ALTERNATIVES to BENZODIAZEPINES

Treatment of Insomnia[1] and Anxiety Disorders

The use of Benzodiazepines (BZ) should be considered last resort after all other non-BZ treatments have been tried. Please see BHRS Benzodiazepines Guidelines for additional information.

Below are ALTERNATIVE steps to consider in the treatment of insomnia and anxiety disorders.

Step 1: No medications

- Sleep hygiene: Walks after dinner, warm milk, warm bath or shower, quiet environment, soothing music…
- Cognitive behavioral therapy, yoga, meditation, relaxation breathing techniques…

Step 2: Medication with no known abuse potential

Insomnia[1] (see flow chart on page 2, with alternatives to benzodiazepine receptor agonists):

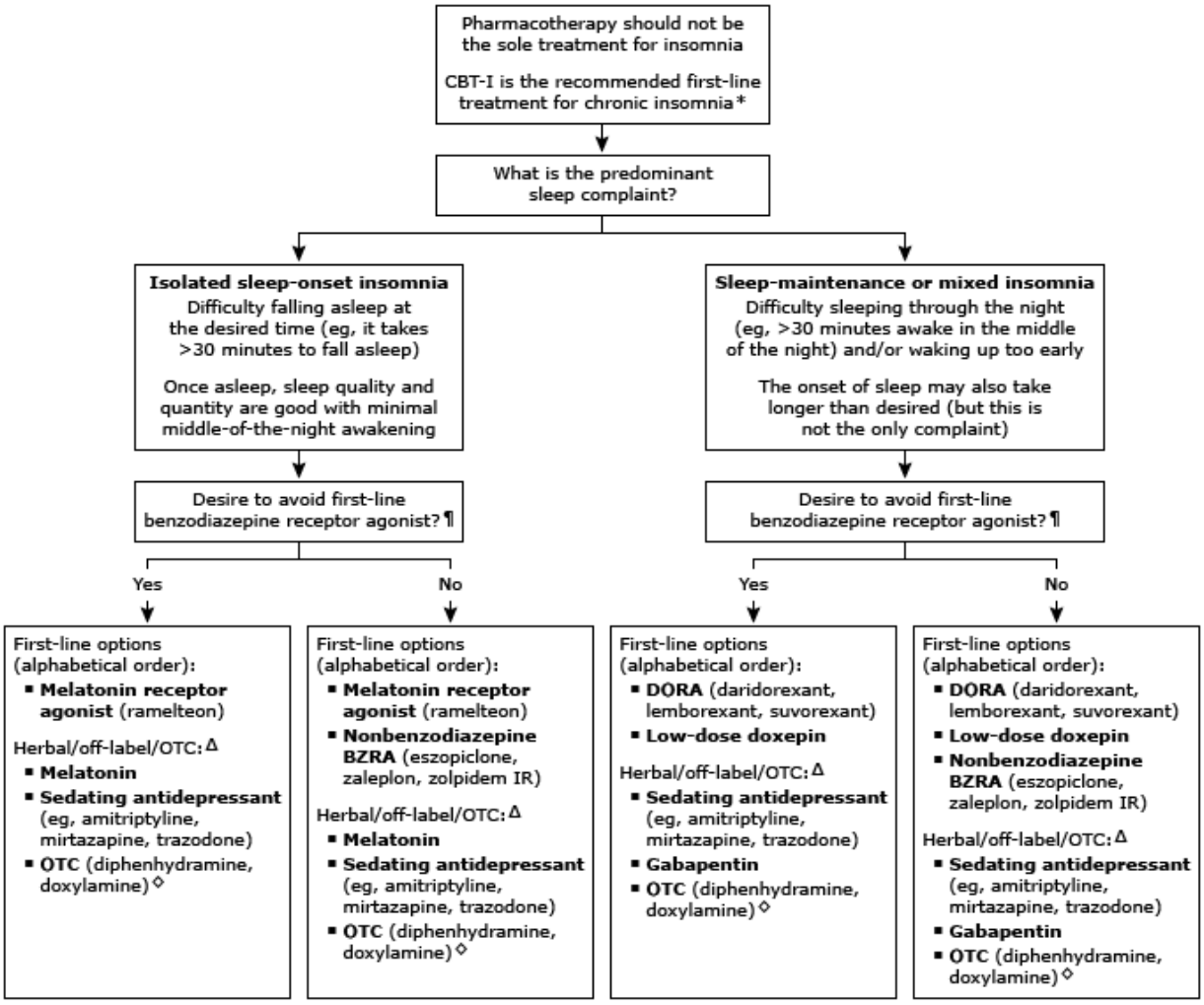
- Melatonin[3] 0.3 – 5mg q HS, or Ramelteon 8mg q HS
- Trazodone[2] usually 25-50mg q HS, but up to 100-200mg
- TCA such as Amitriptyline or Doxepin 10-50mg q HS
- Hydroxyzine or Diphenhydramine usually 25-50mg q HS, but up to 100-150mg

