Deuterated Drugs

WEIGHTY TIMES AHEAD FOR THE LAB?

KARSTEN STEMMERICH[1], ADRIAN C. SEWELL[2] & TORSTEN ARNDT[1] | [1]BIOSCIENTIA INSTITUT FÜR MEDIZINISCHE DIAGNOSTIK, [2]INGELHEIM, *GERMANY* | karsten.stemmerich@bioscientia.de

Deuterium, a stable isotope of hydrogen, contains simply an extra neutron which virtually doubles the mass compared to hydrogen. This gives deuterium a special place among all isotopes of all known elements together with unique properties.

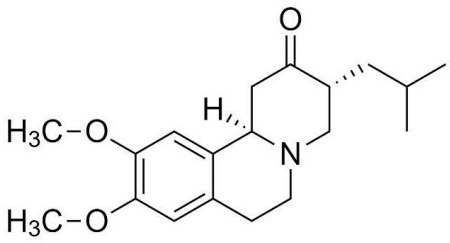
"The most fruitful basis for the discovery of a new drug is to start with an old drug." [1]
Sir James Whyte Black (1924 – 2010), Nobel Prize for Medicine 1988

1. Introduction

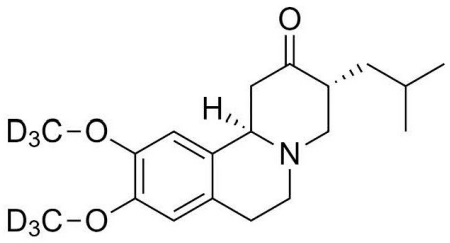
In 2017, the US Food and Drug Administration (FDA) approved the first deuterated drug deutetrabenazine (Austedo) (Figure 1) which paved the way for deuterated medications [2]. At this time, a kind of 'gold rush' atmosphere developed in parts of the pharmaceutical industry and producers of deuterated substances were bought up by large pharmaceutical companies for considerable sums of money [3]. For example, the rights to a deuterated analogue of the immunomodulator lenalidomide were sold for 42 million dollars even before the product was finally developed [4].

The development of the drug deutetrabenazine by Auspex Pharmaceuticals was a huge financial success: this company specialising in deuterated compounds was taken over by Teva Pharmaceuticals for approximately 3.5 billion dollars [4].

Interestingly, the FDA approved deutetrabenazine not as a 'me-too-product', i.e. not as a drug with only a minimal structural change compared to the already available 'native' drug. The American authorities have *de facto* recognized the deuterated drug as an entirely new molecular entity (NME), which brings commercial advantages through the associated patent protection [5].



Tetrabenazine



Deutetrabenazine

FIGURE 1. STRUCTURES OF TETRABENAZINE AND DEUTETRABENAZINE.

The FDA based its decision in part on the dossier for the active ingredient tetrabenazine, which had been approved since 2008 [3]. This procedure was unparalleled in that the approval of deuterated drugs via the FDA could be achieved, at least in part, using the regulatory dossier of the non-deuterated analogues [3].

Deutetrabenazine was given FDA approval although there have been no clinical studies directly comparing tetrabenazine and deutetrabenazine. At that time there were only indirect comparisons in separate studies reported, each using a single compound [6]. Now there have been studies described using both compounds [7], the results of which confirm those findings declared in the course of the FDA approval.

A literature search reveals a number of deuterated substances (see Appendix) which are either under development or in - or have been in - various stages of clinical trials.

Wider use of deuterated analogues of drugs could also lead to their infiltration as deuterated analogues of substances of abuse into the 'drug scene'. Before we address this point, we would like to discuss some basic aspects of the pharmacological action of deuterated compounds.

2. Deuterium

2.1. Discovery and occurrence

Deuterium was first detected in 1931 by Harold Clayton Urey (1893 – 1981), Ferdinand Graft Brickwedde (1903 – 1989) and George Moseley Murphy (1903 – 1968) [8,9]. This was one year before the identification of the neutron (!) [10,11] which is vital for the existence of elemental isotopes. Urey was awarded the Nobel Prize for Chemistry for the discovery of deuterium three years later (!) in 1934 [12].

Hydrogen occurs naturally in three isotopic forms which differ from each other simply by the number of neutrons present in the atomic nucleus. Protium (^{1}H) has no neutron, deuterium (^{2}H heavy hydrogen) has one and tritium (^{3}H superheavy hydrogen) has two. The nomenclature of hydrogen isotopes is unique: only these have names different to the parent element and only these have their own chemical symbol – D for deuterium and T for tritium [13].

Whereas protium and deuterium are stable, tritium decays with a half-life of 12.32 years [12]. So far, isotopes up to ^{7}H can be produced artificially [14] but decay extremely rapidly ($t_{1/2}<10^{-21}$ s) [15].

Protium is the commonest naturally occurring isotope of hydrogen (>99.9%) [5]. Deuterium occurs naturally predominantly as either semi-heavy water (HDO) or heavy water (D_2O) with a fraction of 0.0156% or 156 ppm. This amount makes enrichment of heavy water economically viable [11,12,16,17]. Only traces of tritium occur naturally (1.1×10^{-18}) [12][1].

