Recent Advances in the Pharmacology of Tardive Dyskinesia

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Tardive dyskinesia (TD) is a syndrome of abnormal involuntary movements that follows treatment with dopamine D2-receptor antagonists. Recent approval of vesicular monoamine transporter-2 (VMAT2) inhibitors offers hope for reducing the impact of TD. Although these drugs represent a significant advance in patient care and a practical step forward in providing relief for patients with TD, understanding of the pharmacology of TD that could inform future research to prevent and reverse TD remains incomplete. This review surveys evidence for the effectiveness of VMAT2 inhibitors and other agents in the context of theories of pathogenesis of TD. In patients for whom VMAT2 inhibitors are ineffective or intolerable, as well as for extending therapeutic options and insights regarding underlying mechanisms, a review of clinical trial results examined as experimental tests of etiologic hypotheses is worthwhile. There are still compelling reasons for further investigations of the pharmacology of TD, which could generate alternative preventive and potentially curative treatments. Finally, benefits from novel drugs are best realized within an overall treatment strategy addressing the condition and needs of individual patients.

KEY WORDS: Tardive dyskinesia; Parkinsonian disorders; Antipsychotic agents; Dopamine antagonists; VMAT2 vesicular monoamine transport proteins; Movement disorder.

INTRODUCTION

Tardive dyskinesia (TD) is an involuntary movement disorder associated with dopamine-receptor antagonists, most often antipsychotic drugs [1-4]. TD is characterized by repetitive polymorphous movements that are commonly observed in the orofacial region but can also affect the neck, trunk, and extremities. TD is often delayed in onset, suppressed by ongoing dopamine-receptor antagonist treatment, and potentially irreversible.

Until recently, limited understanding of the neurobiology of TD and disappointing attempts at treatment led to relative neglect. However, TD remains relevant in clinical practice for several reasons. The prevalence of TD among patients receiving antipsychotics is estimated to be 20−30%, and even higher among the elderly [5]. Newer

antipsychotics are less likely to cause TD but the risk is still significant [6,7]. The absolute number of people at risk of TD may be growing due to expanding indications and off-label prescribing of antipsychotics [8-11]. While recent studies confirm the impact of TD on quality of life that was often overlooked in the past [12,13], effective treatment of TD using vesicular monoamine transporter-2 inhibitors (VMAT2s) is now available [14,15]. Finally, research into the pharmacology underlying TD may shed light on basal ganglia organization and function.

Specific treatments for TD are best prescribed within a comprehensive management strategy including preventive screening for early signs, differential diagnosis, and informed discussion with patients and caregivers (Table 1) [1,16-20]. Numerous agents have been tested as treatments for TD based on competing theories of pathophysiology [21-26]. The statistical designs of these clinical trials have been extensively reviewed [18,26-32]. Unfortunately, most trials have been methodologically flawed such that questions on the effectiveness of many agents and the validity of the underlying theories remain unresolved (Table 2).

By comparison, recent clinical trials of VMAT2 inhibitors

Table 1. Summary of proposed stepwise treatment algorithm for tardive dyskinesia (TD)

1. Recognition and diagnosis of TD
2. Documentation of severity, distribution and phenomenology of TD (AIMS examination)
3. Differential diagnosis and laboratory investigation
4. Neurological consultation (for diagnostic dilemmas, atypical or severe cases)
5. Discussion of treatment options with patient and caregivers
6. Review of antipsychotic (dopamine D2-receptor antagonist) treatment:
   a. Patients who can be safely tapered off treatment if alternative therapies are available
   b. Patients who require antipsychotic maintenance treatment
      i. Maintain current treatment
      ii. Switch to an alternative antipsychotic or clozapine
7. Review of anticholinergic treatment:
   a. Patients who can be safely tapered off treatment
   b. Maintain or reduce dosages in patients who require anticholinergic treatment for acute movement disorders or tardive dystonia
   c. Consider amantadine in patients who require concurrent treatment for acute movement disorders and TD
8. Specific anti-dyskinetic treatment on an individualized basis:
   a. Valbenazine or Deutetrabenazine
   b. Positive findings but evidence is insufficient for recommendation, e.g., tetrabenazine, amantadine, botulinum toxin (specific benefit for focal tardive dystonia), levetiracetam, propranolol, Gingko biloba extract, and vitamin B6

AIMS, Abnormal Involuntary Movement Scale.
Adapted from the article of Caroff *et al.* (Expert Rev Neurother 2017;17:871-881) [18]. Reprinted by permission of the publisher, Taylor & Francis Ltd, http://www.tandfonline.com.

