

# Treatment of Insomnia with Comorbid Mental Illness

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## 1. Introduction

Insomnia is the most prevalent sleep disorder; especially in the elderly.<sup>1-3</sup> It is diagnosed in women (55-60%) more often than men (40-45%).<sup>4-6</sup> It can occur acutely (as known as transient insomnia) or become a chronic disorder (occurring at least three or more times per week, usually one to six months in duration and with some degree of daytime dysfunction).<sup>4</sup> Epidemiological studies indicate that at least one symptom of insomnia occurs in approximately one-third of the adult population with about 10 to 15 percent of these cases suffering from chronic insomnia with daytime consequences lasting for months or for many years.<sup>4-10</sup>

Chronic insomnia is frequently associated with depression and other psychiatric disorders including generalized anxiety disorder (GAD).<sup>11-14</sup> For some patients, insomnia symptoms may be a predictor for the onset of clinical depression.<sup>12-16</sup> Thus, given the potential for insomnia or its symptoms to reflect and/or trigger the onset of concomitant disease states, a thorough diagnostic examination is warranted in these patients.

Treatment guidelines for insomnia patients with comorbid mental illness are aimed at addressing the underlying psychiatric problem in order to improve sleep disturbances.<sup>5,13</sup> Successful treatment can only be achieved by a thorough understanding of the extent of the problem and the proper choice of interventions. A combination of lifestyle changes, psychiatric, complementary and alternative medicine, as well as pharmacotherapy are often employed to achieve a positive and lasting outcome.

## 2. Psychiatric comorbidities

The connection between insomnia and psychiatric comorbidities can be attributed to more than a simple cause and effect relationship. A bidirectional relationship has been identified in the literature.<sup>17,18</sup> Researchers have also determined that patients diagnosed with severe insomnia are 6 times more likely to have had a prior mental illness.<sup>14</sup> One study found that the odds of having at least one psychiatric diagnosis was 5.04 times greater in patients with severe insomnia as compared to those without insomnia and that increasing insomnia severity was associated with increased chronic medical and psychiatric illnesses.<sup>19</sup> Moreover, insomnia has been confirmed as a risk factor for future mental illness.<sup>18</sup>

### 3. Anxiety and depression

A prospective study conducted in Sweden showed that both anxiety and depression were associated with future insomnia and insomnia was associated with future anxiety and depression.<sup>17</sup> A baseline diagnosis of anxiety significantly predicted future insomnia, while an insomnia diagnosis at baseline significantly predicted future depression. A community-based retrospective study identified that chronic insomnia sufferers were about 10 times more likely to have clinically significant depression and about 17 times more likely to have clinically significant anxiety.<sup>20</sup> Chronic insomnia has been found to increase the risk of developing depression anywhere from 2 to 40 fold and those being treated for depression and have concomitant chronic insomnia are 2 to 4 times more likely to remain depressed if the insomnia remains untreated.<sup>21-23</sup>

### 4. Generalized anxiety disorder

The strong bidirectional association between chronic insomnia and anxiety disorders may indicate that they share an overlapping neurobiological abnormality with common symptoms and physiological markers (e.g. hyperarousal).<sup>24</sup> It is estimated that 70 to 90% of anxiety patients have insomnia as a complaint.<sup>24,25</sup> Two anxiety disorders, generalized anxiety disorder (GAD) and post traumatic stress disorder (PTSD) include sleep disturbance as part of the DSM-IV TR diagnostic criteria.

GAD has the highest comorbidity rate with insomnia; exceeding the comorbid rate of depression and insomnia.<sup>11,25-27</sup> Research estimates are as many as 50 to 70% of GAD sufferers have insomnia.<sup>26</sup> Additionally, sleep disturbances seem to worsen or trigger GAD-related symptoms of fatigue and irritability which are also hallmark consequences of insomnia.<sup>26-27</sup> Other overlapping symptomatology include excessive worry, significant daytime impairment, decreased sleep efficiency, increased nocturnal awakenings, and rapid eye movement (REM) sleep disturbances.<sup>25,26</sup>

