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CURRENT OPINION

An Evidence-Based Update on Anticholinergic Use for Drug-Induced Movement Disorders

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Abstract

Drug-induced movement disorders (DIMDs) are associated with use of dopamine receptor blocking agents (DRBAs), including antipsychotics. The most common forms are drug-induced parkinsonism (DIP), dystonia, akathisia, and tardive dyskinesia (TD). Although rare, neuroleptic malignant syndrome (NMS) is a potentially life-threatening consequence of DRBA exposure. Recommendations for anticholinergic use in patients with DIMDs were developed on the basis of a roundtable discussion with healthcare professionals with extensive expertise in DIMD management, along with a comprehensive literature review. The roundtable agreed that "extrapyramidal symptoms" is a non-specific term that encompasses a range of abnormal movements. As such, it contributes to a misconception that all DIMDs can be treated in the same way, potentially leading to the misuse and overprescribing of anticholinergics. DIMDs are neurobiologically and clinically distinct, with different treatment paradigms and varying levels of evidence for anticholinergic use. Whereas evidence indicates anticholinergics can be effective for DIP and dystonia, they are not recommended for TD, akathisia, or NMS; nor are they supported for preventing DIMDs except in individuals at high risk for acute dystonia. Anticholinergics may induce serious peripheral adverse effects (e.g., urinary retention) and central effects (e.g., impaired cognition), all of which can be highly concerning especially in older adults. Appropriate use of anticholinergics therefore requires careful consideration of the evidence for efficacy (e.g., supportive for DIP but not TD) and the risks for serious adverse events. If used, anticholinergic medications should be prescribed at the lowest effective dose and for limited periods of time. When discontinued, they should be tapered gradually.

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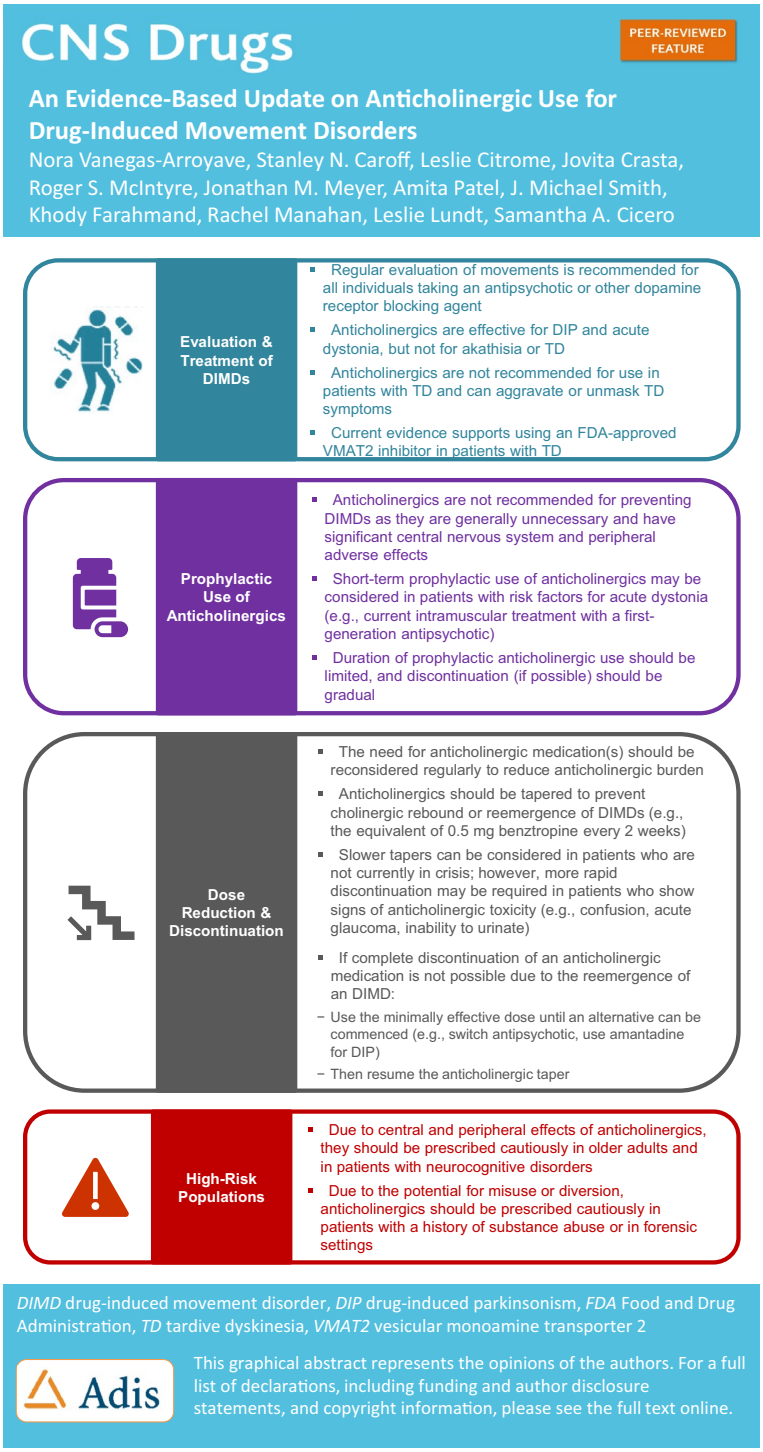
Graphical Abstract



Key Points

Anticholinergic medications can be effective in treating drug-induced parkinsonism and dystonia, but they are not recommended for the treatment of tardive dyskinesia, akathisia, or neuroleptic malignant syndrome.

Appropriate use of anticholinergics requires careful consideration of effectiveness and risk of side effects, especially in older adults and other vulnerable populations, and should be prescribed at the lowest effective dose.

When discontinuing use of anticholinergics, they should be tapered gradually.

1 Introduction

Antipsychotic medications have achieved widespread utilization on the basis of a robust body of evidence for the treatment of psychiatric conditions, and use of these medications is on the rise. In the USA, antipsychotic prescriptions in noninstitutionalized individuals increased from 2.2 million in 1997 to 6.1 million in 2018 [1, 2]. Moreover, in North America, antipsychotic polypharmacy for schizophrenia increased from the 1980s to the 2000s, reflecting an uptick in the combined use of second-generation antipsychotics (SGAs) with first-generation antipsychotics (FGAs) [3]. Contributing to the expanding use of antipsychotics are the on-label uses for approved indications such as bipolar disorder, major depressive disorder, and agitation associated with dementia due to Alzheimer's disease, along with the off-label uses for unapproved indications such as dementia-related psychosis and personality disorders [4–6].