For a short time at least, Urey was also interested in heavy water. He personally carried out tasting trials and concluded that heavy water (D_2O) had a neutral taste and thus could not be differentiated from 'light' water (H_2O) [20]. Perhaps the number of test persons in Urey's trial was too small (n = 2); recent publications using a modern sensory panel have described heavy water as having a distinctly sweet taste [21].

2.2. Metabolism and toxicity

Deuterium as HDO and D_2O has a low systemic toxicity [16,22]. The human body physiologically contains about 15 mg/kg deuterium [23], bound mostly as D_2O [5]. The deuterium inventory of a 70 kg person is about 1 g. According to Gant [11], this deuterium can be incorporated into almost all molecules within the organism.

Heavy water (D_2O) together with water (H_2O) forms an 'ideal solution' [24]. They are not in *strictu sensu* 'metabolised' in the body. The renal excretion of both forms is given as a half-life of approximately 10 days [24]. Experimentally, the water content of the body can be exchanged very easily for heavy water – by drinking heavy water! Within 2-3 h the heavy water has reached a stable distribution [25]. When the body water of standard laboratory animals (such as mice, rats, dogs) is replaced by heavy water, up to approximately 15% exchange shows no effect [26]. Kushner et al. [27] reported that such laboratory animals remained healthy in the long term even when 25% of their body water was exchanged for heavy water. Higher concentrations are eventually lethal [22,25], for example in mice with 100% D_2O within a week [24].

The data obtained in experimental animals were used to estimate the non-toxic and toxic doses for humans and were later confirmed by experiment. Thus the administration, even in large amounts, of D_2O to healthy persons (including infants and pregnant women) showed no effects [5]. The exchange of 15-23% body water for heavy water is reported to have no negative effect on the health of humans [25].

Assuming that about 60% of the body mass is water, then a 70 kg person would have to imbibe 4.2 L of heavy water to exchange approximately 10% of body water [26]. This would correspond to a D_2O concentration of about 60 g/kg body mass. According to Schloeb et al. [24], ingestion of 100 g D_2O resulted in a serum level of 0.2% (v/v) deuterium in the form of heavy water.

For clinical studies, undesirable deuterium effects are suspected from 200 to 400 mg D_2O/kg body mass, corresponding to 14-28 g for a 70 kg person [28]. The nature of the effects is not discussed in detail in [28]. It is important to consider that the amount of deuterium ingested with common doses of deuterated pharmaceuticals would be 2 to 3 orders of magnitude lower. Thus the safety of deuterium-containing drugs is generally considered uncritical [17,28].

2.3. Deuterium substitution and drug pharmacokinetics

The difference in atomic mass between protium and deuterium is far more pronounced than that of isotopes of all other elements. The atomic mass of protium is given as 1.008 atomic mass units (u) whereas that of deuterium, because of the extra neutron, is 2.014 u [22]. The extra neutron of deuterium effectively doubles the atomic mass relative to protium but the isotope remains stable. As opposed to isotopes of heavier elements, the mass difference between ^{1}H and ^{2}H is large enough to alter the physicochemical properties of deuterated molecules compared to their non-deuterated analogues. The pharmacodynamic properties are, however, virtually identical. The chemical reactivity of deuterium is almost identical to that of protium whereby an exchange of protium for deuterium becomes possible [5,22]. Although the C-D bond is stronger than the C-H bond, protium and deuterium are freely exchangeable in synthesis reactions [5].

The shape of a molecule is defined by the electron clouds of the atoms but not by the number of neutrons in the atomic nuclei. Therefore, shape and size of deuterated substances are almost indistinguishable from their protium analogues. Small differences can be observed, e.g. reduced hydrophobicity of deuterated analogues, reduced acidity of carbonic acids and phenols or increased alkalinity of amines [22].

As mentioned above, the double mass of deuterium due to an extra neutron compared to protium, is unique for all isotopes of all elements. This large difference leads to a lower vibration frequency of the C-D bond compared to that of the C-H bond and thus to an increased activation energy necessary for cleavage of the C-D bond [12].

Kinetic Isotope Effect (KIE)

The increased bond strength can lead to lower reaction rates, particularly in oxidation reactions [5,29]. This phenomenon is called the kinetic isotope effect (KIE) of deuterium or simply deuterium isotope effect (DIE). Thermodynamic details and a detailed description of KIE are given in [11,12].

A deuterium bond compared to that of protium is more resistant to cleavage, particularly in oxidation reactions (e.g. by cytochrome P450, CYP450) [28]. Thereby the metabolism of deuterated molecules may be altered with respect to reaction rates and the metabolite profile - a phenomenon called "metabolic switching" [5,22,30]. In fact, significant differences in pharmacokinetics have been reported for some deuterated substances and their non-deuterated analogues [5,22,31]. The KIE – given as the ratio of the reaction rate constants of protonated and deuterated compounds k_H/k_D [28] – can theoretically be 9x as maximum [32]. A prediction of the KIE for a specific substance in cytochrome P450-catalyzed oxidations is not possible [32].

