Akathisia

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Introduction

Overview

Akathisia is the abnormal state of motor restlessness that is most commonly caused by neuroleptic therapy. It can be an acute side effect that improves with withdrawal of medication, or it can be tardive that worsens with drug withdrawal. Literature demonstrates that it occurs with atypical antipsychotics although perhaps less commonly than is seen with typical agents. This is a matter to be debated. The treatment has changed. In the past, the primary therapies included anticholinergics and propranolol. It has been demonstrated that anticholinergics are not effective. Propranolol remains a useful choice, but other medications, mirtazapine and trazodone, have also been found to be effective to an equal extent; the 3 drugs should be considered initial choices.

Key points

- Akathisia is a sensorimotor syndrome.
- Motor symptoms appear to be in response to sensory symptoms and are stereotyped and suppressible, and they decrease with distraction.
- Sensory symptoms are urges or other uncomfortable phenomena that improve with movement.
- Akathisia occurs acutely or subacutely with dopamine receptor-blocker therapy and improves with removing the drug, or it is chronic or tardive after chronic therapy with dopamine receptor-blocking agents and worsens with removing the drug.
- Mechanisms relate to impact of dopamine, serotonin, and noradrenergic systems on the somatosensory system in the brain.
- There should be a high index of suspicion as akathisia is frequently underrecognized.
- Akathisia is a complication of all atypical antipsychotics.
- First-line therapies include propranolol, mirtazapine, or trazodone.

Historical note and terminology

The term “akathisia” is from the Greek “inability to sit,” but it generally refers to an aversion to being still that is relieved by movement. The term was first used medically by Haskovec (Haskovec 1901) who thought the symptoms were the result of psychological disorders (Adler et al 2005). A Czech neuropsychiatrist and a former student of Charcot, Haskovec obviously described this phenomenon in the pre-antipsychotic era (Mohr and Volavka 2002). Akathisia was recognized as a complication of parkinsonism during the epidemic of encephalitis lethargica in the 1920s, and later, Parkinson disease. Dopamine receptor-blocking drugs for the treatment of psychosis were developed during the 1940s, and akathisia was recognized as a side effect of promethazine in 1947 (Adler et al 2005). Tardive akathisia, occurring after chronic neuroleptic therapy and remaining and worsening after withdrawal of the drug, was first reported in 1960 (Kruse 1960) but was not labeled “chronic akathisia” until 1983 (Braude and Barnes 1983). Akathisia is 1 of the most troublesome aspects of tardive dyskinesia (Waln and Jankovic 2013a).

Clinical manifestations

Presentation and course

Akathisia is the abnormal state of excessive restlessness. It fundamentally has 2 components: (1) a sensory component, which includes a sensation of inner restlessness, an urge to move, and dysphoria and (2) a motor component, manifested as movements that result from the sensation (Lohr et al 2015). Thus, akathisia is 1 of many movement disorders manifested by both motor and sensory components (Patel et al 2014). Patients describe feeling an overwhelming inability to remain still. This feeling is usually generalized, but it is occasionally focal in origin (Hirose

2001). The sensation is often unbearable and unpleasant, and patients may feel an associated tension, anxiety, irritability, aggressiveness, and impatience (Leong 2003). The patients describe feeling jittery, fidgety, and nervous. Akathisia is often accompanied by depression, including suicide attempts. Some studies suggest that suicide attempts are more closely associated with subjective sensory symptoms than motor symptoms, and attentional impairment (Kim et al 2002; Seemuller et al 2012a; Seemuller et al 2012b). However, a systematic study indicated no clear association between akathisia and suicide risk (Reutfors et al 2016). This requires further study. Worst of all, movement provides only brief relief. The sensory components can also be relieved by passive movement or a perception of movement, such as riding in a car (Patel et al 2014). The movements secondary to restlessness are often stereotyped and include pacing, walking in place, body-rocking, leg-swinging, toe-tapping, and an inability to stay in 1 place (tasikinesia) (Adler et al 2005). Akathisia particularly involves the lower limbs (Braude et al 1983; Burke et al 1989). Akathisia can interfere with activities of daily living and can be disabling. The restless movements in the legs associated with akathisia must be differentiated from those involved in the leg stereotypy disorder, which is a much more common movement disorder (Jankovic 2016a). In contrast to akathisia, leg stereotypy disorder is not associated with uncomfortable restlessness; it typically consists of stereotypical, repetitive, flexion-extension, abduction-adduction movement of the legs or tapping of the feet. The movements are suppressible and decrease with distraction.

