What Is the Role of Sedating Antidepressants, Antipsychotics, and Anticonvulsants in the Management of Insomnia?

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Abstract Psychiatric medications such as antidepressants, antipsychotics, and anticonvulsants are commonly prescribed by physicians for the off-label use of improving sleep. Reasons for preferential prescription of these medications over FDA-approved insomnia drugs may include a desire to treat concurrent sleep problems and psychiatric illness with a single medication, and/or an attempt to avoid hypnotic drugs due to their publicized side effects. However, there have been few large studies demonstrating the efficacy and safety of most off-label medications prescribed to treat insomnia. In addition, many of these medications have significant known side effect profiles themselves. Here we review the pertinent research studies published in recent years on antidepressant, antipsychotic, and anticonvulsant medications frequently prescribed for sleep difficulties. Although there have been few large-scale studies for most of these medications, some may be appropriate in the treatment of sleep issues in specific well-defined populations.

Keywords Sleep disorders · Insomnia · Comorbid insomnia · Slow wave sleep · SWS · Off-label · Antidepressants · Antipsychotics · Anticonvulsants · Hypnotics · Psychiatry

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Introduction

The off-label prescription of antidepressants, antipsychotics, and anticonvulsants for the treatment of sleep problems is a common practice among physicians. In fact, analyses in the past decades have found that certain off-label medications have been prescribed more commonly than FDA-approved medications for insomnia [1, 2]. One analysis of data from a national service tracking physician prescription activity in 2002 found that the number of prescriptions of antidepressants for insomnia had passed the use of FDA-approved hypnotics for insomnia, with 5.28 million prescriptions for antidepressants and 3.4 million prescriptions for insomnia medications that year. The most commonly prescribed medication of all was trazodone, which was prescribed 32 % more than the most widely prescribed insomnia drug [2].

A survey of 1273 members of the American Academy of Child and Adolescent Psychiatry in 2003–2004 found that trazodone was also the most commonly prescribed medication for the treatment of insomnia in children with concurrent mood and anxiety disorders, with other antidepressants, atypical antipsychotics, anticonvulsants, and short-acting hypnotics also being commonly prescribed for sleep complaints in children with mood disorders [3].

Some reasons for prescribing off-label medications over FDA-approved medications for insomnia include: (1) the benefit of using a single medication with sedating properties to manage both a psychiatric or medical disorder and concurrent insomnia; (2) using a medication with sedating properties to offset sleep difficulties caused by another medication; and (3) avoiding the use of hypnotics due to concerns about dependence and side effects. In children, the American Academy of Pediatrics and the National Sleep Foundation have stated that there are inadequate data to

guide pharmacologic treatment of insomnia in children [4]. Thus, the physician who wishes to prescribe pharmacotherapy for insomnia in the child or adolescent must choose a medication without an approved indication or adequate research on the effects of these medications in this population.

In adults, the frequent prescription of sedating antidepressants, antipsychotics, and anticonvulsants for insomnia implies that prescribers believe these medications are more effective, or safer, or less prone to dependence or side effects when compared with hypnotic medications. It is true that until recently the FDA included a warning with Schedule-IV hypnotics that these medications not be taken for more than 2 consecutive weeks without reevaluation. Patients and physicians may also be concerned about using hypnotics such as zolpidem after much-publicized reports of sleep driving and other complex behaviors occurring with its use [5]. However, there also remains a paucity of research establishing the safety and efficacy of most antidepressants, antipsychotics, and anticonvulsants for the purpose of treating insomnia. Furthermore, many of these medications may be both expensive and associated with a significant known side effect profile. In the case of antidepressants, side effects may include sleep disturbances such as increased wakefulness after sleep onset (WASO), exacerbation of restless leg syndrome and increased periodic limb movements [6, 7].