In human metabolism, CYP450 enzymes are responsible for about 75% of the metabolic reactions of pharmaceuticals [33]. Here a C-H bond is oxidatively cleaved. This cleavage is usually the rate-limiting step and therefore the KIE of deuterium can significantly decelerate this oxidative metabolism [33].

Table 1 summarizes possible pharmacokinetic effects of drug deuteration together with the resulting clinical implications.

[1]Further information on the background, the synthesis of deuterated compounds or the industrial use of hydrogen isotopes can be found in comprehensive reviews such as that of Atzrodt et al. [18,19] or Kopf et al. [12].

TABLE 1. CLINICAL IMPORTANCE OF DEUTERIUM LABELLING OF PHARMACEUTICALS [4,28].

Possible pharmacokinetic effects	Clinical importance
c_{max} ↑	Dosage ↓ possible
$t_{1/2}$ ↑	Elimination ↓ Dosage interval ↑
AUC ↑	Elimination ↓ Dosage interval ↑
t_{max} almost ± 0	Timepoint of initial effect practically unchanged

Deuterated drugs are highly similar to their non-deuterated analogues regarding the selectivity for biological receptors and thus the biochemical (and pathobiochemical) effects - the pharmacodynamics are almost identical. The differences in metabolism are, however, large enough to be clinically relevant compared to the non-deuterated forms [34].

Common goals of drug deuteration could be: (a) reduction in the rate of metabolism and prolongation of the half-life of the drug with (b) subsequent reduction of the required drug dose and thereby (c) fewer adverse drug reactions.

For example, deutetrabenazine given in a maximal daily dose of up to 48 mg achieves a pharmacological effect equivalent to 100 mg tetrabenazine [6]. Such reductions in administrated doses can minimize adverse drug effects. In addition, fewer injections or tablets are required which simplifies administration and thus increases acceptance.

The metabolism of tetrabenazine and deutetrabenazine (Figure 2) begins with a ketone reduction to dihydrotetrabenazine (HTBZ) and dihydrodeutetrabenazine. This step is not affected by the deuterium substitution [7]. HTBZ and its deuterated analogue each consist as a pair of stereoisomers (α- and β-HTBZ or deuterated α- and β-HTBZ, depending on the orientation of the OH-group in position 4). All these are pharmacologically active [35].

Then follows a rapid degradation of the active metabolites via O-demethylation at positions 9 or 10 catalysed by CYP450 2D6 (CYP2D6). This step is, however, affected by the above-mentioned KIE. The deuterated methoxy-groups of deutetrabenzine are more resistant to cleavage, slowing the catabolism of (the pharmacologically active) deuterated HTBZ and thus prolonging the effect of the drug. Finally, a phase II sulphation reaction follows leading to renal excretion [7].

Deutetrabenazine is a good example of the utilization of the KIE: deuterium hinders the oxidative metabolism of the methoxy-groups and thereby slows down the metabolization of the drug [36] (Figure 2). Compared to tetrabenazine, the deuterium effect on the metabolism allows for a reduction in dose and the longer half-life allows for longer dosing intervals.

A highly simplified diagram (Figure 3) illustrates these effects using a fictional, non-deuterated substance (black curve, whole tablet) and its deuterated analogue (red curve, half tablet) under steady-state conditions.

Due to the initially higher plasma levels of the deuterated substance (slower degradation) caused by the isotope effect, the dose could be reduced (half tablet). The reduced dose maintains the level of the deuterated substance within the therapeutic range (green) over the whole time interval. In contrast, the non-deuterated analogue has peak levels above the therapeutic range and must be more frequently administered because of the more rapid catabolism.

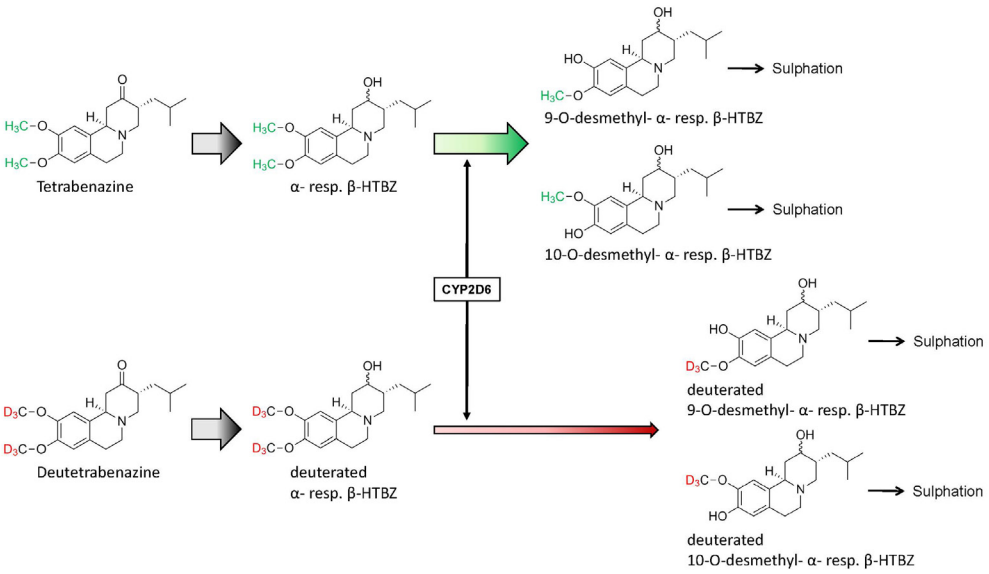


FIGURE 2. METABOLISM OF TETRABENAZINE AND DEUTETRABENAZINE. INITIALLY THERE IS A RAPID CONVERSION OF BOTH SUBSTANCES. THE SUBSEQUENT CATABOLISM OF THE EFFECTIVE COMPOUNDS α- AND ß-HTBZ VIA CYP2D6 IS MUCH SLOWER (RED) FOR DEUTETRABENAZINE AS FOR TETRABENAZINE (GREEN).

