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Selective VMAT Inhibitors for Tourette Syndrome

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Abstract

The search for improved treatment options for patients with Tourette Syndrome (TS) has led to exploration of additional pharmacologic means of modulating dopaminergic pathways in the brain. Specifically, the goal has been to find agents which may avoid unwanted side effects (e.g., sedation, metabolic syndrome) associated with dopamine receptor blocking medications. One such target may be the Vesicular Monoamine Transporter 2 (VMAT2), a presynaptic neuron protein important for dopamine signaling. In this review, emerging data are presented from clinical trials using investigational medications active at VMAT2 and the implications for TS are discussed.

Keywords: Tourette syndrome; VMAT; Dopamine; Antipsychotic

Introduction

Tourette Syndrome (TS) is a childhood-onset neurodevelopmental disorder defined by the presence of chronic motor and vocal tics. While the causes of TS remain largely unknown, current evidence does point to the importance of genetic factors [1]. The detailed neurobiological mechanisms underlying TS remain uncertain as well, but the presence of central Dopamine (DA) hypersensitivity is implicated by several lines of evidence [2-4]. In support of this so-called "DA hypothesis" of TS, historically it has been the DA receptor antagonist (antipsychotic) drugs that have shown the most consistent tic-suppressing effects, and these are still the mainstay of pharmacotherapy for the disorder [5,6]. Medications that reduce dopamine neurotransmission by other mechanisms, such as by depleting presynaptic DA (e.g., tetrabenazine) have also been reported to be effective in reducing tics [7-9]. Recent attention has been directed to next generation drugs that can modulate presynaptic dopamine release at the synapse, specifically those that inhibit the Vesicular Monoamine Transporter 2 (VMAT2) [10,11]. These medications are of special interest now because of the recent development of new selectively acting agents that may be more effective and better tolerated than previous drugs and they are the focus of this review.

The "Dopamine Hypothesis" of TS

The first observations pointing to a disturbance of DA neurotransmission in the pathophysiology of TS occurred after the introduction of antipsychotic medications in the 1960's when a substantial improvement in tics in treated patients was often seen [5,6]. Not only did this experience have a dramatic impact on changing etiological views of TS from a psychodynamically-based to a biologically-based condition, since these drugs were known to block dopamine receptors, a state of excessive brain dopaminergic activity was implicated as a potential mechanism [5,6]. Over time it became clear that the efficacy of an antipsychotic drug in suppressing tics was directly related to its potency in blocking Dopamine-2 (D2) receptors. The findings of reduced levels of the DA metabolite homovanillic acid in the cerebrospinal fluid of patients with TS [12] and normal receptor numbers on functional neuroimaging studies of the basal ganglia suggested [3,4] underlying DA receptor hypersensitivity rather than increased DA release or receptor density. At this time, the exact mechanism of central dopaminergic hypersensitivity in TS remains to be established.

Alternative Drugs to Antipsychotics

While D2-receptor antagonist drugs, including both classical and the newer atypical antipsychotic medications continue to be the most predictably effective tic-suppressing medications, some patients fail to respond and many find them to be poorly tolerated [13-16]. Sedation and depression occur commonly and the atypical antipsychotics often lead to weight gain and the metabolic syndrome. Due to these tolerability difficulties, there has been interest in other types of medications to treat tics. α2-adrenergic agonists like clonidine and guanfacine, the antiepileptic drug topiramate, and the benzodiazepine, clonazepam have demonstrated benefit in some patients [17-19]. Local intramuscular injections of botulinum toxin can be effective when there are a small number of disabling tics, but the benefits are temporary. Non-pharmacologic behavioral interventions e.g., Comprehensive Behavioral Intervention for Tics (CBIT) have also been shown to be of benefit in reducing tic severity [20].

Tetrabenazine (TBZ) is another alternative to antipsychotic medications in the treatment of TS. Although it has had limited availability in the U.S, TBZ is a drug that depletes presynaptic DA and has shown evidence of reducing tics in TS in retrospective or open-label studies [6-8]. Tetrabenazine has VMAT2 inhibitory activity and, unfortunately, is often poorly tolerated due to the side effects of excessive monoamine depletion, including sedation, depression, akathisia and parkinsonism, and thus requires slow and careful titration and careful clinical monitoring. There is also the potential concern that off-target binding by one of the stereoisomer metabolites to the post-synaptic D2 receptor may be a risk for tardive dyskinesia [21].

Recent advances in pharmacology related to VMAT2 inhibition have stimulated renewed interest in this approach to treating TS with the hope of developing new agents that may have both better efficacy and tolerability.