Although antipsychotics are highly effective for many conditions and have positive impacts on patients' lives, they can have significant side effects. Moreover, greater antipsychotic exposure due to higher cumulative doses and polypharmacy can increase these risks [7]. Drug-induced movement disorders (DIMDs) are among the more debilitating adverse consequences associated with antipsychotics and other dopamine receptor blocking agents (DRBAs), including certain agents used for gastrointestinal disorders such as metoclopramide. The DIMDs described in this review are all associated with exposure to DRBAs, including currently available FGAs and SGAs. As new antipsychotic therapies emerge, including those that target muscarinic receptors, the potential efficacy and safety of emerging antipsychotic therapies will also need to be considered [8].

DIMDs are classically categorized by phenomenology, with different times to onset and varying responses to DRBA discontinuation and treatment. Accurate diagnosis is therefore imperative to achieve optimal clinical outcomes [9]. Anticholinergic medications have been shown to be effective for treating drug-induced parkinsonism (DIP) and acute dystonic reactions, but not for treating tardive dyskinesia (TD), akathisia, or neuroleptic malignant syndrome (NMS). Anticholinergics are also not generally recommended for the prophylaxis of DIMDs except in certain clinical situations (e.g., when combined with an intramuscular FGA in patients with a history of DIMDs). Misuse and over-prescription of anticholinergics, especially in older adults and patients taking multiple medications with anticholinergic properties (Fig. 1), contribute to high anticholinergic burden and even higher risks of cognitive dysfunction and peripheral adverse effects.

Appropriate use of anticholinergics in patients with DIMDs requires careful consideration of several important factors: the evidence for efficacy; the potential for various peripheral and central adverse events that may impact tolerability of each anticholinergic medication, especially with long-term use in at-risk populations; and the cumulative adverse effects (i.e., anticholinergic burden) that may occur in patients taking multiple medications with anticholinergic properties. The need for continued education on these topics was recently illustrated in a real-world study that found inappropriate and potentially harmful use on the basis of a survey of 315 healthcare professionals (HCPs) and a pharmacy claims analysis of 738,207 patients with benztropine prescriptions [10]. In the survey, 159 (50.5%) HCPs reported using benztropine to treat TD and 153 (48.6%) reported using this medication in adults ≥ 65 years of age. In the claims analysis, 55.7% of patients took benztropine for > 3 months and 59.1% were taking > 10 medications—many of which were associated with moderate or high anticholinergic burden, as determined using the ACB calculator (https://www.acbcalc.com) [10].

To raise awareness about these issues and review the evidence of how and when anticholinergics should be used, a roundtable discussion with psychiatrists, neurologists, nurse practitioners, and physician assistants was conducted in June 2021. All roundtable participants had vast expertise in the management of DIMDs, and topics of discussion included the following: pharmacology of anticholinergic drugs and rationale for their use in DIMDs; adverse effects of anticholinergic medications; differentiation and appropriate treatment of DIMDs; prophylactic use of anticholinergics; discontinuation and tapering of anticholinergic medications; and treatment considerations for high-risk populations. This report summarizes key points from the roundtable discussion, supplemented by a literature review.

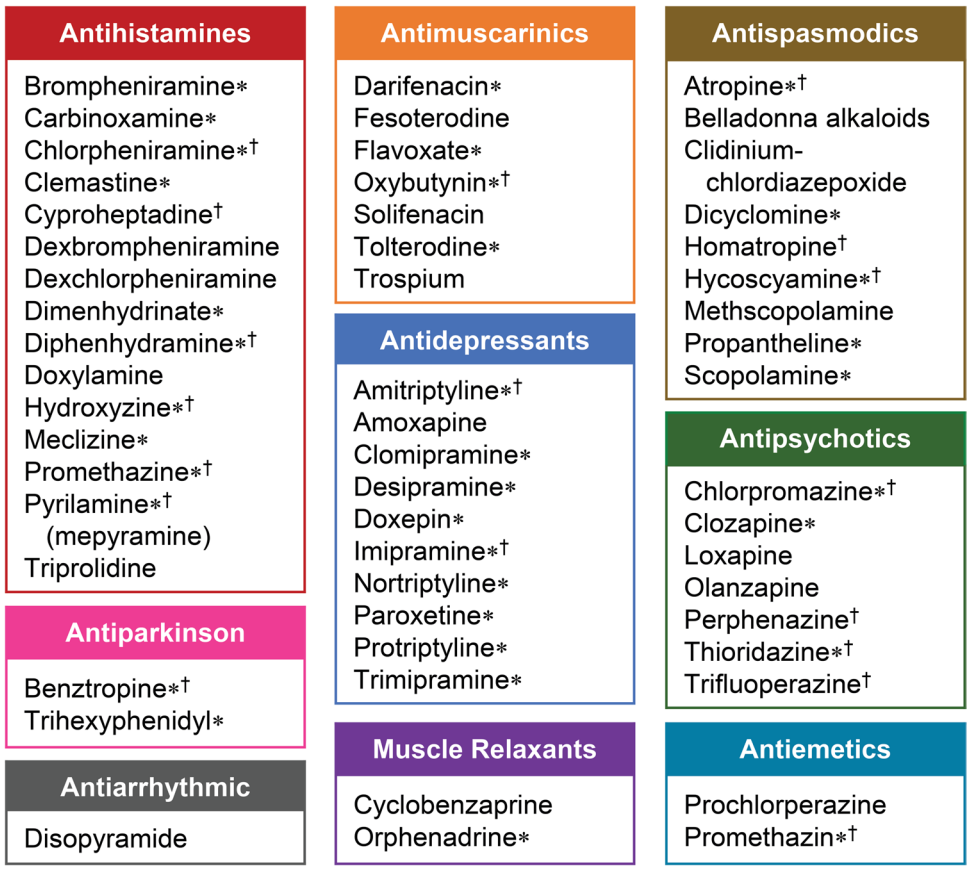


Fig. 1 Selected common medications with strong anticholinergic properties, based on American Geriatric Society Beers® criteria [110]. Medications that have a level 3 rating on the Anticholinergic Drug Scale (*) or a 3-point score on the Anticholinergic Risk Scale (†) are also noted [88, 89]