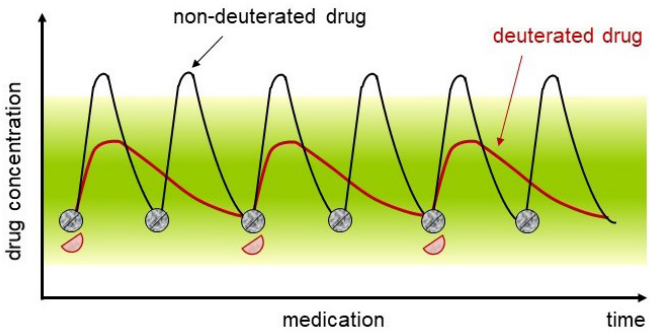


FIGURE 3. TIME VS. PLASMA CONCENTRATION OF A FICTIONAL DEUTERATED PHARMACEUTICAL (RED) GIVEN ORALLY COMPARED WITH THE NON-DEUTERATED ANALOGUE (BLACK). THE THERAPEUTIC RANGE IS SHOWN IN GREEN.

Further potential advantages of deuterated drugs are a possible regulation of metabolism (reduced undesirable metabolites and thus a lower toxicity) or a stabilisation of stereoisomers [28]. For example, a deuterated form of vitamin A shows a lower rate of dimer formation which leads to much lower levels of metabolites which are associated with degenerative ophthalmological disease [5].

Deuterium labelling must not always lower the effective overall rate of biotransformation – the exact opposite is possible (Figure 4). For example CTP-347 (d2-paroxetine) shows a more rapid rate of catabolism compared to the non-deuterated form. Paroxetine inhibits CYP2D6 and therefore an accelerated metabolism of the deuterated drug could result from a reduction of this inhibition [5]. Thus a lowered metabolic activity leads to a more rapid total effect. This shows that many factors can mask or even reverse the effects of deuteration [37].

Deuteration may alter the pharmacokinetics without specifically altering the pharmacodynamics of the substance; however, these effects on the metabolic profile of a drug are not predictable and must be investigated on an individual basis [16].

2.4. Deuterium substitution and economic viability of pharmaceuticals

In financial terms, the major advantage of deuterium labelling for the manufacturer results from lower production costs. Deuterated drugs have a longer effectivity and can be administered at lower doses. Usually, the increase in production costs for the more expensive material is roughly 1-5% whereon the reduction in dosage is about 10-70%, overcompensating for the higher production costs [11].

It is estimated that deuteration of less than 10% of all medications approved by the FDA would be considered viable [37]. The chemical structure or catabolism of these few substances favour a KID [37]. The approval of deutetrabenazine opened the door to commercialisation for a new class of compounds and it is expected that more deuterated substances will follow [5].

That the FDA has categorised deutetrabenazine as a new substance rather than a modified tetrabenazine suggests that a sufficiently large KIE is seen as significant and thus patentable [4]. Major pharmaceutical manufacturers are now including deuterated variants of the compounds in the patents right from the start. This is seen as an important barrier to competitors [37]. Since a 100% pure deuterated product can probably never be available and since residues of the protium form will always remain in the product, points for legal disputes could arise here.

Conversely, there will probably always be a small amount of natural deuterium in a product. Many pharmaceutical companies are therefore trying to protect themselves by buying up patents and patenting as many deuterated analogues as possible [4].

The situation regarding deuterated drugs is often compared to the development on bioisosteric exchange of hydrogen for fluorine [38], an important recent trend in medicinal chemistry. In the 1970s, roughly 2% of registered active ingredients were fluorinated; now it is around 25%. Similar developments for deuterated drugs are expected [17,28].

What has all of this to do with clinical and/or forensic toxicology?

3. Deuterated compounds in the clinical and forensic toxicology laboratory

In our opinion, deuterated active pharmaceutical ingredients and deuterated (il)legal drugs could herald 'difficult times' for the clinical and forensic toxicology laboratory. As described above, they exhibit altered pharmacokinetics and because there is little experience, lead to difficulties in the interpretation of analytical results. Common MS and MS/MS databases include data on certain deuterated compounds, these, however, are mostly compounds and deuteration levels used as internal standards (ISTD). Thus, differently deuterated drugs (of abuse) could theoretically, as of now, invalidate MS-based toxicological analyses.

