglandins, endocannabinoids, ion-specific channels, and scavenger cells all play a key role in the transformation of acute to chronic pain. A better understanding of the interplay among these substances will assist in the development of agents designed to ameliorate or reverse chronic pain.

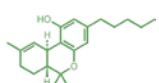
Voth, E. A. and R.H. Schwartz (1997) "Medicinal applications of delta-9-tetrahydrocannabinol and marijuana (see comments)." Annals of Internal Medicine **126** (10): 791-798.

The use of crude marijuana for herbal medicinal applications is now being widely discussed in both the medical and lay literature. Ballot initiatives in California and Arizona have recently made crude marijuana accessible to patients under certain circumstances. As medicinal applications of pure forms of Δ -9-tetrahydrocannabinol (THC) and crude marijuana are being considered, the most promising uses of any form of THC are to counteract the nausea associated with cancer chemotherapy and to stimulate appetite. We evaluated the relevant research published between 1975 and 1996 on the medical applications, physical complications, and legal precedents for the use of pure THC or crude marijuana. Our review focused on the medical use of THC derivatives for nausea associated with cancer chemotherapy, glaucoma, stimulation of appetite, and spinal cord spasticity. Despite the toxicity of THC delivered in any form, evidence supports the selective use of pure THC preparations to treat nausea associated with cancer chemotherapy and to stimulate appetite. The evidence does not support the reclassification of crude marijuana as a prescribable medicine.

Voth, E.A. and R.M. Swift (1995) "Marijuana and its reviews." New England Journal of Medicine **322** (4): 274-275.

As I pointed out in my review of the book in the *Annals of Internal Medicine*, Grinspoon and Bakalar have only assembled anecdotes that they use to justify the rescheduling of marijuana. Like the members of the pro-marijuana lobby during hearings held by the Drug Enforcement Agency to consider rescheduling marijuana, these authors believe that marijuana should be used to treat nausea associated with cancer chemotherapy, glaucoma, wasting in AIDS, depression, menstrual cramps, pain, and virtually limitless ailments. In their anecdotes there are no controls, no standardization of the dose, no quality control, and no independent medical evaluation for efficacy or toxicity. According to Grinspoon and Bakalar, the Chinese used marijuana to "quicken the mind, induce sleep, cure dysentery, stimulate appetite, relieve headaches, and cure venereal disease." One of the references from 1860 states purported beneficial effects "without interfering with the actions of the internal organs" (a statement known to be inaccurate). Potions and remedies were common in those earlier years. Many were absolutely useless, or conversely were harmful to unsuspecting subjects.

The medical issue surrounding the smoking of marijuana can best be summarized by an opinion from Dr. Philip Lee in a letter to Congress after the



"medical marijuana" issue was submitted to the National Institutes of Health. He states, Scientists at the National Institutes of Health indicate that, after carefully examining the existing preclinical and human data, there is no evidence to suggest that smoked marijuana might be superior to currently available therapies for glaucoma, weight loss associated with AIDS, nausea and vomiting associated with cancer chemotherapy, muscle spasticity associated with multiple sclerosis, or intractable pain:
We do not smoke medicine anywhere in our society. We should turn to truly medical solutions to solve our medical problems.

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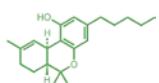
On December 7, 1993, the Surgeon General of the United States, Joycelyn Elders, fired a shot heard around the world when she publicly stated that the legalization of drugs should be explored. Although Dr. Elders's statement gained considerable media exposure, legalization of certain drugs has many other distinguished advocates within the health care profession. One of these is Dr. Lester Grinspoon, associate professor of psychiatry at Harvard Medical School. Dr. Grinspoon has long felt that certain psychopharmacologic agents labeled illicit by American society should be legalized because of their therapeutic value.

In this easy-to-read book, coauthored by James B. Bakalar, Grinspoon presents cogent and convincing arguments for the legalization of marijuana and its pharmacologically active components. The book focuses on the medical, rather than the sociological, benefits of decriminalization but does present a detailed history of the regulation and proscription of marijuana. The arguments are mostly supported by referenced scientific literature and a logic of common sense. They are highlighted by vignettes of desperate people who benefited from the medicinal properties of marijuana but who came into conflict with the law because of their use of the substance.

There is no doubt that the psychoactive components of marijuana have therapeutic properties. The authors present a concise summary of the therapeutic uses of marijuana and its components. The main active components, $\Delta 9$ -tetrahydrocannabinol (THC) and other cannabinoids, have antiemetic, analgesic, and muscle-relaxant properties, reduce intraocular pressure, and stimulate appetite. As yet unidentified components of the plant also have medicinal effects. Marijuana has reported therapeutic value in treating glaucoma, side effects of cancer chemotherapy, muscle spasticity associated with neurologic disorders, and various psychiatric disorders.

Although some of the reports of therapeutic efficacy are anecdotal, the authors emphasize that there have been few controlled studies. The recent identification of the THC receptor -- a neuronal THC-binding site coupled to a G protein -- has increased our understanding of the mechanism of action of the cannabinoids and will stimulate new research with these compounds.

The authors present a compelling argument for unrestricted access to these therapeutic agents derived from marijuana. The federal, state, and local laws regarding marijuana or its active components and the criminal penalties for its use are inconsistent among jurisdictions and inconsistently enforced. The Food and Drug Administration, which regulates the medicinal use of THC and other marijuana components, sometimes permits medicinal use, sometimes does not. The authors argue that THC does not produce drug dependence or lead to addiction, whereas comparable legal pharmacologic agents such as



opiates and benzodiazepines produce substantial drug dependence and withdrawal symptoms.

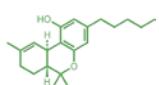
This book is written to enlist the reader in the cause of the legalization of marijuana, and the authors tend to underemphasize reports of its negative medical effects. Nevertheless, whether or not one personally supports the decriminalization or legalization of marijuana, this book provides an excellent overview of the subject from a medical perspective.

Wade, D. (2012) "Evaluation of the safety and tolerability profile of Sativex: is it reassuring enough?" *Expert Review of Neurotherapeutics* **12** (4, Suppl.): 9-14.

The adoption of new drug therapies involves an assessment of risk:benefit based upon the best clinical evidence, including clinical trials but also everyday clinical practice data collection. However, in the case of Sativex, a cannabinoid medicine containing the two main active ingredients of cannabis, Δ-9-tetrahydrocannabinol and cannabidiol, the picture is somewhat clouded by preconceived views regarding the world's most widely used illicit drug, herbal cannabis. In this review, I aim to look beyond these preconceptions and evaluate the body of published data concerning this medicine currently approved in different countries for the management of one of the most frequent and disabling symptoms associated with multiple sclerosis, spasticity. In particular, data relevant to areas of concern such as tolerability, safety, psychoactivity, effects on withdrawal (including possible drug tolerance) and finally the potential for abuse/dependence are evaluated. Balancing these risk factors, the main positive clinical data published over the years by the Oxford Centre for Enablement, following on from the first pilot study in 2004, are presented. Based upon our experience, the benefits that are seen initially with Sativex when treating multiple sclerosis spasticity patients are generally maintained during long-term treatment. Furthermore, following withdrawal of Sativex, symptoms often return, but, beyond this, sudden cessation is generally safe with no evidence of physiological or psychological dependence. Dose escalation has not usually been observed in clinical trials or clinical practice after the first titration weeks. Adverse effects occur relatively frequently, but they are usually mild to moderate in intensity and rarely require drug discontinuation. Overall, Sativex appears to be well-tolerated and a useful addition for patients who have failed treatment with traditional antispastic agents.

Wade, D.T., C. Collin, C. Stott and P. Duncombe, (2010) "Meta-analysis of the efficacy and safety of Sativex® (nabiximols), on spasticity in people with multiple sclerosis." *Multiple Sclerosis Journal* **16** (6): 707-714.

Objective: To determine the efficacy of Sativex (USAN: nabiximols) in the alleviation of spasticity in people with multiple sclerosis. Methods: The results from three randomized, placebo-controlled, double-blind parallel group studies were combined for analysis. Patients: 666 patients with multiple sclerosis and spasticity. Measures: A 0-100 mm Visual Analogue Scale (VAS, transformed to a 0-10 scale) or a 0-10 Numerical Rating Scale (0-10 NRS) was used to measure spasticity. Patients achieving a > or =30% improvement from baseline in their spasticity score were defined as 'responders'. Global impression of change (GIC) at the end of treatment was also recorded. Results: The patient populations were similar. The adjusted mean change of



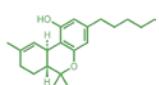
the numerical rating scale from baseline in the treated group was -1.30 compared with -0.97 for placebo. Using a linear model, the treatment difference was -0.32 (95% CI -0.61, -0.04, $p = 0.026$). A statistically significant greater proportion of treated patients were responders (odds ratio (OR) = 1.62, 95% CI 1.15, 2.28; $p = 0.0073$) and treated patients also reported greater improvement: odds ratio 1.67 (95% CI 1.05, 2.65; $p = 0.030$). High numbers of subjects experienced at least one adverse event, but most were mild to moderate in severity and all drug-related serious adverse events resolved. Conclusion: The meta-analysis demonstrates that nabiximols is well tolerated and reduces spasticity.

