# Deuterium Tetrabenazine for Tardive Dyskinesia

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## Abstract

Tardive dyskinesia remains a significant, potentially stigmatizing or crippling adverse effect for any patient treated with an antipsychotic medication. While second- and third-generation antipsychotics have exhibited lower annual incidence rates for tardive dyskinesia than classic or first-generation agents, 3.9% versus 5.5%, the estimated incidence rate is only modestly lower. When coupled with the fact that second- and third-generation antipsychotic medications have come to be employed in treating a wider range of disorders (e.g., autism spectrum disorders, mood disorders, personality disorders, etc.), it is clear that the population of patients exposed to the risk of tardive dyskinesia has expanded. On April 3, 2017, the U.S. Food and Drug Administration (FDA) approved a deuterated version of tetrabenazine (Xenazine®) for the treatment of the involuntary choreic movements associated with Huntington's disease. More recent data, however, have indicated that deuterium tetrabenazine or deutetrabenazine (Austedo®) is effective in treating tardive dyskinesia. Moreover, like the other derivative of tetrabenazine, valbenazine (Ingrezza®), deutetrabenazine offers less frequent dosing and a better short-term adverse effect profile than that of tetrabenazine. Longer use in a broader range of patients, however, will be required to identify risks and benefits not found in short-term trials, as well as optimal use parameters for treatment of tardive dyskinesia.

**Key Words:** Huntington's Disease, Tardive Dyskinesia, Schizophrenia, VMAT-2 Inhibitor, Deutetrabenazine

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## Introduction

Historically, tardive dyskinesia has imposed significant stigmatization and motor impairment on patients and legal liability on clinicians (1). First-generation or conventional antipsychotic treatment has been associated with a 5.5% annual incidence rate of tardive dyskinesia, while second-generation and third-generation antipsychotic medications have been associated with a modestly lower average rate of 3.9% (2). Indication and clinical application in a range of disorders in addition to psychotic disorders (e.g., autism spectrum disorders, mood disorders, personality disorders, etc.) has, however, expanded the population at risk of tardive dyskinesia to an estimated 5 million in the U.S., with an estimated 14% of this population likely to develop tardive dyskinesia (3, 4). In this context, it is worth noting that persons suffering from nonpsychotic disorders, women, and the elderly are at higher risk than schizophrenia-spectrum disordered patients to develop tardive dyskinesia (5, 6). In addition, an estimated 9% of patients with schizophrenia

may exhibit dyskinesia as part of their illness and the elderly may exhibit spontaneous dyskinesia (7, 8). Further complicating the issue of tardive dyskinesia is that tardive dyskinesia tends to persist even when antipsychotic medications are withdrawn, with recovery rates estimated as high as 33% and as low as 2% to 13% (9, 10). Moreover, the chronic nature of schizophrenia-spectrum disorders means that most such patients cannot discontinue antipsychotic treatment without a substantial risk of relapse (11). Clearly, going forward, psychiatry will need effective pharmacological tools with which to address tardive and other dyskinesias.

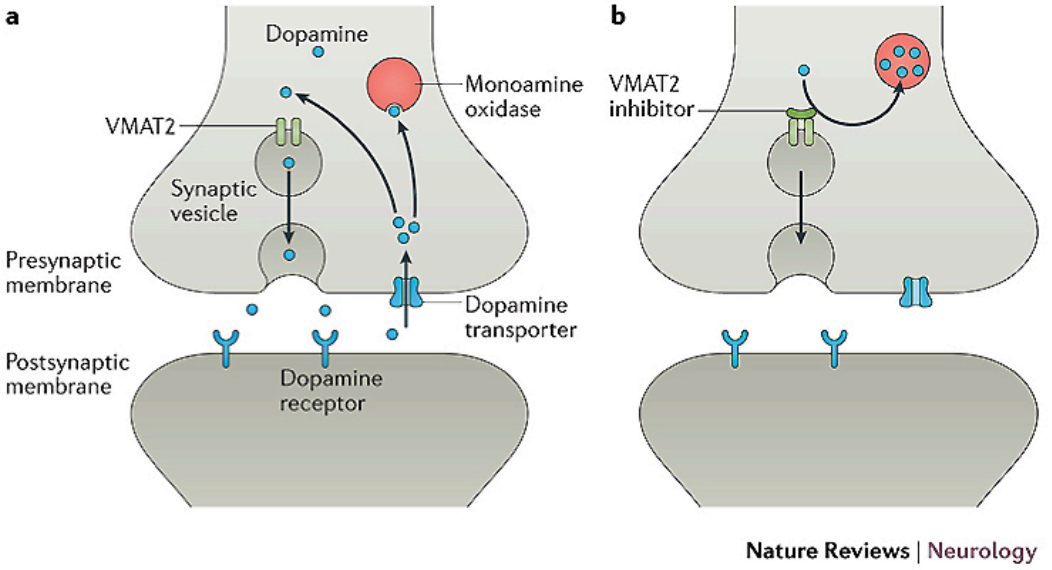
Importantly, in this context, in 2013 the American Academy of Neurology concluded that a large array of attempted treatment approaches for tardive dyskinesia had been either ineffective or lacked adequate data to recommend their use. These included: acetazolamide; baclofen; biperiden discontinuation; botulinum toxin, type A; bromocriptine; buspirone; diltiazem; eicosapenteanoic acid; electroconvulsive therapy; galantamine; levetiracetam; melatonin, methyldopa; nifedapine; pallidal deep brain stimulation; reserpine; selegiline; thiamine; vitamin B-6; vitamin E; and, yi-gan san (12). Other agents showed positive, but limited, efficacy: Amantadine at 300 mg per day and ginkgo biloba standard extract at 240 mg per day were reported to have produced 15% and 22% reductions in abnormal movement ratings on the Abnormal Involuntary Movement Scale (AIMS), respectively (13-15).

