Pharmaceutical update

Marijuana in the management of amyotrophic lateral sclerosis

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Note

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Abstract

Marijuana has been proposed as treatment for a widening spectrum of medical conditions. Marijuana is a substance with many properties that may be applicable to the management of amyotrophic lateral sclerosis (ALS). These include analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, and sleep induction. In addition, marijuana has now been shown to have strong antioxidative and neuroprotective effects, which may prolong neuronal cell survival. In areas where it is legal to do so, marijuana should be considered in the pharmacological management of ALS. Further investigation into the usefulness of marijuana in this setting is warranted.

Key words: ALS, cannabidiol, cannabinoids, cannabinol, marijuana, symptom management

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Introduction

This paper is dedicated to the memory of Linda Santos.

Over the past few decades, there has been widening interest in the viable medicinal uses of marijuana.[1] The National Institutes of Health (NIH), the Institute of Medicine (IOM), and the Food and Drug Administration (FDA) have all issued statements calling for further investigation.[2-4] There is a large body of literature on the effects of cannabinoids on chemotherapy-induced nausea and vomiting, lowering intraocular pressure in patients with glaucoma, and treating anorexia in patients with cancer and AIDS-associated weight loss.[5-8] Beyond these clinical applications, there is limited literature describing other appropriate uses for medicinal marijuana. The intent of this article is to provide an overview of the potential pharmacological role marijuana may have in the management of amyotrophic lateral sclerosis (ALS).

To date, clinical studies on the medicinal value of marijuana have often reached differing conclusions. Some of this inconsistency in the scientific literature likely results from the fact that marijuana is a complex plant, containing over 400 chemicals.[9] Approximately 60 are cannabinoids, chemically classified as 21 carbon terpenes.[9,10] Among the most psychoactive of these is delta-9-tetrahydrocannabinol (THC).[9,10] Because of

this biochemical complexity, characterizing the clinical pharmacology of marijuana is difficult. Further complicating the evaluation of marijuana is the variable potency of the plant material used in research studies. The clinical pharmacology of marijuana containing high concentrations of THC may well differ from plant material containing small amounts of THC and higher amounts of the other cannabinoids. Moreover, the bioavailability and pharmacokinetics of inhaled marijuana are substantially different than those taken by ingestion. THC is not soluble in water, but is lipid soluble.[11] Varying proportions of other cannabinoids, mainly cannabidiol (CBD) and cannabinol (CBN), are also present in marijuana, sometimes in quantities that might modify the pharmacology of THC or have distinct effects of their own. CBD is not psychoactive, but has significant anticonvulsant, sedative, and other pharmacologic activity likely to interact with THC.[12,13] The concentration of THC and other cannabinoids in marijuana varies greatly, depending on growing conditions, plant genetics, and processing after harvest.[13] In the usual mixture of leaves and stems distributed as marijuana, concentration of THC ranges from 0.3 percent to 4 percent by weight.[13,14] However, specially grown and selected marijuana can contain 15 percent or more THC. Thus, one gram of marijuana might contain as little as 3 mg or more than 150 mg of THC.[13] THC is a potent psychoactive drug, and large doses may produce mental and perceptual effects similar to hallucinogenic drugs.[15,16] Despite this, THC and other cannabinoids have remarkably low toxicity and lethal doses in humans have not been described.[17,18]

Prior to the last decade, there was little known about the specific pharmacological and molecular effects of marijuana. However, important advances have recently taken place that have greatly increased the understanding of the receptors and ligands composing the cannabinoid system. Research has shown that two major cannabinoid receptor subtypes exist, and subtype 1 (CB1) is expressed primarily in the brain, whereas subtype 2 (CB2) is expressed primarily in the periphery.[19,20] A variety of ligands for these receptors, based on the cannabinoid structure, have been synthesized and studied. These novel ligands are of interest as both experimental tools and lead compounds for therapeutic agents. Experiments performed with several types of neural cells that endogenously express the CB1 receptor suggest the activation of protein kinases may be responsible for some of the cellular responses elicited by the CB1 cannabinoid receptor.[21] The recent discovery of the endocannabinoids, *i.e.* endogenous metabolites capable of activating the cannabinoid receptors, and the understanding of the molecular mechanisms leading to their biosynthesis and inactivation, has created a new area in research on the pharmaceutical applications of cannabinoids.[22]