Wade, D.T., P.M. Makela, H. House, C. Bateman and P. Robson, (2006) "Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis." *Multiple Sclerosis Journal* **12** (5): 639-645.

The object of this study was to monitor the safety and efficacy of long-term use of an oromucosal cannabis-based medicine (CBM) in patients with multiple sclerosis (MS). A total of 137 MS patients with symptoms not controlled satisfactorily using standard drugs entered this open-label trial following a 10-week, placebo-controlled study. Patients were assessed every eight weeks using visual analogue scales and diary scores of main symptoms, and were followed for an average of 434 days (range: 21 -814). A total of 58 patients (42.3%) withdrew due to lack of efficacy (24); adverse events (17); withdrew consent (6); lost to follow-up (3); and other (8). Patients reported 292 unwanted effects, of which 251 (86%) were mild to moderate, including oral pain (28), dizziness (20), diarrhoea (17), nausea (15) and oromucosal disorder (12). Three patients had five 'serious adverse events' between them--two seizures, one fall, one aspiration pneumonia, one gastroenteritis. Four patients had first-ever seizures. The improvements recorded and dosage taken in the acute study remained stable. Planned, sudden interruption of CBM for two weeks in 25 patients (of 62 approached) did not cause a consistent withdrawal syndrome, although 11 (46%) patients reported at least one of--tiredness, interrupted sleep, hot and cold flushes, mood alteration, reduced appetite, emotional lability, intoxication or vivid dreams. Twenty-two (88%) patients restarted CBM treatment. We conclude that long-term use of an oromucosal CBM (Sativex) maintains its effect in those patients who perceive initial benefit. The precise nature and rate of risks with long-term use, especially epilepsy, will require larger and longer-term studies.

Wade, D.T., P. Makela, P. Robson, H. House, and C. Bateman (2004) "Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients." *Multiple Sclerosis Journal* **10** (4): 434-441.

The objective was to determine whether a cannabis-based medicinal extract (CBME) benefits a range of symptoms due to multiple sclerosis (MS). A parallel group, double-blind, randomized, placebo-controlled study was undertaken in three centres, recruiting 160 outpatients with MS experiencing significant problems from at least one of the following: spasticity, spasms, bladder problems, tremor or pain. The interventions were oromucosal sprays of matched placebo, or whole plant CBME containing equal amounts of Δ -9-tetrahydrocannabinol (THC) and cannabidiol (CBD) at a dose of 2.5-120 mg of



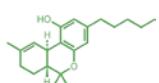
each daily, in divided doses. The primary outcome measure was a Visual Analogue Scale (VAS) score for each patient's most troublesome symptom. Additional measures included VAS scores of other symptoms, and measures of disability, cognition, mood, sleep and fatigue. Following CBME the primary symptom score reduced from mean (SE) 74.36 (11.1) to 48.89 (22.0) following CBME and from 74.31 (12.5) to 54.79 (26.3) following placebo [ns]. Spasticity VAS scores were significantly reduced by CBME (Sativex) in comparison with placebo ($P = 0.001$). There were no significant adverse effects on cognition or mood and intoxication was generally mild.

Wade, D.T., P. Robson, H. House, P. Makela and J. Aram (2003) "A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms." Clinical Rehabilitation **17** (1): 21-29.

Objectives: To determine whether plant-derived cannabis medicinal extracts (CME) can alleviate neurogenic symptoms unresponsive to standard treatment, and to quantify adverse effects. Design: A consecutive series of double-blind, randomized, placebo-controlled single-patient cross-over trials with two-week treatment periods. Setting: Patients attended as outpatients, but took the CME at home. Subjects: Twenty-four patients with multiple sclerosis (18), spinal cord injury (4), brachial plexus damage (1), and limb amputation due to neurofibromatosis (1). Intervention: Whole-plant extracts of Δ -9-tetrahydrocannabinol (THC), cannabidiol (CBD), 1:1 CBD:THC, or matched placebo were self-administered by sublingual spray at doses determined by titration against symptom relief or unwanted effects within the range of 2.5-120 mg/24 hours. Measures used: Patients recorded symptom, well-being and intoxication scores on a daily basis using visual analogue scales. At the end of each two-week period an observer rated severity and frequency of symptoms on numerical rating scales, administered standard measures of disability (Barthel Index), mood and cognition, and recorded adverse events. Results: Pain relief associated with both THC and CBD was significantly superior to placebo. Impaired bladder control, muscle spasms and spasticity were improved by CME in some patients with these symptoms. Three patients had transient hypotension and intoxication with rapid initial dosing of THC-containing CME. Conclusions: Cannabis medicinal extracts can improve neurogenic symptoms unresponsive to standard treatments. Unwanted effects are predictable and generally well tolerated. Larger scale studies are warranted to confirm these findings.

Wade; D:T.; P: Robson; H: House, P: Makela and J. Aram (2003) "A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms." Clinical Rehabilitation **17**: 18-26.

Objectives: To determine whether plant-derived cannabis medicinal extracts (CME) can alleviate neurogenic symptoms unresponsive to standard treatment, and to quantify adverse effects. Design: A consecutive series of double-blind, randomized, placebo-controlled single-patient cross-over trials with two-week treatment periods. Setting: Patients attended as outpatients, but took the CME at home. Subjects: Twenty-four patients with multiple sclerosis (18), spinal cord injury (4), brachial plexus damage (1), and limb amputation due to neurofibromatosis (1). Intervention: Whole-plant extracts of Δ -9-tetrahydrocannabinol (THC), cannabidiol (CBD), 1:1 CBD:THC, or



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Walker, J.M. and A.G. Hohmann (2005) "Cannabinoid mechanisms of pain suppression." Handbook of Experimental Pharmacology **168** (509-554).

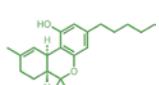
A large body of literature indicates that cannabinoids suppress behavioral responses to acute and persistent noxious stimulation in animals. This review examines neuroanatomical, behavioral, and neurophysiological evidence supporting a role for cannabinoids in suppressing pain at spinal, supraspinal, and peripheral levels. Localization studies employing receptor binding and quantitative autoradiography, immunocytochemistry, and in situ hybridization are reviewed to examine the distribution of cannabinoid receptors at these levels and provide a neuroanatomical framework with which to understand the roles of endogenous cannabinoids in sensory processing. Pharmacological and transgenic approaches that have been used to study cannabinoid antinociceptive mechanisms are described. These studies provide insight into the functional roles of cannabinoid CB1 (CB1R) and CB2 (CB2R) receptor subtypes in cannabinoid antinociceptive mechanisms, as revealed in animal models of acute and persistent pain. The role of endocannabinoids and related fatty acid amides that are implicated in endogenous mechanisms for pain suppression are discussed. Human studies evaluating therapeutic potential of cannabinoid pharmacotherapies in experimental and clinical pain syndromes are evaluated. The potential of exploiting cannabinoid antinociceptive mechanisms in novel pharmacotherapies for pain is discussed.

Wandtner, R. (2003) "Cannabis-Wirkstoffe – Was hat Hanf, was "Hanf" nicht hat?" Frankfurter Allgemeine Zeitung, **239** (15.10.2003): N1.

Schmerzen können heute besser behandelt werden denn je. Das Arsenal an Therapiemöglichkeiten ist so vielfältig, daß oft sogar Spezialisten ihre Mühe haben, für Patienten mit hartnäckigen chronischen Schmerzen die passende Kombination an Behandlungsverfahren zu ermitteln.

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Auf dem Deutschen Schmerzkongreß, der Ende der vergangenen Woche in



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Münster stattgefunden hat, war dies eine der am leidenschaftlichsten diskutierten Fragen. Das hing freilich stark damit zusammen, daß es sich bei dem umstrittenen Medikament um einen Cannabis-Wirkstoff handelt, also um eine Substanz aus dem "Dunstkreis" von Haschisch und Marihuana. Anders als in den Niederlanden, wo seit kurzem sogar Haschisch auf Rezept erhältlich ist, steht in Deutschland nur ein einziger - zumal teurer - Inhaltsstoff des Hanfs legal für die Therapie zur Verfügung. Es ist das Tetrahydrocannabinol, bezeichnet auch als Dronabinol.

