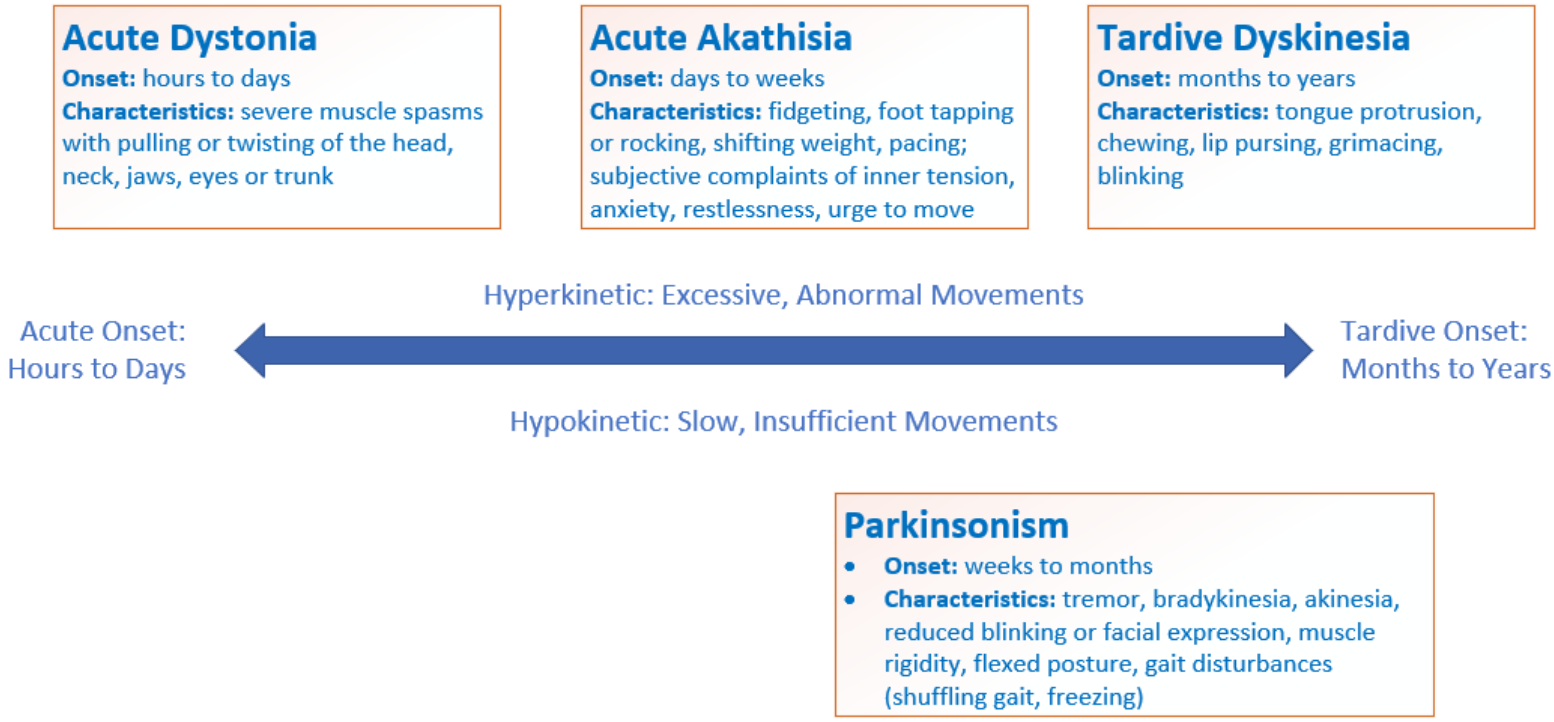
Recognition and Management of Antipsychotic-induced Movement Disorders

