Psychiatr. Pol. 2023; 57(3): 495–516
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/OnlineFirst/161597

Treatment of insomnia in older adults. Recommendations of the Polish Sleep Research Society, Polish Society of Family Medicine and the Polish Psychiatric Association

Adam Wichniak[1], Przemysław Bieńkowski[2], Rafał Dąbrowski[3], Agnieszka Mastalerz-Migas[4], Joanna Rymaszewska[5]

[1] Third Department of Psychiatry, Institute of Psychiatry and Neurology in Warsaw
[2] Department of Psychiatry, Medical University of Warsaw
[3] Department of Coronary Artery Disease and Cardiac Rehabilitation, National Institute of Cardiology, Warsaw
[4] Department of Family Medicine, Wroclaw Medical University
[5] Department of Psychiatry, Wroclaw Medical University

Summary

Insomnia is one of the most common health problems in developed countries. Its prevalence increases with age, with up to one in two people over the age of 65 experiencing symptoms of insomnia. The older people are also the patients who mostly commonly are among chronic sleep medication users. The aim of this article is to present the current recommendations for the management of insomnia in people over 65 years of age.

The recommendations were prepared as a position of an expert panel, which included people from a number of clinical disciplines: family medicine, cardiology, psychiatry, sleep medicine and clinical psychopharmacology.

The first step in treating sleep disorders is to establish proper diagnosis and, if possible, to initiate causal treatment. Moreover, cognitive and behavioural therapy for insomnia should also be used as the primary form of treatment, which can be supplemented, if not sufficiently effective, with pharmacological treatment. The main group of drugs used for treating insomnia are nonbenzodiazepine sedative hypnotics (zolpidem, zopiclone, eszopiclone, zaleplon). However, these drugs do not fully meet the needs of people over 65 years of age, primarily with regard to treatment safety. Therefore, other classes of medicines, which are used for treatment of mental disorders, are prescribed off-label in this group of patients. Melatonin in a prolonged-release form is also indicated for this age group due to the high safety of the therapy.

The management of insomnia in people over 65 years of age is a challenging task, given the need to seek compromise between treatment efficacy and safety. The treatment plan also has to take into account comorbidities as well as drugs used to treat them.

Key words: insomnia, older people, treatment

Introduction

Lifestyle changes associated with the development of civilisation have significantly increased the prevalence of many medical conditions. These disorders, referred to as civilisation diseases, include among others insomnia. Over the past 20 years, the prevalence of insomnia in developed countries has increased from around 6% to 10%, which is also accompanied by an increasing number of people continuously taking sleep medication [1]. Such a significant increase in the prevalence of insomnia is seen as a growing health problem [1]. Chronic insomnia with a sleep duration of less than 6 hours is associated with the risk of significant health deterioration. It is a risk factor for somatic diseases, e.g. cardiovascular diseases [2], mental disorders such as depression [3], it reduces the quality of life [4], increases the frequency of healthcare use, reduces productivity and increases absenteeism from work and the risk of accidents [5].

The major problem with the treatment of insomnia is that in many countries it is still dominated by pharmacotherapy, which is often used as the only treatment modality. This is inconsistent with the current recommendations for the treatment of insomnia, which unanimously indicate that symptomatic pharmacological treatment with sleep medication is an effective treatment option only for episodic or short-term sleep problems which do not meet the diagnostic criteria for insomnia. If these criteria are met, the primary form of treatment should be cognitive behavioural therapy for insomnia, which can be supplemented with pharmacological treatment if not sufficiently effective. In older people, it is worth considering prolonged-release melatonin due to its high safety profile [1, 6, 7]. Behavioural interventions are needed to reinforce the physiological mechanisms that regulate sleep: the homeostatic sleep need and circadian rhythm [8]. Cognitive interventions, on the other hand, can change the patient's dysfunctional beliefs and attitudes related to sleep, thus reducing the fear of insomnia.

The use of non-pharmacological treatments for insomnia became particularly important during the COVID-19 pandemic which, through the emotional burden and lockdown- and telework-related changes in the activity and rhythm of life, further increased the prevalence of sleep problems [9].

