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# CNS SPECTRUMS

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**CME Review Article**

**The Clinical Challenges of Akathisia**

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CME credit expires: November, 2018

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- Employ strategies to accurately recognize and diagnose akathisia
- Implement evidence-based treatment strategies for addressing akathisia

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No writing assistance was utilized in the production of this article.

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Additionally provided by the American Society for the Advancement of Pharmacotherapy.

### **Acknowledgment of Financial Support**

This activity is supported by an unrestricted educational grant from Vanda Pharmaceuticals Inc.

# The clinical challenges of akathisia

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Akathisia is one of the most vexing problems in neuropsychiatry. Although it is one of the most common side effects of antipsychotic medications, it is often difficult to describe by patients, and is difficult to diagnose and treat by practitioners. Akathisia is usually grouped with extrapyramidal movement disorders (ie, movement disorders that originate outside the pyramidal or corticospinal tracts and generally involve the basal ganglia). Yet, it can present as a purely subjective clinical complaint, without overt movement abnormalities. It has been subtyped into acute, subacute, chronic, tardive, withdrawal-related, and “pseudo” forms, although the distinction between many of these is unclear. It is therefore not surprising that akathisia is generally either underdiagnosed or misdiagnosed, which 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. In this article, we will attempt to address some of the confusion surrounding the condition, its relationship to other disorders, and differential diagnosis, as well as treatment alternatives.

Received 14 October 2015; Accepted 27 October 2015

**Key words:** akathisia, antipsychotic, movement disorder, Parkinson, review.

## History and Phenomenology

“Akathisie” was originally coined by the Czechoslovakian neuropsychiatrist Ladislav Hascovec shortly after the turn of the 20th century,<sup>1–3</sup> probably in 1901. He created the term in Czech from the Greek  $\alpha$  (not) +  $\kappa\acute{\alpha}\theta\iota\zeta\omega$  (to be made to sit down) – ie, inability to sit. Hascovec considered akathisia (as the term later came to be spelled) to be primarily a movement disorder (but one with a more psychiatric etiology, such as a hysterical or conversion disorder), and only 1 of the 2 patients he initially described appeared to have the characteristic accompanying subjective discomfort and “need to move” that we now associate with the condition. In 1923, akathisia was described in patients with post-encephalitic parkinsonism by Paul Robert Bing and Jean-Athanase Sicard, but again it was considered more of a psychiatric condition.<sup>3</sup>

After the discovery that antipsychotic medications frequently caused the disorder in the 1950s, it was later grouped with other movement problems that commonly occur with antipsychotics, including parkinsonism and dystonia, all of which came to be referred to as extrapyramidal side effects (EPSE) or extrapyramidal signs (EPS).<sup>3</sup>

Although the term “akathisia” is often pronounced as rhyming with dyskinesia (and sometimes even spelled akathesia),<sup>4</sup> it derives from very different Greek roots (there is no “kinesis” or movement in the etymology of akathisia) and is more correctly spelled “akathisia,” and pronounced æ.kə.'θɪ.si.ə (using International Phonetic Alphabet symbols, where “i” is pronounced as in “kit” or “bin” and “i” is pronounced as in “glorious”).

Akathisia straddles the boundary between being a symptom (ie, a subjective problem described by the patient) and a sign (an objective problem observed by the 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—a troublesome concept discussed below.

The subjective discomfort of akathisia is often extraordinarily difficult for the patient to describe, to

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† We would like to thank Dr. Stephen Stahl and the staff of the Neuroscience Education Institute for their assistance in preparing this article.

This activity is supported by an unrestricted educational grant from Vanda Pharmaceuticals Inc.

some extent because there are few subjective states to which it can be compared. Hence, patients often use terms such as “anxiety” or “itching,” even though these do not really capture the essence of the condition. In addition, since many clinicians have never experienced it, there is often a lack of common ground in communicating the problem. Characteristic descriptions that two of us (JBL and MAS) have heard over the years include, “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,” and “I want to jump out of my skin.” The severity of subjective discomfort ranges from “mildly annoying” (and easily relieved by moving a limb or shifting position) to “absolutely intolerable,” which is associated with extreme dysphoria and a sense of “impending doom.” The most severe cases have been linked to suicidal ideation, aggression, and violence.<sup>5–9</sup> Akathisia is an important cause of poor medication adherence.<sup>10–12</sup> The presence of akathisia also exacerbates any psychiatric symptoms present,<sup>12–16</sup> often leading clinicians to increase inappropriately the offending agents, such as selective serotonin reuptake inhibitors (SSRIs) or antipsychotics.