Akathisia may be found during any stage of Parkinson disease (Lang and Johnson 1987) but may be associated with greater severity of motor symptoms (Comella and Goetz 1994). About 50% of patients experience akathisia as a fluctuating phenomenon that may be present when on or off (Witjas et al 2002; Bayulkem and Lopez 2011). Parkinson disease has been associated with restless leg syndrome, with prevalence as high as 20%, but some of those patients may have akathisia (Ondo et al 2002b). The 2 entities are often difficult to differentiate.

In relation to dopamine receptor-blocking agents, akathisia may occur as an early acute or subacute side effect (Olsen et al 2000) or as a tardive phenomenon after chronic administration and a worsening with withdrawal of the agent (Braude and Barnes 1983). In the early acute form, patients occasionally develop akathisia abruptly at the onset of oral treatment, sometimes within an hour of receiving the drug (Braude et al 1983), but most patients with neuroleptic-induced akathisia have a gradual onset after several weeks of continued therapy and 90% of cases occur within 90 days of onset of therapy (Caroff and Cambell 2016). It appears to be dose-dependent. Akathisia may aggravate the psychopathology for which the neuroleptic is given, partially because of noncompliance with the medication (Duncan et al 2000). However, some have reported a worsening of psychosis without noncompliance that improves with anticholinergics or beta-blockers (Van Putten 1974).

Tardive akathisia occurs after prolonged exposure to neuroleptic drugs (typical and atypical, including aripiprazole and clozapine) (Mossaheb and Kaufmann 2012) and has a similar pharmacologic profile as tardive dyskinesia. It can occasionally evolve from acute to tardive akathisia, so-called acute persistent akathisia (Skidmore et al 2005). In contrast to the early subacute variety, tardive akathisia typically appears or worsens with dosage reduction or drug withdrawal (Lang 1994) and is suppressed by dosage increases. Diagnostic criteria include the occurrence during or within 3 months of cessation of neuroleptic therapy and must be persistent when the neuroleptic is stopped for at least 1 month (Skidmore et al 2005). In most cases, tardive akathisia is associated with other tardive syndromes. The persistent nature of tardive akathisia is similar to tardive dyskinesia in that it rarely remits (Cloud et al 2014; Zutshi et al 2014). One study suggested that motor symptoms and distress are less severe in tardive versus acute akathisia (Kim et al 2005), but that remains to be demonstrated.

Some patients have the movements of akathisia without the sensory component, which is referred to as pseudoakathisia (Adler et al 2005). This may occur in psychotic patients who cannot verbalize the sensory phenomena but also is associated with the movements of tardive dyskinesia or tardive stereotypy. These patients may be misdiagnosed with other psychiatric states such as mania or agitated depression.

Prognosis and complications

Akathisia found in association with Parkinson disease responds inconsistently to antiparkinsonian therapy (Lang and Johnson 1987). Subacute drug-induced akathisia will persist as long as the agent is taken; however, the severity may fluctuate. It will resolve on discontinuation of the drug. Tardive akathisia remits only rarely (Burke et al 1989), usually persisting indefinitely without treatment. Particular importance should be connected with the risk of medication noncompliance and suicide.

Clinical vignette

A 68-year-old woman with Huntington disease for over 10 years had chorea, gait disorder with occasional falls, and cognitive dysfunction. She also had a history of obsessive-compulsive symptoms and anxiety treated with sertraline. For increasing chorea, she was placed on tetrabenazine with an escalating dose to 12.5 mg 3 times daily. After about 6 months, she developed what appeared to be increased movements and depression. The tetrabenazine was initially decreased but then in the emergency room was increased again because of concern that the movements represented increasing chorea. On admission, it was found that the movements were, in fact, severe restlessness. She was getting up constantly. She described dysphoria and a need to move. Because of this, her frequency of falling was increased substantially. The symptoms were so severe she was not sleeping and she had suicide ideation. The tetrabenazine was tapered off, and low-dose quetiapine was initiated along with an increase in her sertraline. Her chorea increased, but the akathisia, depression, and suicidality all improved, and she was discharged.