Cannabinoide aus dem eigenen Körper

Seit mehr als 4000 Jahren nutzt der Mensch Aufbereitungen der Hanfpflanze (*Cannabis sativa*) als Droge und Heilmittel. Darauf wies Shahnaz Christina Azad vom Max-Planck-Institut für Psychiatrie in München hin. Die Forscherin, die aufgrund ihrer Tätigkeit in der Schmerzambulanz der Ludwig-Maximilians-Universität auch über einschlägige klinische Erfahrungen verfügt, präsentierte eine Reihe von Argumenten für die Anwendung von Cannabis-Inhaltsstoffen. Der Körper verfügt über ein endogenes Cannabinoid-System. Im Gehirn finden sich massenweise Bindungsstellen für Cannabinoide. Diese sprechen keineswegs nur auf von außen zugeführte Substanzen an, sondern auch auf körpereigene Cannabinoide, sogenannte Anandamide und Arachidonoylglycerol.

Besonders viele Bindungsstellen weist der Mandelkern auf, eine Hirnstruktur, die an der Verarbeitung von Schmerz und Angst beteiligt ist. Cannabinoide scheinen neuen Untersuchungen an Tieren zufolge eine wichtige Rolle beim Schmerzerleben zu spielen. Wenn Mäuse die Erfahrung machen, daß einem bestimmten Signal ein schmerzhafter Reiz folgt, nehmen sie schon nach der Wahrnehmung des Signals eine Angsthaltung ein. Sie sind dann entsprechend konditioniert. Bleibt das Schmerzerlebnis aber fortan aus, reagieren sie bald nicht mehr auf das Signal. Mäuse mit defektem körpereigenem Cannabinoid-System indessen können die Angst vor dem Schmerz nicht verlernen.

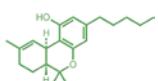
Mehr Behandlungsmöglichkeiten durch Cannabinoide

Die Forscherin mißt dieser Beobachtung erhebliche Bedeutung bei, denn auch bei Patienten mit chronischen Schmerzen spielt konditionierte Angst eine große Rolle. Wie andere Experimente ergaben, hemmen Cannabinoide in Hirnregionen, die an der Schmerzverarbeitung mitwirken, die Übertragung erregender Nervensignale. Gestützt auf die zahlreichen ermutigenden Ergebnisse aus der Grundlagenforschung, plädierte Frau Azad dafür, in der Schmerztherapie gegebenenfalls auf Cannabinoide zurückzugreifen.

Die Substanzen sollten ergänzend angewendet werden. Vor allem biete sich die Kombination mit Opioiden an, weil es dabei zu einer Wirkungssteigerung komme. Cannabinoide erweiterten die Behandlungsmöglichkeiten etwa bei Tumorpatienten mit starken Schmerzen und bei Patienten mit spastischem Schmerz. Die Forscherin verwies auf eine Umfrage bei Patienten mit multipler Sklerose und Spastik. 70 Prozent berichteten dabei über eine Verbesserung durch Cannabinoide, 60 Prozent auch über Appetitsteigerung.

Mehr Hunger und bessere Laune

Wenig beeindruckt von dem Plädoyer zeigte sich Michael Strumpf vom Roten-Kreuz-Krankenhaus in Bremen. Die Begeisterung für die Forschung dürfe keine falschen Hoffnungen wecken. Es sei zu bezweifeln, daß Cannabinoide beim Menschen schmerzlindernd wirkten. Nur bei einzelnen Patienten mit



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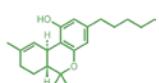
sonst nicht zu behandelnder Spastik sei eine Anwendung denkbar. Es "nerve" ihn, wenn Patienten aufgrund von Medienberichten, in denen Ergebnisse "einseitig ausgeschlachtet" würden, eine Behandlung mit Cannabinoiden wünschten. Die Medien übten Druck aus, der zu einer Erwartungshaltung führe. Er jedenfalls verschreibe solche Mittel nicht.

Nicht ganz so hart prallen die Meinungen aufeinander, wenn es um die Anwendung von Cannabinoiden in der Palliativmedizin geht. Wie Birgit Kraft von der Medizinischen Universität Wien ausführte, sprechen ungefähr 90 Prozent der Tumorpatienten, die aufgrund einer Chemotherapie an Übelkeit und Erbrechen leiden, gut auf moderne Gegenmittel (Antiemetika) an. Das gilt aber nur für die frühe Phase. Erbrechen im späteren Verlauf der Chemotherapie bekomme man bei rund 60 Prozent der betroffenen Patienten schlecht in den Griff. In dieser Situation biete sich die zusätzliche Anwendung von Cannabinoiden an.

Nicht zu unterschätzen ist nach Ansicht der Befürworter der appetitsteigernde Effekt, der häufig beobachtet wird. Wenn der bei Tumorpatienten verbreiteten Auszehrung entgegengewirkt werden kann, ist das, zusammen mit der ebenfalls berichteten Stimmungsaufhellung, mitunter die wichtigste therapeutische Maßnahme. Auch manche Aidspatienten profitieren davon. Die Befürchtung, ihr Immunsystem könnte unter dem Mittel leiden, hat sich nach Aussage der Wiener Forscherin nicht bestätigt. Geprüft wurde allerdings nur eine kurzzeitige Anwendung.

Langzeitstudien fehlen

Ohnehin ist es der gravierende Mangel an aussagekräftigen Studien, an dem die Diskussion um die Cannabinoide krankt. Das Urteil stützt sich immer auf Einzelfälle. Entsprechend widersprüchlich sind die Erfahrungen. Auch der Palliativmediziner Lukas Radbruch vom Universitätsklinikum Aachen konnte seine insgesamt skeptische Haltung lediglich auf einzelne Beispiele gründen. Den günstigen Wirkungen, die er bisweilen sah, standen erhebliche Nebenwirkungen gegenüber. Das "therapeutische Fenster" ist sehr schmal, wie er sagte. Andererseits räumte Radbruch ein, einer seiner Patientinnen werde er das Cannabinoid nicht vorenthalten, denn sie habe jetzt erstmals wieder Appetit. Auf Cannabinoide würde auch der Präsident des Verbandes Deutscher Ärzte für Algesiologie, Dietrich Jungck aus Hamburg, nicht verzichten. Er kann ebenfalls über beachtliche Behandlungserfolge berichten. Der Nutzen der Cannabinoide, so wurde in Münster deutlich, steht und fällt mit der genauen Abstimmung der Dosis auf den jeweiligen Patienten. Gerade weil es sich um eine derart individuelle, die Kunst des Arztes fordernde Therapie handelt, dürfte sie sich in gewisser Weise der Überprüfung durch eine große Studie entziehen. Denn in solchen Untersuchungen kommt es auf eine möglichst umfassende Standardisierung an, auch was die Homogenität des Patientenkollektivs betrifft. Wie repräsentativ die Ergebnisse dann sind, ist eine andere Frage. Einer Studie mit einer großen Zahl von Patienten stehen auch die hohen Kosten des aufwendig hergestellten Dronabinols entgegen. Der Preis ist zudem einer der Gründe, daß viele Schmerzspezialisten dafür plädieren, Haschisch von definierter Zusammensetzung für den Vertrieb durch Apotheken zuzulassen - zum Vorteil jener Patienten, denen die Krankenkasse das teure Cannabinoid verweigert.



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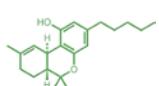
Ward, A. B. and M. Kadies (2002) "The management of pain in spasticity." Disability and Rehabilitation **24** (8): 443-453.

Pain is a common feature of spasticity and muscle spasms and the reasons for this are discussed in this article. However, the causes of this spasticity have to be determined and for successful management, knowing the underlying mechanisms, which produce spasticity, is necessary. In addition to knowing the range of available treatments, one has to know their particular contribution to the overall management of the patient. The assessment and management of the spastic patient is multi-disciplinary and painful spasticity changes over time. This therefore requires repeated assessments and the direction of the treatment may also change. Pain may be a dominant feature, but is rarely the sole symptom. This article looks at a strategy for the overall management of the patient with the focus on managing pain.

Ware, M.A., T. Wang, S. Shapiro, A. Robinson, T. Ducruet, T. Huynh, A. Gamsa, G.J. Bennett, and J.P. Collet (2010) "Smoked cannabis for chronic neuropathic pain: a randomized controlled trial." Canadian Medical Association Journal – CMAJ **182** (14): E694-701.

Background: Chronic neuropathic pain affects 1%-2% of the adult population and is often refractory to standard pharmacologic treatment. Patients with chronic pain have reported using smoked cannabis to relieve pain, improve sleep and improve mood. **Methods:** Adults with post-traumatic or postsurgical neuropathic pain were randomly assigned to receive cannabis at four potencies (0%, 2.5%, 6% and 9.4% tetrahydrocannabinol) over four 14-day periods in a crossover trial. Participants inhaled a single 25-mg dose through a pipe three times daily for the first five days in each cycle, followed by a nine-day washout period. Daily average pain intensity was measured using an 11-point numeric rating scale. We recorded effects on mood, sleep and quality of life, as well as adverse events. **Results:** We recruited 23 participants (mean age 45.4 [standard deviation 12.3] years, 12 women [52%]), of whom 21 completed the trial. The average daily pain intensity, measured on the 11-point numeric rating scale, was lower on the prespecified primary contrast of 9.4% v. 0% tetrahydrocannabinol (5.4 v. 6.1, respectively; difference = 0.7, 95% confidence interval [CI] 0.02-1.4). Preparations with intermediate potency yielded intermediate but nonsignificant degrees of relief. Participants receiving 9.4% tetrahydrocannabinol reported improved ability to fall asleep (easier, $p = 0.001$; faster, $p < 0.001$; more drowsy, $p = 0.003$) and improved quality of sleep (less wakefulness, $p = 0.01$) relative to 0% tetrahydrocannabinol. We found no differences in mood or quality of life. The most common drug-related adverse events during the period when participants received 9.4% tetrahydrocannabinol were headache, dry eyes, burning sensation in areas of neuropathic pain, dizziness, numbness and cough. **Conclusion:** A single inhalation of 25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep and was well tolerated. Further long-term safety and efficacy studies are indicated. (International Standard Randomised Controlled Trial Register no. ISRCTN68314063).

