

# Antidepressant management of insomnia disorder in the absence of a mood disorder

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## ABSTRACT

Insomnia is the most common sleep disorder, and antidepressants are increasingly being used for its management. This article reviews the existing data concerning the use of antidepressants in the treatment of primary insomnia.

## KEYWORDS

insomnia, antidepressant, sleep disorder

## INTRODUCTION

Insomnia is the most common sleep complaint and for many individuals it can become a chronic problem.<sup>1</sup> Concerns about potential side effects of hypnotics, especially those affecting the benzodiazepine receptor, have prompted clinicians to seek alternative classes of medications for the treatment of sleep disorders. With the exception of doxepin, the use of antidepressants in the treatment of primary and secondary insomnia is not Food and Drug Administration (FDA)-approved; however, this practice has grown substantially in recent decades. Over a 10-year period from 1987-1996, antidepressant use for insomnia increased by 146% while hypnotic drug use declined by 53.7%.<sup>2</sup> In 2002, antidepressants were prescribed for insomnia approximately 1.53 more times than a hypnotic medication and comprised three of the four top medications prescribed.<sup>3</sup> Trazodone, amitriptyline, mirtazapine and doxepin are among the most commonly used agents.

The growing practice of antidepressant use for the management of insomnia contrasts the paucity of data available for the use of these agents in patients with sleep disorders. A majority of the available data in relation to the sedating properties of this medication class comes from experience with depressed individuals. Clinical guidelines from 2008 based on literature and consensus recommendations for the evaluation and management of chronic insomnia in adults recommend sedating antidepressants when insomnia is accompanied with depression or when other treatments have failed. However, these guidelines note that evidence is weak for the practice of antidepressant management of insomnia.<sup>4</sup> The aim of this article is to review the limited data that exist regarding the use of antidepressants in the treatment of primary insomnia in adults and to further understand the risk-benefit profile. A summary of the data is provided in Table 1.

## NOVEL ANTIDEPRESSANTS

### Trazodone

Trazodone is a serotonin (5HT) modulator approved by the FDA in 1981 under the original brand name Desyrel. It is indicated for major depressive disorder (MDD) at doses between 150-400mg/d (up to 600mg/d in the inpatient setting).<sup>5</sup> Trazodone has further been classified as a serotonin antagonist/reuptake inhibitor (SARI) based on its antagonism of 5HT<sub>2A</sub>, 5HT<sub>2C</sub> and serotonin reuptake receptors. This makes trazodone a "multifunctional" antidepressant. At low doses it acts mainly to antagonize 5HT<sub>2A</sub>, histamine H<sub>1</sub> and  $\alpha$ <sub>1</sub>-adrenergic receptors. This combination of receptor pharmacology is believed to contribute to trazodone's hypnotic actions.<sup>6</sup>

Use of trazodone for depression has decreased substantially, mainly due to unacceptable daytime sedation. Trazodone at the lower hypnotic dose (50-150mg)<sup>6</sup> is currently the most commonly prescribed antidepressant being used for primary insomnia,<sup>7</sup> and although limited, it has the most data for this off-label use. Walsh and colleagues compared the hypnotic efficacy of trazodone 50mg, zolpidem 10mg and placebo in 278 primary insomniacs with a double-blind, parallel-group design.<sup>8</sup> After one week, both zolpidem and trazodone produced significantly shorter self-reported sleep latency and significantly prolonged self-reported sleep duration compared to placebo. By week two zolpidem, but not trazodone, continued to show significant benefits in sleep duration. The authors concluded that at the doses studied, zolpidem might have some advantage over trazodone in primary insomnia.