Table 2. Modified list of evidence supporting efficacy of agents studied as treatment for TD [18,25,27,28,46]

Established	Probably	Possibly	Inconclusive data	Ineffective
Valbenazine Deutetrabenazine	Tetrabenazine	Amantadine Ginkgo biloba extract Switch antipsychotic or clozapine Antipsychotic withdrawal (in early cases) Clonazepam	Reserpine α-methyldopa Bromocriptine Cholinesterase inhibitors Muscarinic agonists Nicotinic agonists Anticholinergics (tardive dystonia) Melatonin Vitamin B6 Selegiline Yi-gan san/kamishoyosan Baclofen Levetiracetam Nifedipine Buspirone Botulinum toxin (tardive dystonia) Branched chain amino acids Neurosurgey Electroconvulsive therapy Deep brain stimulation	Eicosapentaenoic acid Diltiazem Vitamin E

set a high standard for treatment studies of TD. Approval of these dopamine-depleting drugs represents an important practical step toward improving the lives of patients with TD. Nevertheless, while these agents effectively suppress TD, they do not advance theoretical understanding. Better understanding of mechanisms is essential in advancing research and developing more effective drugs that could prevent or reverse TD [33]. Thus, in order to extend therapeutic options and broaden insights, a review of alternative agents and underlying theories is presented.

PHARMACOTHERAPY OF TARDIVE DYSKINESIA

Dopaminergic Drugs

Rationale
Drawn from observation of dyskinesias in Parkinson's

and Huntington's disease patients, and from denervation studies in animal models, the notion that TD is the result of postsynaptic supersensitivity of dopamine D2-receptors following prolonged drug-induced receptor blockade became the prevailing theory [1,33-37]. This theory has heuristic value in predicting the effects of agents that affect dopaminergic activity. For example, TD is unique to treatment with antagonists of dopamine D2-receptors [38], can be suppressed by drugs that block or deplete dopamine, and precipitated or worsened by drugs that increase dopamine activity.

However, this hypothesis provides an incomplete picture [1,25,33]. Evidence on dopamine D2-receptor supersensitvity associated with dyskinesias in animals, which develop quickly and resolve rapidly after drug discontinuation, has been questioned as an inexact model for TD in humans. Antipsychotics have multiple other effects on pre- and post-synaptic receptors or second messenger systems [39], on dopamine D1- or D3-receptors [40], on differences in D2-receptor supersensitivity measured by receptor numbers, affinity states or functional behavioral assays [41], and a range of genetic products and other neurotransmitters that affect the development of supersensitivity. The D2-receptor supersensitvity model fails to explain why TD does not affect all patients, why it develops over variable periods of time, why it is not preceded necessarily by parkinsonism but yet may coexist with parkinsonism in the same patient, and why it strongly correlates with age. In humans, functional imaging and post-mortem studies have not consistently demonstrated correlations between D2-receptor numbers and TD [21]. Nevertheless, treatment trials are consistent with the notion that dopamine D2-receptor antagonism is a necessary initial step that triggers reactive changes in striatal circuits leading to a potentially permanent state of dopaminergic hyperactivity associated with the manifestations of TD. As a result, agents that inhibit dopamine synthesis, metabolism or receptor function are effective at suppressing symptoms but not necessarily reversing the mechanisms underlying TD.

Dopamine-receptor agonists

Evidence of drug-induced dopamine D2-receptor supersensitivity in animal models implies that dopamine agonists could theoretically downregulate post-synaptic receptors and reverse TD. However, they are limited by worsening psychotic symptoms and increasing hyperkinetic movements at least initially. Several direct and indirect dopamine agonists have been tested in TD patients with mostly negative or inconclusive results [25,27,28,42,43]. Whether the partial dopamine-receptor agonist properties exhibited by drugs like aripiprazole have a possible modulating effect in preventing, reducing or reversing TD may be a related question to explore [44].

Dopamine-receptor antagonists

Depending on dopamine D2-receptor binding affinity, antipsychotics and other dopamine receptor antagonists are paradoxically the primary trigger for TD development as well as the most potent agents for suppressing TD [45]. It has been considered inadvisable to use them to treat and possibly perpetuate the very disorder they caused [18,26-29,46]. While this is understandable from a purely neurological point of view, prescribing decisions on antipsychotics in patients with mental illnesses and TD are complex illustrated by the following options.

