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Modern standards for pharmacological treatment of insomnia

Współczesne standardy farmakologicznego leczenia bezsenności

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Abstract

In clinical practice, insomnia can be classified as temporary and chronic. They differ in duration. Chronic insomnia lasts over 3 months, with symptoms occurring at least 3 times a week. Insomnia treatment standards were defined e.g. by the American Academy of Sleep Medicine in 2017. There are two treatment approaches. First, non-pharmacological methods should be applied, which are the basis of treatment and guarantee its sustained effect. These methods include abiding hygiene of sleep rules, sleep period limits, stimuli control and cognitive therapy. The second form of treatment is pharmacotherapy. It is based on benzodiazepine receptor agonists, which have replaced previous benzodiazepines. They have less side effects and lower addictive potential. This group includes zolpidem, zaleplon and zopiclone. Dosing regimen mainly depends on the form of insomnia being treated: temporary or chronic. Accidental and temporary insomnia should be treated with hypnotics without delay. It is advised to have a pill near one's bed and take it only when the patient waits too long to fall asleep after laying down or after an arousal. Such dosing scheme significantly reduces the risk of addiction and lowers the risk of transformation of insomnia into the chronic form. In chronic insomnia, when benzodiazepines are taken daily, 2 week period cannot be exceeded. Prolonged time is only allowed when using the drugs 2–3 times a week (or up to 10 times a month). Such pharmacotherapy guidelines are easier to tolerate, when the patient simultaneously complies with behavioural therapy. Besides that, a tricyclic antidepressant drug can also be used – doxepin. The list of inadvisable medications for the treatment of insomnia is composed of: trazodone, tiagabine, diphenhydramine, melatonin, tryptophan, valerian.

Keywords: insomnia, pharmacotherapy of insomnia, insomnia treatment

Streszczenie

W praktyce klinicznej bezsenność można podzielić na krótkotrwałą i przewlekłą. Różnią się one kryterium czasowym. Bezsenność przewlekła trwa dłużej niż 3 miesiące, dolegliwości występują co najmniej 3 razy w tygodniu. Standardy leczenia bezsenności określiła m.in. w 2017 roku Amerykańska Akademia Medycyny Snu. Leczenie jest dwutorowe. W pierwszej kolejności powinny być stosowane metody niefarmakologiczne, które są podstawą terapii i gwarantują jej długotrwały efekt. Metody te obejmują przestrzeganie zasad higieny snu, ograniczenie pór snu, kontrolę bodźców oraz terapię poznawczą. Drugi rodzaj leczenia stanowi farmakoterapia. Podstawą są agoniści receptora benzodiazepinowego. Nowe substancje z tej grupy zastąpiły tradycyjne benzodiazepiny, należą do niej zolpidem, zaleplon i zopiklon. Agoniści receptora benzodiazepinowego wykazują mniej działań niepożądanych oraz przede wszystkim mają niższy potencjał uzależniający. Ich schemat dawkowania zależy głównie od tego, czy leczenie dotyczy bezsenności krótkotrwałej czy przewlekłej. W przypadku bezsenności przygodnej i krótkotrwałej należy jak najszybciej włączyć leki nasenne. Zaleca się położenie jednej tabletki koło łóżka i sięganie po nią tylko wtedy, gdy pacjent po położeniu się, lub w razie wybudzenia w nocy, zbyt długo czeka na zaśnięcie. Taki schemat dawkowania znacznie zmniejsza ryzyko uzależnienia, a większość pacjentów unika przejścia bezsenności krótkotrwałej w przewlekłą. W przypadku bezsenności przewlekłej przy codziennym stosowaniu agonistów benzodiazepin nie wolno przekroczyć okresu 2 tygodni. Warunkiem dłuższego stosowania jest doraźne przyjmowanie, czyli 2–3 razy w tygodniu (lub do 10 razy w miesiącu). Taki sposób leczenia ułatwi jednoczesne stosowanie przez pacjenta metod behawioralnych. Ponadto w terapii można uwzględnić trójpierścieniowy lek przeciwdepresyjny – doksepinę. Do leków niezalecanych w leczeniu bezsenności należą trazodon, tiagabina, difenhydramina, melatonina, tryptofan i waleriana.

Słowa kluczowe: bezsenność, farmakoterapia bezsenności, leczenie bezsenności

INTRODUCTION

There are traditionally two types of treatment for insomnia: pharmacological and non-pharmacological. According to modern standards, non-pharmacological methods are the basis for the treatment of chronic insomnia. Therefore, pharmacological treatment of insomnia, using e.g. hypnotic drugs, should be accompanied by at least basic non-pharmacological strategies, such as sleep hygiene.

The treatment of insomnia should begin as early as possible, i.e. when the condition lasts longer than 2–3 weeks and begins to adversely affect daytime functioning. The earliest possible implementation of treatment will prevent activation of mechanisms maintaining insomnia[1,2].

The treatment of chronic and short-term insomnia differs. In chronic insomnia, sleep-related symptoms are present for over a period of 3 months and occur at least 3 times a week[3–5].