Ware, M.A. (2008) "Marijuana as medicine: does it have a future?" Clinical Pharmacology and Therapeutics **83** (4): 515-517.



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Crude preparations of herbal cannabis have been used for thousands of years to treat many symptoms, including pain, spasms, and nausea...

Cannabis has not yet been formally evaluated in clinical trials, but safety and efficacy studies are under way and further studies should be designed and conducted. Without such trials it is premature to consider prescribing cannabis, but based on what is known of a drug that has been around for thousands of years, based on the safety data generated from 2 generations of recreational users, and based on the mechanism of action of cannabinoids, it is reasonable for family physicians to become more familiar with cannabis. Its undignified position as a drug of abuse with no known medical value deserves to be reconsidered.

Ware, M.A. (2007) "Is there a role for marijuana in medical practice? Yes" Canadian Family Physician **53** (1): 22-25.

Ware, M.A., M. Kahan and A. Srivastava (2006) "Is there a role for marijuana in medical practice?" Canadian Family Physician **52** (12): 1531-1533, 1535-1537.

Yes

Editor's Key Points There is solid scientific rationale for therapeutic use of cannabis.

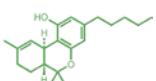
- Pharmaceutical cannabinoid preparations should always be considered.
- Mechanisms exist in Canada for herbal cannabis to be used legally.
- Ongoing research and education regarding cannabis is needed.

Crude preparations of herbal cannabis have been used for thousands of years to treat many symptoms, including pain, spasms, and nausea. Preparations historically included extracts of roots, leaves, and flowering heads but were not commercially standardized or characterized. Modern pharmacology has identified the principal psychoactive ingredient of cannabis as delta-9-tetrahydrocannabinol; specific cannabinoid receptors have been identified in the central and peripheral nervous system as well as in immune cells, endothelial tissue, and other visceral organs. Animal studies have confirmed that many of the effects of cannabis in humanbeings have solid neurophysiologic bases, particularly with respect to pain control. The cannabinoid system is, therefore, a major target for drug development.

History of medical cannabis policy in Canada In 1999 the Court of Appeal for Ontario ruled that it was unconstitutional to enforce the rule of law with respect to cannabis. Since 2001, the Marihuana Medical Access Regulations (MMAR) have made cannabis possession legal for authorized patients in Canada.

Since July 2005 the streamlined MMAR application requires that physicians sign a form confirming the diagnosis, the symptoms, the fact that prior treatments have been tried or considered, that the use of cannabis has been discussed, and that cannabis is not an approved drug.

There are 2 main categories of complexes recognized under the MMAR: those requiring approval from family physicians and those requiring approval from both family physicians and specialists. For the second category, family physicians must discuss the case with a specialist; whose name and the date of consultation, but not signature, are required. Amending this process appears to have increased the number of applications. As of September 2006, 1492 persons were authorized to possess medical marijuana and 917 physicians had supported applications under this program.



Herbal cannabis, cultivated by Prairie Plant Systems Inc under licence to Health Canada, is distributed to authorized patients for \$5/g. This herbal cannabis is cultivated under controlled conditions, is free of contaminants, and is irradiated to destroy pathogenic microorganisms. It is delivered as a milled herb with 10 mm particles and moisture content of 15%. The potency is standardized at $12\% \pm 2.0\%$ delta-9-tetrahydrocannabinol.

Cannabis and family physicians

What do family physicians need to know about the MMAR? First, there is a legal means by which patients can obtain quality-controlled cannabis for medical use. Second, physicians do not “prescribe” cannabis under this approach but instead support a patient’s application for authorization to possess the drug. This process reduces the risk of prosecution for patients whose cannabis use is part of a therapeutic approach. Third, medical cannabis use can be documented and monitored as part of standard care. Prescribed cannabinoids offer an alternative to herbal cannabis and should be considered in all cases where cannabis is discussed. Inhaled cannabinoids have the potential pharmacokinetic advantages of bypassing the first-pass effect of hepatic metabolism, of rapid onset of action, and of easy titration. Risks include irritation of the upper airways, cognitive effects of central cannabinoid activity, and stimulation of reward mechanisms.

Considerations Advocates for medical marijuana are often involved in political action to change policy. For every placard-carrying marijuana activist, however, many more silent sufferers have turned to cannabis where all else has failed. These patients might be afraid to discuss cannabis with their doctor and might not be aware that they have other legal and safe options.

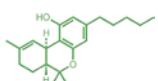
Physicians will formulate their own moral and scientific positions based on available evidence. Cannabis has not yet been formally evaluated in clinical trials, but safety and efficacy studies are under way and further studies should be designed and conducted. Without such trials it is premature to consider prescribing cannabis, but based on what is known of a drug that has been around for thousands of years, based on the safety data generated from 2 generations of recreational users, and based on the mechanism of action of cannabinoids, it is reasonable for family physicians to become more familiar with cannabis. Its undignified position as a drug of abuse with no known medical value deserves to be reconsidered.

No

Editor's Key Points

- Cannabis use has been associated with multiple medical problems, including bronchitis, psychosis, and cognitive impairment.
- The dose of dried cannabis recommended by Health Canada far exceeds the recommended doses of approved products that contain THC and thereby puts patients at risk for dependence and psychomotor impairment.
- There is no good evidence for medical marijuana, and physicians might be liable for prescribing an unapproved and unproven product.

In its Marihuana Medical Access Regulations, Health Canada authorizes physicians to prescribe dried cannabis, an unproven and potentially dangerous substance, under the guise of medical treatment. The program is intended to help patients with serious illnesses, such as HIV infection and cancer, but severe arthritis is also listed as an indication. Surveys confirm that chronic pain and arthritis are common reasons for medical cannabis use. As



analgesics, however, pharmaceutical cannabis products are weaker and less well tolerated than opioids. While cannabis users testify to its therapeutic benefits, they also commonly report pleasant psychoactive effects that are easily confused with direct analgesia.

Safer alternatives available The main active ingredient in marijuana is delta-9-tetrahydrocannabinol (THC), but both an oral THC and a buccal spray of THC and cannabidiol are available and are far safer than smoking dried cannabis. Cannabis smoke contains many of the same carcinogens as tobacco, and case-control studies suggest that cannabis smokers are at increased risk for prostate cancer and for head and neck cancer. Cannabis smokers are also at increased risk for bronchitis. Even if cannabis were vaporized and inhaled rather than smoked, the rapid delivery of high THC doses increases the risk of psychomotor impairment and addiction.

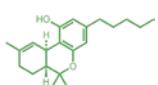
Risks associated with use While many people smoke cannabis occasionally without obvious harm, regular cannabis smoking can be dangerous. Cannabis use is a major risk factor for psychosis and schizophrenia, aggravates psychotic symptoms, and might have long-term cognitive effects.⁷ Adolescents who smoke cannabis have higher rates of other substance use, school failure, criminal activity, and suicidal thoughts. Cannabis impairs driving ability and so is a risk factor for motor vehicle accidents. In utero cannabis exposure is associated with attention deficit disorders, behavioural problems, and poor academic performance in childhood.

Health Canada states that “the average daily amount approved for over 90% of patients ... is 5 grams or less per day (5 to 10 joints)”. Based on Health Canada’s calculations, 5 joints with 12.5% THC concentration will contain approximately 400 mg of THC, or 20 times the maximum daily dose of oral THC. A single oral 5-mg dose reaches a peak plasma THC level of 5 to 10 ng/mL within 2 to 4 hours, whereas a single joint reaches 200 to 300 ng/mL within 6 to 9 minutes. This disparity puts patients at substantial risk for adverse effects, including dependence and psychomotor impairment. Even at therapeutic doses, symptoms of intoxication affected 40% of subjects in trials of the THC and cannabidiol buccal spray, and 8% to 24% in the trials of oral THC.

Legal complications Physicians are relatively safe from legal sanctions in cases of adverse drug reactions as long as they have exercised due precaution. This standard, however, will not protect physicians who prescribe an unapproved drug, such as marijuana. The Canadian Medical Protective Association waiver purportedly absolves physicians of legal responsibility for untoward events related to cannabis prescribing, but it cannot protect physicians from legal action brought by third-party victims.

