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Managing Antipsychotic-Induced Acute and Chronic Akathisia

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Abstract

Akathisia is a frequent and common adverse effect of treatment with antipsychotic (neuroleptic) drugs. This syndrome consists of subjective (feeling of inner restlessness and the urge to move) as well as objective components (rocking while standing or sitting, lifting feet as if marching on the spot and crossing and uncrossing the legs while sitting). Antipsychotic-induced akathisia can be classified according to the time of onset in the course of antipsychotic treatment (acute, tardive, withdrawal and chronic akathisia). Reported prevalence rates vary widely between 5 and 36.8%. Numerous risk factors for acute akathisia have been described and the exact pathophysiology of akathisia is still unknown.

Since akathisia is a drug-induced adverse effect, optimal management involves its prevention rather than treatment. Standardised titration and the use of novel antipsychotics are successful measures of prevention.

This paper reviews different forms of therapeutic approaches for the treatment of akathisia. Based on the available literature, propranolol or other lipophilic β-blockers seem to be the most consistently effective treatment for acute akathisia. There is nothing in the literature to guide a clinician when treatment with β-blockers fails. Addition of benzodiazepines would appear to be a sensible next choice, especially if subjective distress persists. If all of these drugs are unsuccessful, amantadine or clonidine can be tried. Other agents that have been inves-

tigated include ritanserin, piracetam, valproic acid (sodium valproate) and tricyclic antidepressants. Evidence on the treatment of tardive akathisia is unsatisfactory.

1. Diagnosis, Prevalence and Pathophysiology

Akathisia is a common and serious adverse effect of treatment with antipsychotics (neuroleptics). It manifests itself as a subjective feeling of inner restlessness and the urge to move. There are also objective signs, such as rocking while sitting or standing, lifting the feet as if marching in on the spot and crossing and uncrossing the legs while sitting. While the patient is lying down, it is possible to observe foot movements and/or myoclonic jerks of the feet.

To diagnose akathisia the patient must usually be observed in more than one position.[1,2] A strict adherence to the originally proposed definition requires the presence of subjective as well as of objective signs.[3,4] If only objective symptoms are seen, the term 'pseudoakathisia' has been proposed.[5]

The term 'pseudoakathisia' was first introduced by Munetz and Cornes[5] to refer to lower extremity tardive dyskinesia, or a form fruste of tardive dyskinesia, that was mistaken for akathisia. Barnes and Braude[3] applied a different meaning when they suggested use of the term for the objective manifestation of akathisia without the subjective component. For these authors pseudoakathisia was in fact true akathisia, but with limited manifestations. Stahl[6] suggested that this was inappropriate and wondered if this should not be described as a variation of tardive dyskinesia. Sachdev[7] is of the opinion, that pseudoakathisia is an ambiguous term which should be dropped.

The clinical diagnosis of akathisia may be difficult. It has to be to differentiated from psychotic agitation, anxiety, drug withdrawal syndromes or from some neurological disorders like Parkinson's disease, Huntington's disease or Ekbom syndrome. Differential diagnosis is reviewed in Sachdev.[7] Antipsychotic-induced akathisia can be classified according to its onset in relation to the administration of the antipsychotic drug and its duration (see table I[8]).

Reports of the prevalence rates of antipsychotic-induced akathisia in patients receiving antipsychotic drugs vary widely between 5% (National Institute of Mental Health and Psychopharmacology survey centre collaborative study group[9]) and 36.8%.[10]

Incidence rates for antipsychotic-induced akathisia also have a wide range from 25[1] to 75%.[11] This discrepancy in prevalence and incidence rates is mainly due to varying diagnostic approaches. All the authors reporting lower figures stress the objective phenomena of antipsychotic-induced akathisia, reports that emphasise the subjective features find higher rates[11] antipsychotic-induced akathisia has been reported to be a dose-dependent adverse effect. An influence of a recent increase of antipsychotic dose has also been described.[12-14] The risk of antipsychotic-induced akathisia with some newer antipsychotics may differ from that of conventional drugs. The results of clozapine are conflicting with rates between 0,[15] 5,[16] to 39%.[17] For risperidone a point prevalence of 13% was calculated.[18]

Studies about the epidemiology of tardive akathisia and chronic akathisia have limitations as tardive akathisia is generally overshadowed by tardive dyskinesia.

