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Extrapyramidal side effects with nonantipsychotic medications

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Case Report

PK is a 35-year-old male patient who presents to the psychiatry clinic for a routine follow-up visit. He denies any mood complaints but does report arm stiffness, slowness of his movements, and a slight left-handed tremor that is observed during rest on a few occasions during the visit. PK has a 15-year history of bipolar I disorder; the most recent episode was depressed. He has been stable on his current medication regimen of lithium 600 mg twice a day and lamotrigine 150 mg once daily for the last 3 years. He denies any history of substance use and does not recall ever being given an antipsychotic as "lithium worked for me from the start." He also denies taking any other medications, prescribed or over the counter, and has no other chronic medical conditions. An appropriately drawn lithium concentration obtained that morning was therapeutic at 1.0 mEq/L.

Discussion

Extrapyramidal side effects (EPS) are also referred to as medication-induced movement disorders, and they include dystonias, akathisia, parkinsonism, and dyskinesias.[1] Table 1 provides a summary of these EPS and commonly associated features. Typical and atypical antipsychotics are the most common causes of EPS due to their antagonist effects at dopamine receptors in the nigrostriatal pathway of the brain. In addition to antipsychotic medications, a number of other psychiatric medications, including mood stabilizers and antidepressants, have been associated with EPS with unknown causative mechanisms.[2] A summary of some specific nonantipsychotic, psychotropic agents implicated in contributing to EPS are outlined as follows.

Lithium

The conventional mood stabilizer lithium is associated with parkinsonism and, in a few case reports, tardive dyskinesia.[3,4] More commonly, lithium is associated with postural and action tremors (estimates of frequency range from 4% to 65%). It is important to note that lithium-induced tremors are not characteristic of the tremor featured in parkinsonism, which is a resting tremor. Parkinsonism is diagnosed by the presence of bradykinesia (slowness of the movements) along with at least 1 of 3 other symptoms: resting tremor, rigidity, and/or postural instability.[5] Although the exact prevalence of lithium-induced parkinsonism is unknown, this EPS seems to be relatively rare. Interestingly, 1 retrospective study evaluated the use of lithium, valproic acid (VPA), or antidepressants in individuals aged ≥66 years old and initiation of an antiparkinson medication. This study found a significant increase in the prescribing of an antiparkinson medication in patients treated with lithium for at least 1 year.[6] Although it is possible that the patients prescribed an antiparkinson medication may have had parkinsonism secondary to lithium therapy, the investigators questioned the accuracy of diagnosis. There was some question as to whether these patients may have had the more common lithium-associated adverse effect, a postural or action tremor, which was inappropriately treated with antiparkinson medication.[6] As a health care provider, it is important to determine whether a patient on lithium is presenting with symptoms that are diagnostic of

Practice Points:

1. Extrapyramidal side effects are associated with nonantipsychotic medications, including lithium, valproic acid, and antidepressants.
2. If a patient is presenting with what seems to be a possible medication-induced movement disorder, evaluation should include the use of a validated assessment scale found in Table 1.
3. Most often, discontinuation of the offending medication leads to resolution of the movement disorder; however, this may not be possible for some patients, so dose adjustment and addition of another medication (such as propranolol) may be required.

parkinsonism or an action/postural tremor as the management may vary. For either side effect, a reduction in lithium dose or discontinuation should alleviate symptoms. In the case of an action or postural tremor, the continuation of lithium, upon verifying an appropriate concentration, may include the addition of propranolol or primidone.[7]

VPA/Divalproex Sodium

The antiseizure medication VPA/divalproex sodium is often used for psychiatric purposes and is also reported in limited cases to cause parkinsonism. Several studies of patients treated with VPA report that parkinsonism occurred within therapeutic concentrations of the agent and at normal serum ammonium concentrations, so it does not appear to be dose dependent.[2] Most patients' parkinsonism resolved with the discontinuation of VPA. If parkinsonism is diagnosed secondary to VPA, the best course of treatment is discontinuation of VPA in favor of another mood-stabilizing agent when possible.

As with lithium, VPA commonly causes a non–dose-dependent tremor. The most common type of tremor induced by VPA includes a postural or action tremor followed by a resting tremor (without other features of parkinsonism).[2,7] The treatment for VPA-induced tremor includes the addition of a beta-blocker, such as propranolol, or reduction/discontinuation of VPA.[7]

Antidepressants

Antidepressants are associated with causing various EPS, including dystonia, akathisia, dyskinesia, and parkinsonism.[1] Of these EPS, akathisia is most reported secondary to antidepressant use.[8] Akathisia tends to occur within the first few days to weeks of antidepressant initiation and dose escalation. Akathisia can be more difficult to recognize in patients and may be misdiagnosed as agitation, acute anxiety, restless leg syndrome, or withdrawal, resulting in improper management and possible worsening of the akathisia. A patient's self-report of what they are experiencing in addition to the use of the Barnes Akathisia Rating scale can aid in proper diagnosis and management.[9] If antidepressant-induced akathisia is identified, treatment can include a dose reduction, discontinuation of therapy, or the addition of propranolol to the current regimen.[8]

Just as with lithium and VPA, antidepressants are also associated with medication-induced tremors. Antidepressant-induced tremors may be treated by reducing the dose, discontinuing the offending agent, or adding propranolol.[7] However, it is important to rule out medication nonadherence as a tremor may occur during antidepressant discontinuation. Additionally, it is important to rule out tremors secondary to serotonin syndrome. Table 2 provides a summary of the EPS from nonantipsychotic medications along with possible management strategies.

Case Report Follow-Up

Based upon a literature search, lithium is found to be a possible cause of parkinsonism. An evaluation of PK with the Simpson-Angus Scale is positive.[10] Based upon this information and current clinical control of PK's bipolar disorder, the decision is made to decrease his current lithium dose from 600 mg twice daily to 300 mg every morning

TABLE 1: Extrapyramidal side effects and rating scales[1,9–12]

Extrapyramidal Side Effect	Description	Rating Scales
Dystonia	Involuntary muscle contractions	The Extrapyramidal Symptom Rating Scale[a]
Akathisia	A feeling of inner restlessness	Barnes Akathisia Rating Scale
Parkinsonism	Characterized by bradykinesia (slowness of the movements) plus at least 1 of 3 other symptoms: resting tremor, rigidity, or postural instability	The Simpson-Angus Scale
Dyskinesias	Involuntary, purposeless movement	The Abnormal Involuntary Movement Scale

[a]The Extrapyramidal Symptom Rating Scale is not specific just for dystonia.

TABLE 2: Extrapyramidal side effects associated with nonantipsychotic medication and possible management[2,6,8]

Extrapyramidal Side Effect	Possible Nonantipsychotic Medication	Management Strategies
Parkinsonism	Lithium VPA	Dose reduction, discontinuation
Akathisia	Antidepressants, most commonly SSRIs	Dose reduction, discontinuation Addition of propranolol
Tremor	Lithium VPA Antidepressants (most commonly SSRIs)	Dose reduction, discontinuation Addition of primidone, propranolol

SSRI = selective serotonin reuptake inhibitor; VPA = valproic acid.

and 600 mg at bedtime and to increase his lamotrigine from 150 mg daily to 200 mg daily.

One month later, PK returns to the clinic for follow-up and reports a resolution of his symptoms and continued control of his mood symptoms. PK is counseled to let his providers know if he is prescribed any chronic medications as well as to maintain his current caffeine and salt intake to maintain a steady lithium level.

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