The characterization of endocannabinoids, such as anandamide, and the detection of widespread cannabinoid receptors in the brain and peripheral tissues, suggests that the cannabinoid system represents a previously unrecognized, ubiquitous network in the nervous system. Cannabinoid receptors are protein-coupled, transmembrane nucleotides, similar to the receptors of other neurotransmitters such as dopamine, serotonin, and norepinephrine.[20,22] Dense receptor concentrations are found in the cerebellum, basal ganglia, and hippocampus, likely accounting for the effect of marijuana on motor tone and coordination as well as mood state.[20-22] Low concentrations are found in the brainstem, accounting for the low potential for lethal overdose.[21,22] A growing number of strategies for separating sought-after therapeutic effects of cannabinoid receptor agonists from the unwanted consequences of CB1 receptor activation are now emerging. Recently, ligands have been developed that are potent and selective agonists for CB1 and CB2 receptors as well as potent CB2-selective antagonists and inhibitors of endocannabinoid uptake or metabolism.[21,22] This knowledge may lead to the design of synthetic cannabinoid agonists and antagonists with high therapeutic potential.

Current pharmacological management of ALS

Amyotrophic lateral sclerosis, with an incident rate of five to seven per 100,000 population, is the most common form of adult motor neuron disease.[23-26] ALS is a rapidly progressive neuromuscular disease that destroys both upper and lower motor neurons, resulting in weakness, spasticity, and ultimately death from respiratory failure. The vast majority of ALS cases are acquired and occur sporadically. Emerging evidence suggests that increased oxidative stress from free radical toxicity or excessive glutamate activity is what leads to motor neuron cell death in the brain and spinal cord.[24,27]

There is not yet a known cure for ALS, although significant research advances are being made. Riluzole is approved by the FDA for treatment of ALS.[24] This drug inhibits the presynaptic release of glutamate and reduces neuronal damage in experimental models of ALS. In 1995, two clinical trials showed that riluzole slowed disease progression.[27] Both of these studies showed prolonged survival for patients taking riluzole as opposed to placebo, although the benefit was modest. However, there are serious, but rare, complications of riluzole treatment, including renal tubular impairment, hepatitis, and pancreatitis.[27]

Because oxidative stress is one of the proposed pathogenic factors in ALS, antioxidants are recommended,

Table 1. Properties of marijuana applicable to ALS symptom management

ALS symptom	Marijuana effect
Pain	Nonopioid analgesia and anti-inflammatory
Spasticity	Muscle relaxant
Wasting	Appetite stimulant
Dyspnea	Bronchodilation
Drooling	Dry mouth
Depression	Euphoria
Dysautonomia	Vasodilation
Neuronal oxidation	Neuroprotective antioxidant

including vitamin E, vitamin C, coenzyme Q, B-carotene, and N-acetylcysteine.[28,29] Creatine, an amino acid naturally found in skeletal muscle and other tissues, may also have some benefit in ALS. Creatine given to "ALS mice," a transgenic mouse model of ALS, improved motor performance, prolonged survival, and slowed loss of motor neurons.[30] At present, trials of neurotrophic factors, anti-oxidants, glutamate antagonists, and creatine are ongoing. It is currently felt that a "cocktail" approach may be the ideal treatment strategy, including glutamate antagonists, antioxidants, and neurotrophic factors.

Application of marijuana for symptom management of ALS

Amyotrophic lateral sclerosis presents a multitude of difficult clinical problems. This section will overview these problems and discuss the potential role marijuana may play in their management. There are both direct and theoretical applications for using marijuana to manage ALS symptoms. Marijuana has easily observable clinical effects with rapid onset (*e.g.*, analgesia, muscle relaxation, dry mouth, etc.). It also has neuroprotective properties that may help prolong neuronal cell survival over extended use. This next section will delineate specific clinical problems encountered in ALS and describe the potential use of marijuana to address these.

