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Mirtazapine for antipsychotic-induced acute akathisia: a systematic review and meta-analysis of randomized placebo-controlled trials

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Abstract

Objective: To conduct a systematic review and meta-analysis of randomized placebo-controlled trials of mirtazapine for the treatment of antipsychotic-induced acute akathisia (AIAA).

Methods: Studies were identified using online searches of PUBMED/MEDLINE and Cochrane database (CENTRAL), along with websites recording trial information such as www.clinicaltrials.gov, www.controlled-trials.com, and www.clinicalstudyresults.org. The study eligibility criteria were randomized, double-blind clinical trials comparing mirtazapine with placebo for AIAA with standardized rating for akathisia as outcome measure. The methodological quality of included trials was assessed using the Jadad Scale. Separate meta-analyses were undertaken for each outcome (response rate and complete remission) and treatment effects were expressed as Mantel–Haenszel risk ratio (RR). Fixed-effect meta-analysis was performed as heterogeneity was not significant. Number need to treat (NNT) as a measure of relative treatment effectiveness was calculated.

Results: A systematic review of the literature revealed six studies that had assessed mirtazapine for the treatment of AIAA. Of these, two studies ($n = 86$) met the review inclusion criteria and were included in the final analysis. A meta-analysis was performed to see the effect size of response rate and complete remission. For response rate, RR was 6.67 [95% confidence interval (CI) 2.14–20.78], favoring mirtazapine compared with placebo, and the overall effect was significant ($p = 0.001$, NNT 4, 95% CI 2.6–8.6). For complete remission, RR was 6.20 (95% CI 1.74–22.08), favoring mirtazapine compared with placebo, and the overall effect was significant ($p = 0.005$, NNT 5, 95% CI 2.9–11.6).

Conclusions: Although limited to only two studies and small sample, existing data support the efficacy of mirtazapine for the treatment of AIAA, with one in four patients showing partial response and one in five patients showing complete remission.

Keywords: akathisia, meta-analysis, mirtazapine, systematic review

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Introduction

Akathisia is a clinical syndrome characterized by the subjective sense of unease or restlessness, or observable motor manifestations including shuffling or tramping movements of the legs and feet [Barnes and Braude, 1985]. It is commonly associated with antipsychotic medications, both first generation and atypical [Kumar and Sachdev, 2009], as well as antidepressants, including tricyclics and selective serotonin reuptake inhibitors (SSRIs). Estimates of the prevalence of akathisia in people treated with antipsychotics vary from 20% to 75%, occurring more frequently in the first 3 months of treatment [Ayd, 1961; Sachdev, 1995].

There are several clinical implications of identifying akathisia. Its presence suggests higher rates of psychopathology and poor response to pharmacotherapy [Van Putten *et al.* 1984; Newcomer

et al. 1994; Duncan *et al.* 2000]. It is also identified as a predictor for development of tardive dyskinesia [Goswami and Channabasavanna, 1984]. Furthermore, the marked distress associated with akathisia has been associated with impulsive suicide attempts [Shear *et al.* 1983; Drake and Ehrlich, 1985; Wirshing *et al.* 1992; Hansen and Kingdom, 2006]. All these can contribute to noncompliance with antipsychotic drug treatment leading to increased risk for relapse [Barnes, 2003]. All these factors warrant early identification and treatment.

Antipsychotic-induced akathisia has been described as acute or tardive: the former occurs within 6 weeks of starting antipsychotics, whereas the later occurs after 3 months [Sachdev, 1995]. There is evidence to suggest differences in the clinical manifestation and response to treatment in acute and tardive akathisia. The pathophysiology of antipsychotic-induced acute akathisia (AIAA) is unknown. Involvement of dopaminergic and serotonergic pathways has been suggested as a possible mechanism. β blockers, benzodiazepines, and anticholinergics are currently recommended as the first-line treatment options in AIAA [Miller and Fleischhacker, 2000]. The high rate of nonresponse and their side effects prompted the search for effective anti-AIAA treatment alternatives. Recently, agents with marked serotonin 5-HT_{2A} antagonism (ritanserin, cyproheptadine, and mianserin) were found efficacious for AIAA [Miller *et al.* 1990, 1992; Weiss *et al.* 1995; Poyurovsky and Weizman, 1997, 2001b; Stryjer *et al.* 2004].