Maintenance of antipsychotics

In patients with psychiatric illness at high risk for relapse who have mild, localized TD with minimal subjective impact, maintenance of antipsychotic treatment may be justified. TD is usually not progressive even with continued antipsychotic treatment. In several studies of antipsychotic maintenance treatment, TD was reported to show no change, worsening in some cases, or significant improvement over time albeit at risk of increased parkinsonism and diminished odds of reversibility [31,47,48]. The evidence suggests that TD is persistent and fluctuates in most cases with continued antipsychotic treatment, with only a minority of patients showing worsening [47]. Importantly, TD could be masked by antipsychotics and may first become apparent or worsen only after drug withdrawal in 5 − 67% of patients [49,50]. Patients with TD should consent to maintenance treatment and be monitored for any signs of progression.

Withdrawal of antipsychotics

Ideally, antipsychotics could be tapered off. In TD patients without a chronic underlying psychotic disorder, such as those with episodic depression, maintenance with antipsychotics may be safely discontinued. However, patients with schizophrenia or some cases of bipolar dis-

order may incur a significant risk of psychotic relapse and require ongoing treatment [51]. Although drug withdrawal has been recommended [27,31,52], about 33% to 53% of patients experienced worsening of dyskinesias initially, while only 36% to 55% showed improvement over time after older antipsychotics were discontinued [53]. Potential reversibility of TD after drug cessation is controversial. While recent surveys suggest a grim prognosis with as few as 2% of patients showing resolution of TD after drug withdrawal [54-56], older reports found remission of TD after drug cessation occurring in 50−75% of patients if detected early [57,58]. While these early cases may represent reversible withdrawal dyskinesias, they support the potential efficacy of drug cessation in nonpsychotic patients if implemented soon after the diagnosis of TD is made. These cases suggest that there may be a period of consolidation during which the mechanisms underlying TD are reversible.

Dose reduction of antipsychotics

Another option has been dose reduction of antipsychotics, which has resulted in increased remissions in some studies [32,59,60]. However, meta-analyses concluded that available data are insufficient to either support or refute treatment of TD by dose reduction [27,29,42,56], which may temporarily unmask or worsen movements. Recent evidence suggests that dose reduction, like drug cessation, may contribute to relapses in psychiatric symptoms in some cases, further limiting this intervention for TD [61,62].

Switching antipsychotics

If TD develops, another alternative is to switch antipsychotics if maintenance treatment is necessary. A change to higher doses or potent antipsychotics may increase dopamine D2-receptor blockade and suppress symptoms of TD in up to 67% of patients, although limiting remission of TD and potentially exacerbating parkinsonism [29,45,63]. These agents have not been recommended because of their propensity to mask symptoms and cause parkinsonism, and because of concern that long-term use will worsen TD [27]. However, they have been used in severe cases to provide symptom relief [1]. A previous study of the effects of high potency antipsychotics on TD suggested the suppressive effect may be only temporary and TD symptoms may re-emerge during follow-up [64].

The role of newer antipsychotics in managing TD is less clear [26]. Recent meta-analyses have judged the evidence as insufficient to support recommendations for using newer antipsychotics specifically to treat TD [27,28]. However, individual studies of newer agents have shown significant reduction in TD severity, with some studies showing greater suppression, lesser suppression, or no difference compared with older agents [18,27,47,65-67]. Studies of newer antipsychotics in suppressing TD have shown nearly an identical drop in the percentage of patients showing persistent TD and in the total Abnormal Involuntary Movement Scale (AIMS) severity scores compared to decreases observed in recent trials of VMAT2 inhibitors [17,47,65]. But antipsychotic suppression of TD comes at a cost of continued dopamine-receptor blockade perpetuating the etiologic mechanism of TD and restricting chances of remission [18,44,47,48,65,67].

Dopamine depleting agents

Reserpine

Drugs that deplete presynaptic stores of dopamine have been useful in reducing TD [25,43,68-70]. Two depleting agents, α-methylparatyrosine and α-methyldopa which interfere with dopamine synthesis, were found to significantly reduce severity of TD in small early studies [25,27]. More enduring interest in dopamine depletion as a treatment strategy for TD was stimulated by the effects of reserpine. When it is not sequestered into presynaptic vesicles because of inhibition of VMAT, dopamine is rapidly degraded by monoamine oxidase resulting in pre-synaptic depletion and reduced availability for release into the synapse. VMAT occurs in two isoforms; VMAT1 which is distributed primarily in the peripheral nervous system and VMAT2 which is found primarily in the central nervous system. The actions of reserpine are irreversible and nonselective, inhibiting both VMAT1 as well as VMAT2, resulting in tolerability problems with blood pressure, gastric motility, impotence and nasal congestion and potentially prolonged depression and extrapyramidal side effects [69]. Initially used as an antihypertensive treatment, reserpine was observed to have significant effects as an antipsychotic as well as a treatment for Huntington's chorea [25]. In addition, early studies of reserpine showed at least a 50% improvement in TD move-

ments, although the evidence is not considered sufficient to support its use [27].