Cognitive-behavioural therapy is the standard treatment of chronic insomnia. It should be the first line method introduced for every patient. The next step involves pharmacotherapy, which remains the second most important strategy, especially as there is a group of patients who, for various reasons – whether organisational or simply because of a lack of conviction – will not benefit from cognitive-behavioural therapy. In such cases, pharmacotherapy is either adjuvant or the sole method used. Furthermore, the treatment should not overlook possible overlapping diseases and disorders, both mental and somatic[1,2,6,7].

NON-PHARMACOLOGICAL TREATMENT OF INSOMNIA

There are many recognised non-pharmacological treatment methods for insomnia. Sleep hygiene, sleep time restriction, stimulus control, and cognitive therapy are considered most important. Techniques useful in insomnia treatment include also relaxation techniques, biofeedback, chronotherapy, and phytotherapy[1,2,6,7].

Sleep hygiene includes fixed sleeping and waking hours, refraining from taking naps during the day, avoiding caffeine, alcohol, and nicotine, avoiding physical exercise and emotionally engaging activities before bedtime, and ensuring silence and optimal bedroom temperature[8].

Sleep restriction consists in arbitrary determination of the time the patient is allowed to stay in bed, which is established on the basis of data from a sleep diary kept by the patients. Sleeping time is gradually increased as the method progresses[9].

Stimulus control consists in associating the bedroom and the bed exclusively with sleep. The patient should only go to bed if they feel sleepy, any other activity (except sexual) in bed is not allowed. If the patient does not fall asleep within 10 minutes (perceived subjectively) after lying down, they should get up and go to another room. They should return to bed once they feel sleepy again. The same time should be always set on the alarm clock, regardless of the duration of night sleep or the day of the week[10].

The core of **cognitive therapy** involves changing the patients' negative thoughts related to insomnia. Education in this area can reduce their fears concerning sleep deprivation and break the vicious circle which leads to arousal[11].

PHARMACOLOGICAL TREATMENT OF INSOMNIA

It consists in administering various medications "improving" sleep. Benzodiazepine receptor agonists are the most commonly used medications in insomnia. This group includes all traditional benzodiazepines and the new generation hypnotics – zolpidem, zopiclone and zaleplon[1,2,7].

Hypnotics in temporary and short-term insomnia

In the case of transient and short-term insomnia, new generation hypnotics (zolpidem, zopiclone, zaleplon) should be prescribed as soon as possible to prevent the development of factors maintaining insomnia. It is advisable, under these circumstances, to place one pill (half a pill for women) near the bed and use it only when it takes too long for the patient to fall asleep, or in the case of middle-of-night-insomnia[2,7]. Such use of hypnotics will significantly reduce the risk of addiction, and most patients with short-term insomnia will avoid transitioning to the chronic phase.

In **chronic insomnia**, benzodiazepine receptor agonists must not be administered chronically, and their daily use should be limited to a period of 2 weeks. They can be used for prolonged periods as needed, 2–3 times a week (or up to 10 times a month). Administering medicine this way is easier when the patient simultaneously uses behavioural methods[12,13].

Pharmacological "alternatives" (antidepressants)

In recent years, substances from other groups are being increasingly proposed as an adjunctive treatment of insomnia, especially antidepressants and natural medicines, which are available without prescription in increasing quantities[14–16].

In clinical practice, if a long-term use of a sleep-enhancing or sleep-inducing medication is necessary, antidepressants with sedative-hypnotic properties may be used as an alternative to hypnotic drugs, especially in patients with symptoms of insomnia and depression. Trazodone, mianserin, mirtazapine, and doxepin are the most commonly used drugs with this profile. They have been shown to improve sleep in patients with insomnia and increase the amount of NREM sleep. No set dose for insomnia treatment has been established. Unlike in depression, the treatment of insomnia usually uses low doses[15,16].

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Over-the-counter drugs

When reviewing medications for insomnia, OTCs cannot be ignored. These include melatonin, antihistamines, and herbal remedies. These medications are commonly used[17], though systematic studies on their subject are still sparse. On the basis of the scant available literature, it is estimated that natural remedies are used by 4 to 18% of the general population and by 30 to over 70% of people complaining of insomnia symptoms[17–19]. Thus far, few proper placebo-controlled trials have been conducted. Therefore, it is difficult to make clear judgments about the efficacy of OTCs. A 2011 review of the available studies on natural remedies and methods used in the treatment of insomnia showed that preparations containing valerian and hops have some advantage over other preparations in improving certain sleep parameters[18].

Modern standards for pharmacological treatment of insomnia (according to AASM)

Current guidelines, published in 2017 by the American Academy of Sleep Medicine (AASM)[20], include a list of recommended and non-recommended agents for treating chronic insomnia. It is worth pointing out that no preparation is recommended as a drug of choice. The decision to choose a specific substance must be made individually in each case. The recommendations are given in the form of a meta-analysis. Despite significant efforts within the framework of evidence-based medicine (EBM), the strength of the individual recommendations is weak. This is due to limitations identified at various steps in the vast majority of the studies. However, this does not change the fact that pharmacotherapy remains a crucial part of treatment. Also, the need for an individualised approach is further emphasised. Therefore, a range of factors must be considered before each decision on the inclusion of pharmacotherapy: treatment goals, comorbid disorders, response to previous treatment attempts, availability and safety of a given preparation, patient preferences, and the cost of therapy.