The objective sign of akathisia is a movement disorder. When mild to moderate in severity, the lower extremities are predominantly involved, usually from hips to ankles, and the movements take the form of shifting positions while standing, and rocking or moving the feet around while sitting. The predilection to affect primarily the lower extremities is often helpful in differentiating akathisia from other antipsychotic-induced side effects that tend to affect other body regions (described more below). With increasing severity, however, akathisia can involve the entire body, resulting in near incessant writhing and rocking movements often accompanied by jumping around, running, and occasionally flinging oneself out of a chair or a bed.<sup>17</sup> Although we have never personally seen a case of akathisia that did not affect the lower extremities to some degree, there are reports of akathisia occurring primarily in other body regions (such as suboccipital muscles)<sup>18</sup> or in strange distributions, such as hemiakathisia (affecting only one side of the body).<sup>19</sup> Strange or unusual distributions of either subjective or objective components of akathisia should increase concern that there may be another process present influencing the clinical presentation, such as an infarction or abscess.<sup>19</sup>

Although commonly considered a type of movement disorder or EPS, in fact akathisia should be considered more a *sensorimotor disorder* because of the powerful sensory component, which is a defining characteristic of the condition. In fact, the sensory component may be the

primary problem, with motor signs being secondary to the restlessness and need to move.

### Potential Subtypes

Akathisia has been divided into several subcategories, mainly in relation to drug-induced forms of the condition. The differences between these subtypes are generally based on the time course of the condition, because the actual clinical presentations (save for pseudoakathisia) are indistinguishable from one another.

- **Acute, subacute, and chronic akathisia:**<sup>20,21</sup> Akathisia usually occurs within a few days to weeks of initiating an antipsychotic medication or increasing the dose. During the initial weeks, it is considered acute, and later it is considered subacute or chronic. Akathisia may develop within days and maintain severity at that level over time, or it may gradually increase or decrease in severity over time. When increasing in severity, the subjective and objective components become more pronounced and spread to other body regions. Chronic akathisia simply refers to akathisia that has been present a long time, usually several months or more, and is a different concept from tardive akathisia, described below.
- **Withdrawal akathisia:**<sup>22</sup> This condition, indistinguishable phenomenologically from acute akathisia, occurs upon dosage decrease or withdrawal of antipsychotic agents. Withdrawal akathisia usually appears within about 2 weeks of discontinuation, and disappears within about 6 weeks. If it lasts longer, then it probably represents tardive akathisia, as described below.
- **Tardive akathisia:**<sup>23,24</sup> Again, tardive akathisia is indistinguishable in clinical appearance from acute akathisia, but its time of onset and course resembles those of tardive dyskinesia. In other words, it (1) occurs late in the course of treatment with antipsychotics (usually after 3 months or more), (2) may emerge initially after antipsychotic discontinuation or dosage reduction, (3) can often be reduced in severity by increasing the antipsychotic dosage, and (4) may persist from months to years, even in the absence of drug—all of which are hallmarks of tardive syndromes in general.
- **Pseudoakathisia:**<sup>25,26</sup> This was a term invented to describe a condition in which there are the objective signs of akathisia without the subjective component. Because akathisia occurs commonly in patients with psychiatric disorders such as schizophrenia, it is not clear if pseudoakathisia should actually be considered a “pseudo” form of the disorder, because many patients experience discomfort that they are unable to understand or express clearly. Thus, we, like

others,<sup>21</sup> are skeptical about the existence of pseudoakathisia as a true subtype of akathisia, as opposed to one where other factors may simply reduce or alter the subjective complaints.

- **Bing–Sicard akathisia.**<sup>27</sup> This is a term that has been used to describe the occurrence of akathisia in parkinsonian disorders such as Parkinson’s disease (PD) and post-encephalitic parkinsonism, discussed below.

