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Treatment of insomnia – effect of trazodone and hypnotics on sleep

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Summary

Sedative antidepressants are commonly used drugs in the treatment of insomnia. However, some recommendations claim that only hypnotics have been proven effective in the treatment of sleep initiation and maintenance disorders. The aim of this article is to compare the effect of hypnotics and trazodone on sleep, and to analyse the evidence for the use of trazodone in the treatment of insomnia.

Three studies investigated the effects of trazodone on sleep in primary insomnia, 5 studies on insomnia in the course of affective disorders and 6 studies on insomnia in other indications (PTSD, Alzheimer's disease, alcohol and opiate dependence, somatoform disorder, and insomnia during pregnancy).

In the treatment of insomnia, 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-HT_2 serotonin receptors, while hypnotics are agonists of gamma-aminobutyric acid $GABA_A$ 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.

Key words: insomnia, pharmacotherapy, sleep-inducing drugs, trazodone

Introduction

Insomnia is one of the most common health issues; 6% to 19% of adults in European countries suffer from it [1]. The presence of insomnia symptoms that do not meet the diagnostic criteria of insomnia is even higher. In a representative sample of the Polish population, 50.5% of respondents experienced symptoms of insomnia (58.9% of women and 41.4% of men) [2]. The onset and prolonged presence of insomnia is associated with a higher risk of depression (double the risk), anxiety and psychotic disorders [3]. Insomnia also increases the likelihood of alcohol dependence [3], cognitive impairment in old age [4], cardiovascular disorders [5], and type 2 diabetes [6]. In patients with mental disorders, insomnia increases the risk of suicide [7]. Insomnia also leads to impaired daytime functioning and increases the risk of falls and involvement in fatal traffic accidents [8].

Effective treatment of insomnia requires, in the first place, for the cause of the disorder to be established [1, 9]. A differential diagnosis of insomnia should include an assessment of mental and somatic disorders, administered medications and substance use, behavioural, environmental and lifestyle factors and other primary sleep disorders, especially sleep apnoea, restless leg syndrome, and circadian rhythm sleep-wake disorders, which are often omitted in the diagnostic assessment [10, 11]. Current guidelines for the treatment of chronic insomnia underline the role of dysfunctional beliefs and attitudes about sleep as factors hindering sleep. For this reason, cognitive-behavioural therapy of insomnia (CBT-I) is indicated as the primary treatment of chronic insomnia [1, 9, 12]. Pharmacotherapy should be offered to patients who do not respond to CBT-I, for whom this form of therapy is unavailable or who have concomitant conditions (e.g. mental disorders) that decrease the effectiveness of cognitive-behavioural interventions and justify the use of pharmacotherapy [1, 9, 12].

Choosing the right drug to treat insomnia is not an easy task. A rigorous assessment of available sleep-promoting drugs carried out by experts from the American Academy of Sleep Medicine established that only a few of them have been proven to be effective and safe in the treatment of insomnia. Based on the results of studies objectively assessing the effects of drugs on sleep architecture using polysomnography (PSG), only 8 of the evaluated drugs were recommended for the treatment of insomnia: 3 drugs for the treatment of both sleep-onset and sleep-maintenance insomnia – eszopiclone (laevorotatory enantiomer of zopiclone, available in Poland since March 2021), zolpidem and temazepam, 2 drugs only for treatment of sleep-maintenance insomnia – suvorexant (not available in Poland) and doxepin, and 3 drugs solely for the treatment of sleep-onset insomnia – zaleplon, triazolam (not available in Poland) and ramelteon (not available in Poland) [13]. This does not imply that other drugs cannot be used for treating sleep disorders. Recent British guidelines indicate, for example, that sedative antidepressants should be considered for insomnia treatment when there is co-existent mood disorder [9]. Therefore, it is vital to know how these other drugs affect sleep and in what group of insomnia

patients they might be more effective than the above-mentioned drugs indicated for the treatment of insomnia.

The aim of this article is to compare the effect of hypnotics and trazodone on sleep, and to analyse the evidence for the use of trazodone in the treatment of patients with insomnia.

Method

The views presented here are based on the analysis of published studies available in electronic literature databases (PubMed, Embase, Web of Science, Cochrane Library), current guidelines [1, 9, 13], and meta-analyses [14, 15] published till end of December 2019. The key words used for literature searches were: trazodone and insomnia, trazodone and polysomnography or actigraphy. This assessment is based primarily on randomized clinical trials, including crossover trials performed with objective sleep assessment using polysomnography.

