Introduction: medication-induced movement disorders

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Adverse drug events (ADE) are, unfortunately, very common events (Jha AK; Davey et al. 2008). They constituted over 2% of pediatric emergency visits to a Canadian hospital and 1.4% of admissions to a US hospital. ADE may be defined as an unwanted effect of the medication, whether anticipated or not, which is not due to a medical error.

Ascribing an ADE to a drug exposure is often difficult, especially in the setting of a rare reaction. A temporal relationship between starting a medication and experiencing a rare syndrome does not mean that the two are related. Nor does a seeming lack of temporal relationship indicate a lack of causality, as some effects may take weeks to months to appear. Ideally, one can follow the postulates Koch espoused for determining infectious etiologies: identify a syndrome, isolate the presumed causal agent, and demonstrate that this agent causes the same syndrome in other hosts. That, of course, is not always feasible, possible, or ethical.

Sometimes in the field of movement disorders the connection between drug and movement is straightforward: lithium causes tremor, anticonvulsants cause ataxia, clozapine causes asterixis, etc. In some cases this has been less straightforward, as the history of the recognition of the tardive syndromes makes clear. Many years elapsed before the connection between neuroleptics and tardive dyskinesia was made, partly because, unlike other movement disorder adverse effects, this did not resolve when the offending medication was stopped. More unusual was the observation that the movements typically got worse when the dose was reduced and improved when the dose was increased, which seemed paradoxical for an ADE. Compounding the difficulty was the longstanding association between psychotic behaviors and movement disorders, that long predated the use of antipsychotic drugs.

Movement disorder side effects may go unnoticed, as is often the case with parkinsonism or tardive dyskinesia, but usually the side effects are perceived and are often troublesome. Some disorders are flagrant and life threatening, as with neuroleptic malignant syndrome and serotonin syndrome, while some are functionally disabling, although not "medically" serious, as is often the case with tremor. In middle aged and older patients, the development of a parkinsonian syndrome, perhaps from psychiatric or gastrointestinal motility drugs, raises the always worrisome concern about the unmasking of idiopathic PD. These issues are often important, first requiring recognition, then appropriate evaluation and treatment, when possible.

ADEs have a special place in the field of movement disorders. The field of movement disorders really began in the 1970s, and initially focused primarily on two major problems, Parkinson's disease and neuroleptic-induced movement disorders. There was a mirror image symmetry between the disciplines of neurology and psychiatry with these disorders, for the treatment of motor problems in Parkinson's disease caused the psychotic symptoms of hallucinations and delusions, while the treatment of hallucinations and delusions in psychotic patients caused motor signs that exactly replicated those of idiopathic Parkinson's disease. In addition, chronic treatment of PD with L-Dopa induced dyskinesias, which were often quite similar to the tardive syndromes induced by longstanding use of dopamine receptor antagonists. And the early approaches to the treatment of PD and schizophrenia developed in parallel as well, with some neurologists advocating titrating doses of

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L-Dopa until dyskinesias appeared, then reducing slightly, while some psychiatrists advocated increasing doses of neuroleptics until parkinsonism appeared. Both approaches now are considered outdated, and the appearance of parkinsonism is no longer viewed as a goal, since its occurrence was clearly divorced from antipsychotic effects with the development of clozapine.

It is not rare for patients to have suffered with movement disorders for years before the connection with a chronic medication was recognized. Certainly the number of lawsuits based on excessively long use of metoclopramide and prochlorperazine supports this unfortunate connection. This book will hopefully help reduce these problems. It is not always possible to follow the first commandment of medical practice, primum non nocere, but certainly we can always be alert to identifying and then reducing that harm.

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Chapter 1

Acute akathisia

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Introduction

Akathisia, a term coined by Ladislav Haksovec in 1901 from the Greek meaning "not to sit," is an inner sensation of restlessness that is alleviated by movement.[1] It was first described in patients with Parkinson's disease (PD); however, it is more commonly considered an adverse effect of antipsychotics (neuroleptics). Akathisia is the most common and distressing symptom in patients administered antipsychotics.