## Etiology and Epidemiology

Although most commonly considered a side effect of antipsychotic medications, akathisia was described long before the advent of these drugs, and can still occur in other conditions:

### *Antipsychotic-induced akathisia*

Akathisia is commonly observed after treatment with first-generation antipsychotic medications with reports of prevalence 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 range in prevalence, with differences in reports probably due in part to some of the recognition factors described below, and also to differences in age, dosage, and timing of assessment. Although it is commonly thought that akathisia is not a significant problem with second-generation (“atypical”) antipsychotic medications, this is not true. The reported prevalence of akathisia with second-generation drugs has varied widely, but it is often quite high, although in general lower than first-generation drugs.<sup>28,29</sup> There has also been a lot of variability of reported prevalence rates across agents, with aripiprazole (23–42%)<sup>30–32</sup> and risperidone (7–50%)<sup>33</sup> being among the highest and olanzapine (3–16%), quetiapine (2–13%), and iloperidone (appears to be very low, 0%?)<sup>34–38</sup> being among the lowest. Clozapine is interesting, as the prototypical second-generation agent, with some reports of very low incidence and prevalence<sup>39</sup> and other reports where the prevalence was quite high (15–31%),<sup>40</sup> and the incidence was not different from first-generation antipsychotics (39% vs 45%).<sup>41</sup> At this time it appears that quetiapine<sup>33</sup> and iloperidone<sup>35,36</sup> may be associated with the lowest rates of akathisia, but further studies are warranted. Anti-dopaminergic anti-emetics (such as prochlorperazine and metaclopramide), as well as dopamine-depleting agents (reserpine and tetrabenazine, which impede reuptake of dopamine into presynaptic vesicles), have also been reported to commonly cause akathisia.<sup>42,43</sup>

### *Antidepressant-induced akathisia*

There is growing awareness that akathisia can occur during treatment with antidepressant drugs, of which SSRIs have received the most reports of an

association,<sup>44–52</sup> with relatively fewer reports of tricyclic antidepressants (TCAs)<sup>53,54</sup> or monoamine oxidase inhibitors (MAOIs).<sup>54</sup>

### *Other drug-induced akathisia*

There have also been reports of akathisia with the antibiotic azithromycin,<sup>55</sup> with calcium channel blockers,<sup>56</sup> lithium,<sup>56</sup> and with drugs often used for recreational purposes such as gamma-hydroxybutyrate (GHB), methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), and cocaine.<sup>57</sup>

### *Akathisia in parkinsonian conditions*

Akathisia has been described in conjunction with a variety of Parkinson-related disorders including PD itself,<sup>58</sup> as well as post-encephalitic parkinsonism, cortico-basal degeneration (CBD), and multiple system atrophy (MSA). There is a complex relationship between the use of L-DOPA and akathisia, with some reports suggesting that its occurrence may relate to time-of-dosing or to “off” effects, and other reports finding no clear association.

### *Spontaneous akathisia*

Akathisia has been reported to occur in untreated schizophrenia<sup>59</sup> where it has also been termed “spontaneous akathisia.”

## Risk Factors for Drug-Induced Akathisia

Although acute antipsychotic-induced akathisia is often thought of in conjunction with schizophrenia, it appears that patients with mood disorders, particularly bipolar disorder, may actually be at higher risk.<sup>60–62</sup> Other risk factors may include higher dose or rapid dose increase,<sup>63</sup> traumatic brain injury,<sup>64,65</sup> cancer,<sup>43</sup> and possibly iron deficiency.<sup>66,67</sup> There is no clear evidence of risk associated with age, gender, or ethnic background.<sup>56,68</sup> Chronic or tardive akathisia may be associated with advanced age and female gender, just as is tardive dyskinesia.<sup>21</sup>

## Recognition and Differential Diagnosis

### *Under-recognition and misdiagnosis of akathisia*

These are very significant clinical problems<sup>12,15,69–72</sup> because they contribute to profound suffering of patients, both directly—from the signs and symptoms of akathisia itself—and indirectly, because of secondary effects on medication adherence by patients as well as inappropriate medication dosing by clinicians. When Hirose<sup>70</sup> reviewed the literature on under-



recognition, he divided the factors contributing to poor recognition and treatment into “patient” and “clinician” components. The patient factors included (1) mild severity of akathisia, (2) lack of apparent motor restlessness, (3) no voluntary expression of inner restlessness, (4) no clear communication of inner restlessness, (5) restlessness in body parts other than the legs, (6) atypical expressions of inner restlessness, (7) other prominent psychiatric symptoms, and (8) absence of other extrapyramidal signs. The clinician factors included (1) emphasis on objective restlessness, (2) failure to consider akathisia during antipsychotic therapy, (3) failure to fully implement anti-akathisia treatments in ambiguous cases, and (4) strict adherence to research diagnostic criteria.<sup>70</sup>

### **Differential diagnosis**

There are several conditions that are commonly confused with akathisia:

#### *Anxiety*

Anxiety can be extremely difficult to distinguish from akathisia. Subjectively, patients with anxiety are less likely to complain about a need to move, or about how movement reduces the severity of their discomfort. Objectively, anxiety is associated with a greater degree of autonomic arousal, and observable excesses in movement usually manifest in upper extremity and facial fidgetiness, which is less common in akathisia.