Society pays From a public health perspective, the Health Canada program is fundamentally unjust and harmful. The program diverts resources to an unproven substance of uncertain efficacy with abuse liability, contributing to the public’s perception of cannabis as a harmless recreational product with therapeutic benefits.

Forty-seven percent of 18- to 19-year-olds in Canada have smoked cannabis in the past year, and 5% of Canadians report at least 1 concern related to cannabis. Six thousand patients were treated for cannabis dependence in Ontario in 2000, which likely represents a small fraction of those who need help. As one author stated, “... the costs to society are continuing to mount



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from past neglect of this continuing health problem."

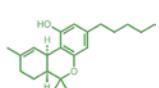
If legislators wish to decriminalize cannabis possession, they should do so without disguising it as medical therapy. Smoked medical marijuana is unnecessary and unsafe, especially in the doses allowed by Health Canada, and it distracts physicians and the public from the widespread harm caused by cannabis use and dependence.

Ware, M.A., T. Ducruet, and A.R. Robinson (2006) "Evaluation of herbal cannabis characteristics by medical users: a randomized trial." *Harm Reduction Journal* **3**: 32.

Background: Cannabis, in herbal form, is widely used as self-medication by patients with diseases such as HIV/AIDS and multiple sclerosis suffering from symptoms including pain, muscle spasticity, stress and insomnia. Valid clinical studies of herbal cannabis require a product which is acceptable to patients in order to maximize adherence to study protocols. **Methods:** We conducted a randomized controlled crossover trial of 4 different herbal cannabis preparations among 8 experienced and authorized cannabis users with chronic pain. Preparations were varied with respect to grind size, THC content and humidity. Subjects received each preparation on a separate day and prepared the drug in their usual way in a dedicated and licensed clinical facility. They were asked to evaluate the products based on appearance (smell, colour, humidity, grind size, ease of preparation and overall appearance) and smoking characteristics (burn rate, hotness, harshness and taste). Five-point Likert scores were assigned to each characteristic. Scores were compared between preparations using ANOVA. **Results:** Seven subjects completed the study, and the product with highest THC content (12%), highest humidity (14%) and largest grind size (10 mm) was rated highest overall. Significant differences were noted between preparations on overall appearance and colour ($p = 0.003$). **Discussion:** While the small size of the study precludes broad conclusions, the study shows that medical cannabis users can appreciate differences in herbal product. A more acceptable cannabis product may increase recruitment and retention in clinical studies of medical cannabis.

Ware, M.A., H. Adams and G.W. Guy (2005) "The medicinal use of cannabis in the UK: results of a nationwide survey." *International Journal of Clinical Practice* **59** (3): 291-295.

The use of cannabis for medical purposes is a controversial but an important topic of public and scientific interest. We report on the results of a self-administered questionnaire study conducted in the United Kingdom between 1998 and 2002. The questionnaire consisted of 34 items and included demographic data, disease and medication use patterns and cannabis use profiles. Subjects were self-selected; 3663 questionnaires were distributed and 2969 were returned [1805 (60.9%) women, mean age 52.7 years (SD 12.7)]. Medicinal cannabis use was reported by patients with chronic pain (25%), multiple sclerosis and depression (22% each), arthritis (21%) and neuropathy (19%). Medicinal cannabis use was associated with younger age, male gender and previous recreational use ($p < 0.001$). While caution must be exercised in interpreting these data, they point to the need for clinical studies of cannabis and cannabinoids with standardised and quality-controlled products.



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Whelan, J. (2002) "New cannabinoid for multiple sclerosis." Drug Discovery Today **7** (14): 745-746.

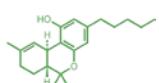
A new synthetic cannabinoid could provide symptomatic relief from muscle spasticity and tremor in people with multiple sclerosis (MS), without psychoactive side effects. Ajulemic acid (CT-3) has already completed Phase I clinical trials to determine its safety and tolerability, and has recently demonstrated anti-spastic activity in a mouse model of MS.

Wilsey, B., T. Marcotte, A. Tsodikov, J. Millman, H. Bentley, B. Gouaux, and S. Fishman (2008) "A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain." The Journal of Pain **8** (6): 506-521.

The Food and Drug Administration (FDA), Substance Abuse and Mental Health Services Administration (SAMHSA), and the National Institute for Drug Abuse (NIDA) report that no sound scientific studies support the medicinal use of cannabis. Despite this lack of scientific validation, many patients routinely use "medical marijuana," and in many cases this use is for pain related to nerve injury. We conducted a double-blinded, placebo-controlled, crossover study evaluating the analgesic efficacy of smoking cannabis for neuropathic pain. Thirty-eight patients with central and peripheral neuropathic pain underwent a standardized procedure for smoking either high-dose (7%), low-dose (3.5%), or placebo cannabis. In addition to the primary outcome of pain intensity, secondary outcome measures included evoked pain using heat-pain threshold, sensitivity to light touch, psychoactive side effects, and neuropsychological performance. A mixed linear model demonstrated an analgesic response to smoking cannabis. No effect on evoked pain was seen. Psychoactive effects were minimal and well-tolerated, with some acute cognitive effects, particularly with memory, at higher doses. Perspective This study adds to a growing body of evidence that cannabis may be effective at ameliorating neuropathic pain, and may be an alternative for patients who do not respond to, or cannot tolerate, other drugs. However, the use of marijuana as medicine may be limited by its method of administration (smoking) and modest acute cognitive effects, particularly at higher doses.

Wilkinson, J.D., B.J. Whalley, D. Baker, G. Pryce, A. Constanti, S. Gibbons and E.M. Williamson (2003) "Medicinal cannabis: is Δ-9-tetrahydrocannabinol necessary for all its effects?" Journal of Pharmacy and Pharmacology **55** (12): 1687-1694.

Cannabis is under clinical investigation to assess its potential for medicinal use, but the question arises as to whether there is any advantage in using cannabis extracts compared with isolated Δ-9-trans-tetrahydrocannabinol (Δ-9-THC), the major psychoactive component. We have compared the effect of a standardized cannabis extract (SCE) with pure Δ-9-THC, at matched concentrations of Δ-9-THC, and also with a Δ-9-THC-free extract (Δ-9-THC-free SCE), using two cannabinoid-sensitive models, a mouse model of multiple sclerosis (MS), and an in-vitro rat brain slice model of epilepsy. Whilst SCE inhibited spasticity in the mouse model of MS to a comparable level, it caused a more rapid onset of muscle relaxation, and a reduction in the time to maximum effect compared with Δ-9-THC alone. The Δ-9-THC-free extract or cannabidiol (CBD) caused no inhibition of spasticity. However, in the in-vitro epilepsy model, in which sustained epileptiform seizures were induced by the



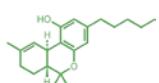
muscarinic receptor agonist oxotremorine-M in immature rat piriform cortical brain slices, SCE was a more potent and again more rapidly-acting anticonvulsant than isolated Δ-9-THC, but in this model, the Δ-9-THC-free extract also exhibited anticonvulsant activity. Cannabidiol did not inhibit seizures, nor did it modulate the activity of Δ-9-THC in this model. Therefore, as far as some actions of cannabis were concerned (e.g. antispasticity), Δ-9-THC was the active constituent, which might be modified by the presence of other components. However, for other effects (e.g. anticonvulsant properties) Δ-9-THC, although active, might not be necessary for the observed effect. Above all, these results demonstrated that not all of the therapeutic actions of cannabis herb might be due to the Δ-9-THC content.

Wingerchuk, D. (2004) "Cannabis for medical purposes: cultivating science, weeding out the fiction." *Lancet* **364** (9431): 315–316.

In this trial, no significant clinical effect was seen on this primary outcome for treatment with either Δ-9-THC or C sativa extract. However, the authors argue that the Ashworth scale may be too insensitive to detect a difference between the groups. Nevertheless, this study was powered (90%) to test specifically the hypothesis that marijuana was at least as effective as other spasticity treatments on the Ashworth scale. The fact that the results do not show an effect raises the question of how much additional benefit marijuana could provide relative to available treatments.

Numerous secondary outcomes—including irritability, pain, spasticity, fatigue, depression, tremor, sleep, and mobility—were also investigated. The authors report several positive findings that led them to conclude that there might be some beneficial effect of cannabinoids in MS. This benefit may, however, be wishful thinking. For example, improved mobility, assessed by the time taken to walk 10 m, was improved in the Δ-9-THC group compared with the placebo group ($p<0.05$). By contrast, C sativa extract provided no such benefit. This suggests either that the original observation is spurious or that other cannabinoids inhibit the beneficial effect of Δ-9-THC. The former explanation seems more plausible. Similarly, the subjective reports of reduced pain, decreased spasticity, improved sleep, and reduced spasms (all $p<0.05$) are suggestive but unconvincing, especially because of the unblinding of the treating physicians and the patients ($p<0.001$). Moreover, none of these findings would survive even a modest statistical adjustment for multiple comparisons. In addition, the fact that few patients reached their target dose because of side-effects also suggests that the therapeutic potential of either Δ-9-THC or C sativa extract in the symptomatic management of MS is limited. Perhaps most intriguing, in light of the expression of CB2 receptors on the surfaces of immune system cells, is the observation that exacerbation rates were lower in both cannabinoid groups compared with placebo ($p<0.05$). Nevertheless, even this result requires replication before it can be considered reliable, because it relates only to undocumented attacks and is statistically marginal.