FDA approval of new medications for insomnia requires at least 2 randomized, placebo-controlled trials in insomnia patients that show more effective induction and/or maintenance of sleep compared with placebo. Approval also requires evidence of this effectiveness using both objective measurement of sleep and subjective patient report. To a large extent, trials of this magnitude have not been conducted for many off-label prescriptions of these medications for insomnia. One notable exception is doxepin, a tricyclic antidepressant, which was approved by the FDA in 2010 for the treatment of insomnia after 3 large phase III trials demonstrated improved WASO, total sleep time (TST), and sleep efficiency (SE) compared with placebo [8]. The FDA does not prohibit the use of approved medications for off-label purposes; however, the decision to use a medication for a purpose other than its approved indication warrants discussion with the patient concerning the clinical rationale for choosing the medication, as well as documentation of the discussion in the patient's medical record [9, 10].

The off-label prescription of medications for insomnia has been described extensively in the past [11••]. For the purposes of this article, we will briefly summarize previous research on the sleep effects of specific sedating antidepressants, antipsychotics, and anticonvulsants commonly prescribed for insomnia, with subsequent focus on more recent studies performed in the last 2 years.

Antidepressants

Trazodone

Background

Trazodone is a triazolopyridine antidepressant that blocks post-synaptic serotonin receptors 5-HT_{1A}, 5-HT_{1C}, and $5\text{-HT}2$, as well as post-synaptic α_1-adreneregic receptors. It is a relatively weak SSRI with an elimination half-life of 5–9 hours. Typical doses for depression are ≥ 150 mg daily.

Since its introduction in the United States in 1983, few studies have investigated the beneficial effects of trazodone on sleep in people with primary insomnia; however, it is one of the most prescribed off-label medications for sleep difficulties in both adults and children [2, 3, 12]. In small studies with primary insomniacs and normal sleepers, trazodone 50–200 mg has been found to increase slow wave sleep (SWS) over short periods of time, compared with placebo [13–15]. It may be noted that although the clinical significance of increased SWS is not entirely clear, it is often assumed to be a sign of improved sleep. Many more small studies examining the use of trazodone for sleep have been conducted in depressed patients, and in patients whose insomnia is depression-associated or antidepressant-induced. These studies also report increases in SWS and improvements in sleep quality; however, there is no clear trend of benefits in sleep continuity [16–18].

The most common side effects of small doses at bedtime are residual morning sedation and orthostatic hypotension from peripheral adrenergic blockade. Priapism, though often cited as a concerning side effect, is a relatively rare occurrence [19–22].

Recent Studies

There are still few studies on the efficacy and safety of trazodone for primary insomnia, despite its popularity among providers. One within-subjects, randomized, double-blind, placebo-controlled study administered 50 mg to 16 insomniacs 30 minutes before bedtime for 7 days, and found that trazodone produced small but significant impairments of short-term memory, verbal learning, equilibrium, and arm muscle endurance across time-points. Relative to placebo across test days, trazodone was associated with fewer night-time awakenings, minutes of Stage 1 sleep and self-reports of difficulty sleeping. On day 7 only, slow wave sleep was greater and objective measures of daytime sleepiness lower with trazodone than with placebo [23•].

Two recent studies have demonstrated improvement of both depression and insomnia with trazodone. Fourteen patients with primary insomnia and high Beck Depression Inventory (BDI) scores (>10), and 15 sex- and age-matched

patients with primary insomnia and low BDI scores (≤10) were treated with trazodone CR 25–150 mg/d for 3 months and followed for 1 month after discontinuation of the medication. Significant improvements in subjective sleep time and several sleep rating scales occurred in both high and low BDI groups. No significant differences were found with actigraphic measurements of sleep [24]. In another double-blind study, 412 patients with major depressive disorder were randomized 1:1 to receive either Trazodone Contramid® OAD (150–375 mg) or placebo for 8 weeks. There was a statistically significant difference between trazodone and placebo on the mean 17-item Hamilton Depression Rating Scale score; secondary findings included improvements in quality of sleep as measured by self-report. This study did not include objective measures of sleep [25].