2 Pharmacology

2.1 Mechanism of Action of Anticholinergic Medications

Broadly speaking, anticholinergics block acetylcholine from binding to its receptors in the peripheral and central nervous systems. There are two major classes of acetylcholine receptors: G protein-coupled muscarinic receptors and ionotropic ligand-gated nicotinic receptors [11]. Muscarinic receptors comprise five subtypes (M_1 through M_5) that are associated with a wide range of functions, including cognition, smooth muscle contraction, sweating, and motor control, with M_1 and M_4 receptors implicated in disorders such as schizophrenia [12]. Nicotinic receptors are composed of various subunits (α1–α10, β1–β4, γ, δ, ε), with α7 and α4β2 receptors implicated in disorders such as schizophrenia, depression, Parkinson's disease, and Alzheimer's disease [13]. The centrally acting anticholinergic medications approved for all forms of parkinsonism (e.g., benztropine and trihexyphenidyl [11]) are nonselective muscarinic receptor antagonists, with the primary target being M_1 receptors present on medium spiny neurons (MSNs) in the striatum and nearby cholinergic interneurons (CINs). Blocking acetylcholine M_1 receptors restores the imbalance between dopamine and acetylcholine signaling on MSNs caused by insufficient dopaminergic signaling resulting from dopamine D_2 receptor blockade by antipsychotics and other DRBAs [14].

2.2 Interactions Between Dopamine and Acetylcholine in Motor Circuitry

The nigrostriatal dopamine pathway, which projects from the substantia nigra to the dorsal striatum [11], is especially important for movement control. Decreased dopamine signaling is associated with hypokinetic movement disorders, while excessive dopamine signaling is associated with hyperkinetic disorders (Fig. 2) [15]. On the basis of early clinical experience with anticholinergic drugs in patients with Parkinson's disease, it was postulated that dopamine and acetylcholine have opposing and balancing effects in the striatum; however, interactions between these neurotransmitter systems are more dynamic and complex than originally thought [16].

Dopaminergic activity is modulated by cholinergic neurons that project from the laterodorsal tegmentum and pedunculopontine tegmentum, two acetylcholine-rich nuclei located in the pons region of the brainstem, along with CINs located within the striatum [11, 15]. Cholinergic projections from the laterodorsal tegmentum

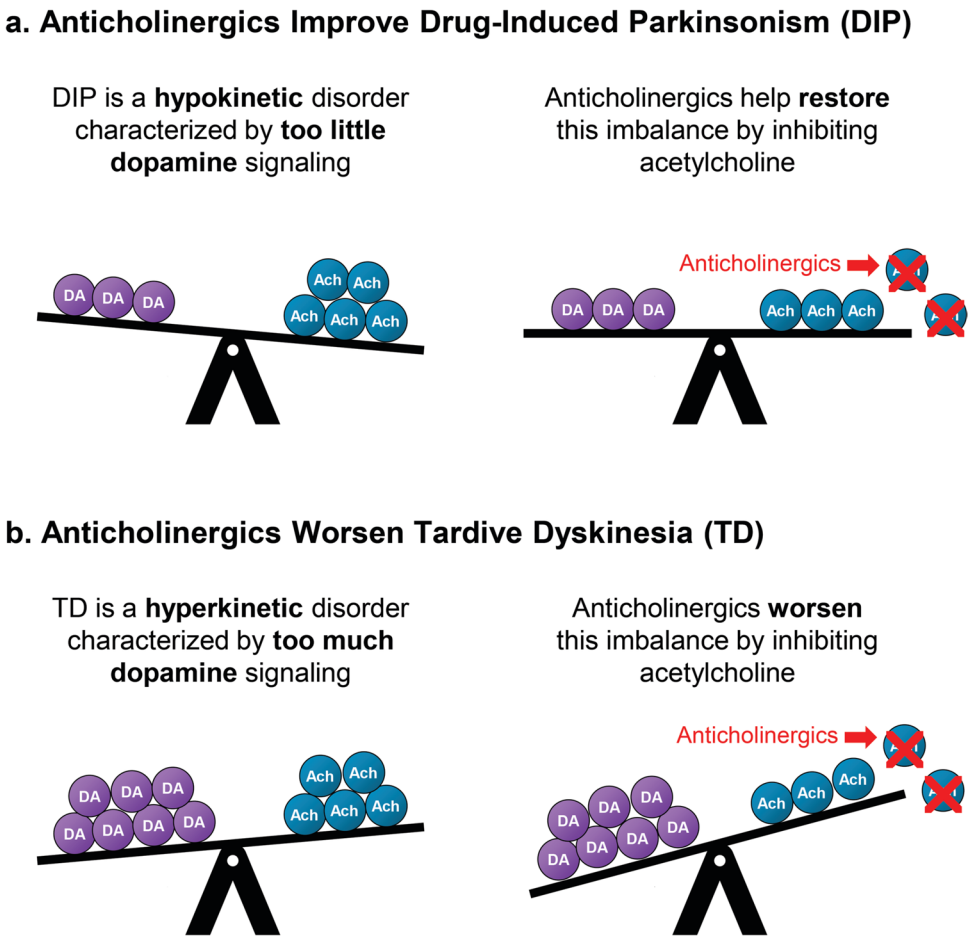


Fig. 2 Hypokinetic movement disorders, such as drug-induced parkinsonism, are characterized by a decrease in dopamine signaling, which amplifies cholinergic activity. Anticholinergics can be effective in treating these disorders by restoring dopamine–acetylcholine balance. Hyperkinetic disorders, such as tardive dyskinesia, are characterized by an increase in dopamine signaling, which dampens cholinergic activity. Thus, anticholinergic medications are not effective in treating these disorders and may even worsen hyperkinetic symptoms

are primarily involved in non-motor systems that control reward, motivation, cognition, and aversion via their interactions with dopaminergic neurons in the ventral tegmental area. Cholinergic projections from the pedunculopontine tegmentum directly and indirectly (via subthalamic nuclei) innervate dopamine-containing cells in the substantia nigra, thereby stimulating dopamine release into areas of the sensorimotor striatum that are primarily involved in motor control (Fig. 3).