Mirtazapine is a novel antidepressant that acts centrally to increase both noradrenergic and serotonergic neurotransmission. It is structurally and pharmacologically similar to mianserin and exhibits marked 5-HT_{2A} antagonism. Common side effects include sedation, weight gain and increased appetite. Recent studies have shown that mirtazapine is useful for the treatment of AIAA [Poyurovsky and Weizman, 2001a; Wilson, 2005; Ranjan *et al.* 2006; Poyurovsky *et al.* 2003, 2006, 2014], although a few case reports of akathisia, both acute and tardive, induced by mirtazapine have been reported [Girishchandra *et al.* 2002; Gulsun and Doruk, 2008; Ozyildirim and Kosecioglu, 2009; Markoula *et al.* 2010]. As the effect of first-line agents for AIAA is variable, we reviewed existing literature to identify if enough evidence is available for mirtazapine. We conducted a systematic review and meta-analysis with an objective to determine whether mirtazapine is effective for the treatment of AIAA.

Methods

In our systematic review and meta-analysis, we adhered to the recent update of preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [Moher *et al.* 2009]. The flow of studies is summarized in Figure 1.

Data sources and search strategy

Studies were identified using online searches of PUBMED/MEDLINE and Cochrane database (CENTRAL). Also, websites recording trial information such as www.clinicaltrials.gov, www.controlled-trials.com, and www.clinicalstudyresults.org were searched for relevant studies. Searches were conducted using combination of terms 'antipsychotics', 'neuroleptic', 'akathisia', and 'mirtazapine'. We inspected the reference lists of all identified studies, including existing reviews for relevant citations. The search was restricted to publications in the English language.

Study selection: inclusion criteria

One reviewer (SKP) initially evaluated the abstracts from the literature search. The following criteria were used to identify the studies:

1. Randomized, double-blind clinical trials comparing mirtazapine with placebo for AIAA.
2. Outcome measures including standardized rating on a scale for akathisia (e.g. Barnes Akathisia Rating Scale).

Data extraction

Two reviewers (SKP and SK) decided, independently, whether individual studies met the inclusion criteria. Any discrepancy was resolved after discussion with RVB. A standardized form was used, and extracted data which included patient and study characteristics, outcome measures, and study results.

Assessment of methodological quality of studies

The methodological quality of included trials in this review was assessed using the Jadad Scale [Jadad *et al.* 1996]. It includes three items: (1) Was