Clinical presentation

Patients with akathisia commonly develop both subjective and objective symptoms. The recently revised Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) defines medication-induced akathisia as a syndrome with subjective symptoms often accompanied by objective findings.[2] Subjective symptoms are described as an inner tension, anxiety, irritability, discomfort, restlessness, or sleeplessness. The objective findings include movements that are semivolitional, purposeful and suppressible, repetitive, complex, and stereotypical. Patients with akathisia are unable to remain motionless and present as restless. These movements are most commonly evident in the legs, seen as crossing and uncrossing, swinging one leg lateral to medial or anterior to posterior, or pacing. Other movements include rubbing the scalp or anterior thighs, rocking while sitting, swaying while standing, swinging arms, and changing positions from sitting to standing. Forty percent of patients notice improvement in the supine position and worsening when standing compared with sitting.[3]

Typically the symptoms of akathisia are generalized; however, there are rare case reports of focal akathisia. An unusual presentation of akathisia affecting the oral and genital regions described as extremely uncomfortable and with burning pain has also been reported.[4] In addition, patients may make noises, including moaning and grunting. It is debatable whether these vocalizations are due to discomfort or are a component of akathisia with the purpose of providing subjective relief.

Akathisia is a distressing and disabling condition affecting an individual's quality of life. Acute akathisia often will result in noncompliance and may be associated with new onset suicidal ideation. It is possible that patients with underlying psychiatric disease are less able to cope with the distressing symptoms of akathisia, increasing the potential for suicide. However, there are rare reports of suicidal thoughts manifesting in patients with no history of mental illness. Consequently, clinicians need to be aware of this potential risk and monitor patients diligently.

Diagnosis

Accurate diagnosis of akathisia is challenging and the disorder is likely underdiagnosed. Some patients, especially those with mental illness or dementia, and children, may lack the ability to communicate subjective symptoms of akathisia effectively. Symptoms may also be minimal, not reaching a threshold of concern by the patient to warrant discussion with the physician. In addition, akathisia severity can vary greatly and symptoms may be delayed, intermittent, or suppressed. This may result in objective symptoms being minimal or absent during a physician appointment. In research studies designed to evaluate effectiveness of treatment, potential adverse effects may not be fully evaluated. Therefore, in a brief examination, when other concerns and symptoms are evaluated, it is

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possible to not recognize akathisia and the true prevalence may be underreported.

Patients with mental illness including bipolar disorder, depression, and schizophrenia may present with psychosis mimicking akathisia. Distinguishing akathisia from underlying psychiatric symptoms is difficult and misinterpretation may result in inappropriate medical management. For example, a patient with acute akathisia misinterpreted as having worsening of psychosis may be prescribed higher dosages of antipsychotics with resultant worsening of symptoms due to escalation of the offending medication. Akathisia may also overlap with psychiatric symptoms, making distinguishing between them nearly impossible. Akathisia may be associated with other "extrapyramidal" side effects including parkinsonism and tardive dyskinesias, though it has been reported to be less commonly present with oral tardive dyskinesias. Finally, recreational drugs such as cocaine may induce symptoms that appear to be akathitic in nature but other symptoms not consistent with akathisia also manifest, including psychomotor agitation and an altered level of consciousness.

It remains unclear whether the "jitteriness/anxiety syndrome" and akathisia are separate entities or part of a spectrum. Jitteriness/anxiety syndrome is a poorly characterized syndrome described in patients treated with selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants. There is great variation in symptoms, including insomnia, anxiety, irritability, hypomania, and restlessness, that may also cause the urge to move. There is also variability in onset of presentation with the majority of symptoms occurring within two weeks of the start of antidepressants. Some authors have even incorporated akathisia as an essential component of the definition of jitteriness/anxiety syndrome.

Additionally, there are a number of movement disorders that mimic akathisia, including restless leg syndrome (RLS), stereotypies, tics, paradoxical dystonia (dystonia relieved with movement), punding, and withdrawal syndromes. RLS is characterized by an urge to move and unpleasant sensations in the legs predominately occurring in the evening and in repose. Relief is obtained by moving the affected limbs. In comparison, akathisia is much more generalized, does not have a diurnal component, and is often less in the lying position. Stereotypies are involuntary, typically continuous and repetitive non–goal directed movements that often begin prior to the age of two years. Examples include hand waving, head nodding, head banging, covering of ears, chewing movements, and pacing. This disorder is most often seen in patients with developmental disorders including autism and Rett syndrome. Tics can be simple or complex, motor or phonic, often brought on by an urge to perform gestures with relief upon making them. In comparison, akathisia has a more restless feature to the movements. Punding is a compulsive behavior of repetitive, purposeless movements often involving mechanical tasks including shuffling, sorting, arranging and reorganizing environments, disassembly and assembly of items, and collecting objects. Patients with punding do not express an inner sense of restlessness as occurs in akathisia.