### 5. Post traumatic stress disorder

PTSD patients commonly (70-90%) experience sleep disturbances.<sup>26,27</sup> These patients report sleep disturbance symptoms such as poor sleep quality, decreased total sleep time, nightmares, and hyperarousal.<sup>26,27</sup> Of important note, is that research has not demonstrated a bidirectional relationship between insomnia and PTSD given that an intervening trauma is necessary to establish a diagnosis of PTSD. Insomnia may predict the development of PTSD after trauma exposure however, and patients with more severe insomnia symptoms within a month of the trauma incident are at greater risk of developing PTSD within the following 12 month period.<sup>26</sup> Moreover, the severity of insomnia appears to be correlated with PTSD severity.<sup>18</sup>

### 6. Panic disorder

Empirical evidence exists to support the association between insomnia and panic disorder with about 67% of panic patients reporting difficulty falling asleep and 77% with difficulty maintaining sleep.<sup>26,27</sup> Approximately 44 to 77% of panic patients experience nocturnal panic attacks which have different pathology from those experienced during daylight hours.<sup>27</sup> A degree of hyperarousal may also be present.<sup>25</sup>

## 7. Comorbidity treatment strategies

Nearly 80% of patients diagnosed with major depressive disorder (MDD) have sleep disturbances with disturbed sleep and fatigue remaining after successful treatment of the mood disorder.<sup>21,23,24,28,30</sup> Lingering insomnia following treatment of depression is associated with increased risk of relapse (more than 50% of cases).<sup>21,24,30</sup> Therefore, insomnia is a significant independent predictor of future depression.<sup>14,22-24,29</sup> Clinical sequelae of insomnia such as negative affect, fatigue, anhedonia, poor concentration, and irritability are also symptoms found in depression. As mentioned earlier, a bidirectional relationship between depression and insomnia exists thereby emphasizing the importance of treating the insomnia independent of the comorbid condition.<sup>24,28,31</sup>

## 8. Treatment strategies

Several treatment strategies are utilized, often in various combinations, for the treatment of insomnia. These include psychological and behavioral therapy (PBT), pharmacotherapy, over-the-counter (OTC) medications, herbal and dietary supplements, complementary and alternative medicine (CAM), mind-body and lifestyle interventions (Table 1).

<b>Lifestyle:</b> sleep hygiene, weight control, low impact exercise, dietary (e.g. elimination of caffeine, nicotine, alcohol)
<b>OTC medications:</b> Not recommended by AASM and NIH
<b>Herbal/ Dietary supplements:</b> melatonin (for changes in circadian rhythm, jet lag, shift work, or documented deficiency only); valerian (for acute treatment only)
<b>PBT:</b> stimulus control, coping skills, relaxation training (e.g. progressive muscle relaxation, guided imagery, abdominal breathing), CBT-I, multi-component therapy, sleep restriction, paradoxical intension, biofeedback, grief management
<b>Mind and Body:</b> yoga, meditation, mindfulness-based programs (MBSR, MBCT, MBT-I, MBRP), tai chi, acupuncture, acupressure
<b>Pharmacological:</b> SSRI or SNRI, augmentation with sedating antidepressant (low dose), BzRA (for acute treatment only), or benzodiazepine (minimal use: for acute or "as needed" treatment of anxiety symptoms only), prazosin

**KEY:** AASM = American Academy of Sleep Medicine; BzRA = benzodiazepine receptor agonist; CBT-I = cognitive behavioral therapy for insomnia; MBSR = mindfulness-based stress reduction; MBCT = mindfulness-based cognitive therapy; MBT-I = mindfulness based therapy for insomnia; MBRP = mindfulness-based relapse prevention; NIH = National Institutes of Health; OTC = over-the-counter; PBT Psychological and Behavioral Therapy; SNRI - serotonin norepinephrine receptor inhibitor; SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant

Table 1. Treatment Options for Insomnia with Co-Morbid Mental Illness

Unfortunately, clinicians are not routinely probing the level of sleep difficulties in their patients other than a simple identification (yes or no) of sleep disturbance.<sup>32-38</sup> Treatment seeking behavior for insomnia is based on disease severity, fatigue, daytime consequences and comorbidities.<sup>32-33</sup> A study of primary care patients with insomnia determined that the principal motivator for seeking treatment after controlling for insomnia severity was found to be the negative impact on daytime functioning.<sup>32</sup> A community based study identified that daytime fatigue and psychological distress were the main predictors of treatment seeking

behavior.<sup>5</sup> Moreover, when patients seek treatment for their insomnia symptoms, health care providers (HCPs) are significantly more prone to prescribe pharmacotherapy than to refer patients for behavioral interventions.<sup>34</sup> Additionally, HCPs are more likely to diagnose one or more of the comorbidities as opposed to insomnia; there is a greater probability of obtaining reimbursement for these diagnoses by insurance carriers.<sup>10,37,38</sup> Thus, behavioral interventions which presume a diagnosis of insomnia remain underutilized.<sup>37</sup>

## 9. Sleep hygiene

A thorough evaluation of sleep hygiene is required at initial evaluation of all patients with sleeping difficulties. These simple and basic sleep practices offer a consistent routine to assist patients to return to a normal sleep schedule.<sup>34,38-40</sup> Adherence to good sleep hygiene practices is imperative in establishing a stable baseline to work from in order to improve sleeping difficulties. Sleep hygiene counseling includes the following:

- Follow a regular sleep pattern; go to bed and arise at about the same time each day.
- Eliminate daytime naps.
- Make the bedroom comfortable for sleeping by avoiding temperature extremes, noise and light.
- Make sure the bed is comfortable.
- Go to bed only when sleepy.
- Engage in relaxing activities before bedtime.
- Use the bed and bedroom only for sleep and sexual activities only.
- If unable to fall asleep, do not become anxious. Leave the bedroom and participate in relaxing activities for 20 to 30 minutes.
- If tense, practice relaxation exercises (e.g. deep breathing, meditation).
- If hungry, eat a light snack, but avoid eating meals or large snacks immediately before bedtime.
- Avoid using caffeine after noon.
- Avoid using alcohol or nicotine later in the evening.

Sleep hygiene is most effective when used in conjunction with other behavioral treatments. The overall goal is to decrease or eliminate sleep-reducing behaviors such as inconsistent sleep and wake cycle, daytime napping, clock monitoring, and exercising or consuming caffeine-containing beverages too close to bedtime.<sup>39</sup> One barrier to the success of sleep hygiene, is patient's perception that their compensatory behaviors of napping and drinking caffeinated beverages enable them to function during the day making them resistant to abandon these behaviors.<sup>40</sup> It is therefore recommended that HCPs be persistent in communicating their expectations on the importance of maintaining good sleep hygiene habits.

## 10. Over-the-counter remedies

Self-help remedies are a major source of treatments for many patients with insomnia. The most frequently used include over-the-counter (OTC) antihistamines (10-25%), herbal supplements, alcohol (10-25%), caffeinated beverages, or a diet high in carbohydrates and/or sugars throughout the day to combat fatigue.<sup>5,41</sup> None of these are suitable choices for the treatment of insomnia. Alcohol may reduce sleep-onset latency via its CNS

depressive effects but it also disrupts sleep architecture causing disruption in REM and slow wave sleep.<sup>42-44</sup>

OTC antihistamines (e.g. diphenhydramine and doxylamine) are available for short term treatment of mild cases of insomnia only and should not be used for chronic insomnia. There is minimal evidence that these antihistamines are effective in improving sleep parameters but they may actually reduce sleep quality.<sup>42,43</sup> While these agents may help with mild cases of acute insomnia, they are not without potential serious adverse effects including daytime drowsiness, dizziness, fatigue, headaches, vomiting, and anticholinergic properties (e.g. blurred vision, urinary retention, confusion).<sup>44-45</sup> Moreover, the American Academy of Sleep Medicine (AASM) and the United States National Institutes of Health (NIH) both agree that there is insufficient evidence supporting the use of OTC antihistamines for the treatment of insomnia. This is of great concern as patients may experiment with various self-help remedies for a significant amount of time before consulting their HCP about their sleeping difficulties.