In more recent years, five trials further explored the role of trazodone at doses varying from 25-150mg.<sup>9-13</sup> One trial administered caffeine to healthy volunteers to stimulate insomnia,<sup>9</sup> otherwise, the other four trials were conducted in primary insomniacs. Overall objective and

**Table 1. Antidepressants used in the treatment of insomnia**

AGENT/ STUDY	DOSES USED FOR INSOMNIA (mg/day)	USE CONSIDERATIONS/ COMMENTS	PHARMACO- KINETICS (Tmax and T½:)	PSG DATA <sup>14</sup>
<b>Novel Antidepressants</b>				
Trazodone	25-150	Risk of priapism Orthostatic hypotension	Tmax: 1-2 hours T½: 9 hours	TST ~SL ~W ? SWS Minimal ~REM
Mirtazapine	7.5-30	Increase weight gain	Tmax: 2 hours T½: 20-40 hours	TST ~SL ~S1 ? SWS
<b>Tricyclic Antidepressants (TCA)</b>				
Doxepin*	3-6	Take at least 3 hours after a meal Orthostatic hypotension Confusion and over-sedation in the elderly	Tmax: 3.5 hours fasting; 6.5 hours with a meal T½: 15 hours	TST ~W ~SL ~REM
Amitriptyline	10-100	Caution in overdose Cardiac conduction changes Orthostatic hypotension Anticholinergic effects Confusion and over-sedation in the elderly	Tmax: 2-5 hours T½: 15 hours	PLMs
Trimipramine	50-200	Caution in overdose Cardiac conduction changes Orthostatic hypotension Anticholinergic effects Confusion and over-sedation in the elderly	Tmax: 2 hours T½: 24 hours	
<b>Selective Serotonin Reuptake Inhibitors (SSRI)</b>				
Paroxetine	10-40	High anticholinergic activity Increase weight gain	Tmax: 5-6 hours T½: 15-21 hours	W ~TST S1 SL ~REM

\* Indicates an FDA approved indication for insomnia by the trade name Silenor

PLM: Periodic Limb Movement

PSG: Polysomnography

REM: Rapid Eye Movement

S1: stage 1 sleep

SL: Sleep Latency

SWS: Slow Wave Sleep

TST: Total Sleep Time

W: wake

subjective improvements in sleep were noted in all studies. This included decreased scores on a variety of sleep scales, increased total sleep time (TST), decreased sleep latency (SL), increased slow wave sleep (SWS), fewer nighttime awakenings and improvement in self-reported difficulty sleeping. These results show promise for trazodone as a hypnotic, but are limited by small sample sizes (not greater than 30 in any trial) and a short

study duration (all but two<sup>11,12</sup> did not exceed one week in duration).

The observations seen in trials with trazodone are congruent with polysomnography studies that demonstrate that trazodone may increase TST, decrease SL, increase SWS and has little to no effect on rapid eye movement (REM) sleep.<sup>14</sup> Trazodone has been investigated in a variety of other co-morbid conditions

including alcoholism, fibromyalgia, dysthymia, dementia and mainly depression.<sup>15</sup> These studies of varying methods support the notion that trazodone may be efficacious at improving sleep quality and/or duration.

As a hypnotic, trazodone offers some advantages over benzodiazepine and non-benzodiazepine hypnotics, which are currently approved for the treatment of insomnia. It is available as a generic agent, has low abuse potential,<sup>16</sup> has a relatively short half-life of 10-11 hours, has less impairment of performance compared to benzodiazepines,<sup>16</sup> has an unscheduled drug status, and lacks prescribing restrictions. These advantages should be considered in the context of the potential for serious side effects with trazodone, which include dizziness, orthostatic hypotension that increases fall risk, residual daytime sedation, psychomotor impairment, cardiovascular side effects and priapism.<sup>17</sup> At the present time, larger randomized trials of a longer duration are necessary to validate the popular use of trazodone in primary insomnia.

