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SAGE

The Assessment and Treatment of Antipsychotic-Induced Akathisia

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Abstract

Background: Akathisia is a common and distressing neuropsychiatric syndrome associated with antipsychotic medication, characterised by subjective and objective psychomotor restlessness. The goal of this guideline is to provide clinicians with recommendations on the assessment and treatment of akathisia.

Methods: We performed a systematic review of therapeutic studies assessing the treatment of antipsychotic-induced extrapyramidal symptoms. Forty studies on akathisia and 4 systematic reviews evaluating the adverse effects of antipsychotics were used in the formulation of recommendations. Studies were rated for methodological quality using the American Academy of Neurology Risk of Bias Classification system. The overall level of evidence classifications and grades of recommendation were made using the Scottish Intercollegiate Guidelines Network framework.

Results: As a good practice point, clinicians should systematically assess akathisia with a validated scale before starting antipsychotics and during antipsychotic dosage titration. For the management of akathisia, there was adequate evidence to allow recommendations regarding antipsychotic dose reduction, antipsychotic polypharmacy, switching antipsychotic medication, and the use of adjuvant medications including beta-blockers, anticholinergics, $5HT_{2A}$ antagonists, benzodiazepines, and vitamin B6.

Conclusion: The treatment of antipsychotic-induced akathisia should be personalised, with consideration of antipsychotic dose reduction, cessation of antipsychotic polypharmacy, and switching to an antipsychotic with a perceived lower liability for akathisia, before the use of adjuvant medications. The choice of adjuvant medications should favour the more established treatments, with careful consideration of contraindications and side effects. Limitations in the evidence should be acknowledged and prompt cautious prescribing, particularly with respect to the duration of use of adjuvant medications, is warranted.

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Abrégé

Contexte : L'acathisie est un syndrome neuropsychiatrique commun et éprouvant associé aux médicaments antipsychotiques, caractérisé par une agitation psychomotrice subjective et objective. Le but de ce guide est d'offrir aux cliniciens des recommandations sur l'évaluation et le traitement de l'acathisie.

Méthodes : Une revue systématique des études thérapeutiques du traitement des symptômes extrapyramidaux induits par antipsychotique a été menée. Quarante études sur l'acathisie et quatre revues systématiques évaluant les effets indésirables des antipsychotiques ont été utilisées pour formuler les recommandations. Les études ont été classées pour leur qualité méthodologique à l'aide du système de classification du risque de biais de l'académie américaine de neurologie. Le niveau global des classifications des données probantes et des catégories de recommandations a été déterminé à l'aide du cadre du Scottish Intercollegiate Guidelines Network (SIGN).

Résultats : Un bon point de la pratique serait pour les cliniciens de systématiquement évaluer l'acathisie avec une échelle valide avant de commencer les antipsychotiques et durant l'ajustement posologique de l'antipsychotique. Pour la prise en charge de l'acathisie, il y avait des données probantes adéquates pour permettre des recommandations sur la réduction de la dose d'antipsychotique, la polypharmacie antipsychotique, le changement d'antipsychotique, et l'emploi de médicaments adjuvants dont les bêtabloquants, les anticholinergiques, les antagonistes 5-HT_{2A}, les benzodiazépines, et la vitamine B6.

Conclusion : Le traitement de l'acathisie induite par antipsychotique devrait être personnalisé, en prenant en considération la réduction de la dose d'antipsychotique, la cessation de la polypharmacie antipsychotique, et le changement pour un antipsychotique perçu comme étant moins favorable à l'acathisie, avant l'utilisation de médicaments adjuvants. Le choix des médicaments adjuvants devrait privilégier les traitements mieux établis, et un examen soigneux des contre-indications et des effets secondaires. Les limitations des données probantes doivent être reconnues et inciter à une prescription prudente, surtout à l'égard de la durée d'utilisation des médicaments adjuvants.