Dopamine input to MSNs within the striatum is also modulated by CINs, which account for 1–2% of striatal neurons. These CINs are the main source of striatal acetylcholine and have extensive modulatory effects on MSNs via their widespread projections [16, 17]. MSNs play key roles in the motor circuitry by releasing gamma-aminobutyric acid (GABA), which modulates the opposite motor effects of the direct and indirect pathways. The activation and inhibition of MSNs and CINs by dopamine from substantia nigra depend on dopamine receptor type and location (Fig. 3). Normal motor function requires that these dopamine-acetylcholine interactions remain in dynamic balance [16, 17].

2.3 Adverse Consequences of Dopamine Receptor Blockade on Motor Circuitry

In patients with DIP, blockade of D_2 receptors by DRBAs leads to diminished dopamine signaling [18]. Findings from preclinical studies suggest that blocking D_2 receptors may also have the following effects: (1) disinhibition of indirect MSNs, leading to increased release of inhibitory GABA from these MSNs; and (2) disinhibition of CINs, leading to greater binding of acetylcholine to excitatory M_1 receptors on indirect and direct MSNs (and further augmenting GABA release from indirect MSNs) (Fig. 3) [16, 17, 19]. These cumulative effects of D_2 receptor blockade on MSN and CIN activity may contribute to the abnormal movements associated with DIP and other acute, reversible movement disorders. For these conditions, anticholinergics are believed to restore the dynamic balance between dopamine and acetylcholine (Fig. 2) [16].

Furthermore, for the case of hyperkinetic movements such as TD, it has been hypothesized that chronic blockade of postsynaptic D_2 receptors induces upregulation of D_2 receptors on MSNs, along with conformational changes

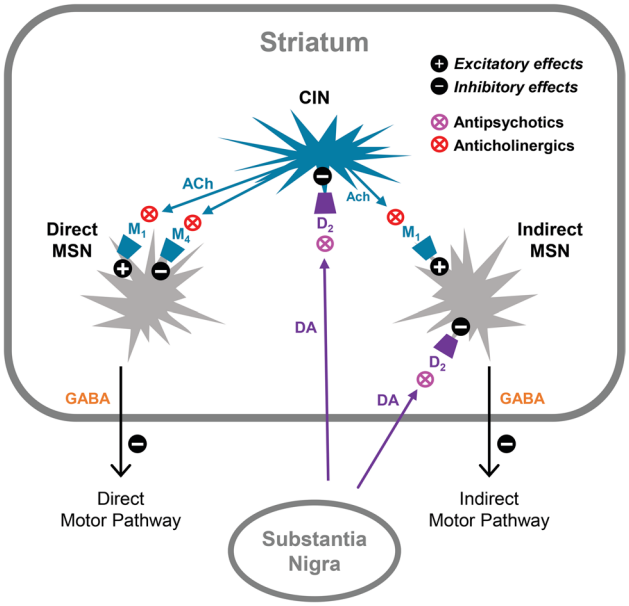


Fig 3 Dopamine (DA) is released from the substantia nigra to the striatum. Within the striatum, antipsychotics prevent DA from binding to D_2 receptors on indirect medium spiny neurons (MSNs) and cholinergic interneurons (CINs). Anticholinergics prevent the binding of acetylcholine (ACh) to muscarinic M_1 and M_4 receptors on direct MSNs and to M1 receptors on indirect MSNs. Adapted with permission from Lester 2010 [15] and Paz 2021 [17]

in the receptors themselves that render a state of hypersensitivity [18, 20]. The net result is enhanced dopamine signaling, leading to increased inhibition of indirect MSNs and CINs, along with decreased cholinergic and GABAergic signaling [21]. Clinically, these effects present as the potentially persistent and excessive abnormal involuntary movements associated with TD. Further inhibition of acetylcholine activity could exacerbate the imbalance between dopamine and acetylcholine (Fig. 2), which is consistent with the lack of evidence supporting the use of anticholinergics in TD [22, 23] and reports of TD worsening with anticholinergics and improving after anticholinergic discontinuation [24–27].

3 Adverse Effects of Anticholinergic Medications

Medications with anticholinergic properties are used to treat a wide range of peripheral somatic and central nervous system conditions, including parkinsonism, chronic obstructive pulmonary disease (COPD), overactive bladder, hyperhidrosis, poor sleep, flu/cold symptoms, and allergies [28]. Anticholinergics have long been used to treat Parkinson's disease, even before levodopa was introduced; however, their cognitive side effects may be particularly concerning in this older patient population [29]. Evidence on the efficacy of anticholinergics in DMDs, as covered in greater detail below, has generally been low quality in previous reviews [18, 30, 31]. Ideally, an evidence-based approach should be taken when prescribing anticholinergic medication for any condition. Recent meta-analyses, such as those for COPD [32, 33] and overactive bladder [34, 35], are valuable resources for such information.

More than 600 prescription and over-the-counter medications with anticholinergic properties are currently available, including commonly used antipsychotics, antidepressants, antihistamines, antiemetics, antispasmodics, and nonprescription flu/cold remedies (Fig. 1). Anticholinergic burden is increased when these drugs are used concomitantly, and accidental or intentional overexposure to one or more of these medications can lead to anticholinergic toxicity [36]. For M_1/M_4 receptor agonists in development for schizophrenia [8, 37], as well as M_4 receptor positive allosteric modulators [38], the potentially deleterious effects of centrally acting anticholinergics on antipsychotic efficacy remains to be determined.

The range of adverse effects with anticholinergics is extensive. Peripheral or systemic effects include dry mouth (associated with dental caries), anhidrosis (contributing to heatstroke), tachycardia, constipation or decreased bowel motility, vomiting, urinary retention, blurred vision, and narrow-angle glaucoma [28, 39]. Central effects include impaired cognition and memory loss [28]. Acute anticholinergic toxicity can present as a medical emergency presenting with arrhythmias, seizures, hyperthermia, agitation, and delirium [40]. Treatment of acute toxicity consists of supportive medical care including hemodynamic support, fluid resuscitation, treatment of dysrhythmias, cooling elevated temperatures, treatment of seizures, and consideration of benzodiazepines or physostigmine for agitation and delirium [41].