Despite these essentially negative results, Zajicek's study is unlikely to resolve or even substantially add to the heated political debate. Enthusiasts for the medicinal use of marijuana will be unconvinced by the negative result and will, no doubt, focus on the suggestive (but subjective) reports in favour of treatment. Conversely, opponents of the medicinal use of marijuana will



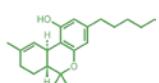
readily accept the negative findings on the primary outcome measure and will dismiss the other findings as meaningless and not worthy of further study. Unfortunately, neither viewpoint represents a balanced assessment because both are tainted by preconceived biases. On the one hand, because cannabinoids activate specific receptor systems within the brain, it is possible, and indeed probable, that marijuana will ultimately prove to be medically valuable in some clinical settings; if not in MS, then in some other diseases. On the other hand, the medical community should demand solid evidence from carefully designed clinical trials in support of any particular use. The present study is an excellent example of such a study, which, as it turned out, did not substantiate a role for marijuana in the management of spasticity. Whether the subjective reports of benefit found by these authors are accurate or spurious will await further, and more focused, investigation, but the therapeutic potential of marijuana should not simply be dismissed.

Wissel, J., T. Haydn, J. Muller, C. Brenneis, T. Berger, W. Poewe and L.D. Schelosky (2006) "Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial." Journal of Neurology **253** (10): 1337-1341.

About 30% of patients with chronic upper motor neuron syndrome (UMNS) suffer from disabling spasticity-related pain not sufficiently correctable by conventional treatment. Δ -9-tetrahydrocannabinol (Δ -9-THC) was reported to add benefit in the treatment of pain in patients with multiple sclerosis (MS). The question arose whether synthetic cannabinoids with lower potential for psychotropic side effects could be effective as well. To evaluate the safety and efficacy of low dose treatment with the synthetic cannabinoid Nabilone (1 mg per day) on spasticity-related pain a placebo-controlled double-blind crossover trial was performed. 11 out of 13 included patients completed the study. The 11-Point-Box-Test showed a significant decrease of pain under Nabilone ($p < 0.05$), while spasticity, motor function and activities of daily living did not change. 5 patients reported side effects: one moderate transient weakness of the lower limbs (Nabilone phase, drop out), three mild drowsiness (two Nabilone, one placebo) and one mild dysphagia (placebo). One patient was excluded from the study due to an acute relapse of multiple sclerosis (Nabilone phase, drop out). Nabilone 1 mg per day proved to be a safe and easily applicable option in the care of patients with chronic UMNS and spasticity-related pain otherwise not controllable.

Yates, M.L. and E.L. Barker (2009) "Inactivation and biotransformation of the endogenous cannabinoids anandamide and 2-arachidonoylglycerol." Molecular Pharmacology **76** (1): 11-17.

The cannabinoid field is currently an active research area. Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the most characterized endogenous cannabinoids (also known as endocannabinoids). These neuromodulators have been implicated in various physiologically relevant phenomena, including mood, the immune response, appetite, reproduction, spasticity, and pain. Pharmacological manipulation of AEA and 2-AG signalling should prove to have significant therapeutic applications in disorders linked to endocannabinoid signalling. One way to alter endocannabinoid signalling is to regulate the events responsible for termination of the endocannabinoid signal-



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cellular uptake and metabolism. However, to pharmacologically exploit AEA and/or 2-AG signalling in this way, we must first gain a better understanding of the proteins and mechanisms governing these processes. This review serves as an introduction to the endocannabinoid system with an emphasis on the proteins and events responsible for the termination of AEA and 2-AG signalling.

Young, C., T. Nurmikko and, D. Rog (2005) "A randomised controlled trial of cannabis based medicinal extract in central neuropathic pain due to multiple sclerosis." The Journal of Pain **6** (3 Suppl.): S38.

Young, C.A. and D.J. Rog (2003) "Randomised controlled trial of cannabis based medicinal extracts (CBME) in central neuropathic pain due to multiple sclerosis." IV. Congress of the European Federation of IASP Chapters (EFIC), September 2-6 2003, Prague.

Background: Central neuropathic pain can be an intractable problem for some multiple sclerosis (MS) patients. Aim: To evaluate the efficacy and safety of THC:CBD CBME in the relief of central neuropathic pain due to MS, using the Neuropathic Pain Scale (NPS) and single Box Scale-11 (BS-11) pain severity score. Methods: A 5-week (1 week run-in, 4 week treatment), randomised, double-blinded, placebo-controlled, parallel group trial in 66 MS patients was conducted. The study medication was an oro-mucosal preparation of a whole plant extract which delivered 2.7mg of THC and 2.5mg CBD per spray.

Patients were allowed to self-titrate up to a maximum of 48 sprays per day.

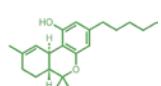
Results: Sixty-four patients (96.9%) completed the trial (n=32 CBME, n=32 placebo). Efficacy: Significant mean reductions in pain were observed at Week 4 for CBME compared to placebo, using both BS-11 score ($p=0.005$) and Neuropathic Pain Scale (NPS) scores ($p=0.039$). A statistically significant reduction in sleep disturbance using a 0-10 scale ($p=0.003$), and a greater overall impression of change ($p=0.005$) in favour of CBME was observed.

Safety: Thirty patients (88.2%) on CBME and 22 (68.8%) on placebo had at least one adverse event; however only 1 patient (CBME) withdrew from the study. There was a small, but statistically significant mean difference between treatments in the long term storage component of the Selective Reminding Test, in favour of placebo ($p = 0.009$). Conclusion: CBME showed significant reductions in both neuropathic pain and pain-related sleep disturbance in patients with MS. CBMEs appear well tolerated by most patients.

Young, C.A., D.J. Rog and N. Sarantis (2006) "A randomised controlled study of Sativex[®], a Cannabis based medicine, in central neuropathic pain due to Multiple Sclerosis." European Journal of Pain **10** (Suppl. 1): S126.

Zafonte, R., L. Lombard, and E. Elovic (2004) "Antispasticity medications: uses and limitations of enteral therapy." American Journal of Physical Medicine & Rehabilitation **83** (10 Suppl.): S50-S58.

Zajicek, J. "Cannabinoids on trial for multiple sclerosis." (2002) Lancet Neurology **1** (3): 147.



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Zajicek, J., P. Fox, H. Sanders, D. Wright, J. Vickery, A. Nunn and A. Thompson. (2003) "Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial." *Lancet* **362** (9395): 1517-1526.

Background: Multiple sclerosis is associated with muscle stiffness, spasms, pain, and tremor. Much anecdotal evidence suggests that cannabinoids could help these symptoms. Our aim was to test the notion that cannabinoids have a beneficial effect on spasticity and other symptoms related to multiple sclerosis.

Methods: We did a randomised, placebo-controlled trial, to which we enrolled 667 patients with stable multiple sclerosis and muscle spasticity. 630 participants were treated at 33 UK centres with oral cannabis extract (n=211), Δ-9-tetrahydrocannabinol (Δ-9-THC; n=206), or placebo (n=213). Trial duration was 15 weeks. Our primary outcome measure was change in overall spasticity scores, using the Ashworth scale. Analysis was by intention to treat.

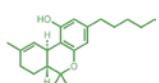
Findings: 611 of 630 patients were followed up for the primary endpoint. We noted no treatment effect of cannabinoids on the primary outcome ($p=0.40$). The estimated difference in mean reduction in total Ashworth score for participants taking cannabis extract compared with placebo was 0.32 (95% CI -1.04 to 1.67), and for those taking Δ-9-THC versus placebo it was 0.94 (-0.44 to 2.31). There was evidence of a treatment effect on patient-reported spasticity and pain ($p=0.003$), with improvement in spasticity reported in 61% (n=121, 95% CI 54.6-68.2), 60% (n=108, 52.5-66.8), and 46% (n=91, 39.0-52.9) of participants on cannabis extract, Δ-9-THC, and placebo, respectively.

Interpretation: Treatment with cannabinoids did not have a beneficial effect on spasticity when assessed with the Ashworth scale. However, though there was a degree of unmasking among the patients in the active treatment groups, objective improvement in mobility and patients' opinion of an improvement in pain suggest cannabinoids might be clinically useful.

