Comprehensive Reviews

A Brief Overview of Iatrogenic Akathisia

Claire Advokat [1]

Abstract

Akathisia is a significant and serious neurological side effect of many antipsychotic and antidepressant medications. It is most often expressed as a subjective, uncomfortable, inner restlessness, which produces a constant compulsion to be in motion, although that activity is often not able to relieve the distress. Because it can be extremely upsetting to the patient, akathisia is a common cause of nonadherence to psychotropic treatment. Unfortunately, its subjective nature makes quantitative assessment difficult. Although its pathophysiology is not well-established, a decrease in dopaminergic activity appears to be an important etiological factor. In addition to reducing the dose of the offending drug, the most effective treatment of akathisia includes administration of either a beta-adrenergic antagonist or a serotonergic 5HT2 receptor antagonist. The therapeutic effect of monoaminergic antagonists is believed to result from blockade of inhibitory noradrenergic and serotonergic inputs onto dopaminergic pathways in the striatum and limbic system. If so, medications with intrinsic beta-adrenergic and 5HT2 receptor antagonism might produce less akathisia, and dopaminergic (but not adrenergic) agents, (e.g., the antidepressant bupropion, or the dopamine agonist ropinirole) might reduce akathisia. To evaluate these hypotheses, better treatments—as well as more precise ways of detecting akathisia—are needed. Currently, akathisia is inadequately controlled, and there is evidence that it may be increased when antipsychotic and antidepressant drugs are combined, such as in the treatment of bipolar disorder.

Brief History

Literally translated from the Greek, akathisia means "not to sit." Although best-known for its association with neuroleptic medications, akathisia was recognized long before such drugs were developed. The earliest medical description is attributed to Willis in 1685 (1, 2); and, the earliest 19th century account to Wittmaack (1861), who referred to it as *anxietas tibiarum*. Subsequently, Beard (1880) described a phenomenon of: "Fidgetiness and nervousness, inability to keep still-a sensation that amounts to pain-[and] is sometimes unspeakably distressing. When

[1] *Department of Psychology, Louisiana State University, Baton Rouge*

Address for correspondence: Claire Advokat, PhD, Department of Psychology, 236 Audubon Hall, Louisiana State University, Baton Rouge, LA 70803 Phone: 225-578-8500; E-mail: cadvoka@lsu.edu

the legs feel this way the sufferer must get up and walk or run even if he is debilitated."

In 1923, Bing noted that although Haskovec originally described it in 1901 and first used the term "akathisia," Haskovec mistakenly thought it had an hysterical origin, when, instead, it is an organically based symptom of extrapyramidal dysregulation. This was supported by Wilson who noted it in patients with postencephalic or idiopathic parkinsonism (1940). But Sigwald was probably the first to recognize drug-induced akathisia when using promethazine in 1947, and it was frequently reported in the 1950s and 1960s as a component of neurologic side effects induced by antipsychotic drugs (1-4).

Diagnosis

Akathisia consists of two components. One is a subjective, uncomfortable, inner restlessness which may be accompanied by cognitive impairments in attention, or perceptual disorders (5). This sensation differs from anxiety, is most referable to the legs, and produces a constant compulsion

Clinical Implications

Akathisia is a significant and serious side effect of many antipsychotic and antidepressant medications. It is extremely distressing to the patient, and a common cause of medication nonadherence, even when the drugs are therapeutically effective. The primary etiology appears to involve a decrease in dopaminergic activity. Treatment includes reducing the dose of the offending drug, or administration of a beta-adrenergic blocker, such as propranolol, or a 5HT2 antagonist. Because 5HT2 antagonism seems to be at least partially effective, antipsychotics and antidepressants with intrinsic anti-serotonergic activity may be less likely to induce akathisia. With the development of the newer second-generation antipsychotics, it was thought that the prevalence of akathisia, along with the parkinsonian side effects of the older neuroleptics, might be substantially reduced. But the situation is not as benign as hoped, and akathisia remains a serious problem. Furthermore, these drugs are now approved and prescribed for bipolar disorder and for anxiety, as well as schizophrenia and depression, with the increased possibility of combined exposure to both antipsychotics and antidepressants (83). Recognition of the growing population at risk for this extremely unpleasant psychotropic side effect, and the most current treatment, is becoming increasingly important. Improvements in quantifying akathisia, and in understanding its pathophysiology, might provide insight into more effective therapy.

to be in motion that is often not able to relieve the distress. The second characteristic is an objective component of restless movements that can be seen by an observer (6). Bratti, Kane and Marder (7) provide a concise, yet comprehensive table summarizing the core diagnostic criteria of iatrogenic akathisia, as adapted in Table 1.

Currently, there are two rating scales that are most commonly used for assessing akathisia. One is the Barnes Akathisia Rating Scale (BARS) (8), which rates observable, characteristic restless movements, and a combination of the patient's awareness of the restlessness and the patient's distress related to the restlessness, on a 4-point scale, with a score of 2 denoting the diagnostic threshold. It also includes a clearly defined 6-point global severity rating scale. It provides brief examination instructions and takes less than five minutes to complete, with a maximum score of 14. Interrater reliabilities range from 0.74 to 0.95.

The second instrument, the Hillside Akathisia Scale (9), is more extensive. First, it includes two Subjective items: inner restlessness and urge to move. Each of these are rated from 0 (absent) to 4 (present and not controllable). Second, it includes three Objective items: akathisia presents in head, hands and arms, or feet and legs. These are rated from 0 (no akathisia) to 4 (large amplitude movements, all of the time). Third, this scale includes a positional component in that each of these items is evaluated with the patient sitting, standing and lying down. Fourth, each category may be rated under activation conditions, such as counting or finger tapping. Last, there are Global Impression items for severity and improvement.

While it has long been appreciated that a more quantitative index of akathisia is needed, this has proven difficult, particularly because the symptoms are covert and not easily characterized in a consistent manner.

Problems of communication make akathisia hard to diagnose. Some of the pacing, bizarre movements, impul-

sive actions, aggressive or self-abusive behaviors may be mistakenly attributed to the patient's disorder, and doses of the potentially causal medication may be increased, which may worsen the condition (1, 10).

Manifestation

It is difficult to convey the extremely distressful nature of the phenomenon; the inner agitation and restlessness are difficult to articulate (10). In many cases, patients could not tell that akathisia was a drug effect—they thought their illness had taken such a turn for the worse that life was not worth living (11). One report of thirty patients with schizophrenia before they "completed suicide" noted that patients made "requests or demands that something be done to relieve their tensions" and "appeared driven to find some kind of relief" (cited in Drake and Ehrlich [11] , p. 499).