Antipsychotic-induced movement disorders commonly seen in clinical practice include parkinsonism, akathisia, tardive dyskinesia and acute dystonia. The prevalence of antipsychotic-induced movement disorders is about 37% (95% CI, 18-55%), where 20% of people on an antipsychotic medication experience parkinsonism, 11% experience akathisia, and 7% experience tardive dyskinesia.[1] Acute syndromes manifest within days or weeks, whereas tardive syndromes might develop after months or years of antipsychotic use. These movement disorders can cause distress, fear, social shame and isolation, and psychological impact from not being able to control one's body. Their impact can erode patient trust, result in less medication adherence, lead to poor quality of life and increased morbidity and mortality.[2]

Key features of common antipsychotic-induced movement disorders [adapted from Warren, et al.[3]].



Acute Dystonia

Acute dystonia is characterized by uncontrollable, painful movement (twisting or repetitive) or posturing of the neck (head tilt and rotation) due to prolonged or intermittent muscle contraction.[4] It may also present as oculogyric crisis with uncontrollable, upward movement of the eye. Dystonic reactions may be sustained, fluctuating, or episodic, and last a few seconds or several hours.[5] Acute dystonia may be incorrectly attributed to catatonic signs or misdiagnosed as seizure activity.[6] Some symptoms may precede dystonia, including anxiety, muscle pain, cramps or tightness of the jaw, or tongue swelling.[5]

In most cases, dystonia appears suddenly within the first 5 days of starting antipsychotic treatment.[5] Less often, dystonic reactions may appear after increasing the antipsychotic dose, after a dose of a long-acting agent is administered, or when a second antipsychotic agent is added to a treatment regimen.[5]

Risk factors: potent antidopaminergic first-generation antipsychotics, younger age, previous dystonic reactions, family history of dystonia, cocaine use, mood disorders, hypocalcemia, hypoparathyroidism, hyperthyroidism, and dehydration.[5] Drug dose, potency and the rate of titration also correlate with risk of dystonia.[5]

Treatment [6]

1. **IM diphenhydramine** (or administer IV if life-threatening laryngospasm present).
2. **IM benztropine** is an alternative option.
3. Transition to a short-term course of a long-acting oral anticholinergic medication like **benztropine** or **trihexyphenidyl** once acute symptoms resolve. Continue anticholinergic medication at the lowest effective dose for several weeks or months to prevent recurrence. Long-term treatment is not usually necessary. Treat for the shortest duration possible after the patient is stabilized on a different antipsychotic medication or at a reduced dose of the original antipsychotic medication.

KEY POINT: *Anticholinergic medications should be used on a short-term basis. These medications can negatively impact quality of life and cognition. Long-term use may increase risk of dementia and tardive dyskinesia.*

- Other side effects include dry mouth, blurred vision, precipitation of angle-closure glaucoma, constipation, tachycardia, and urinary retention.
- Be aware of anticholinergic toxicity with delirium, somnolence and hallucinations.

Evidence

Overall quality of evidence is low because of lack of data from clinical trials; however, sufficient evidence from a large amount of real-world clinical experience suggests these treatments may be useful to reverse acute dystonia. No studies are available to suggest that these anticholinergic medications differ in their effectiveness or safety when used to treat acute dystonia.

Acute Akathisia

Akathisia is commonly unrecognized and confused with agitation or anxiety.

KEY POINT: *Akathisia should be distinguished from agitation or anxiety so that unnecessary increasing of the antipsychotic dose is avoided.*[7]

Akathisia can be difficult to diagnose and is defined as much by subjective symptoms as by objective features. Akathisia can develop within a few weeks of first starting an antipsychotic medication or after rapidly increasing the dose.[7] After an antipsychotic medication is initiated or the dose is increased, regularly ask patients about feelings of the need to move, restlessness, or anxiety.[5] Excessive movements may also be observed, such as fidgeting legs, rocking feet, pacing incessantly, or a general inability to sit or stand still.[5] Most patients are bothered by akathisia, and it can be a strong disincentive to accepting antipsychotic treatment.[7]