Keywords

antipsychotics, extrapyramidal syndromes, evidence-based medicine

Introduction

Akathisia, a term derived from the Greek for 'inability to sit',[1] refers to a neuropsychiatric syndrome characterised by subjective and objective psychomotor restlessness. Although recognised soon after the introduction of antipsychotic medication,[2,3] it was largely overlooked for 30 years[4,5] until the clinical presentation was delineated in the 1980s.[6-8] The core of the condition is a subjective experience of mental unease and dysphoria, characterised by a sense of restlessness that may sometimes drive impulsive behaviour.[9,10] When the condition is severe, there is an irresistible urge to move around, partly to achieve some respite. Patients may complain of a mounting sense of tension when required to stand still; for example, when waiting in line. The observable features include the inability to sit, stand or lie still. When sitting, the legs tend to swing, cross and uncross, or tramp up and down. When standing, there is a tendency for the body weight to shift from one foot to the other ('marching on the spot') or for the person to pace back and forth.

Akathisia usually occurs during the early days of treatment with antipsychotic medication, when it is considered as acute akathisia. But it can be, and often is, a persistent problem when not addressed; chronic akathisia is usually defined as the continuation of the signs and symptoms for more than 3 months. Akathisia may also arise following reduction of dosage or cessation of antipsychotic medication,[11-13] referred to as withdrawal akathisia; although, it is generally considered to be indistinguishable phenomenologically from acute akathisia.[7] The term 'tardive akathisia' has been inconsistently applied in the literature to refer to akathisia that occurs late in the course of treatment, is exacerbated or provoked by antipsychotic dose reduction or withdrawal, and improves at least temporarily when the dose is increased; these are pharmacological characteristics shared with tardive dyskinesia.[7,11] However, it has also been used to refer to late-onset akathisia occurring in the absence of any change in drug dose or type, or provoked by stopping anti-akathisia medication[14] as well as persistent akathisia that is particularly disabling and often refractory to treatment.[15]

Where a patient exhibits the objective signs of akathisia in the absence of awareness of the typical subjective experience, this is sometimes called pseudoakathisia. However, it remains uncertain whether such a presentation reflects chronic akathisia, where the patient is either unable to verbalise the subjective dysphoria or this component has faded over time, or whether it is a variant of tardive dyskinesia.[12,16-18]

Akathisia is a common and distressing motor syndrome associated with antipsychotic drug treatment. Its development can be a disincentive to medication acceptance and thus it can have an adverse effect on long-term treatment outcomes. Further, the signs and symptoms of akathisia can confound clinical assessment of the mental state. In clinical practice, the condition often goes unrecognised or misdiagnosed as psychotic agitation or excitement, restless legs syndrome, anxiety, substance intoxication/withdrawal or tardive dyskinesia.[19-21] The extent to which akathisia is a risk factor for suicide[22,23] remains uncertain; although, it has been found to be associated with suicidality, in individuals with

first-episode psychosis,[24] as well as the development of violent or aggressive behaviour.[25]

Methods

A systematic review of the literature was performed for therapeutic studies on the treatment of antipsychotic-induced extrapyramidal symptoms. We searched Medline and CENTRAL in November 2016, using the search strategy in Supplemental Appendix 1. We hand-searched the Cochrane Library for systematic reviews on this topic and searched for published guidelines on this topic as well, and included all references from these papers. Our Medline and CENTRAL search found 5,053 abstracts, which were reviewed independently by 2 researchers, and of which 250 were chosen for full-text review. From the 9 identified Cochrane reviews on this topic,[26-34] American Academy of Neurology (AAN) guideline on tardive syndromes,[35] and the Canadian Alliance on Monitoring of Safety and Effectiveness of Antipsychotic (CAMESA) guideline on the management of extrapyramidal symptoms,[36] we identified an additional 94 articles for full-text review, bringing the total to 344 articles for full-text review. Forty clinical studies pertaining to the treatment of akathisia and 4 systematic reviews evaluating adverse effects of antipsychotics from randomised controlled trials were used in the formulation of recommendations on the assessment and management of antipsychotic-induced akathisia. We included any type of therapeutic study, including case reports, case series, and controlled trials. If controlled trials were available for a specific therapeutic intervention, case reports and case series were not included in our analysis. Studies were rated for methodological quality using the American Academy of Neurology Risk of Bias Classification system. Each study was given a class rating of I, II, III, or IV based on the fulfilment of these criteria (see Table 1). Rating of risk of bias and data extraction were performed by a single researcher and checked by a second researcher for accuracy. Discrepancies were resolved by discussion. The overall level of evidence classifications were made using the Scottish Intercollegiate Guidelines Network framework (see Table 2). For each therapeutic study that was included, the risk of bias, population, intervention, comparator, trial length, number of participants, and main outcomes are described in full in Supplemental Appendix 2, and summarised below with the recommendations. Initial recommendations were drafted by a team of researchers and then voted on by the entire panel for inclusion in the guideline. The grade of recommendations was made using the SIGN framework. Recommendation statements were formulated based on the evidence obtained from the systematic review, the magnitude of benefit associated with the intervention, and the risk of harm, cost, availability, and variation in patient preference. Each recommendation required agreement by 80% of the panel for inclusion in the guideline. The panel consisted of movement disorders specialists, psychiatrists, and psychopharmacologists with expertise in the therapeutic use of antipsychotic medication and the adverse effects associated with such medication.

