Drug-Induced EPS, Akathisia, and Tardive Dyskinesia
Learning Objectives

• Differentiate antipsychotic treatment options based on risk for drug-induced movement disorders

• Implement updated evidence-based treatment guidelines for managing drug-induced movement disorders

• Explain the mechanisms and clinical data for novel agents under investigation for drug-induced movement disorders
What Are Extrapyramidal Signs (EPS) and Extrapyramidal Side Effects (EPSE)?

• Movement disorders that occur with antipsychotics
• Thought to involve structures outside of the pyramidal tract
• Occur in acute and late (tardive) forms
• Reason for the older term "neuroleptic" to describe antipsychotics
ACUTE AND SUBACUTE EPSE
Extrapyramidal Side Effects

• Acute extrapyramidal side effects
  – Dystonia
    • Disturbance in muscle tone leading to prolonged contractions of groups of muscles
    • Occurs within 24–48 hours of antipsychotic initiation
    • Only acute EPS that is less common in the elderly
  – Parkinsonism
    • Classic triad of bradykinesia, rigidity, and tremor
    • Occurs within days of treatment in one-fourth to one-third of patients
    • Can occur in up to 75% of older patients
Pathophysiology and Treatment

• Pathophysiology
  – Probably due to D2 blockade in various brain regions

• Treatment
  – Reduction in dose
  – Anticholinergics and other antiparkinsonians
  – Beta-blockers
  – Benzodiazepines
A 38-year-old woman was diagnosed with schizophrenia approximately 2 years ago, and after multiple trials of atypical and typical antipsychotic medications, she has been maintained on haloperidol for the last several months with good response. Two weeks ago, she began exhibiting mild motor symptoms of parkinsonism. Which of the following would be the most appropriate adjunct medication for this patient?

1. Alpha 1 adrenergic agonist
2. Cholinesterase inhibitor
3. Histamine 1 antagonist
4. Muscarinic 1 antagonist
What would be the most appropriate adjunct medication for this patient with EPS?

1. Alpha 1 adrenergic agonist
   - Alpha 1 stimulation may decrease striatal DA release; thus, antagonism would be expected to reduce EPS

2. Cholinesterase inhibitor
   - Reduces metabolism of ACh, causing a further increase in ACh activity

3. Histamine 1 antagonist
   - Some antihistamines are M1 antagonists, but their H1 antagonist properties do not regulate EPS

4. Muscarinic 1 antagonist
   - Prevents ACh from binding at M1 receptor and thus reduces its effects, potentially relieving EPS

Distribution of Parkinsonian Tremor
Distribution of Acute Dystonia
Videos

Dystonic Reaction—Oculogyric Crisis

Neuroleptic-Induced Parkinsonism—Pill-Rolling Tremor

Neuroleptic-Induced Parkinsonism—Rigidity

Parkinson’s Gait
AKATHISIA
Akathisia Overview

• Akathisia is one of the most vexing problems in neuropsychiatry and is *still common with second-generation antipsychotics*

• Although it is one of the most common side effects of antipsychotics, it is often difficult to describe by patients and difficult to diagnose and treat by practitioners

• It is therefore not surprising that akathisia is generally either underdiagnosed or misdiagnosed; this is a serious problem because it can lead to such adverse outcomes as poor adherence to medications, exacerbation of psychiatric symptoms, and in some cases, aggression, violence, and suicide
History and Pronunciation

• "Akathisie" – coined in 1901 by the Czechoslovakian neuropsychiatrist Ladislav Hascovec, who created the term in Czech from the Greek $\alpha$ (not) + κάθιςω (to be made to sit down) – i.e., inability to sit

• Although the term "akathisia" is often pronounced as rhyming with dyskinesia (and sometimes even spelled "akathesia"), it derives from very different Greek roots (there is no "kinesis," or movement, in the etymology of akathisia)

• It is more correctly spelled "akathisia" and pronounced æ.kə.'θi.sɪ.ə, where "ɪ" is pronounced as in "kit" or "bin" and "i" is pronounced as in "glorious"
Phenomenology

- Straddles the boundary between a symptom (a subjective problem described by a patient) and a sign (an objective problem observed by a clinician)

- The subjective component can exist independently of the objective component, particularly when the condition is mild; the opposite—if there is an objective component but no subjective discomfort—has been called pseudoakathisia.

