

FPIN's Clinical Inquiries

Antidepressants for the Treatment of Insomnia in Patients with Depression

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Clinical Question

Which antidepressant medications are most effective for treating insomnia in patients with depression?

Evidence-Based Answer

There is no single antidepressant or class of antidepressants that is most effective for the treatment of insomnia in patients with depression. The use of antidepressant medications can have a positive impact on sleep physiology, but does not seem to improve subjective ratings of sleep quality. (Strength of Recommendation: B, based on one qualitative study and one meta-analysis.)

Evidence Summary

The relationship between depression, insomnia, and treatment is complex. A meta-analysis of sleep and psychiatric disorders found that patients with comorbid sleep disturbances and depression typically have increased sleep latency, increased rapid eye movement (REM) sleep, increased midcycle awakening, decreased slow wave sleep, and shortened REM latency.¹ Therefore, selecting antidepressant agents that increase sleep continuity (i.e., uninterrupted sleep), prolong REM latency, and decrease REM sleep is one strategy for treating insomnia in patients with depression.²⁻⁵ Research on the impact of antidepressants on objective sleep measures is summarized in *Table 1*.²

Studies have consistently demonstrated differences between objective and subjective sleep measures in patients taking antidepressants.⁶ In a study comparing objective and subjective sleep measures in patients with depression, 18 patients (78 percent) showed at least a 30-minute over- or underestimation of

total sleep time. Twelve patients (52 percent) over- or underestimated total sleep time by at least 60 minutes when comparing their subjective sleep ratings with polysomnography.⁷

Research measuring the effect of antidepressants on subjective sleep ratings is sparse. There are no systematic reviews or meta-analyses. Subjective measures of sleep quality are often included as secondary outcomes in clinical trials of antidepressants. Existing studies are further limited by small sample size, short duration, incomplete data reporting, lack of a placebo arm, concurrent hypnotic use, or heterogeneity in rating instruments of perceived sleep quality.

Studies that measured subjective sleep ratings used the three sleep items on the Hamilton Rating Scale for Depression or the Leeds Sleep Evaluation Questionnaire.² These studies found that selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) improved subjective sleep measures in patients with depression. In addition, studies have shown that nefazodone, trazodone, or mirtazapine (Remeron) also can improve subjective sleep ratings compared with placebo, SSRIs, or TCAs in patients with depression.²

Recommendations from Others

For patients with depression and comorbid insomnia, the American Academy of Sleep Medicine recommends the addition of a low-dose, sedating antidepressant if not contraindicated. Low-dose trazodone, mirtazapine, doxepin, amitriptyline, or trimipramine (Surmontil) may be given in addition to another full-dose antidepressant.⁸ Guidelines from the American College of Physicians report conflicting evidence, with some studies indicating

Table 1. Impact of Antidepressants on Objective Sleep Measures

Drug	Short term (five to 10 days)			Long term (more than 21 days)			
	Continuity	REM sleep	REM sleep latency	Continuity	REM sleep	REM sleep latency	Withdrawal REM rebound
MAOI							
Phenelzine (Nardil)	∞	***	†††	∞	***	†††	†
SSRI							
Citalopram (Celexa), fluvoxamine, paroxetine (Paxil), and sertraline (Zoloft)	↔	**	†††	↔	**	††	†
Fluoxetine (Prozac)	↓	**	†	↓	*	†	∞
TCA							
Amitriptyline	↔	**	††	↑	*	††	†
Imipramine (Tofranil)	↔	**	†††	↔	*	††	∞
Other							
Bupropion (Wellbutrin)	∞	∞	∞	↔	↔/↓	†/↔	∞
Mirtazapine (Remeron)	↑	↔	↔	↑	↔	†/↔	∞
Nefazodone	↑	↔	↔	↑	↔	↔/↓	∞
Trazodone	↔/↑	*	†	↑	↔	†	∞

MAOI = monoamine oxidase inhibitor; REM = rapid eye movement; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

↔ = no change; ∞ = no data; ↑ = increase; ↓ = decrease; * = 10 to 30 percent decrease; ** = 30 to 60 percent decrease; *** = greater than 60 percent decrease; † = 30 to 100 percent increase; †† = 100 to 200 percent increase; ††† = greater than 200 percent increase.

Adapted with permission from Wilson S, Argyropoulos S. Antidepressants and sleep: a qualitative review of the literature. *Drugs*. 2005;65(7):932.

improved sleep ratings with escitalopram (Lexapro) over citalopram (Celexa), nefazodone over fluoxetine (Prozac), and trazodone over fluoxetine. However, the authors caution that in randomized controlled trials and multiple head-to-head trials, there is limited evidence for the comparative effectiveness of antidepressants in treating insomnia in patients with depression.⁹

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REFERENCES

1. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders. A meta-analysis. *Arch Gen Psychiatry*. 1992;49(8):651-668.
2. Wilson S, Argyropoulos S. Antidepressants and sleep: a qualitative review of the literature. *Drugs*. 2005;65(7):927-947.

3. Winokur A, Gary KA, Rodner S, Rae-Red C, Fernando AT, Szuba MP. Depression, sleep physiology, and antidepressant drugs. *Depress Anxiety*. 2001;14(1):19-28.
4. Gursky JT, Krahn LE. The effects of antidepressants on sleep: a review. *Harv Rev Psychiatry*. 2000;8(6):298-306.
5. Mayers AG, Baldwin DS. Antidepressants and their effect on sleep. *Hum Psychopharmacol*. 2005;20(8):533-559.
6. Ware JC. Tricyclic antidepressants in the treatment of insomnia. *J Clin Psychiatry*. 1983;44(9 pt 2):25-28.
7. Tsuchiyama K, Nagayama H, Kudo K, Kojima K, Yamada K. Discrepancy between subjective and objective sleep in patients with depression. *Psychiatry Clin Neurosci*. 2003;57(3):259-264.
8. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4(5):487-504.
9. Qaseem A, Snow V, Denberg TD, Forciea MA, Owens DK; Clinical Efficacy Assessment Subcommittee of American College of Physicians. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians [published correction appears in *Ann Intern Med*. 2009;150(2):148]. *Ann Intern Med*. 2008;149(10):725-733. ■