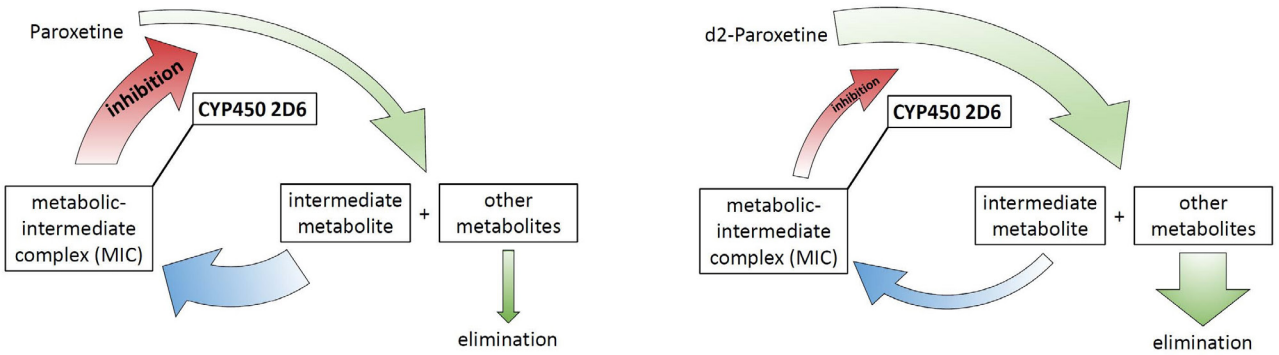


FIGURE 4. SELF-INHIBITORY FEEDBACK-LOOP OF PAROXETINE METABOLISM: PAROXETINE METABOLIZES CATALYZED BY CYP450 2D6. ONE OF THE METABOLITES FORMED BINDS TO THE ENZYME THUS INHIBITING THE PAROXETINE METABOLISM. ACCORDING TO [49] D2-PAROXETINE FORMS LESS METABOLIC-INTERMEDIATE COMPLEX (MIC), CAUSING A REDUCED INHIBITION OF THE ENZYME. THUS D2-PAROXETINE METABOLIZES TO A LARGER EXTENT AND IS ELIMINATED FASTER COMPARED TO THE NON-DEUTERATED PAROXETINE.

3.1. 'Heavy' drugs and deuterated internal standards

The first deuterated biologically active substances were described in the mid 20th century [28,39]. In one of these reports in 1961 (one year before the discovery of CYP450 was published [40]), a reduced rate of biotransformation of d3-morphine compared to the non-deuterated analogue was described in mice [41]. This d3-morphine is exactly one of those substances still in use today as an common laboratory ISTD, even in commercially available LC-MS/MS test kits [42]. In the case of (il)legal use of d3-morphine, this could be detected by a conspicuously strong signal of the internal standard. More problematic would be when the ingested amount of d3-morphine or the remaining residues in the body are low compared with the added amount of ISTD. If there is no detectable increase in the ISTD signal e.g. because the change is insignificant, then a d3-morphine ingestion would remain undetected.

The points mentioned above raise the following questions:

- When is an increase in ISTD signal reliably detectable, even under changing suppression effects by individual samples?
- How can these effects be checked and validated?
- Can strictly defined criteria be applied to reliably detect discrepancies in ISTDs?
- How can a deuterated ISTD be chosen in method development so that interference by the same substance in biological samples can be prevented or at least be rendered unlikely?

Further possible problematic areas are summarised in Figure 5.

A possible solution could be the general use of several ISTDs, e.g. a primary and secondary, per analysed compound. Thus, in suspicious cases, the result could be obtained using either the primary or the secondary ISTD. Such a procedure, however, would severely complicate the development, validation and documentation of an analytical test not to mention the calculation of the end-result.

The question would still remain as to which criteria would be used to select between the primary and secondary ISTD for the evaluation of a sample. This would be particularly interesting when the results calculated via the different ISTDs are significantly different from each other!

An alternative and pragmatic approach would be to run the test twice – one with an ISTD, the other without. The latter would prove the presence of interfering substances with the ISTD.

The choice of an ISTD for a mass-spectrometric analysis is limited by the retention time – to compensate for matrix effects, this should be as identical as possible to the analyte. In our experience, deuterated compounds usually elute earlier in gradient HPLC with reversed phase (RP) columns than the non-deuterated analogues. The extent of the retention time shift depends on the elution conditions and the degree of deuteration. A multi-deuterated ISTD with a respective shift in retention time would therefore certainly be suitable to differentiate between the ISTD and less highly deuterated drugs. A high degree of deuteration can, however, lead to too much retention time shift where an effective compensation for matrix effects is no longer valid.

From an analytical point of view, standard addition would certainly be an effective solution to this problem, but is probably only feasible to a limited extent due to the effort involved and the number of samples.

Whether high-resolution mass spectrometry can help to answer these questions remains to be seen. It could be possible if the relevant isotopes of hydrogen (^{2}H) and of carbon (^{13}C, in case of switching to ^{13}C-labelled ISTDs) can be included in the calculation of the molecular formula. Thus the labeled ISTDs can be reliably identified.