Many herbal and dietary supplements are marketed directly to the consumer as sleep aids however, consistent scientific evidence supporting their use is very limited.<sup>42,44,46</sup> Valerian and melatonin are the only supplements with sufficient research of adequate rigor evaluating their use in insomnia.<sup>46</sup> Unfortunately, recent meta-analyses of randomized clinical trials (RCTs) for valerian as monotherapy, or in combination with other herbal supplements, did not find significant improvement in sleep quality or sleep latency.<sup>47,48</sup>

Melatonin is a naturally occurring hormone that regulates sleep and circadian schedules. Research on melatonin's usefulness for insomnia is mixed. It has been primarily useful in decreasing sleep latency (e.g. jet lag, shift work-related insomnia) with no significant impact on sleep maintenance or total sleep time.<sup>43-44</sup> Additionally, melatonin has been associated with adverse effects such as residual fatigue, dizziness, headache, and irritability.<sup>43,44</sup> Therefore, it is not routinely recommended for treatment of chronic insomnia.

## 11. Psychological and behavioral therapy

PBT is considered first line treatment in chronic insomnia.<sup>44</sup> Unfortunately, it is underutilized by practitioners even though there is significant evidence proving its effectiveness in chronic insomnia with or without comorbid illness.<sup>30,36,44,49-51</sup> Behavioral modification may actually be more useful for insomnia sufferers with comorbid illness as these patients are often burdened with a multitude of medications that enhance their risk for medication-related adverse effects, interactions, and/or dependency / addiction.<sup>37</sup>

It is hypothesized that physiological and cognitive hyperarousal contribute to the development and chronicity of insomnia.<sup>44</sup> Moreover, patients tend to develop problematic sleep hygiene practices such as remaining awake in bed for long periods of time which causes heightened anxiety and frustration about inability to sleep, increased efforts to sleep, wakefulness, negative expectations, and distorted attitudes about their insomnia and its consequences on their work/life. PBT is specifically targeted to address these perpetuating negative learned responses. The goal of PBT is to elicit a change in the patient's belief system, through education and awareness, which enhances the patient's sense of self-efficacy concerning their insomnia management.<sup>44</sup>

<p><b>Relaxation training</b> is often utilized with CBT-I and involves the use of progressive muscle relaxation, guided imagery, or abdominal breathing in order to lower somatic and cognitive arousal states that interfere with sleep.</p> <p><i>Instructions:</i> PRM training involves the methodical tensing and relaxing of different muscle groups throughout the body. Techniques are widely available in written and audio formats.</p>
<p><b>Stimulus control</b> is for the patient to establish a clear and positive association between the bed and sleep, as well as, creating a stable sleep-wake schedule. It is designed to eliminate the negative association between the bed and undesirable outcomes (e.g. wakefulness, frustration, worry)</p> <p><i>Instructions:</i> Follow appropriate sleep hygiene</p>
<p><b>CBT-I</b> is a combination of cognitive therapy with behavioral interventions (e.g., stimulus control, sleep restriction) with or without relaxation therapy. Cognitive therapy uses a psychotherapeutic method to reconstruct cognitive pathways with positive and appropriate concepts about sleep and its effects. CBT-I works to change the patient's overall beliefs and unrealistic expectations about sleep.</p>
<p><b>Multi-component therapy [without cognitive therapy]</b> is employed by a majority of practitioners. It uses various combinations of behavioral interventions (e.g. stimulus control, relaxation, sleep restriction) and sleep hygiene education.</p>
<p><b>Sleep Restriction</b> is used to improve sleep continuity by using sleep restriction to enhance sleep drive. The TIB to the TST is limited initially through the use of baseline sleep logs. As sleep drive increases and the window of sleep opportunity remains restricted with daytime napping prohibited, sleep becomes consolidated. As soon as sleep continuity significantly improves, TIB is slowly increased to provide adequate sleep time to feel rested during the day, while preserving the newly acquired sleep consolidation.</p> <p><i>Instructions:</i> Patients should be cautioned that sleep restriction may create possible sleepiness and reduce cognition. Maintain sleep log and determine mean TST for a 1-2 week baseline; Set bedtime and wake-up times to approximate mean TST to achieve &gt; 85% SE (TST/TIB x 100) over 1 week; the goal is for the TIB (not &lt; 5 hrs) to be about the TST; Make weekly adjustments for SE &gt; 85% to 90% over 1 week, TIB is increased by 15-20 minutes, for SE &lt; 80%, TIB is decreased by 15-20 minutes; Repeat TIB adjustment every week until TST goal is achieved.</p>
<p><b>Paradoxical intention</b> is used to eliminate anxiety over sleep performance. It is a targeted cognitive therapy which trains the patient to confront the fear of staying awake and its potential effects.</p>
<p><b>Biofeedback</b> training is used to reduce somatic arousal. It trains the patient to control a selected physiologic variable through auditory or visual feedback.</p>
<p><b>Sleep hygiene</b> teaches the patient healthy lifestyles that improve sleep. It is used in conjunction with stimulus control, relaxation training, sleep restriction, and/or CBT-I.</p> <p><i>Instructions:</i> include, but are not limited to, keeping a regular sleep wake cycle, healthy dietary choices, regular daytime exercise program, maintaining a quiet sleep environment, avoidance of daytime napping, caffeine, nicotine, alcohol, other stimulants, excessive fluids, or stimulating activities before bedtime.</p>