#### *Agitation with medical conditions*

Agitation can occur in a variety of medical conditions, such as hyperthyroidism, sedative (including alcohol) or opiate withdrawal, AIDS, respiratory alkalosis, pre-eclampsia and eclampsia, meningitis, septicemia, pulmonary edema, and hyponatremia. These diagnoses can usually be made by their individual clinical features, and the agitation that accompanies them does not have a preferential lower extremity involvement, feeling of a need to move, or relief with movement.

#### *Psychomotor agitation*

This type of agitation is considered to be part of the primary presentation of a mental disorder, such as depression, bipolar disorder, schizophrenia, or post-traumatic stress disorder (PTSD), but it is not clear if “psychomotor agitation” relates to the same underlying mechanism in these different disorders. Unlike anxiety, which is a symptom, agitation is a sign, and hence a clinically observable entity, and the two may or may not be associated. Akathisia is often described as a type of agitation, but can usually be differentiated by the specific

movement-impelling aspect of the subjective discomfort and the preferential involvement of the lower extremities when mild or moderate in severity.

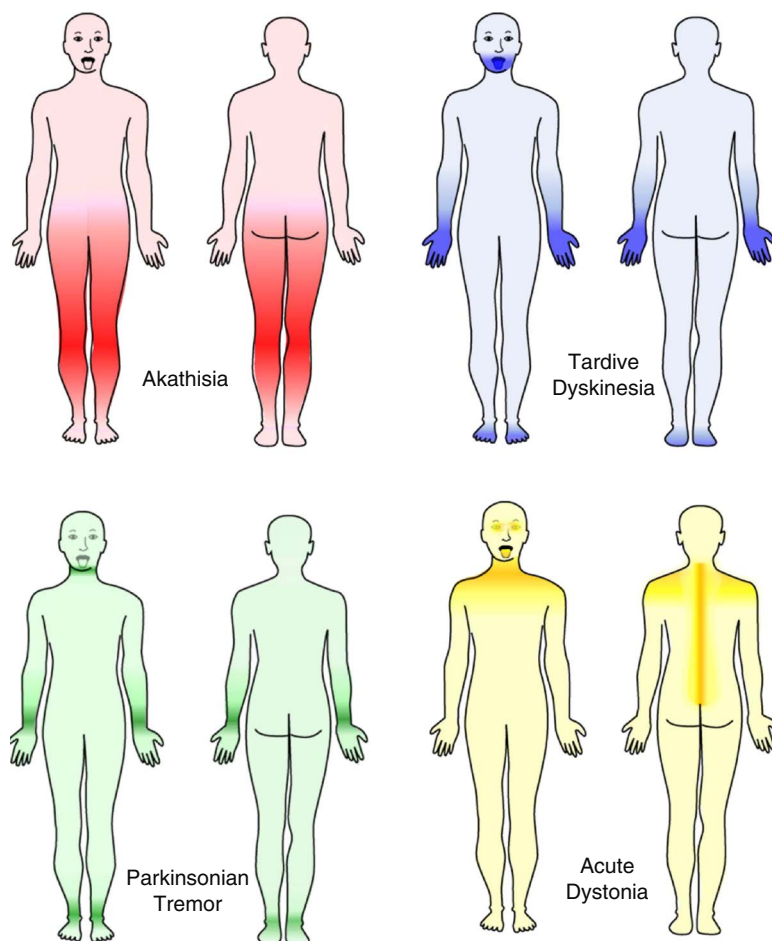
#### *Tics and Tourette disorder*<sup>16,73</sup>