3.2. 'Heavy' drugs as medication

The problems associated with choosing a suitable ISTD are also relevant to therapeutic drug monitoring (TDM). The advantage here is that the drugs to be assayed are known and well-defined which allows a reliable choice of ISTD and consequent validation. Deuterated drugs, however, must be seen as individual medications and therefore the altered kinetics, administration profile and subsequent detection time window must also be considered. It is unclear whether there will also be changes in the therapeutic ranges.

3.3. 'Heavy' drugs as drugs of abuse

In experiments with mice, d2-MDMA (d2-3,4-methylenedioxymethamphetamine) showed properties comparable to the stimulatory effects of MDMA [43]. Consequently, d2-MDMA could show potential as a substance of abuse. Berquist et al. [43] suggested that a different deuteration could maximise the therapeutic effect in the treatment of patients with post-traumatic stress disorder (PTSD) while minimising the adverse effects of MDMA. This may be equally true in reverse for the abusive properties, which could also be altered by appropriate deuteration of the molecule.

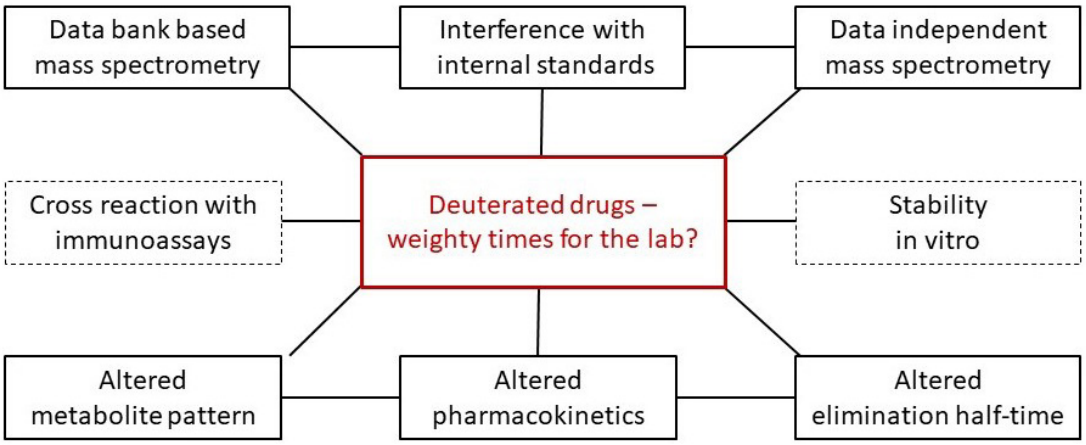


FIGURE 5. PROBLEM AREAS SHOULD DEUTERIUM-LABELLED DRUGS OF ABUSE OCCUR.

The literature contains information on deuterated analogues of substances with a high level of potential for improper use. These include d9-venlafaxine, d4-GHB (d4-gamma-hydroxybutyric acid), d9-tramadol, d2-ketamine and dx-psilocybin (see Appendix).

There are different and sometimes contradictory accounts in the literature on the production of deuterated drugs. Whether these apply to illegal drug laboratories is not clear.

Heavy water is a comparably cheap, safe and easily available source of highly pure deuterium [11] and the synthesis of deuterated products is quite well developed [5]. Nevertheless, the synthesis of deuterated compounds is not without problems. High costs of deuterated substrates or synthesis reactions with a low selectivity and yield are limiting factors [37]. Harsh and less environmentally friendly reaction conditions could play an additional role [37], although probably not so important for the drugs scene.

Assuming technical feasibility, the deuteration of drugs of abuse appears economically rather lucrative. An extension or increase of effect via deuterium labelling and thus a dose reduction could lead to maximum profit. This, however, is not something for the small, illegal back-street drug lab, but for a professional - almost industrial - manufacture of drugs of abuse.

3.4. 'Heavy' alcohol – "Ethanol-D"

There have been – or there still are – thoughts on deuterium labelling of foodstuffs, in particular spirits: according to Anthony Czarnik [44], deuterated alcohol, "Ethanol-D", is to revolutionise the beverage industry! Compared to 'normal' protonated ethanol, deuterium-labelled ethanol is metabolised 4.5x slower by alcohol dehydrogenase [44], therefore producing less acetaldehyde per time unit. Acetaldehyde is held mostly responsible for the 'hangover' and also the hepatic toxicity. At the same time, aldehyde dehydrogenase, which converts acetaldehyde to acetate, remains unaffected. Czarnik [45] proposed that there would be fewer side-effects, i.e. no hangover, after the consumption of deuterated alcohol. In 2009, he founded the company "Deuteria Beverages" to promote this concept. He holds or has applied for worldwide patents for these products [44]. Up to now, however, no commercial product containing deuterium-labelled ethanol is available and the patents for "Ethanol-D" are up for sale [46].