Numerous risk factors for acute akathisia have been described.[12-14,19] Age as well as gender or the psychiatric diagnosis do not have any significant influence on the occurrence of acute akathisia. Acute akathisia is mostly associated with classical antipsychotics. A dose increase in the first days of treatment also augments the risk for acute akathisia significantly.[12-14]

The exact pathophysiological mechanism of akathisia is still unknown. Marsden and Jenner[20]

speculated that dopamine A_{10} neurons, originating in the ventral tegmental area, are mainly involved in the pathophysiology of antipsychotic-induced akathisia. This is substantiated not only by the fact that blockers of serotonergic[21] and noradrenergic[22] transmission can increase the firing rate of these neurons, thereby possibly counteracting the dopamine blockade of antipsychotic drugs, but also by the observation, that β-blockers usually do not influence classical nigrostriatal antipsychotic adverse effects like parkinsonism. The role of serotonin (5-hydroxytryptamine; 5-HT) antagonists or selective serotonin reuptake inhibitors in akathisia is still under investigation.[23-26]

2. Prevention

Since akathisia is a drug-induced adverse effect, optimal management involves its prevention rather than treatment. Ideally, antipsychotic-induced akathisia should be avoided. Therefore, the use of novel antipsychotics as first-line drugs should be recommended, because of their lower risk of inducing akathisia.[27]

The association of akathisia with antipsychotic dose is generally accepted.[12] Smaller dosages are therefore recommended, without compromising antipsychotic efficacy.[28] The role of dosage increment also plays an important role in the incidence of akathisia.[14] It is therefore useful to increase the dose gradually, especially in drug-naive patients. Another factor, which may be important, is the type of antipsychotic used. Of the 'classical' antipsychotics, akathisia is more likely to occur in those with higher potency.

3. Pharmacological Treatment of Acute Akathisia

Studies in which 2 different drugs were compared are described in the following sections under the type of drug which produced the most pronounced effect during the trial.

Table I. Classification of antipsychotic-induced akathisia according to the time of onset in the course of antipsychotic treatment[8]

Diagnosis	Symptoms
Acute akathisia	Rapid onset within hours or days after an exposure with antipsychotics. In most cases, this form of akathisia occurs within the first 3 days to 2 weeks of treatment
Tardive akathisia	Symptoms begin at least 3 months after initiation of the antipsychotic drug; there should have been no increase in dose or change in type of the drug in the 6 weeks prior to the onset; a concurrently administered therapeutic drug should not have been decreased or discontinued in the 2 weeks before the onset of the symptoms
Withdrawal akathisia	Starts within 6 weeks following discontinuation or a significant decrease in the dose of the antipsychotic. A further criterion is that a concurrent drug was not discontinued in the 2 weeks before the onset of the symptoms
Chronic akathisia	Persistence of akathisic symptoms for more than 3 months. The term does not express whether the beginning of the symptoms was acute or tardive or withdrawal. This term only describes the duration of the symptoms

3.1 β-Blockers

β-Blockers are currently considered to be the most helpful treatment for antipsychotic-induced akathisia. Two pharmacological properties of β-blockers are relevant with regard to their anti-akathisic effects. First, they have to be lipophilic and to be able to cross the blood-brain barrier and secondly, they should block β_2-receptors.

The first report of the efficacy of propranolol, which is a nonselective β-blocker, in the treatment of akathisia was published by Lipinski et al.[29] They reported 12 patients, mostly with bipolar disorders, treated with propranolol for antipsychotic-induced akathisia. All patients showed improvements, with 9 experiencing complete remission. The same group published an nonblind trial with propranolol in 14 patients with antipsychotic-induced akathisia.[30] Of the 14 patients, 10 also had other extrapyramidal symptoms (EPS) and therefore received concomitant benzatropine (benztropine). Patients with mania received lithium and all showed tremor thought to be secondary to this treatment. They reported that all patients

improved while receiving propranolol, with 9 obtaining complete remission. The improvement was rapid. Also lithium-induced tremor responded but other antipsychotic-induced EPS did not improve. Hypotension and bradycardia were not observed, nor was significant sedation.

A randomised, double-blind comparison of propranolol with placebo utilising a crossover design was conducted by Adler and co-workers.[31] Treatment periods lasted from 6 to 10 days and patients received up to 60 mg/day of propranolol. Eight of the 12 received concomitant anticholinergics and 1 received amantadine. Three received benzodiazepines on an as needed basis. The authors reported that propranolol treatment resulted in improvements in both objective and subjective ratings of akathisia. Placebo had no effect on any of the measures. The efficacy of propranolol was also confirmed in comparison with benzatropine[32] and lorazepam.[33] Propranolol was superior to the comparator in both trials. In comparison with benzatropine, treatment with propranolol resulted in a mean improvement on objective and subjective scores of 50%. The authors[32] pointed out that the magnitude of this decrease is similar to that seen in their other studies.

