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REVIEW ARTICLE

Revisiting amantadine as a treatment for drug-induced movement disorders

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BACKGROUND: Amantadine, an aliphatic primary amine with complex actions on neurotransmitter systems in the basal ganglia, is approved for treating Parkinson's disease and drug-induced movement disorders (DIMDs). These disorders have a significant impact on clinical outcomes and quality of life in patients receiving antipsychotic treatment.

METHODS: We searched PubMed up to June 1, 2019 to identify relevant studies. The following search terms were used: "amantadine" AND "dystonia," "parkinsonism, " "akathisia," "tardive dyskinesia," "catatonia," "neuroleptic malignant syndrome." Reference lists were reviewed for additional material.

RESULTS: Evidence from multiple, small, controlled trials supports the efficacy of amantadine as a treatment for drug-induced parkinsonism. Studies show amantadine has a more favorable tolerability profile than anticholinergic medications in these patients. Clinical evidence from observational studies and case reports suggests that further trials might be warranted to support use of amantadine in select patients for preventing dystonic reactions and as a second-line agent for treating catatonia, neuroleptic malignant syndrome, and tardive dyskinesia. Evidence is lacking on the use of amantadine specifically for akathisia relative to other treatments.

CONCLUSIONS: Amantadine is an evidence-based pharmacologic strategy for treating drug-induced parkinsonism and might be an alternative treatment for other DIMDs in select patients. Additional randomized controlled trials are needed.

INTRODUCTION

Amantadine was developed as an antiviral agent for the prophylaxis and treatment of influenza A.[1-4] The mechanism of its antiviral action is not clear, but appears related to transmembrane domain interference of the viral M2 protein via ion channel inhibition, as well as prevention of viral assembly during replication.[1,5] Although amantadine was effective for treating influenza A, increasing viral resistance diminish its potential usefulness in future epidemics.[5]

In 1969, an older woman with Parkinson's disease (PD) taking amantadine hydrochloride (100 mg twice daily) to prevent influenza reported remission of rigidity, tremors, and akinesia.[6,7] A pilot study corroborated the anti-parkinsonian effects of amantadine, which led to additional trials in patients with PD.[6] The positive results in these trials resulted in FDA approval for treating PD and drug-induced extrapyramidal reactions.[1]

Parkinsonism and other drug-induced extrapyramidal reactions (also called drug-induced movement disorders [DIMDs]) continue to present a challenge for antipsychotic therapy. Although the incidence and prevalence of DIMDs has diminished with the development of newer antipsychotics, the risk remains because of increasing drug indications, expansive marketing, and off-label prescribing.[8-12] Symptoms of DIMDs can result in poor treatment adherence or response, reduced symptom remission, longer hospital stays, greater risk of relapse, lower quality of life and functioning, and higher mortality among affected individuals.[13-16]

The recommended first-line treatment for DIMDs involves reassessing the need for and selection of antipsychotic agents depending on treatment history and the patient's susceptibility to neurologic adverse effects. If possible, antipsychotic treatment should be reduced or modified to alleviate DIMD symptoms.[13] For patients who require long-term maintenance treatment with antipsychotics or who do not respond to changes in antipsychotic therapy, several medications have been used to manage DIMDs. However, controlled safety and efficacy studies of these drugs in DIMD treatment remain limited. Adjunctive medications can contribute additional adverse effects, which are particularly problematic for geriatric patients. Furthermore, patients might have concurrent DIMDs in different body areas, such as tardive dyskinesia (TD) and parkinsonism, which could require multiple or contradictory treatments.[16-18]

There is an unmet need for evidence-based, tolerable, effective DIMD pharmacotherapy.[8,19] The purpose of this report is to critically review the history of amantadine, its pharmacology, and the evidence available on its role in treating specific DIMDs.