There is no universally held consensus on the diagnosis of akathisia. Diagnosis is most accurately made using both subjective and objective findings and a classification system of akathisia has been proposed based upon these.[5] Medication-induced akathisia is categorized into subtypes including acute, tardive, and withdrawal tardive. Acute akathisia is commonly defined as subjective and objective restlessness of ≤ 6 months duration often coinciding with the onset of starting, increasing, or changing to a more potent medication. Medication-induced acute akathisia decreases with drug reduction. In contrast, tardive akathisia occurs late in the treatment course without any provocation. An arbitrary duration is commonly considered as greater than three months. Analogous to tardive dyskinesias, tardive akathisia may worsen with abrupt drug withdrawal (in contrast to acute akathisia) and is challenging to treat. Withdrawal tardive akathisia is subjective, and objective restlessness presents within days to weeks after drug reduction or withdrawal. An arbitrary cutoff is 6 weeks. Chronic akathisia is not a distinct subtype. This refers to the duration of symptoms being more prolonged, typically greater than three months. It may have an acute, tardive, or withdrawal onset; however, the literature is inconsistent, often combining tardive, chronic, and withdrawal akathisia. "Pseudoakathisia" is a term used to describe motor restlessness unaccompanied by subjective symptoms and may be a symptom on a spectrum of akathisia or, in many patients, is probably a form of tardive dyskinesia, sometimes called "tardive stereotypy." The pathophysiology of the akathisia subtypes likely differs based upon variability of treatment effects and symptomatology. Most cases of akathisia are acute. The severity of subjective symptoms in acute akathisia may not significantly differ compared with tardive

(chronic) akathisia. However, it is claimed that objective motor findings are more severe in acute akathisia although many patients with tardive akathisia can have very striking clinical features.[6] Therefore, clear definitions are needed for our current and future understanding akathisia.

There are several scales used to measure akathisia and the response to treatment.[7] The Barnes Akathisia Rating Scale (BARS) is an assessment composed of subjective, objective, and distress aspects of akathisia and has a high inter-rater reliability. The total score ranges from 0 to 9 with higher scores representing more severe akathisia. The Prince Henry Hospital Rating Scale of Akathisia (PHH) is a comprehensive diagnostic and grading instrument using duration and intensity of akathisia in rating. An abridged version of the PHH has also been developed with a 100% sensitivity and 99% specificity to PHH.[8] The Hillside-Akathisia-Scale (HAS) was designed to evaluate the frequency and severity of akathisia in clinical psychopharmacological research. There is no consensus on the best scale to use, although the BARS is the most commonly applied.

Pathogenesis

Despite longstanding recognition of akathisia, its pathophysiology is not fully understood. It is likely that multiple complex pathways are involved and that more than one pathophysiological mechanism can result in akathisia. Since akathisia is predominately induced by antipsychotics and it often occurs in association with other "extrapyramidal" symptoms, much research has focused on the dopaminergic system either directly or indirectly.

Blockade of dopamine D2 receptors is believed to be a major factor in the pathophysiology of akathisia. Antipsychotics are potent D2 antagonists and are associated with the greatest risk of akathisia. Studies using positron emission tomography (PET) imaging have demonstrated that akathisia is associated with high degrees of antagonism of D2 receptors in the basal ganglia.[9] In patients with schizophrenia, D2 occupancy of greater than 78% was associated with extrapyramidal symptoms including haloperidol-induced akathisia.[10] However, this theory fails to explain other causes of akathisia, including antidepressants, dopamine depleting drugs, and PD. Furthermore, antipsychotics with low D2 potency, including clozapine and quetiapine, are also known to induce akathisia. Consequently, other theories need to be considered.