Terabenazine

Tetrabenazine (TBZ) was developed in the 1950s as an antipsychotic [68,70-73]. It replaced reserpine because of its VMAT2 selectivity, shorter duration and reversible action on VMAT, relative lack of hypotensive side effects, and less severe depressive effect. Approved in the United States as a treatment for Huntington's chorea, it was studied off-label and has been approved for treatment of TD in several countries (Table 3). TBZ undergoes rapid first-past hepatic metabolism to two main metabolites, α-dihydrotetrabenazine (α-HTBZ) and β-HTBZ, which are potent inhibitors of VMAT2 [68,70]. Peak plasma concentrations of α-HTBZ and β-HTBZ are reached within 1 − 1.5 h [68] with a duration of clinical effect estimated to be 5 hours requiring multiple daily dosing [68], with chorea recurring within 12 − 18 hours after the last dose [73]. Apart from binding to VMAT2, TBZ and its metabolites have affinity for other receptors, contributing to unwanted side effects that can be dose-limiting [68,70]. Due to its tolerability and pharmacokinetic profile, use of TBZ in Huntington's disease includes recommendations for CYP2D6 genotyping to screen for poor metabolizers when exceeding doses of 50 mg/day [68].

Recent reviews of TBZ for TD found one double-blind, crossover study and seven open-label studies [72-74]. TBZ doses ranged from 6.25 to 300 mg/day. At least moderate improvement was reported in 41% to 93% of patients, with a mean improvement of 54% in the total AIMS score. Long-term observational studies support the sustained efficacy of TBZ. Dose-related side effects included sedation, parkinsonism, akathisia, and depression. Guidelines concluded that TBZ is only possibly effective for TD,

because of a lack of double-blind, randomized, placebo controlled trials [27,28,72]. Two long-term retrospective studies reported that TD severity recurred when TBZ was discontinued [73].

Valbenazine

The positive effect of TBZ on TD prompted efforts to improve upon its shortcomings. Valbenazine (VBZ) is a reversible, selective VMAT2 inhibitor approved for the treatment of TD (Table 3) [18,28,68,70-73,75]. VBZ is the parent drug of the α-dihydrotetrabenazine isomer of TBZ which has the strongest affinity for VMAT2 and the least affinity for off-target receptor binding. VBZ is metabolized slowly with peak concentrations of the active metabolite reached within 4 − 10 hours and a half-life of 20 hours. VBZ and its metabolites are metabolized by CYP3A4 as well as CYP2D6 making it less dependent on genotyping of the CYP2D6 enzyme.

Evidence on the efficacy and safety of VBZ for TD has been tested in randomized, placebo-controlled, double-blind trials [18,28,68,71,73,75], including a 6-week dose-escalation study (KINECT 2) and a 6-week fixed-dose trial (KINECT 3) [76,77]. Treatment with VBZ was associated with significant improvement in total AIMS scores in both KINECT 2 and KINECT 3. Patients receiving VBZ were significantly more often "much improved" or "very much improved" compared with placebo and were significantly more likely to show ≥ 50% reduction in the AIMS score [72]. Pooling data from short-term trials provides an overall number needed to treat (NNT) estimate for AIMS response of VBZ vs. placebo of 5 [75].

In a 42-week extension study, efficacy measures continued to improve but trended back to baseline after VBZ was discontinued [72,73,75,78]. An interesting finding was that 25% to 30% of patients enrolled in long-term ex-

Table 3. Vesicular monoamine transporter-2 (VMAT2) inhibitors

VMAT2 inhibitor	Half-life	Dose range	T max	CYP2D6 metabolism	%Responders (≥50% ↓ AIMS) [77,82]	NNT/NNH [69,75,80]	Approved indications
TBZ	5.5 hr	12.5 − 50 mg/d in divided doses	1 − 1.5 hr	Genotyping required for doses > 50 mg/d	-	-	Huntington's chorea
VBZ	20 hr	40 − 80 mg QD	4 − 10 hr	Consider dose reduction for poor metabolizers	40% (80 mg) 24% (40 mg)	5/15 − 500	TD
DTBZ	8.6 hr	6 − 24 mg BID with food	3 − 4 hr	Maximum dose = 18 mg BID in poor metabolizers	33% (36 mg) 35% (24 mg)	7/34 − 100	Huntington's chorea, TD