**KEY:** CBT-I = cognitive behavioral therapy for insomnia; PBT = psychological and behavioral therapy; SE = sleep efficiency; TIB = time in bed; TST = total sleep time.

Table 2. Common PBT for Chronic Insomnia

There are a number of different psychological and behavioral therapies available to address these aberrant behaviors (Table 2).<sup>37,39,40,51-53</sup> Standard therapies of stimulus control, relaxation training, and cognitive behavioral therapy for insomnia (CBT-I) with or without relaxation therapy are well supported in the scientific literature.<sup>42,39,40,52,53</sup> CBT-I is the most common form of PBT for chronic insomnia. CBT-I is individualized and combines several behavioral / multimodal interventions. CBT-I usually includes stimulus control, sleep restriction, cognitive psychotherapy, light and dark exposure, sleep hygiene education, bedroom modification, relaxation training, and gradual tapering of hypnotic medications (when applicable).<sup>44</sup>

## 12. Complementary and alternative medicine

Pharmacotherapy and PBT interventions continue to be the mainstays of treatment for chronic insomnia patients with mental illness comorbidity. However, the use of complementary and alternative medicines (CAMs) has increased dramatically in the 21<sup>st</sup> century. CAMs (e.g. acupuncture, mindfulness-based stress reduction, yoga, meditation) are an integral part of the holistic medicine approach which aims to treat the “whole patient.”<sup>54</sup> Patients are expected to play an active role in their health when receiving CAMs which appeals to many chronic sufferers who have experienced ineffective relief from conventional medicine practices. CAMs are increasingly becoming part of mainstream medicine as more research on their effectiveness is published.<sup>54-60</sup>

CAMs are more commonly used by those with psychiatric disorders especially patients with anxiety, depression and insomnia.<sup>61-63</sup> CAMs have shown to improve sleep in 4.5% of insomnia patients translating to 1.6 million U.S. citizens.<sup>64</sup> Herbal supplements or nutritional medicine, tai chi, and yoga are the most common CAMs utilized with 56% of patients reporting that CAMs were important in maintaining their health and 72% thought there was a significant improvement in their insomnia symptoms.<sup>64</sup>

Supportive evidence for acupuncture and acupressure in the treatment of insomnia is now available.<sup>65-68</sup> However, while acupuncture and acupressure may assist to improve sleep quality, the efficacy of these interventions was inconsistent between studies for many sleep parameters, including sleep onset latency, total sleep duration, and time to waking.<sup>65-68</sup> A recent study using electroacupuncture for chronic insomnias demonstrated beneficial effects on sleep quality which, as the authors stated, may be associated with valuable repair of sleep architecture, reconstructing sleep continuity, prolonging slow wave sleep time and rapid eye movement (REM) sleep time.<sup>57</sup> Research using acupuncture and acupressure remains in progress and will hopefully demonstrate the full benefits as more rigorous studies are completed and published.