Akathisia also may involve antagonism of two dopaminergic pathways originating in the midbrain: the mesocortical system with projections from the ventral tegmental area (VTA) to the frontal lobes, and the mesolimbic pathway with connections from the VTA to the nucleus accumbens.[11] In animal models, bilateral lesions of the VTA result in locomotor hyperactivity.[12] Furthermore, haloperidol administration produces an increase of neuronal activation determined by increased Fos (the protein produced from the immediate early gene *c-fos* and marker to visualize the pattern on neuronal activity in the CNS) neuronal expression in regions with high D2 expression, including the prefrontal cortex, striatum, nucleus accumbens, lateral septal nucleus, and dorsolateral striatum. Pretreatment with propranolol (an effective treatment for akathisia; see treatment section below) reduced the number of Fos-positive nuclei within the cortex, piriform cortex, and parietal cortex.[13] The nucleus accumbens is composed of two regions: the core and surface portions. Akathisia may result as a consequence of an imbalance between these two. The surface portion is involved in unconditional defense behaviors and receives noradrenergic input from the locus coeruleus. Reduced dopaminergic input from the VTA to the core portion permits unopposed stimulation of the surface portion from the locus coeruleus. Consequently, beta blockers may act by inhibiting this input. Theoretically, the mesocortical pathway may also be hyperactive due to impaired feedback mechanisms, as D1 receptors that predominate in the cortex, especially the orbitofrontal cortex, are less inhibited by antipsychotics. The orbitofrontal cortex also stimulates the locus coeruleus, further increasing noradrenergic input to the surface portion of the nucleus accumbens (see Figure 1.1). However, direct evidence for impairment of this system is lacking, and it fails to explain akathisia occurring with SSRIs and in PD.

The existence of SSRI-induced akathisia suggests that the serotoninergic system is also involved. The role of 5-HT2 receptors in the pathophysiology of akathisia is supported by the presence of these receptors in the VTA, the response of akathisia to 5HT2A antagonists, and treatment failure of buspiron, a 5-HT1a partial agonist, and granisetron, a 5-HT3 receptor antagonist (see treatment section below).[14,15] The dorsal raphe nucleus has serotonergic projections directly to

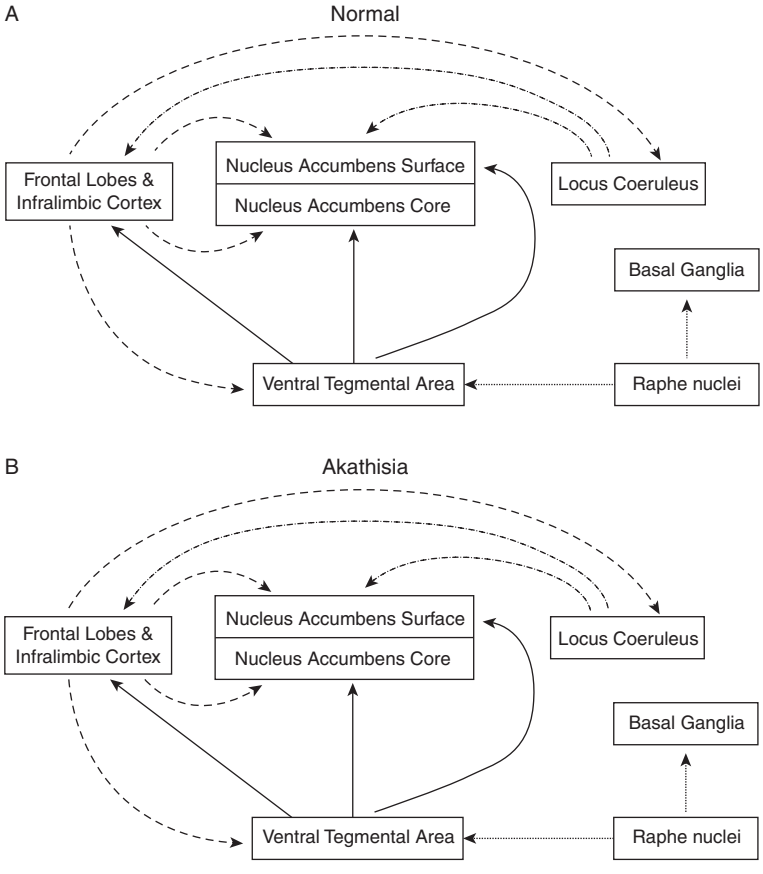

Figure 1.1 Schematic proposal of pathways comparing normal (A) to akathisia (B). Reduced dopaminergic stimulation from the ventral tegmental area (VTA) may create unopposed stimulation of the pathway from the locus coeruleus to the surface portion of the nucleus accumbens. Thickness of arrows represent strength of input. Increased thickness of the serotonin input in bottom right corner of figure (B) exclusively relates to possible explanation of selective serotonin reuptake inhibitors (SSRI)-induced akathisia. Blue arrows = noradrenergic, Green arrows = glutamatergic, Red arrows = serotonergic, Black arrows = dopaminergic. Figure adapted from 11,86.