- Although commonly considered a type of movement disorder or EPS, akathisia should be considered more of a sensorimotor disorder because of the powerful sensory component, which is a defining characteristic of the condition.
Subjective Symptoms

• Often extraordinarily difficult for the patient to describe, to some extent because there are few subjective states to which it can be compared

• Patients often use terms such as "anxiety" or "itching," although these do not really capture the essence of the condition

• Since many clinicians have never experienced it, there is often a lack of common ground in communicating the problem
Patient Descriptions

• "It feels like my legs are on fire inside"
• "It makes me want to run around the room or leap out of my bed"
• "It's like a deep itching and tingling inside my bones, and moving around relieves it a little"
• "It's sort of like that feeling you get after your leg falls asleep and then wakes up, but it doesn't go away"
• "I want to jump out of my skin"
Severity of Subjective Problems

- Severity ranges from "mildly annoying" (and easily relieved by moving a limb or shifting position), to "absolutely intolerable," associated with extreme dysphoria and a sense of "impending doom"

- An important cause of medication nonadherence

- May exacerbate any psychiatric symptoms present, often leading clinicians to inappropriately increase the offending agents, such as SSRIs or antipsychotics

- Severe cases have been linked to suicidal ideation, aggression, and violence
Objective Signs

- The objective sign of akathisia is a **movement disorder**
- When mild to moderate in severity, the lower extremities are predominantly involved, usually from the hips to the ankles, and the movements take the form of shifting positions while standing and rocking or moving the feet around while sitting
- With increasing severity, akathisia can involve the entire body, resulting in nearly incessant writhing and rocking movements often accompanied by jumping around, running, and occasionally jumping out of a chair or a bed
- There are isolated reports of akathisia occurring primarily in other body regions (such as suboccipital muscles) or in strange distributions, as in hemi-akathisia (affecting only 1 side of the body)
- **Strange or unusual distributions** of either subjective or objective components should increase concern that there may be another **process** influencing the clinical presentation, such as an infarction or abscess
Characteristic Distribution
Videos

Akathisia—Mild

Akathisia—Severe
POTENTIAL SUBTYPES OF AKATHISIA
Acute, Subacute, and Chronic Akathisia

- Usually occurs within a few days to weeks of initiating or increasing the dose of an antipsychotic.

- During the initial weeks, it is considered acute; later, it is considered subacute or chronic.

- Chronic akathisia simply refers to akathisia that has been present for a long time, usually for at least several months; it is different from tardive akathisia.
Withdrawal Akathisia

- Phenomenologically indistinguishable from acute akathisia
- Occurs upon antipsychotic dosage decrease or withdrawal
- Usually appears within 2 weeks of discontinuation and disappears within 6 weeks
- If it lasts longer, it is probably tardive akathisia
Tardive Akathisia

- Indistinguishable in clinical appearance from acute akathisia, but its time of onset and course resemble those of tardive dyskinesia; in other words, it:
  1. Occurs late in the course of treatment with antipsychotics (usually after at least 3 months)
  2. May emerge after antipsychotic discontinuation or dosage reduction
  3. Can often be reduced in severity by increasing the antipsychotic dosage
  4. May persist from months to years, even in the absence of drug
Pseudoakathisia

- Describes a condition in which there are objective signs of akathisia without subjective symptoms

- Because akathisia commonly occurs in patients with psychiatric disorders such as schizophrenia, it is unclear whether pseudoakathisia should actually be considered a "pseudo" form of the disorder, as many patients experience discomfort that they are unable to understand or express clearly

- I am skeptical about the existence of pseudoakathisia as a true subtype of akathisia as opposed to one in which other factors may simply reduce or alter the subjective complaints
• Prevalence with first-generation antipsychotics (FGAs) is in the range of 8-76% of treated patients, making it arguably the most common side effect of these medications; this is quite a large prevalence range; differences in reports are probably due in part to some of the recognition factors described below and to differences in age, dosage, and timing of assessment.