These central adverse effects of anticholinergics are particularly concerning in older individuals due to decreasing cholinergic reserves in the aging brain [42]. Studies have shown that centrally acting anticholinergics can exacerbate cognitive dysfunction related to schizophrenia, with negative repercussions for cognitive and psychosocial rehabilitation and activities of daily living [43, 44]. In one study, high serum anticholinergic activity was associated with decrements in verbal working memory, verbal learning, and response to cognitive training, independent of age, intelligence quotient, or disease severity [45]. In another study, use of highly anticholinergic medications was associated with poorer cognition, especially immediate memory recall and executive function, along with reduced cortical volume and temporal lobe atrophy [46]. These results may be linked to synaptic loss and neurodegeneration in the cortex and medial temporal lobe caused by decreased cholinergic innervation

and activity in these areas due to cholinergic receptor blockade by anticholinergic medications.

4 Differentiation of Drug-Induced Movement Disorders and Their Response to Anticholinergic Treatment

With their wide-ranging phenomenology, differentiating one DIMD from another can be challenging, especially in patients who exhibit simultaneous abnormal movements [4, 9]. DIMDs related to antipsychotic exposure include DIP, akathisia, dystonia, and TD. Historically, these sequelae of D_2 receptor antagonism have collectively been referred to as "extrapyramidal symptoms" or "EPS." The panelists agreed, however, that this terminology is non-specific and encompasses a range of abnormal movements with distinct pathophysiology and clinical presentation, thereby requiring divergent treatment approaches. As such, "EPS" is not useful for conveying a precise clinical characterization, which is critical for effective treatment. However, "extrapyramidal disorder" remains in use in the Medical Dictionary for Regulatory Activities (MedDRA) terminology and is therefore included in product labeling.

The panelists agreed that standards for DIMD evaluation and treatment are covered in the 2020 American Psychiatric Association (APA) guidelines for the treatment of adults with schizophrenia (Table 1) [47]. Per these guidelines, all antipsychotic-treated individuals should be evaluated for DIMDs at every clinical encounter. More formal assessments with a structured instrument, such as the Abnormal Involuntary Movement Scale (AIMS) for TD, are recommended at least every 12 months or every 6 months in patients with high risk for TD (e.g., older age).

4.1 Drug-Induced Parkinsonism

DIP is a form of secondary parkinsonism that is predominantly associated with the use of D_2 receptor-blocking antipsychotics. Older adults may be at particular risk, even if they have tolerated these types of medications in the past. Motor symptoms, which include bradykinesia, rigidity, and tremors, generally emerge within days to weeks of antipsychotic initiation or dosage increase [4, 9, 18]. These symptoms often subside when the medication is stopped, the dose is reduced, or the treatment is switched to a different antipsychotic with a lower propensity to cause DIP (e.g., from FGA to SGA) [18]. However, remission of symptoms can take weeks to months, especially in older patients, and symptoms may persist in up to 15% of patients possibly due to tardive parkinsonism or to unmasking of underlying Parkinson's disease [30].

Anticholinergics that are FDA approved for all forms of parkinsonism include benztropine, trihexyphenidyl, and biperiden. These medications can be used for short-term management while adjustments are made to the patient's antipsychotic regimen [47]. The panelists agreed that in such cases, anticholinergic treatment could be considered at the lowest effective dose. Although anticholinergic-like symptoms such as dry mouth and constipation have also been reported in previous trials with amantadine, it is a weak uncompetitive N-methyl-D-aspartate (NMDA) receptor with no measurable direct anticholinergic receptor activity. Amantadine has shown beneficial effects in secondary parkinsonism with relatively less peripheral or central adverse effects compared with anticholinergic medications [31]. An extended-release form of amantadine is specifically approved for the treatment of "drug-induced extrapyramidal reactions in adults" in addition to Parkinson's disease [48]. Strong consideration should be given to preferential use of amantadine for managing DIP, especially in patients who cannot tolerate anticholinergic medications or are at risk for their central and peripheral adverse effects.

4.2 Dystonia

Acute dystonia can occur within hours of initiating antipsychotic treatment or incremental dose adjustment [30]. Risk factors for dystonia include parenteral administration, high doses of high-potency FGAs, younger age, male sex, or recent cocaine use [47]. Dystonia is manifested as the contraction of both agonist and antagonist muscles, resulting in abnormal postures, pain, and cramping sensations [4, 9, 47]. These contractions often occur in the head, neck, face, and back, although the trunk and extremities can also be affected. Characteristic symptoms include torticollis, retrocollis, trismus, grimacing, oculogyric crisis, blepharospasm, and opisthotonos. In rare instances, laryngeal dystonia could impact breathing and swallowing, requiring emergency treatment [4, 47].

Per APA recommendations, intramuscular administration of diphenhydramine or benztropine—both of which have anticholinergic properties—can provide rapid relief of acute dystonic symptoms [47, 49]. In emergency situations where an injectable antipsychotic is indicated (e.g., for a highly agitated patient), an anticholinergic medication is often administered in combination with an antipsychotic and benzodiazepine for rapid control [49]. Alternative approaches for the emergency treatment of agitation include an injectable SGA that has reduced risk of dystonia (e.g., olanzapine, ziprasidone) or sublingual dexmedetomidine [50, 51].

After dystonia is suppressed, oral anticholinergics can be continued for 1–2 days if the antipsychotic was discontinued and for several days if the antipsychotic was not discontinued [30]. The anticholinergic medications should be used at the

Table 1 APA Guidelines for Evaluation and Treatment of DRBA-Induced Movement Disorders[a]