Treatment of a restless leg syndrome misdiagnosis with a dopamine agonist will worsen psychosis and may lead to increased antipsychotic dosage and further compounding of akathisia.[5]

Risk factors: first-generation antipsychotic, increased age, negative symptoms, cognitive dysfunction, iron deficiency, mood disorders, concomitant parkinsonism.[5]

Treatment [6,8]

1. **Lower the dose of antipsychotic medication** after weighing benefits of reduced akathisia with potential risk for increased psychotic symptoms.
2. **Switch to another antipsychotic medication** with a lower likelihood of akathisia (see Side Effect Profiles of Second-generation Antipsychotic Medications).
3. Akathisia is often resistant to pharmacological treatment. However, **mirtazapine** 15 mg/day has shown to reduce symptoms of akathisia. Benzodiazepines have **not** shown to improve symptoms of akathisia.

Evidence

Overall quality of evidence for most treatments is low because of lack of data from clinical trials; however, sufficient evidence from a large amount of real-world clinical experience and clinical evidence suggest mirtazapine may be useful for antipsychotic-induced akathisia.[8] Adding a benzodiazepine may result in undesirable side effects without improvement in akathisia.[8] Individualize treatment based on patient preferences.

Parkinsonism

Symptoms of antipsychotic-induced parkinsonism develop weeks or months after starting or increasing the dosage of antipsychotic medication, and may include parkinsonian tremor, muscular rigidity, loss of movement or difficulty initiating movement (akinesia), or slow movement (bradykinesia).[6] Parkinsonism symptoms are less acute than acute dystonia, but it is a more common condition and more difficult to treat.[5] Patients may initially complain of fatigue, weakness, cognitive slowing, or depression, even in the absence of motor symptoms.[5]

It can be difficult to differentiate drug-induced parkinsonism from negative symptoms of schizophrenia or idiopathic parkinsonism.[9] Symptoms of Parkinson's disease are progressive, more likely to be asymmetric, are characterized by greater prominence of rigidity, tremor, and gait disturbance, and will not subside after stopping or switching antipsychotic medications.[9] Differential diagnoses also include tardive dyskinesia, where movements are non-rhythmic and slower than the fast, rhythmic tremors associated with parkinsonism (3-6 cycles/sec). **Treatment that helps antipsychotic-induced parkinsonism will make tardive dyskinesia worse**.[10]

Risk factors: first-generation antipsychotics, higher dose or duration of antipsychotic medication, older age, and family history of Parkinson's disease.[9]

Treatment [6]

1. **Lower the dose of antipsychotic medication** after weighing benefits of reduced parkinsonism with potential risk for increased psychotic symptoms.
2. **Switch to another antipsychotic medication** with a lower likelihood of parkinsonism (see Side Effect Profiles of Second-generation Antipsychotic Medications).
    - Clozapine may be considered for individuals highly sensitive to antipsychotic-induced parkinsonism.
3. Start a short-term course of a long-acting oral anticholinergic medication like **benztropine, trihexyphenidyl** or **diphenhydramine** to alleviate symptoms. Continue anticholinergic medication until the necessary adjustments to the antipsychotic medication changes are completed.

    KEY POINT: *Anticholinergic medications should be used on a short-term basis. These medications can negatively impact patient's quality of life and cognition. Long-term use may increase risk for dementia and tardive dyskinesia.*
    - Other side effects include dry mouth, blurred vision, precipitation of angle-closure glaucoma, constipation, tachycardia, and urinary retention.
    - Be aware of anticholinergic toxicity with delirium, somnolence and hallucinations.
    - **Amantadine** is an alternative when an anticholinergic medication is not an option for an individual.
- Use of dopaminergic medications like levodopa can exacerbate psychosis.

Evidence

Overall quality of evidence is low because of lack of data from clinical trials; however, sufficient evidence from a large amount of real-world clinical experience suggests these treatment options may be useful for antipsychotic-induced parkinsonism. No studies are available to suggest that one option is more effective than another option, but adding an anticholinergic may result in undesirable side effects. Individualize treatment based on patient preferences.