Biological basis

Etiology and pathogenesis

Because akathisia is a sensorimotor disorder, the causative abnormality involves the complex somatosensory system. The basal ganglia are central to most movement disorders, and although they do not directly receive sensory information, they process sensory information indirectly and serve as the gate keeper for sensory input to motor and other nonmotor features (through their anatomically distinct loops) at various levels. Abnormal sensorimotor integration may be key in the pathogenesis of akathisia and other movement disorders that involve sensory features (Patel et al 2014). The situations whereby akathisia occurs would represent clues to the lesion location. Akathisia arises in 3 main clinical situations, but all impact dopaminergic systems: (1) Parkinson disease, (2) dopamine receptor blocking drug (neuroleptic) treatment, and (3) treatment with other medications including selective serotonin reuptake inhibitors (SSRIs) and VMAT2 inhibitors (eg, tetrabenazine and reserpine) (Ondo et al 2002a; Jankovic and Clarence-Smith 2011) can also be responsible. Although it is suggested that atypical antipsychotics have a lower propensity to cause akathisia than typical agents, it is known that both have the potential (Lawford et al 2013). It is important to remember that antiemetic dopamine receptor blockers (metoclopramide and Compazine for example) can also cause profound akathisia (Akagi and Kumar 2002). Subacute akathisia is a dose-related phenomenon. Individual susceptibility to anti-dopaminergic drug-induced akathisia may be determined by genetic factors (eg, in the dopamine D3 receptor gene or the A1+ variants of the DRD2/ANKK1 Taq1A allele) (Eichhammer et al 2000; Lawford et al 2013). Up to 25% of those treated with fluoxetine may develop akathisia (Lipinski et al 1989; Gerber and Lynd 1998). Other drugs that rarely cause akathisia include calcium-channel blockers, lithium, and carbamazepine. Rarer causes of akathisia include head trauma (Silver and Yablon 1996) and carbon monoxide intoxication (Stuppaeck et al 1995).

The association with parkinsonism and pharmacological blockade of dopamine receptors suggests that akathisia reflects a state of hypoactivity of dopaminergic systems. Decreased dopamine signaling results in the reduced ability to generate automatic movements. On the other hand, increased dopaminergic signaling might result in repetitive and stereotyped movements such as seen in akathisia (Patel et al 2014). Acute akathisia may result from decreased activity in mesocortical and mesolimbic dopaminergic pathways (Marsden and Jenner 1980). This attractive hypothesis may be overly simplistic; for example, low-dose apomorphine (reducing dopamine release) suppresses the movements associated with tardive akathisia but not the sensation of restlessness (Sachdev and Loneragan 1993). Tardive akathisia may relate to the hypersensitivity of dopamine receptors.

Pharmacologic studies have also implicated nondopaminergic pathways in the pathophysiology of akathisia. The development of akathisia with atomoxetine therapy and the response of many patients to beta-blockers suggests that noradrenergic hyperactivity may play a role (Ratey et al 1985; Yazici and Percinel 2014). Serotonin mechanisms, and specifically 5-HT2 receptor stimulation, have been implicated by pharmacologic studies demonstrating that SSRI agents such as fluoxetine can cause akathisia (Lipinski et al 1989), and relief may be seen with 5-HT2A/2C receptor antagonists (Poyurovsky et al 2006; Laoutidis and Luckhaus 2014). Serotonin results in the inhibition of dopamine release. Opiate systems may also be involved, although perhaps only indirectly (Walters et al 1986). Finally, Sigma-1 receptors, which are connected to the development of endoplasmic reticulum stress, may play a role in the development of akathisia. Haloperidol, a major cause of akathisia, is a sigma-1 antagonist. Sigma-1 agonists, including fluvoxamine, improve akathisia (Albayrak and Hashimoto 2013). These receptors may possibly modulate dopaminergic neurotransmission in the limbic area via chaperone activity.