Trazodone

Trazodone is a 5-HT_2 serotonin receptor antagonist and reuptake inhibitor (SARI). Its sleep-inducing effect is mostly associated with blocking 5-HT_2 serotonin receptors, which is a mechanism that also leads to improving sleep depth. This medication also exerts a mild sedative effect by blocking H1 histamine receptors and alpha-1 adrenergic receptors [16]. The immediate-release (IR) trazodone reaches its maximum serum concentration within 0.5-2 hours after ingestion depending on the amount of food in the stomach, and the half-life is approximately 4.4 hours. For the controlled release (CR) formulation, the maximum blood serum concentration is achieved 4 hours after administration, and the half-life of trazodone is 12 hours. This means that this dosage form is helpful in treating sleep-maintenance insomnia, especially in the second half of the night, including early morning awakenings. However, in order to be effective in sleep-onset insomnia it needs to be administered significantly earlier than in the case of IR trazodone or non-benzodiazepine hypnotics, i.e. at least 1-2 hours before bedtime. Taking the trazodone too late may cause early morning sedation more often than it is observed with non-benzodiazepine hypnotics [17]. The studies did not assess whether the differences in the pharmacokinetic parameters of the two pharmaceutical forms of trazodone (IR and CR) are important for the drug efficacy and tolerance in the treatment of sleep onset and maintenance insomnia. The studies discussed below mostly evaluated the IR drug form, administered within 1 hour before bedtime, while the CR form of trazodone was used in two studies [18, 19].

The main argument adduced by opponents of trazodone use for insomnia treatment is the limited number of studies conducted with this drug in patients with insomnia that was not concomitant with or caused by other disorders or conditions [20]. There

are only three studies (Table 1) assessing the effects of trazodone on sleep in primary insomnia, including only one multicentre study [21].

Table 1. **Studies assessing the effect of trazodone on sleep in insomnia patients and patients reporting poor sleep quality**

Study	Study groups and observation period	Assessment method	Results	Notes
Walsh et al. 1998 [21]	Insomnia patients, aged 21-65 years, treated with 50 mg of trazodone (n = 100), 10 mg of zolpidem (n = 102) or receiving a placebo (n = 104). Duration of treatment 2 weeks.	A randomized, placebo-controlled, double-blind study. Assessment by means of sleep and well-being diaries in the mornings and evenings, and Sheehan Disability Scale.	After 7 days, decreased sleep latency and prolonged sleep time with both medications. After 14 days, decreased sleep latency only with zolpidem; none of the medications significantly prolonged total sleep time.	Increasingly shorter sleep latencies and longer sleep time have been observed in the placebo group. Both drugs were well tolerated.
Roth et al. 2011 [23]	16 insomnia patients with an average age of 44 years. 7 days of treatment with 50 mg of trazodone and 7 days of administering placebo separated by 7 days without medication/ placebo.	A randomized, placebo-controlled, double-blind, crossover study. Assessment by means of polysomnography, MSLT, neuropsychological tests, car simulator.	Trazodone decreased the number of awakenings, the amount of light sleep (stage 1), and increased the amount of deep sleep. Extended mean sleep latency in MSLT after 7 days (decreased daytime sleepiness).	Lack of trazodone's negative effect on the ability to drive vehicles. A slight impairment of short-term memory, verbal learning, equilibrium and arm muscle endurance during trazodone treatment.
Montgomery et al. 1983 [22]	Patients reporting poor sleep quality (n = 9), aged 50-70 years. Two weeks of placebo, 3 weeks of 150 mg/d of trazodone, 1 week of placebo.	Single-blind study. Sleep assessment by means of polysomnography.	Decreased time of wake after sleep onset; in the first week: – 30.6 min; in the third week: – 40.1 min.	Shortened time of wake after sleep onset was accompanied by improved sleep quality: less light sleep (stage 1 and 2), more deep sleep. A slightly shortened time of REM sleep with trazodone treatment. Decreased sleep quality was observed during the second night after discontinuation of trazodone.