Zajicek J.P., J.C. Hobart, A. Slade, D. Barnes, P.G. Mattison (2012) "Multiple Sclerosis and Extract of Cannabis: results of the MUSEC trial." *Journal of Neurology, Neurosurgery and Psychiatry*: Epub ahead of print.

Zajicek, J.P., H.P. Sanders, D.E. Wright, P.J. Vickery, W.M. Ingram, S.M. Reilly, A.J. Nunn, L.J. Teare, P.J. Fox and A.J. Thompson (2005) "Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up." *Journal of Neurology, Neurosurgery, and Psychiatry* **76** (12): 1664-1669.

Objective: To test the effectiveness and long term safety of cannabinoids in multiple sclerosis (MS), in a follow up to the main Cannabinoids in Multiple Sclerosis (CAMS) study. **Methods:** In total, 630 patients with stable MS with muscle spasticity from 33 UK centres were randomised to receive oral Δ-9-tetrahydrocannabinol (Δ-9-THC), cannabis extract, or placebo in the main 15 week CAMS study. The primary outcome was change in the Ashworth spasticity scale. Secondary outcomes were the Rivermead Mobility Index, timed 10 metre walk, UK Neurological Disability Score, postal Barthel Index, General Health Questionnaire-30, and a series of nine category rating scales. Following the main study, patients were invited to continue medication, double blinded, for up to 12 months in the follow up study reported here. **Results:** Intention to treat analysis of data from the 80% of patients followed up for 12 months showed evidence of a small treatment effect on muscle spasticity as



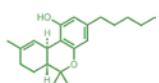
measured by change in Ashworth score from baseline to 12 months (Δ -9-THC mean reduction 1.82 (n = 154, 95% confidence interval (CI) 0.53 to 3.12), cannabis extract 0.10 (n = 172, 95% CI -0.99 to 1.19), placebo -0.23 (n = 176, 95% CI -1.41 to 0.94); p = 0.04 unadjusted for ambulatory status and centre, p = 0.01 adjusted). There was suggestive evidence for treatment effects of Δ -9-THC on some aspects of disability. There were no major safety concerns. Overall, patients felt that these drugs were helpful in treating their disease. Conclusions: These data provide limited evidence for a longer term treatment effect of cannabinoids. A long term placebo controlled study is now needed to establish whether cannabinoids may have a role beyond symptom amelioration in MS.

Addendum: Einsatz von Cannabis bei geclusterten Kopfschmerzen

„Die heftigen und einseitigen Attacken dauern meist zwischen 15 und 180 Minuten und treten unvermittelt vornehmlich aus dem Schlaf heraus auf. ... Der Kopfschmerzcharakter wird als unerträglich reißend, bohrend, manchmal als brennend geschildert. Seine Haupt-Lokalisation ist meist um das Auge herum, seltener im Bereich des Hinterkopfs. Besonders typisch ist ein während der Kopfschmerzattacken bestehender Bewegungsdrang.“ Wikipedia, 27.08.2012 "Cluster-Kopfschmerz" <https://de.wikipedia.org/wiki/Cluster-Kopfschmerz>.

Donnet, A., M. Lanteri-Minet, E. Guegan-Massardier, G. Mick, N. Fabre, G. Geraud, C. Lucas, M. Navez and D. Valade (2007) "Chronic cluster headache: a French clinical descriptive study." *Journal of Neurology, Neurosurgery & Psychiatry* **78** (12): 1354-1358. [Boschert, S. (2010) "Variable Effects Reported for Cannabis in Cluster." *Internal Medicine News (Neurology)* 8/2010: 45. <http://www.internalmedicinenews.com/specialty-focus/neurology/single-article-page/variable-effects-reported-for-cannabis-in-cluster.html>]

Background: Cluster headache (CH) is a relatively rare disease and episodic CH is more frequent than chronic CH. Few studies have described the characteristics of patients with chronic CH. Methods: This was a descriptive study carried out by eight tertiary care specialist headache centres in France participating in the Observatory of Migraine and Headaches (OMH). From 2002 to 2005, OMH collected data from 2074 patients with CH, of whom 316 had chronic CH. From January to June 2005, 113 patients with chronic CH were interviewed using standardised questionnaires during a consultation. Results: The male to female ratio was 4.65:1. Median age was 42 years. The majority of patients were smokers or former smokers (87%). 46% had primary chronic CH (chronic at onset) and 54% secondary chronic CH (evolving from episodic CH). Most patients had unilateral pain during attacks and 7% had sometimes bilateral pain during an attack. 48% reported a persisting painful state between attacks. Symptoms anteceding pain onset (mainly discomfort/diffuse pain, exhaustion, mood disorders) and auras were reported by 55% and 20% of patients, respectively. The functional impact of chronic CH was estimated as severe by 74% of patients, and 75.7% suffered from anxiety, as assessed by the Hospital Anxiety and Depression scale. There was no substantial difference in clinical presentation between primary and secondary CH. Discussion: This study confirms the existence of auras and interictal signs

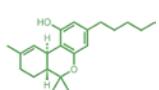


Cannabis, Dronabinol und die Behandlung schwerer Erkrankungen

and symptoms in patients with chronic CH, and male sex and smoking as CH risk factors. Primary and secondary chronic CH appear equally prevalent. Male sex does not appear to favour the shift from episodic to chronic CH.

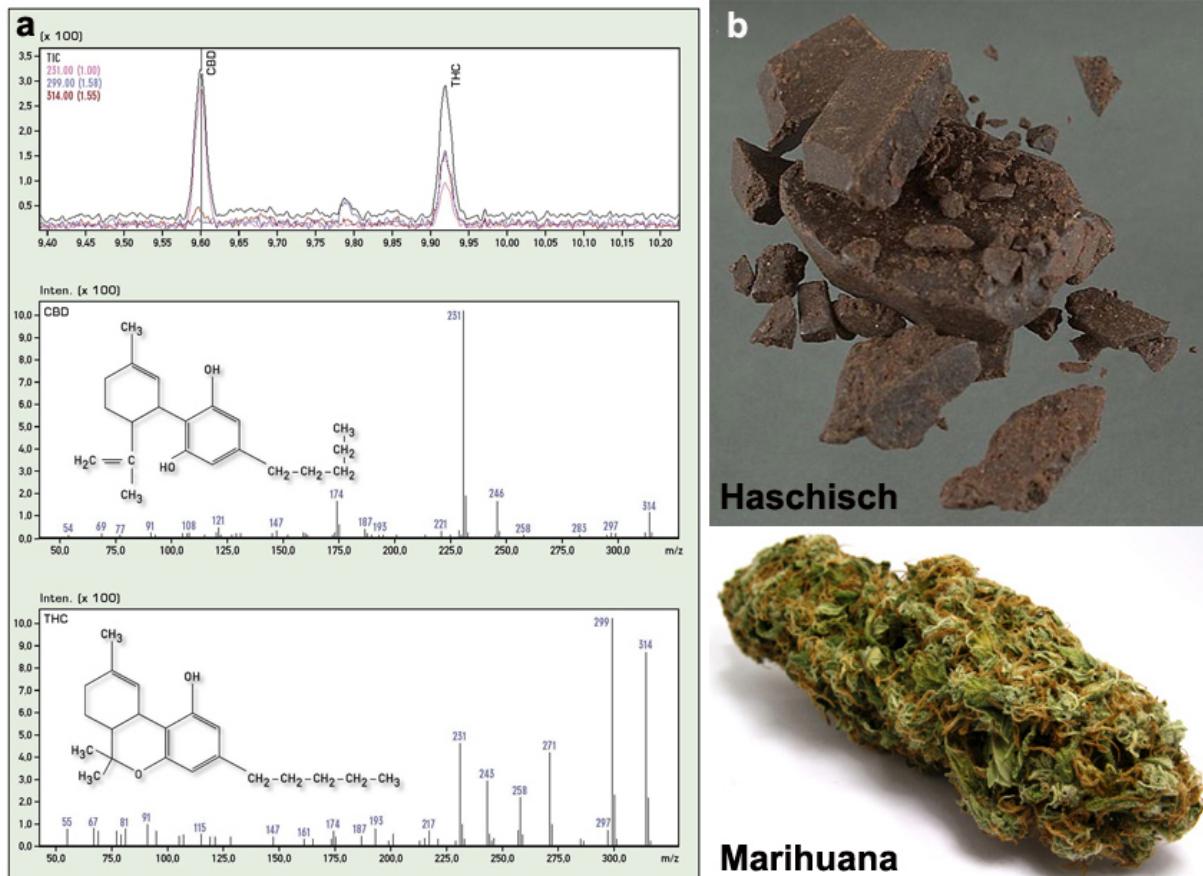
Robbins, M.S., S. Tarshish, S. Solomon, and B.M. Grosberg (2009) "Cluster attacks responsive to recreational cannabis and dronabinol." *Headache* **49** (6): 914-916.