TBZ, tetrabenazine; VBZ, valbenazine; DTBZ, deutetrabenazine; QD, once daily; BID, twice daily; TID, Thrice daily; T max, time to maximum concentration; AIMS, Abnormal Involuntary Movement Scale; NNT/NNH, number needed to treat/number needed to harm; TD, tardive dyskinesia.

tension studies continued to show response in reduction of TD 4 weeks after withdrawal from VBZ [79]. VBZ was well-tolerated. Based on pooled data, the only adverse event that reached the incidence threshold of ≥ 5% and twice that of placebo was fatigue/sedation. QTc prolongation was not clinically significant at regular doses, but should be monitored in those with QTc prolongation or arrhythmias. Number needed to harm (NNH) values for adverse events ranged from 15 to 500 [75].

Deutetrabenazine

Deutetrabenazine (DTBZ) is a reversible, selective VMAT2 inhibitor approved for the treatment TD (Table 3) [68,70-72,80]. It differs from TBZ in that deuterium atoms have been substituted for hydrogen atoms in the molecule. Because a carbon-deuterium chemical bond is stronger than a carbon-hydrogen bond, substitution of deuterium results in slower drug metabolism, longer duration of action, less frequent dosing, greater drug exposure, reduced variability in metabolism, reduced drug interactions and adverse effects, and less impact of CYP2D6 activity, eliminating the need for genotyping. DTBZ has lower peak concentrations and less plasma fluctuation without altering VMAT2 inhibition compared to TBZ. Peak plasma concentrations of deuterated α-HTBZ and β-HTBZ are reached within $3-4$ hours after dosing. The half-life of DTBZ is about $9-10$ hours. Deuteration does not appear to cause a significant difference in off-target receptor binding compared with TBZ, however the affinity for other receptors is low.

DTBZ has been tested in 12-week, randomized, placebo-controlled, double-blind trials [81,82]. In the ARM-TD study, DTBZ was associated with a statistically significant reduction in AIMS score versus placebo. In the AIM-TD study, DTBZ showed statistically significant changes in AIMS score compared with placebo. In addition, significantly more patients taking DTBZ were "much improved" or "very much improved" compared with placebo. The proportion of patients showing 50% or more reduction in AIMS score was also significantly greater for DTBZ. Using AIMS reduction as a definition of response, DTBZ resulted in a NNT of 7 [80].

In an open-label extension study, patients continued to have significant improvements in AIMS scores and categorical measures of treatment success [80,83]. DTBZ was well-tolerated, demonstrating reduced rates of depres-

sion, somnolence, and akathisia compared to those seen in TBZ trials [28,71,80]. As DTBZ is also approved for Huntington's chorea, it has a black box warning like TBZ for depression and suicidality, but data from trials in TD did not show an increased risk of suicide [72]. In pooled TD trials, no adverse events were reported in ≥ 5% of patients and twice that of placebo but those occurring in ≥ 2% and more common than placebo were akathisia, depression and diarrhea. DTBZ may prolong the QT interval and should be avoided in patients with QT prolongation and arrhythmias. NNH values for adverse events ranged from 34 to 100 [69].

Additional questions on long-term outcomes of TD with VMAT2 inhibitors in association with combined treatment with antipsychotics remain to be investigated. VMAT2 inhibitors could possibly prevent TD if used adjunctively to allow for lower dosages of dopamine antagonists for the treatment of psychosis, or VMAT2 inhibitors could allow for natural reversal of TD if substituted for antipsychotics in patients who could be safely tapered off the latter [79]. However, it is also possible that dopamine depletion from VMAT2 inhibitors may add to the risk of supersensitivity and TD (similar to denervation) in association with concurrent antipsychotic-induced dopamine receptor blockade [35,84-87]. Also, head-to-head trials are needed to compare outcomes between competing VMAT2 inhibitors, low potency antipsychotics, and alternative treatment strategies.

Glutamatergic Drugs

Rationale

A potential unifying theory that complements the dopamine-receptor supersensitivity hypothesis is based on the concept of maladaptive synaptic plasticity mediated by medium spiny neurons in the striatum [23,24,33,88]. These interneurons play an integral role in coordinating output from direct and indirect pathways to striatal structures, the thalamus and ultimately the motor cortex to ensure adaptive motor behavior. These neurons receive cortical glutamatergic input through N-methyl-D-aspartate-(NMDA)-receptors, which confers the ability to learn sequences of activation to execute complex movements by means of an increase or decrease of synaptic plasticity of neurotransmission based on previous experience.