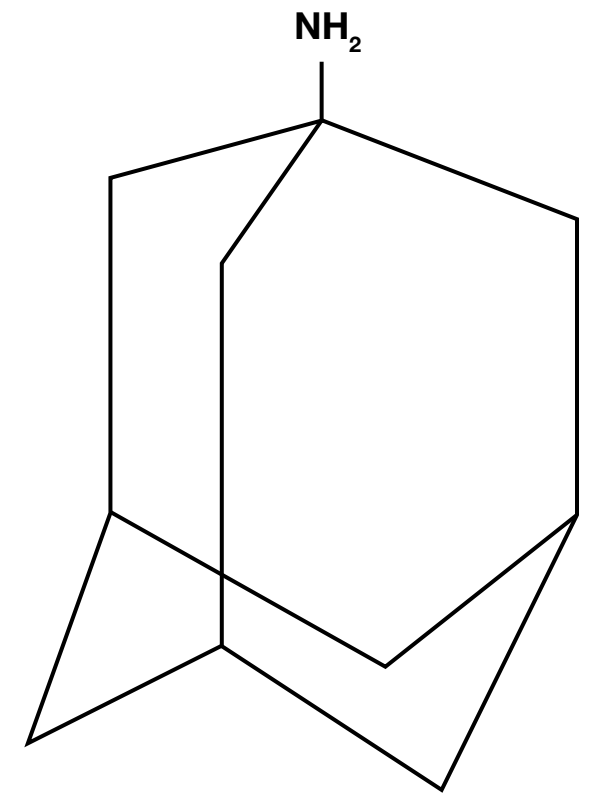
Pharmacology of amantadine

Amantadine (1-adamantanamine hydrochloride) is a synthetic aliphatic primary amine derived from adamantane (**FIGURE**). Amantadine is well-absorbed when administered orally. Plasma concentrations of amantadine are dose-proportional up to 200 mg/d. Dosages >200 mg/d could result in disproportional increases in maximum plasma concentrations, with greater likelihood of central nervous system stimulation (agitation, ataxia, seizures, delirium, and psychosis), and other adverse effects (including constipation, dizziness, dry mouth, headache, nausea, hallucinations, confusion, and falls).[20,21] Amantadine is primarily excreted unchanged in the urine through glomerular filtration and tubular secretion.[1,22,23] The time to maximum concentration for immediate-release (IR) formulations is approximately 3 hours in healthy adults.[24,25] Amantadine clearance is significantly reduced in geriatric patients and those with renal insufficiency.[1,22,23,26] Although traditionally given twice daily, amantadine IR has an average plasma half-life of 13 to 15 hours in healthy volunteers, suggesting that daily dosing might be sufficient.[24,25] Studies of extended-release (ER) formulations report average time to maximum concentration of 9 to 16 hours, and recommend a once-daily dosing schedule.[24,25]

Amantadine's mechanism of action for treating PD and DIMDs is not completely understood.[1] Dopamine signaling plays an important role in the pathophysiology of movement disorders. In vitro binding and single-photon emission computerized tomography studies demonstrate that all antipsychotics bind to dopamine D2 receptors.[27,28] Dopamine D2 receptor blockade by antipsychotic drugs is thought to play a principal role in producing parkinsonism and other DIMDs, possibly by altering the balance between dopamine and acetylcholine signaling in the neostriatum.[29,30] Patients exhibiting DIMDs have a mean striatal D2 receptor occupancy of 77% compared with 62% occupancy in patients who do not exhibit DIMDs.[28]

Amantadine might exert antiparkinsonian effects by pre- and post-synaptic activity that enhances dopamine neurotransmission.[31] In vitro findings suggest that at pre-synaptic sites, amantadine stimulates the release of dopamine from striatal dopaminergic nerve terminals

FIGURE
Chemical structure of amantadine



and also might inhibit pre-synaptic dopamine reuptake. However, this activity occurs in vitro at dosages that significantly exceed those typically prescribed clinically.[29,31,32] Dopaminergic activity could account for the adverse central nervous system toxicity seen with higher doses of amantadine. Some evidence suggests amantadine might also increase the number of post-synaptic dopamine receptors.[31]

Although it is unclear from in vitro studies whether amantadine possesses any direct anticholinergic activity,[32,33] it exhibits anticholinergic-like adverse effects in clinical studies (blurred vision, dry mouth, urinary retention, and constipation).[1,34,35] Some of its anticholinergic activity, at least in the CNS, could be the indirect result of inhibition of *N*-methyl-D-aspartate (NMDA) receptor-mediated acetylcholine stimulation.[29] Previous studies demonstrated that amantadine is a weak, non-competitive NMDA receptor antagonist.[36-38] Amantadine exhibits stronger anticholinergic, rather than dopaminergic, effects at therapeutic dosages. The concentration of amantadine required to inhibit the NMDA-evoked release of acetylcholine from neostriatal tissue is approximately 30 times lower than the concentration needed to affect dopamine release.[29] An early clinical trial demonstrated that plasma levels of amantadine in the 400 to 900 nM range corresponded to reduced DIMDs.[39] These concentrations of amantadine were too low to induce dopamine release, but were able to inhibit the NMDA-induced release of acetylcholine.[29] It is therefore possible the antiparkinsonian effect of amantadine depends more on its ability to inhibit NMDA-receptor stimulation of cholinergic neurons than on inducing dopamine release.