Trazodone has also been extensively studied in the treatment of fibromyalgia. One study with 66 fibromyalgia patients treated with flexibly dosed trazodone (50-300 mg/day) over 12 weeks found that trazodone significantly improved global fibromyalgia severity, sleep quality, and depression, as well as pain interference with daily activities although without showing a direct effect on bodily pain [26]. In another study, a flexible dose of trazodone (50–300 mg/day), was administered to 66 fibromyalgia patients for 12 weeks. The primary outcome measure was the Pittsburgh Sleep Quality Index (PSQI). Trazodone markedly improved sleep quality, with large effect sizes in total PSQI score as well on sleep quality, sleep duration and SE. Significant improvements, although with moderate effect sizes, were also observed in standardized fibromyalgia, anxiety, and depression rating scores, as well as pain interference with daily activities [27].

A retrospective study on sleep effects of trazodone in patients with dementia found that trazodone was among the antidepressants used with good tolerability in this sample, showing effectiveness in resolving sleep complaints and caregiver distress in 2/3 of patients. "Effectiveness" was defined as improvement of the sleep complaint and reduction in distress of the caregiver as rated on the Neuropsychiatric Inventory Scale (Nighttime Behavior items). One third terminated treatment with trazodone due to a lack of effectiveness but not due to adverse effects [28].

A study on 137 people receiving methadone who reported a Pittsburgh Sleep Quality Index (PSQI) score of 6 or higher found that trazodone did not improve subjective or objective sleep in this sample [29].

Summary

Trazodone may be effective in improving night-time awakenings, subjective sleep difficulties, and objective daytime sleepiness in patients with primary insomnia, but there is evidence that it may also produce significant cognitive and motor impairment. Research on the efficacy of trazodone for sleep difficulties in the last several years has focused on patients with depression and those with fibromyalgia. In these patient groups, significant improvements have been observed in both sleep and comorbid disorder, though without improvements in objective sleep parameters.

Amitriptyline

Background

Amitriptyline is a tricyclic antidepressant (TCA) that inhibits reuptake of serotonin and norepinephrine, with cholinergic, histaminergic, and α_1-adreneregic receptor blockade. It has an elimination half-life of 20–30 hours. Typical antidepressant dosages are ≥75 mg.

Before the introduction of fluoxetine in the US in 1987, tricyclic antidepressants were first-line treatment for depression, and were commonly prescribed to improve sleep in that patient population. However, there have been no data on the effects of amitriptyline on sleep in patients with primary insomnia and little data on sleep effects in patients with depression. There is limited evidence that in depressed patients, amitriptyline may improve PSG sleep measures of TST, sleep latency (SL), early morning awakening, and total REM time; however, this research was performed without placebo comparison or patient self-report [30].

Recent Studies

We found no studies on the effects of amitriptyline on sleep in primary insomniacs in the last 3 years. One study with healthy male subjects investigated the impact of evening doses of 75 mg amitriptyline over 2 nights on PSG-recorded nocturnal sleep and day-time sleepiness measured by the multiple sleep latency test, in comparison to 10 mg escitalopram and placebo. While amitriptyline did reduce PSG-determined WASO, compared with placebo, it also was associated with greater rates of periodic limb movements (PLM) and a higher PLM-arousal index. In turn, amitriptyline was associated with increased daytime sleepiness compared with placebo, as reflected in shorter mean sleep latencies [31].

Amitriptyline has also been studied in sleep disturbance associated with fibromyalgia. A randomized, double-blind, active-control, equivalency crossover trial compared nabilone (0.5–1.0 mg before bedtime) to amitriptyline (10–20 mg before bedtime) in patients with fibromyalgia with chronic insomnia. Although sleep was improved by both amitriptyline and nabilone, nabilone was superior to amitriptyline as rated on the Insomnia Severity Index. No objective measure was reported [32].

Summary

There remains little data on the benefits of amitriptyline for the treatment of sleep difficulties, whether in insomnia or fibromyalgia. Large research efforts in recent years have focused on other TCAs such as doxepin, which has shown promise in the treatment of insomnia at low dosages with minimal side effects.