• Prevalence with second-generation ("atypical") antipsychotics (SGAs) varies widely but is often quite high, although in general, it is lower than with FGAs:
  – Aripiprazole (23–42%)
  – Risperidone (7–50%)
  – Olanzapine (3–16%)
  – Quetiapine (2–13%)
  – Iloperidone (appears very low, 0%?)
Clozapine has highly variable reports of prevalence from very low to rates similar to those seen with FGAs (39% vs. 45%).

At this time, it appears that quetiapine and iloperidone may be associated with the lowest rates of akathisia, but further studies are warranted.

Antidopaminergic antiemetics, such as prochlorperazine and metoclopramide, as well as dopamine-depleting agents, such as reserpine and tetrabenazine, which impede the reuptake of dopamine into presynaptic vesicles, have also been reported to commonly cause akathisia.
Antidepressant-Induced Akathisia

• There is growing awareness that akathisia can occur during treatment with antidepressants

• Selective serotonin reuptake inhibitors (SSRIs) have received the most reports of an association with akathisia

• Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have received fewer such reports
Other Drug-Induced Akathisia

• There have also been reports of akathisia with:
  – The antibiotic azithromycin
  – Calcium channel blockers
  – Lithium
  – Recreational drugs such as:
    • Gamma-hydroxybutyrate (GHB)
    • Methamphetamine
    • 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)
    • Cocaine
Akathisia in Parkinsonian Conditions

• Akathisia has been described in conjunction with a variety of parkinson-related disorders, including:
  – Parkinson's disease (PD) itself
  – Postencephalitic parkinsonism
  – Corticobasal degeneration (CBD)
  – Multiple system atrophy (MSA)

• There is a complex relationship between L-DOPA and akathisia, with some reports suggesting that the occurrence of akathisia may relate to the time of dosing or to "off" effects and other reports finding no clear association between the two
Spontaneous Akathisia

- Akathisia has been reported to occur in untreated schizophrenia, in which it has also been termed "spontaneous akathisia"
Risk Factors for Antipsychotic-Induced Akathisia

- Bipolar disorder
- Higher dose or rapid dose increase of antipsychotic
- Traumatic brain injury
- Cancer
- Possibly iron deficiency
- There is no clear evidence of risk associated with age, gender, or ethnicity
- Chronic or tardive akathisia may be more common with advanced age and female gender
Pathophysiological Mechanisms of Akathisia: Part 1

• The pathophysiology of akathisia is unknown

• Dopamine blockade might be involved

• More than 30 years ago, Marsden and Jenner suggested that akathisia may be caused by the blockade of mesocortical dopaminergic pathways; this is still a viable but unproven hypothesis

• May relate to an imbalance between the serotonergic and dopaminergic systems, as akathisia appears to be less common after treatment with SGAs, which are serotonergic antagonists, than with FGAs, which have much less serotonergic activity
Loonen and Stahl have suggested another mechanism of akathisia, in which a generalized reduction in dopamine in the brain (as is seen with antipsychotics and PD) may trigger compensatory mechanisms, particularly in the form of increased noradrenergic activity from the locus coeruleus.

Because adrenergic fibers innervate the shell of the nucleus accumbens to a greater extent than the core, a mismatch may occur, resulting in dysphoric feelings and semi-purposeful movements.

This would also help explain the possible utility of beta-blockers and the fact that akathisia is not seen in everyone treated with FGAs, which powerfully block dopamine receptors.
It is possible that mechanistic clues for akathisia can be found in studies of restless legs syndrome (RLS).

For RLS, it has been suggested that dopamine reduction in the substantia nigra or in dopamine A11 neurons, which originate in the hypothalamus and terminate in the spinal cord, may be involved.

Recently, however, it has been observed that domperidone, which is a dopamine receptor antagonist that does not cross the blood-brain barrier, can cause a worsening of RLS in PD, suggesting that peripheral dopaminergic factors may be involved.