Regardless of severity, patients feel "restless inside" *if this terminology is suggested to them*. Vague feelings of apprehension, irritability and general unease are common, and patients may be more comfortable standing up or moving about. Although they may be able to sit without moving, they are usually fidgety, tap their feet and frequently change posture. Sometimes the intensity is severe enough for running, agitated dancing or rocking (12). Hirose (13) even described five cases of respiratory dyspnea appearing several weeks after starting antipsychotics, in schizophrenic or bipolar patients, characterized subjectively by the patients' inner feeling of restlessness in respiration such as gasping or sighing.

The phenomenon may also occur in individuals with intellectual disabilities (14) and even in nonpsychotic research subjects, one of whom reported, "The sense of a foreign influence forcing me to move was dramatic." It has been described as a panic attack, agitation, reduced concentration, anxiety and dysphoria; "a paralysis of volition, a lack of physical and psychic energy" (15). Van Putten (10) cites

Table 1	Diagnostic Criteria for Akathisia
Required for Diagnosis	
Exposure to medications or drugs that can cause akathisia, including first-generation antipsychotics, second-generation antipsychotics, selective serotonin reuptake inhibitors, lithium, buspirone, amoxapine, and calcium channel blockers.	
Presence of characteristic subjective and/or objective features of akathisia.	
Absence of other known causes of akathisia symptoms, including restless legs syndrome, Parkinson disease, and subthalamic lesions. Absence of peripheral neuropathy, myelopathy, or myopathy.	
Diagnosis	
Acute akathisia: symptoms begin within 6 weeks of drug initiation or dosage increase, and another therapeutic agent has not been decreased or discontinued in the 2 weeks prior to symptom onset.	
If symptoms persist more than 3 months, the diagnosis is chronic akathisia with acute onset.	
Tardive akathisia: symptoms begin 3 or more months after initiation of an antipsychotic medication, there has been no change in dosage or medication in the 6 weeks prior to onset of symptoms, and another therapeutic agent has not been decreased or discontinued in the 2 weeks prior to symptom onset.	

Modified from research diagnostic criteria in: Sachdev P. Research diagnostic criteria for drug-induced akathisia: conceptualization, rationale, and proposal. Psychopharmacology (Berl) 1994;114(1):181-186. See also the research criteria for akathisia in *DSM-IV-TR*, Appendix B, p. 802.

Source: Bratti IM, Kane JM, Marder SR. Chronic restlessness with antipsychotics. Am J Psychiatry 2007;164(11):1648-1654.

Kalinowsky's comment (1958) that it can be "more difficult to endure than any of the symptoms for which [the patient] was originally treated."

Prevalence

Prevalence varies from 12.5 to 75%, mostly determined from data obtained with first-generation antipsychotics. Sachdev and Kruk (16) reported an incidence rate of 25% for acute akathisia, while Van Putten (10) reported that 45% of his subjects had it at one time during treatment. He attributed the higher rate in his study to the fact that subtler forms of akathisias were included, antiakathisia drugs were not administered and patients were continuously observed by staff that was trained to recognize the condition. Braude et al. (17) stated that all 26 of his patients showed the reaction within 14 days of reaching the maximum dose, 3 of them within 12 hours of their first dose. Most reviews cite the typical prevalence rate as approximately 20 to 30% (6, 18). However, Modestin et al. (19) reported a prevalence of 14% in 200 inpatients treated in 1995 with typical neuroleptics or clozapine. When the 83 surviving patients were reevaluated in 2003–2004, the prevalence was the same, 14%.

Differential Diagnosis of Akathisia Subtypes

Distinguishing akathisia from other neuroleptic-induced neurological side effects can be difficult. This is most evident when the akathisic symptoms have persisted for three months or longer. In that case, the terms "chronic" or "tardive akathisia" (20-22) have been applied, as opposed to "acute" akathisia with onset within weeks or less. However, the distinction between late onset of akathisia and the development of movement disorders, particularly tardive (late onset) dyskinesia (TD), may be challenging. TD refers to involuntary movements that occur late in treatment, often after drugs are stopped, which may persist for years and for which there is no definite treatment. Most responses are in the oral region, but motor restlessness can occur, although it is not associated with an inner sense of anxiety or discomfort.

Because of the difficulty of this differential diagnosis, the concepts of "chronic," "tardive" or "withdrawal akathisia" (21) have sometimes been proposed to be an "atypical" form of TD. The term "pseudoakathisia" has been suggested to define such involuntary movements without a subjective aspect, as a variant of TD, although Sachdev argues that this term is not very useful (2). Patients with akathisia have been considered at risk for the development of TD, and it has been proposed that the syndromes represent a continuum—from subjective and objective components to wholly objective, involuntary movements. That is, the subjective distress may disappear and the movements become involuntary (1). As suggested by Blaisdell (6), the relevant question may be: "Is the patient moving because of inner restlessness or moving uncontrollably and therefore anxious?"

In summary, akathisia usually occurs early in the course of neuroleptic treatment. It is reversible, may be treatment responsive and is not an involuntary movement disorder per se, but "a subjective desire to be in constant motion" (22), resulting in an inability to sit still and a compulsion to move. Though driven, the movements are voluntary reactions to the subjective discomfort. TD occurs late, may be irreversible, is typically unresponsive to treatment and is an involuntary movement disorder characterized by "slow, rhythmical,

automatic, stereotyped movements, particularly in buccolingual masticatory area, extremities and trunk muscles" (22).

Akathisia may occur in patients with Parkinson disease (PD), and was first noted in this disorder before the advent of antipsychotics. Van Putten (10) reported that it occurred in about 59% of patients with PD. In fact, a subjective feeling of a need to move was thought to be a reaction to the immobility produced by PD: "There are patients in whom immobility is actually a prominent symptom and yet who complain in a paradoxical way that they 'cannot sit still' or only 'with an effort.' After a time they simply must get up…" (22).

On the other hand, there is no association between severity of akathisia and parkinsonian symptoms (7). Patients with akathisia do not always have extrapyramidal symptoms (EPS), and akathisia frequently does not improve with antiPD drugs.

Restless legs, although similar in some ways, is also not the same as akathisia. First described in the 17th century, it is an unpleasant, painful creeping or crawling sensation, usually bilateral and symmetrical in the legs and starts five to thirty minutes before bedtime. Restless legs syndrome is associated with polio, vitamin deficiency, cold, diabetes, pregnancy, iron deficiency anemia, carcinoma, uremia, chronic pulmonary disease, multiple sclerosis, neuropathy, or gastric surgery. In contrast, akathisia affects the whole body, occurs during the day, and does not interfere so much with sleep (12).

Finally, there is the distinction between akathisia and general anxiety disorder (GAD). Akathisia is more often referable to the legs and perceived as "unnatural," "abnormal," or "driven." Benzodiazepines are effective for anxiety and have been used in the symptomatic relief of akathisia (1). Catalano et al. note that while "lorazepam, clonazepam and diazepam have all been reported to have some efficacy in treating akathisia, few scientifically rigorous studies have been done" (23 [p. 297]). Propranolol, however, is not indicated for GAD. See Bratti et al. (17) for an excellent summary of differential diagnoses.