Three recent events hold forth the promise of more effective treatment tools. These include: the availability of tetrabenazine as a generic medication; U.S. Food and Drug Administration (FDA) approval of valbenazine for treatment of tardive dyskinesia; and, FDA approval of deuterated tetrabenazine or deutetrabenazine. For a detailed review of valbenazine, the reader is referred to a previous article in this journal by Freudenreich and Remington (16), available free online at www.clinicalschizophrenia.net.

## Background

Monoaminergic neurons which use dopamine, epinephrine, norepinephrine, and serotonin as synaptic signaling molecules depend, in large part, on presynaptic reuptake to maintain their neurotransmitter stores (17). A critical step in this neurotransmitter recycling is storage of the neurotransmitter in presynaptic vesicles associated with the

**Figure 1 Mechanism of Actions of VMAT-2 Inhibitors**




Source: Jankovic J. (2017) Progress in Parkinson disease and other movement disorders. Nat Rev Neurol. doi:10.1038/nrneurol.2016.204.

(a) Normally, vesicular membrane transport type 2 (VMAT-2) mediates loading of dopamine into synaptic vesicles for release. Breakdown of dopamine is mediated by monoamine oxidase. (b) VMAT-2 inhibitors block transport of dopamine into synaptic vesicles, reducing dopamine release and depleting dopamine levels through its breakdown by monoamine oxidase.

axon bouton membrane (18). If these monoamine signaling molecules were left in the neuron cytoplasm, they would be vulnerable to enzymatic degradation by monoamine oxidase (19). Central to this process of vesicular neurotransmitter storage is vesicle membrane transporter proteins, vesicular monoamine transporter, type 2 (VMAT-2) a.k.a. solute carrier family 18 member 2 (20).

Tetrabenazine was developed in the 1950s as an antipsychotic (21). Shortly thereafter, however, its capacity to deplete dopamine via inhibition of VMAT-2 in the nigrostriatal tract was found to be effective in reducing the rapid involuntary or choreic movements of Huntington's disease (22). Subsequently, it was also found to be effective in reducing tics associated with Tourette's syndrome and the movements associated with tardive dyskinesia (23). That is, tetrabenazine's depletion of dopamine by inhibition of VMAT-2 was hypothesized to counteract postsynaptic dopamine receptor supersensitivity and loss of plasticity thought to underlie the hyperkinetic movements observed in Huntington's disease, Tourette's syndrome, and tardive dyskinesia (24).