Treatment of insomnia is particularly challenging in older patients. Physiological changes in sleep, associated with ageing, include a decrease in the total sleep time, an increase in sleep latency, an increase in the number and duration of awakenings from sleep, a decrease in sleep efficiency and a decrease of the deep sleep [10]. Complaints about poor sleep are often the predominant symptom in this group of people [11]. Difficulties with starting or maintaining sleep can occur in up to one in two people over 65 years of age [12, 13] and are caused not only by age-related deterioration of sleep

quality, but also by co-occurring somatic diseases and psychiatric disorders. At least one chronic somatic disease is present in more than 80% of people of this age, two or more somatic conditions are present in about two-thirds of people over 65 [14].

Despite the numerous risks associated with taking sedative hypnotics and their low efficacy at this age [15], the older people are among patients in whom sedative hypnotics are often used chronically, despite the high risk of developing tolerance and dependence on sleep medication [16, 17]. These data indicate the need to educate physicians about effective treatment options for insomnia in people over 65 years of age, with focus on non-pharmacological methods and pharmacological treatment associated with a low risk of falls and other side effects.

The aim of this article is to present the current recommendations on the diagnosis and treatment of insomnia in people over 65 years of age.

Method

The recommendations were prepared as a position of an expert panel, which included people from a number of clinical disciplines: family medicine, cardiology, psychiatry, sleep medicine and clinical psychopharmacology. Experts were invited by the first author to develop recommendations. Each expert was asked to elaborate a series of recommendations directly related to their specialisation, based on their professional experience and the available recommendations from scientific societies and relevant references in the literature. The resulting recommendations were put forward in the form of a presentation and discussed during the expert panel meeting, which resulted in a common position statement.

The diagnosis of insomnia

A proper diagnosis is the first step towards an effective treatment of sleep disorders. When differentiating the causes of insomnia, a careful assessment of the patient in five areas is recommended: 1) mental health, 2) somatic diseases and general health, 3) medications and psychoactive substances taken, 4) lifestyle, environmental factors, 5) primary sleep disorders.

Differentiation and co-occurrence of insomnia against mental disorders

Insomnia or difficulty sleeping are often the only symptoms a patient with a mental disorder will complain about to a doctor. Sometimes only a longer conversation with an assessment of the patient's sleep problems can reveal additional psychopathological symptoms and syndromes. Sleep problems can occur as a symptom or even a diagnostic criterion in the course of most psychiatric disorders: mood disorders (depressive episode, mania, dysthymia), anxiety disorders (generalised anxiety disorder, anxiety disorder with panic attacks [nocturnal attacks], post-traumatic stress disorder, adjust-

ment disorder), psychotic disorders (schizophrenia, schizoaffective disorder, delusional disorder) and organic mental disorders (dementia, delirium).

Insomnia as a disorder can co-occur with psychiatric disorders and requires due medical attention. More than 30% of older people with insomnia have an accompanying mental disorder [18]. Findings indicate that therapy for insomnia leads to better treatment outcomes for co-occurring mental disorders [19]. The importance of diagnosing insomnia in mental disorders is underlined by hard evidence, such as the fact that insomnia is a risk factor for relapse in people treated for depression and even a marker for increased risk of suicidal thoughts [20]. Furthermore, a link has been shown between suicidal thoughts and sleep disturbances in people with no other mental disorders [21].

Sleep problems occur in around 60% of people with depression and are associated, similarly to those occurring in older age, with reduced sleep length and depth. However, a shortened REM sleep latency is more common in depression than in other mental disorders. The most common sleep-related symptom in the course of depression in older age is waking up too early in the morning. The quality of sleep is also affected by chronic pain which often affects older people. In chronic pain clinics, between 50% and 88% of patients complain of sleep disturbances [22].