Tardive Dyskinesia

Tardive dyskinesia is insidious in onset and typically arises 1-2 years after starting antipsychotic medication, though it can occur earlier.[11] It is an involuntary movement disorder characterized by non-rhythmic, repetitive and purposeless orofacial movements of the jaw, lips, tongue and eyes (e.g., chewing or bruxism of the jaw; protrusion, curling, twisting tongue movements; lip smacking, puckering, sucking and pursing; grimacing or bridling of the mouth; eye blinking and blepharospasm).[5,12]

KEY POINT: *Symptoms may be irreversible despite reducing the dose or discontinuing the antipsychotic medication.[13] It is essential to have an informed consent conversation when starting medications that may result in tardive dyskinesia.*

Most patients who develop tardive dyskinesia have mild symptoms. Subjectively, symptoms may be denied or described as minimal

by patients with mild tardive dyskinesia; however, people who develop moderate or severe tardive dyskinesia can have symptoms that are quite disturbing and socially or emotionally intolerable.[5] Severe cases can disfigure the patient's face and compromise their ability to eat, speak, breath or ambulate.[5]

Diagnosis is complicated and requires a systematic approach. Symptoms fluctuate and may be influenced by psychosocial factors. Differential diagnoses include antipsychotic-induced parkinsonism, which typically occurs soon after an antipsychotic medication is started, or after the dose is increased. In contrast to tardive dyskinesia, parkinsonian tremor is rhythmic and faster (3-6 cycles/sec).[10] **Anticholinergics that help antipsychotic-induced parkinsonism will make tardive dyskinesia worse**.[10] Huntington's disease is one of the most important differential diagnoses of tardive dyskinesia, where psychiatric disease can precede the development of hyperkinetic movements by several years.[14]

A complete assessment should be conducted, including a neurological examination, history of motor symptoms, past and current medication and drug use history, and laboratory testing (liver function tests, thyroid function tests, serum calcium, complete blood count and antiphospholipid antibodies).[6] If dyskinetic movements have begun or have increased after decreasing the dose of an antipsychotic medication, assess the longitudinal course of symptoms for up to several months because spontaneous reductions or resolution of dyskinesia may occur.[6] If tardive dyskinesia is suspected, the 12-item Abnormal Involuntary Movement Scale (AIMS) is the accepted standard to confirm diagnosis and to facilitate ongoing assessment.[10]

Risk factors: first-generation antipsychotic medications are higher risk than second-generation agents, and risk increases with higher doses, longer duration of treatment, and advancing age.[4,15]

Treatment [6,12,15-18]

Note: The medications mentioned below are costly, so verify insurance coverage and prior authorization criteria. Discount cards (e.g., ArrayrRx discount card) are available and may be help mitigate some cost for uninsured or underinsured individuals. If prescribed, payers may require going through a specialty pharmacy.