Conversely, mechanisms for proposed beneficial effects of amantadine on tardive DIMDs must be different, because dopaminergic stimulation or cholinergic inhibition are associated with worsening TD.[40] However, an alternative hypothesis of TD based on maladaptive synaptic plasticity proposes that drug-induced dopamine-receptor supersensitivity affects medium spiny neurons in the striatum, with secondary effects on NMDA receptor-mediated synaptic plasticity. The resulting imbalance of the direct and indirect pathways produces abnormal output to the sensorimotor cortex, resulting in dyskinesias.[41] According to this hypothesis, low-affinity NMDA antagonists, such as amantadine, might inhibit development of and reverse dyskinesias, thereby suggesting a role for amantadine in treating TD.[42]

Treatment of DIMDs with amantadine

Acute dystonia. Dystonias are a group of movement disorders characterized by briefly sustained, intermittent, or prolonged spasms or contractions resulting in involuntary twisting, and repetitive movements or postures.[43-45] Drug-induced dystonia is an acute movement disorder that can be painful and distressing, and can negatively impact medication adherence.[8,46] Dystonia typically is observed within a few hours of antipsychotic exposure, especially via parenteral administration, and appears within the first 5 days of treatment in 95% of cases.[8,43,47] Drug-induced dystonia can affect any muscle group, but usually is focal and restricted to 1 or a few muscle groups. Common areas affected are the head, jaw, mouth, eyes, and neck.[47]

The overall incidence of dystonia is estimated to be 2% to 5% with use of first-generation antipsychotics (FGAs). However, up to 90% of young men on parenteral, high-potency antipsychotics could be affected; dystonia is

less common in patients age >45.[8] Drug potency, dosage, and titration rate correlate with dystonia risk. This risk is reduced with second-generation antipsychotics (SGAs), and antipsychotics with weak dopamine antagonism and prominent anticholinergic effects.[48]

Dystonic reactions can last from a few seconds to several hours and might be sustained, episodic, or fluctuating. The movements can be alarming and could be life threatening if pharyngeal or laryngeal dystonia compromises breathing. Rapid parenteral administration of antihistamines, anticholinergics, or benzodiazepines is indicated to treat acute dystonia. These drugs are highly effective, and usually begin to alleviate symptoms within 10 to 20 minutes.[8,49] Oral administration of these drugs might be sufficient in less acute cases. If the antipsychotic is discontinued, oral anticholinergics are continued for 24 to 48 hours after dystonia suppression. If the antipsychotic is not stopped, oral anticholinergics are continued for several days after dystonia suppression and are gradually tapered to prevent recurrence.[19]

The use of anticholinergics for acute dystonic reaction prophylaxis is controversial.[8,45] Preventing dystonia outweighs potential adverse effects in high-risk populations, including patients who are young, paranoid, ambivalent about treatment, receiving parenteral antipsychotics, or receiving high-potency antipsychotics. However, prophylactic anticholinergics can cause adverse events, which are of particular concern in geriatric patients. Prophylactic anticholinergics commonly cause serious atropinic adverse effects (blurred vision, dry mouth, constipation, cognitive impairment, or memory loss), and could precipitate urinary retention or acute narrow-angle glaucoma.[50] The risk of acute dystonic reactions can be mitigated by the use of less-potent SGAs or by concomitant administration of anticholinergics given prophylactically with FGAs.[51]

Amantadine has not been tested for dystonia treatment in controlled trials, but a study of 37 participants reported that 6 individuals with oculogyric crises reported relief after oral administration of 100 mg of amantadine in liquid form.[52] However, amantadine is of limited value in emergency situations because of the lack of a parenteral preparation in the United States.