Evaluation	
Initial/baseline assessment	Clinical assessment of akathisia, dystonia, parkinsonism, and other abnormal involuntary movements, including tardive dyskinesia Assessment with a structured instrument (e.g., AIMS, DISCUS) if such movements are present
Follow-up assessments	Clinical assessment of akathisia, dystonia, parkinsonism, and other abnormal involuntary movements, including tardive dyskinesia, at each visit Assessment with a structured instrument (e.g., AIMS, DISCUS) as follows: At least every 6 months in patients at high risk of tardive dyskinesia[b] At least every 12 months in other patients
Treatment	
Parkinsonism	If possible, reduction in antipsychotic dose or change in antipsychotic medication Anticholinergics may also be used, but at the lowest effective dose for the shortest amount of time The antiparkinsonian medication amantadine can also be tried if anticholinergics are not preferred, cannot be tolerated, or are contraindicated After weeks to months, anticholinergics can often be reduced or withdrawn
Dystonia	Initial therapy with intramuscular diphenhydramine or benztropine If needed, treatment with an oral anticholinergic (e.g., trihexyphenidyl, benztropine) to prevent recurrence or until appropriate changes in antipsychotics and/or other medications can be made Anticholinergics should be used at the lowest dose needed to treat acute dystonia and for the shortest duration needed to prevent dystonia from recurring After weeks to months, anticholinergics can often be reduced or withdrawn
Akathisia	If possible, reduction in antipsychotic dose or change in antipsychotic medication Treatment with a benzodiazepine, propranolol, or mirtazapine may be tried after considering any relevant warnings, precautions, adverse reactions, and/or drug interactions Anticholinergics are not recommended
Neuroleptic malignant syndrome	Antipsychotics should be discontinued with supportive medical care to maintain hydration, reduce temperature, and manage potential cardiovascular and renal complications Benzodiazepines, dopamine agonists, amantadine, dantrolene, or electroconvulsive therapy can also be considered as needed (e.g., lorazepam for catatonia) Anticholinergics are contraindicated
Tardive dyskinesia	Treatment with a reversible VMAT2 inhibitor; strongest evidence is for valbenazine and deutetrabenazine, which are FDA approved for tardive dyskinesia Abnormal involuntary movements can emerge or transiently worsen with antipsychotic cessation or dose reduction; however, cessation can be considered in early onset cases if antipsychotic maintenance is not essential Anticholinergics are contraindicated

AIMS Abnormal Involuntary Movement Scale, *APA* American Psychiatric Association, *DRBA* dopamine receptor blocking agent, *DISCUS* Dyskinesia Identification System: Condensed User Scale, *FDA* United States Food and Drug Administration, *VMAT2* vesicular monoamine transporter 2

[a]From *The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, Third Edition* [40].

[b]Includes the following risk factors: age ≥ 55 years; female sex; history or presence of a mood disorder, substance use disorder, intellectual disability, or central nervous system injury; high cumulative exposure to antipsychotic medications, particularly high-potency dopamine D_2 receptor antagonists; and experience of acute dystonic reactions, clinically significant parkinsonism, or akathisia.

minimal effective dose and tapered off as soon as changes in the antipsychotic regimen are made to lower the risk of dystonic reactions (e.g., switch to SGA). As discussed in section 5, anticholinergics can also be used prophylactically, although the potential benefits need to be weighed against the risks associated with anticholinergic burden.

Tardive dystonia, sometimes described as belonging to a "tardive syndrome" along with tardive akathisia and TD, can be distinguished from acute dystonic reactions by the delayed time of onset and persistence despite antipsychotic discontinuation [9, 47]. Although controlled clinical trials are needed to determine the best first-line approach for tardive dystonia, early studies suggest that either a vesicular monoamine transporter 2 (VMAT2) inhibitor or relatively high anticholinergic dose may benefit some [52–54]. However, VMAT2 inhibitors may be preferred if clinicians want to avoid serious adverse effects of high-dose anticholinergics or potential worsening of concomitant stereotypic TD movements with these medications. Other options for tardive dystonia include antipsychotic modification (e.g., decreasing or increasing dosing, switching to clozapine), botulinum toxin, and neurosurgical interventions [9, 55].

4.3 Akathisia

Patients with akathisia usually experience overwhelming feelings of restlessness and the urge to move, resulting in pacing, walking in place, rocking back and forth, leg swinging, toe tapping, squirming, and fidgeting [4, 9, 30, 56]. Due to similarity in symptoms, akathisia may be misdiagnosed as anxiety, potentially resulting in exacerbation of symptoms if the antipsychotic dosage is increased [56]. Although related to DRBA exposure, akathisia responds poorly to anticholinergics. The lack of supportive evidence for anticholinergic medication in patients with akathisia is documented in a 2006 Cochrane review [57].

Acute akathisia can occur within hours to a few weeks after initiation of antipsychotic treatment or dose change [58]. For many patients, akathisia symptoms improve when the antipsychotic is stopped, the dose is reduced, or the medication is switched to another antipsychotic agent. However, the benefits of these strategies need to be weighed against the possibility of worsening psychiatric symptoms. As a tardive syndrome, tardive akathisia usually can be distinguished from the acute disorder by delayed onset and persistence after antipsychotic discontinuation.

If changing the antipsychotic regimen is not feasible or effective, adjunctive treatment with propranolol, low-dose mirtazapine (7.5–15 mg at bedtime), or a high-potency benzodiazepine (e.g., clonazepam) may be considered for acute akathisia [47, 56]. However, the warnings, precautions, adverse reactions, and drug interactions associated with these medications also need to be considered. Data on treatment of tardive akathisia are limited and may differ from the acute form in the response to DRBA dose modification or specific agents. An early clinical report suggested that reserpine (irreversible and nonselective VMAT2 inhibitor) and tetrabenazine (reversible VMAT2 inhibitor) may be beneficial in the tardive form [59], but they would be expected to worsen acute akathisia. Although a few early clinical reports suggested amantadine may be beneficial in acute persistent akathisia [60], and anticholinergics may reduce symptoms in some patients with acute akathisia especially if experiencing concurrent parkinsonism, the evidence is limited and benefits may be outweighed by risks of anticholinergic side effects [57].

4.4 Tardive Dyskinesia

TD usually emerges after three or more months of DRBA exposure, although some at-risk patients including older adults may develop symptoms more quickly [61]. TD is typically characterized by abnormal involuntary movements in the orofacial region, such as lip smacking, chewing, tongue protrusions, excessive blinking or squinting, and jaw clenching. Symptoms can also arise in other body regions, with writhing, twisting, rocking, and finger/toe tapping among the more common types of movements found in the trunk, limbs, and extremities [4, 9, 18, 62].