Pain and immobility

The majority of ALS patients experience significant pain.[24] The pain is due largely to immobility, which can cause adhesive capsulitis, mechanical back pain, pressure areas on the skin, and, more rarely, neuropathic pain.[24,31] Synthetic cannabinoids have been shown to produce an anti-inflammatory effect by inhibiting the production and action of tumor necrosis factor (TNF) and other acute phase cytokines.[32] Additionally, marijuana may reduce pain sensation, likely through a brainstem circuit that also contributes to the pain-suppressing effects of morphine.[33] Cannabinoids produce analgesia by modulating rostral ventromedial medulla neuronal activity in a manner similar to, but pharmacologically distinct from, that of morphine. This analgesic effect is also exerted by some endogenous cannabinoids (anandamide) and synthetic cannabinoids (methanandamide), and may be prevented by the use of selective antagonists.[34] Thus, cannabinoids are centrally acting analgesics with a different mechanism of action than opioids, although the analgesia produced by cannabinoids and opioids may involve similar pathways at the brainstem level.[35-37] Despite this promising basic science research, no clinical trials currently involving marijuana have been performed in patients with naturally occurring pain. There are two well-controlled clinical studies using marijuana in cancer pain that show significant evidence of analgesic efficacy, although these studies indicate there is a narrow therapeutic margin between the doses that produce useful analgesia and those producing euphoria and other CNS effects.[38,39]

Concern for drug overuse, within reason, is pointless in a terminal disease, and the medication should be given on a regular dosing schedule and titrated to the point of comfort.[40] Concomitant use of narcotics may also be beneficial, since the opioid receptor system appears to be separate and distinct from the cannabinoid system. In that regard, the anti-emetic effect of marijuana may help with the nausea sometimes associated with narcotic medications. Untoward effects are the possibly significant psychoactive effects of marijuana, which may include euphoria, but can also include confusion and paranoia (see *Mood state*). Some of these side effects, such as euphoria, may be quite acceptable in the final phases of life, when respiratory insufficiency or severe pain require increased doses of analgesia.[40] However, patients and caregivers should be made aware of these issues and monitor for unwanted effects.

Spasticity

Spasticity in ALS is induced at

both the motor cortex and the spinal cord level through the loss of motor neuron inhibition.[24] Marijuana has an inhibitory effect on the gamma-amino-butyric acid (GABA) pathways in the central nervous system.[41] This produces motor neuron inhibition at spinal levels in mice.[42-45] Baclofen also works via the GABA pathways and would theoretically be potentiated by marijuana. Tizanidine, another commonly used anti-spasticity drug, works as an alpha-2 agonist, which is a different mechanism. Like baclofen and tizanidine, marijuana does not cause respiratory depression. This is a distinct advantage of these drugs over the benzodiazepines. Despite this, clinical evidence that marijuana relieves spinal cord spasticity is largely anecdotal. Large-scale trials or controlled studies to compare marijuana or THC with currently available therapies have not been performed and there is no published evidence that cannabinoids are necessarily superior to available therapies.

ALS wasting

The term "ALS cachexia" refers to a phenomenon experienced by some patients in which weight loss occurs in excess of that caused by muscle atrophy and reduced caloric intake.[24] Both subcutaneous fat and peritoneal fat are lost, presumably because of acceleration of the basal metabolic rate.[25] In patients with ALS cachexia, greater than 20 percent of body weight is typically lost over a six-month period. Clinical studies and survey data in healthy populations have shown a strong relationship between marijuana use and increased eating.[42,46,47] Marijuana is reported to increase food enjoyment and the number of times individuals eat per day.[14,42] Mechanistic studies of marijuana on taste and satiety have shown that it does not affect taste or produce a collapse of normal satiety mechanisms.[46] Dronabinol has been shown to increase appetite and produce weight gain in AIDS and cancer patients, although the weight gain is not in lean body mass.[47] Dronabinol is approved for the treatment of anorexia in patients with AIDS-associated weight loss.[47]