Although amantadine might not be practical as a rescue drug for acute dystonia, its use as a prophylactic agent might have overlooked advantages in certain high-risk patients (eg, young males treated with high-potency parenteral antipsychotics or those with recent or prior dystonic reactions) by avoiding unnecessary peripheral atropinic adverse effects seen with anticholinergic treatment.[47]

Parkinsonism. Drug-induced parkinsonism is characterized by bradykinesia, rigidity, and tremor. It is a subacute syndrome that mimics idiopathic PD; the 2 conditions can be clinically indistinguishable.[53] Although less acute than dystonia, parkinsonism is more common, more difficult to treat, and may cause significant disability. Although parkinsonism could appear relatively early after initiating treatment with antipsychotics, onset could be delayed from days to weeks. Most cases (50% to 75%) occur within 1 month, and 90% occur within 3 months.[8,16,43]

Parkinsonism occurs in 13% to 46% of patients receiving antipsychotics. Reported rates of parkinsonism vary depending on age, duration of follow-up, sensitivity of diagnosis, and potency of antipsychotics used in the populations studied.[16,54-56] Drug-induced parkinsonism is the second most common cause of parkinsonism after PD itself.[8] Although parkinsonism is correlated with increased antipsychotic dosage and potency, dose-response relationships have been unclear in view of differences in individual susceptibility. While SGAs have reduced liability for parkinsonism compared with high-potency FGAs, even SGAs could cause significant parkinsonism, especially in susceptible individuals (eg, those with underlying PD or Lewy body dementia), with the exception of clozapine and possibly quetiapine.[57,58] Additionally, even if the risk of parkinsonism is lower with selected SGAs, their widespread use for both on- and off-label indications results in a significant overall burden of SGA-associated parkinsonism. Because of the often gradual or subacute onset of parkinsonism, patients should be monitored closely. Upon detection of parkinsonism, consider antipsychotic discontinuation, dosage reduction, or switching to lower-risk antipsychotics. Clinicians should weigh these adjustments against the risk of psychotic relapse. Symptoms of parkinsonism usually are reversible after discontinuing antipsychotics, but in approximately 15% to 25% of cases, symptoms could reflect underlying PD unmasked by antipsychotic treatment and might persist.[8,55,59] Prophylaxis with anticholinergic drugs to prevent parkinsonism is even less compelling than for dystonia, introducing significant risk of anticholinergic toxicity with questionable benefit.

If a given antipsychotic cannot be changed in a patient with parkinsonism, treatment with anticholinergics might be effective. However, there is surprisingly limited controlled evidence for anticholinergic use.[60,61] A survey of the prevalence of parkinsonism among patients

with schizophrenia found a correlation between parkinsonism and anticholinergic treatment and concluded that anticholinergics might not be effective. However, it is more likely that these findings simply represent a prescribing bias of attempts to treat extant parkinsonism.[54] Once patients are successfully maintained on adjunctive anticholinergic therapy for 3 to 6 months, cautious tapering can be attempted.[43] However, several studies show that 62% to 96% of patients on maintenance antipsychotics could still experience parkinsonism after anticholinergic drug discontinuation.[62]

Evidence for dopamine replacement therapy (eg, levodopa) to treat drug-induced parkinsonism has been inconsistent. Dopaminergic agents are believed to be ineffective because of ongoing drug-induced blockade of dopamine receptors, and also could raise the risk of worsening psychotic symptoms.[53,63]

Therefore, amantadine could offer an alternative for patients at high risk of developing parkinsonism. Because of amantadine's efficacy in PD, the drug was tested as a treatment for drug-induced parkinsonism.[7] Initial reports from open-label studies with amantadine showed promising effects with a favorable safety profile.[64-66]

An early, small, double-blind crossover study found no difference in antiparkinsonian efficacy between amantadine and benztropine.[67] Another double-blind crossover trial of amantadine vs benztropine in 37 patients with DIMDs found that although both drugs were effective, amantadine showed a more rapid onset of action and fewer adverse effects.[52] In another early, randomized, double-blind trial involving 41 patients, amantadine and benztropine were equally effective in reducing parkinsonism, but differed in anticholinergic adverse effects.[68] A randomized, controlled, double-blind crossover trial of amantadine in 39 psychiatric inpatients treated with amantadine vs trihexyphenidyl found that both drugs were equally effective in achieving improvement of approximately 50% in parkinsonian symptoms while amantadine produced fewer and less severe adverse effects.[69] A randomized, double-blind trial comparing amantadine with benztropine in 44 patients with schizophrenia concluded that amantadine appeared equally effective and as rapid-acting as benztropine.[70] Although benztropine had a slight advantage in reducing rigidity, it produced more atropinic adverse effects. This led the authors to recommend amantadine in patients for whom anticholinergic effects might be contraindicated. Another randomized controlled trial of 55 inpatients with schizophrenia reported that amantadine was equally effective as benztropine.[71] Similarly, a 2-week, double-blind trial of 42 patients with schizophrenia reported significant and equivalent improvement in ratings of parkinsonism between amantadine and biperiden.[72]