Recommendations

Assessment of Akathisia

Clinical examination procedures designed to identify and assess extrapyramidal side effects in people prescribed antipsychotic medication have been described.[37,38] The overall detection and management of antipsychotic-induced akathisia as well as its assessment before starting antipsychotic medication and during titration to a therapeutic dosage may be improved by using a validated scale. The most widely used rating scale for the measurement of akathisia symptoms is the Barnes Akathisia Rating Scale, which measures objective signs and subjective (awareness and distress) symptoms of akathisia, and includes a global assessment item, on which a score of 2 or more indicates the presence of akathisia.[8] The instrument is easy to administer and score, with established reliability, validity, and clinical utility.[39-42] If an instrument assessing all types of extrapyramidal symptoms is preferred for use, the Extrapyramidal Symptom Rating Scale[43] includes one item on the symptoms of akathisia, one item assessing objective signs of akathisia, and a clinical global impression of severity of akathisia. The Extrapyramidal Rating Scale has been extensively deployed and has established inter-rater reliability.[43]

Recommendation (Good Practice Point). Before starting antipsychotic medication and during antipsychotic dosage titration, clinicians should systematically assess the symptoms and signs of akathisia using a validated scale. The use of such a scale can provide a reliable baseline measure for subsequent monitoring of akathisia.

Antipsychotic Polypharmacy and Dose Reduction (Level of Evidence 3)

Naturalistic studies of psychiatric inpatients have shown that acute akathisia develops within hours or days of initiation of antipsychotic treatment. The evidence suggests that the risk of akathisia is greater in patients prescribed antipsychotic medication for the first time—i.e., antipsychotic-naïve, or for whom antipsychotic drug dosage is rapidly escalated[6,44]—and that akathisia tends to improve following dose reduction. Prescribing more than one antipsychotic drug for patients is also a risk factor. A recent study of 372 community-dwelling individuals with schizophrenia on stable antipsychotic medication treatment regimens for at least 4 weeks found an overall prevalence of akathisia of 18.5%.[45] In this community survey, polypharmacy with 2 first-generation antipsychotics was associated with the highest prevalence of akathisia at 40%, v. a prevalence of 21% in those on first-generation antipsychotic monotherapy. For those receiving second-generation antipsychotic monotherapy, the prevalence was 11%, whereas

Table 1. American Academy of Neurology Risk of Bias Classification System.

Class I
Randomized controlled clinical trial (RCT) in a representative population
Triple masked studies (i.e. the patient, treating provider and outcome assessors are unaware of treatment assignment)
Relevant baseline characteristics of treatment groups (or treatment order groups for cross-over trials) are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences
Additional Class I criteria:
a. Concealed allocation
b. No more than 2 primary outcomes specified
c. Exclusion and inclusion criteria clearly defined
d. Adequate accounting of dropouts (with at least 80% of participants completing the study) and crossovers
e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority
ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
iii. The inclusion and exclusion criteria for participant selection and the outcomes of participants on the standard treatment are comparable with those of previous studies establishing efficacy of the standard treatment
iv. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers
f. For crossover trials, both period and carryover effects are examined and statistical adjustments performed, if appropriate
Class II
RCT that lacks one or 2 Class I criteria a–e (see above)
Cohort studies employing methods that successfully match treatment groups on relevant baseline characteristics (e.g., propensity score matching) meeting Class I criteria b–e (see above)
Randomized crossover trial missing one of the following 2 criteria:
a. Period and carryover effects described
b. Baseline characteristics of treatment order groups presented
All relevant baseline characteristics are presented and substantially equivalent across treatment groups (or treatment order groups for crossover trials, or there is appropriate statistical adjustment for differences
Masked or objective** outcome assessment
Class III
Controlled studies (including studies with external controls such as well-defined natural history controls)
Crossover trial missing both of the following 2 criteria:
c. Period and carryover effects
d. Presentation of baseline characteristics
A description of major confounding differences between treatment groups that could affect outcome**
Outcome assessment performed by someone who is not a member of the treatment team
Class IV
Studies not meeting Class I, II or III criteria.

