Anticholinergics are Not Appropriate Treatments for Tardive Dyskinesia: Insights from an Expert Panel of Psychiatry and Neurology Healthcare Professionals

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ABSTRACT DESCRIPTION

Recommendations from movement disorder experts are presented regarding appropriate and inappropriate use of anticholinergics in patients with drug-induced movement disorders (DIMDs). Key topics include differentiation of tardive dyskinesia (TD) from other DIMDs, prophylactic and chronic use of anticholinergics, treatment considerations in high-risk populations (e.g., elderly patients), and safe anticholinergic discontinuation.

INTRODUCTION

- TD is a persistent and often disabling hyperkinetic movement disorder associated with prolonged exposure to dopamine receptor blocking agents (e.g., antipsychotics, antiemetics)[1]
- Before the approval of valbenazine for TD, followed by deutetrabenazine, various off-label medications (e.g., anticholinergics, tetrabenazine) and treatment strategies (e.g., antipsychotic switching) were used to manage TD despite the lack of supportive evidence[2,3]
- TD is sometimes classified as an "extrapyramidal symptom" (EPS), which is an outdated umbrella term that collapses various acute and tardive neuroleptic-induced movement disorders into a single category, despite the fact that these disorders are distinct in terms of pathophysiology, presentation, and treatment
- Conflating all neuroleptic-induced movement disorders can result in similar and inadequate treatment; in some cases, this can diminish benefits and even exacerbate the symptoms of the DIMD
- Hence, despite a lack of evidence and the availability of approved TD medications (valbenazine and deutetrabenazine) for several years, anticholinergics are still commonly used to treat TD
- To better understand this practice, an advisory panel of movement disorder experts from neurology and psychiatry was convened to gather real-world insights into how and why clinicians continue to use anticholinergics for TD

OBJECTIVES

- Recognize that TD should be treated with an approved vesicular monoamine transporter 2 (VMAT2) inhibitor, as anticholinergics are not recommended and may aggravate or unmask TD symptoms
- Understand the importance of anticholinergic dose reduction and gradual discontinuation when possible
- Describe the risks associated with inappropriate anticholinergic use in patients who are older, have cognitive difficulties, or have a history of substance abuse or dependence

METHODS

- The initial expert panel (4 psychiatrists, 1 geriatric psychiatrist, 1 psychiatric physician assistant [PA], 1 psychiatric nurse practitioner [NP], 1 neurologist specializing in movement disorders [MDS]) convened virtually in November 2020 to discuss anticholinergic use for TD
- In June 2021, a follow-up panel (5 psychiatrists, 1 geriatric psychiatrist, 1 psychiatric PA, 1 psychiatric NP, 1 MDS neurologist) reconvened to discuss 13 potential consensus statements and corresponding data, categorized by topic as follows:
  - Appropriate use of anticholinergics for DIMDs (4 statements)
  - Prophylactic use of anticholinergics (3 statements)
  - Considerations for high-risk patients and special populations (3 statements)
  - Dose reduction and discontinuation of anticholinergics (3 statements)
- For each statement, panel members discussed supportive data and made changes needed to obtain consensus
- Consensus was defined as verbal agreement from all expert panelists that the revised statement was accurate
- Following the meeting, each expert separately confirmed agreement to all statements

RESULTS

APPROPRIATE USE OF ANTICHOLINERGICS (TABLE 1)

- Per guidelines from the American Psychiatric Association (APA), all patients taking an antipsychotic should be monitored regularly for TD and other DIMDs
- Anticholinergics do not improve and may worsen TD symptoms
- Food and Drug Administration (FDA)-approved VMAT2 inhibitors (e.g., valbenazine and deutetrabenazine) are recommended as first-line TD therapies
- Misunderstanding and misuse of "EPS" contribute to a fundamental gap in knowledge on the differences between various DIMDs
- In turn, these knowledge gaps contribute to inappropriate treatment of TD with anticholinergics and other medications with poor or limited evidence of efficacy