Second-Generation Antipsychotics (SGAs)

The SGAs were specifically developed with the goal of producing less parkinsonism and tardive dyskinesia. For the most part, this was successful. It was assumed that akathisia would similarly be less prevalent with these agents. Overall, this seems to be the case although there is much variability among the drugs (24-26).

In clinical trials, the akathisia prevalence of the first SGA, clozapine, was reported to be 7.3% (27). However, Cohen et al. (28) stated that, in a blind survey, akathisia was

similar in prevalence and severity in patients treated with clozapine and in those getting standard neuroleptics.

Not surprisingly, risperidone-induced akathisia increases with dose. At <5 mg, prevalence was around 13%; at 5–8 mg prevalence was 32% (compared with 23.8% of patients on conventional agents reporting this symptom) (27). However, in a recent, randomized, placebo-controlled study of the extended release formulation of paliperidone (the active metabolite of risperidone), BARS scores were zero at both baseline and the six-week endpoint (29). During a dose-finding study for olanzapine (23), akathisia was the most commonly reported neurological side effect, at 6.4%. Even the low-potency antipsychotic agent, quetiapine, has been associated with the reaction (30). Grace (23) describes two cases of patients given low doses of quetiapine for depression and anxiety, who experienced this side effect. In one case: "After one dose of 25 mg of quetiapine she complained of 'body anxiety,' and started pacing. She was unable to sleep through the night and woke up to perform bicycling movements to relieve the tension in her legs. Akathisia stopped when quetiapine was stopped."

However, quetiapine reportedly reduced akathisia when patients with this side effect were switched from other antipsychotics (31).

Akathisia has also been reported with ziprasidone, in 5 to 17% of patients; and, in one four-week study, in 20% of patients taking aripiprazole. Because most of these patients had been treated with conventional neuroleptics before initiation of the new agents, these rates might be somewhat elevated (23, 32). Most recently, a brief, four-week, placebo-controlled, double-blind study compared ziprasidone with the investigational drug iloperidone (33). Akathisia was rare, occurring in 4/300 patients on iloperidone compared to 11/150 on ziprasidone. Kane et al. (34) and Weiden et al. (35) also report minimal akathisia with iloperidone. Padder et al. (36) cite a case of a 23-year old Hispanic man with bipolar spectrum disorder who had difficulty controlling anger and inability to focus. After a failed trial of antidepressants, he was started on 5 mg of aripiprazole, and was doing well. Three days after the dose was increased to 10 mg the patient:

> … called the clinic in great distress and reported he felt extremely restless and irritable with an inability to sit still and a constant desire to move. He was experiencing suicidal ideations. These symptoms had never occurred before and started suddenly. He felt so unsafe he insisted his mother call 911.

Aripiprazole was stopped and propranolol started, with benzodiazepines. He was ultimately discharged on bupropion and gabapentin. These authors also cite another report of suicidal ideation and attempts in five patients taking aripiprazole. A case of tardive akathisia has also been described

Table 2 Extrapyramidal Symptoms Associated with Antidepressant Treatment					
Antidepressant Class/Drug*	Drug-Induced Parkinsonism†	Akathisia‡	Dystonia§	Reversible Dykinesia‖	NMS¶
TCAs					
Imipramine	—	1	—	1	—
Desipramine	—	1	—	—	1
Clomipramine	—	2	—	4	—
Doxepin	—	1	1	2	—
Amitriptyline	—	1	3	5	—
Miscellaneous Agents					
Trazodone	1	2	1	1	—
Amoxapine	4	10	5	6	5
MAOIs					
Tranylcypromine	—	1	1	2	—
Phenelzine	2	—	—	—	—
SSRIs					
Fluoxetine	17	35	15	9	1
Fluvoxamine	2	2	5	1	—
Sertraline	—	9	2	1	—
Paroxetine	4	2	17	1	—

*NMS=neuroleptic malignant syndrome; MAOI=monoamine oxidase inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant. †Masked facies; bradykinesia; shuffling gait; cogwheel rigidity; tremor; worsening of underlying Parkinson disease. ‡Restlessness; pacing; inability to sit still; agitation; irritability. §Opisthotonos; torticollis; oculogyria; trismus; truncal rigidity. ‖Lingual-facial-buccal dyskinesias; choreiform movements; limb-truncal choreoathetoid movements. ¶ Hyperthermia, muscular rigidity; dysautonomia; altered mental status; elevated creatine phosphokinase.

Source: Gill HS, DeVane CL, Risch SC. Extrapyramidal symptoms associated with cyclic antidepressant treatment: a review of the literature and consolidating hypotheses. J Clin Psychopharmacol 1997;17(5):377-389.

in one patient given aripiprazole for treatment of depression and anxiety (37). Of particular concern, in one study of patients with bipolar disorder, five out of twelve (42%) developed akathisia to aripiprazole, given to augment antidepressants (38). Similarly, in a second study of adjunctive aripiprazole in major depressive disorder, 25.9% of patients receiving aripiprazole in combination with an antidepressant were reported as having akathisia—but an additional 9.5% were said to have "restlessness" (39). This raises the concern that neuroleptic augmentation of antidepressant treatment may increase the likelihood of eliciting akathisia. Given the fact that aripiprazole was developed as a partial dopamine agonist, rather than an antagonist, it seems surprising that the amount of akathisia reported in these studies is not lower (40 [and references therein]).

Antidepressant-Induced Akathisia

Although less discussed (41), akathisia may also occur with antidepressant (AD) medications (42). Gill et al. (43) (see Table 2) summarized all reports available at that time concerning the role of ADs in producing akathisia. Several points are suggested by the data.

First, the older medications are less likely to produce akathisia than the selective serotonin reuptake inhibitor (SSRI) type, with the possible exception of amoxapine (44). During clinical trials, akathisia or jitteriness was even observed in patients taking the newest SSRIs, citalopram and escitalopram, and it has been reported in response to the "atypical" ADs nefazodone (45) and mirtazapine (at doses of 30 mg) (46).

In a case series review of SSRI-induced movement disorders (47), akathisia was the most common at 45.1%, with dystonia at 28.2%, PD at 14.1%, and TD at 11.3%. All sixteen parkinsonian patients in the group had their PD worsen, either on fluoxetine, fluvoxamine or paroxetine, and it was suggested that this had not been reported more often because of antiPD medications. Akathisia was more likely in younger (<50 years) individuals and in females—although more females are treated for depression. Fluoxetine was the most commonly prescribed SSRI that induced akathisia (74.6% of cases, at doses of 5 to 140 mg/day), but 57.7% of the patients were prescribed other medications.

Second, patient descriptions of the phenomenon are the same as those for neuroleptic-induced akathisia (NIA). Lipinski et al. (48) described five patients given fluoxetine for obsessive-compulsive disorder or major depression who

developed akathisia. Patients who had experienced NIA said that fluoxetine-induced akathisia was the same but milder. Clinical case reports of imipramine- or desipramine-induced akathisia state that the overt motor restlessness was indistinguishable from idiopathic or neuroleptic-induced akathisia (49).