Anxiety Disorders or Depression with Anxiety sx should consider monotherapy or combination of

- SSRIs, SNRIs, Buspirone, Clonidine, Mirtazapine, Trazodone, Bupropion,TCAs.

Overview of pharmacotherapy for insomnia in adults[1]

(UptoDate)



CBT-I: cognitive behavioral therapy for insomnia; DORA: dual orexin receptor antagonist; OTC: over the counter; BZRA: benzodiazepine receptor agonist; IR: immediate release; ER: extended release; MOTN: middle of the night.

* When used, medications should be part of a holistic approach that includes healthy sleep habits, adequate opportunity for sleep, treatment of relevant comorbidities, and CBT-I when appropriate and available. Treatment selection is individualized based on the nature of the insomnia symptoms, past treatment responses, medication availability and cost, side effects, comorbidities, and patient preferences.

¶ BZRAs include benzodiazepines and nonbenzodiazepine BZRAs such as zolpidem. Common reasons to avoid may include older age, history of substance use disorder, or patient preference.

Δ Off-label prescribing of sedating medications for insomnia should be considered primarily for patients who do not have an adequate therapeutic response to first-line medications with regulatory approval for insomnia, when a different mechanism of action is desired, or when there is a specific reason to avoid BZRAs. Doses of such medications for insomnia purposes are generally subtherapeutic for the relevant comorbidity.

◊ Not recommended for chronic use. Avoid use in older adults.

Trazodone for Sleep[2]

Trazodone has been used for the past 40 years and is also commonly used off-label for insomnia. It's use at lower doses (compared to approved indications), may represent a safer alternative to BZRAs in some patients, even if the evidence for efficacy is not as strong. Off-label prescribing must be done with caution specially in older adults (due to unintended consequences such as a hypotensive effect that increases fall risk) as the risk-benefit ratio in treating insomnia may be different compared to the indicated disorder.

The American Academy of Sleep Medicine practice guideline (Sateia et al. 2017) recommends against trazodone as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults (weak recommendation) based on paucity of data.

Pochiero et al (2022) studied the real-world characteristics and treatment patterns of patients with insomnia prescribed trazodone in the US. Findings of the study suggest that trazodone is widely used among patients with insomnia, especially when this condition is associated with other specific comorbidities, such as psychiatric conditions.