In this model, TD may result from drug-induced dop-

amine D2-receptor supersensitivity that affects medium spiny neurons in the striatum causing maladaptive NMDA-mediated synaptic plasticity, resulting in an imbalance of the direct and indirect pathway, which in turn, produces abnormal output to the sensorimotor cortex and dyskinesias. A related corollary proposes increases in the sensitivity of indirect pathway medium spiny neurons to excitotoxicity induced by the stimulation of glutamatergic NMDA receptors from cortico-striatal synapses [24,89].

Amantadine

Amantadine is approved for both Parkinson's disease and drug-induced movement disorders [46,90-92]. The exact mechanism of action of amantadine is unclear. Amantadine stimulates the release of dopamine from striatal nerve terminals, may also inhibit its pre-synaptic reuptake, and may increase the number and availability of post-synaptic dopamine receptors although these actions occur at concentrations exceeding those observed in patients [1]. Previous studies demonstrated that amantadine is also a weak, non-competitive NMDA-receptor antagonist [1,93,94], and shows anticholinergic activity as the result of inhibition of NMDA-receptor mediated stimulation of acetylcholine at concentrations roughly 100 times lower than the concentration needed to affect dopamine release suggesting that this activity is more clinically relevant in explaining its antiparkinsonian efficacy [95].

However, mechanisms for proposed beneficial effects of amantadine on TD must be different, as both dopaminergic stimulation and NMDA-mediated inhibition of cholinergic activity through NMDA receptor blockade both predict worsening of dyskinesias. An alternative mechanism is suggested by the glutamate-synaptic plasticity hypothesis, namely that NMDA-receptor blockade by amantadine could interrupt excitotoxicity from cortico-striatal input and reduce maladaptive synaptic plasticity [96].

Early case reports reported mixed results on amantadine as a preventative or treatment of TD [97-99]. Recent reviews of the evidence on antidyskinetic properties of amantadine have shown reductions in levodopa-induced dyskinesias in Parkinson's disease patients [90,91,96], and it has been considered "possibly effective" for TD [27]. A few case series examined the addition of amantadine to an antipsychotic for TD with inconsistent results [26,46].

Two small, short-term, double-blind, placebo-controlled, cross-over trials reported a significant decrease in AIMS scores compared to placebo [100,101]. Although amantadine may be considered for short-term use to treat TD, the evidence base of controlled trials is limited [27]. However, amantadine may have a unique role for patients who have both TD and parkinsonism [88,102]. In such patients, amantadine may be effective for both movement disorders, and is better tolerated than a VMAT2 inhibitor prescribed for TD which may worsen parkinsonism, or an anticholinergic prescribed for parkinsonism which may worsen TD [103]. This approach is strengthened by recent trials of extended-release amantadine for dyskinesias in Parkinson's disease, which found reduced severity of dyskinesias as well as reductions in hypokinetic "off" times [90,91]. Because it acts as an antagonist of central NMDA-mediated cholinergic stimulation, amantadine may also be as effective as anticholinergics and worth testing in treating tardive dystonia but with better tolerability.

Cholinergic Drugs

Rationale

The proposed balance between dopamine and acetylcholine in the striatum has long served as a rationale to use cholinergic agents for TD to counteract a presumed imbalance. Miller and Chouinard proposed that prolonged dopamine receptor blockade results in the loss of dopamine-mediated inhibition of striatal cholinergic interneurons, creating a state of hyperexcitability and eventual cell death or damage which accounts for the dyskinesias of TD [104]. While the results of early trials of non-specific cholinergic agents were discouraging, advances in technology as well as the development of specific cholinergic receptor ligands have highlighted the central role of cholinergic interneurons in basal ganglia function [105]. As a result, the potential role of cholinergic agents in treating TD should receive renewed attention.

Anticholinergics (Antimuscarinics)

In contrast to reversing drug-induced parkinsonism, antimuscarinic drugs have not been effective in reducing TD [106]. In fact, worsening of TD associated with anticholinergic agents was demonstrated while improvement in the severity of TD has been noted in up to 60% of patients who had these agents withdrawn [18,25,27,29],

supporting the conjecture that TD reflects relative acetylcholine deficiency. One exception is tardive dystonia, for which high doses of antimuscarinics may be effective. Caution should be taken in decisions to reduce antimuscarinics if acute drug-induced movements or tardive dystonia are present as these disorders could re-emerge or worsen after withdrawal. Amantadine may be a reasonable alternative to antimuscarinics in patients with both TD and parkinsonism [103].