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The Vesicular Monoamine Transporter and its Pharmacology

Given the importance of basal ganglia function and DA circuits in TS, and the aforementioned limitations of currently available treatments (i.e., DA antagonist medications), alternative pharmacologic targets for the dopaminergic system have been sought [5,6]. VMAT2 is specifically attractive as a means for achieving tic reduction in that the transporter is localized primarily in the motor-control circuits of the striatum [22,23]. Modulation of presynaptic DA release can be achieved via VMAT2 inhibition without necessitating post-synaptic receptor blockade. This offers the theoretical advantage of avoidance of up regulation of post-synaptic DA receptors and associated downstream changes implicated in tardive dyskinesia. In addition, selective VMAT2 targeting may also avoid the metabolic syndrome side effects associated with the newer generation of antipsychotic medications (atypical antipsychotics).

VMAT2 is a transporter which is present in the membrane of presynaptic vesicles in monoaminergic neurons [23]. The primary function appears to be packaging monoamines (e.g., DA) from the cytoplasm of the presynaptic neuron into vesicles for subsequent release into the synapse. VMAT2 may also have a role in dopamine production via interactions with tyrosine hydroxylase in the presynaptic neuronal membrane [24]. Inhibition of VMAT2 results in decreased activity in the associated neuronal circuits. Increasing inhibition of VMAT2 results in predictable signs of pharmacologic effect in animals including slowing of movement, ptosis, and sedation [23].

It is not clear whether various disease states are associated with alterations in VMAT2 function directly. Genetic polymorphism may contribute to functional differences in VMAT2 and it has been proposed that VMAT2 over activity due to such polymorphism may result in behavioral abnormalities [25].

New VMAT Inhibitors

Novel approaches to VMAT2 therapeutics have been undertaken over the past few years, including the development of a deuterated form of tetrabenazine and a new highly selective VMAT2 inhibitor, valbenazine [26]. The former (SD-809ER) is a tetrabenazine analog with replacement of select hydrogen groups with deuterium. The concept is that deuterium substitution alters hepatic metabolism of the compound, providing similar overall exposure (i.e., Area Under Curve [AUC]) to the four active stereoisomer metabolites but at a lower dose and with lower peak concentration levels than with tetrabenazine [unpublished]. All 4 stereoisomers of deuterated tetrabenazine are present upon reduction, with the same pharmacological properties of binding to VMAT2 along with dopamine D2 and serotonergic (5HT) receptors as tetrabenazine. SD-809ER (also described as SD-809) uses an extended release formulation to extend the half-life such that twice daily dosing is possible following titration (compared to three times daily with tetrabenazine) [27,28].

Valbenazine (NBI-98854)is a new molecular entity developed by Neurocrine Biosciences with no "off-target" pharmacology; it has potent binding at VMAT2 and no significant binding at VMAT1 or over100 other receptors, channels, transporters and enzymes tested in an extensive screen (data on file at Neurocrine, manuscript in preparation). The molecule was designed to deliver a pharmacokinetic profile with limited daily peak-to-trough fluctuation providing a lower risk of side effects associated with higher peak exposures, while allowing for appropriate overall exposure (AUC) for symptom reduction. Pharmacokinetic studies of valbenazine have demonstrated predictable dose-proportional exposures in the clinically relevant dose ranges, and the 20-hour half-life of valbenazine enables once daily dosing [26]. To date, the adverse event profile in adults suggests that slow titration is not required. Valbenazine is metabolized by multiple routes (primarily liver) with minimal risk of drug-drug interactions (data on file, manuscript in preparation).

Clinical Trials in TS

Regulatory approval of the first pharmacological treatment for tics, the D2-blocker haloperidol, relied almost entirely on clinical case studies/series and anecdotal reports of significant tic reduction following drug administration [13]. In the 1980's, both open-label and small randomized double-blind clinical trials provided the requisite data for the approval of pimozide to treat TS under the then newly ratified Orphan Drug Act [13]. Improvement of TS symptoms in these studies was determined using a variety of clinician-based and patient-based instruments, including clinical global impression scales and TS severity scales [14,15]. The state of regulatory science regarding study endpoints for use in clinical trials, and the burden of regulatory proof for therapeutic efficacy, progressed over the next three decades and culminated in the 2014 approval of the atypical antipsychotic, aripiprazole (Abilify®) for the indication of TS [16,29]. To date, haloperidol, pimozide, and aripiprazole are the only pharmacotherapies specifically indicated and labeled for the treatment of TS.