A paper expanded the hypothesis, relating akathisia to the dopaminergic blockade of the nucleus accumbens and nondopaminergic pathways (Stahl and Lonnen 2011). The authors suggest that the decreased dopaminergic stimulation of the nucleus accumbens leads to compensatory increase in the adrenergic input from the locus ceruleus to the shell portion of the accumbens but not the core. This mismatch between activities of the core and shell lead to the seemingly senseless and purposeless movements associated with activation of the shell region (which receives projections from the infralimbic cortex) and immediate reward-seeking behavior due to decreased activity of the core region, both related to akathisia. This may explain response to beta-blocking agents.

An association between akathisia and abnormalities of iron metabolism has been proposed based on the similar association of iron and restless legs syndrome. Several studies have found low iron and ferritin levels and high total iron-binding capacity in schizophrenic patients with akathisia (Kuloglu et al 2003). In 1 study, schizophrenic patients without akathisia posted results on all 3 tests that were intermediate between those of akathitic patients and controls (Kuloglu et al 2003). However, this is not a consistent finding, and the role of iron in this disorder remains to be clarified (Sachdev and Loneragan 1991).

In examining the neuroanatoomic correlates of akathisia using [18]-FDG-PET imaging in 1 patient, researchers showed reduced metabolic activity in the thalamus and cerebellum (Landgrebe et al 2006).

Epidemiology"

The prevalence of akathisia with first-generation neuroleptics over many studies and many years is variable, from 3% to as high as 75%, with an estimate 20% to 30% overall for acute/subacute akathisia (Adler et al 2005). One study found that the prevalence of subjective, objective, and mixed akathisia was 11.3%, 6.3%, and 16.9%, respectively (Kim and Byun 2003). The variation depended on the definition of akathisia as well as risk factors including type, dose, and potency of the neuroleptic, female gender, age, ethnicity of the patient population, concomitant features, and recognition of the disorder. In a prevalence study through the FACE-SZ data set from 10 schizophrenia centers in France, a majority of patients were on second-generation antipsychotics. Of the 372 schizophrenia and schizoaffective disorder patients evaluated, the global prevalence was 18.5 % (Berna et al 2015). In other studies, the frequency was thought to be higher in patients with bipolar disorder than with schizophrenia (Brune 1999; Kane et al 2009). No age or gender predisposition was found.

Akathisia is a complication of therapy with all atypical (second-generation) antipsychotics as well (Kane et al 2009; Kumar and Sachdev 2009). In a review of over 70 trials, the frequency was consistently lower than that seen with first-generation drugs (Kane et al 2009; Kumar and Sachdev 2009). Another study came to the same conclusion when accounting only for low doses of first-generation agents (Markkula et al 2007). One additional study demonstrated lower frequency of akathisia in first-episode psychosis (Haddad et al 2012). The frequency was suggested to be about 15% overall (De Fruyt et al 2012). In a study from Estonia the frequency of akathisia was compared in an inpatient cohort when they were mainly on first-generation agents, then 8 years later when a larger percent were changed to second-generation drugs (Parksepp et al 2016). About 30% of patients had neuroleptic-induced akathisia at both time points. The results of such comparison studies with first-generation agents depended on the comparator agent; studies with haloperidol were different from those with perphenazine (Caroff and Cambell 2016). Other studies depended on the potency of the second-generation agent as well; for example, risperidone is more likely to cause akathisia than quetiapine (Adler et al 2005). With risperidone the frequency is dose-related with figures ranging from 13% to 32% and higher (Miller et al 1998; Wirshing et al 1999). With olanzapine the frequency was less than 10% in clinical trials compared with much higher frequencies with its comparator haloperidol (Sanger et al 1999). With aripiprazole, the prevalence was 17% in older and 26% in younger depressed patients (Steffens et al 2011), and 24% in bipolar patients (Pena et al 2011; De Fruyt et al 2012). A meta-analysis of 24 clinical trials indicated that the risk of akathisia with aripiprazole, asenapine, and lurasidone was higher than with other second-generation agents, with a relative risk of nearly 3 (Thomas et al 2015). However, in 1 long-term study of asenapine the figures ranged from 1% to 8% depending on duration and dose (Ketter et al 2017). Lower figures have been reported with quetiapine and clozapine, and they can still be implicated (Miller et al 1998; Shah et al 2010). In a community-dwelling population, the frequency of akathisia with second-generation drugs was similar for all (including clozapine) except quetiapine and amisulpride, which had the lowest prevalence figures of 1% to 6% (Berna et al 2015). A study in patients with bipolar disorder demonstrated a frequency of 5% with 300 and 600 mg per day of quetiapine (De Fruyt et al 2012). It should be noted that frequencies with haloperidol in these comparator studies was quite varied, as earlier studies noted.