*Numbers i–iii in Class Ie are required for Class II in equivalence trials. If any one of the 3 is missing, the class is automatically downgraded to Class III.
**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

polypharmacy with 2 second-generation antipsychotics was associated with a prevalence of 34%.

The Canadian Agency for Drugs and Technology in Health published optimal use recommendations for antipsychotic polypharmacy and high-dose treatment strategies in adolescents and adults with schizophrenia based on a systematic review of the literature and expert consensus.[46] This report recommended against the use of antipsychotic combination therapy and high-dose strategies, based on inadequate evidence of efficacy and evidence of harm (including higher rates of extrapyramidal symptoms) associated with these practices.

A randomised controlled trial addressed the risks and benefits of staying on antipsychotic polypharmacy or switching to monotherapy in adults with schizophrenia.[47] Outpatients taking 2 antipsychotics were randomised to stay on polypharmacy or switch to monotherapy by discontinuing one antipsychotic. After 6 months, 86% of those assigned

Table 2. Scottish Intercollegiate Guidelines Network Framework.

LEVELS OF EVIDENCE
1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 - Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++ High quality systematic reviews of case control or cohort studies, or High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 - Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3 Non-analytic studies, e.g. case reports, case series
4 Expert opinion
GRADES OF RECOMMENDATION Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.
A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GOOD PRACTICE POINTS Recommended best practice based on the clinical experience of the guideline development group

to stay on polypharmacy were still taking both medications, whereas 69% of those assigned to switch to monotherapy remained on monotherapy. Most individuals who discontinued monotherapy resumed their original polypharmacy. Those switching to monotherapy lost weight, and had no worsening of symptom control or increase in hospitalization compared with those on polypharmacy.

Recommendation (Grade D). To reduce the risk of developing acute akathisia, clinicians should seek to avoid rapid escalation of antipsychotic dosage.

Recommendation (Grade D). Clinicians should consider dose reduction in patients with persistent akathisia on a stable dose of antipsychotic medication, considering the potential risk of clinical deterioration of the psychiatric disorder.

Recommendation (Grade D). When considering the risks and benefits of using combined antipsychotics in a patient, clinicians should account for the increased risk of akathisia and inadequate evidence for clinical efficacy with such a strategy.

Recommendation: (Grade D). Where antipsychotic polypharmacy is being prescribed and there is persistent, clinically significant akathisia, clinicians should attempt to achieve mono-antipsychotic therapy, by tapering and discontinuing one of the antipsychotic medications or switching to a different single antipsychotic, if this can be accomplished without clinical deterioration.

Antipsychotic Switching (Level of Evidence 1-)

To our knowledge, a systematic and comprehensive review comparing the liability for akathisia specifically across all antipsychotic medication trials has not been published. Several reviews have analysed akathisia risk in specific subsets of published studies. A systematic review and meta-analysis of head-to-head comparisons of antipsychotic medications for the treatment of schizophrenia published before 2009[48] found that aripiprazole produced more akathisia (as measured on the Barnes Akathisia Rating Scale) than olanzapine, and clozapine more than ziprasidone. Risperidone was associated with more akathisia than sertindole and ziprasidone. Haddad[49] performed a systematic review of head-to-head comparisons of antipsychotic medications for first-episode psychosis. Three trials comparing haloperidol with olanzapine, and 2 trials comparing haloperidol with olanzapine and risperidone demonstrated a significantly higher risk of treatment-emergent akathisia with haloperidol. Two trials comparing haloperidol with risperidone found significantly higher scores on the Extrapyramidal Symptom Rating Scale akathisia subscale with haloperidol. One trial comparing clozapine to chlorpromazine found akathisia was more frequent over 1 year of follow-up with chlorpromazine. A more