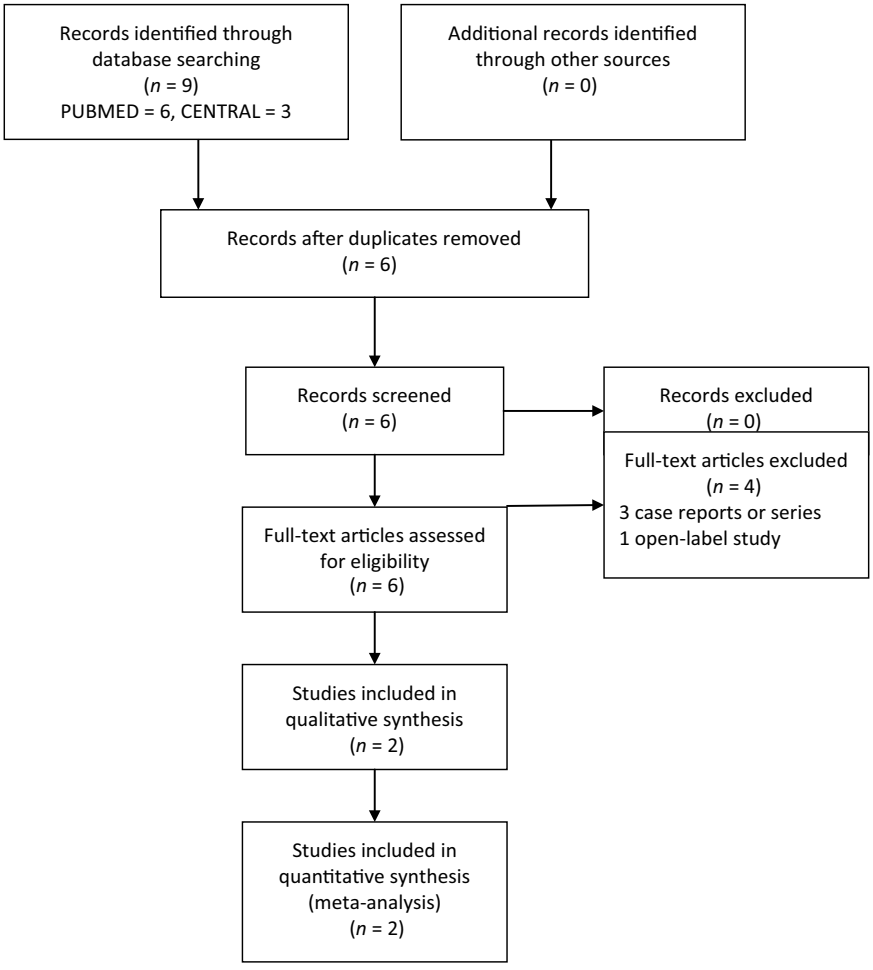

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 flow diagram.

the study described as randomized? (2) Was the study described as double blind? (3) Was there a description of withdrawals and drop outs? Scoring was done as follows: one point for a positive answer and one point deducted if either the randomization or the blinding/masking procedures was inadequate. Cutoff of two points on the Jadad Scale was considered.

Quantitative data synthesis

Meta-analyses were undertaken to estimate overall treatment effects where the trials were considered to be similar enough to combine using RevMan 5 version. This decision was based on assessing similarity of trial characteristics as well as results. A separate meta-analysis was undertaken for response rate (at least two-point reduction in the Barnes Akathisia Scale (BAS) Global Scale) and complete remission (0 or 1 on BAS Global Scale) as outcome measures. Treatment effects were expressed as Mantel–Haenszel risk ratio (RR) as outcome was categorical with 95% confidence interval (95% CI). Homogeneity among studies was tested using Cochran's Q test and I^2 statistic, in which more than 50% indicates a moderate amount of heterogeneity [Higgins *et al.* 2003]. If significant statistical heterogeneity was detected (Cochran's Q test $p < 0.1$ or I^2 value $> 50\%$), random effects estimates were calculated. Otherwise, the fixed-effect model was used for analysis. When overall results were significant, the number need to treat (NNT) as a measure of relative treatment effectiveness was calculated on an intent-to-treat basis.

Results

Studies included

The combined search strategies identified six papers on use of mirtazapine in AIAA after removing duplications (Figure 1). Among the three papers in CENTRAL, two [Poyurovsky *et al.*

Table 1. Characteristics of included studies.

Study	Methods	Participants	Intervention	Outcome
Poyurovsky *et al.* [2003]	Allocation: randomized Blinding: double Duration: 5 days	Diagnosis: schizophrenia *N* = 26	1. Mirtazapine 15 mg daily, *N* = 13 2. Placebo, *N* = 13	BAS, PANSS, HAM-D, SAS
Poyurovsky *et al.* [2006]	Allocation: randomized Blinding: double Duration: 7 days	Diagnosis: schizophrenia, delusional disorder, major depressive disorder with psychotic features *N* = 60	1. Mirtazapine 15 mg daily, *N* = 30 2. Placebo, *N* = 30	BAS, BPRS, HAM-D, SAS

BAS, Barnes Akathisia Scale; BPRS, Brief Psychiatric Rating Scale; HAM-D, Hamilton Rating Scale for Depression; PANSS, Positive and Negative Syndrome Scale; SAS, Simpson–Angus Scale.