Third, rapid dose increases often induced the reaction (50), and dose reduction or discontinuation of the drug, as well as administration of propranolol (an adrenergic beta-blocking drug), produced relief (51, 52). These characteristics are also the same as in NIA.

Fourth, concomitant use of antidepressants and neuroleptics may increase the risk. In fact, the first published case of fluoxetine-induced akathisia was in a thirty-nine year old woman with bipolar disorder, after fluoxetine was added to other drugs including the neuroleptic haloperidol. Some of these cases may be due to interference with metabolism of neuroleptic drugs, as fluoxetine has been reported to inhibit the metabolism of haloperidol (cited in 43). Currently, it is difficult to evaluate the effect of psychotropic combinations because bipolar disorder itself may be associated with an increased risk of NIA (53).

Fifth, as with NIA, suicidal ideation has been noted as a reaction to AD-induced akathisia. Rothchild and Locke (54) describe three patients who said previous exposure to fluoxetine had made them feel suicidal and precipitated their suicide attempts. Both suicidal ideation and akathisia stopped after discontinuation of the drug or addition of propranolol.

Currently, NIA and SSRI-induced akathisia appear to be clinically indistinguishable, although it remains unclear whether or not they have the same pathophysiology.

Treatment of Akathisia

The fact that akathisia occurs in Parkinson disease, which is characterized by a loss of dopaminergic neurons (in the nigrostriatal pathway), with exposure to antipsychotic drugs, which block dopamine receptors (in all dopamine pathways), and by serotonergic agents (which inhibit dopaminergic pathways), indicates that the loss of dopamine function is a primary cause. This is also consistent with a recent report that 7.6% of patients, given the dopamine-depleting drug tetrabenazine (recently approved for the treatment of Huntington chorea), also developed akathisia (55). As noted earlier, antiemetics may also elicit this symptom, and, in situations such as pregnancy, or cancer treatment (56) in which antiemetics may be administered, akathisia may be misinterpreted as a psychiatric disorder (57). Moreover, Sekine et al. (58) recently compared the clinical incidences of seven different types of drug-induced adverse reactions to the affinity constants of the same drugs

to several neurotransmitter receptor types. They found significant correlations between the affinity constants for the dopamine D2 receptor and the clinical incidences of akathisia and dyskinesia.

Anticholinergic Medications

Because akathisia and parkinsonian movement disorders generally occur at the beginning of drug treatment, the use of anticholinergic medications has also been reported to improve akathisia (1975). However, Braude et al. (17) found only six of twenty patients with NIA improved with anticholinergics and Ratey and Salzman (15) and Lipinski et al. (59) concluded that akathisia does not improve with anticholinergics. More recently, the effectiveness of anticholinergics for akathisia has been questioned in a Cochrane review (60), which prompted the most recent study (61). Patients were treated with either biperiden or placebo, in a randomized, double-blind study. About one-third of each group improved. There was no difference between the groups, and the authors concluded that biperiden is not a first-line treatment for NIA. One interpretation of these results is that responders to antiPD agents are really exhibiting parkinsonian symptoms, not akathisia. Moreover, anticholinergic drugs have their own significant side effects, particularly memory problems, as well as constipation, blurred vision and other adverse reactions.

Benzodiazepines have often been used for symptomatic relief. Adler et al. (1) cite several studies that reported improvement after administration of diazepam, lorazepam, clonazepam, or even antihistamines (diphenhydramine). More recently, Parlak et al. (62) compared the benzodiazepine midazolam to diphenhydramine and found them both effective, although midazolam, while working faster, was also more sedating. Similarly, amantadine, which is believed to act by releasing dopamine from nerve terminals, has been effective, but, unfortunately, tolerance develops to its antiakathisic action (49).

Beta-Adrenergic Receptor Blockade

Although it may not be effective in every case, propranolol is unquestionably a first-line drug treatment for akathisia (1, 58, 63, 64), even in postencephalic cases (65). Adler et al. (1) attribute the discovery of this therapeutic effect to a report by Strang, in 1967, which described the syndrome of "restless legs," in 40 of 600 consecutive PD patients, and reported that propranolol was effective in treating this condition. Lipinski noted the article and, appreciating the similarity in the symptoms, reported the first use of propranolol for NIA, in 1983. All 12 patients improved (9 completely) in response to a mean dose of 30 mg/day. Improvement was quick, starting in an hour and reaching a maximum in 24 to

48 hours. Conversely, parkinsonian symptoms were unaffected.

Efforts to determine which pharmacological property is responsible for propranolol's effectiveness have not been completely successful. As seen in Table 3 (taken from Adler et al. [1]), propranolol is a nonspecific antagonist of both beta 1 and beta 2 receptor subtypes. It is also lipophilic, and easily penetrates the blood-brain barrier. Among these drugs, pindolol has an additional stimulatory action (ISA), and so does not lower the blood pressure as much as other beta-blocking drugs.

Research has shown that atenolol and sotalol, which are less lipophilic beta blockers, are not very effective—indicating that the therapeutic effect is due to an action of the drug in the brain. The best agents seem to be those that block beta 1 receptors AND are lipophilic, like betaxolol. This is supported by a randomized, double-blind, crossover, placebo-controlled trial showing comparable efficacy of propranolol and betaxolol (66). One issue with this interpretation is a study reporting that metoprolol was less effective than propranolol, and the response required high doses. Therefore, the role of beta 1 versus beta 2 receptors is not yet clear, and antagonism at both receptors might contribute to efficacy.

One problem with propranolol is that high doses (up to 800 mg/day) increased the blood levels of at least one neuroleptic, thioridazine (although not haloperidol), which would worsen akathisia. Another adrenergic drug that has been used with some success is clonidine, a central alpha 2 agonist which decreases central norepinephrine activity. Presumably, clonidine's antiakathesic effect, like its antihypertensive action, is due to activation of presynaptic adrenergic autoreceptors. The negative feedback of autoreceptor stimulation would be expected to reduce norepinephrine release and decrease activation of both alpha and beta adrenergic receptors. While reportedly effective, it is sedating and may decrease blood pressure. However, clonidine decreased anxiety while propranolol did not (1).

Serotonergic Receptor Antagonists

Recognition of SSRI-induced akathisia emphasized the significance of the diffuse interconnections between dopaminergic and serotonergic nuclei. In particular, serotonergic input is known to have an inhibitory effect on dopamine release by an action at dopaminergic nerve terminals. Accordingly, several case reports described the successful treatment of akathisia with serotonergic, specifically 5HT2, antagonists (67, 68). Although mianserin is a commonly investigated 5HT2 antagonist for NIA, other drugs in this class have been found effective. As described by Poyurovsky et al. (68), Miller was the first to test ritanserin (1990) and found about 50% improvement in ten patients, even in those who had not responded to anticholinergics, benzodiazepines, or propranolol. Weiss (cited in Fischel et al. [69]) first showed benefit from the 5HT2 antagonist cyproheptidine, which was replicated by Fischel et al. (69) in a double-blind, placebo-controlled comparison with propranolol. The NIA decreased significantly with both drugs (cyproheptadine by 46%; propranolol by 42%), and worsened when the drugs were discontinued (two patients refused to stop propranolol because of its benefit).