A study in adolescents also demonstrated an approximately 11% frequency with atypical antipsychotics (Gebhardt et

al 2006). Risk factors include higher doses, high potency agents, or polytherapy with combinations of atypical agents with other psychotropic drugs (as high as 35% prevalence or 2-3 fold increased risk), and bipolar disorder (Gao et al 2008; Kumar and Sachdev 2009; Berna et al 2015). In a study of 40 patients with ages ranging from 8 to 18 years treated for ADHD, mood, anxiety, and eating disorders, 10% developed akathisia. An additional 10% experienced subjective restlessness and 33% of those receiving second-generation antipsychotics developed symptoms suggestive of akathisia. Most patients had mild symptoms. One with severe symptoms was treated with a combination of methylphenidate extended release and fluoxetine (Forcen et al 2017).

Studies examining the frequency of akathisia in migraine patients who received a single dose of prochlorperazine or metoclopramide had a frequency of 5% to 6% with a definitive diagnosis of akathisia, but 34% treated with prochlorperazine had symptoms suggesting a possible diagnosis of akathisia (Trottier et al 2012; Friedman et al 2014). The rate of delivery of antiemetics (metoclopramide) may impact the frequency of akathisia (Wijemanne et al 2016). In 1 blinded trial, the incidence of akathisia was observed to be 26% with bolus therapy and 7% in those given a slow infusion (Tura et al 2012).

The prevalence of tardive akathisia is estimated at approximately 20% to 30% of cases treated chronically with neuroleptics (Braude and Barnes 1983), a figure similar to that of classical tardive dyskinesia, but 2 centers have reported large numbers of patients (Burke et al 1989), suggesting wide variations in the frequency of diagnosis. Studies have suggested that tardive akathisia occurs in younger patients treated with higher doses, but it is unclear if there is a gender predilection.

Patients with Parkinson disease show a comparable rate of development of akathisia--26% in 1 series (Lang and Johnson 1987) and 45% in another (Comella and Goetz 1994). For up to half of the patients, akathisia relates to nonmotor fluctuations (Witjas et al 2002; Bayulkem and Lopez 2011).

In a naturalistic study, 209 chronically institutionalized psychotic patients were evaluated for akathisia and other movement disorders with at least 2 examinations over a minimal period of 3 months (Bakker et al 2011). Mean duration of institutionalization was 22 years. These patients were frequently treated with multiple medications, including first- and second-generation antipsychotics. Akathisia was seen at first evaluation in 8.8% of cases, at second evaluation in 10.4%, and at both evaluations in 4.6%; therefore, the later were considered persistent. The frequency decreased with age. Unlike prior cross-sectional studies, there was no difference in frequency with first- and second-degree agents.

There have been several studies implicating serotonin reuptake inhibitors, such as fluoxetine and sertraline. The frequency of akathisia with these agents is unknown, but it appears to be less than that seen with antipsychotics (Adler et al 2005). One study, however, suggested a frequency as high as 25% (Lipinski et al 1989). In a double-blind, placebo-controlled study of Huntington disease patients treated with tetrabenazine, the frequency of akathisia was 9% of 54 patients (Huntington Disease Study Group 2006). The figures for the newer VMAT2 inhibitors deutetrabenazine and Valbenazine, which could be available in the coming year, appear to be lower (O'Brien et al 2015; Huntington Study Group 2016; Jankovic 2016b).