Because RLS is similar to akathisia, these possible mechanisms may be worth studying in akathisia as well.
Assessment of Akathisia

• Akathisia is a diagnosis made purely by clinical observation and patient report

• There is no confirmatory blood test, imaging assessment, or neurophysiological study available

• When assessing the severity of akathisia, it can be quite helpful to observe the patient when they do not know they are being evaluated, such as when sitting in the waiting area; this is because many individuals can exert a great deal of suppressive control over the motor aspects of the condition, especially when it is only of mild to moderate severity, causing a falsely low estimate of its severity

• The most commonly used tool for assessment is the Barnes Akathisia Rating Scale (BARS)
Treatment of Akathisia: Part 1

- The evidence base for the treatment of akathisia is very small; many recommendations are based on clinician experience, case reports, and reports from drug studies in which akathisia was not a primary concern.
- **Step 1:** The cause of the akathisia should be identified, and initial treatment should be aimed at that cause.
- **Step 2:** Since the majority of patients with akathisia probably develop it secondary to psychotropic medications, an initial recommendation is to reduce or switch medications, if possible.
  - In patients on FGAs, an attempt should be made to switch to SGAs such as quetiapine and iloperidone, which appear to cause less akathisia.
  - It should be remembered that occasionally, withdrawal akathisia can occur, so one should not judge the effectiveness of a dose reduction or a medication switch for at least 6 weeks, as the akathisia may show a temporary exacerbation.
  - If the akathisia worsens but does not disappear, tardive akathisia may be present; the treatment guidelines follow those of acute akathisia, with the exception that when severe, tardive akathisia can be suppressed by reinstating the offending agent at the previous dose.
- **Step 3:** If iron deficiency is present, correcting this may be of some benefit.
• **Step 4:** If the akathisia is still present after these steps, *it may be very difficult to treat*; a host of different medications have been reported to be useful, but without much corroborating evidence; these medications include:

  – Anticholinergic drugs (e.g., biperiden, trihexyphenidyl, benztropine)
  
  – Beta-blockers (e.g., propranolol, metoprolol)
  
  – Serotonin 5HT2A antagonists (e.g., mianserin, mirtazapine, cyproheptadine)

• Recent meta-analyses of these treatments have been performed, with the results for anticholinergic drugs and beta-blockers being negative (both of these were Cochrane Reviews); however, a recent meta-analysis of serotonergic antagonists for akathisia was positive
Treatment of Akathisia: Part 3

- Isolated reports of success with:
  - Vitamin B6
  - N-acetylcysteine
  - Tetrabenazine (although this is also reported to cause akathisia)
  - Clonidine
  - Dopamine agonists (bromocriptine and amantadine)
  - Piracetam
  - Buspirone
  - Opiates

- Benzodiazepines have proven useful but do not appear to relieve akathisia as much as associated anxiety
TARDIVE DYSKINESIA (TD)
Clinical Presentation of TD

• Athetoid or choreoathetoid movements usually associated with lower facial and distal extremity musculature
• Not associated with direct sensory problems
• Has been of considerable clinical, medical, and legal concern because of potential persistence despite drug discontinuation
Characteristic Distribution of TD
Course and Epidemiology of Tardive Dyskinesia: Part 1

- May appear as early as 1 month
- Prevalence as high as 60–70%
- Course is variable
- One-third of patients who discontinue neuroleptics show improvement
• Lifetime prevalence as high as 33% in patients treated with FGAs
  – Risk is approximately 5%/year with FGAs
  – Risk is 80% lower for SGAs but is not 0%
• Geriatric patients: increased movement disorders even in neuroleptic-naïve patients
  • TD rates of 26–31% after 1-year exposure to FGA
  • TD rates of 2.5% after 1-year exposure to atypical antipsychotic (risperidone, quetiapine)
• Children: higher rates in patients taking haloperidol
Tardive Syndromes

- Tardive dyskinesia
- Tardive dystonia
- Tardive akathisia
- Tardive parkinsonism (tremor)
- Tardive myoclonus
Tardive Dyskinesia—Moderate

Tardive Dyskinesia—Severe

Tardive Dyskinesia—Severe in Tongue

Tardive Dystonia—Severe

Tardive Dystonia

Tardive Tic
Is TD Disappearing?