Respiratory failure

The terminal event in ALS is usually directly related to respiratory failure. Restrictive breathing problems usually develop in ALS and are due to weakness of the diaphragm, chest wall, and abdominal musculature.[24,25] Although cannabinoids will not likely improve respiratory muscle performance, the cannabinoids are strong bronchodilators, and pharmacologically active, aerosolized forms of THC have recently been developed.[48] This was done via a small particle nebulizer that generated an aerosol, which could penetrate deeply into the lungs. Inhalation exposure to aerosolized THC in mice elicited anti-nociceptive and bronchodilation effects that were dependent on concentration and exposure time. The anti-nociceptive and bronchodilation effects occurred within five minutes of exposure. Cannabinoid receptor antagonists, but not naloxone, blocked these effects, again indicating a cannabinoid receptor mechanism of action separate from that of the opioids.[48,49] These results demonstrate that the development of an aerosolized form of cannabinoids for human medicinal use is feasible.

Dysphagia

Patients with ALS and bulbar symptoms also usually have difficulty controlling and swallowing the amounts of saliva that are normally present in the oral cavity. Marijuana is a potent anti-salivatory compound that swiftly dries the oral cavity and upper airway.[48,5] Marijuana may be used alone or in conjunction with other anti-cholinergic medications to help dry up secretions. This potentially reduces the risk for aspiration pneumonia and may make the patient more comfortable.

Mood state

Reactive clinical depression is expected in ALS. Marijuana will improve appetite and sleep, two problems that may be related to depression. Marijuana is often used recreationally for the "euphoria"-inducing properties, but, in some patients, it may exacerbate depression.[51] Further, it is not clear what effect marijuana will have on the pseudobulbar palsy or emotional lability of ALS. Usually, the mental and behavioral effects of marijuana consist of a sense of well-being (often termed a "high"), feelings of relaxation, altered perception of time and distance, intensified sensory experiences, laughter, talkativeness, and increased sociability when taken in a social setting.[51-53] Impaired memory for recent events, difficulty concentrating, dreamlike states, impaired motor coordination, impaired driving and other psychomotor skills, slowed reaction time, impaired goal-directed mental activity, and altered peripheral vision are commonly associated effects.[54] With repeated exposure, varying degrees of tolerance rapidly develop to many subjective and physiologic effects.[55,56] Thus, intensity of acute effects is determined not only by THC dose, but also by past experience, setting, expectations, and poorly understood individual differences in sensitivity. Large inhaled or oral marijuana doses or even ordinary doses taken by a sensitive, inexperienced, or predisposed person can produce transient anxiety, panic, feelings of depression and other dysphoric mood changes, depersonalization, bizarre behaviors, delusions, illusions, or hallucinations.[53,56] Depending on the mix of symptoms and behaviors, the state has been termed an acute panic reaction,

toxic delirium, acute paranoid state, or acute mania. These unpleasant effects are usually of sudden onset, during or shortly after smoking, or appear more gradually an hour or two after an oral dose, often lasting a few hours, and completely clear without any specific treatment other than reassurance and a supportive environment. Subsequent marijuana doses may be better tolerated.[56,57]

Dysautonomia

Although dysautonomia is not generally a predominant feature of ALS, it can cause some unique clinical problems. Patients may complain of feeling quite hot, due to alterations in the autonomic control of peripheral circulation and perspiration. Marijuana produces a transient hypothermia and vasodilation, which may ease these symptoms. Skin temperature may drop four to six degrees centigrade.[50,58,59] However, marijuana is also a mild diuretic and may produce dehydration and hypotension. Thus, blood pressure and fluid intake need to be monitored in ALS patients that use marijuana and have dysautonomia.[58,59]

Neuroprotective and antioxidant effects

Cannabinoids have significant neuroprotective and antioxidative effects. Recent studies have demonstrated the neuroprotective effects of synthetic, nonpsychotropic cannabinoids, which appear to protect neurons from chemically-induced excitotoxicity.[60-63] Direct measurement of oxidative stress reveals that cannabinoids prevent cell death by antioxidation. The antioxidative property of cannabinoids is confirmed by their ability to antagonize oxidative stress and consequent cell death induced by the powerful oxidant, retinoid anhydroretinol. Cannabinoids also modulate cell survival and growth of B-lymphocytes and fibroblasts.[63]