It is interesting that the improvement seen with propranolol in the patients with schizophrenia treated by Adler et al.[31,33] does not seem to be as great as the almost complete remission reported by Lipinski et al.[29,30] Perhaps these differences can be explained by the different patient populations treated by the 2 groups.[34]

Deron et al.[35] were the first to compare propranolol with atenolol, a selective β_1-blocker. They found that atenolol was as effective as propranolol. Other authors performed studies with pindolol, a nonselective antagonist with intrinsic sympathomimetic activity.[36] They reported successful treatment. On the other hand, Adler et al.,[37] found that pindolol was less effective than propranolol. They emphasised that pindolol is less lipophilic and a partial agonist and that these features are responsible for lesser efficacy.

Zubenko et al.[38] compared metoprolol, a lipophilic selective β_2 antagonist, with propranolol. They found that metoprolol was less effective and required administration at higher dosages to obtain improvement. Significant changes in pulse and blood pressure were also reported in the metoprolol group. The authors pointed out that at only high doses metoprolol may have significant β_2-receptor blocking effects and their data support a mechanism of action involving central β_2-receptor blockade. Another interpretation of their data might be that both β_1- and β_2-receptor blockade is required to reduce akathisia.

The efficacy of betaxolol, another selective β_1 antagonist, was investigated twice by the same research group.[39,40] The first study was a nonblind trial involving 4 patients, the second study was a randomised comparison versus propranolol. Both papers describe an effectiveness of this drug in the treatment of akathisia.

The question of whether the therapeutic effect of β-blockers is a central or a peripheral one has been addressed by studying the effect of hydrophillic drugs like nandolol, sotalol and atenolol, that do not cross the blood-brain barrier.

The therapeutic efficacy of nadolol was evaluated in a placebo-controlled, double-blind study by Wells et al.[41] Patients received nadolol 40 to 80 mg/day and were rated daily for 4 days and on alternate days for 15 days. The authors found no significant differences between nadolol and placebo either in the subjective or in the objective symptoms of akathisia, while both groups showed an improvement in the objective manifestations on day 9 compared with day 1. Deron et al.[35] reported the ineffectiveness of atenolol in comparison with propranolol. Reiter and co-workers[42] also compared these 2 drugs. They also found that atenolol was ineffective in the treatment of antipsychotic-induced akathisia. The published evidence therefore suggests that these hydrophillic drugs are not effective.

In summary, based on a review of the literature, propranolol or other lipophilic β-blockers must be considered to be the most effective treatment. A

careful review of the antipsychotic requirements of the patient should be the first step in the treatment of antipsychotic-induced akathisia. A reduction in dosage or replacement of high potency antipsychotics with atypical antipsychotics, if at all possible may be considered at this point. Propranolol therapy should be instituted at a low dosages, e.g. 10mg 3 times daily, which can be increased every few days to a maximum of 90 to 120 mg/day. Above this level, response is unlikely.

There is nothing in the literature to guide the clinician when treatment with propranolol fails. Addition of benzodiazepines, such as lorazepam 1.5 to 3 mg/day in divided doses or clonazepam 0.5 mg/day would appear to be a sensible next choice, especially if subjective distress persists.[34]

3.2 Benzodiazepines

The rationale for the use of benzodiazepines in the treatment of akathisia stems from 3 observations: (i) the level of anxiety influences the manifestation of akathisia; (ii) the subjective part of akathisia resembles anxiety and; (iii) restless legs syndrome (Ekbom Syndrome[43]), which resembles akathisia phenomenologically, has been reported to respond to treatment with benzodiazepines.[44]

The focus of the mode of action of the benzodiazepines has been on their γ-aminobutyric acid–mimetic properties. The results of nonblind trials with lorazepam as well as clonazepam have shown that benzodiazepines can be effective in the treatment of acute and chronic akathisia.[45-47] Donlon[48] reported from an open study with diazepam of 13 patients with akathisia in whom treatment with diphenhydramine 75 mg/day had been unsuccessful. He reported that diazepam effectively relieved the akathisia in 10 patients within 3 days.

Gagrat et al.[49] performed a double-blind study of a single intravenous dose of diazepam 5mg versus diphenhydramine 50mg. Diazepam-treated patients did not do as well, although the difference was not statistically significant. Akathisia was rated at baseline and 4 times up to 2 hours after infusion. The ratings after the infusion were significantly lower than baseline in the diazepam group as well as in the anticholinergic group.

In a single blind crossover study by Adler et al.,[33] the authors compared lorazepam with propranolol. Lorazepam 2 mg/day produced improvements in the subjective but not in the objective ratings of akathisia and was inferior to propranolol.