Mindfulness-based programs (utilizing meditation with or without yoga) have emerged as novel approaches to behavior modification, stress / anxiety reduction, pain management, and relapse prevention. Historically, meditation has been used to regulate physical and mental health and for spiritual development. Mindfulness meditation is an outgrowth from a Buddhist practice called *vipassana* (“to see a special way”).<sup>69</sup> Mindfulness-based meditation is surfacing in Western cultures as a beneficial approach to patient healing for many chronic conditions (e.g. insomnia, chronic back pain, fibromyalgia, cancer, psoriasis)<sup>70-73</sup> This meditation technique fosters acute awareness of the present moment and the impermanent nature of things.<sup>74</sup> The patient is thereby able to cultivate the ability to respond to stimuli in

a nonjudgmental way; allowing them to navigate their life in a manner that does not involve attachment to particular beliefs.<sup>74</sup> This form of self-compassion is the mechanism for reducing negative emotional reactions, enhancing resilience, and promoting self-healing.

There is a growing emphasis in applying mindfulness-based meditation in behavioral medicine. The first formal program, mindfulness-based stress reduction (MBSR) was created by Jon Kabat-Zinn over 2 decades ago and involves an 8-week program with an experiential component (formal mindfulness meditation) and group processing / support.<sup>75</sup> The MBSR program teaches patients how to make appropriate lifestyle changes by incorporating mindfulness techniques into their day-to-day life and encourages them to maintain a regular meditation practice. Several mindfulness-based programs have been designed from MBSR and adapted to meet the needs of specific populations. Mindfulness-based cognitive therapy (MBCT) is a program with assists in prevention and relapse of depression among individuals with recurrent major depressive disorders (MDD). MBCT could therefore be of benefit to those with insomnia and comorbid depressive illness.<sup>76</sup> Most recently, preliminary work on mindfulness-based therapy for insomnia (MBT-I) has been described as an effective treatment choice.<sup>58-60</sup> Additionally, there are also a mindfulness-based relapse prevention (MBRP) programs for depression, craving, as well as, alcohol and substance abuse.<sup>77,78</sup>

Low impact exercise, *Tai chi* and yoga are increasing in popularity as published research on mind-body interventions supports their use to improve sleep quality and reducing latency and insomnia severity.<sup>79-81</sup> Not all of these studies recruited chronic insomnia patients. Therefore, more yoga research is needed to validate its benefit for insomnia. Mainstream CAM studies including homoeopathy, massage, and aromatherapy are lacking at this time.

### 13. Pharmacotherapy

Currently there are no established treatment algorithms for insomnia with comorbid mental illness. While research has established the linkages between insomnia and psychiatric comorbidities, there is limited to no data to guide HCPs other than the reported recommendation to treat comorbidities (e.g. depression, GAD, PTSD, panic) concurrently, at recommended therapeutic doses, and in concert with PBT, sleep hygiene, and CAMs.<sup>44</sup>

Pharmacotherapy for comorbid insomnia can be effective, however, in improving targeted sleep parameters and improving symptoms of depression and anxiety disorders.<sup>44,82-85</sup> As mentioned earlier, treatment should address the insomnia and the comorbid mental illness simultaneously. Therapeutic choices include: benzodiazepine receptor agonists, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine receptor antagonists (SNRIs), sedating antidepressants, anticonvulsants, and atypical antipsychotics.<sup>44</sup> Pharmacotherapy is not curative and therefore the best outcomes are realized when used in combination with other previously mentioned interventions (e.g. sleep hygiene, PBT, CAMs). Table 3 summarizes pharmacotherapy choices for insomnia with comorbid mental illness, as well as, various treatment considerations.

### 14. Sedative / hypnotics

While sedative hypnotic medications like eszopiclone, zolpidem, zaleplon, benzodiazepines (e.g. alprazolam, lorazepam, temazepam) have demonstrated efficacy for short-term treatment of insomnia, very little evidence exists to confirm their usefulness in chronic situations.<sup>44</sup>

Moreover, sedative hypnotics can produce residual sedation, memory and performance impairment, increased risk of falls and fractures, as well as, undesirable behaviors while sleeping (e.g. sleep walking, sleep driving, sleep talking).<sup>44</sup> Triazolam, for example, has been associated with rebound anxiety and is no longer considered a first line hypnotic.<sup>44</sup> Thus, these medications are best reserved for initial short-term therapy with the goal of little to no utilization once other interventions (e.g. antidepressant, PBT, sleep hygiene, CAMs) are successfully employed. Benzodiazepines, such as lorazepam, can be useful for immediate relief of breakthrough anxiety symptoms (e.g. panic attack) and prescribed on a limited “as needed” basis.<sup>44</sup> Buccal or sublingual administration of benzodiazepines provides rapid response and is very useful for these intense anxiety situations.