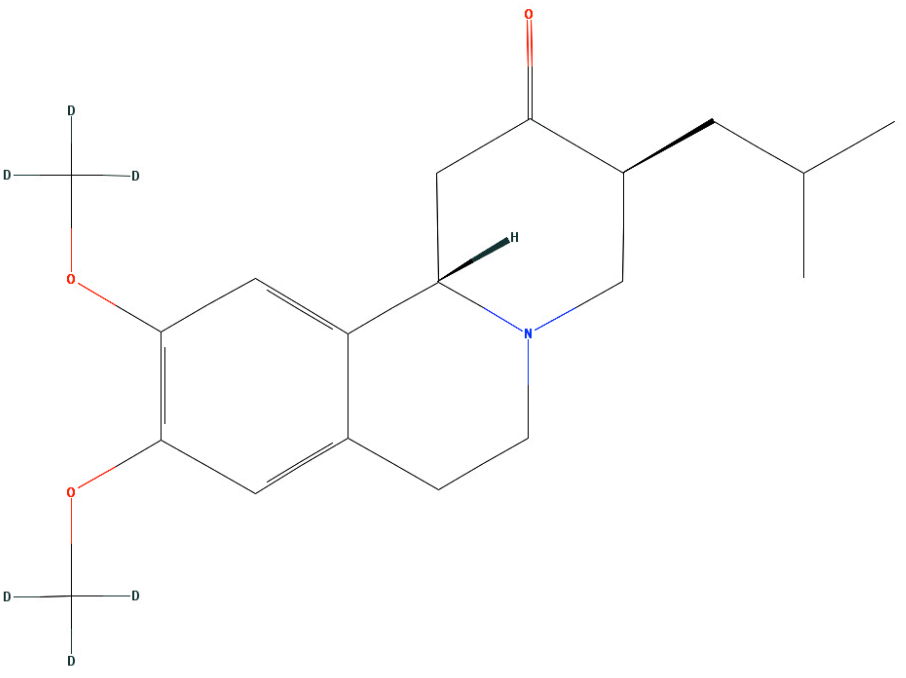
Nevertheless, tetrabenazine has several clinically undesirable characteristics. These include adverse effects such as insomnia, sedation, akathisia, pseudoparkinsonism, ortho-

**Table 1 Hydrogen Isotopes**

| Isotope | Nuclear Composition | Decay Type | Emitted Particles at Decay | Half-Life |
|---|---|---|---|---|
| Protium | Proton | Stable | None | Stable |
| Deuterium | Proton plus neutron | Stable | None | Stable |
| Tritium | Proton plus 2 neutrons | Beta | Energetic electron plus antineutrino<br><br>Energetic positron plus neutrino | 12.32 years |

Theoretically, the standard model of physics suggests that nuclei such as protium and deuterium may undergo proton decay; however, the half-life for this decay may exceed the estimated age of the universe. Hydrogen isotopes with more than two neutrons have been made by neutron bombardment, but half-lives are on a nanosecond time scale.

**Figure 2 Structure of Deutetrabenazine Showing Deuterium Substitutions**




Source: PubChem; National Library of Medicine (2017).

static hypotension during titration, depression, and suicidality (25). The latter two cited adverse effects carry a black box warning in tetrabenazine's package insert. In addition, tetrabenazine requires frequent dosing due to the short half-life of its principle active metabolite, (+)-α-H-tetrabenazine (26). Tetrabenazine is a racemic mixture of (+) and (-) enantiomers, which are catabolized by carbonyl reductase to four different dihydro-tetrabenazine metabolites: (+)-α-H-tetrabenazine, (+)-β-H-tetrabenazine, (-)-α-H-tetrabenazine, and (-)-β-H-tetrabenazine. While (+)-α-H-tetrabenazine is a potent and highly selective inhibitor of VMAT-2, the other metabolites are prone to off-target actions and may be responsible for some of the undesirable effects of tetrabenazine (27).

To date, two pathways have been pursued in attempting to improve on the undesirable clinical characteristics of tetrabenazine. These have been development of the most desirable metabolite of tetrabenazine as an independent medication (i.e., valbenazine) and alteration of tetrabenazine's pharmacokinetics by deuteration. In this latter context, six of the hydrogen, or protium, atoms of tetrabenazine have been converted to the heavier, stable isotope of hydrogen, deuterium, by precision bombardment with neutrons (28, 29). Because deuterium bonds are more stable than protium bonds, the effect of deuteration is to slow the catabolism of tetrabenazine, thereby reducing the frequency of dosing and, perhaps owing to lower peak plasma concentrations, ameliorating tetrabenazine's adverse effects (30, 31).

## Clinical Data

Deutetrabenazine (known prior to FDA approval as tetrabenazine 6D or SD-809) was approved by the FDA for treatment of the chorea associated with Huntington's disease (32). Subsequently, beginning in May 2017, data were published describing deutetrabenazine as effective in treating the hyperkinetic movements of tardive dyskinesia, leading to FDA approval for this indication as well (33, 34). Comparative structural models of tetrabenazine and deutetrabenazine are shown on Figure 2.

The Huntington Study Group found in a prospective, randomized, double-blind trial of 90 patients suffering from Huntington's disease given deutetrabenazine or placebo for a period of 12 weeks that deutetrabenazine treatment resulted in a significant (p<0.001) decline in the total maximal chorea score from a mean of 12.1 to 7.7, while patients taking placebo showed a decline in scores from a mean of 13.2 to 12.2 (35). Also, as with Huntington's disease, clinical research data have found deutetrabenazine to be effective in reducing the tic frequency in Tourette's syndrome (36).