It has been established that after 7 days of treatment with trazodone (in a dose of 50 mg/d) or zolpidem (10 mg/d), in subjective patients' reports both drugs significantly shortened sleep latency and increased total sleep time. After 14 days of treatment, benefits remained significant only with regard to shorter sleep latency during zolpidem treatment. Both drugs were well tolerated [21]. The other two studies, although conducted on much smaller patient populations, have however yielded very valuable data. In both studies, sleep was objectively assessed using polysomnography [22, 23]. In addition, the study conducted by Roth et al. [23] included an objective assessment of trazodone's effect on cognitive functions, the ability to operate vehicles and the presence of daytime sleepiness. In both studies there was found a significant reduction in wake time after sleep onset (amount of wake time during sleeping period) accompanied by an improvement in sleep quality, a reduction in light sleep and an increase in deep sleep during treatment with trazodone (Table 1). An objective assessment using the multiple sleep latency test (MSLT) showed decreased daytime sleepiness during trazodone treatment, which indicates that patients slept better. Trazodone 50 mg/d did not have a negative effect on the ability to drive vehicles. However, neuropsychological tests showed a slightly negative effect of trazodone on cognitive function [23].

The results of studies indicating an improvement of sleep-maintenance and quality in patients with primary insomnia during trazodone treatment are strengthened by the observations assessing the effect of trazodone on sleep in patients with comorbid insomnia or caused by other disorders.

Especially well-documented is the beneficial effect of trazodone in a dosage of 50-100 mg/d on sleep in patients with depression who are treated with activating antidepressants, like fluoxetine and other selective serotonin reuptake inhibitors (SSRIs), venlafaxine and bupropion [24–26]. The observed improvements included mainly awakenings from sleep and sleep depth, and to a lesser extent sleep-onset insomnia (sleep latency). In studies assessing the effects of trazodone on sleep in patients with dysthymia, no significant effect on sleep continuity (latency, effectiveness, and length of sleep) was observed, but trazodone treatment did have a positive effect on sleep depth [19, 27]. The improvement of sleep quality was accompanied with a decrease of dysthymia symptoms [19].

Aside from affective disorders, other indications in which polysomnography indicated a beneficial effect of trazodone on sleep included insomnia in patients with Alzheimer's disease [28], somatoform disorder [18] and in pregnant women [29]. No improvement in sleep quality was found during treatment with trazodone of insomnia in the course of opiate addiction [30]. Studies conducted in alcohol-dependent patients after detoxification showed a positive effect of trazodone on sleep, but their conclusions were not unanimous. While the study conducted by Le Bon et al. [31] showed that a positive effect of trazodone on sleep may decrease the risk of relapse in alcohol-dependent patients, Friedman et al. [32] noted a reduction in patients' treatment compliance in subsequent months, as well as their drinking more often and in bigger amounts on the days they were not taking the medication.

In addition to the above-mentioned indications and the registered indication for the prescription of trazodone, which is the treatment of depression of various aetiologies [16], including depression with anxiety, trazodone effects on sleep were investigated in further indications that are not registered for this medication. In studies without polysomnography a beneficial effect of trazodone on sleep was shown in post-traumatic stress disorder – dosage 25-600 mg [33, 34] and in primary insomnia in two other studies – dosage 50-150 mg [35, 36].

In the treatment of depression, trazodone normalizes sleep architecture disturbances caused by this disease. These include prolonged sleep latency, increased number and duration of awakenings (reduced sleep efficacy), decreased duration of deep sleep, and increased duration of REM sleep with its early occurrence in the first sleep cycle (shortened REM sleep latency) [37].

Hypnotics

Hypnotics are the most thoroughly documented drugs as regards efficacy and safety for treating insomnia. For short-term treatment, especially the treatment of sleep-onset insomnia, hypnotics are the pharmacological treatment of choice [1, 9, 13]. They significantly decrease sleep latency, while trazodone and other sedative antidepressants have the same effect only if they are administered significantly earlier– at least 1 hour before bedtime.

Some hypnotics (zolpidem, zopiclone, and temazepam) also significantly decrease the time of wakefulness after sleep onset. However, in this indication, the treatment of sleep-maintenance insomnia, sedative antidepressants are no less effective than hypnotics. These are important observations, since sleep-maintenance insomnia affects approximately 70% of patients with insomnia [38] and is a very common sleep-related symptom in patients with mental disorders. Another significant issue is the effect of hypnotics on sleep quality. There is no doubt that they shorten the time to sleep onset and improve sleep continuity by decreasing the number and duration of awakenings and increasing sleep efficacy. Unfortunately, this drug class does not significantly improve sleep depth and can even decrease it (Table 2).