A 26-day placebo-controlled crossover trial of the relationship between clinical response and plasma levels of amantadine in 15 psychiatric patients with parkinsonism not well controlled on anticholinergic drugs found significant improvement in parkinsonism with amantadine.[39] Another randomized, double-blind, placebo-controlled, 2-week crossover trial of amantadine compared with biperiden found that both drugs were more effective than placebo in relieving parkinsonism without worsening TD.[73] In contrast, a double-blind trial of 43 inpatients with schizophrenia reported neither amantadine nor orphenadrine was better than placebo in alleviating parkinsonism symptoms.[74] It should be noted that these findings are difficult to interpret because of the complexity of the multiple drug crossovers employed in the trial. Another randomized trial of amantadine vs benztropine found that among 22 patients with DIMDs previously maintained on anticholinergics, one-half of amantadine-treated patients could not complete the trial because of distressing movements and psychotic symptoms.[75]

Although these trials of amantadine for drug-induced parkinsonism are limited by small samples, variable outcome measures, different rating instruments, carryover effects inherent in crossover designs, absence of placebo controls, and short-term durations, the evidence is mostly consistent that amantadine is as effective as anticholinergics and might have a more favorable adverse effect profile. These cumulative findings suggest that amantadine could be considered a first-line agent in patients with drug-induced parkinsonism who are at risk for developing anticholinergic adverse effects. This is a special concern when anticholinergics are used with other psychotropic drugs that have anticholinergic properties (eg, quetiapine, paroxetine).

It is unclear whether amantadine affects peripheral muscarinic receptors, which are largely responsible for many of the toxic effects of anticholinergic drugs. Many of the trials comparing amantadine to anticholinergics focused on patients with schizophrenia. It might be that anticholinergic adverse effects are even less well tolerated among higher-functioning patients, or patients with mood disorders. Geriatric patients are at particular risk both for parkinsonism and confusion or delirium from anticholinergics.[76] Consistent with our understanding of

NMDA-mediated central anticholinergic effects, clinical experience suggests that amantadine might also adversely affect cognition in geriatric patients. However, earlier studies suggested an advantage with amantadine compared with specific anticholinergic agents. Therefore, the impact of amantadine on cognition in geriatric patients requires further study.[76,77] Finally, anticholinergics can directly worsen existing choreiform or stereotyped forms of TD.[78,79] Considering that a not insignificant percentage of patients with parkinsonism also might have TD,[80] amantadine could be a useful alternative to mitigate adverse effects on concurrent TD.

Akathisia. Akathisia is distinctive among DIMDs because it is defined as much by subjective features (irritability, anxiety, inner tension, or discomfort) as by objective findings. Signs of akathisia include pacing, persistent fidgeting, or repeatedly crossing and uncrossing the legs. Misdiagnosis of akathisia as anxiety or agitation can result in symptom exacerbation if the clinician increases the antipsychotic dosage.[81-83] Although symptom severity varies with stress and arousal, it can become intolerable. Symptoms also have been associated with violence and suicide.[8,84] Akathisia might begin within days, but prevalence increases with duration of treatment. It occurs within 1 month in up to 50% of cases, and within 3 months in 90% of cases.[8,43] A tardive form of akathisia also might arise after antipsychotic discontinuation or dosage decrease.[81]

Depending on the population susceptibility, sensitivity of diagnosis, and the potency of drug treatment, 15% to 35% of patients on antipsychotics could develop akathisia, and akathisia often co-exists with parkinsonism.[81,85] Akathisia occurs with SGAs, but is more likely with high-potency drugs[84,86,87] and can be induced by non-antipsychotic drugs, including antiemetics, selective serotonin reuptake inhibitors, preoperative sedatives, and calcium channel blockers.[87] Understanding the pathophysiology of akathisia is difficult because of these disparate causes. A proposed mechanism of induction involves an overstimulation of the locus coeruleus. Another theory suggests akathisia is caused by dysregulation of the dopaminergic/cholinergic and dopaminergic/serotonergic systems.[87]