Poyurovsky and Weizman (70) found the antidepressant mirtazapine effective in treating akathisia in a schizophrenic patient. They postulated that mirtazepine's marked antagonism of 5HT2A/2C receptors was responsible for the therapeutic effect. Wilson (71) described the first successful

Table 3	Characteristics of Beta-Blockers				
Drug	Blockade of β-1 Receptors	Blockade of β-2 Receptors	ISA	Lipophilicity	β−1 Blockade Potency Ratio (Propranolol=1)
Propranolol	++	++	0	+++	1.0
Metoprolol*	++	0 – +	0	++	1.0
Nadolol	++	++	0	0 – +	1.0
Atenolol	++	0	0	0	1.0
Pindolol	++	++	++	++	6.0
ICI 118,551	0	++	0	+++	—
Betaxolol[†]	++	0	0	++	3.0–10.0
Sotalol	++	++	0	0	0.3

*Metoprolol is selective for β-1 receptors at doses ≤100 mg/day (Koch-Weser, 1979). †Betaxolol has a β-1 blockade potency ratio of 3.0–10.0 based on animal data; preliminary human studies indicate a potency ratio of 4.0–8.0 (Guidicelli et al., 1983; Gieseker, personal communication).

Source: Adler LA, Angrist B, Reiter S, Rotrosen J. Neuroleptic-induced akathisia: a review. Psychopharmacology (Berl) 1989;97(1):1-11.

Table 4	In Vitro Binding Affinities (K_i values in nM*) of Currently Available Atypical Antipsychotics for 5HT Receptor Subtypes				
	5HT1A	**5HT2A**	**5HT2C**	**5HT3**	**5HT6**
Clozapine	145	9.6	13	108	4
Risperidone	420	0.52	48	>10000	425
Olanzapine	2720	2.5	7.1	84	2.5
Quetiapine	320	96	3800	4060	NA
Sertindole	280	0.39	1.9	3200	NA
Ziprasidone		0.39	0.72		
Aripiprazole		3.4	15		

*The lower the K_i values, the higher the affinity for the receptor; K_i=inhibition constant. Modified from data based on Leysen JE, Gommeren W, Shotte A. Serotonin receptor subtypes: possible roles and applications in antipsychotic drug action. In: Kane JM, Moller HJ, Awouters F, editors. Serotonin in antipsychotic treatment. Mechanisms and clinical practice. New York: Marcel Dekker; 1996. p. 51-75.

Sources: 1) Poyurovsky M, Weizman A. Serotonin-based pharmacotherapy for acute neuroleptic-induced akathisia: a new approach to an old problem. Br J Psychiatry 2001;179:4-8. 2) Nemeroff CB, Lieberman JA, Weiden PJ, Harvey PD, Newcomer JW, Schatzberg AF, et al. From clinical research to clinical practice: a 4-year review of ziprasidone. CNS Spectr 2005;10(11 Suppl 17):1-20.

use of mirtazapine in three patients treated with olanzapine or aripiprazole for bipolar disorder. Most recently, Hieber et al. (72) published a review of case studies confirming the effectiveness of mirtazapine in the treatment of NIA, with overall response rates of 43 to 54%.

In their review, Poyurovsky and Weizman (73) argue that 5HT2 blockade must be the mechanism of serotonin-based pharmacotherapy for akathisia, because buspirone, a 5HT1A partial agonist, was ineffective (although those patients improved with mianserin) and the 5HT3 antagonist, granisetron, was also ineffective. Although currently there are no selective specific 5HT2A antagonists available, the authors proposed that the SGAs should produce less akathisia because of their intrinsic 5HT2 antagonism (summarized in Table 4).

The existence of antidepressants with an intrinsic anti-serotonergic action has the obvious advantage of providing alternatives for patients who develop SSRI-induced akathisia. In fact, Chelben et al. (74) described two patients who developed akathisia from fluoxetine and paroxetine, respectively, and found relief when switched to nefazodone, not only of the akathisia but of the depression as well.

Miscellaneous Treatments

There have been scattered reports of other successful akathisia treatments. Fehr et al. (75) described a substantial reduction of both TD and NIA after piracetam (24 g/day) in a patient who had been taking haloperidol for eight years. The mechanism of action of piracetam is unknown. Dietary supplementation with omega-3 fatty acids and vitamins E and C reportedly decreased akathisia in seven-teen schizophrenic patients treated with haloperidol (76). Anfang and Pope (77) reported successful treatment of NIA with nicotine patches in sixteen nonsmoking patients. The study only lasted three days—baseline, patch day and non-patch day. There was a significant decrease in rating scores (i.e., a decrease in akathisia) from baseline to patch day and a significant increase from patch day to nonpatch day. Mean scores on the rating scale went from 8.9 (out of 14) to 4.8 and back to 8.2. This interesting result might be due to the fact that nicotine increases dopamine release. On the other hand, a review of 250 schizophrenic outpatients found no association between heavy smoking (>30 cigarettes a day) and akathisia. Forty-one percent of patients with akathisia were heavy smokers compared to 39% of patients without akathisia (78). However, the prevalence of akathisia in this study was low: only 7% when "scored as usual," and 14% when a broad definition of "any response >0" was used. Perhaps the high overall smoking rate of 69% contributed to the low prevalence of akathisia, in which case cessation of smoking might result in an increase in akathisia. Last, one case report described dramatic relief of tardive and withdrawal akathisia (from aripiprazole) (37) with the dopamine agonist ropinirole (approved for treating restless legs syndrome). Because this patient was diagnosed with anxiety and depression, dopamine treatment was not contraindicated, which may be a problem in patients with schizophrenia and patients with bipolar disorder.

Pathophysiology

It is clear that akathisia is associated with disorders and drugs that reduce dopaminergic activity in the brain,

including nonpsychiatric agents such as emetics, which may produce akathisia in medical settings, although patients may not report it (79). Even a brief, forty-eight hour, reversible, experimental dopamine depletion, produced by the synthesis blocker, alphamethylparatyrosine, elicited akathisia in medication-free schizophrenic patients (80). Current evidence, described above, indicates that the most effective treatment of akathisia involves indirect serotonergic and noradrenergic modulation of dopaminergic systems in the brain (43).