Medication	Therapeutic Considerations
<i>BRAs:</i> eszopiclone, zolpidem, zaleplon	For short term treatment of insomnia only; no evidence of efficacy in chronic situations.
<i>BZDs:</i> alprazolam, lorazepam, triazolam, temazepam	Best reserved for initial short term treatment of insomnia symptoms with the goal of little to no utilization once other interventions (e.g. SSRI, SNRI, PBT, sleep hygiene, CAMs) are successfully employed. May be used on a limited “as needed” basis for immediate relief of breakthrough anxiety symptoms (i.e. panic attack).
<i>SSRIs:</i> citalopram, escitalopram, fluoxetine, paroxetine, sertraline <i>SNRIs:</i> duloxetine, venlafaxine	“First line” for comorbid depression and/or anxiety disorders. Higher doses are often needed for anxiety disorders than for depression. Selection of medication is guided by treatment history, side effect profile, interactions with other medications, and expense. Citalopram and escitalopram have lowest propensity to interact with other medications.
<i>Sedating Antidepressants:</i> amitriptyline, doxepin, mirtazapine, nefazodone, trazodone, trimipramine	Use in low doses only; best used in combination as augmentation to SSRI or SNRI for treatment of persistent insomnia symptoms after an adequate trial of other interventions (e.g. SSRI, SNRI, PBT, sleep hygiene, CAMs). Limited evidence for trazodone and nefazodone as augmentation in PTSD. Do not use as monotherapy (weak efficacy).
<i>Anticonvulsants:</i> gabapentin, tiagavine <i>Atypical Antipsychotics:</i> olanzapine, quetiapine	Generally not recommended; limited evidence to support their use for chronic insomnia. Atypical antipsychotics show some promise in the treatment of anxiety disorders but their side effect profile (e.g. weight gain, metabolic syndrome) and noncompliance continue to limit their use.
<i>Alpha Blocker:</i> prazosin	For treatment of sleep disturbances (nightmares, disturbing dreams, insomnia) in PTSD. Recommended by the <i>AASM Best Practice Guide</i> for treatment of PTSD-related nightmares.

**Key:** AASM = American Academy of Sleep Medicine; BRA = benzodiazepine receptor agonist; BZD = benzodiazepine; CAM = complementary and alternative medicine; PBT = psychological and behavioral therapy; PTSD = post traumatic stress disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Table 3. Pharmacotherapy Choices for Insomnia and Comorbid Mental Illness

## 15. Antidepressants

Antidepressant (AD) medications, primarily SSRIs (e.g. citalopram, escitalopram, fluoxetine, paroxetine, sertraline) and SNRIs (e.g. duloxetine, venlafaxine), are first line for treatment of MDD, GAD, panic disorder, and PTSD.<sup>86-88</sup> These agents may or may not be effective in completely alleviating sleep disturbances. Therefore, low dose sedating antidepressants such as mirtazapine, doxepin, amitriptyline, or trimipramine, may be considered as augmentation when insomnia complaints continue even with adequate dosing of the SSRI or SNRI.<sup>44</sup> Moreover, low dose ADs are best used in combination with other antidepressant pharmacotherapy as their evidence for efficacy as monotherapy is rather weak.<sup>89-94</sup> Selection is primarily guided by treatment history, side effect profile, medications interactions and expense.<sup>44</sup> Elderly patients, for example, may not tolerate the anticholinergic side effects of trazadone, doxepin and amitriptyline. The weight gain associated with mirtazipine could be deleterious to diabetics, hyperlipidemics, or cardiovascular patients.