Clear evidence of the tic suppressing effects of atypical D2-blocking drugs was demonstrated in the two adequately-sized, randomized controlled trials of aripiprazole [16,29]. Similar to previously published studies of the α2-adrenergic agonists clonidine and guanfacine [17,18] and the antiepileptic drug topiramate [19], the pivotal clinical trials for aripiprazole [16] utilized a primary endpoint measurement of the Yale Global Tic Severity Scale [30]. More specifically, the Total Tic Score (TTS), which represents the sum of motor and phonic tic severity scores across 5 measurement domains of the YGTSS (number, frequency, intensity, complexity, and interference), was used to quantify treatment response of active drug versus placebo. The clinical significance of TTS improvement has been examined in a rigorous meta-analysis of both controlled and uncontrolled interventional trials in TS patients [29]. In this meta-analysis, the TTS was evaluated against the clinical response status of "improved" or "very much improved" on the Clinical Global Impression Scale (CGI), demonstrating that a 6 to 7 point reduction from baseline/pre-drug values in the TTS, an approximate 35% decrease, was indicative of a clinically meaningful response in TS patients.

The effectiveness of dopaminergic system modulation through VMAT2 inhibition has also been investigated in TS. The clinical response to TBZ administration in these studies was exclusively based on retrospective chart reviews and case reports/series, and relied on more global assessments of treatment response and not the YGTSS [7-9].

Recent clinical trials of the new VMAT2 inhibitors have been designed with clinical outcomes specific and relevant to the condition to assess both efficacy in improving the primary symptoms, as well as safety and tolerability in patients in the context of comorbid conditions, and frequently complex concomitant medication regimens.

Preliminary Clinical Experience with the New Drugs

To date, there have been five randomized, placebo-controlled Phase 2 and 3 trials of valbenazine for the treatment of Tardive Dyskinesia (TD), a hyperkinetic movement disorder that can be permanent and disabling following chronic use of dopamine D2 receptor antagonists. It is hypothesized that chronic administration of these D2 blockers also results in basal ganglia dysfunction and dopamine hypersensitivity [31]. In the Phase 2b ("Kinect 2") and Phase 3 ("Kinect 3") studies, valbenazine treatment resulted in significant reductions in tardive dyskinesia [32] severity of >3 points (least-squared means change from baseline) measured by the Abnormal Involuntary Movement Scale (AIMS) compared to placebo, after 6 weeks of treatment. Improvement was also seen based on Clinical Global Impression scores of improvement and significantly higher proportions of responders in the valbenazine-treated groups [10,26]. Notably, rates of adverse events and study discontinuation were similar in active and placebo groups, and systematic assessments of depression, suicidality, and psychiatric symptoms did not indicate a safety signal. SD-809 has also shown significant reduction of chorea severity in Huntington's disease in a Phase 3 study [28] and in tardive dyskinesia severity in a Phase 2 study [11]. More recently, pilot studies with valbenazine and SD-809 have been conducted in children and adolescents with TS. The open-label pilot study of SD-809 in adolescents with TS, titrating over 6 weeks up to 36mg/day (given as divided twice a day dosing) followed by 2 weeks of maintenance, was reported to show a mean 37% reduction in YGTSS TTS [5]. The open-label Phase 1b study of valbenazine in children and adolescents with TS, given as fixed once-daily doses over 14 days, was reported to show a mean 31% reduction in YGTSS TTS (www.clinicaltrials.govNCT02256475). With the safety, tolerability, and pharmacokinetic profiles from these valbenazine studies, Neurocrine Biosciences, Inc has initiated Phase 2 double-blind, randomized, placebo-controlled clinical trials to evaluate valbenazine in adults with TS (NCT02581865) and in children and adolescents (NCT02679079), that are currently underway. These studies will use the YGTSS (as primary endpoint) and CGI to quantify TS improvement over 6 to 8 weeks of treatment. Further long-term studies to evaluate the safety and efficacy of valbenazine for TS in these patient populations are being planned.

Conclusion

Tourette syndrome remains an unmet medical need as current therapies are limited by insufficient efficacy, poor tolerability or unacceptable safety profiles, particularly with young children. While the spectrum of neurological and behavioral phenomena most likely require different types of pharmacologic and non-pharmacologic interventions, DA modulation clearly can be useful for reduction of phonic and motor tics. VMAT2 is a rational target for new therapies and dose-proportional inhibition of presynaptic DA release appears to be useful for management of hyperkinetic movement disorders. Availability of a Selective VMAT2 Inhibitor (SVI) with a favorable preclinical and human safety profile has led to Phase 2 studies in TS and data are eagerly awaited.

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