- A vesicular monoamine transporter-2 (VMAT-2) inhibitor **valbenazine** or **deutetrabenazine** is suggested in individuals with moderate, severe or disabling tardive dyskinesia:
    - **Valbenazine (INGREZZA)**
        - Initiate at 40 mg/day and increase to 80 mg/day after 1 week.
        - A dose response has been observed up to 80 mg/day, but doses of 40 mg/day or 60 mg/day may be considered based on tolerability.
        - Limit dose to 40 mg/day in people with moderate or severe hepatic impairment.
    - **Deutetrabenazine** (**AUSTEDO; AUSTEDO XR**)
        - Initiate at 12 mg/day and increase by 6 mg each week.
        - A dose response has been observed up to 24 mg/day; it is unclear if there are additional benefits for most patients at doses greater than 24 mg/day, though some individuals may benefit from higher doses. The maximum dose is 48 mg/day.
        - Contraindicated in people with hepatic impairment.
    - Specific dosing is recommended for certain CYP2D6 metabolic phenotypes. Cytochrome P450 genotyping is not currently widely utilized in clinical practice and drug labeling does not require genotype testing before treatment.
    - Regularly assess symptoms using validated tools like the Abnormal Involuntary Movement Scale (AIMS) which can be performed by any clinician with appropriate training.[19]
        - Obtain a baseline score and reassess symptoms with the AIMS after 12 weeks of treatment.
        - Discontinue if no clinically meaningful improvement is documented (e.g., at least a 2-point reduction[20,21]).
- Consult with psychiatric services before discontinuing the offending antipsychotic medication or switching to a different agent with low risk for tardive dyskinesia, such as clozapine.
- Avoid VMAT-2 inhibitors when treating other tardive syndromes, such as tardive dystonia, which may be more generalized and disabling than tardive dyskinesia and may respond to anticholinergic agents or injections of botulinum neurotoxin. Akathisia, tics and other movement disorders also occur as tardive variants.
- Amantadine and benzodiazepines are not helpful, and use should be avoided for treatment of tardive dyskinesia.

Evidence

Evidence for reducing symptoms of tardive dyskinesia by lowering the antipsychotic dose or switching to another antipsychotic is insufficient.[13] We recommend that the clinician consult with a psychiatrist or movement disorder specialist before making changes to the antipsychotic regimen. There is low quality evidence that deutetrabenazine and valbenazine may produce meaningful reduction the total AIMS score, which is the tool used in clinical trials to assess the efficacy VMAT-2 inhibitors.[15,16] With regard to safety, there is low quality evidence that both VMAT-2 inhibitors are generally well tolerated.[15] Evidence does not suggest that the risk for depression and suicidality possibly associated with VMAT-2 inhibitors in people with Huntington's disease is observed in people with tardive dyskinesia.[6] No studies have directly compared VMAT-2 inhibitors, so it is unclear if there are differences in efficacy or safety between them. There is insufficient evidence to support the use of amantadine or benzodiazepines for tardive dyskinesia.[6]