Kutcher et al.[47] performed a double-blind trial of clonazepam (n = 7) versus placebo (n = 7). All patients who received clonazepam showed an amelioration of their symptoms of akathisia, whereas symptoms in 5 of the patients in the placebo group were unchanged.

On the whole, most studies report effectiveness on benzodiazepines in antipsychotic-induced akathisia, although the duration of treatment was generally brief. Clonazepam may be preferable to diazepam because of its long half-life. Lorazepam has been shown to have similar success in the treatment of this disturbance.

3.3 Anticholinergic Drugs

Anticholinergic drugs can also be useful in the treatment of akathisia.[11,50,51] Only a few controlled studies have been performed with these substances.

Di Mascio et al.[52] in a double-blind study, compared the efficacy of amantadine with benzatropine in the reduction of EPS, including akathisia. He included 44 patients in this study. Benzatropine was reported as almost completely effective in eliminating akathisia over the 4-week period of this comparison. This study had some methodological problems. The dose was not controlled. Another disadvantage was the lack of a placebo group.

Another double-blind comparison was reported by Gagrat and co-workers.[49] They compared the efficacy of intravenous diphenhydramine with intravenous diazepam. Patients receiving diphenhydramine began to show improvements in their symptoms 5 minutes after the infusion. The benefits were still evident 2 hours later. There were no statistically significant differences between diphenhydramine and diazepam. Again, this study had no placebo control.

In a study comparing akathisia in patients treated with tiotixene (thiothixene) versus haloperidol, van Putten and colleagues[11] reported the proportion of patients with akathisia who responded to an anticholinergic drug. In the haloperidol group, of the 32 patients treated with anticholinergic, 14 showed complete alleviation of the akathisia. All but 3 of the tiotixene patients (n = 27) treated with an anticholinergic also experienced an alleviation in their symptoms. The authors concluded that akathisia secondary to the administration of haloperidol was relatively refractory to treatment with anticholinergics, while akathisia occurring in tiotixene-treated patients was easier to suppress. The authors suggested prophylactic treatment with antiparkinsonian drugs to prevent the emergence of akathisia.

Sachdev and Loneragan[53] challenged 6 patients with acute akathisia using benzatropine 2mg, propranolol 1mg and placebo. The study was a randomised, double-blind, crossover design. Benzatropine produced a significant amelioration of antipsychotic-induced akathisia which was more apparent in the subjective component.

In an interim analysis of a placebo-controlled, double-blind comparison of benzatropine and propranolol, Adler et al.[54] reported that 6 patients treated with benzatropine showed a slight improvement in the subjective symptoms of akathisia. In contrast to propranolol, benzatropine treatment had no effect on the objective signs of antipsychotic-induced akathisia.

Only 1 benzatropine-treated participant in the negative report of Adler et al.[54] experienced severe parkinsonism, while in the reports of Friis et al.[51] and Gagrat et al.[49] the incidence of concomitant parkinsonian adverse effects was considerably higher. These data lend support to the hypothesis of Braude et al.,[12] that akathisia only responds to treatment with anticholinergic agents when it is accompanied by parkinsonism. Also worth considering in the treatment of akathisia is that serum anticholinergic activity levels may be better correlated with efficacy than dosage of these agents. Tune et al.[55] found an inverse relationship between the severity of acute EPS and anticholinergic plasma concentrations in patients receiving these drugs. Taken together, the efficacy of anticholinergic agents in the treatment of antipsychotic-induced akathisia is far from established.

3.4 Clonidine

Clonidine is an α_2 agonist that decreases central noradrenergic activity.[56] Zubenko et al.[38] treated 6 patients with akathisia with this drug in dosages ranging from 0.2 to 0.8 mg/day. All 6 patients showed some improvement, 4 experiencing complete remission of symptoms. Adler et al.[57] also treated 6 patients with antipsychotic-induced akathisia with clonidine. The initial dosage was 0.05 to 0.20 mg/day, which was titrated to avoid akathisia over 3 to 15 days to a maximum tolerated dosage of 0.15 to 0.40 mg/day. All patients received concomitant benzatropine. Improvement in the objective features of akathisia was seen in all patients at the time of maximum clonidine dose. All patients also showed a positive subjective response at that dosage. The dosage increase was limited by adverse effects such as sedation and hypotension.

The limited studies of the role of clonidine suggest that this substance may be beneficial, but adverse effects limit its clinical use. Further clarification is necessary.

