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Akathisia

Schizophrenia and related psychoses CHAPTER 1 Akathisia Akathisia is a fairly common adverse effect of most antipsychotic medications, although the risk of developing akathisia varies markedly between such medications.1–3 For example, a 2023 dose–response meta-analysis4 investigating antipsychotic-induced akathisia with haloperidol and 16 SGAs (not including clozapine) found that the risk was minimal with sertindole and quetiapine but high with haloperidol and lurasidone. The risk of akathisia tended to increase with dose, but the dose–response curves differed between medications, plateauing at a certain dose with some medications, such as amisulpride, haloperidol and risperidone, but increasing beyond the licensed dose range with others, such as lurasidone and lumateperone. This meta-analysis4 also confirmed the risk of akathisia with partial agonist to be greatest with cariprazine and lowest with brexpiprazole. The core feature of akathisia is mental unease and dysphoria characterised by a sense of restlessness.5,6 There is commonly a compulsion to move and a characteristic pattern of motor restlessness, which, when severe, can cause patients to pace up and down and be unable to stay seated for more than a short time.5,6 There is a phenomenological overlap between antipsychotic-induced akathisia and the restless legs syndrome and possibly an overlap in pathophysiology.7,8 The subjective experience of akathisia can be discomfiting and distressing; an association with suicidal ideation has been postulated9,10 but remains uncertain. There is some evidence to suggest that the risk of akathisia may be mitigated by avoiding high-dose antipsychotic medication, antipsychotic polypharmacy and a rapid increase in dosage.5,11–13 There is limited evidence on the benefit–risk balance for pharmacological treatments of antipsychotic-induced akathisia, even those most commonly used, such as switching to an antipsychotic medication with a lower risk of akathisia or adding a beta-adrenergic blocker, 5-HT2A antagonist or anticholinergic agent.14,15 Nevertheless, a 2024 systematic review and meta-analysis of adjunctive treatments identified 15 eligible studies of 10 treatments.16 Mirtazapine, biperiden and vitamin B6 emerged as the most efficacious, with vitamin B6 judged to have the most favourable efficacy and tolerability profile. Trazodone, mianserin and propranolol were considered effective alternative treatments, albeit with a slightly less favourable risk–benefit balance. However, given the lack of robust evidence of efficacy for such adjunctive treatments, particularly in the medium to long term, it is probably prudent to initially consider reduction of the antipsychotic dose or switching to an antipsychotic medication with a lower liability for the condition. The following diagram suggests a programme of treatment options for persistent, antipsychotic-induced akathisia.

Reduce the dose of the patient’s current antipsychotic medication, switch from antipsychotic polypharmacy to monotherapy (if possible) or slow rate of dosage increase17,18 CHAPTER 1 Ineffective/not appropriate Switch to an antipsychotic medication with a lower liability for akathisia,

such as quetiapine or olanzapine19–21 (lowest effective dose possible) (Clozapine also an option in treatment-resistant schizophrenia)22 Ineffective/not appropriate to switch Consider propranolol: 30–80mg/day11,23,24 (start at 10mg three times a day) NB Note contraindications (asthma, bradycardia, hypotension etc.) Not effective/contraindicated Consider mirtazapine (15mg/day) or trazodone (50mg/day) or mianserin (30mg/day) (5HT2A antagonists)16,25–28 Not effective/not tolerated Consider an antimuscarinic drug18 (e.g. benzatropine 6mg/day) Weak support for efficacy29–31 and risk of anticholinergic adverse effects, including cognitive impairment, but may be effective where other EPS present5,11,14 Ineffective/no other EPS Consider cyproheptadine 16mg/day24,32 Ineffective Consider a benzodiazepine17,18 (e.g. diazepam up to 15mg/day, clonazepam 0.5–3mg/day) Ineffective Consider clonidine 0.2–0.8mg/day18,33 Effective Continue at reduced dose Effective Continue Effective Continue if no contraindications Continue Effective Continue, but attempt withdrawal after several months Effective Effective Continue, if no contraindications Continue, but attempt slow withdrawal after 2–4 weeks (risk of dependence) Effective Effective Continue if tolerated; withdraw very slowly (Continued)

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