

Mirtazapine is sedating at low doses and stimulating at high doses: fact or myth? A systematic review of randomized controlled trials.

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Introduction

Mirtazapine is a widely prescribed psychotropic medication approved by the FDA for the treatment of major depressive disorder. In addition to its antidepressant effects, it is often used off-label to manage insomnia because of its sedating properties. Trainees are commonly taught that mirtazapine produces greater sedation at lower doses, whereas higher doses may have more activating effects due to increased noradrenergic activity that partially counteracts its antihistaminergic sedation. Although this teaching is frequently cited in clinical settings, it remains unclear whether these dose-dependent effects are strongly supported by empirical evidence or primarily derived from clinical observation. This systematic review of randomized controlled trials aimed to assess the literature for evidence supporting the widely held belief that lower doses of mirtazapine are more sedating, while higher doses are more stimulating.

Aims and Objectives

Aim:

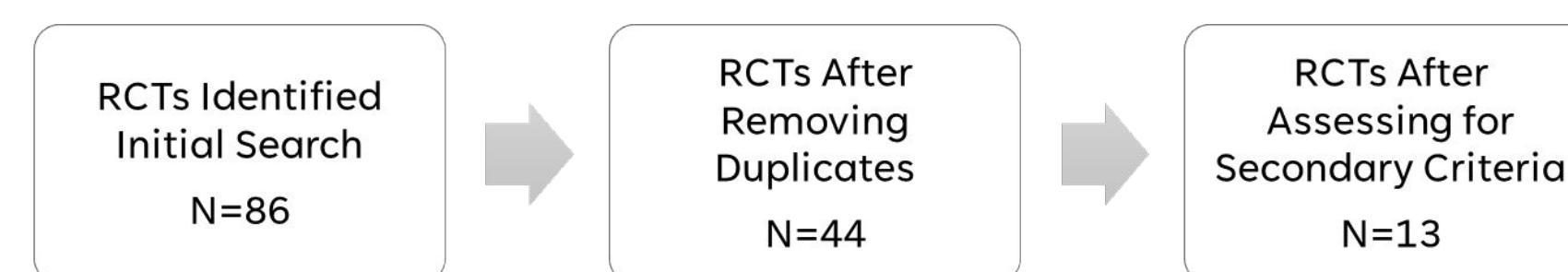
To determine whether randomized controlled trial evidence supports the widely held belief that mirtazapine is more sedating at lower doses and less sedating at higher doses.

Objectives:

- Conduct a systematic review of randomized controlled trials examining mirtazapine across a range of doses.
- Compare the effects of different mirtazapine dose ranges on sedation and sleep outcomes.
- Assess the statistical significance of reported sedative effects using validated sleep measures.
- Determine whether higher doses are associated with reduced sedation compared to lower doses.
- Identify gaps in the literature to inform future research on dose-dependent sedative effects.

Methods

A literature search of PubMed and OVID databases was conducted. The phrase “Mirtazapine AND Sleep” was utilized on both databases. The primary inclusion criteria encompassed randomized control trials involving mirtazapine. Secondary inclusion criteria encompassed: (1) article included medication dosages, (2) the effect of sedation was assessed in the article, (3) not confounded by other sedative medication, (4) not confounded by substance use, and (5) not confounded by significant medical issues. The research publications passing inclusion criteria were assessed, and their corresponding outcomes on sedation were included (Figure 1).



Results

A total of 86 randomized controlled trials were initially identified through the electronic database search. After removing duplicates, 44 articles remained and were further evaluated using secondary inclusion criteria. Ultimately, 13 independent, non-overlapping studies were included in the review, representing 1,005 participants from trials conducted between 1985 and 2022. The studies examined mirtazapine at doses ranging from 7.5 mg to 45 mg, compared with placebo and/or other antidepressants. Sedation was assessed using several measures, including the Jenkins Sleep Scale, Stanford Sleepiness Scale, and Pittsburgh Sleep Quality Index. Each study was analyzed to determine mirtazapine’s impact on sleep and sedation, as well as statistical significance. Across the 13 studies, there was no statistically significant reduction in sedation at doses above 15 mg, and two studies reported greater sedation at higher doses.