There are no data on akathisia prophylaxis, and there is no compelling evidence for a definitive treatment. Because of its subacute onset, the best preventative measure is close observation for early signs. Once akathisia is detected, clinicians should consider reducing antipsychotic dosage, discontinuing antipsychotic treatment, or switching to a less potent dopamine antagonist, although these options all incur the risk of psychotic exacerbation or relapse.[81] In some reports, lipophilic beta-adrenergic blockers such as propranolol were effective, but were limited by hypotension, bradycardia, and medical contraindications. Anticholinergics traditionally have been used, but evidence of their efficacy is mixed. In a meta-analysis to support or refute the use of anticholinergics in akathisia, there were no randomized clinical trials that met rigorous inclusion criteria.[88] It also has been suggested that anticholinergics might be more effective for akathisia in the presence of concomitant parkinsonism, but this is untested.[31,89] Benzodiazepines have been useful because of their anxiolytic and sedative properties.[90] Recently, serotonin (5-HT2A) receptor antagonists have attracted interest in treating akathisia, with mirtazapine showing equal efficacy and better tolerability compared with propranolol.[91] The clinician should evaluate the patient's comorbidities to guide treatment decisions.[81]

Several early trials of amantadine as treatment for DIMDs included outcomes among patients with akathisia. A trial of amantadine in 4 patients with akathisia reported encouraging results.[65] A controlled crossover trial of amantadine vs benztropine found that amantadine reduced symptoms of akathisia, but results were comparable to patients receiving benztropine.[52] Another randomized controlled trial of amantadine vs benztropine reported reductions in akathisia scores, but could not compare amantadine with benztropine because of the small number of patients with akathisia in the study.[68] A controlled, parallel, double-blind trial reported significant improvement in akathisia among 24 patients receiving amantadine or benztropine.[70] Another controlled trial reported that amantadine proved superior to benztropine for alleviating akathisia.[71] A different trial reported improvement in akathisia with amantadine but diminished after 1 week of treatment.[92] These few trials provide limited support for placing amantadine in a treatment paradigm for akathisia, a condition for which first-line treatment remains uncertain. Amantadine might be worth exploring as an alternative treatment for akathisia only if more conventional approaches (antipsychotic modification, serotonin antagonists, beta-adrenergic blockers, anticholinergics) have failed.[31]

Tardive dyskinesia. In contrast with acute DIMDs, TD is delayed after initiation of antipsychotic treatment, and often is masked by ongoing treatment with dopamine receptor blocking agents. The onset of TD often occurs within weeks or months of treatment initiation. Tardive

dyskinesia most often affects the face and mouth, manifesting as classic orobuccolingual dyskinesia, although it also affects the trunk and limbs.[8] Tardive dyskinesia typically describes hyperkinetic movements that are involuntary, purposeless, heterogeneous, non-rhythmic and repetitive, appearing stereotyped and/or choreiform. However, other tardive syndromes are dominated by tics, dystonia, or akathisia. Although usually mild in amplitude or frequency, TD can compromise eating, speaking, breathing, or ambulation. Tardive dyskinesia also can become socially disfiguring. Symptoms of TD might transiently worsen after antipsychotic discontinuation, and appear to be irreversible in most patients if antipsychotics are continued.[19,93]

Studies have shown a cumulative TD incidence of approximately 4% to 5% annually, and a prevalence rate of 20% to 43%.[9,94,95] Recent studies confirmed that the relative risk of TD with FGAs is significantly higher than with SGAs.[9]

Clinicians are encouraged to routinely monitor patients receiving antipsychotic therapy for incipient signs of TD.[96] Once TD is noted, patients and caregivers should collaborate on decisions of antipsychotic dosage modification and anticholinergic prescribing. Prompt diagnosis and antipsychotic cessation in patients who can be safely tapered off treatment may allow for resolution of early or withdrawal TD. If TD remains persistent and bothersome, consider specific anti-dyskinetic agents. A broad spectrum of drugs has been tested for TD treatment, but controlled evidence has been uninformative because of methodological limitations.[97] However, recent controlled trials of novel vesicular monoamine transporter-2 inhibitors (valbenazine, deutetrabenazine) have shown promising efficacy.[98,99] These agents have now become the first-line, FDA-approved treatments for TD.[100,101]

In early, open-label case series, amantadine treatment resulted in significant decreases in dyskinetic movements.[64,102,103] However, other clinical reports found no effect on TD with amantadine.[104-107] Interestingly, an animal study reported that amantadine prevented dopamine receptor supersensitivity, which led them to propose that the agent might have a prophylactic effect in preventing TD when given concurrently with antipsychotics.[108] Other studies support this finding, which contrasts with the finding that anticholinergics might augment supersensitivity.[42,109,110] Clinical trials of amantadine to prevent TD have not been reported.