• No direct evidence of decrease in prevalence
• Incidence in SGAs is about one-tenth of that in FGAs, but:
  – SGAs are more widely used
  – It is unclear whether TD is more persistent when it occurs with SGAs
• Increased numbers of older patients receiving antipsychotics
Tardive Dyskinesia Risk Factors

- Older age (risks are 26%, 52%, 60% after 1, 2, 3 years in geriatric patients)
- Length of treatment
- Alcohol abuse/dependence
- Early-onset EPS
- Medical comorbidity
- Female gender
- Presence of mood disorder
Tardive Dyskinesia: Other Risk Factors

- Early onset of psychosis
- Negative symptoms
- Cognitive symptoms
- Comorbid substance abuse
- Ethnicity?
- 5% of medication-naïve patients with schizophrenia exhibit spontaneous movements
Pathophysiology: 2 Hypotheses

• Dopamine supersensitivity hypothesis
  – May contribute, but lots of problems
  – Probably better model for withdrawal-emergent dyskinesia

• Neuronal degeneration hypothesis
  – Oxidative and/or excitotoxic damage
  – Considerable basic science evidence
  – May offer avenues for clinical treatment
Treatment of TD

• Reduce FGA
• Switch to SGA (not much evidence that SGAs treat TD, though)
• Be patient
• Other strategies
Switching Antipsychotics to Address Tardive Dyskinesia

- Dopamine antagonism can mask dyskinesia
- Severe TD
  - Switch to clozapine
- Mild to moderate TD on conventional antipsychotic
  - Switch to SGA
- Mild to moderate TD on SGA
  - No clear evidence
  - Theory is that risk of TD is proportional to agent's propensity to cause EPS, so consider agents with lowest risk of EPS
    - Iloperidone, quetiapine, clozapine
Other Strategies if TD Does Not Reverse

• Reserpine and tetrabenazine (dopamine-depleting agents) have been first line
• Other options with some evidence of efficacy, per the American Academy of Neurology:
  – Clonazepam and ginkgo biloba
  – Amantadine
  – Botulinum toxin injections for focal symptoms
  – Vitamin E for protecting against deterioration
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<th>Compound</th>
<th>Company</th>
<th>Stage</th>
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<td>Phase III ongoing</td>
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A 54-year-old woman with schizophrenia and a history of depression has developed tardive dyskinesia after taking haloperidol 15 mg/day for 2 years. Her depression is currently poorly controlled. Which of the following would be the most appropriate pharmacological option for managing this patient's tardive dyskinesia?

1. Amantadine
2. Donepezil
3. Reserpine
4. Tetrabenazine
**What would be the most appropriate pharmacological option for managing this patient's TD?**

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1. Amantadine</td>
<td>Not usually first line, but the best of these choices because some of the other options are <strong>contraindicated</strong></td>
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<tr>
<td>2. Donepezil</td>
<td>Cholinesterase inhibitor; limited data show that it has negligible benefit for tardive dyskinesia</td>
</tr>
<tr>
<td>3. Reserpine</td>
<td>Contraindicated in patients with a history of depression</td>
</tr>
<tr>
<td>4. Tetrabenazine</td>
<td>Contraindicated in patients with poorly controlled depression</td>
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</table>
A 44-year-old man with schizophrenia has been taking a second-generation antipsychotic since his initial diagnosis 12 years ago. Four weeks ago, he discontinued his medication and began experiencing difficulty with fluid movement of his arms as well as involuntary facial grimaces and tongue protrusions. Which of the following likely underlies these symptoms?

1. Upregulation of 5HT2A receptors
2. Downregulation of 5HT2A receptors
3. Upregulation of D2 receptors
4. Downregulation of D2 receptors
What likely underlies this patient's symptoms?

1. Upregulation of 5HT2A receptors
2. Downregulation of 5HT2A receptors
3. Upregulation of D2 receptors
4. Downregulation of D2 receptors

Withdrawal dyskinesia does not result from changes in 5HT2A receptors.
DIFFERENTIAL DIAGNOSIS OF EPS
Anxiety vs. Akathisia

- Extremely difficult to distinguish anxiety from akathisia

- Anxiety
  - Subjectively, patients are less likely to complain about a need to move or about how movement reduces the severity of their discomfort
  - Objectively, associated with a greater degree of autonomic arousal; observable excesses in movement usually manifest in the upper extremities and the face
Psychomotor Agitation vs. Akathisia

• Considered part of the primary presentation of a mental disorder, such as depression, bipolar disorder, schizophrenia, or posttraumatic stress disorder (PTSD)

• It is unclear whether "psychomotor agitation" relates to the same underlying mechanism in these disorders

• Unlike anxiety, which is a symptom, agitation is a sign; the two may or may not be associated