2002, 2003] were identical studies based on sample, methodology and results, but the Poyurovsky *et al.* [2003] paper used intent-to-treat analysis and reported results from 26 patients. Both the Poyurovsky studies were also identified through a PUBMED search [Poyurovsky *et al.* 2003, 2006]. Four studies were excluded as they were case reports or case series [Poyurovsky and Weizman, 2001a; Wilson, 2005; Ranjan *et al.* 2006; Poyurovsky *et al.* 2014]. In a case study, Poyurovsky and Weizman observed a reduction of AIAA (that did not improve with trial of biperiden 4 mg twice daily for 5 days, and subsequently diazepam 10 mg for 3 days) after the second day, with the addition of a morning dose of 15 mg mirtazapine [Poyurovsky and Weizman, 2001a]. There was recurrence of akathisia with discontinuation of mirtazapine, which improved after restarting medication. It was tolerated well with mild transient sedation as an adverse effect. Wilson found low-dose mirtazapine (7.5 mg) reduced akathisia with antipsychotics in three patients having bipolar disorder, without induction of mania [Wilson, 2005]. Improvement was noted after 2–7 days, and only case 3 could be weaned off mirtazapine over a month without recurrence, whereas case 1 could be maintained on 3.75 mg dose. In another case series (n = 5), Ranjan and colleagues reported reduction in AIAA with the addition of 15 mg mirtazapine, with an additional benefit for depressive symptoms [Ranjan *et al.* 2006]. Improvement was noted after 3 days in three patients, and in the other two patients after 1–2 weeks. In an open-related trial, Poyurovsky and colleagues studied mirtazapine 15 mg daily for the treatment of aripiprazole-related akathisia. They found significant improvement in five of eight (62.5%) patients, and partial improvement in another patient. There was mild transient sedation in three patients, without any aggravation of psychosis [Poyurovsky *et al.* 2014]. Finally, two studies [Poyurovsky *et al.* 2003, 2006] met the review inclusion criteria (total 86 subjects) and were included in the final analysis. Characteristics of included studies are summarized in Table 1. In one study, only mirtazapine and placebo arm values were included in the meta-analysis [Poyurovsky *et al.* 2006].

Study quality

Both of the studies were described as randomized and were double blind. Dropout rates were mentioned in both the studies, and varied from 11.2% to 14.2%. Concealment of allocation was not adequately reported in both studies. Therefore, as it was unclear how randomization sequences were kept concealed, it is likely that the studies are prone to at least a moderate degree of bias [Juni *et al.* 2001].

Meta-analysis

Forest plots for meta-analyses for response rate (at least two-point reduction in BAS Global Scale) and complete remission (0 or 1 on BAS Global Scale) are presented in Figures 2 and 3. For response rate, test for heterogeneity was not significant (p = 0.95, I^2 = 0%); therefore the fixed-effects model was used. Mantel–Haenszel RR for response rate was 6.67 (95% CI 2.14–20.78), favoring mirtazapine compared with placebo, and the overall effect was significant (p = 0.001). NNT for response rate in the mirtazapine group compared with placebo was calculated as 4 (95% CI 2.6–8.6). For complete remission of akathisia, the test for heterogeneity was not significant (p = 0.62, I^2 = 0%); therefore the fixed-effects model was used. The Mantel–Haenszel RR for complete remission was 6.20 (95% CI

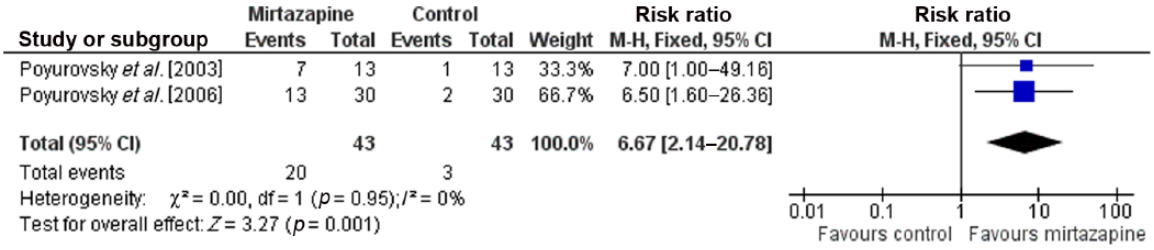

Figure 2. Forest plot showing response rate (at least two-point reduction in BAS Global Scale) in randomized controlled trials comparing mirtazapine with placebo for antipsychotic-induced acute akathisia ($N = 86$). CI, confidence interval; M-H, Mantel–Haenszel.