There are three major dopamine pathways in the brain (excluding a fourth small pathway from the hypothalamus to the pituitary). Two pathways originate in the ventral tegmental area and ascend to terminate in the temporal lobe limbic structures (the mesolimbic pathway) and the prefrontal cortex (the mesocortical pathway), respectively. These two pathways are believed to be responsible for mediating psychotic symptomatology. The nigrostriatal pathway is composed of ascending dopaminergic neurons projecting from the substantia nigra to the striatum, and dopamine released by these projections activates postsynaptic dopamine receptors in the striatum. Blockade of these receptors by antipsychotics is presumed to be responsible for EPS, just as degeneration of this projection is responsible for Parkinson disease.

The raphe nuclei, which are the source of most of the 5HT in the brain, project to both the substantia nigra and the striatum. 5HT is inhibitory, and its release suppresses spontaneous firing activity of dopamine neurons, and dopamine release. Blockade of 5HT reuptake into raphe neurons by SSRIs increases synaptic serotonin concentrations. As a result, dopamine release is further suppressed, which may promote the development of akathisia. Conversely, blockade of the 5HT2 receptor would counteract this serotonergic-induced suppression of dopamine release and reduce akathisia. In support of this hypothesis, systemic administration of fluoxetine, sertraline, and paroxetine produced a significant decrease in extracellular dopamine levels in rodents in the striatum, and citalopram decreased striatal dopamine levels in humans (research by Ichikawa and Meltzer, cited in Gill et al. [43]). More difficult to account for is the observation that clomipramine and imipramine increased dopamine in the striatum (43).

A similar argument has been made for norepinephrine to explain the therapeutic benefit of propranolol (43). Wilbur and coworkers proposed that direct noradrenergic modulation is exerted by a pathway that projects from the locus ceruleus (the source of norepinephrine in the brain) to the striatum and limbic system. Accordingly, blockade of noradrenergic outflow from the locus ceruleus to the limbic system, by beta-adrenergic receptor antagonists, might explain the clinical effectiveness of propranolol in treating patients with akathisia and, in certain cases, tardive dyskinesia. After high-dose propranolol administration, studies have demonstrated statistically significant elevations of homovanilic acid, the major metabolite of dopamine, in the mesolimbic area but not in the striatum. Presumably, this is due to increased dopamine release (43).

These hypotheses raise the obvious question of whether or not dopamine agonists would be good antiakathesic agents. In that regard, it may be noted that the catecholaminergic antidepressant, bupropion, did not elicit akathisia in a patient (mentioned above) who developed akathisia from aripiprazole. The fact that it is not listed in Table 2, which summarizes reports of antidepressant-induced akathisia, also suggests that it does not elicit this symptom. Furthermore, the dopamine releasing drug, amantadine, is known to be antiakathesic, although tolerance develops to this therapeutic action. Moreover, the dopamine agonist ropinirole was recently found effective for aripiprazole-induced akathisia. These observations imply that, while presumably contraindicated for treatment of NIA, dopaminergic agents may be useful in treating antidepressant-induced akathisia (and, perhaps, simultaneously augmenting antidepressant effects as well). Last, considering the efficacy of the adrenergic beta-blocker, propranolol, a corollary of this interpretation may be that, conversely, antidepressants with a predominant adrenergic action such as duloxetine or venlafaxine, would not be expected to reduce akathisia.

Conclusions

Better methods of quantifying akathisia and other neurological side effects (81) would greatly improve our understanding of its pathophysiology and facilitate the development of psychotropic drugs that remain effective without inducing akathisia. Efforts to identify specific movement patterns for NIA in a naturalistic schizophrenic population, by using actometry (82), have been partially successful. The technique discriminated NIA from non-NIA groups (those with other types of movement disorders and those with no movement disorders). However, as acknowledged by the authors, their criteria did not identify subclinical cases, even though 75% of the non-movement disorder subjects showed some overt evidence for such a symptom. There is also some physical limitation to this method, in that actometric recordings are most easily made from the ankle or wrist, but may not provide data from other parts of the body.

In summary, akathisia is a significant and serious side effect of many antipsychotic and antidepressant medications. It is extremely distressing to the patient, and a common cause of medication nonadherence, even when the drugs are therapeutically effective. The primary etiology appears to involve a decrease in dopaminergic activity. Treatment includes reducing the dose of the offending drug,

or administration of a beta-adrenergic blocker, such as propranolol, or a 5HT2 antagonist. Because 5HT2 antagonism seems to be at least partially effective, antipsychotics and antidepressants, with intrinsic antiserotonergic activity may be less likely to induce akathisia.

With the development of the newer second-generation antipsychotics it was thought that the prevalence of akathisia, along with the parkinsonian side effects of the older neuroleptics, might be substantially reduced. But the situation is not as benign as hoped, and akathisia remains a serious problem. Furthermore, these drugs are now approved and prescribed for bipolar disorder and for anxiety, as well as schizophrenia and depression, with the increased possibility of combined exposure to both antipsychotics and antidepressants (83). Recognition of the growing population at risk for this extremely unpleasant psychotropic side effect, and the most current treatment, is becoming increasingly important. Improvements in quantifying akathisia, and in understanding its pathophysiology, might provide insight into more effective therapy.

Financial Disclosure and Conflicts of Interest

Dr. Advokat reports no biomedical financial interests or potential conflicts of interest.

References

1. Adler LA, Angrist B, Reiter S, Rotrosen J. Neuroleptic-induced akathisia: a review. Psychopharmacol (Berl) 1989;97(1):1-11.

2. Sachdev P. The development of the concept of akathisia: a historical overview. Schizophr Res 1995;16(1):33-45.

3. Gibb WR, Lees AJ. The clinical phenomenon of akathisia. J Neurol Neurosurg Psychiatry 1986;49(8):861-866.

4. Mohr P, Volavka J. Ladislav Haskovec and akathisia: 100th anniversary. Br J Psychiatry 2002;181:537.

5. Kim JH, Byun HJ. Association of subjective cognitive dysfunction with akathisia in patients receiving stable doses of risperidone or haloperidol. J Clin Pharm Ther 2007;32(5):461-467.

6. Blaisdell GD. Akathisia: a comprehensive review and treatment summary. Pharmacopsychiatry 1994;27(4):139-146.

7. Bratti IM, Kane JM, Marder SR. Chronic restlessness with antipsychotics. Am J Psychiatry 2007;164(11):1648-1654.

8. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672-676.

9. Fleischhacker WW, Bergmann KJ, Perovich R, Pestreich LK, Borenstein M, Lieberman JA, et al. The Hillside Akathisia Scale: a new rating instrument for neuroleptic-induced akathisia. Psychopharmacol Bull 1989;25(2):222-226.

10. Van Putten T. The many faces of akathisia. Compr Psychiatry 1975;16(1):43-47.

11. Drake RE, Ehrlich J. Suicide attempts associated with akathisia. Am J Psychiatry 1985;142(4):499-501.

12. Raskin DE. Akathisia: a side effect to be remembered. Am J Psychiatry 1972;129(3):345-347.

13. Hirose S. Restlessness of respiration as a manifestation of akathisia: five case reports of respiratory akathisia. J Clin Psychiatry 2000;61(10):737-741.