The tics of Tourette disorder are divided into motor and phonic types, with motor tics typically appearing as rapid movements of eyes, lips, shoulders, fingers, and other areas, and phonic tics typically involving coughs, grunts, whistles, and animal noises. Although tics can involve the lower extremities, they are much more common in the face and upper extremities. Tics are often complex in nature, consisting of connected strings of separate motor and phonic tics. Some tic disorders, particularly Tourette disorder, are associated with a sensory disturbance that precedes the actual tic, sometimes called “a premonition” or “an itch,” which builds in intensity until it is relieved when the tic occurs. Thus, Tourette disorder is also a sensorimotor disorder, like akathisia. The upper torso distribution and the presence of phonic tics are distinguishing features from akathisia. Many patients with Tourette disorder may develop akathisia because of treatment with dopamine blocking drugs, which can serve to worsen the tics.<sup>74</sup> Patients who have both tics and akathisia can readily tell the difference in the subjective experience, as tics are not experienced as restlessness, but rather as a buildup of an uncomfortable feeling in a specific body part that culminates in a motor or phonic tic. There is also a tardive form of Tourette disorder that follows the course of tardive dyskinesia and is usually seen accompanying the more typical signs of tardive dyskinesia.<sup>75,76</sup>

For the remaining discussion of the differential diagnosis of antipsychotic-induced movement disorders, we have prepared Figure 1, which illustrates the relative preferred somatic region involved in mild to moderate cases of antipsychotic-induced akathisia, tardive dyskinesia, dystonia, and parkinsonian tremor. This differential distribution is often extremely helpful in making a diagnosis.

#### *Antipsychotic-induced tardive dyskinesia (TD)*<sup>77–82</sup>

Because akathisia frequently occurs secondary to treatment with antipsychotic drugs, it is important to distinguish it from other antipsychotic-induced movement disorders. Perhaps the most commonly confused disorder is TD, which occurs late in the course of treatment and with which tardive akathisia is often associated. TD can be differentiated from acute akathisia on the basis of the timing of the appearance (late vs early), the nature of the movements, as well as the preferred somatic distribution of the movements (see Figure 1). TD consists of writhing athetoid or choreo-athetoid movements predominantly of the



Relative prevalence of body region involvement of different antipsychotic-induced EPS, when they are present with mild to moderate severity. It can be seen that the preferred regional distribution can be of use in differentiating akathisia from other antipsychotic-induced conditions.

**FIGURE 1.** Relative prevalence of body region involvement of different antipsychotic-induced EPS, when they are present with mild to moderate severity. It can be seen that the preferred regional distribution can be of use in differentiating akathisia from other antipsychotic-induced conditions.

lower face and distal extremities (although it can involve the trunk, and the pharynx and diaphragm when severe). When the legs are involved, the movements are usually more pronounced in the toes than the more proximal muscles.

#### *Antipsychotic-induced dystonia*<sup>77–81</sup>

Acute antipsychotic-induced dystonias (also called dystonic reactions) occur very soon, within 24–48 hours, after initiating or increasing antipsychotic dosing. There is also a tardive form, which shares the timing characteristics with TD (described earlier in the tardive akathisia section). Dystonias tend to involve the eyes (oculogyric crises), the tongue, the neck (torticollis), the shoulders, and trunk (see Figure 1).

#### *Antipsychotic-induced parkinsonian tremor*<sup>77–81</sup>

Although when assessed carefully, parkinsonian tremor can involve virtually all body regions to some extent, it is usually most clinically obvious in the hands and wrists when at rest (see Figure 1), where it assumes a pill-rolling characteristic consisting of alternating contractions of agonist and antagonist muscles in a very rhythmic rate of 4–7 cycles/second.

#### **Akathisia vs Restless Legs Syndrome (RLS)**

We are considering RLS separately from the other differential diagnostic entities because it is not clear whether akathisia and RLS truly represent different disorders. To see how difficult it can be to distinguish



from akathisia, let us examine Ekbom's original description<sup>83</sup>:

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. (p 198)

RLS has more alternative names than most other medical disorders, being also known as Ekbom syndrome, Wittmaack-Ekbom syndrome, Willis-Ekbom disease, *anxietas tibiaram*, and *anxietas tibialis*. Ekbom himself originally called the disorder *asthenia crurum paresthetica*, highlighting the uncomfortable paresthesias in the lower extremities. RLS appears to be quite common and may affect 3–9% of the population, being more common in women, with advanced age, and with iron deficiency.<sup>84</sup> The critical features of RLS are (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, and (4) worsening of symptoms later in the day or at night. As can be seen, apart from criterion 4, there is essentially no definitional difference between akathisia and RLS. This association with night-time and sleep is the essential clinical difference between RLS and akathisia, and was noted by Ekbom:<sup>83</sup>