Pharmacological preparations of cannabinoid compounds have a variety of therapeutic uses in medicine, including different pain syndromes, but have not been previously reported as beneficial for cluster headache. We present a patient with cluster headache who was refractory to multiple acute and preventive medications but successfully aborted his attacks with recreational marijuana use; subsequent use of dronabinol provided equally effective pain relief. The beneficial effect may be related to the high concentration of cannabinoid receptors in the hypothalamus, which has been implicated as a site of dysfunction in neuroimaging studies of patients with cluster headache.



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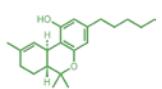
Abbildung 1



a) Chromatogramm und Massenspektren von CBD und Dronabinol (THC) von

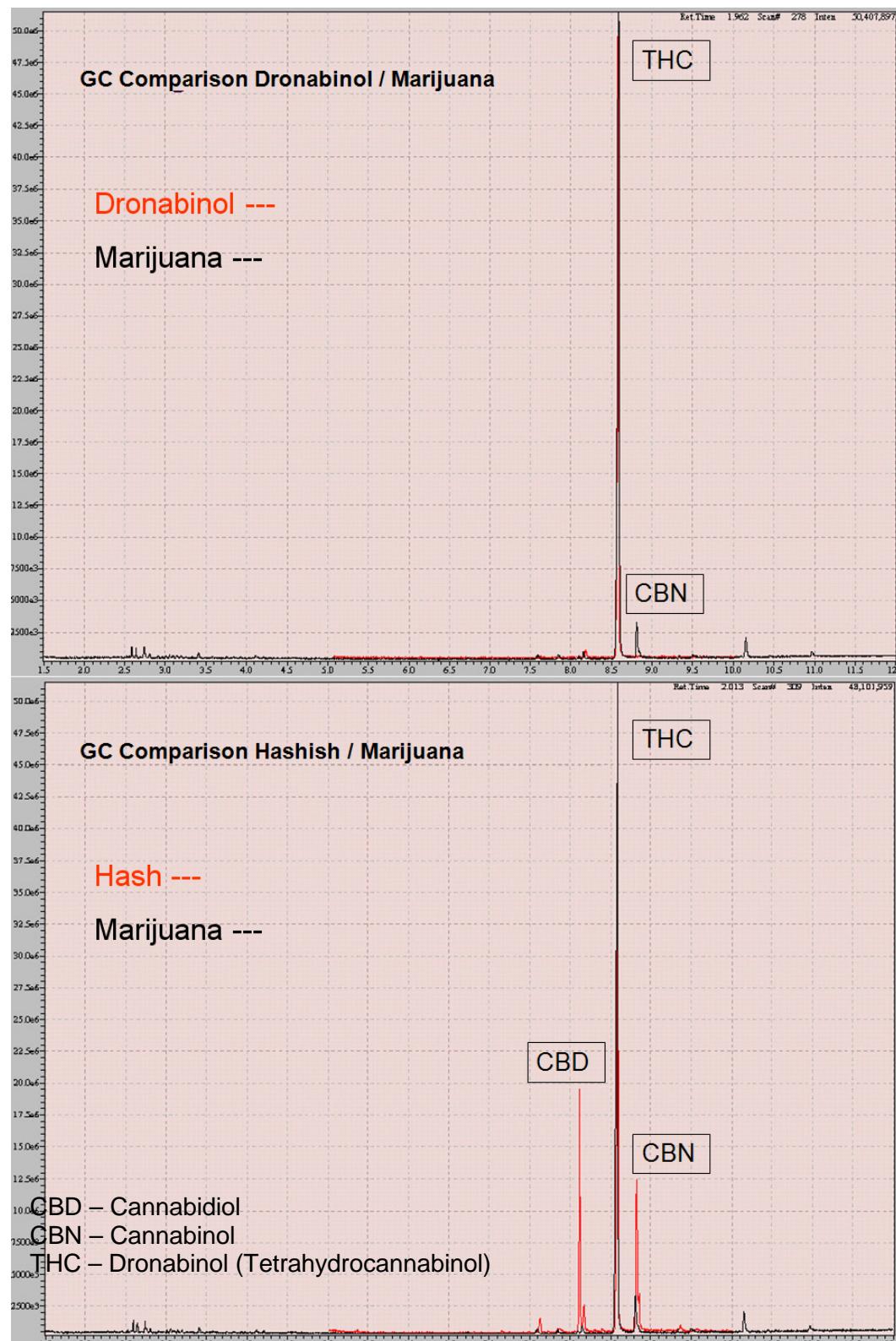
The Health Concept

b) Illegale Cannabispräparationen Haschisch und Marihuana



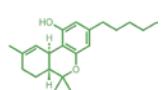
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Abbildung 2 Gaschromatographischer Vergleich von Dronabinol, Marihuana und Haschisch



Die Verbrennungsprodukte der Pflanzenbestandteile und -öle sind bei dieser Präparation nicht sichtbar.

Von der Fa. THC Pharm GmbH The Health Concept



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Abbildung 3 Rezepturset von Dronabinol der Fa. THC Pharm GmbH

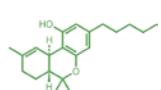
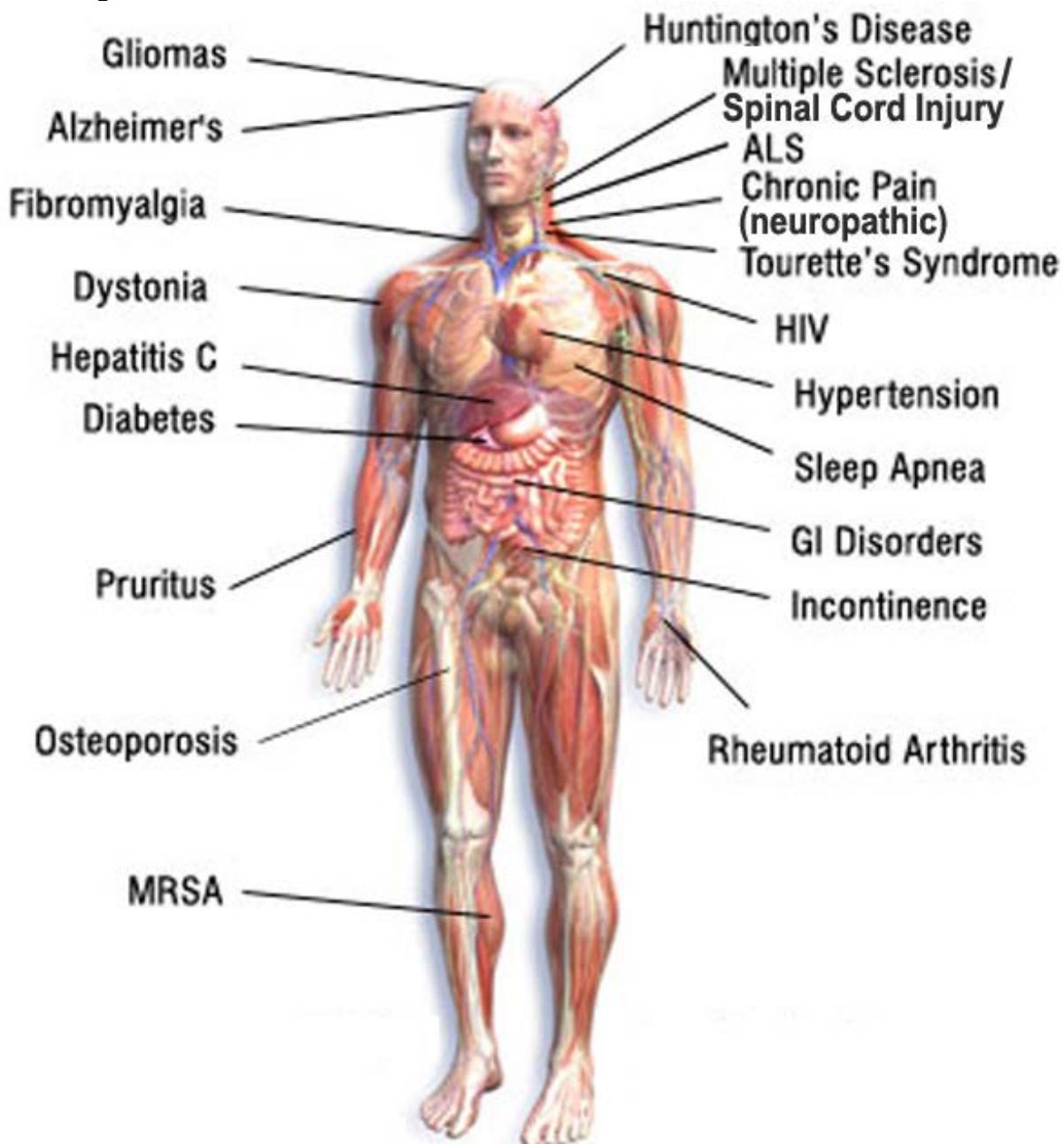


Abbildung 4



Potentielle Therapieziele von Medizinischem Marihuana