14. Garcia MJ, Matson JL. Akathisia in adults with severe and profound intellectual disability: a psychometric study of the MEDS and ARMS. J Intellect Dev Disabil 2008;33(2):171-176.

15. Ratey JJ, Salzman C. Recognizing and managing akathisia. Hosp Community Psychiatry 1984;35(10):975-977.

16. Sachdev P, Kruk J. Clinical characteristics and predisposing factors in acute drug-induced akathisia. Arch Gen Psychiatry 1994;51(12):963-974.

17. Braude WM, Barnes TR, Gore SM. Clinical characteristics of akathisia: a systematic investigation of acute psychiatric inpatient admissions. Br J Psychiatry 1983;143:139-150.

18. Janno S, Holi M, Tuisku K, Wahlbeck K. Prevalence of neuroleptic-induced movement disorders in chronic schizophrenia inpatients. Am J Psychiatry 2004;161(1):160-163.

19. Modestin J, Wehrli MV, Stephan PL, Agarwalla P. Evolution of neuroleptic-induced extrapyramidal syndromes under long-term neuroleptic treatment. Schizophr Res 2008;100(1-3):97-107.

20. Burke RE, Kang UJ, Jankovic J, Miller LG, Fahn S. Tardive akathisia: an analysis of clinical features and response to open therapeutic trials. Mov Disord 1989;4(2):157-175.

21. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. Drug Saf 2000;22(1):73-81.

22. Munetz MR, Cornes CL. Distinguishing akathisia and tardive dyskinesia: a review of the literature. J Clin Psychopharmacol 1983;3(6):343-350.

23. Catalano G, Grace JW, Catalano MC, Morales MJ, Cruse LM. Acute akathisia associated with quetiapine use. Psychosomatics 2005;46(4):291-301.

24. Bhattacharjee J, El-Sayeh HG. Aripiprazole versus typicals for schizophrenia. Cochrane Database Syst Rev 2008 Jul 16;(3):CD006617. DOI: 10.1002/14651858.CD006617.pub2.

25. Haddad PM, Dursun SM. Neurological complications of psychiatric drugs: clinical features and management. Hum Psychopharmacol 2008;23 Suppl 1:15-26.

26. Markkula J, Helenius H, Lauerma H. On the relationship of atypical and low-dose conventional antipsychotics with akathisia in a clinical patient population. Nordic J Psychiatry 2007;61(2):152-157.

27. Miller CH, Mohr F, Umbricht D, Woerner M, Fleischhacker WW, Lieberman JA. The prevalence of acute extrapyramidal signs and symptoms in patients treated with clozapine, risperidone, and conventional antipsychotics. J Clin Psychiatry 1998;59(2):69-75.

28. Cohen BM, Keck PE, Satlin A, Cole JO. Prevalence and severity of akathisia in patients on clozapine. Biol Psychiatry 1991;29(12):1215-1219.

29. Meltzer HY, Bobo WV, Nuamah IF, Lane R, Hough D, Kramer M, et al. Efficacy and tolerability of oral paliperidone extended-release tablets in the treatment of acute schizophrenia: pooled data from three 6-week, placebo-controlled studies. J Clin Psychiatry 2008;69(5):817-829.

30. Bharadwaj R, Grover S. Parkinsonism and akathisia with quetiapine: three case reports. J Clin Psychiatry 2008;69(7):1189-1191.

31. Cortese L, Caligiuri MP, Williams R, Schieldrop P, Manchanda R, Malla A, et al. Reduction in neuroleptic-induced movement disorders after a switch to quetiapine in patients with schizophrenia. J Clin Psychopharmacol 2008;28(1):69-73.

32. Levine J, Chengappa KN. Second thoughts about clozapine as a treatment for neuroleptic-induced akathisia. J Clin Psychiatry 1998;59(4):195.

33. Cutler AJ, Kalali AH, Weiden PJ, Hamilton J, Wolfgang CD. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. J Clin Psychopharmacol 2008;28(2 Suppl 1):S20-S28.

34. Kane JM, Lauriello J, Laska E, Di Marino M, Wolfgang CD. Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. J Clin Psychopharmacol 2008;28(2 Suppl 1):S29-S35.

35. Weiden PJ, Cutler AJ, Polymeropoulos MH, Wolfgang CD. Safety profile of iloperidone: a pooled analysis of 6-week acute-phase pivotal trials. J Clin Psychopharmacol 2008;28(2 Suppl 1):S12-S19.

36. Padder T, Skodnek K, Hashmi S, Samad M, Udyawar A, Azhar N, et al. Acute akathisia with suicidal ideation associated with low dose aripiprazole. Psychiatry 2006;3(4):40-43.

37. Hettema JM, Ross DE. A case of aripiprazole-related tardive akathisia and its treatment with ropinirole. J Clin Psychiatry 2007;68(11):1814-1815.

38. Kemp DE, Gilmer WS, Fleck J, Straus JL, Dago PL, Karaffa M. Aripiprazole augmentation in treatment-resistant bipolar depression: early response and development of akathisia. Prog Neuropsychopharmacol Biol Psychiatry 2007;31(2):574-577.

39. Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 2008;28(2):156-165.

40. Poyurovsky M, Weizman R, Weizman A. Aripiprazole's receptor pharmacology and extrapyramidal side effects. Am J Psychiatry 2008;165(3):398.

41. Iqbal N, Lambert T, Masand P. Akathisia: problem of history or concern of today. CNS Spectr 2007;12(9 Suppl 14):1-13.

42. Lane RM. SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. J Psychopharmacol 1998;12(2):192-214.

43. Gill HS, DeVane CL, Risch SC. Extrapyramidal symptoms associated with cyclic antidepressant treatment: a review of the literature and consolidating hypotheses. J Clin Psychopharmacol 1997;17(5):377-389.

44. Hullett FJ, Levy AB. Amoxapine-induced akathisia. Am J Psychiatry 1983;149(6):820.

45. Eberstein S, Adler LA, Angrist B. Nefazodone and akathisia. Biol Psychiatry 1996;40(8):798-799.

46. Girishchandra BG, Johnson L, Cresp RM, Orr KG. Mirtazepine-induced akathisia. Med J Aust 2002;176(5):242.

47. Leo RJ. Movement disorders associated with the serotonin selective reuptake inhibitors. J Clin Psychiatry 1996;57(10):449-454.

48. Lipinski JF Jr, Mallya G, Zimmerman MG, Pope HG Jr. Fluoxetine-induced akathisia: clinical and theoretical implications. J Clin Psychiatry 1989;50(9):339-342.

49. Zubenko GS, Barreira P, Lipinski JF Jr. Development of tolerance to the therapeutic effect of amantadine on akathisia. J Clin Psychopharmacol 1984;4(4):218-220.