### Mirtazapine

Mirtazapine is commercially available under the trade name Remeron and was FDA approved solely for MDD in 1996.<sup>18</sup> As an antidepressant it is used at doses ranging from 15-45 mg/d, however, it is unclear if these doses are appropriate in the treatment of insomnia. Mirtazapine is a novel antidepressant, which acts as a potent inhibitor of 5HT<sub>2</sub> and 5HT<sub>3</sub>, central  $\alpha$ -2-adrenergic and histamine H<sub>1</sub> receptors. It is hypothesized that the action of mirtazapine on 5HT<sub>2</sub> and H<sub>1</sub> contribute to its highly sedating activity.<sup>14</sup> To the best of our knowledge, there is no research evaluating the use of mirtazapine in primary insomnia. All clinical trials assessing the role of mirtazapine on sleep parameters have been conducted either in healthy volunteers or in patients with co-morbid conditions, primarily depression. In healthy volunteers, mirtazapine increased sleep efficiency (SE), enhanced sleep continuity, decreased SL and reduced the frequency of awakening without any apparent decreases in the percentage of time spent in REM sleep.<sup>19,20</sup>

Winokur and colleagues evaluated the acute effects of mirtazapine across the full spectrum of antidepressant dosage range (15-45 mg/d) in six patients with MDD and subjective sleep complaints.<sup>21</sup> After two weeks, mirtazapine was associated with a significant increase in TST and SE and decrease in SL. A follow-up extension study of 19 subjects was conducted comparing the effects of mirtazapine (15-45 mg/d) versus fluoxetine (20-40 mg/d) on sleep physiology measures in an eight-week, double-blind, double dummy trial.<sup>22</sup> The same results

were concluded with regards to SE, SL and sleep continuity. Improvements in Hamilton Depression Rating Scale and sleep disturbance scores were further noted. As with healthy volunteers, no significant changes in total REM time or percentage of time spent in REM sleep were observed in either study.

More recently, the effect of mirtazapine on sleep quality in outpatients with MDD was assessed using the Pittsburg Sleep Quality Index (PSQI). After treatment with mirtazapine, the global PSQI score was significantly lower and SE was significantly higher compared to baseline.<sup>23</sup> Other studies have investigated the role of mirtazapine in improving insomnia in other co-morbid conditions, such as cancer and in perimenopausal women, and found similar results.<sup>15</sup>

In placebo-controlled trials, rates of somnolence with mirtazapine exceed 50%.<sup>24</sup> With a half-life of 20-40 hours, concerns for residual daytime sedation prompted investigation of mirtazapine's effect on psychomotor and driving performance in healthy volunteers and patients with depression. Initial doses of mirtazapine produced driving and psychomotor impairment; however, these effects lost significance over time and with increases in dose.<sup>24-26</sup> Significant subjective reports of feeling lethargic, drowsy, weak and decreased alertness and concentration were also detected.

While mirtazapine demonstrates robust effects in improving sleep continuity, efficiency and latency in depressed patients, it is unclear to what extent these findings can be generalized to primary insomnia. The importance of large-scale randomized clinical trials assessing the role and dose of mirtazapine in primary insomnia is especially of high demand as no trials have been conducted in this setting. Moreover, it appears that mirtazapine's sedating properties may be offset by noradrenergic activity at higher doses.<sup>24</sup>

### TRICYCLIC ANTIDEPRESSANTS

Sedating tricyclic antidepressants (TCAs) are widely used for their sleep-promoting effects. They may serve as alternatives to benzodiazepine receptor agonists when used at relatively lower than antidepressant doses. Unlike benzodiazepines, TCAs are not known to suppress deep sleep.<sup>27</sup> The sedating effects are attributed primarily to histamine-1 (H<sub>1</sub>) receptor blockade.<sup>28</sup> However, it is suggested that not all TCAs are sedating. Imipramine and desipramine are associated with insomnia and greater sleep disturbance.<sup>29,30</sup> Sedating TCAs include doxepin, amitriptyline, and trimipramine. Others include clomipramine, nortriptyline and dothiepin (not available

in the US). The evidence appears less clear for clomipramine.<sup>31</sup>

Factors in choosing a TCA over other sedating antidepressants may include co-morbid pain disorders, for which relatively lower doses of TCAs will manage both insomnia and pain. In addition, the lack of controlled drug status makes TCAs more favorable in individuals with a history of substance abuse. Compared to other sedating antidepressants, however, lower safety in overdose should be evaluated before recommending a TCA for insomnia in certain patients.