There is insufficient evidence for changing antipsychotic regimens or discontinuing antipsychotics to treat TD [63–65]. Maintenance of antipsychotic treatment is often necessary in patients with severe psychotic disorders who are at high risk for relapse, stable on their current antipsychotic therapy, and experiencing mild or localized TD symptoms with minimal self-reported impact. Dose reduction can temporarily unmask or worsen motor symptoms while increasing the risk of psychotic decompensation [9, 66]. Antipsychotics with lower D_2 receptor affinity or occupancy still carry a risk for TD; however, switching to these medications can be considered in patients who have developed TD, particularly if there are overriding benefits (e.g., switching to clozapine in patients who have treatment-resistant schizophrenia or who are at risk for suicidal behavior) [47, 67]. Discontinuation of antipsychotics has been used in clinical practice, especially in younger patients who have early onset of mild TD, but with limited supportive evidence for remission. This type of approach should only be considered in patients who are likely to safely tolerate withdrawal and have conditions that might not require continuous antipsychotic exposure (e.g., adjunctive treatment for mood disorders).

As reported in a 2018 Cochrane review, there is an absence of compelling evidence to recommend the use of anticholinergics in patients with TD [22]. Moreover, the prescribing labels for both benztropine and trihexyphenidyl indicate that they should not be used for TD and may even aggravate TD (Fig. 2) [68–70]. Withdrawal of anticholinergics in patients with TD should be done with cautious tapering after considering the impact on concurrent conditions that may worsen upon anticholinergic withdrawal (e.g., DIP, tardive dystonia), [53].

Once the patient's antipsychotic and anticholinergic regimens are reassessed and stabilized, specific antidyskinetic strategies can be employed. In the USA, two medications are currently approved for TD in adults: valbenazine and deutetrabenazine. The APA recommends that these medications be considered for adults with moderate-to-severe TD and in adults with milder symptoms on the basis of factors such as patient preference, associated impairment, and impact on psychosocial functioning [47].

Valbenazine, the first medication approved in the USA for TD, is the valine ester of [+]-α-dihydrotetrabenazine, a highly potent and selective VMAT2 inhibitor [71]. Valbenazine is available in three dosing options (40, 60, and 80 mg), all of which are taken as a single capsule once daily [72]. Although patients have been observed to improve with a low dose of 40 mg/day [73, 74], escalation to the target dose of 80 mg/day can be achieved after 1 week of initial treatment with 40 mg [72]. The second

VMAT2 inhibitor to be approved in the USA for TD is deutetrabenazine, a deuterated formulation of tetrabenazine. Deutetrabenazine is available as twice-daily tablets (6, 9, and 12 mg) or once-daily extended release tablets (6, 12, and 24 mg) [75]. Treatment for TD requires titration in 6-mg increments weekly after starting treatment at 12 mg/day. As evident from the clinical trials, the effective dose range for TD is 24–48 mg/day, with an observed mean dose of approximately 39 mg/day in a long-term, open-label extension study [76–78]. Both valbenazine and deutetrabenazine carry warnings about secondary parkinsonism as a potential adverse effect.

Treatment can be challenging when TD and DIP are both present. In these cases, medication selection should be guided by the primary and most bothersome phenomenology [18]. When dyskinetic movements are the predominant symptom, a VMAT2 inhibitor can be prescribed while monitoring DIP severity. When parkinsonian symptoms are most bothersome, an antiparkinsonian medication should be considered. VMAT2 inhibitors and anticholinergics can be prescribed concurrently, although valbenazine was the only VMAT2 inhibitor that allowed for concomitant anticholinergic use in TD studies. The combined risk of side effects from polypharmacy of VMAT2 inhibitors and anticholinergics should be carefully considered. Amantadine has been suggested as a possible alternative in patients who have both TD and DIP [18, 63]. If modification of the antipsychotic regimen is feasible, switching agents to reduce or eliminate DIP may be considered [18].

4.5 Neuroleptic Malignant Syndrome

NMS is a relatively rare and potentially life-threatening reaction to DRBAs, with high-potency FGAs posing the greatest risk [79]. The clinical manifestations include severe muscle rigidity and tremor along with catatonic symptoms (stupor, mutism) and hypermetabolic systemic signs (hyperthermia, autonomic instability) [30]. The primary recommended approach is DRBA cessation and supportive care [47, 80]. Treatments that have been tried empirically in observational studies, with variable success, include benzodiazepines, dopamine agonists, dantrolene, and electroconvulsive therapy [80].

Anticholinergics are contraindicated in NMS and other cases of hyperthermia or heat-related illness because they block sympathetic innervation of sweat glands, resulting in anhidrosis and potentially complete loss of ability to dissipate a heat load. Consequently, these medications are a major contributing factor to potentially fatal heatstroke in the elderly and in mentally ill patients during increasingly common summer heat waves [81, 82].

5 Prophylactic Use of Anticholinergic Medications

Historically, many clinicians were trained to prescribe anticholinergics concomitantly with antipsychotics—especially FGAs—to prevent the emergence of DIMDs. However, prophylaxis with anticholinergics is not generally recommended, particularly with SGAs that have a lower propensity for DIMDs [83, 84]. Early studies indicated effective prophylaxis with anticholinergics for acute dystonia [85–87], but findings have not been consistent and there is no evidence that these medications have an effect in preventing DIP, akathisia, TD, or NMS [83]. Moreover, patients at high risk for DIP are usually older and susceptible to cognitive impairment. Given the potentially deleterious effects of anticholinergics in patients with these characteristics, prophylactic use to prevent DIP should be avoided or monitored carefully [18, 30, 47].

The strongest evidence for prophylactic anticholinergic use is for the prevention of acute dystonia in at-risk individuals (e.g., young, male) [30, 47]. Although prophylactic anticholinergics can be problematic in older adults owing to adverse anticholinergic effects, the benefits of preventing dystonia outweigh the potential risks in younger patients who are receiving parenteral high-potency FGAs and in patients who are paranoid or ambivalent about treatment [9, 30, 47]. The risk of acute dystonia can be largely mitigated by using SGAs [30].

6 Discontinuation and Dose Reduction

The panelists noted that clinicians may not appreciate the need to discontinue anticholinergics if the patient's clinical status appears unchanged, but they emphasized the need for routine evaluation of anticholinergic need and pharmacological burden. Evaluation can be performed using instruments such as the Anticholinergic Drug Scale (ADS) or Anticholinergic Risk Scale (ARS) [88, 89]. Both scales include a list of medications that are assigned different levels of anticholinergic burden, ranging from 0 to 3 (highest burden). Regular evaluation of each patient's total medication regimen is needed because many medications have anticholinergic properties (e.g., antipsychotics, antidepressants) that can contribute to anticholinergic burden, even if they are not typically classified as an anticholinergic agent. High anticholinergic burden has been associated with serious adverse outcomes, including increased risks for mortality, fractures, falls, delirium, and dementia or other cognitive impairments [68, 90–97]. Studies have shown that anticholinergic medications can

be safely discontinued in those with severe mental illnesses such as schizophrenia, with beneficial outcomes in terms of cognition, mood, and quality of life, along with reduced fall risk in older patients [98–100].