50. Chong SA, Tan CH. Fluvoxamine and akathisia. J Clin Psychopharmacol 1996;16(4):334-335.

51. Baldassano CF, Truman CJ, Nierenberg A, Ghaemi SN, Sachs GS. Akathisia: a review and case report following paroxetine treatment. Compr Psychiatry 1996;37(2):122-124.

52. Bauer M, Hellweg R, Baumgartner A. Fluoxetine-induced akathisia does not reappear after switch to paroxetine. J Clin Psychiatry 1996;57(12):593-594.

53. Gao K, Kemp DE, Ganocy SJ, Gajwani P, Xia G, Calabrese JR. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. J Clin Psychopharmacol 2008;28(2):203-209.

54. Rothschild AJ, Locke CA. Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. J Clin Psychiatry 1991;52(12):491-493.

55. Kenney C, Hunter C, Jankovic J. Long-term tolerability of tetrabenazine in the treatment of hyperkinetic movement disorders. Mov Disord 2007;22(2):193-197.

56. Back I, Taubert M. Akathisia and an unusual symptomatic treatment: a case report. Palliat Med 2007;21(8):713-715.

57. Wright MT. Antiemetics, akathisia, and pregnancy. Psychosomatics 2007;48(6):461-466.

58. Sekine Y, Rikihisa T, Ogata H, Echizen H, Arakawa Y. Correlations between in vitro affinity of antipsychotics to various central neurotransmitter receptors and clinical incidence of their adverse drug reactions. Eur J Clin Pharmacol 1999;55(8):583-587.

59. Lipinski JF Jr, Zubenko GS, Cohen BM, Barreira PJ. Propranolol in the treatment of neuroleptic-induced akathisia. Am J Psychiatry 1984;141(3):412-415.

60. Rathbone J, Soares-Weiser K. Anticholinergics for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev 2006 Oct 18;(4):CD003727. DOI: 10.1002/14651858.CD003727.pub3.

61. Baskak B, Atbasoglu EC, Ozguven HD, Saka MC, Gogus AK. The effectiveness of intramuscular biperiden in acute akathisia: a double-blind, randomized, placebo-controlled study. J Clin Psychopharmacol 2007;27(3):289-294.

62. Parlak I, Erdur B, Parlak M, Ergin A, Ayrik C, Tomruk O, et al. Midazolam vs. diphenhydramine for the treatment of metoclopramide-induced akathisia: a randomized controlled trial. Acad Emerg Med 2007;14(8):714-721.

63. Comaty JE. Propranolol treatment of neuroleptic-induced akathisia. Psychiatr Ann 1987;17:150-153.

64. Kulik AV, Wilbur R. Case report of propranolol (Inderal) pharmacotherapy for neuroleptic-induced akathisia and tremor. Prog Neuropsychopharmacol Biol Psychiatry 1983;7(2-3):223-225.

65. Goyal R, Chandrasekaran R, Nanda MR. Propranolol-responsive akathisia following acute encephalitis. Gen Hosp Psychiatry 2007;29(3):273-274.

66. Dumon JP, Catteau J, Lanvin F, Dupuis BA. Randomized, double-blind, cross-over, placebo-controlled comparison of propranolol and betaxolol in the treatment of neuroleptic-induced akathisia. Am J Psychiatry 1992;149(5):647-650.

67. Poyurovsky M, Fuchs C, Weizman A. Low-dose mianserin in treatment of acute neuroleptic-induced akathisia. J Clin Psychopharmacol 1998;18(3):253-254.

68. Poyurovsky M, Shardorodsky M, Fuchs C, Schneidman M, Weizman A. Treatment of neuroleptic-induced akathisia with the 5-HT2 antagonist mianserin. Double-blind, placebo-controlled study. Br J Psychiatry 1999;174:238-242.

69. Fischel T, Hermesh H, Aizenberg D, Zemishlany Z, Munitz H, Benjamini Y, et al. Cyproheptadine versus propranolol for the treatment of acute neuroleptic-induced akathisia: a comparative double-blind study. J Clin Psychopharmacol 2001;21(6):612-615.

70. Poyurovsky M, Weizman A. Mirtazepine for neuroleptic-induced akathisia. Am J Psychiatry 2001;158(5):819.

71. Wilson MS 2nd. Mirtazepine for akathisia in bipolar disorder. J Clin Psychopharmacol 2005;25(4):394-395.

72. Hieber R, Dellenbaugh T, Nelson LA. Role of mirtazapine in the treatment of antipsychotic-induced akathisia. Ann Pharmacother 2008;42(6):841-846.

73. Poyurovsky M, Weizman A. Serotonin-based pharmacotherapy for acute neuroleptic-induced akathisia: a new approach to an old problem. Br J Psychiatry 2001;179:4-8.

74. Chelben J, Strous RD, Lustig M, Baruch Y. Remission of SSRI-induced akathisia after switch to nefazodone. J Clin Psychiatry 2001;62(7):570-571.

75. Fehr C, Dahmen N, Klawe C, Eicke M, Szegedi A. Piracetam in the treatment of tardive dyskinesia and akathisia: a case report. J Clin Psychopharmacol 2001;21(2):248-249.

76. Sivrioglu EY, Kirli S, Sipahioglu D, Gursoy B, Sarandol E. The impact of omega-3 fatty acids, vitamins E and C supplementation on treatment outcome and side effects in schizophrenia patients treated with haloperidol: an open-label pilot study. Prog Neuropsychopharmacol Biol Psychiatry 2007;31(7):1493-1499.

77. Anfang MK, Pope HG Jr. Treatment of neuroleptic-induced akathisia with nicotine patches. Psychopharmacol (Berl) 1997;134(2):153-156.

78. de Leon J, Diaz FJ, Aguilar MC, Jurado D, Gurpegui M. Does smoking reduce akathisia? Testing a narrow version of the self-medication hypothesis. Schizophr Res 2006;86(1-3):256-268.

79. Akagi H, Kumar TM. Lesson of the week: Akathisia: overlooked at a cost. BMJ 2002;324(7352):1506-1507.

80. Voruganti LN, Awad AG. Subjective and behavioural consequences of striatal dopamine depletion in schizophrenia--findings from an in vivo SPECT study. Schizophr Res 2006;88(1-3):179-186.

81. Loonen AJ, van Praag HM. Measuring movement disorders in antipsychotic drug trials: the need to define a new standard. J Clin Psychopharmacol 2007;27(5):423-430.

82. Janno S, Holi MM, Tuisku K, Wahlbeck K. Neuroleptic-induced movement disorders in a naturalistic schizophrenia population: diagnostic value of actometric movement patterns. BMC Neurol 2008;8:10. DOI: 10.1186/1471-2377-8-10.

83. Hansen LK. Akathisia--seen from the patients' perspective. J Psychopharmacol 2008;22(5):572-573.