On point for this review, Fernandez et al. conducted a randomized, double-blind, placebo-controlled, multi-center trial of deutetrabenazine in a sample of 117 patients suffering from moderate to severe tardive dyskinesia. Study entry required that patients score 6 or greater on a blinded, centralized video rating of their movements and that their psychiatric status and psychoactive medications be stable. The primary outcome measure was change in AIMS score across the 12 weeks of the study, while secondary measures were success on the Clinical Global Impression of Change (CGIC) scale and patient impression of change. Deutetrabenazine achieved a significant (p=0.019) reduction in dyskinetic movements compared to placebo, a reduction of mean+/-S.E.M. of 3.0+/-0.45 for deutetrabenazine vs. 1.6+/-0.46 for placebo. Change on the CGIC favored deutetrabenazine, 48.2% vs. 40.4%, but was not significant. Both deutetrabenazine and placebo groups showed low rates of psychiatric adverse effects: anxiety (3.4% vs. 6.8%); depressed mood/depression (1.7% vs. 1.7%); and, suicidal ideation (0% vs. 1.7%), respectively. Finally, no increase was seen in pseudoparkinsonism among deutetrabenazine-treated patients (37).

Similarly, Anderson et al. published a randomized, double-blind, placebo-controlled, multi-center, fixed-dose study of deutetrabenazine in August 2017. Patients, aged 18 to 80 years (n=298), were randomly assigned to receive fixed doses of deutetrabenazine 12 mg (n=75), 24 mg (n=74), 36 mg (n=75) or matching placebo tablets (n=74). Doses were titrated during the first four weeks of the study and then held steady for the last eight weeks. The primary outcome measure was change in AIMS score from baseline to week 12. Ultimately, 222 patients were included in the modified intention-to-treat analysis, while 293 patients were included in the safety analysis. From baseline to week twelve the two higher tested doses of deutetrabenazine produced a significant decline in AIMS score compared to placebo (see Table 2).

**Table 2 Fixed Dose Deutetrabenazine Outcomes**

| Deutetrabenazine Dose | Decline in AIMS (Mean+/-S.E.M.) | Significance |
|---|---|---|
| 36 mg/day | 3.3+/-0.42 | p=0.001 |
| 24 mg/day | 3.2+/-0.45 | p=0.003 |
| 12 mg/day | 2.1+/-0.42 | p=0.217 |

Placebo produced a mean +/-S.E.M. decline in AIMS score of 1.4+/-0.41.

As in the earlier study by Fernandez et al., the safety arm of the Anderson et al. study found relatively infrequent adverse events among deutetrabenazine-treated patients: 5% in the 36 mg per day group; 8% in the 24 mg per day group; and, 3% in the 12 mg per day group. In comparison, 6% of

those given placebo exhibited adverse events. Two patients died during the study, one each in the treatment and placebo groups, but the death in the treatment group was judged to be unrelated to deutetrabenazine (38).

Of interest, an open, prospective trial in 37 Huntington's disease patients indicated that switching abruptly from tetrabenazine to deutetrabenazine was associated with a low rate of adverse neuropsychiatric effects, while showing a significant decline in the maximal chorea score on the Unified Huntington's Disease Rating Scale over eight weeks, mean decline +/-S.D.=2.1+/-3.2 ($p<0.001$). This study suggested that deutetrabenazine's favorable tolerability may have permitted titration to more effective doses than had been possible with prior tetrabenazine treatment (39). Similarly, a recent meta-analysis suggested that tetrabenazine and deutetrabenazine were comparable with respect to overall efficacy and adverse events, but indicated that deutetrabenazine may be less prone to cause sedation or depression (40).

A comparison of tetrabenazine and deutetrabenazine is shown in Table 3.

**Table 3 Comparison of Deutetrabenazine and Tetrabenazine**

| Medication | Deutetrabenazine | Tetrabenazine |
|---|---|---|
| Mol. Wt. | 323.466 G/Mol | 317.429 G/Mol |
| Plasma Protein Binding | 82 to 85% | 82 to 85% |
| Half-life (primary active metabolite) | 9 to 10 hours | 4 to 8 hours |
| Major Metabolic Pathway | Carbonyl reductase | Carbonyl reductase |
| | Cytochrome P-450 2D6 | Cytochrome P-450 2D6 |
| Minor Metabolic Pathway | Cytochrome P-450 1A2 and 3A4 | Cytochrome P-450 1A2 and 3A4 |
| Elimination | Renal (major) | Renal (major) |
| | Fecal (minor) | Fecal (minor) |

Source: PubChem; National Library of Medicine (2017).