Acetylcholine precursors

Initial trials of acetylcholine precursors, deanol, choline, and lecithin, in the treatment of TD discouraged work in this area [25,107]. However, these drugs may have failed for several reasons; questions about whether precursors were able to reach cholinergic neuronal targets in pharmacological concentrations; whether they could increase acetylcholine neurotransmission; nonspecific actions on multiple acetylcholine receptor subtypes; and finally, whether or not the targeted cholinergic interneurons were impaired in the ability to synthesize and release acetylcholine [104].

Acetylcholinesterase inhibitors

The notion that impairment of cholinergic interneurons precluded the efficacy of precursors prompted trials of acetylcholinesterase inhibitors, marketed for Alzheimer's disease, to circumvent cell loss. Results with physostigmine, tacrine, donepezil and galantamine were mixed [107,108], leading reviewers to conclude that evidence supporting cholinesterase treatment was insufficient [27,109]. The only small, controlled trial using galantamine showed a trend for efficacy in reducing TD that was reversed after switching to placebo [108]. Moreover, cholinesterase inhibitors, by increasing acetylcholine levels in general may not be sufficiently precise to target specific receptor subtypes which may have markedly different and contradictory actions on acetylcholine transmission and movements.

Muscarinic and nicotinic receptor subtypes

With elaboration of complex neurotransmitter interactions in the basal ganglia and novel agents becoming available to target specific receptor subtypes, future trials may yet confirm selective muscarinic or nicotinic agents that could reduce TD movements [105,110-112]. Given the dense localization of muscarinic receptors (mAChRs) in the striatum, they may constitute a viable target affecting TD [110,113]. Antagonists of two mAChRs, m1 and m4, improve parkinsonism but exacerbate stimulant-induced motor stereotypy, whereas allosteric modulators potentiating m4-receptor activity reduce dyskinesias in preclinical models.

The role of diminished nicotinic receptor (nAChR) function underlying TD is suggested by the fact that D2-receptor blockade may result in reduced binding and loss of nAChRs [105]. Since activation of nAChR normally evokes release of striatal dopamine, nicotinic agonists should acutely worsen TD, but long-term administration leading to nAChR desensitization may reduce dopamine release and potentially suppress dyskinesias [111,114]. In fact, chronic administration of nicotine does indeed attenuate haloperidol-induced vacuous chewing movements in rodent and primate models [115,116]. However, effects of nicotinic drugs on TD in humans is unclear. Varenicline, a partial nicotinic agonist acting at several nAChRs and used for smoking cessation, has been reported to have inconsistent effects on parkinsonism and TD [117].

Gamma-aminobutyric Acid Drugs

Rationale

Gamma-aminobutyric acid (GABA) agents could theoretically improve TD symptoms by reversing decreases in GABA, a major inhibitory component of basal ganglia pathways, resulting from antipsychotic treatment [18,25,27,46]. Based on animal and human studies, this hypothesis suggests that prolonged dopamine D2-receptor blockade in the striatal indirect pathway results in damage to GABAergic medium spiny interneurons which generates dyskinesias [23,24,88].

GABA agonists

A meta-analysis of treatment options for TD found no significant difference between benzodiazepines and placebo in TD [29]. A trial examining clonazepam indicated improvement that was subsequently lost suggesting that tolerance develops. Similarly, treatment with non-benzodiazepine GABA agonists (e.g., baclofen, sodium valproate) showed no significant improvement in TD compared with placebo. Treatment with baclofen and sodium

valproate tended to increase ataxia and sedation, and two patients experienced seizures after anticonvulsant drug withdrawal.

A second meta-analysis examined non-benzodiazepine agents in patients with TD [118]. Patients receiving GABAergic medications were more likely to show deterioration in mental status, fail to complete the study and experience ataxia or sedation. Although some reviewers recommend benzodiazepines as "probably" effective in TD [25,27], the evidence for GABA-ergic drugs in general is of low quality and balanced by sedation, addiction potential and the possibility of a nonspecific and transient anxiolytic effect [118,119].

Other anticonvulsant drugs (levetiracetam, piracetam, zonisamide) acting via GABA-ergic or other mechanisms have been tried in TD with promising results but require replication [27,46]. In a well-conducted 12-week randomized, double-blind, placebo controlled clinical trial (n = 50), levetiracetam reduced severity of TD significantly compared with placebo [120].