recent systematic review comparing the incidence of akathisia in the treatment of schizophrenia with aripiprazole, asenapine and lurasidone, including studies published before June 2014, found that the risk of akathisia was elevated for these newer antipsychotics compared with risperidone, olanzapine, ziprasidone and quetiapine.[50] Compared with olanzapine, asenapine had an odds of akathisia of 2.23 (1.45 to 3.42), aripiprazole had an odds of akathisia of 1.49 (1.13 to 1.99) compared with risperidone, ziprasidone, and olanzapine, while lurasidone had an odds of 1.83 (1.27 to 2.63) relative to ziprasidone, risperidone, olanzapine and quetiapine. The Maudsley Prescribing Guidelines in Psychiatry[51] identify a 'very low' liability for akathisia with aripiprazole, lurasidone and ziprasidone; although, it has also been argued that a switch to iloperidone might be most favourable for patients exhibiting akathisia.[13]

Recommendation (Grade C). For patients on continuing antipsychotic treatment who have persistent and clinically significant akathisia symptoms, clinicians should consider switching to an agent with a perceived lower liability for extrapyramidal side effects, such as clozapine, olanzapine or quetiapine.

Propranolol and Other Beta Blockers (Level of Evidence 1-)

Propranolol, a nonselective beta-adrenergic antagonist, is the most studied treatment intervention for antipsychotic-induced akathisia. There are 7 published trials comparing propranolol with placebo for the treatment of akathisia. These trials were published between 1986 and 2006, and the risk of bias was low in 2 trials (Class II),[52,53] but high (Class III) in 5 trials.[54-58] Most trials were conducted in people with schizophrenia and were of short duration, ranging from 2 to 12 days of propranolol treatment. In total, 194 individuals participated in these 7 trials. The dose of propranolol ranged from 20 to 120 mg daily. Six of the 7 trials reported improvement in akathisia in individuals receiving propranolol relative to placebo. The negative trial[56] consisted of treatment with propranolol for 2 days; yet, subsequent trials[57,58] found no difference between propranolol and placebo at 2 days, but a significant improvement relative to placebo at 5 days, suggesting that the short duration of the previous study may have resulted in the negative response. There are no reports of worsening psychosis associated with propranolol use.

Four studies have compared propranolol exclusively with another drug. None of these 4 studies used a non-inferiority design, and were rated as having a low (one class II study)[59] or high (2 class III and one class IV study)[60-62] risk of bias. Like studies comparing propranolol to placebo, trials were of short duration, ranging from 1 to 7 days duration, and included 88 participants. Doses of propranolol ranged from 40 to 120 mg daily. All trials reported benefit with propranolol from baseline to endpoint, as well as with the other agents studied (metoprolol, zolmitriptan, cyproheptadine), except for benztropine, which showed no change in objective ratings of akathisia.

Metoprolol and nadolol have been evaluated for the treatment of akathisia in one trial each. Both studies had a high risk of bias (Class III) and included a small number of participants. Metoprolol and propranolol were not found to be different (no placebo control group),[60] and there was no significant difference between nadolol and placebo in subjective or objective restlessness scores.[63]

If the treatment of akathisia requires the addition of a new medication (rather than dose lowering or antipsychotic switching), overall, propranolol has the most evidence to support its use. Although published trials have methodological limitations, the overall body of evidence suggests some benefit with propranolol for subjective and objective symptoms of akathisia, as well as global ratings. Limitations in the current evidence include the short duration of all treatment trials, making it difficult to decide how long propranolol, if helpful, should be continued. Evidence to support the use of metoprolol is extremely limited and at a high risk of bias. The limited evidence available for nadolol suggests it is no better than placebo. If propranolol is prescribed, clinicians should review its contraindications before starting treatment and monitor blood pressure and heart rate in the supine and standing position, as propranolol can cause hypotension and bradycardia, which can be exacerbated by antipsychotic medications. Treatment should be started at a low dose (e.g., 10 mg twice daily), and gradually titrated based on clinical response and adverse effects. For patients requiring higher doses, a sustained release formulation is available (60 mg capsules or higher), which may reduce dosing frequency to daily or twice daily. A minimum treatment duration of 5 days is suggested to evaluate efficacy, unless intolerable adverse effects occur.