the basal ganglia inhibiting dopaminergic neurons, potentially via 5-HT2 receptors. The midbrain raphe nuclei also projects inhibitory serotonergic input to the VTA and substantia nigra. Studies evaluating SSRI-induced inhibition of the dopamine system have provided inconsistent results. This may relate to the varying distribution of different serotonin receptors in the midbrain and basal ganglia.

Etiologies

Akathisia is most often iatrogenic, caused by antipsychotic medications, but also by SSRI antidepressants. Medication-induced acute akathisia typically begins within hours of administering the offending drug but may be delayed up to several days after initiation, during escalation of treatment, or upon switching to a more potent dopamine receptor blocking agent. There are several other etiologies of acute akathisia that have also been reported (see Table 1.1).

Antipsychotics

Antipsychotics have been classified into two categories: first generation (typical) and second generation (atypical) antipsychotics. This classification system was originally developed partially by the pharmaceutical industry with the expectation that newer developed antipsychotics created in the 1990s would have less extrapyramidal adverse effects compared with the traditional first generation antipsychotics developed in the 1950s. First generation antipsychotics are potent dopamine D2 antagonists. In contrast, second generation antipsychotics, which are also D2 antagonists, are characterized by relatively low-affinity or rapid dissociation from D2 receptors and are potent antagonists of serotonin 5HT2A receptors (see Table 1.2).

Second generation antipsychotics are thought to be less prone to cause extrapyramidal symptoms, including akathisia, due to lower affinity for D2

receptors, although clinical evidence is conflicting. However, they do have more antimuscarinic and antiadrenergic activity, resulting in greater sedation and hypotension compared with first generation antipsychotics. For example, the risk of akathisia with haloperidol, a first generation antipsychotic, may be as high as 75%, while it is approximately 5% with clozapine, a second generation antipsychotic.[16] In a three arm double blind 8-week treatment study, akathisia developed in 19% and 22% of patients treated with second generation antipsychotics, olanzapine and risperidone, respectively, in comparison to 45% of patients treated with the first generation agent, molindone, with 18% of patients in this treatment arm reporting moderate to severe symptoms.[17] Furthermore, in comparing medications within the second generation class, those with higher D2 affinity are more likely to cause akathisia. Certain D2 receptor blockers are used as antiemetics, particularly chlorpromazine and prochlorperazine. In the emergency department, the incidence of akathisia with these medications has been reported to be 44%.[18]

Acute akathisia is the most common important adverse effect of antipsychotics. The reported incidence of antipsychotic-induced akathisia (AIA) ranges greatly, from 8%–76%, but more conservative estimates utilizing clear subjective and objective findings report an incidence of 20%–30%.[19] As noted above, accurate epidemiological data comes from studies using validated rating scales that include subjective and objective findings to consistently diagnose akathisia. Other causes of inaccurate prevalence estimates include the facts that patients are less inclined to spontaneously report milder

Table 1.1 Etiologies of acute akathisia

Medications:
Antipsychotics (including metoclopramide, prochlorperazine & droperidol)
SSRI antidepressants
Mood stabilizers (lithium)
Catecholamine-depleting agents (tetrabenazine & reserpine)
Antiepileptics (carbamazepine, ethosuximide, gabapentin & pregabalin*)
Calcium channel blockers and antihistamines (flunarizine, cinnarizine)
Calcium channel blocker (diltiazem)*
Toxic:
Central stimulants (amphetamine and cocaine)*
Neurodegenerative:
Parkinson's disease
Spinocerebellar ataxia 3*
Wilson's disease*
Structural
Traumatic brain injury*
Encephalitis*
Stroke*