Antioxidants

Rationale

Another popular concept reflecting the potentially irreversible nature of TD invokes cell loss and damage resulting from oxidative free radicals generated by reactive overproduction and turnover of dopamine associated with dopamine-receptor blockade. This hypothesis is consistent with the reported association between TD and variants in the gene that encodes manganese super-oxide dismutase, an enzyme that scavenges free radicals, along with imaging studies showing decreases in basal ganglia volumes in antipsychotic treated patients [23,24]. However, prophylactic effects of antioxidants in pre-clinical models have not consistently supported this hypothesis [121].

Nutritional and herbal antioxidants

Trials of several drugs with antioxidant properties have been reviewed with insufficient evidence to support their recommendation (Table 2) [25,27,46]. While antioxidants may have a role when given with antipsychotics early in treatment or in early stages of TD to prevent oxidative cell damage, they have been tested primarily in patients who already have established TD. For example, vi-

tamin B6 (pyridoxal 5'-phosphate) may have some benefits in reducing the severity of TD but the quality of evidence is low and high doses have been associated with neuropathy [46,122]. Positive results in reducing TD were reported in a meta-analysis of 3 randomized, placebo-controlled clinical trials of EGb-761 (Gingko biloba extract) [123]. Melatonin achieved only mixed results in two small controlled studies [27,46]. Convincing evidence from randomized trials suggests that vitamin E (α-tocopherol) does not improve TD in comparison with placebo, although it may prevent worsening of symptoms in mild cases and could have a prophylactic effect in diminishing oxidative damage [124]. Observational studies of the traditional herbal medicines, yi-gan san and kamishoyosan which may have effects on multiple neurotransmitter systems as well as prevent cell damage, reported significant decreases in AIMS scores [18,27,46]. While some studies of antioxidants have shown possible efficacy, the quality of evidence has been low. Moreover, in considering nutritional and herbal remedies, lack of product reliability and market availability of unregulated herbal compounds need to be considered.

Drugs Based on Alternative Mechanisms

Based on other theoretical neurotransmitter or properties, several alternative agents have been tested for antidyskinetic activity [18,25]. Noradrenergic agents have been tried with variable results in mostly open studies and case reports. Propranolol, a β-adrenergic antagonist, resulted in moderate or better response of TD in one retrospective study [125]. Interestingly, since propranolol has shown efficacy in akathisia [126], further studies may be worthwhile in patients with tardive akathisia or in patients with concurrent TD and acute akathisia. An α-adrenergic agonist (clonidine), serotonergic agents (buspirone, serotonin reuptake inhibitors), calcium channel blockers, and branched-chain amino acids have had mixed success and have not been recommended based on insufficient evidence [27,46]. Botulinum neurotoxin acts to weaken muscle by decreasing neuromuscular transmission of acetylcholine, and has been reported to be effective when injected to decrease focal orofacial TD and tardive dystonia [25,46].

CONCLUSIONS AND FUTURE DIRECTIONS

TD is likely to remain important in clinical practice and may even increase in prevalence as antipsychotics are expansively marketed. The ideal goals of future research should be the elimination of TD as a consequence of antipsychotic treatment and the development of interventions to reverse TD once it occurs. Approval of VMAT2 inhibitors offers an effective treatment to reduce the severity and impact of TD. By comparison, past clinical trials of other treatments were most often methodologically limited. Several of these alternative strategies merit a second look in adequately powered trials. It is important to develop treatments targeting patients who do not respond to or cannot tolerate VMAT2 inhibitors and for patients with phenomenological and pharmacological subtypes of TD.

In addition, the VMAT2 inhibitors do not advance our understanding of the pathophysiology underlying the disorder. Emerging research suggests that movement is a result of a complex interplay of multiple neurotransmitters and receptor subtypes orchestrated to shape synaptic plasticity in cortical-thalamic-striatal circuits. While dopamine D2-receptor blockade is the necessary trigger and dopaminergic hyperactivity the inevitable consequence of antipsychotic treatment, the potential irreversibility of TD appears to stem from selective damage to striatal interneurons that may implicate glutamate, acetylcholine, GABA, oxidative or other mechanisms. It follows that there may be multiple therapeutic targets that could be actuated to forestall irreversible changes and maximize prevention and treatment of TD. In view of advances in elucidating basal ganglia functions, further research on interventions targeting non-dopaminergic, and more integrative multi-circuit nodal points may be productive in the future.

■ Conflicts of Interest

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