Recommendation (Grade B). If adjunctive medication is required for the treatment of akathisia, clinicians should consider a trial of propranolol as a first-choice option, after reviewing contraindications and associated precautions on a per-patient basis.

Anticholinergic Medications

Benztropine (Level of Evidence 1-). There are 2 trials of the anticholinergic benztropine v. placebo for the treatment of antipsychotic-induced akathisia.[54,64] Both trials had a high risk of bias (class III). One trial evaluated oral benztropine at an unusually high dose of 6 mg for 12 days in 28 participants, most of whom were diagnosed with schizophrenia (Adler 1993). Benztropine treatment resulted in significant improvement in akathisia compared to placebo. The other trial evaluated intravenous benztropine at a dose of 2 mg in 6 individuals with schizophrenia or bipolar disorder. All patients received a single injection and were evaluated up to 60 min after the injection. Global and subjective rating of

akathisia were significantly lower with benztropine than placebo, whereas the objective ratings were not.

Two trials have compared benztropine to other drugs for the treatment of antipsychotic-induced akathisia.[65,66] Both trials had a high risk of bias (class III and IV), and neither employed a non-inferiority design. The Class IV trial of 17 individuals treated for 2 to 5 days with up to 4 mg of benztropine found that, compared with propranolol,[65] benztropine was less effective, with no change in objective ratings of akathisia and only a small decrease in subjective ratings. Significant worsening in tests of recent memory were associated with benztropine use. The Class III trial[66] of 44 individuals treated for 28 days with up to 8 mg of benztropine reported a significant improvement in akathisia from baseline to endpoint, which was similar in magnitude to amantadine.

Biperiden (Level of Evidence 1-). Two trials have compared biperiden to placebo[67,68] for the treatment of antipsychotic-induced akathisia. Both trials had a high risk of bias (Class III). One trial[68] compared up to 18 mg per day of oral biperiden to placebo for 4 weeks in 15 psychiatric in-patients with antipsychotic-induced akathisia. Compared to placebo, treatment with biperiden resulted in a significant decrease in akathisia scores. The other trial[67] compared the intramuscular injection of 2.5 mg of biperiden (up to 3 times, every 2 hours) to placebo for 6 hours in 30 individuals. Over time, there was a decline in akathisia scores on all Barnes Akathisia Rating Scale items, but this was not different between the treatment groups.

One trial with a high risk of bias (Class IV) compared a single injection of intravenous biperiden to intramuscular biperiden in 23 individuals requiring the rapid relief of antipsychotic-induced akathisia.[69] Intravenous administration of biperiden resulted in the rapid relief of symptoms and amelioration of akathisia for at least 4 hours in 17 individuals. Side effects included confusion, drowsiness, dizziness, palpitations, and dry mouth.

The evidence to support the use of the anticholinergic medications benztropine and biperiden for the treatment of antipsychotic-induced akathisia is extremely limited and at high risk of bias, with inconsistent findings among trials regarding efficacy. The doses used exceed those currently recommended, and the adverse effects of anticholinergic medications, including memory impairment, are of great concern in patients with schizophrenia. Some data suggest that anticholinergic medications may be preferentially helpful in patients with akathisia and co-existing parkinsonism. A naturalistic study of 20 patients with akathisia treated with anticholinergic medications found that only those with clinically significant co-existing parkinsonism experienced amelioration of their akathisia symptoms with anticholinergic medication.[6] Further, treatment trials of anticholinergic medications for akathisia that included a higher proportion of individuals with co-existing parkinsonism have reported greater benefit with therapy.[70]

Recommendation (Grade B). Considering the limitations of the available evidence on anticholinergic medications and the risk of cognitive and anticholinergic adverse effects with these drugs, anticholinergic medications should not be routinely used for the treatment of akathisia.