## 16. Anticonvulsants and atypical antipsychotics

Evidence to support the use of anticonvulsants (gabapentin, tiagabine) and atypical antipsychotics (quetiapine, olanzapine) for chronic insomnia is insufficient at this time.<sup>44</sup> Off-label use of these medications should not be recommended as they increase the potential for significant adverse effects (e.g. seizures with tigabine; weight gain and metabolic syndrome with quetiapine and olanzapine).<sup>44</sup> Additionally, atypical antipsychotics have been evaluated as monotherapy or augmentation in the treatment of anxiety disorders with or without comorbid MDD, schizophrenia, or bipolar disorder.<sup>89</sup> This recent critical evaluation of the available research confirmed that although atypical antipsychotics showed promising results in the treatment of anxiety disorders, their side effect profiles continue to limited their use.<sup>89</sup> Atypical antipsychotic side effects were found to be a source of non-compliance and resulted in premature discontinuation of treatment with higher dropout rates found in the majority of randomized clinical trials.<sup>89</sup>

## 17. Nefazodone, trazodone, and prazosin for PTSD

Nightmares and insomnia produce significant distress and daytime impairment in those with PTSD. There is limited evidence supporting the efficacy of nefazodone and trazodone augmentation in PTSD.<sup>89</sup> The *AASM Best Practice Guide* describes "low grade to sparse" data supporting trazadone use in this population and recommends against the use of nefazodone for the treatment of nightmares.<sup>90</sup> Fortunately, there is promising research using prazosin to treat sleep disturbances in PTSD.<sup>85,91-93</sup> Prazosin is the only medication to receive a grade of "recommended" by the *AASM Best Practice Guide* for the treatment of PTSD-related nightmares.<sup>90</sup>

## 18. Conclusions and recommendations

Successful treatment of insomnia with comorbid mental illness is dictated by individualized treatment regimens where all appropriate options are considered. Treatment of both the insomnia and comorbid condition is important in achieving the best outcomes. Several treatment strategies in various combinations are often employed including sleep hygiene, PBT, CAMs, and pharmacotherapy. Behavioral modifications may actually be more useful

for insomnia sufferers with comorbid illness as these patients are often burdened with a multitude of medications. Standard therapies of stimulus control, relaxation training, and CBT-I with or without insomnia are well supported in the literature. CAMs are commonly utilized in patients with anxiety, depression, and insomnia. Additionally, mindfulness-based programs (MBSR, MBCT, MBT-I, MBRP) are promising interventions and appear to be appropriate. Research on low-impact exercise (e.g. Tai chi and yoga) is currently emerging but certainly may be a beneficial lifestyle intervention in this population.

Selection of pharmacotherapy is based on a patient's treatment history, side effect profile, potential medication-related interactions, and expense. There are no established medication-related treatment algorithms for insomnia with comorbid mental illness. Sedative hypnotics have a limited role in these patients and are best reserved for initial short-term therapy with the goal of limited to no use after positive outcomes are demonstrated with other interventions. SSRIs and SNRIs are first line pharmacotherapy for MDD, GAD, panic disorder, and PTSD. SSRIs or SNRIs as monotherapy, however, may not be effective in completely alleviating the sleeping disturbances in these patients and augmentation therapy with sedating low-dose AD may be useful. The use of anticonvulsants and atypical antipsychotics in these patients is currently not well supported in the literature and the side effect profiles are problematic. Prazosin is now an AASM recommended medication for the treatment of sleep disorders associated with PTSD patients.

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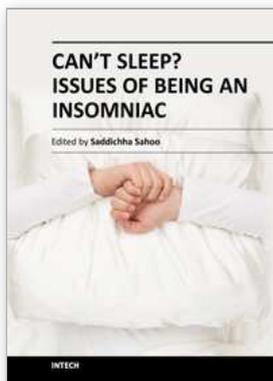
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## **Can't Sleep? Issues of Being an Insomniac**

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The word insomnia originates from the Latin "in" (no) and "somnus" (sleep). It is a disorder characterized by an inability to sleep or a complete lack of sleep. Various studies have noted insomnia to be quite a common condition, with symptoms present in about 33-50% of the adult population. This book provides a comprehensive state of the art review on the diagnosis and management of the current knowledge of insomnia and is divided into several sections, each detailing different issues related to this problem, including epidemiology, diagnosis, management, quality of life and psychopharmacology. In order to present a balanced medical view, this book was edited by a clinical psychiatrist.

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