## Prescribing Information

Deutetrabenazine is supplied as 6 mg, 9 mg, and 12 mg oral tablets. The initial recommended dose for Huntington's disease is 6 mg per day, while for tardive dyskinesia it is 6 mg twice per day. It is recommended that all doses >12 mg per day be divided into a twice per day schedule. The recommended rate of titration is 6 mg per week to a maximum of 48 mg per day (24 mg twice per day). Tablets should be taken with food and should not be chewed.

If the patient is being switched from tetrabenazine, it is advised that deutetrabenazine be initiated the day after tetrabenazine is discontinued. See Table 4 for initial dose conversions.

**Table 4 Tetrabenazine to Deutetrabenazine Dosing**

| Tetrabenazine Daily Dose | Deutetrabenazine Initial Dose |
|---|---|
| 12.5 mg q day | 6 mg q day |
| 25 mg q day | 6 mg bid |
| 37.5 mg q day | 9 mg bid |
| 50 mg q day | 12 mg bid |
| 65.2 mg q day | 15 mg bid |
| 75 mg q day | 18 mg bid |
| 87.5 mg q day | 21 mg bid |
| 100 mg q day | 24 mg bid |

With respect to metabolism and drug interactions, it is recommended that in patients who are poor metabolizers at cytochrome P-450 2D6 or who are taking a potent 2D6 inhibitor that the total dose not exceed 36 mg, with no single dose exceeding 18 mg. It is recommended that combination with drugs that potently inhibit cytochrome P-450 2D6 (e.g., fluoxetine, paroxetine, or bupropion) and drugs that alter dopamine signal transduction (e.g., dopamine antagonist antipsychotics, reserpine, or monoamine oxidase inhibitors) be avoided or approached with caution. For patients known or suspected to have cardiac QT interval prolongation, measurement of the QT interval at baseline and after initiation and following dose increase is recommended. Additionally, based on studies of tetrabenazine, severe hepatic impairment is viewed as a contraindication to deutetrabenazine treatment. Also, based on trials and clinical experience with tetrabenazine, the FDA continued warnings for depression and suicidality.

For deutetrabenazine, adverse effects observed in 12-week trials at a rate greater than placebo and at least a 2% incidence rate included nasopharyngitis, insomnia, depression or dysthymia, and akathisia/restlessness. Altogether, adverse effects which resulted in dose reductions occurred in 4% of deutetrabenazine-treated patients and in 2% of patients taking placebo. Additional potential risks noted to be theoretically present included hyperprolactinemia and neuroleptic malignant syndrome. Deutetrabenazine may accumulate in melanin-containing tissues (e.g., the eye), but data are insufficient to know whether this poses any risk of long-term toxicity. Nevertheless, prescribers should be aware of this property of deutetrabenazine. Animal studies did not reveal any teratogenic adverse effects during pregnancy; however, human data are lacking. Similarly, data are lacking regarding secretion of deutetrabenazine in breast milk (41, 42).

## Conclusions (Take-Home Points)

- Although second- and third-generation antipsychotics carry a modestly lesser risk of inducing tardive dyskinesia than first-generation antipsychotics, their use in a broader array of psychiatric disorders is likely to maintain tardive dyskinesia as a substantial stigmatizing and sometimes disabling condition among patients exposed to antipsychotic medications.

- Tetrabenazine, a vesicular monoamine transporter, type 2 (VMAT-2) inhibitor, was historically effective in reducing rapid dyskinetic movements in Huntington's disease, Tourette's syndrome, and tardive dyskinesia; however, it had several problematic properties, including need for frequent dosing, sedation, orthostasis during titration, and induction of depression and suicidality.

- Precision deuteration of tetrabenazine, replacing six hydrogen (protium) atoms with deuterium, resulted in deutetrabenazine. Because deuterium bonds are more stable than hydrogen bonds, the half-life of the principle active metabolite is extended and peak plasma concentrations are reduced. This permits once or twice per day dosing and may be responsible for the favorable tolerability observed in short trials.

- Whether improved tolerability will be maintained for deutetrabenazine over longer periods will require longer duration trials and accumulated clinical experience. Longer trials and clinical experience also will be needed to determine to what extent induction of depression and suicidality are problematic for deutetrabenazine.

- Nevertheless, deutetrabenazine, along with valbenazine, promise to provide a broader range of effective tools for treating tardive dyskinesia.

## Disclosures

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