Table 1: RCTS Meeting Eligibility Criteria

1st Author, Year	Sample Size	Dosage(s) (mg)	Sleep Measurement Used	Notes
Karsten, 2017	n=19	7.5 mg	Leeds Sleep Evaluation Questionnaire Karolinska Sleepiness Scale	Mirtazapine increased total sleep time by half an hour and reduced the number of awakenings by 35–40%, increased deep sleep stage N3 compared to placebo.
Huang, 2022	n=450	Initiated at 15mg and increased to 30 mg within 1 week, max dose of 45mg	Hamilton Depression Rating Scale (HAMD) Quick Inventory of Depressive Symptomatology (QIDS-16-SR)	Patients showed significantly greater improvements in difficulty falling asleep and early wake, and significantly greater improvement in the depth of sleep from 2 to 8 weeks of treatment, and significantly greater improvement in difficulty falling asleep and early wake in weeks 2, 4, 6, and 8.
Winokur, 2003	n=19	Week 1, 15 mg Week 2 30 mg Week 3-8 45 mg	Polysomnographic (PSG)	Significant improvement in objective sleep physiology measures at 8 weeks. Improvements in sleep latency, sleep efficiency, and wake after sleep onset were significant after only 2 weeks of mirtazapine treatment.
Radhakishun, 1999	n=140	2 Groups: Fixed at 30 mg and Increasing from 15 to 30 mg	Bond and Lader’s Visual Analogue Mood Rating Scale (VAMRS) LSEQ	Patients receiving the fixed dose reported earlier sleep onset and longer duration. Mirtazapine in fixed and ascending nocturnal dosing regimens was found to facilitate sleep, but it does not generally reduce daytime alertness. The higher starting dose had greater beneficial effects on sleep initiation and duration.
Sato, 2013	n=5	15 mg	Line Analog Rating Scale (LARS) indicating present subjective alertness and sleepiness	Subjective sleepiness was significantly greater after mirtazapine administration in comparison to fluvoxamine and placebo at 120 minutes after administration and 180 minutes after administration. There was also a correlation between H1 receptor occupancy and subjective sleepiness during these periods.
Davis, 2020	n=78	15mg titrated up to 45 mg for 8 week period	Pittsburgh Sleep Quality Index (PSQI)	Fewer participants in the mirtazapine group required a rescue sleep medication. 28.2% of participants in the placebo group required rescue sleep medication in comparison to 7.7% in the mirtazapine group. In the mirtazapine group, 2 participants experienced increased sedation to the extent that they required a decreased dosage. PSQI scores between the groups did not show significant differences but this may be attributed to the usage of rescue sleep medications as needed.
Benkert, 2006	n=172	Day 1-4: 30mg Day 5-42: 45	HAMD	Changes in the HAM-D Sleep disturbance factor were greater with mirtazapine than with venlafaxine at all assessments. The difference was statistically significant on days 5, 8, 11, and 43.
Koshmura, 2013	n=19	15mg	Stanford Sleepiness Scale (SSS)	Mirtazapine increased subjective sleepiness on both day 2 and day 9. The difference was statistically significant on day 2 (p=0.00).
Sorensen, 1985	n=250	5mg group, 15mg group, 30mg group	Sleep Questionnaire consisting of 11 items	All mirtazapine doses were superior to placebo in improving sleep (5 mg p <0.01, 15mg p <0.001, 30 mg p <0.001). 15mg of mirtazapine had an optimal effect on sleep because 5mg had no significant beneficial effect on the number of nighttime awakenings when compared to the placebo and 30mg was associated with significantly more sleepiness in the morning. A dose-response relationship is demonstrated.
Yeepu, 2013	n=40	Started at 7.5 mg titrated to 15mg or 30mg	Jenkins Sleep Scale	The mirtazapine 30 mg group was found to have the highest proportion of insomnia responders at 90.91%, with the next highest being the mirtazapine 15 mg group at 75%, and placebo with the fewest at 40%.
Carly, 2007	n=12	4.5 mg, 15 mg, or placebo in 3 way crossover	SSS PSG	High-dose mirtazapine group had significantly lower arousal index on polysomnogram. Mirtazapine groups had lower daytime sleepiness scores than placebo but not significantly so.
Aslan, 2002	n=20	30 mg	PSG	Mirtazapine increased sleep efficiency index, decreased number of awakenings & duration of awakenings, increased slow wave sleep, and decreased time spent in stage 1 sleep.
Shen, 2009	n=28	30 mg	Maintenance of Wakefulness test (MWT)	Mean sleep latency decreased on day 2, but within a week was not significant and then normalized. After day 2 of treatment, alertness ratings recovered and by day 14, alertness ratings had increased to 18% higher than baseline levels.

Conclusions

This review supports the conclusion that, among the randomized controlled trials analyzed, there is no statistically significant evidence suggesting that mirtazapine becomes less sedating at higher doses. These findings challenge the commonly taught clinical assumption of dose-dependent activation and highlight the need for clinicians to rely on evidence-based guidance when counseling patients about expected side effects. Future research should focus on randomized controlled trials that directly compare the sedative effects of mirtazapine across multiple dose ranges to better clarify any potential differences. Greater clarity in this area may improve individualized treatment planning and optimize medication selection for patients with depression and comorbid sleep disturbances.

References

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