Although 2 randomized, double-blind, controlled trials of DIMDs reported that amantadine had a significant effect in suppressing existing dyskinetic movements, anticholinergic drugs had an equivalent effect, raising questions about the phenomenology of movements in these studies.[70,73] More recently, amantadine was tested in an 18-week, randomized, double-blind, placebo-controlled trial of 16 patients receiving antipsychotics with symptoms of TD.[111] Overall, the mean improvement was 15% with amantadine, which was significantly greater than placebo.[111] The only adverse effects were drowsiness and fatigue, which occurred with significantly higher frequency in patients receiving amantadine than placebo.[111] Another double-blind, placebo-controlled, crossover study examined the effects of 2 weeks of amantadine on TD in 22 patients.[112] The study found the mean symptom scores decreased 21.8% in patients receiving amantadine compared with no reduction seen in patients receiving placebo.[112] Only minor adverse effects were reported.[112]

Based on this limited evidence and recent consensus guidelines, amantadine might be considered as effective for short-term use to treat TD.[97] A potentially unique niche for amantadine might apply to patients experiencing concurrent parkinsonism and TD.[16] Tardive dyskinesia and parkinsonism could coexist in ≥13% of patients.[80] There is no treatment strategy to address TD and parkinsonism concurrently (eg, anticholinergic treatment of parkinsonism could worsen TD while dopamine-depleting agents effective in suppressing TD could excerbate parkinsonism).[80] Recent trials of ER amantadine in levodopa-induced dyskinesias in PD found that amantadine treatment results in reduction of both parkinsonian "off-time" and dyskinesias.[113] By extrapolation, amantadine could have positive effects in patients with both drug-induced parkinsonism and TD.[16] Considering recent interest in potential antidepressant properties of NMDA-receptor antagonists, amantadine could be useful for patients with TD who do not respond to vesicular monamine transporter-2 inhibitors, or who present with risks for comorbid depression or suicidality.[114] However, further clinical studies in these patient populations are needed.

Catatonia. Although symptoms of catatonia extend beyond movement disorders to include disorders of consciousness and volition, catatonia has been associated with antipsychotics. Drug-induced catatonia often presents as rigidity, akinesia, mutism (akinetic mutism), and stupor. It can be associated with waxy flexibility and catalepsy, but these occur less frequently.[8,115-117] Drug-induced catatonia develops within hours to days of antipsychotic treatment initiation, and should resolve in a similar period of time after drug discontinuation.

Catatonia onset with antipsychotics can occur after discontinuing concomitant benzodiazepines or antiparkinsonian agents, including amantadine.[8] Although signs of idiopathic catatonia could occur in up to 18% of psychiatric inpatients,[118] only 6 cases of "catatonic neuroleptic syndrome" were attributed to antipsychotics among 86,439 patients in a retrospective drug surveillance program.[119] Catatonia primarily is associated with high-potency drugs, but SGAs are not without risk.[119] Published case reports document the occurrence and worsening of catatonia with SGAs, including precipitation of malignant catatonia[120] or neuroleptic malignant syndrome (NMS).[57,121] However, SGAs also have been proposed as treatments for catatonia.[122,123]

There are no data on whether prophylaxis with benzodiazepines or other agents could prevent catatonia. A more conservative approach would be to limit antipsychotic use in patients with catatonia, and to treat pre-existing catatonia with benzodiazepines or electroconvulsive therapy (ECT).[8] Catatonia can occur in schizophrenia or mood disorders, independent of antipsychotic treatment. This results in the "catatonic dilemma," in which it might be difficult to distinguish primary catatonia from the effect of drug treatment.[124] This dilemma could be resolved by discontinuing the antipsychotic medication, which leads to resolution of catatonia in drug-related cases. There have been no controlled studies of treatment of drug-induced catatonia. Treatment should include reconsidering the offending antipsychotic agent to prevent medical complications, including NMS. Although most patients with catatonia of all causes respond to benzodiazepines or ECT, some patients have a partial response, non-response, or might not be candidates because of comorbid medical conditions.[125] A systematic review of alternative treatments for catatonia, including use of amantadine in 18 cases, reported that amantadine monotherapy often led to resolution after a few doses.[125,126] Another study concluded that NMDA antagonists were effective, even in cases of catatonia that were secondary to medical conditions.[127] Animal studies of drug-induced catatonia have reported the reversal of antipsychotic-induced catalepsy by NMDA antagonists in rats.[128] A study of 8 patients reported that drug-induced catatonia that occurred with parkinsonism responded to amantadine (200 to 300 mg/d) but not to benztropine (up to 6 mg/d).[115]