The paresthesia is mostly felt during the night, generally within an hour after retiral (in one case not until the early morning, however)... The patients cannot sleep, but are forced to lie and move their legs and continually change their position, to sit on the edge of the bed and kick, or to walk about on the floor. It is quite impossible to stay in bed. The paresthesia may keep on the whole night, according to the patients at least, but they often disappear in the early morning.... During the day, the paresthesiae are either entirely absent or are of mild degree, coming on when the legs are kept still, especially in the evenings, e.g., at the theatre or cinema, or if the patients take a nap to try to make up for their lost night sleep. (p 198)

The relationship between akathisia and RLS often receives very little attention in discussions of the differential diagnosis of either of these conditions, which is surprising considering the large degree of clinical overlap between them. Part of the reason for this may be

related to the different heritage of these concepts, with RLS studies coming more from the neurological and sleep literature, and akathisia from the psychiatric and psychopharmacological literature. An example of the diagnostic confusion is seen with PD, for example, where in some instances the restlessness is referred to as RLS,<sup>85–89</sup> and in others, akathisia,<sup>90,91</sup> but it is unclear if there is a real distinction present. For example, it is very confusing diagnostically when investigators report the occurrence of akathisia at nighttime<sup>92</sup> and RLS during the day.<sup>93</sup>

It has been suggested that RLS can be distinguished from akathisia in that RLS occurs more commonly at night, is associated with greater sleep disturbance, is marked by myoclonus when severe, is exacerbated by lying down (akathisia may be somewhat *relieved* by lying down in some patients), and is experienced more as paresthesias (akathisia may be experienced more as restlessness).<sup>94</sup> However, none of these distinctions forms a firm basis for differentiating the conditions, and in fact RLS and akathisia may actually be closely related disorders, if not in fact variants of the same underlying pathophysiology. One distinguishing feature usually not addressed is that the two conditions may have different treatment responses. Although both have been described as responding to benzodiazepines, the use of dopamine agonists such as L-DOPA and opiates is standard treatments for RLS, but rarely if ever used for akathisia, whereas anticholinergic drugs and beta-adrenergic blockers are often used for akathisia (though the evidence is inconsistent; see below), but they are rarely used for RLS. These differences may not so much relate to differences in the underlying conditions, however, as to the fact that akathisia commonly occurs in individuals with psychiatric disorders, where the use of dopaminergic agonists may exacerbate manic or psychotic symptoms,<sup>95</sup> and the use of opiates is usually avoided because of abuse potential.

We should also mention periodic limb movement disorder (PLMD), which is also known as periodic leg movements of sleep (PLMS), which is a condition that clinically overlaps and is frequently associated with RLS. In fact, it has been considered to be simply a milder form of RLS (in which only the sleep component occurs) by some investigators. However, because RLS and PLMD can occur independently of one another, and there are differences in the sleep architecture between RLS and PLMD, they may actually represent different conditions.<sup>96</sup> In any case, PLMD is different from akathisia in that it occurs during sleep, whereas akathisia is a condition of wakefulness.

### Pathophysiology

The pathophysiology of akathisia is unknown. Because akathisia is so commonly observed in the context of treatment with first-generation antipsychotic medications and in parkinsonian states, it is reasonable to assume that

dopamine blockade may be involved in its genesis, but this is not certain. More than 30 years ago, Marsden and Jenner<sup>95</sup> suggested that akathisia may be caused by a blockade of mesocortical dopaminergic pathways, which is still a viable but unproven hypothesis.

Stahl and Loonen<sup>97</sup> have suggested another mechanism for akathisia, in which a generalized reduction in dopamine in the brain (such as is seen with antipsychotics and PD) may trigger compensatory mechanisms, particularly in the form of increased noradrenergic activity from the locus ceruleus. Because these adrenergic fibers innervate the shell portion of the nucleus accumbens to a greater extent than the core portion, a mismatch may occur resulting in dysphoric feelings and semipurposeful movements. This would also help explain the possible utility of beta-blocking drugs and the fact that akathisia is not seen in everyone when treated with first-generation antipsychotic drugs, which powerfully block dopamine receptors.