• Akathisia is often described as a type of agitation, but the two can usually be differentiated by:
  – The specific movement-impelling aspect of the subjective discomfort
  – The preferential involvement of the lower extremities when mild or moderate in severity
TD vs. Akathisia

• The disorder perhaps most commonly confused with akathisia; occurs late in the course of treatment; often associated with tardive akathisia

• TD can be differentiated from acute akathisia on the basis of:
  – Timing of the appearance (late vs. early)
  – Nature of the movements (writhing athetoid or choreoathetoid movements)
  – Preferred somatic distribution of movements, predominantly of the lower face and distal extremities
  – When the legs are involved in TD, the movements are usually more pronounced in the toes than in the more proximal muscles
Antipsychotic-Induced Dystonia

- Acute antipsychotic-induced dystonias (also called dystonic reactions) occur within 24–48 hours of initiating or increasing antipsychotic dosing.
- There is also a tardive form, which shares the timing characteristics of TD.
- Dystonias tend to involve the eyes (oculogyric crises), tongue, neck (torticollis), shoulders, and trunk.
TD vs. Parkinsonian Tremor

- Usually most clinically obvious in the hands and wrists when at rest
- Pill-rolling characteristic consisting of alternating contractions of agonist and antagonist muscles in a rhythmic rate of 4-7 cycles/second
AKATHISIA VS. RESTLESS LEGS SYNDROME (RLS)
Restless Legs Syndrome (RLS)

• RLS has more alternative names than most other medical disorders
  – Also known as Ekbom syndrome, Wittmaack-Ekbom syndrome, Willis-Ekbom Disease, *anxietas tibiarum*, and *anxietas tibialis*
  – Ekbom himself originally called the disorder *asthenia crurum paraesthetica*, highlighting the uncomfortable paresthesias in the lower extremities

• It is unclear whether akathisia and RLS are truly different disorders

• To see how difficult it can be to distinguish from akathisia, witness Ekbom's original description…
"The paresthesia is felt in the lower legs (not the feet). It is never experienced superficially in the skin, but deep down in the calf or sometimes the shin. The patient has difficulty in finding the right words to describe it. It is a crawling sensation, irritating and enervating. As a rule it is not a question of real pain....I have asked the patients whether it is experienced as a kind of anxiety, but they all said no. But all agreed that it was something very unpleasant....The sensations disappear or lessen when the legs are moved about, but they soon return."
Critical Features of RLS

1. A desire to move the extremities usually associated with some definable discomfort

2. Motor restlessness

3. Worsening of symptoms at rest with at least temporary relief by activity

4. Worsening of symptoms later in the day or at night
   • Aside from criterion 4, there is essentially no definitional difference between akathisia and RLS
   • The association with nighttime and sleep is the essential clinical difference between RLS and akathisia, as Ekbom noted
Relationship Between Akathisia and RLS

- Often receives very little attention
- May relate to the different heritage of these concepts
- RLS studies come more from the neurological and sleep literature, whereas akathisia studies come more from the psychiatric and psychopharmacological literature
- The diagnostic confusion is seen with PD, for example; in some instances, restlessness is referred to as RLS; in others, akathisia; however, it is unclear whether there is a real distinction
- Diagnostically, it is very confusing when investigators report the occurrence of akathisia at nighttime and RLS during the day
Possible Distinguishing Characteristics

• **RLS may be clinically distinguished from akathisia as follows:**
  - Occurs more commonly at night
  - Associated with greater sleep disturbance
  - Marked by myoclonus when severe
  - Exacerbated by lying down (akathisia may be somewhat relieved by lying down in some patients)
  - Experienced more as paresthesias (akathisia may be experienced more as restlessness)

• **May also be distinguished in terms of treatments:**
  - Dopamine agonists and opiates are standard treatments for RLS but are rarely if ever used for akathisia
  - Anticholinergic drugs and beta-adrenergic blockers are often used for akathisia but are rarely used for RLS

• **These differences may relate not so much to the underlying conditions, but to the fact that akathisia commonly occurs in individuals with psychiatric disorders**
  - In these individuals, dopaminergic agonists may exacerbate manic or psychotic symptoms, and opiates are usually avoided because of abuse potential