Table 1. Appropriate Use of Anticholinergics

Original Statements	Consensus Statements	Rationale for Edits
• It is appropriate to follow guidelines on treatment of DIP and acute dystonia	• **The APA guidelines are recommended for the treatment of DIMDs**	• The umbrella term **"EPS" is often used incorrectly**, resulting in a fundamental knowledge gap on specific DIMDs • The **APA guidelines are most current** and include treatment recommendations for DIP, dystonia, and TD
• All patients treated with an antipsychotic should be regularly evaluated for DIMDs	• **All patients treated with an antipsychotic should be regularly evaluated for DIMDs**	• Due to the **cognitive and peripheral effects associated with anticholinergics**, it is important to **evaluate the patient for DIMDs**–DIP, dystonia, TD–**and then address the specific problem with its specific solution**
• It is not appropriate to use anticholinergics to treat TD	• **Anticholinergics are not recommended to treat TD and may aggravate or unmask TD symptoms**	• It is documented in the medical literature and is consistent with APA guidelines that **anticholinergics can exacerbate TD risk and symptoms**
• In accordance with existing guidelines, the use of FDA-approved VMAT2 inhibitors indicated for TD should be considered as first-line treatment for TD	• **In accordance with APA guidelines, the use of FDA-approved VMAT2 inhibitors indicated for TD should be considered as first-line treatment for TD**	• **APA guidelines recognize VMAT2 inhibitors as first-line treatment options**, which have shown efficacy in clinical trials for TD

APA, American Psychiatric Association; DIMD, drug-induced movement disorder; DIP, drug-induced parkinsonism; EPS, extrapyramidal symptom; FDA, Food and Drug Administration; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter 2.

PROPHYLACTIC USE OF ANTICHOLINERGICS (TABLE 2)

- The prophylactic use of anticholinergics to prevent DIMDs is not appropriate or recommended
- Anticholinergics may be used prophylactically in patients with a high risk of acute dystonia
- However, prolonged use of anticholinergics for any reason is not recommended due to potential cognitive and peripheral adverse effects
- Anticholinergics should be tapered off slowly when discontinuing

Table 2. Prophylactic Use of Anticholinergics

Original Statements	Consensus Statements	Rationale for Edits
• Generally, it is not appropriate to use anticholinergics prophylactically	• **Generally, anticholinergics are not recommended for prophylactic use to prevent DIMDs** • **Prophylactic use of anticholinergics may be considered in patients with high risk for acute dystonia (young age, high potency, acute IM injections, previous episodes of dystonia)**	• Use of a **FGA + anticholinergic** is outdated and **often misused as a "one-size-fits-all" protocol to prevent DIMDs in general** versus consideration on a case-by-case basis • There is a paucity of clinical trials on prophylactic anticholinergic use in DIMDs
• In treatment-naive patients, it is recommended to initiate an anticholinergic prophylactically when starting a first-generation AP, but not when starting a second-generation AP	• **Statement deleted**	
• If anticholinergics are used prophylactically, the duration of use should be limited to 4 weeks	• **If anticholinergics are used prophylactically, the duration of use should be limited** • **The patient should be re-evaluated for discontinuation** • **If discontinuation is possible, patients should be tapered off**	• When considering anticholinergics, clinicians should always strive to **minimize burden to lessen the cognitive and peripheral adverse effects**

AP, antipsychotic; DIMD, drug-induced movement disorder; FGA, first-generation antipsychotic; IM, intramuscular.

CONSIDERATIONS FOR HIGH-RISK PATIENTS AND SPECIAL POPULATIONS (TABLE 3)

- Anticholinergics are not recommended in older patients (≥55 years) since cognitive and other side effects may be more pronounced in this population
- Anticholinergics should also be avoided in patients with cognitive difficulties, except for emergent treatment of acute dystonia
- Anticholinergics should be used with great caution in forensic settings and in patients with a history of substance abuse or dependence