Not all medicines are available on the Polish market. Examples of drugs not available in Poland:

- suvorexant – an orexin receptor antagonist, recommended for treating insomnia in the form of difficulty maintaining sleep;
- ramelteon – a melatonin receptor agonist, recommended at doses of 8 mg for treating insomnia in the form of difficulty falling asleep.

Due to their unavailability in Poland, they will not be discussed further.

Medicines recommended for treating specific forms of insomnia (note that some preparations are recommended for both forms):

1. For difficulties with falling asleep:

- Eszopiclone – a benzodiazepine receptor agonist, recommended at doses of 2 mg and 3 mg. It decreases sleep latency (as evidenced by objective studies), increases total sleep time (TST; in subjective studies), improves sleep quality and effectiveness, though on a subthreshold level of clinical significance. It involves a low risk of side effects; a beneficial effect of eszopiclone in peri- and postmenopausal women has been reported. However, its beneficial effect is so small that the benefits of administration only slightly outweigh the risk of possible side effects.
- Zaleplon – a benzodiazepine receptor agonist, recommended at a dose of 10 mg. It decreases sleep latency (as evidenced by objective studies), though no clinically significant differences for other sleep parameters have been reported. Benefits of administration outweigh the potential risks only to a slight degree.
- Zolpidem – a benzodiazepine receptor agonist. It decreases sleep latency, increases TST, reduces wake after sleep onset (WASO), and increases sleep quality (all confirmed by objective studies). The above benefits outweigh the risk for 10 mg doses and 12.5 mg extended release doses (not available on the Polish market). For preparations with immediate and extended release, the recommended doses are lower. Zolpidem was the first benzodiazepine receptor agonist (3-Z) introduced into the market, and is currently the longest-used and most popular medication of this type. Zolpidem is also available in a sublingual form, and in this form is especially intended for middle-night-insomnia because it shortens falling sleep again. Rebound insomnia (worsening of sleep after discontinuation of medicine) is a problem faced by every doctor planning to include a benzodiazepine receptor agonist in the treatment. This topic has been extensively studied for zolpidem. It has been shown that rebound insomnia symptoms occur most frequently during the first night after discontinuation (though they do not have to occur at all). This is regardless of the administration regimen – whether the medicine was used each night or intermittently. Naturally, the treatment must be limited in duration. In clinical studies, zolpidem was used for 6 months at most. Moreover, impairment in daytime functioning was not observed in the vast majority of participants. These symptoms mostly occur with 10 mg doses taken less than 8 hours before waking time.
- Triazolam – a benzodiazepine derivative with a recommended dose of 0.25 mg. It decreases sleep latency (in subjective ratings); sleep quality is lower in comparison to placebo; in geriatric population, it increases TST; one study has shown a reduction in sleep interruptions (other studies have not confirmed this effect); in general, the benefits are considered to virtually equal the risks. The medication is not available on the Polish market. It was never registered, though it enjoyed popularity in the 1980s and 90s.
- Temazepam – a benzodiazepine derivative with a recommended dose of 15 mg. It decreases sleep latency and increases TST (in subjective ratings).

2. For difficulties with sleep maintenance:

- eszopiclone – described above;
- zolpidem – described above;

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- temazepam – described above;
- doxepin – a tricyclic antidepressant with recommended doses of 3 mg and 6 mg. Increases TST (with 6 mg dose being more effective), shortens WASO, increases sleep quality and effectiveness.

Medications not recommended for the treatment of insomnia:

- Trazodone – antidepressant medication, 5-HT2 serotonin receptor antagonist and selective serotonin reuptake inhibitor. Does not improve any sleep parameter, though side effects are more common than with placebo.
- Tiagabine – anticonvulsant medication, GABA reuptake inhibitor. No improvements on any sleep parameter, slight worsening of sleep latency, TST, WASO, number of awakenings during night and sleep effectiveness.
- Diphenhydramine – first-generation antihistamine medication. No improvement on most sleep parameters; slight improvement of sleep quality; side effects more common than with placebo.
- Melatonin – natural hormone produced by the pineal gland when in darkness. Shortens sleep latency (immediate and extended release preparations), especially among seniors, increases sleep effectiveness.
- Tryptophan – exogenous amino acid. No improvement on most sleep parameters, slight reduction of sleep interruptions.
- Valerian – no improvement on any sleep parameter.

CONCLUSIONS

1. Medical consultation is necessary in each case of sleep difficulties persisting for more than 2–3 weeks and beginning to negatively impact daytime functioning.
2. Modern standards suggest that treatment should begin as early as possible to avoid activating the mechanisms maintaining insomnia – its "chronicalisation."
3. In cases of transient or short-term insomnia, the primary and usually sufficient method of treatment involves the use of appropriate hypnotics and education on sleep hygiene.
4. In cases of chronic insomnia, the primary method of treatment is behavioural therapy, which can be supplemented pharmacologically, e.g. using hypnotics as needed (no more than 2–3 times per week).

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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