### **Doxepin**

Doxepin, approved under the trade name Silenor (Somaxon Pharmaceuticals) in March 2010, is the only antidepressant currently approved for insomnia. This product is marketed in lower dosage strengths (3 and 6mg non-scored tablets) compared to the product strengths originally marketed for MDD in 1969 (i.e., 10, 25, 50, 75, 100, 150mg capsules; 10mg/mL oral concentrate) such as Sinequan (Pfizer). Generics of some of these higher strengths are also available. Doxepin 3-6mg is specifically approved for the treatment of insomnia characterized by difficulties with sleep maintenance.<sup>32</sup> It is highly specific for the H<sub>1</sub> receptor at lower doses.<sup>28</sup> There have been several clinical trials confirming the efficacy of doxepin 1-6mg/day in adult<sup>33-35</sup> and elderly<sup>36-38</sup> patients with primary chronic insomnia. One of the earlier doxepin studies for primary insomnia in adults utilized 25-50mg for 4 weeks, improving TST in 20 adults.<sup>39</sup> Subsequent controlled studies systematically assessed significantly lower doses of doxepin for its effects on sleep.

Roth et al. evaluated the efficacy and safety of doxepin 1, 3, and 6mg in adults with primary insomnia.<sup>33</sup> The study evaluated traditional sleep maintenance parameters and found significant improvement, with the effect notably stronger for 3 and 6mg doses compared to 1mg. The adverse side effects profile was similar to placebo and no anticholinergic effects were reported. A similarly designed study evaluated sleep improvement in the elderly population (average age of 71 years).<sup>36</sup> As with the previous study, clinically relevant improvement in objective and subjective sleep maintenance occurred. The longest duration studied was 12 weeks of doxepin 1 and 3 mg in the elderly with chronic primary insomnia.<sup>37</sup> Rates of study discontinuation were lower in both doxepin groups (1mg: 9%; 3mg: 10%) compared to placebo (14%). Results indicated that both doses were well tolerated with no next-day residual impairment.

Nearly all trials of doxepin indicate improvement in wake after sleep onset (WASO), TST and SE on polysomnography. The effects on improving sleep latency and number of awakenings is mixed, however. Based on clinical trials, it appears that low-dose doxepin has a role in managing insomnia, even in the elderly. It may prove to be an agent with an enhanced benefit/risk ratio in this population. However, more long-term and head-to-head comparative trials with traditional hypnotics are needed to determine any advantages of this TCA when used for insomnia. It is unknown whether or not a 1 mg dosage strength of doxepin will be available by the manufacturer in the future.

### **Amitriptyline**

There are no controlled trials evaluating amitriptyline for insomnia in the absence of other medical conditions. Amitriptyline has been used for decades in providing long-term sleep-improving benefits in fibromyalgia (FM)<sup>40</sup> and is an antidepressant approved by the European League Against Rheumatism (EULAR) for the management of pain and improving function associated with FM.<sup>41</sup> A meta-analysis comparing amitriptyline 10-50mg/day, duloxetine and milnacipran to placebo in managing insomnia associated with FM found that amitriptyline was superior to the other two serotonin norepinephrine reuptake inhibitors (SNRIs) in reducing sleep disturbance, pain, and fatigue.<sup>42</sup> However, the methodological quality of the amitriptyline trials was poor.