3.5 Amantadine

Amantadine was first marketed as an antiviral drug, but has later been demonstrated to have antiparkinsonian effects. Three articles on amantadine in the treatment of akathisia have been published.

Di Mascio et al.[52] compared amantadine and benzatropine in the treatment of antipsychotic-induced EPS. Out of 44 patients, 24 had akathisia. By the third day of treatment both groups showed marked improvements. The authors concluded that benzatropine and amantadine were equally effective in the treatment of antipsychotic-induced EPS. Gelenberg[58] gave amatadine 200 to 300 mg/day to patients who had benzatropine refractory EPS. Of 14 patients, 2 had akathisia and parkinsonism.

Of these 2 patients, 1 improved substantially and the other only minimally. Symptoms in 1 patient, with akathisia alone, deteriorated. Casting doubt on the efficacy of this drug in the treatment of acute akathisia is a paper by Zubenko et al.[59] They studied 4 patients, who responded to amantadine but developed tolerance within a week. This report reinforces the need for more controlled trials of amantadine in the treatment of antipsychotic-induced akathisia.

3.6 Ritanserin

A promising approach in the treatment of akathisia is the use of drugs that act on the $5HT_2$ receptor. There is 1 report of improvement of EPS with ritanserin, a specific $5HT_2$-receptor antagonist.[24] Ritanserin only had a positive effect on akathisia and tremor. We investigated ritanserin in patients with akathisia in a single blind open study. Of our 10 patients, 8 were receiving concomitant medications, but all drugs were kept constant during the study and during the week prior to the study. Ritanserin resulted in a significant decrease in Hillside Akathisia Scale[60] scores within 3 days of treatment in all patients. The effect was generally apparent by the first day, and no adverse effects were noted.[25]

3.7 Piracetam

Piracetam is labelled as a nootropic drug and it said to influence neuronal metabolism,[61] but it does not affect any of the known neurotransmitters. Kabes et al.[62] used intravenous piracetam to treat patients receiving antipsychotic medication who had mild akathisia along with other EPS. The authors reported a significant beneficial effect of piracetam on acute akathisia compared with placebo. They hypothesise that piracetam may alter membrane permeability in the CNS and cited this as a possible mechanism of action. Replication of this study is warranted.

3.8 Valproic Acid (Sodium Valproate)

Friis et al.[51] examined valproic acid (sodium valproate) as a treatment of akathisia. In this double-blind, placebo-controlled study involving 15 patients, valproic acid did not have any significant effect on acute akathisia when compared with placebo.

3.9 Tricyclic Antidepressants

A case report of a patient with akathisia, who experienced a dramatic improvement with amitriptyline after experiencing no response with trihexyphenidyl, was published by Danel et al.[63] The authors argued that the efficacy of this tricyclic antidepressant was due to postsynaptic β-adrenergic desensitisation induced by this drug. But an additive anticholinergic effect of both substances could not be ruled out either.

4. Tardive/Chronic Akathisia

The assessment of the treatment of tardive and chronic akathisia is difficult, due to the lack of a detailed characterisation of these 2 syndromes. While discontinuation of antipsychotic drugs would be ideal, it is seldom feasible. If a withdrawal of antipsychotics is possible, there may be some worsening of tardive akathisia, but this is often temporary.[7] Burke et al.[64] followed their patients over a mean of 2.3 years after the discontinuation of antipsychotics. They found that 67% of the patients continued to have akathisia.

If a dose decrease or discontinuation of antipsychotic is impossible, alternative drugs should be considered. Some evidence suggests that clozapine may be suitable in these cases.[65] Clearly all the other novel antipsychotics with their reduced propensity to induce EPS must also be considered.[66]

Two case reports describe an efficacy of propranolol in tardive akathisia.[67,68] There are also some case reports evaluating anticholinergic drugs.[69-71]

In summary, the evidence on pharmacological treatment of tardive akathisia is unsatisfactory.

5. Conclusion

Despite the relatively large numbers of studies, the optimal pharmacological treatment of akathisia is yet to be determined. Differences in study design and duration make it difficult to compare the various modalities of treatment. Based on the available literature, propranolol or other lipophilic β-blockers seem to be the most consistently effective treatment for antipsychotic-induced akathisia. The addition of a benzodiazepine would appear to be a sensible next choice, especially when subjective distress persists. If all of the drugs, recommended above, have failed, amantadine or clonidine can be tried. Although there is no evidence that they are any more beneficial than β-blockers or benzodiazepines.

A careful review of the antipsychotic requirements of the patients should be the first approach. This should, wherever possible, be followed by a reduction in dosage or by switching from classical antipsychotics to novel compounds.

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