5-HT2$_A$ Antagonists

Several medications share potent antagonistic activity at 5-HT2$_A$ receptors, and these have been assessed for their anti-akathisic effects, based on observations that antipsychotic agents with high 5-HT2$_A$ antagonist activity relative to D_2 antagonistic activity are associated with reduced risk for extrapyramidal symptoms.[71] Studied medications in this class include mianserin, mirtazapine, trazadone, and cyproheptadine. Mianserin and mirtazapine are noradrenergic and specific serotonergic antidepressants that are highly similar in chemical structure and receptor affinity. Mianserin is infrequently used in clinical practice. Relative to their other pharmacological effects, they both share very high binding affinity to histamine-1 receptors.

Mianserin (Level of Evidence 1-). There are 2 class II studies (low risk of bias) comparing mianserin to placebo for the treatment of antipsychotic-induced akathisia in individuals with schizophrenia or schizoaffective disorder.[72,73] Both trials evaluated mianserin at a dose of 15 mg, for a treatment period of 5 days in 90 individuals. Significant improvement in the Barnes Akathisia Rating Scale subjective, distress, and global subscales with mianserin relative to placebo was seen in both studies, whereas improvement in the objective subscale was only demonstrated in 1 of the 2 studies. The most common adverse effect associated with mianserin use was sedation.

Mirtazapine (Level of Evidence 1-). There are 2 trials comparing mirtazapine to placebo (and also to propranolol in one trial) for the treatment of antipsychotic-induced akathisia in individuals with schizophrenia.[53,74] Both trials used mirtazapine at a dose of 15 mg, and evaluated the response after 5 or 7 days. Trials were rated at low[53] and high[74] risk of bias. Between the 2 studies, 116 individuals participated in the trials. Both studies reported significant improvement in the global subscale of the Barnes Akathisia Rating Scale with mirtazapine relative to placebo. Significant improvement in the objective subscale was also noted in one study,[74] whereas the other study demonstrated a gradual improvement in the objective, subjective, and distress subscales that was not statistically significant.[53] In the more recent study, propranolol was used as an internal control; the study was not powered to compare mirtazapine and propranolol statistically. Improvements were very similar between the 2 active medications. No aggravation of psychotic symptoms was reported, and the most common side effect associated with mirtazapine use was sedation.

Trazodone (Level of Evidence 1-). There is one published study of trazodone v. placebo[75] for the treatment of antipsychotic-induced akathisia, which was rated at a low risk of bias (Class II). This trial included 13 inpatients with schizophrenia or schizoaffective disorder who were treated for 3 days with trazodone 100 mg and placebo in a crossover study. The trial reported significant improvement with trazodone compared with placebo in all subscales of the Barnes Akathisia Rating Scale. No worsening of psychosis or other adverse effects were associated with trazodone treatment.

Cyproheptadine (Level of Evidence 1-). There is one Class II trial comparing cyproheptadine to propranolol[59] in 30 hospitalised adults with schizophrenia. Participants were treated with cyproheptadine 16 mg per day or propranolol 80 mg per day for 4 days. Significant improvement was observed from baseline to endpoint in the total score on the Barnes Akathisia Rating Scale in both cyproheptadine- and propranolol-treated participants, with no difference between groups. Adverse effects of treatment were not assessed.

As a class, there is limited evidence to support the use of 5HT2A antagonists for the treatment of akathisia, with the 2 trials of mirtazapine including the greatest number of participants. All trials were of short duration (longest trial 7 days).

Recommendation (Grade B). When propranolol is contraindicated, ineffective, or not tolerated and long-term pharmacological management of akathisia is anticipated, a trial of a mirtazapine may be considered.

Benzodiazepines: Clonazepam (Level of Evidence 1-)

There are 2 published trials comparing clonazepam to placebo for the treatment of antipsychotic-induced akathisia.[76,77] Both trials were conducted in individuals with psychosis, and were rated at a high risk of bias (Class III). Both trials were small, including 27 participants overall, and treatment duration ranged from 7 to 14 days. Clonazepam dose ranged from 0.5 to 2.5 mg daily. Both trials reported significant improvement in akathisia symptoms relative to placebo. No major adverse effects were reported in either trial, with only one patient having mild drowsiness in one of the studies.