Table 3. Considerations for High-Risk Patients and Special Populations

Original Statements	Consensus Statements	Rationale for Edits
• We do not recommend that patients over the age of 55 be treated with anticholinergics	• **Anticholinergics are not recommended for patients over the age of 55** • **In older populations, cognitive and other side effects are more prominent** • **Amantadine could be considered for DIP at lower doses to avoid anticholinergic side effects**	• The **cognitive effects of anticholinergics are more prominent in older patients** and anticholinergic burden should be minimized
• In patients with cognitive impairment, despite age, we do not recommend the use of anticholinergics except in brief cases of DIP or acute dystonia	• **In patients with neurocognitive disorders,* such as developmental disabilities, mild cognitive impairment, or dementia, anticholinergics are not recommended (except for emergent treatment of acute dystonia)**	• **Cognitive impairment or other adverse effects may worsen** in those with neurocognitive disorders who may be unable to communicate/report these symptoms
• In patients with a history of substance abuse, we do not recommend the use of anticholinergics except in cases of DIP or acute dystonia	• **Anticholinergics may be misused or diverted in forensic settings or in patients with a history of substance abuse or dependence; therefore, anticholinergics are not recommended in these populations (except for the treatment of acute dystonia)**	• **Anticholinergics have abuse potential and may be misused or diverted** by patients in forensic settings or with a history of substance abuse or dependence

*ACs may further worsen cognitive impairment or other adverse effects in these patients, who may be unable to report side effects, which may then go undetected.
AC, anticholinergic; DIP, drug-induced parkinsonism.

DOSE REDUCTION AND DISCONTINUATION OF ANTICHOLINERGICS (TABLE 4)

- When used for appropriate conditions (e.g., acute dystonia), anticholinergics should be prescribed at minimally effective doses and tapered slowly when discontinuing
- Abrupt discontinuation can result in cholinergic rebound
- When stopping inappropriate use of anticholinergics in TD or other DIMDs, abrupt discontinuation can exacerbate symptoms

Table 4. Dose Reduction and Discontinuation of Anticholinergics

Original Statements	Consensus Statements	Rationale for Edits
• Discontinuation of anticholinergics for acute treatment of dystonia and DIP should follow the USPI	• **Even small doses of anticholinergics can cause cognitive impairment; therefore, every attempt should be made to discontinue anticholinergic therapy**	• **Dystonia is sensitive to small doses of anticholinergics**, so there is little need to give a higher dose than necessary—especially given the harmful effects of anticholinergics on all patients, regardless of age
• Anticholinergics should be tapered and should not be abruptly discontinued after long-term use	• **Anticholinergics should be tapered and should not be abruptly discontinued to prevent cholinergic rebound or reemergence of DIMDs**	• When anticholinergics are **abruptly discontinued**, patients can experience **cholinergic rebound** (e.g., sleep disturbance, GI problems, urinary urgency, manifestation of DIMDs) **or exacerbation of TD**
• In general, best practice for discontinuation of long-term anticholinergics is to decrease the dose by 25% every month in order to avoid cholinergic rebound in most patients	• **In general, best practice for discontinuation of long-term anticholinergics is to decrease the dose by no more frequently/faster than 1 mg trihexyphenidyl or 0.5 mg benztropine every 2 to 4 weeks* in order to minimize the risk of cholinergic rebound** • **If not possible to completely eliminate the anticholinergic, at least reduce it to the minimal amount**** • **Tapering too fast may result in failure**	• Too rapid of a taper may result in **cholinergic rebound and prohibit the assessment of ongoing need** for anticholinergics in some patients

*Approach may be flexible on a case-by-case basis. Some patients on shorter-term AC use may be able to be tapered a little more quickly. For those with acute AC side effects, initial taper should be faster (25% dose reduction), then subsequently slowed down. Inpatient vs outpatient treatment is another consideration here.
**Can offer amantadine if DIMD manifestation reemerges.
AC, anticholinergic; DIMD, drug-induced movement disorder; DIP, drug-induced parkinsonism; GI, gastrointestinal; TD, tardive dyskinesia; USPI, United States prescribing information.

CONCLUSIONS

- Anticholinergics are not recommended for the treatment of TD and may aggravate or unmask TD
- The misunderstanding and misuse of the term "EPS" for all DIMDs and the continued educational need on TD differentiation contribute to a lack of knowledge, which can lead to inappropriate treatment[1]
- Even when used appropriately (e.g., for acute dystonia), chronic anticholinergic treatment is not recommended; anticholinergics should be prescribed at minimally effective doses and patients should be tapered off slowly when discontinuing treatment with anticholinergics[4,5]
- Anticholinergics are associated with adverse cognitive effects, which can be particularly harmful in older patients and those with cognitive disorders
- The potential for abuse, addiction, and diversion should be considered when prescribing anticholinergics

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Please email medinfo@neurocrine.com if you have any questions on this presentation.

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