Wichniak et al (2021) compared the effect of hypnotics and trazodone on sleep to analyze the evidence for the use of trazodone in the treatment of insomnia and found that "trazodone is less effective than hypnotics in the treatment of sleep onset insomnia (i.e. disorders of falling asleep). For this indication it needs to be administered earlier than hypnotics, at least 1 hour before bedtime. It is, however, very effective in the treatment of sleep-maintenance insomnia, especially in patients with comorbid mental disorders or patients treated with activating antidepressants. Hypnotics and trazodone have the opposite effect on deep sleep. Trazodone increases the duration of deep sleep, which is associated with better sleep quality as assessed by patients. In contrast, hypnotics decrease slow-wave activity in sleep EEG, which is the biomarker of deep sleep. The main mechanism through which trazodone promotes sleep is its antagonistic effect on 5-HT2 serotonin receptors, while hypnotics are agonists of gamma-aminobutyric acid GABAA receptors, and other sedative antidepressants block H1 histamine receptors. This is associated with a low risk of weight gain, which is rare with trazodone treatment."

Yi et al (2018; a meta-analysis of randomized placebo-controlled trials) investigated the efficacy and tolerability of trazodone compared with placebo and concluded that trazodone was effective in sleep maintenance, and it could significantly improve perceived sleep quality, but no significant improvements in sleep efficiency or other objective measures. Trazodone was well tolerated in short term use for insomnia.

Jaffer et al (2017) conducted a systematic review to examine the evidence for the efficacy and safety of trazodone for insomnia and concluded that there are adequate data supporting the efficacy and general safety of the low dose use of trazodone for the treatment of insomnia.

Walsh et al (1998) conducted a randomized, double blind, 14-day study to compare subjective hypnotic efficacy of trazodone 50 mg, zolpidem 10 mg and placebo and found that both zolpidem and trazodone improved the sleep of non-depressed primary insomniacs. However, after 14 days, the difference between trazodone and the placebo group was insignificant.

Melatonin for Sleep[3]

Literature search indicates mixed results about the clinical effectiveness of melatonin compared to placebo. Many studies suggest small benefits for sleep onset and possibly a small net increase in the total sleep time while others show no difference between patients who received melatonin compared to placebo. Although melatonin's effectiveness for the treatment of insomnia in adults is unclear, the potential benefits may depend on type of insomnia (sleep onset vs sleep maintenance), administration timing, patient's circadian predisposition, comorbidities (such as dementia), and age.

Even though melatonin's benefit compared to placebo is smaller than other pharmacological treatments, melatonin may have a role given its relatively safe side-effect profile. It is generally well tolerated and appears to have mild side effects, however, melatonin adverse effects from controlled studies are not well established and the safety of long-term melatonin use has not been established.

Melatonin appears to augment endogenous circadian alignment and does not help maintain sleep later in the night. Melatonin may be useful in some patients for sleep-onset insomnia (eg. pts for whom benzodiazepine receptor agonists (BZRA) should be avoided such as older adults or clts with cognitive dysfunction). Given the role of melatonin in circadian rhythm regulation and the age-related decline in endogenous production, melatonin may improve sleep quality particularly in older patients (> 55 yo) with primary insomnia and patients with circadian rhythm sleep disorders (e.g blind patients). Circadin is a prescription prolonged-release melatonin, indicated for the short-term treatment of primary insomnia in patients 55 or older and is available in United Kingdom.

Low et al conducted an umbrella review of meta-analyses and systematic reviews and concluded that melatonin results in a "statistically significant improvement in sleep latency and total sleep time, with a lack of consensus on whether these are clinically meaningful."

International Expert Opinions and Recommendations on the Use of Melatonin in the Treatment of Insomnia and Circadian Sleep Disturbances in Adult Neuropsychiatric Disorders (Pagalini et al. 2021) recommends "melatonin at 2–10 mg, 1–2 h before bedtime, might be used in the treatment of insomnia symptoms or comorbid insomnia in mood disorders, schizophrenia, in adults with autism spectrum disorders, neurocognitive disorders and during sedative-hypnotics discontinuation. Immediate release melatonin at <1 mg might be useful in the treatment of circadian sleep disturbances of neuropsychiatric disorders."

Another guideline (Sateia et al. 2017) recommends against melatonin as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults (weak recommendation).

Above algorithm from UptoDate suggesting melatonin use when there is a desire to avoid the side effects and risks of BZRAs.

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