The neuroprotective actions of cannabidiol and other cannabinoids were examined in rat cortical neuron cultures exposed to toxic levels of the excitatory neurotransmitter glutamate, known to be increased in the spinal cords of ALS patients. Glutamate toxicity was reduced by both cannabidiol, a nonpsychoactive constituent of marijuana, and the psychotropic cannabinoid THC.[64] The neuroprotection observed with cannabidiol and THC was unaffected by cannabinoid receptor antagonist, indicating it to be cannabinoid receptor independent. Cannabidiol was more protective against glutamate neurotoxicity than either ascorbate (vitamin C) or alpha-tocopherol (vitamin E).[64,65]

Cannabinoids have shown efficacy as immune modulators in animal models of neurological conditions, such as experimental allergic encephalomyelitis (EAE) and neuritis.[66] These data suggest that cannabinoids might modify the presumed autoimmune cause of other neurological diseases, including multiple sclerosis (MS). Current data suggest that the naturally occurring, nonpsychotropic cannabinoid (cannabidiol) may have a potential role as a therapeutic agent for the neurodegenerative disorders produced by excessive cellular oxidation, such as ALS.

Using marijuana

Smoking anything, including marijuana, is not healthful for the lungs and airway system.[46] Despite risk for bronchitis, the main advantage of smoking is rapid onset of effect and easy dose titration. When marijuana is smoked, THC in the form of an aerosol in the inhaled smoke is rapidly absorbed and delivered to the brain, as would be expected of a highly lipid-soluble drug.[67,68] A healthier option is vaporization. Because the cannabinoids are volatile, they will vaporize at a temperature much lower than actual combustion.[16] Heated air can be drawn through marijuana and the active compounds will vaporize, which can then be inhaled. This delivers the substance in a rapid manner that can be easily titrated to desired effect.[69] Theoretically, this removes most of the health hazards of smoking, although this has not been studied. Additionally, marijuana can be ingested orally or through a feeding tube, although oral ingestion is quite different than inhalation. The onset of action is much slower and titration of dosing is more difficult.[68,69] Maximum THC and other cannabinoid blood levels are only reached one to three hours after an oral dose.[49] The same is true of dronabinol capsules, which also have the disadvantage of containing only synthetic THC and none of the other cannabinoids.[47]

For ALS patients with severe dysphagia, the inhalation route offers additional advantages beyond rapid onset of action, particularly compared to the currently available capsule formulation. This raises many issues concerning the best mode of administration. Ideally, drug administration would be via a delivery route that is safe, easy to titrate, and readily dispersed in the body. Smoking or vaporizing plant material for inhalation poses difficulties in standardizing testing paradigms. The development of alternative dosage forms, including an inhaler form into which a controlled unit dose could be placed and volatilized would make clinical use much easier. Aerosolized cannabinoids have been developed, as described earlier, although they are not yet commercially available.

Legal issues

An in-depth discussion of the legal ramifications of using medicinal marijuana is beyond the scope or intent of this paper. In some states, it is currently legal to use marijuana for medicinal purposes.[70-72] In Washington state, a

not-for-profit cooperative organization, the Green Cross, provides high-quality, medicinal marijuana to patients for a minimal donation, and delivers the marijuana to homebound patients. However, in other states, the use of marijuana for any purpose remains illegal. Health care providers need to know the local laws before recommending medicinal marijuana to avoid legally endangering their patients and themselves.[73-75] All decisions on the ultimate usefulness of a medical intervention should be based on a benefit/risk calculation, and marijuana is no exception to this principle.

Conclusion

Marijuana is a substance with many properties that are directly applicable to the management of ALS. These include analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, sleep induction, and euphoria. In addition, marijuana has now been shown to have strong antioxidative and neuroprotective effects, which may prolong neuronal cell survival. From a pharmacological perspective, marijuana is reasonably safe with minimal possibility of overdose. In states where it is legal to do so, marijuana should be considered in the pharmacological management of ALS.

Moreover, the scientific process should be allowed to evaluate the potential therapeutic effects of marijuana for ALS and other disorders, detached from the societal debate over any potential harmful effects of non-medical marijuana use.

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