The patents describe the use of d1-ethanol up to d5-ethanol. Should the "Ethanol-D" concept finally appear on the market, then many questions would arise. For example:

- What are the clinical signs of an intoxication with deuterated ethanol?
- What role does deuterated ethanol play in the elimination kinetics after consumption as a single substance or in combination with non-deuterated ethanol?
- What is the effect of deuterated ethanol on the assessment of post offence alcohol drinking claims?
- What is the effect of deuterium-labelled ethanol on the analysis of markers of alcohol abuse?
- Would endogenous dx-EtG (dx-ethyl glucuronide), dx-EtS (dx-ethyl sulfate) or dx-PEth (dx-phosphatidyl ethanol) be produced after consumption of deuterated ethanol?
- Would these deuterated metabolites be detected by immunoassays developed for protonated analogues?
- Would these deuterated metabolites be detected by established physicochemical methods, in particular by the widely used LC-MS/MS, as long as mass spectra and MRM data for deuterated substances are not integrated into the corresponding databases?
- Would CDT (carbohydrate-deficient transferrin) remain unaffected as a marker of chronic alcohol abuse or would the modified toxicokinetics of deuterated ethanol lead to different response and decay times compared to non-deuterated ethanol?

4. Summary and outlook

It has taken about half a century from the initial description of deuterium-labelled compounds to the first approval of such a labelled medication, namely deutetrabenzine [28]. The pharmaceutical usage of deuterium labelling demonstrates a fascinating targeted alteration of metabolism so enabling a stronger therapeutic effect over a longer time period. Accordingly, the dose of a deuterium-labelled medication can be decreased and the administration schedule reduced leading to fewer potential adverse effects and an increase in patient compliance.

The possible effects of deuterium-labelling have another aspect. What is advantageous for medications is likely to be applicable to drugs of abuse. Here, too, the effect and duration of action can be increased. A therefore possible reduced dosage would maximise the profit of business in deuterated illegal drugs.

However, deuterated drugs could have an unintended analytical advantage. Depending on the analytical sensitivity, a prolonged effect could also mean a prolonged detectability!

Germany's "Neue psychoaktive Substanzen Gesetz" (NpSG; New Psychoactive Substances Act) at present does not include isotopically labelled derivatives. This approach differs from that of the German "Betäubungsmittelgesetz" (BtmG; German Narcotics Act), which also limits the use of isotopically labelled narcotics. This could possibly indicate a legal loophole (at least in Germany).

At present, we are unaware of any reports of 'heavy drugs' appearing in the illegal drug scene. This might mean on the one hand, that the drug designers are not yet fully acquainted with the latest developments in pharmacology or that the synthesis of deuterated drugs is technically difficult and economically demanding. On the other hand, deuterated drugs may be already available and not detected by the analytical methods focussed on protonated analogues.

We believe that it is only right and prudent that we should turn our attention to the role of deuterium-labelled drugs - both legal and illegal - in our daily routine.

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APPENDIX – SELECTED DEUTERATED DRUGS AND SUBSTANCES

Non-deuterated Form	Deuterated Form	Indication / Effect / Application	Source
[^{18}F]-Fluoroselegiline	d2-[^{18}F]-Fluoroselegiline	Parkinson disease	[17]
3-Fluor-d-alanine	Fludalanine, MK-0641	Antibiotic	[11,16,17,22]
4,6-Benzylidene-D-Glucose	d1-4,6-Benzylidene-D-Glucose	Cytostatic	[17]
Acetaminophen	dx-Acetaminophen	Analgesic	*1
Apalutamide	d3-Apalutamide	Prostate carcinoma	[17]
Apremilast	d5-Apremilast, CTP-730	Anti-inflammatory	[2,17,34]
Ascorbic acid	Zilascorb	Cytostatic	[17]
Atazanavir	d15-Atazanavir, CTP-518	HIV	[17,22]
AVE5638	d2-AVE5638	Tryptase inhibitor	[17]
Brecanavir	deuterated Brecanavir	HIV	[17]
Clopidogrel	d6-Clopidogrel	Platelet adhesion inhibitor	[17]
Caffeine	d9-Caffeine (low-dose)	Food industry	[47,48] *1
Caffeine	d9-Caffeine	Headache, narcolepsy, attention-deficit/hyperactivity disorder (ADHS)	[47,48] *1
Dapaglifozine	d3-Dapaglifozine	Type II diabetes	[17]
Dextromethorphane	C-10068	Anticonvulsive, anti-inflammatory	[5]
Dextromethorphane / Chinidine	d6-Dextramethorphane / Chinidine, AVP-786	Alzheimer disease, schizophrenia, dementia, depression	[2,5]
D-Serine	d3-D-Serine, CTP-692	Schizophrenia	[17]
Efavirenz	d1-Efavirenz	HIV	[16,17]
Enzalutamide	d3-Enzalutamide, HC-1119	Prostate carcinoma	[4,17,37]
Erythromycin B	d1-Erythromycin B	Antibiotic	[17]
Ethanol	dx-Ethanol	Food industry	[44]
Halothane	d1-Halothane	Anaesthetic	[11,17]
Ifosfamide	d4-Ifosfamide	Cytostatic	[17]
Imatinib	d3-Imatinib	Chronic myeloid leucemia, cytostatic	[17]
Indiplon	d3-Indiplon	Hypnotic	[16,22]
Ivacaftor	d9-Ivacaftor, VX-561, CTP-656	Cystic fibrosis	[2,5,17,32]
JNJ38877605	d1-JNJ38877605	Cytostatic	[17]

APPENDIX – SELECTED DEUTERATED DRUGS AND SUBSTANCES (CONTINUED)