It is possible that mechanistic clues for akathisia can be found in studies of RLS. In the case of RLS, it has been suggested that dopamine reduction in the substantia nigra or in the 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.<sup>98</sup> Because of the previously mentioned similarity of RLS and akathisia, these possible mechanisms may be worth studying in akathisia as well.

## Assessment

Currently, akathisia is a diagnosis made purely by clinical observation and patient report, as there is no confirmatory blood test, imaging assessment, or neurophysiological study available. The most commonly used tool for assessment is the Barnes Akathisia Rating Scale (BARS),<sup>99</sup> which is a 4-item scale in which the subjective and objective components of the condition are rated separately, then combined. Each item is rated on a 4-point scale (0 to 3). There is 1 item that assesses objective signs, 2 subjective items that assess awareness and distress related to restlessness, and a global clinical assessment (see the Appendix).

When assessing the severity of akathisia, it can be quite helpful to observe patients 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 on the motor aspects of the condition, especially when it is only of mild to moderate severity, causing a falsely low estimate of its severity.

## Treatment

It is unfortunate that the actual evidence base for treatments of akathisia is very small, and many of the recommendations are based on clinician experience, case reports, and reports from studies of drugs where akathisia was not a primary concern. Nevertheless, the absence of strong evidence does not mean we should not try to address and treat the situation to the greatest possible extent. In our opinion, first and foremost, the cause of the akathisia should be identified and initial treatment aimed at that cause. Since the majority of patients with akathisia probably developed it secondary to psychotropic medications, the initial recommendation is, if possible, to reduce or switch medications. In patients on first-generation drugs, an attempt should be made to switch to second-generation agents that appear to cause less akathisia, including quetiapine and iloperidone. Also, if iron deficiency is present, then correcting this may be of some benefit. It should be remembered that occasionally, withdrawal akathisia can occur, so one should not judge the effectiveness of a dosage reduction or a medication switch for up to 6 weeks or more, as the akathisia may show a temporary exacerbation. If the akathisia worsens but does not disappear, then tardive akathisia may be present, and the general treatment guidelines follow those of acute akathisia below, with the exception that, when severe, tardive akathisia can be suppressed with a reinstatement of the offending agent at the previous dose.

After these maneuvers, if the akathisia is still present, it may be very difficult to treat. A host of different medications has been reported to be useful, but without much corroboration or evidence. These include anticholinergic drugs (such as biperiden, trihexyphenidyl, and benztropine),<sup>100-102</sup> beta-blockers (such as propranolol and metoprolol),<sup>103</sup> and serotonin 5-HT<sub>2A</sub> antagonists (such as mianserin, mirtazapine, and cyproheptadine).<sup>104</sup> There have also been reports of success with vitamin B<sub>6</sub>, n-acetylcysteine,<sup>105</sup> and tetrabenazine,<sup>106,107</sup> although tetrabenazine is also reported to cause akathisia. Benzodiazepines have proven useful, but do not appear to relieve the akathisia as much as any associated anxiety.<sup>104</sup> Interestingly, two of the most commonly used treatments for akathisia, anticholinergic agents and beta-blockers, have both been reported to have poor evidence of efficacy in Cochrane reviews.<sup>100,101,103</sup>

By and large, after adjusting any offending agents (or treating any underlying conditions), there is little in the way of incontrovertible evidence for any therapeutic approach, and the treatment of akathisia becomes largely empirical, with many of the more severely affected patients ending up on double- and triple-drug regimens involving combinations of anticholinergic,

beta-blocking, and serotonin blocking drugs, along with benzodiazepines. Occasionally, clonidine has been recommended, and there is a report of tardive akathisia responding to clonidine.<sup>24</sup> Rarely, dopamine agonists such as bromocriptine and amantadine have been tried.<sup>90</sup> Finally, piracetam,<sup>108</sup> buspirone,<sup>90</sup> and opiates<sup>90</sup> have been suggested to be of benefit in case reports of more serious akathisia.

## Summary

Akathisia is a complex, confusing, and under-recognized problem that causes considerable suffering. It is extremely important for the clinician to be alert to its presence, as addressing akathisia in terms of alterations of current medication regimens can do much to relieve discomfort and to improve patient adherence, thereby reducing psychiatric and medical morbidity.

## Disclosures

The authors do not have anything to disclose.