Prevention

Akathisia complicating Parkinson disease cannot be prevented. Drug-induced akathisia is preventable by avoiding the use of the offending agents. This is particularly true when considering neuroleptic therapy for nonpsychotic disorders and other medical uses. Unfortunately, for many psychotic disorders, no alternatives to anti-dopaminergic drugs are available. Some believe that atypical neuroleptics produce a lower incidence of akathisia, but even clozapine (Gogtay et al 2002) and quetiapine (Prueter et al 2003; Shah et al 2010) cause severe akathisia. The lowest incidence of drug-induced akathisia can be achieved if physicians reserve antipsychotic drugs for situations of absolute necessity, prescribe the lowest dose required for the desired therapeutic effect, and withdraw the drug at the earliest possible opportunity.

Differential diagnosis

In patients taking neuroleptic drugs, akathisia is often difficult to distinguish from the anxiety and agitation caused by the underlying psychiatric condition for which the drugs are being given. Akathisia also occurs in a number of other scenarios for which dopamine blocking agents are used. Cancer patients also seem to be particularly prone as they

often receive dopamine-blocking anti-emetic agents during chemotherapy (Kawanishi et al 2007). Patients treated for gastrointestinal problems with metoclopramide and other similar agents are also prone. Intravenous metoclopramide used in the treatment of migraines was associated with akathisia in 9.2% of cases (Friedman et al 2011). Failure to recognize akathisia may lead to an inappropriate increase in medication and, thus, compounds the problem (Lang 1993). It is important to keep an index of suspicion. Schizophrenic stereotypies may be mistaken for movements of akathisic restlessness. Tardive dyskinesia must also be distinguished from akathisia in those patients who are distressed by their movements. Drug withdrawal is another condition that may be confused with akathisia.

Restless legs syndrome resembles akathisia in many respects and may also be a complication of Parkinson disease. However, in restless legs syndrome, symptoms are generally confined to the lower limbs and tend to occur only at night. Tics also result from a psychic urge to move (Lang 1991) but should be relatively easy to identify when witnessed.

Diagnostic workup

Akathisia is recognized solely by its clinical features. Although nonspecific reduction of serum iron and ferritin and elevation of acute phase reactants have been reported, their clinical importance is questionable (Hofmann et al 2000). No laboratory tests firmly support the diagnosis. The same is true for virtually all disorders that may be considered in the differential diagnosis.

Management

It is important that psychiatric patients be informed about the possible development of akathisia or other movement disorders if neuroleptic therapy is being considered. Recognition is important for patients and physicians, lest they misinterpret the condition as worsening agitation or psychosis; recognition is also important for maintenance of medication compliance and prevention of secondary suicide ideation (Drake and Ehrlich 1985). Should acute or subacute akathisia occur the first step in therapy is to reduce or eliminate intake of the offending drug. Time to reversal after removal of the inciting agent is variable and there may be a worsening before it improves (Caroff and Cambell 2016). If this is not feasible, consider substituting the agent with a less potent one, preferably a second-generation agent. If the substitution is unsuccessful, medical therapy will be necessary. There are no treatments specifically FDA approved for akathisia. However, akathisia may respond to 1 of a variety of medications.

Anticholinergic medications (including diphenhydramine) have historically been utilized to treat akathisia--perhaps because of their usefulness in drug-induced parkinsonism and acute dystonia, but evidence is scant. A Cochrane review in 2006 found no relevant randomized controlled trials and, hence, no reliable evidence to support or refute the use of anticholinergics for patients with acute or subacute akathisia (Rathbone and Soares-Weiser 2006). Open trials have demonstrated mixed results with various agents in the class. In 2007, a double-blind, placebo-controlled study of biperiden injections was completed in 30 patients (15 active vs. controls) with assessments at baseline and 3 times after the first injection at 2-hour intervals. Response was defined as at least a 2-point decline in the global akathisia score. The numbers of responders in the 2 groups were not significantly different, and the changes in the Barnes Akathisia Rating Scale were similar (Baskak et al 2007). One additional study demonstrated that diphenhydramine did not prevent akathisia in those treated with metoclopramide acutely (Erdur et al 2012). Anticholinergics do not appear to be effective treatment of akathisia and should not be used as first-line treatment. Considering the adverse effects associated with this class of medications, they should not be used.