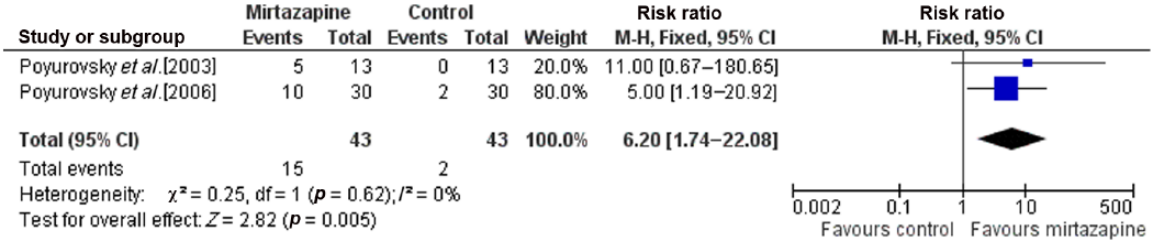

Figure 3. Forest plot showing complete remission (0 or 1 on BAS Global Scale) in randomized controlled trials comparing mirtazapine and placebo for antipsychotic-induced acute akathisia ($N = 86$). CI, confidence interval; M-H, Mantel–Haenszel.

1.74–22.08), favoring mirtazapine compared with placebo, and the overall treatment effect was significant ($p = 0.005$). NNT for complete remission in the mirtazapine group compared with placebo was calculated as 5 (95% CI 2.9–11.6). Mirtazapine was well tolerated in these studies, with sedation as the most common adverse effect.

Discussion

There is a paucity of studies examining the efficacy of mirtazapine for the treatment of AIAA (only two studies, $N = 86$). Nevertheless, existing data support the efficacy of mirtazapine for the treatment of AIAA, with RR 6.67 (95% CI 2.14–20.78) for response and 6.20 (95% CI 1.74–22.08) for complete remission. The effect size (NNT) for the efficacy was high, with one in four patients showing partial response and one in five patients showing complete remission. The dose of mirtazapine used in both studies was 15 mg, given as a morning dose, and the most common adverse effect reported was sedation. Considering the long half life of mirtazapine (20–40 h), it will be worthwhile to study whether bedtime dosing of mirtazapine will be effective for the treatment of AIAA with minimal sedation.

Traditionally, β blockers have been advocated as first-line treatment of AIAA. A meta-analysis [Lima *et al.* 2004] found three small randomized controlled trials (RCTs) (total $N = 51$), but this was considered as insufficient to recommend β blockers for akathisia. Another meta-analysis [Lima *et al.* 2002] found two small RCTs (total $N = 26$) which showed benzodiazepines may reduce the symptoms of AIAA using the outcome criterion of 'at least 50% remission' (two RCTs, $N = 26$, RR 0.09, 95% CI 0.01–0.6). But for the outcome of 'complete remission', pooled data showed no significant difference between the benzodiazepine and control groups (two RCTs, $N = 26$, RR 0.86, 95% CI 0.6–1.2). Also there was no evidence in favor of anticholinergic agents for antipsychotic-induced acute akathisia in another meta-analysis [Rathbone and Soares-Weiser, 2006].

Our review is limited by the number of studies included in the meta-analysis. The small number of studies did not allow us to conduct tests for publication bias. Also a sensitivity analysis was not performed in our study. No heterogeneity was found for the study variables across both the studies; therefore the fixed effects model was used. In both the studies [Poyurovsky *et al.* 2003, 2006], the duration of treatment varied from 5 to 7 days, therefore the longer term effects of mirtazapine are not known. We suggest that all future studies should respect standards of measuring outcomes and of reporting data in order to enhance the

comparability of study results. In addition, binary outcomes (response and remission) should be reported as they are easier to interpret and clinically relevant. Details regarding the allocation sequence and allocation concealment should be clearly described in all studies to prevent bias.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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