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## Appendix:

Name: \_\_\_\_\_ Date: \_\_\_\_\_

### Barnes Akathisia Rating Scale (BARS)

**Instructions:** Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

#### Objective

- 0 Normal, occasional fidgety movements of the limbs
- 1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed
- 2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
- 3 Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

#### Subjective

##### *Awareness of restlessness*

- 0 Absence of inner restlessness
- 1 Non-specific sense of inner restlessness
- 2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
- 3 Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

##### *Distress related to restlessness*

- 0 No distress
- 1 Mild
- 2 Moderate
- 3 Severe

#### Global Clinical Assessment of Akathisia

- 0 *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
- 1 *Questionable.* Non-specific inner tension and fidgety movements
- 2 *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.
- 3 *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
- 4 *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.
- 5 *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.

### Scoring the Barnes Akathisia Rating Scale (BARS)

The Barnes Akathisia Rating Scale is scored as follows:

Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness are rated on a 4-point scale from 0 – 3 and are summed yielding a total score ranging from 0 to 9.

The Global Clinical Assessment of Akathisia uses a 5-point scale ranging from 0 – 4.

Citation: Barnes TR. A rating scale for drug-induced akathisia. *British Journal of Psychiatry* 1989;154(5):672-676. This scale can be reproduced freely.

## Optional CME Posttest and Certificate

*CME Credit Expires: November 30, 2018*

### CME Posttest Study Guide

**NOTE: The posttest can only be submitted online.** The below posttest questions have been provided solely as a study tool to prepare for your online submission. **Faxed/mailed copies of the posttest cannot be processed** and will be returned to the sender. If you do not have access to a computer, contact NEI customer service at 888-535-5600.

1. A 31-year-old patient with schizophrenia is currently exhibiting signs of akathisia. When mild to moderate in severity, akathisia preferentially involves:
  - A. The tongue and jaw
  - B. Upper extremity musculature
  - C. Lower extremities
2. A 26-year-old man with schizoaffective disorder discontinued his antipsychotic treatment several months ago due to the medication making him feel “itchy and tingly”. He now presents with a worsening of psychosis and has agreed to start antipsychotic medication again. Which of the following statements is true regarding antipsychotic-induced akathisia?
  - A. Akathisia is more commonly a side effect of first-generation, conventional antipsychotics
  - B. Akathisia is more commonly a side effect of second-generation, atypical antipsychotics
  - C. Akathisia is an equally common side effect of both first-generation, conventional antipsychotics and second-generation, atypical antipsychotics
3. Jaqueline is a 45-year-old patient with major depressive disorder, currently being treated with a selective serotonin reuptake inhibitor. She has begun to complain of symptoms of akathisia. When symptoms and signs of acute akathisia occur with treatment of SSRI antidepressants, the condition is called:
  - A. Pseudoakathisia
  - B. Withdrawal akathisia
  - C. Bing-Sicard akathisia
  - D. None of the above
4. A 32-year-old patient with a family history of restless leg syndrome (RLS) is currently taking an antipsychotic. She now presents with complaints of discomfort, describing a sensation of “wanting to crawl out of my skin”. In distinguishing RLS from antipsychotic-induced akathisia, it may be most important to note that:
  - A. The severity of RLS symptoms worsens later in the day or at night
  - B. Discomfort is associated with a desire to move extremities in RLS
  - C. Symptoms are often temporarily relieved by activity in RLS
  - D. All of the above distinguish RLS from antipsychotic-induced akathisia
5. Mike is a 53-year-old patient presenting with signs and symptoms of akathisia. Overwhelming clinical consensus suggests that the following class of drugs demonstrates strong evidence as a general treatment for akathisia:
  - A. Anticholinergic drugs
  - B. Beta-blockers
  - C. Serotonin 5HT<sub>2A</sub> antagonists
  - D. Benzodiazepines
  - E. All of the above demonstrate strong evidence as treatments for akathisia
  - F. None of the above demonstrate strong evidence as treatments for akathisia
6. A 19-year-old patient with first-episode schizophrenia is nervous about starting treatment with an antipsychotic due to fears of developing akathisia. Of the second-generation, atypical antipsychotics, which agent demonstrates the lowest association with akathisia?
  - A. Aripiprazole
  - B. Iloperidone
  - C. Risperidone
  - D. There is an equal risk of akathisia associated with all of the above

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