After anticholinergic burden is assessed and all potential beneficial and detrimental outcomes are considered, decisions can be made about which medications could be stopped and/or whether doses could be decreased. Abrupt discontinuation can lead to cholinergic rebound, which is characterized by symptoms such as nausea, vomiting, headache, sweating, muscle spasms, abdominal cramping, and urinary urgency [101]. Therefore, for elective discontinuation in stable outpatients without serious anticholinergic toxicity, anticholinergics should be tapered slowly when stopping treatment or reducing the dose.

Given the potential complexity of treating patients with DIMDs, especially those who have two or more distinct DIMDs, the panelists recommended taking an individualized approach when stopping or decreasing anticholinergics in this population. Factors to consider include age, sex, anticholinergic treatment duration, concomitant medications, and current medical/psychiatric conditions including acuity of anticholinergic toxicity. Moreover, patients should be monitored during the tapering process. Slow tapers may be considered in stable outpatients who chose to discontinue anticholinergics and are not currently in distress or experiencing adverse events (i.e., "elective" tapering). In studies that included outpatients with serious mental illness, tapering schedules ranging from approximately 1 to 4 months were associated with reduced anticholinergic burden and significant improvements in cognition and quality of life [99, 102–104]. However, a more rapid tapering schedule may be required in patients who are exhibiting signs of anticholinergic toxicity, including confusion, acute glaucoma, bladder obstruction, and heatstroke.

In patients who are experiencing cholinergic rebound or reemergence of DIMDs, tapering may require smaller dose-tapering reductions, longer intervals between dose reductions, and/or stopping anticholinergic withdrawal at the minimally effective dose needed to manage the DIMD. If parkinsonism reemerges, amantadine can be considered to help manage the movements while gradual tapering of the remaining anticholinergic medication continues. In the event that antipsychotics are also discontinued, anticholinergics should be continued for an additional 48–72 hours to prevent emergence or recurrence of acute dystonia. Due to the extended half-lives of most DRBAs, break-through dystonic reactions can occur if both drugs are discontinued simultaneously [105, 106].

7 High-Risk Populations

Older adults, women, and individuals with poor cytochrome P450 metabolism (due to genetic polymorphisms or aging) have an increased risk of incurring a high anticholinergic load [107]. Moreover, older patients often have additional risk factors (e.g., polypharmacy, cognitive decline, medical comorbidities) that contraindicate the use of anticholinergics in this population.

Although multiple medications may sometimes be indicated in severely ill patients, the widespread prevalence of polypharmacy in older adult populations has been well documented, especially in long-term care facilities [108]. However, polypharmacy among older adults in the general population is also common, as demonstrated in a recent study that included 2.12 billion outpatient visits in adults aged ≥ 65 years [109]. This study showed that 1.377 billion visits (65.1%) had older patients who were taking ≥ 2 medications of concern, as classified using American Geriatric Society Beers Criteria® for potentially inappropriate medication [110], and 779 million visits (36.9%) had older adults taking > 5 medications of concern. In a study that included 3.238 community-dwelling adults aged > 65 years, 1814 (56.0%) were taking > 3 medications [111]. Longitudinal analyses in this study showed that polypharmacy was associated with accelerated decline and the eventual need for assisted care. Other populations with high polypharmacy and increased exposure to anticholinergic medications include patients with intellectual disabilities, neurocognitive disorders, or serious mental illness [112–114].

As discussed by the expert panel, centrally acting anticholinergics should be used cautiously in patients with cognitive impairment, whether due to advancing age, neurodegenerative disorder, or serious mental illness such as schizophrenia. In a systematic review of patients with preexisting dementia, anticholinergic use was associated with poor clinical outcomes, including mortality, stroke, delirium, poor physical performance, reduced health-related quality of life, and longer hospital stays [115]. Another systematic review, based on studies of patients with schizophrenia, found anticholinergics to be associated with reduced cognitive ability, including impairment in learning, memory, processing speed, attention, and executive function [43].

The potential for anticholinergic abuse and misuse, particularly in forensic settings, is another important consideration. Abuse, defined as taking an anticholinergic for nonmedical or recreational purposes, is attributable to the euphoric, stimulant, and hallucinogenic properties of these drugs [116]. Routes of administration for anticholinergic abuse include ingestion, injection, and smoking

(e.g., mixed with tobacco). Misuse is defined as taking an anticholinergic for medical reasons in nonprescribed ways, including for non-intended symptoms and at non-recommended doses. Anticholinergic misuse can occur for various reasons, but the perceived hedonic effects of these drugs likely contribute to why patients take them in nonprescribed ways. Given the potential for abuse or misuse, anticholinergics should be avoided or used with caution in patients with current or prior substance abuse or dependence. In forensic settings, cautionary measures should be taken to prevent diversion for recreational or other nonprescribed uses [117].

8 Conclusions

Although DIMDs share a common cause (i.e., exposure to antipsychotics, antiemetics, or other dopamine D_2 receptor antagonists), they are neurobiologically and clinically distinct. As such, DIMDs require accurate diagnoses and appropriate treatment approaches. One common misconception is that anticholinergics can be used to treat, prevent, or reduce any DIMDs, despite the well-documented hazards of high anticholinergic burden and the evidence indicating that these medications are effective for DIP and acute dystonia but not for akathisia, TD, or neuroleptic malignant syndrome. As a result, anticholinergics continue to be overprescribed in conjunction with antipsychotics.

Part of the problem of anticholinergic overuse is the tendency to conflate all DIMDs as "EPS," which is a non-specific term that encompasses a wide variety of clinical manifestations and distinct treatment strategies. It is challenging to clinically differentiate DIMDs, and the panelists agreed that continued training on the identification and appropriate treatment of these disorders is warranted. In addition, more education is needed on anticholinergic tapering strategies and the serious adverse effects associated with anticholinergic medications, especially in high-risk populations such as the elderly.

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