TCAs are used in target patients who suffer from opiate-withdrawal insomnia. It is suggested that anticholinergic side effects of amitriptyline 25-100mg/day (mean dose 58mg) may be beneficial in relieving rhinorrhea and lacrimation in these patients while improving awakening from sleep (AFS) scores.<sup>43</sup> Despite lack of evidence of efficacy in large trials, low-dose amitriptyline continues to be one of the most commonly used TCAs in clinical practice for managing insomnia, even in the absence of depression.

### **Trimipramine**

One of the only double-blind studies using another TCA in primary insomnia comes from Riemann et al. comparing trimipramine versus placebo and lormetazepam (available in Germany).<sup>44</sup> Doses of 50-200mg of trimipramine per day for four weeks increased total sleep time by 60 minutes, but the small sample size of 15 contributed to a non-statistically significant result ( $P=0.1007$ ). However, compared to placebo and lormetazepam treatments, imipramine patients reported

improved subjective 'feeling rested in the morning.' Adverse events included dry mouth, dizziness and nausea.

When compared to imipramine (n=16; final dose 144mg), trimipramine (n=14; final dose 188mg) eliminated objective sleep disturbance but imipramine did not in depressed patients with insomnia and anxiety.<sup>27</sup> Depression improved equally with both TCAs. This supports the fact that imipramine is used uncommonly for promoting sleep.

### SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Paroxetine is the only selective serotonin reuptake inhibitor (SSRI) evaluated in the setting of primary insomnia. In a pilot study, Nowell and colleagues assessed the effectiveness of paroxetine 10-30mg in 14 patients over a 6 week period.<sup>45</sup> At the conclusion of the study, 79% of patients were at least "much improved" on the Clinical Global Impression-Improvement scale (CGI-I) and seven patients no longer met DSM-IV criteria for insomnia. Subjective improvements in sleep quality and daytime well-being were also reported. Polysomnography indicated worsening of sleep onset but improvement in total sleep time. The authors noted that paroxetine was well tolerated and side effects diminished with treatment.

Other SSRIs have been assessed for insomnia in the presence of depression.<sup>31</sup> These studies suggest that mechanisms other than sedation contribute to the improvements in sleep quality observed.

### CONCLUSION

Although antidepressants are currently being used to aid with sleep, the data to support such widespread use is minimal and practices are generally anecdotal. With the exception of doxepin, few studies supporting this use were conducted in the absence of a mood disorder. Furthermore, many of the studies are limited by small sample sizes and inadequate control groups and lacked a randomized, double-blind study design. For these reasons, antidepressants are recommended as second line agents if hypnotics are ineffective or as an alternative option in individuals who cannot use a controlled substance or have co-morbid depression.<sup>4</sup>

Reasons postulated for the common practice of off-label use of antidepressants in insomnia, despite insufficient evidence, include unscheduled drug status, lower risks of abuse and dependence, lack of prescribing restrictions, availability as generic agents and reduced performance-impairing effects. Furthermore, long-term care facilities are required to report and monitor the use of

benzodiazepines and sedative drugs; however, these requirements do not apply to antidepressants.<sup>46</sup> The less stringent regulation surrounding antidepressants makes them an attractive option in those individuals residing in long-term care facilities. Nonetheless, antidepressants carry their own potentially significant adverse effects that need to be weighed against these potential benefits.<sup>1</sup> All antidepressants have an FDA-issued black box warning regarding increased risks of suicidal thinking and behavior (i.e., suicidality) in young adults ages 18 to 24 during initial treatment (generally the first one to two months).<sup>47</sup> Whether using lower doses of these agents would carry a lower risk profile is unknown at this time. Moreover, some evidence suggests that tolerance may develop to the sedating effects of histamine H1 blockade as quickly as in four nights.<sup>48</sup>

Small studies of antidepressants in the setting of primary insomnia have provided good proof of concept for their use. With the exception of doxepin, there is a great need for larger studies to determine the safety, efficacy and optimal dosing when using antidepressants in this setting to allow clinicians to make informed, evidence-based decisions when prescribing.

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