A second class of medications used to treat akathisia, and the general first choice, is beta-blockers, which have been in use since 1983. Propranolol is the most commonly prescribed and most effective. Several open-label and controlled trials have shown consistent results with doses of 80 mg/day or less and a 50% improvement (Miller and Fleischhacker 2000; Adler et al 2005). Other nonselective beta-blockers such as nadolol and pindolol have been found to be effective though less so because of diminished blood-brain barrier penetration. B1 selective agents, such as metoprolol and betahexol, have also been utilized with some success. These medications should be used with caution in those with depression, pulmonary disease, diabetes mellitus, or cardiac disease.

Relatively new agents have been examined with some success; these include vitamin B6 and the 5HT2 antagonists mianserin, mirtazapine, and trazodone. In a systemic review and evidenced based meta-analysis, 6 randomized controlled trials were found examining 5HT2a antagonists, 5 of which included a placebo control group (Laoutidis and Luckhaus 2014). The overall effect size in the analysis is substantial, RR=7.10 with 95% CI 3.08–16.40 ($p<0.0001$)

based on change in the Barnes Akathisia Scale. Because of the small number of trials, a difference between the 3 agents: mianserin, mirtazapine, and trazodone, could not be detected. These findings point to the class of 5HT2A antagonists as effective and safe and perhaps the treatment of choice for neuroleptic induced akathisia. Some of these trials will be discussed.

One study compared the efficacy of B6, mianserin and placebo in the treatment of acute akathisia. Sixty schizophrenia and schizoaffective in-patients with akathisia were randomized to receive vitamin B6 1200 mg/d, mianserin 15 mg/d, or placebo for 5 days, in a double-blind design. Compared with the placebo group, the vitamin B6-treated and mianserin-treated patients showed a significant improvement in the subjective symptoms ($P < 0.0001$), subjective distress ($P < 0.0001$), and global ($P < 0.0001$) subscales. A reduction of at least 2 points on the Barnes Akathisia Rating Scale global subscale was noted in the vitamin B6 group (13/23, 56%) as well as in the mianserin groups (13/20, 65%) and in only 1 patient in the placebo group (1/17, 6%; $P < 0.0005$) (Miodownik et al 2006).

Mirtazapine is a potent antagonist of central alpha 2 auto- and hetero-adrenergic receptors, as well as an antagonist of 5-HT2A/2C, 5-HT3, and histaminergic H1 postsynaptic receptors. The use of mirtazapine offers advantages over other anti-akathisia drugs in its better adverse effect profile as well as its ability to treat coexisting depression (Ranjan et al 2006). In a 7-day double-blind trial, 90 antipsychotic-treated patients meeting DSM-IV criteria for akathisia were randomly assigned to mirtazapine (n = 30; 15 mg), propranolol (n = 30; 80 mg), or placebo (n = 30). Twenty-four patients (26.6%) did not complete the study (7 mirtazapine, 8 propranolol, 9 placebo) due to lack of response (n = 19) and adverse events (n = 5). Both mirtazapine and propranolol significantly reduced akathisia severity (Barnes Akathisia Scale: -34% mirtazapine ($p = .012$) and -29% propranolol ($p = .023$) vs. placebo -11%). Thirteen (43.3%) mirtazapine- and 9 (30.0%) propranolol-treated patients versus 2 (6.7%) placebo-treated patients responded (odds ratios 10.7 [95% confidence interval (CI), 2.1-53.3] and 6.0 [95% CI, 1.1-30.7]). Five (16.7%) of 30 propranolol-treated patients and none in the mirtazapine and placebo groups ($p = .0195$ for both) prematurely discontinued the study due to clinically significant hypotension or bradycardia (Poyurovsky et al 2006).