Doxepin

Background

Like amitriptyline, doxepin is a TCA that inhibits reuptake of serotonin and norepinephrine, with cholinergic, histaminergic, and α_1-adreneregic receptor blockade. Typical antidepressant dosage is $\geq$75 mg daily. However, it is likely that at low doses under 10 mg, doxepin's main pharmacologic effect is histaminergic blockade, with little effect on serotonergic or adrenergic receptors [8].

There has been a dramatic increase in research on the sleep effects of doxepin that has led to recent FDA approval in 2010 of doxepin as Silenor® (Somaxon Pharmaceuticals, San Diego, CA) in 3 mg and 6 mg doses for the treatment of insomnia characterized by difficulty with sleep maintenance. Although doxepin is thus no longer considered an off-label prescription for insomnia, we will include it here to illustrate the large research efforts that led to FDA approval of this medication.

Previously, studies on doxepin at lower doses than typically used for antidepressant effect (1, 3, and 6 mg) were found to improve sleep as measured by PSG and patient self-report. Side effects of low-dose doxepin in primary insomniacs are similar to placebo [33].

Recent Studies

FDA approval of Silenor occurred after 3 large phase III clinical trials in adult and elderly patients with chronic primary insomnia demonstrated that low-dose doxepin 3 mg or 6 mg once daily improved PSG-determined WASO, TST, and SE compared with placebo. Five weeks of nightly administration of DXP 3 mg and 6 mg to adults with chronic primary insomnia resulted in significant and sustained improvements in sleep maintenance and early morning awakenings. These sleep improvements were not accompanied by next-day residual effects or followed by rebound insomnia or withdrawal effects upon discontinuation [34••].

Two randomized, double-blind, placebo-controlled trials studied low-dose doxepin in elderly patients with primary insomnia. Elderly adults with primary insomnia were randomized to 4 weeks of nightly treatment with either doxepin 6 mg or placebo. Doxepin 6 mg produced significant improvements in patient-reported WASO, TST, and sleep quality endpoints that were sustained throughout the trial [35••]. Doxepin 1 mg and 3 mg administered nightly to elderly chronic insomnia patients for 12 weeks resulted in significant and sustained improvements in PSG-measured WASO, TST, SE, and WASO compared with placebo; they also noted improvement in patient-reported SOL, TST, and sleep quality. These improvements were not accompanied by evidence of next-day residual sedation or other significant adverse effects [36••].

Summary

The approval of doxepin for the management of insomnia characterized by difficulty in sleep maintenance introduces a medication that has a well-established mechanism of action and few side effects. Perhaps more importantly, it has been studied in geriatric patients, a population with common sleep complaints of early morning awakenings and fragmented sleep. The low anticholinergic effect of this dosage also makes it appropriate for the elderly population.

Mirtazapine

Background

Mirtazapine is a tetracyclic piperazino azepine with potent inhibition of 5-HT$_2$, 5-HT$_3$ and central α_2-adrenergic receptors, with minimal monoamine uptake. It has a half-life of 22–40 hours, and typical antidepressant dosage is $\geq$15 mg daily.

There have been no placebo-controlled randomized clinical trials of mirtazapine in primary insomniacs. Mirtazapine has been shown to reduce PSG-measured SL and increase slow wave sleep and SE in normal sleepers [37, 38]. In depressed insomniacs, 8 weeks of treatment produced greater reductions in PSG SL and increased TST as compared with fluoxetine, with no patient report described. Antidepressants such as mirtazepine have also shown efficacy in treating disturbed sleep associated with hot flashes in perimenopausal women [39].

Side effects of bedtime mirtazapine 30 mg have been observed, include prolonged next-day motor reaction and impaired driving performance when compared with placebo, for acute but not chronic dosing [40]. Mirtazapine may also cause significant weight gain.

Recent Studies

No recent studies were performed in normal sleepers or primary insomniacs. Two studies tested the effects of mirtazapine in patients with depression. In one of the studies, 16 depressed patients experienced significant improvement of

sleepiness and fatigue measures on subjective scales as well as the Multiple Sleep Latency Test (MSLT); there was no placebo comparison [41].