The evidence to support the use of clonazepam for the treatment of antipsychotic-induced akathisia is limited and with a high risk of bias. Both studies, however, reported benefits with treatment and that the treatment is well tolerated. Doses of clonazepam should be started at 0.5 mg, and slowly titrated based on effect, with the goal of using the lowest effective dose. As controlled trials were of short duration, and long-term benzodiazepines use is associated with tolerance, risk of dependence, and cognitive side effects, clinicians should consider gradual tapering of the medication after symptoms stabilize.

Recommendation (Grade B). Clonazepam may be considered as a short-term therapy option for the treatment of antipsychotic-induced akathisia.

Vitamin B6 (Level of Evidence 1+)

There are 2 published trials comparing vitamin B6 with placebo for the treatment of antipsychotic-induced akathisia.[72,78] Both trials were performed in inpatients with schizophrenia or schizoaffective disorder, and were rated at low risk of bias (Class II). In total, 80 individuals participated in these 2 trials, which were both conducted for a period of 5 days, using a dose of 600 mg or 1,200 mg daily. Both trials reported significant improvement with vitamin B6 relative to placebo on the Barnes Akathisia Rating Scale subjective and global subscales, but not on the objective subscale. A significantly greater proportion of vitamin B6-treated individuals had a reduction of at least 2 points on the global subscale in both studies. Adverse effects of treatment were not formally studied or reported in either study.

The evidence to support the use of vitamin B6 has a low risk of bias but limited to 2 short-term studies with relatively small sample sizes. Chronic administration (more than 12 months) of oral vitamin B6 in amounts exceeding 1,000 mg per day can cause a severe and progressive sensory neuropathy.[79,80]

Recommendation (Grade A). In patients failing to respond to alternative treatments for persistent antipsychotic-induced akathisia, short-term treatment with vitamin B6 may be considered. Clinicians prescribing vitamin B6 should exercise caution, given the limitation of the trial evidence (small sample size, short duration) and the ability of this treatment to cause an irreversible and severe neuropathy when used long term.

Other Medications

Many other medications have been assessed as potential treatments for antipsychotic-induced akathisia. Although some results are promising, the current evidence available on the potential risks and benefits for these agents as treatments for akathisia is insufficient to allow for clear practice recommendations. Medications assessed include amantadine (one Class III trial v. benztropine),[66] apomorphine (one Class III trial v. placebo),[81] zolmitriptan (one Class III trial v. propranolol),[61] clonidine (2 class IV studies),[62,82] gabapentin (one Class IV study),[83] and pregabalin (one Class IV study).[84] The results of these trials are described in the Supplemental Appendix.

Conclusion

The treatment of antipsychotic-induced akathisia should be personalised, incorporating thoughtful evaluation of a patient's history of therapeutic response to medication and the adverse effects experienced. The initial approach to treatment should be to consider antipsychotic dose reduction, cessation of antipsychotic polypharmacy, and switching to an

antipsychotic with a perceived lower liability for akathisia, before the use of any additional medication. However, such strategies are not without hazard, and there should be clinical concern around reduction to a sub-therapeutic dose when reducing the dosage and possible destabilization of the illness when switching antipsychotic medications. Further, it could be argued that the relative liability of individual antipsychotic medications for akathisia has not yet been reliably established.

The therapeutic options for akathisia are limited.[10,70] The evidence supporting the most commonly used pharmacological interventions, such as switching to an antipsychotic with a perceived lower liability for the condition, or prescribing a beta-adrenergic blocker or antihistaminic/anticholinergic agent, remains limited. Some of the treatment trials in acute akathisia were published several decades ago and not all used validated scales for the measurement of the condition. Nevertheless, the choice of intervention should probably favour the more established treatments, with careful consideration of any contraindications to use and potential side effects. The limitations of the evidence for risk-benefit should be acknowledged and prompt caution, particularly with respect to the duration of use of concomitant medication.

Further large scale, randomised controlled trials are needed to test potential treatments for antipsychotic-induced akathisia and thus improve the evidence base and expand the therapeutic options. For example, given the success of both gabapentin and pregabalin in the treatment of restless legs syndrome[85] and similarities between restless legs syndrome and akathisia, trials with these agents may be worthwhile. In the meantime, akathisia currently remains a frequent adverse effect of antipsychotic use, and clinicians should strive to prescribe antipsychotic medication judiciously and remain vigilant in monitoring for the symptoms and signs of the condition in their patients.

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Supplemental Material

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