* Case reports or series

Table 1.2 D2 receptor affinity of commonly used first and second generation antipsychotic medications divided into low, medium, and high potency

First Generation		Second Generation		
Low (8–16)	**High (1–4)**	**Low (126–380)**	**Medium (20)**	**High (2–6)**
Chlorpromazine	Haloperidol	Clozapine	Olanzapine	Risperidone
Levomepromazine	Fluphenazine	Quetiapine		Paliperidone
Mesoridazine	Loxapine			Aripiprazole *
Periciazine	Molindone			Ziprasidone
Pipamperone	Perphenazine			Amisulpride
Thioridazine	Pimozide			Lurasidone
	Thiothixene			Iloperidone
	Zuclopenthixol			Cariprazine *

Ranges reported as Ki. * denominate agonists

symptoms to care providers, and symptoms of akathisia may be misinterpreted as psychiatric symptoms. In a study of 100 patients taking antipsychotics for two weeks, 40% developed mild akathisia that did not require a change in therapy. Moderate to severe symptoms necessitating change or reduction of medication were evident in 21% of patients.[20]

The CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study included 1493 patients with schizophrenia randomly assigned to receive ziprasidone (40–160mg/day), olanzapine (7.5–30mg/day), perphenazine (8–32mg/day), quetiapine (200–800mg/day), or risperidone (1.5–6mg/day) for up to 18 months. Surprisingly, this study did not demonstrate significant difference in the incidence of akathisia among the various treatment groups, which ranged from 5%–9%.[21] The lack of difference between first and second generation antipsychotics in this study may partially be the effect of underreporting of mild symptoms (BARS score of ≥ 3) or maybe the fact that all subjects had been taking neuroleptics for long periods of time with only a short washout before enrolling in the study.

Several potential risks factors for the development of AIA have been reported. As previously noted, one of the greatest risks is increasing dosage or switching to more potent medications with greater D2 affinity. A number of studies have also identified an association between other extrapyramidal symptoms and the development of akathisia, indicating that they often occur together; but one does not necessarily predict the occurrence of the other. Patients with bipolar disorder may have twice the risk of developing AIA as patients with schizophrenia.[22] Homozygosity for the Ser9Gly variant of the dopamine D3 receptor (DRD3) gene has been identified in eight of nine patients with schizophrenia and AIA.[23] Interestingly, DRD3 receptors are mainly localized in mesolimbic brain regions and therefore may play a role in the pathogenesis of acute akathisia. In addition, the TaqI_D polymorphism in the DRD2 gene was significantly associated with akathisia in patients treated on antipsychotics. For each extra C-allele a 2.3% times higher risk of having akathisia was found.[24]

Results are inconsistent with respect to several other reported risk factors. Smoking tobacco has been proposed to be protective against akathisia; however, a study of 250 patients with schizophrenia failed to demonstrate any association between akathisia and heavy smoking.[25] There is conflicting data regarding women having a potentially increased risk of AIA. Sandyk and Kay (1990) reported in schizophrenic hospitalized patients that akathisia was more common in women compared with men, although they did not separate acute and tardive akathisia.[26] However, most epidemiology studies have failed to identify any significant gender difference in the occurrence of AIA. Age and race are not associated with akathisia.[20] It is possible that low iron stores increase the risk of AIA. Several studies have been performed supporting this finding. Serum iron and ferritin levels were compared in 33 patients with AIA and 23 patients on antipsychotics without akathisia. Patients with AIA had significantly lower serum ferritin levels, although the differences were small and levels were within a normal range. There was no correlation between serum iron or ferritin levels and akathisia ratings.[27] However, other studies contradict these findings. Two prospective studies failed to demonstrate any differences in serum iron and transferrin levels between patients with and without AIA.[28]

Below we will provide more detail on selected commonly prescribed second generation agents. Table 1.3 summarizes information on AIA induced by other second generation medications not discussed below.