Non-deuterated Form	Deuterated Form	Indication / Effect / Application	Source
Ketamine	d2-Ketamine	Anaesthetic, analgesic	[17]
L-838417	d9-L-838417, CTP-354	Multiple sclerosis	[17]
Lenalidomide	d1-CC-122	Anti-inflammatory, cytostatic	[4,5,17,36]
Levodopa	d3-L-DOPA, SD-1077	Parkinson disease	[5,17]
Linezolid	d10-Linezolid	Antibiotic	[22]
Linolenic acid	d2-Linolenic acid ethyl ester, RT001	Friedreich ataxia	[2,5,17]
Lumateperone	ITI-1284 ODT-SL	Schizophrenia	*2
Lysine	d2-Lysine	Fibrosis, cytostatic	[17]
Maraviroc	d5-Maraviroc	HIV	[17]
ML-337	d3-ML-337	Schizophrenia, depression, Alzheimer disease	[16]
Morphine	d3-Morphine	Opioid analgesic	[17]
Natriumoxybate (GHB!)	d4-Natriumoxybate, JZP-386	Narcolepsy, daytime sleepiness	[4,17,34]
Nerispiridine	d14-Nerispiridine	Multiple sclerosis	[17]
Nevirapine	d3-Nevirapine	HIV	[16,17,22]
Newly developed *3 (similar to Rosuvastatin)	BMS-986165	Psoriasis, systemic lupus erythematosus, chronic inflammatory bowel disease	[2,17,28]
Newly developed *3 (similar to Doxorubicin)	VX-984	Cytostatic, metastasing endometrial carcinoma, psoriasis	[2,17,28]
Nifedipin	d6-Nifedipine	Anti-hypertensive	[11]
NVS-CRF38	d3-NVS-CRF38	Corticotropin-releasing hormone antagonist	[17]
Odanacatib	d6-Odanacatib	Post-menopausal osteoporosis	[16]
Paraxanthine	dx-Paraxanthine	Headache, narcolepsy, attention-deficit/hyperactivity disorder (ADHS)	*1
Paroxetine	d2-Paroxetine, CTP-347	Menopause, vasomotor symptoms, hot flushes	[5,17,22,49]
Pentoxifylline metabolite	CTP-499	Chronic renal insufficiency	[4,34]
Pioglitazone	d1-Pioglitazone, DRX-065, PXL065	Steatohepatitis, adrenoleukodystrophy	[2,5,17]
Pirfenidone	d3-Pirfenidone, SD-560	Idiopathic pulmonary fibrosis	[5,17]
Pirfenidone	Deupirfenidone , LYT-100	Idiopathic pulmonary fibrosis	*4
Psilocybin	dx-Psilocybin	Severe depressive disorders, post-traumatic stress disorder	*1

APPENDIX – SELECTED DEUTERATED DRUGS AND SUBSTANCES (CONTINUED)

Non-deuterated Form	Deuterated Form	Indication / Effect / Application	Source
Retinyl acetate	d3-Vitamin A, C20-d3-Retinyl acetate, ALK-001	Stargardt disease	[5,17]
Rofecoxib	d5-Rofecoxib, BDD-11602	Non-steroidal anti-rheumatic (NSAR)	[16,17,22]
Ruxolitinib	d8-Ruxolitinib, Deuruxolitinib, CTP-543	Alopecia areata	[2,17] *5
Sildenafil	d5-Sildenafil	Phosphodiesterase-5-inhibitor	[17]
Sorafenib	d3-Sorafenib, Donafenib	Thyroid carcinoma	[4,17]
Tamoxifen	d5-Tamoxifen	Breast cancer	[11]
Telaprevir	d1-Telaprevir	Hepatitis C	[16,17,22]
Testosterone	d3-Testosterone	Breast cancer, hypogonadism	*1
Tetrabenazine	d6-Tetrabenazine, Deutetrabenazine, SD-809, TEV-50717	Huntington chorea, tardive dyskinesia, Tourette syndrome	[5,17]
Thalidomide (R-Isomer)	(R)-d1-Thalidomide	Anti-inflammatory and anti-tumourigenic, melanoma	[4,5,17,36]
Tivozanib	d6-Tivozanib	Cytostatic	[17]
Tolperisone	d7-Tolperisone, BDD-10103	Spastic paralysis	[17,22]
Tramadol	d9-Tramadol	Opioid-analgesic	[17,22]
Tyramine	d2-Tyramine	Catecholamine releasing agent	[17,50,51]
Venlafaxine	d9-Venlafaxine, SD-254	Severe depressive disorders	[17,22,34]

*1) https://www.lennham.com/pipeline

*2) https://ir.intracellulartherapies.com/static-files/c9a9b839-b6fe-4b84-b342-bac18a0ce9a7

*3) Examples such as BMS-986165 or VX-984 show that deuterated bioactive substances exist which have been developed solely as deuterated componds and are not analogues of known pharmaceuticals.

*4) https://investors.puretechhealth.com/news-releases/news-release-details/puretechs-lyt-100-deupirfenidone-achieves-50-reduction-healthy/

*5) https://www.concertpharma.com/product-pipeline/ctp-543/

All links last addressed on 24.08.2022.

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