References

1. Ali T, Sisay M, Tariku M, Mekuria AN, Desalew A. Antipsychotic-induced extrapyramidal side effects: A systematic review and meta-analysis of observational studies. *PLoS One*. 2021 Sep 10;16(9):e0257129. doi: 10.1371/journal.pone.0257129.
2. Mulroy E, Balint B, Bhatia KP. Tardive syndromes. *Pract Neurol*. 2020 Oct;20(5):368-376. doi: 10.1136/practneurol-2020-002566.
3. Warren B, Vanderhoef D and Johnson J. VMAT2 Inhibitors for the Treatment of Tardive Dyskinesia. *Issues in Mental Health Nursing*. 2022; 43(1): 22-31. doi: 10.1080/01612840.2021.1948643
4. DynaMed [database online]. Ipswich (MA): EBSCO Information Services. https://www.dynamed.com. Accessed January 23, 2024.
5. Caroff SN, Campbell EC. Drug-Induced Extrapyramidal Syndromes: Implications for Contemporary Practice. *Psychiatr Clin North Am*. 2016 Sep;39(3):391-411. doi: 10.1016/j.psc.2016.04.003.
6. The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia. *Am J Psychiatry*. 2020 Sep 1;177(9):868-872. doi: 10.1176/appi.ajp.2020.177901
7. Pringsheim T, Gardner D, Addington D, Martino D, Morgante F, et al. The Assessment and Treatment of Antipsychotic-Induced Akathisia. Can J Psychiatry. 2018 Nov;63(11):719-729. doi: 10.1177/0706743718760288.
8. Gerolymos C, Barazer R, Yon DK, Loundou A, Boyer L, et al. Drug Efficacy in the Treatment of Antipsychotic-Induced Akathisia: A Systematic Review and Network Meta-Analysis. *JAMA Network Open*. 2024;7(3):e241527. doi:10.1001/jamanetworkopen.2024.1527
9. Ward KM, Citrome L. Antipsychotic-Related Movement Disorders: Drug-Induced Parkinsonism vs. Tardive Dyskinesia-Key Differences in Pathophysiology and Clinical Management. *Neurol Ther*. 2018 Dec;7(2):233-248. doi: 10.1007/s40120-018-0105-0.
10. Citrome L. Tardive dyskinesia: placing vesicular monoamine transporter type 2 (VMAT2) inhibitors into clinical perspective. *Expert Rev Neurother*. 2018 Apr;18(4):323-332. doi: 10.1080/14737175.2018.1455504.
11. Savitt D, Jankovic J. Tardive syndromes. *J Neurol Sci*. 2018 Jun 15;389:35-42. doi: 10.1016/j.jns.2018.02.005.
12. Artukoglu BB, Li F, Szejko N, Bloch MH. Pharmacologic Treatment of Tardive Dyskinesia: A Meta-Analysis and Systematic Review. *J Clin Psychiatry*. 2020 May 26;81(4):19r12798. doi: 10.4088/JCP.19r12798. PMID: 32459404.
13. Bergman H, Rathbone J, Agarwal V, Soares-Weiser K. Antipsychotic reduction and/or cessation and antipsychotics as specific treatments for tardive dyskinesia. *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD000459. DOI: 10.1002/14651858.CD000459.pub3.
14. Mulroy E, Balint B, Bhatia KP. Tardive syndromes. *Pract Neurol*. 2020 Oct;20(5):368-376. doi: 10.1136/practneurol-2020-002566.
15. Solmi M, Pigato G, Kane JM, Correll CU. Treatment of tardive dyskinesia with VMAT-2 inhibitors: a systematic review and meta-analysis of randomized controlled trials. *Drug Des Devel Ther*. 2018 May 14;12:1215-1238. doi: 10.2147/DDDT.S133205.
16. VA/DoD Clinical Practice Guideline (2023). Management of First-Episode Psychosis and Schizophrenia Work Group. Washington, DC: U.S. Government Printing Office. Available at: https://www.healthquality.va.gov/guidelines/MH/scz/index.asp. Accessed 21 Feb 2024.
17. INGREZZA (valbenazine) capsules [Prescribing Information]. Neurocrine Biosciences, Inc., San Diego, CA. Aug 2023.
18. AUSTEDO XR (deutetrabenazine extended-release tablets) and AUSTEDO (deutetrabenazine) tablets [Prescribing Information]. Teva Neuroscience, Inc. Parsippany, NJ. Sept 2023.
19. Kane JM, Correll CU, Nierenberg AA, Caroff SN, Sajatovic M; Tardive Dyskinesia Assessment Working Group. Revisiting the Abnormal Involuntary Movement Scale: Proceedings from the Tardive Dyskinesia Assessment Workshop. *J Clin Psychiatry*. 2018 May/Jun;79(3):17cs11959. doi: 10.4088/JCP.17cs11959.
20. Stacy M, Sajatovic M, Kane JM, Cutler AJ, Liang GS, et al.. Abnormal involuntary movement scale in tardive dyskinesia: Minimal clinically important difference. *Mov Disord*. 2019 Aug;34(8):1203-1209. doi: 10.1002/mds.27769.
21. Hauser RA, Barkay H, Wilhelm A, Wieman M, Savola JM, et al. Minimal clinically important change in Abnormal Involuntary Movement Scale score in tardive dyskinesia as assessed in pivotal trials of deutetrabenazine. *Parkinsonism Relat Disord*. 2022 Apr;97:47-51. doi: 10.1016/j.parkreldis.2022.02.017.

You can get this document in other languages, large print, braille or a format you prefer.
Contact Andrew Gibler, PharmD, at 503-878-1395 or email andrew.n.gibler@oha.oregon.gov
We accept all relay calls or you can dial 711.

4/2024

Oregon Health Authority
HEALTH POLICY AND ANALYTICS
Office of Delivery Systems Innovation