Previously noted side effects of motor impairment were revisited in another study in which 14 depressed patients took mirtazapine 30 mg at bedtime for 30 days. A computerized driving simulator test (DST) and the Maintenance of Wakefulness Test (MWT) were conducted at baseline and on days 2, 9, 16, and 30 after commencement of antidepressant use. Several driving safety measures improved with mirtazepine over time, and several were also superior compared with untreated patients. The authors observed greatest improvement in morning performance, and suggested this may related to the circadian pattern often observed in untreated depression, in which mood is lower in the morning [42].

A case series of 11 perimenopausal women with insomnia without depression found that treatment with mirtazapine 15 mg followed by prolonged-release melatonin add-on therapy significantly improved sleep quality as measured by PSQI scores [43].

Summary

Mirtazapine, as with other sedating antidepressants, may be effective for sleep difficulties in depressed patients, particularly those with a need for weight gain. These studies suggest that it may also improve next-day sleepiness and fatigue, possibly due to its antidepressant effect. Mirtazapine may also be effective in treating insomnia associated with hot flashes in perimenopausal women.

Antipsychotics

Quetiapine

Background

Quetiapine is an atypical antipsychotic with high affinity for 5-HT2A receptors and weak affinity for dopamine, muscarinic, and adrenergic receptors. It has a half-life of 2–3 hours, and a typical antipsychotic dose is 150–800 mg daily.

In small studies of patients with primary insomnia or dementia, quetiapine was previously found to increase PSG or actigraphic TST at doses starting at 25 mg [44–46]. Side effects of quetiapine include weight gain with potential glucose intolerance [47].

Recent Studies

The prescription of quetiapine for sleep difficulties in patients with psychiatric illness and dementia is commonly employed [2]. In 1 retrospective cross-sectional study on the use of quetiapine for sleep in demented patients between January 2007 and December 2009, authors found that 43 of the 101 patients included in the study were prescribed quetiapine, "probably for sleep" [48].

We found only 1 study evaluating the effect of quetiapine in primary insomnia in a randomized controlled trial. Quetiapine 25 mg at night led to nonsignificant improvement of self-reported TST and SOL in patients with primary insomnia [49].

In adolescents with autistic spectrum disorder and aggressive behavior, treatment with 25 mg twice a day (50 mg/d) for the first 4 days of treatment, titrated to a maximum of 150 mg/day based on physician judgment, significantly improved subjective sleep disturbances; a positive correlation was found between the improvements in aggression and sleep [50].

Quetiapine has also been recently studied in regards to generalized anxiety disorder (GAD). One prospectively planned pooled analysis of 3 10-week, randomized, double-blind, placebo-controlled studies evaluated the efficacy and tolerability of acute extended release quetiapine fumarate (quetiapine XR) monotherapy in GAD. Significant improvements vs placebo at Week 8 included Pittsburgh Sleep Quality Index global scores for all quetiapine XR doses (50, 150, and 300 mg/day) [51].

Two studies evaluated adjunctive quetiapine XR in patients with major depressive disorder (MDD) who demonstrated inadequate response to antidepressant treatment. Among the individual Montgomery–Åsberg Depression Rating Scale items, the greatest magnitude of improvement at Weeks 1 and 6 was observed in Item 4 (reduced sleep). Quetiapine XR was also associated with significant improvement in PSQI global score and HAM-D sleep disturbance factor scores at Week 6 [52].

Summary

Quetiapine has been most studied for the treatment of insomnia in disorders characterized by psychosis, frequently with symptoms of agitation. In recent years, a number of studies have suggested it may be useful for treating sleep difficulties in patients with a variety of disorders, including autism with aggressive behavior, GAD, and depression.

Anticonvulsants

Gabapentin

Background

Gabapentin is a GABA analogue that interferes with the influx of calcium into nerve terminals. It is excreted via the kidneys as an unchanged drug, and has a half-life of 5–7 hours. Initial

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