Table 2. **Advantages and disadvantages of trazodone and hypnotics in the treatment of insomnia**

		Trazodone	Hypnotics
Advantages	Effect on sleep	Effective in the treatment of sleep-maintenance insomnia, increases deep sleep, improves sleep quality	Effective in the treatment of sleep-onset insomnia, some of them also in sleep-maintenance insomnia
	Clinical use	Concurrent insomnia and depression treatment (dose >150 mg/d) Insomnia treatment (dose 25-150 mg/d)	Insomnia treatment Concurrent insomnia and anxiety treatment (benzodiazepines)

table continued on the next page

	Tolerance	No risk of drug dependence	Well-tolerated drug group, low risk of interaction with other drugs
Disadvantages	Effect on sleep	Less effective in sleep-onset insomnia, the need to administer 1-2 hours before bedtime	Increase mainly the amount of shallow sleep (stage N2) at the expense of deep sleep (stage N3) and REM sleep (especially benzodiazepines)
	Clinical use	Recommended mainly for insomnia with concomitant depressive or anxiety symptoms, even subclinical ones	Limited use in patients over 65 years of age, contraindicated in patients with obstructive sleep apnoea
	Tolerance	At higher doses the possibility of interactions with other drugs and side effects, only low doses are recommended for insomnia treatment	Risk of drug dependence

This applies especially to benzodiazepines, but also to a lesser extent to non-benzodiazepine hypnotics [39, 40]. This limits the use of these drugs in patients who primarily present with poor sleep quality due to light sleep, which, here again, often affects patients with mental disorders, but also elderly patients. In addition, for the latter group of patients, hypnotics are relatively contraindicated due to their negative effects on cognitive functions and an increased risk of falls. In elderly patients, the risks associated with taking hypnotics may outweigh their beneficial effects on sleep [41]. According to current guidelines for insomnia treatment, both for chronic sleep-maintenance insomnia and poor sleep quality, the primary treatment for elderly patients consists of behavioural interventions, which involve decreasing the time spent in bed at night, avoiding resting in a lying down position and increasing regular age-appropriate physical activity during the daytime [1, 9, 12].

Discussion

Insomnia and poor quality of night sleep are frequent reasons for patients to seek medical advice. Doctors wanting to quickly ease their patient's suffering often decide to introduce pharmacotherapy already during the first visit and prescribe a hypnotic drug. This is understandable and can be compared to administering an analgesic, which rapidly eases pain and gives the physician time to determine the cause of the patient's ailment and decide on an effective form of treatment. In the case of patients suffering from chronic insomnia, this treatment should involve cognitive-behavioural therapy for insomnia [1, 9, 12] and treatment of concomitant conditions. In the case of insomnia comorbid with depression, the treatment of choice is antidepressants that have a beneficial effect on sleep, such as trazodone, mianserin, mirtazapine and agomelatine. Antidepressants that can disturb sleep, such as fluoxetine, duloxetine, and

venlafaxine, should be prescribed with caution [37]. Administering medication that has a positive effect on sleep quality is justified in the treatment of depression, since persistent insomnia is one of the main residual symptoms of depression [42].

Sedative antidepressants are also often used in the treatment of insomnia. The current guidelines of the American Academy of Sleep Medicine state that 3-6 mg of doxepin are effective in the treatment of sleep-maintenance insomnia [13]. The same guidelines also state that trazodone should be avoided for the treatment of insomnia [13], although it is the second most commonly used medication for treating insomnia in the United States [9]. This recommendation is based mostly on the conclusion that the knowledge about the beneficial effects of trazodone on sleep comes primarily from studies performed in patients with insomnia comorbid with mental disorders. There are also some reservations about the tolerance of the drug [20]. Higher doses of trazodone, through serotonergic, alpha-adrenolytic and antihistaminergic action, can cause side effects, most commonly from the gastrointestinal tract (nausea, dry mouth, constipation, diarrhea), headache, dizziness, low blood pressure, and residual morning sedation. A rare side effect of trazodone also includes priapism.

The recommendations of the British Psychopharmacological Society name, next to doxepin, a drug of proven efficacy, trazodone, paroxetine and trimipramine (not available in Poland) as antidepressants with limited evidence of their effectiveness in the treatment of insomnia [9]. The European Sleep Research Society states that sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trazodone, and trimipramine) and agomelatine are effective in short-term insomnia treatment. However, they are not recommended as a long-term treatment option [1], if the insomnia is not accompanied by other psychopathological symptoms, e.g. symptoms of depression and anxiety. Similar recommendations on the use of trazodone in the treatment of insomnia were included in the Polish guidelines. They indicate that trazodone should be considered for insomnia treatment when in the mental state assessment there are symptoms of depression, even subclinical, or when assessment with clinical rating scales shows increased scores for depression, anxiety, insomnia response to stress or excessive physiological arousal [43].