A double-blind, crossover study of trazodone, which has similar pharmacological effects to mirtazapine, 5-HT2A/2C antagonism, has also been found to improve akathisia. This was a 6-day study (3 days active, 3 days placebo with no washout) performed on 13 patients with acute akathisia diagnosed by DSM IV criteria. There was significant improvement of the Barnes Akathisia Rating scale subjective, objective, distress, and global parts with 100 mg at night (Stryjer et al 2010). Other less frequently examined agents thought to benefit patients with akathisia include benzodiazepines, amantadine, and clonidine.

Based on results of the various studies, it is suggested that propranolol, mirtazapine, and perhaps trazodone be considered first-line agents (Poyurovsky 2010). The other classes listed above could be considered if these fail or are contraindicated (for instance, propranolol should not be utilized in patients with asthma or diabetes).

Evidence-based guideline for the treatment of tardive dyskinesia has been provided by the American Academy of Neurology (Bhidayasiri et al 2013). In tardive akathisia, aside from beta-blockers, the catecholamine depletors reserpine and tetrabenazine have been the effective agents (Burke et al 1989; Jankovic and Clarence-Smith 2011), much as in tardive dyskinesia. Zolpidem, which is a GABA-mimetic drug and a selective agonist of the benzodiazepine receptors, and gabapentin, which enhances the activity of GABA, have also been found to be helpful in some patients with akathisia, without causing drowsiness (Jankovic and Clarence-Smith 2011; Waln and Jankovic 2013b; Sullivan and Wilbur 2014). Fluvoxamine, a sigma-1 agonist has also been shown to improve akathisia in single cases (Albayrak and Hashimoto 2013). It is likely anticholinergic agents will make tardive akathisia worse as they do with classical tardive dyskinesia, but there are little data on this. Deep brain stimulation of the subthalamic nucleus has been reported to be effective in patients with Parkinson disease who experienced severe akathisia with or without a relationship to levodopa (Shin et al 2010). It is not clear, however, whether deep brain stimulation would be a suitable treatment for tardive akathisia.

A potential future class of medications that may be effective in treating akathisia is the adenosine A2a antagonist group. A2a antagonists have been studied in large clinical trials for the treatment of Parkinson disease, including motor fluctuations and dyskinesia and are found to be safe and to improve motor symptoms (Smith et al 2012). A first generation agent has been approved for use in Japan (Dungo and Deeks 2013). A study demonstrated that a selective A2A receptor antagonist (compound SCH 412348 10 to 30 mg/kg) can effectively reduce or reverse akathisia-like behavior in nonhuman primates induced by both aripiprazole and the phosphodiesterase 10A inhibitor MP-10 (Bleickardt et al 2014). Studies in humans are pending.

Special considerations

Anesthesia

Akathisia may be seen in surgical patients as dopamine receptor antagonists acquire a wider role in control of emesis and pain (Brown 1988). The butyrophenone droperidol, and phenothiazine metoclopramide used as an adjunctive antiemetic with opiate analgesics, may cause akathisia when administered intravenously (Ward 1989) or epidurally (Athanassiadis and Karamanis 1992). Midazolam, a benzodiazepine often used for preoperative sedation, induced paradoxical akathisia in 3 patients who received epidural anesthesia (Martinez-Telleria et al 1992).

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**References especially recommended by the author or editor for general reading.

Former authors

David E Riley MD (original author)

ICD and OMIM codes

ICD codes

ICD-9:
Abnormal involuntary movements: 781.0

ICD-10:
Other and unspecified abnormal involuntary movements: R25.8

Profile

Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance

male=female

Family history

none

Heredity

none

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

schizophrenic stereotypies
tardive dyskinesia
drug withdrawal
restless legs syndrome
tics
SSRI-induced movement disorders
lithium-induced movement disorders

Associated disorders

Parkinson disease
Postencephalitic parkinsonism
Psychiatric disorders

Other topics to consider

Acute drug-induced movement disorders
Catatonia
Periodic limb movements
Restless legs syndrome
Sleep disorders associated with parkinsonism
Status migrainosus
Stereotypies
Tardive dyskinesia
Tardive dystonia