Clozapine – There are relatively few reports of AIA induced by clozapine. In one, hospitalized schizophrenic patients were enrolled in a double blind multicenter study aimed at comparing treatment with clozapine (N=75) to chlorpromazine (N=76). Akathisia occurred in comparable numbers of clozapine and chlorpromazine treated patients, 5 and 4, respectively. However, other extrapyramidal symptoms including rigidity, tremor, and dystonia were much less common in the clozapine treated group.[29] In a nonrandomized, nonblinded study of patients with a variety of psychiatric disorders the prevalence of akathisia was 39% with clozapine compared with 45% in patients treated with miscellaneous antipsychotics. A greater number of patients taking first generation antipsychotics had severe akathisia.[30] Selection bias was a limitation, as those treated with clozapine had more severe mental illness and often had previously failed conventional medications. In addition, the dose of clozapine was higher from other studies reporting a 7% incidence of akathisia.[31] The majority of patients treated with clozapine had been previously tried on other antipsychotics and it is unclear whether this past exposure increases the risk of developing AIA.

Table 1.3 Summary miscellaneous second generation antipsychotic-induced akathisia

Medication	Study Design	Dosage	Incidence	Reference
Paliperidone	Case Report	37.5mg biweekly	–	64
Aripiprazole	RCT and case reports	2–24mg/day	23%	42,65,66
Ziprasidone	RCT and case reports	80–160mg/day	36%	67,68
Amisulpride	Prospective studies and case reports	~ 400mg/day	11%	69,70
Lurasidone	RCT	20–120mg/day	11–24%	71,72
Iloperidone	RCT	4–24mg/day	1–9%	73
Cariprazine	RCT	1.5–4.5mg/day	10%	74

RCT = Randomized controlled trial

Quetiapine – Overall, similar to clozapine, quetiapine is generally well tolerated with only case reports of akathisia that typically have resolved with reduction of dosage. Data combined from four randomized double blind 3-week to 12-week studies of 1003 patients with bipolar disorder indicated that extrapyramidal symptoms, including akathisia, were comparable between quetiapine and placebo.[32] Furthermore, patients with AIA who switched from conventional antipsychotics to quetiapine (400–800mg/day) have reported resolution of symptoms.[20]

Olanzapine – A pooled analysis from four randomized, open label, parallel trials of 6 weeks in patients with schizophrenia compared olanzapine 5–20mg/day (N=77) to chlorpromazine 200–800mg/day (N=32). Akathisia was reported in 2.4% in the olanzapine and 10% of the chlorpromazine groups.[33] Similar results were reported from a 12-week study comparing olanzapine monotherapy with the combination of olanzapine and other antipsychotics, antidepressants, or mood stabilizers. Three percent of patients in the olanzapine monotherapy group experienced akathisia compared to twice this in the combination medication group.[34] Similar to oral formulations, intramuscular olanzapine injections were also well tolerated with low risk of akathisia.

Risperidone – In a comparison double blind 8-week study involving 296 patients, akathisia was reported in 26% treated with risperidone compared with 32% receiving haloperidol at similar strengths.[16] Risperidone appears to carry a slightly higher risk of developing severe akathisia necessitating medication adjustments compared with second generation antipsychotics with less D2 receptor affinity.[35]

Other Dopamine Antagonists

Antiemetics are also a cause of akathisia. Metoclopramide is a presynaptic D2 antagonist prescribed as an antiemetic and intestinal prokinetic. There are several reports of metoclopramide-induced akathisia. It remains unclear if the rate of infusion is associated with risk of akathisia. A randomized double blind study comparing slow intravenous infusion of metoclopramide at 20mg over 15 min (N=102) compared with a bolus of 20mg (N=103) found no difference in development of akathisia (12% in both groups).[36] In contrast, another randomized prospective double blind study of 10mg metoclopramide in bolus (N=36) or slow infusion over 15 minutes (N=32) reported an incidence of 11% in the bolus treated group while none of the patients in the slow infusion group experienced akathisia.[37] Droperidol, an antidopaminergic used as an antiemetic, but more often for induction of anesthesia and sedation, has also been reported to result in acute dystonia and akathisia.[38]

Antidepressants

Selective serotonin reuptake inhibitors (SSRI) including fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram are associated with akathisia. Fluoxetine is reported to have the greatest risk of akathisia among the SSRIs with an incidence of 9.8%–25%. It is possible that the incidence with newer SSRIs will increase as we gain experience. Similar to antipsychotics, the onset of SSRI-related akathisia typically occurs within 1 week of starting medication. Risk factors for the development of akathisia include simultaneous use of antipsychotics

and higher SSRI dosages. Individuals with variant alleles in the CYP450 gene (involved in the metabolism of antidepressants) may be at increased risk of violent behavior when they develop akathisia.[39]