The popularity of antidepressants in the treatment of insomnia does not only stem from the frequent coexistence of insomnia with affective and anxiety disorders. A very important feature of these drugs is that there is no risk of causing dependence. Both benzodiazepines and non-benzodiazepine hypnotics come with a risk of dependence [44]. Antidepressants are also chosen in the treatment of insomnia because they improve sleep maintenance and decrease the wake time after sleep onset. They can therefore be used successfully in the treatment of sleep-maintenance insomnia and early morning awakenings, where the effectiveness of hypnotics is limited. This frequently causes patients to take a second dose of hypnotic during the night, which significantly increases the risk of dependence and disrupts psychomotor functions during the day. However, the prolonged effect of trazodone and other sedative antidepressants, compared to hypnotic drugs, may also have such negative effects. This includes, for example, the

risk of excessive morning sedation. It should be noted that low doses of trazodone (50 mg) do not increase, but rather decrease, daytime sleepiness and have no negative effect on the ability to drive vehicles. However, they may negatively impact cognitive functions in detailed assessments with the use of neuropsychological tests [23]. Due to the above, sedative antidepressants should be taken in the evening in the lowest possible dose. If the patient also suffers from sleep-onset insomnia, the medication should be taken earlier than hypnotics, usually no later than 1-2 hours before bedtime. This decreases the risk of residual morning sedation and increases the efficacy of the drugs used to treat sleep-onset insomnia. In this indication, antidepressants are less effective than hypnotics [45].

A special feature of trazodone, mianserin, and mirtazapine is their ability to increase the amount of deep sleep. Hypnotics usually have the opposite effect. They increase sleep duration, mainly by increasing the amount of light sleep (stage 2 of NREM sleep, marked currently as N2), but sleep EEGs show a decreased activity of slow waves (< 2 Hz in frequency), which are biological markers of sleep depth [39, 40, 46]. The mechanism associated with the improvement of deep sleep is the antagonistic effect of trazodone on 5-HT_2 serotonin receptors, to which trazodone has a high affinity and is one of the strongest antagonists for this receptor [16, 47]. This action is much more important than trazodone's antihistamine effect, which is stronger in mianserin and mirtazapine, but weaker in the case of trazodone [16, 37]. This is associated not only with a lower risk of morning sedation when using trazodone, as opposed to mianserin and mirtazapine, but also with a low risk of increase in body weight. The latter is a common problem during treatment with sedative antidepressants, with the exception of trazodone. While mianserin and mirtazapine increase body mass by 1.28–2.20 kg (1.74 kg on average) during 4-12 weeks of treatment, for trazodone the change in body mass is between – 0.94 and 0.54 kg (-0.20 kg on average) and is not statistically significant [48].

In conclusion, this article presents the various effects of hypnotics and trazodone on sleep. Hypnotics effectively decrease the time to sleep onset and three of them (zolpidem, zopiclone and temazepam) also improve sleep maintenance. Trazodone gives way to hypnotics in the strength and speed of inducing sleep (falling asleep). It is, however, effective in sleep-maintenance insomnia, especially in patients with concomitant 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 improvement of sleep quality as assessed by patients. Hypnotics decrease the activity of slow waves as demonstrated by sleep EEGs, so this group of drugs is not useful in treating patients who report poor sleep quality, not due to problems with falling asleep and waking up during the night, but due to lightness of sleep, which is not regenerative.

The opponents of using antidepressants in insomnia treatment point to the small number of studies conducted in this indication and a worse tolerance profile for antidepressants compared to hypnotics. It is important, therefore, that the dose of those

antidepressants for treating insomnia be kept as low as possible. This can be done if the physician adheres to current guidelines and prescribes both pharmacotherapy and cognitive-behavioural interventions in the treatment of insomnia.

An important difference between the two groups of drugs is also the risk of causing drug dependence. In the case of antidepressants, it is non-existent. In the case of hypnotics, it may also be low, but only provided that they are used for no longer than 2-4 weeks, and afterwards no more than 2-3 nights a week and no more than 3 nights in a row. The positive experience in treating insomnia with low doses of sedative antidepressants should not be applied to treating other disorders. If the insomnia is concomitant with other mental disorders, such as depression, adequate doses of these drugs should be used – for trazodone, that dosage is > 150 mg/d.

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