Neuroleptic malignant syndrome is a rare but potentially lethal form of DIMD. Neuroleptic malignant syndrome combines features of advanced parkinsonism and catatonia.[129] Classic signs of NMS are generalized muscle rigidity with tremors, altered consciousness, hyperthermia, and autonomic instability.[130,131] Neuroleptic malignant syndrome could develop within hours of antipsychotic initiation, but usually evolves over days. Approximately 66.6% of NMS cases occur during the first 1 to 2 weeks after drug initiation.[8]

Although only approximately 0.02% of patients treated with antipsychotics will experience NMS, it has the potential to be a lethal crisis.[8] Neuroleptic malignant syndrome is more likely to occur with use of high-potency agents, but it has been observed with all antipsychotic drugs. Approximately 50% of all reported cases are associated with haloperidol.[8] Case reports have described NMS after SGA treatment, but large-scale surveys suggest a reduced NMS risk for SGAs compared with FGAs.[119,132]

Neuroleptic malignant syndrome management relies on early diagnosis, dopamine antagonist discontinuation, and supportive medical care. Approximately 63% of NMS cases resolve within 1 to 2 weeks of discontinuating dopamine-blocking drugs, with an average NMS duration of 7 to 10 days.[131] The use of dopamine agonists, dantrolene, benzodiazepines, and ECT have been advocated. However, controlled trials comparing these agents are not feasible because NMS is rare, heterogeneous, and often self-limited after drug discontinuation.[8]

In a review of case reports of NMS, Weller and Kornhuber[133] summarized "good" responses with amantadine in 11 cases, questionable responses in 2 cases, and treatment failures in 5 cases. A comprehensive meta-analysis of published NMS treatment outcomes found that amantadine was judged to be effective by treating clinicians in 16 of 30 cases (53%). Amantadine monotherapy was effective in 12 of 19 cases (63%). The mortality rate among amantadine-treated cases (3%) was significantly lower compared with controls who received supportive care alone (21%). When amantadine was prematurely discontinued, 6 (35%) of 17 patients experienced a recurrence of NMS symptoms.[134] In another clinical report, the risk of catatonia or NMS emerging after amantadine withdrawal was highlighted in 3 cases.[135] It is worth emphasizing that anticholinergics are ineffective for NMS and could contribute to hyperthermia by blocking peripheral muscarinic receptors that enable sweating, whereas amantadine might be effective in NMS without compromising heat-loss mechanisms.[131]

TABLE
Summary: Amantadine in drug-induced movement disorders

DIMD	Role of amantadine in treatment
Acute dystonia	Possible role as second-line prophylactic agent
Parkinsonism	Similar efficacy to anticholinergics Reduced risk of adverse effects compared with anticholinergics
Akathisia	Insufficient evidence for efficacy
Catatonia	Possibly effective
Neuroleptic malignant syndrome	Possibly effective
Tardive dyskinesia	Possibly effective

DIMD: drug-induced movement disorder.

CONCLUSIONS

Long-term treatment with antipsychotics can be highly effective for patients with chronic or relapsing psychotic disorders. Patients with mood disorders or other episodic conditions increasingly are prescribed antipsychotics during acute episodes. These patients sometimes unnecessarily remain on antipsychotic therapy for extended periods. Prolonged exposure to antipsychotics increases the probability of ≥1 DIMDs, which remain a significant concern in clinical practice. This is particularly true of susceptible populations such as geriatric patients and those receiving high-potency antipsychotics.

Amantadine has a long history of clinical use. Multiple, small, controlled trials show it has similar efficacy to anticholinergics in reducing drug-induced parkinsonism with fewer atropinic adverse effects (**TABLE**). Anecdotal evidence suggests it might have a role as a second-line agent in preventing acute dystonia and in treating catatonia and NMS. Akathisia remains challenging to treat and evidence is too limited to consider amantadine for this disorder. Considering its possible ability to suppress movements of both TD and levodopa-induced dyskinesias while limiting parkinsonism and depression, amantadine might have an advantage in selected cases of TD. More rigorous controlled trials of amantadine in clinical practice are warranted. ■

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