Other antidepressants and mood stabilizers have also been associated with akathisia. Atomoxetine, a selective norepinephrine reuptake inhibitor used in the treatment of attention-deficit/hyperactivity disorder (ADHD), has been reported to cause akathisia in a patient receiving a dose of 18 mg/day.[40] Venlafaxine has serotonergic properties at low dose and noradrenergic effects at higher doses. Akathisia was reported in a single patient treated with venlafaxine XR 150mg/day with resolution of symptoms in response to biperidin 4 mg/day.[41] Lithium has been reported to be associated with akathisia. In a double blind 52-week study comparing lithium to aripiprazole, nine of 159 patients treated with lithium experienced akathisia compared with 24 of 154 with aripiprazole.[42]

Miscellaneous Medications

Cinnarizine and flunarizine (calcium channel blockers and antihistamines) have been reported to cause akathisia as well as concurrent dystonia, orofacial tremor, parkinsonism, and even acute dystonic reactions, possibly supporting a dopamine antagonist effect.[43] There are rare case reports of diltiazem, a calcium channel blocker, inducing akathisia. Tetrabenazine (often used in the treatment of tardive akathisia) and reserpine, catecholamine-depleting medications, have also been associated with akathisia with an estimated incidence of 7%–15%.[44] Finally, gabapentin and pregabalin (GABA analogs) have been reported to be associated with akathisia in case reports.[45]

Treatment

As in the other section of this chapter, we will limit our discussion on treatment to the management of acute akathisia. The treatment of chronic tardive akathisia is distinctly different and generally similar to that of other tardive syndromes, which are covered elsewhere in this volume. There are two main treatment strategies for medication-induced acute akathisia: modification of the drug regimen and the addition of antiakathitic medications. The first treatment strategy should be to identify the offending medication and to withdraw this if possible. In situations where this is not possible, a dose reduction or switching to a less potent D2 blocking agent is recommended. Unlike tardive akathisia, acute akathisia typically responds well to this approach. However, in severe acute akathisia or where drug adjustments are not possible, it may be necessary to treat with medication. The most commonly used medications in the treatment of AIA are antiadrenergics (β-adrenergic antagonists and α-2-agonists) and anticholinergics, while other treatments have also been investigated (see Table 1.4). A problem in the literature regarding treatment of AIA is that the majority of studies are small with short duration of follow-up and often combine akathisia subtypes. Studies are open-labeled, and given the marked response these patients have to placebo, interpretation must be made cautiously. We have summarized many studies on AIA treatment in Table 1.4.

Antiadrenergics – β-blockers are the most widely used treatment for akathisia. These medications are classified based on the type of β-receptors antagonized (selective β-1 or β-2 and nonselective blocking both types) and lipophilicity with more lipophilic medications having greater blood-brain barrier penetration. Propranolol, a lipophilic nonselective β-blocker, has been used as a first-line antiakathisia agent for more than two decades with approximately 70% positive response rate. Symptomatic improvement may be seen within 24 hours of starting; the typical dosage range is 60–120mg/day divided twice daily.[46,47] The duration of benefit is unknown but sustained effects of several months have been reported. Pindolol, a lipophilic nonselective β-blocker and partial 5HT1A receptor antagonist, has been reported to be efficacious in 4 of 9 patients with drug-induced akathisia.[48] In those who did not respond, benefit was obtained with propranolol. Metoprolol (75m/day) and betaxolol (5–20mg), lipophilic selective β-1 antagonists, are effective treatments with comparable results to propranolol. A specific lipophilic β-2 antagonist that was subsequently withdrawn from production, ICI 118,551, demonstrated significant improvement of AIA compared to placebo in a double blind study. In contrast to lipophilic β-blockers, the hydrophilic selective and nonselective β-antagonists, including nadolol, sotalolol, and atenolol, are less effective.[46,47]

α2 adrenergic agonist – A number of reports have indicated that clonidine, a central acting α-2 receptor agonist, may be effective in treating akathisia. Maximal beneficial effects are noted within 48 hours of starting medication with dosages ranging from 0.15–0.8 mg/day titrated to beneficial effects.[46] The use of clonidine