Up to two-thirds of patients with Parkinson's disease experience sleep-related disorders, including problems falling asleep as well as night and morning awakenings [23]. Similarly, people with dementia secondary to Alzheimer's disease and other medical conditions often have sleep disturbances associated with the reversal of the diurnal cycle, sleep initiation and maintenance disorders. Older people may experience insomnia associated with abuse or dependence on sedative hypnotics (hypnotic-dependent insomnia, HDI) which are used almost twice as long as by younger people [24]. Geriatric addictions remain under-recognised and under-treated. Doctors do not routinely assess or screen older people for alcohol or other addictive substance use disorders, including medication [25]. A small number of studies in Poland have shown that approximately 30% of the population – including 20% of men and 10% of women – abuse alcohol in old age [26, 27], which is also associated with sleep disorders.

Characteristic of addiction to sedative hypnotics is the emergence of tolerance, resulting in the use of increasingly higher doses of medication, rebound insomnia, excessive sleepiness, depressive symptoms and anxiety after withdrawal. Older people may also experience seizures and hallucinations.

A detailed history and psychiatric examination make it possible to differentiate between primary insomnia and sleep disorders caused by another mental disorder. In almost every scale assessing depressive symptoms, there are questions about sleep disturbances.

To differentiate between insomnia and mental disorders, it is necessary to:

– ask about the patient's day-to-day functioning, how the patient copes with daily chores,

- ask about recent important events in the patient's life, serious concerns or losses,
- use brief and reliable screening tools for the most common mental disorders in older age: for depression – PHQ-9, and anxiety disorders – GAD-7. A score > 10 is the optimal cut-off point for both scales and indicates the need for further diagnostic work-up for a depressive episode or generalised anxiety disorder,
- perform a simple screening test for cognitive impairment (MMSE or TYM (Test Your Memory) self-assessment test),
- gather a brief geriatric history of alcohol dependence (SMAST). A result with > 2 confirmatory responses requires further diagnosis for alcohol use disorders,
- assess what medicines have been used to improve sleep, the timing and frequency of their use, their doses and whether they need to be increased.

Differentiation and co-occurrence of insomnia against somatic diseases

Among somatic diseases, due to its prevalence, insomnia most often co-occurs with cardiovascular disorders. Other somatic diseases frequently associated with insomnia include chronic obstructive pulmonary disease, asthma, allergies, diabetes, chronic renal failure, rheumatic and cancer diseases, cerebrovascular and neurodegenerative diseases, multiple sclerosis, and a number of other conditions associated with pain, endocrine or metabolic disorders, and reduced daytime physical activity [1]. The deterioration of sleep quality may also result from adverse effects of drugs used for the treatment of somatic diseases, e.g. glucocorticosteroids, alpha- and beta-blockers, angiotensin receptor antagonists, second-generation antihistamines, statins.

The relationship between sleep and cardiovascular diseases is bidirectional. On the one hand, it has been shown that people suffering from hypertension, heart failure or ischaemic disease are far more likely to suffer from sleep disorders. The occurrence of nocturnal symptoms, such as pain, frequent urination or dyspnoea, has been cited as a potential cause [28, 29]. On the other hand, insomnia significantly increases the risk of cardiovascular diseases, while reduced sleep duration and sleep fragmentation cause important pathophysiological changes that add to this effect. There is activation of the sympathetic nervous system and dysregulation of the hypothalamic-pituitary-adrenal axis. Increased levels of cortisol, the 'stress' hormone, lead to impaired glucose metabolism and increased secretion of catecholamines. There are also disorders affecting the functions of arterial baroreceptors and chemoreceptors. People with insomnia show signs of a systemic, chronic inflammation – an increase in cytokines (CRP, TNF-α, interleukin 6). In addition, oxidative stress processes are exacerbated and there is an increase in endothelin levels. This causes damage to the vascular endothelium and reduces nitric oxide secretion. Immune system dysfunction has also been demonstrated in people with insomnia [30].

All of these processes can result in heart rhythm disorders and disorders of heart rhythm variability as well as disruption of the diurnal rhythm of blood pressure, including its elevation, adverse metabolic changes, including dyslipidaemia, increased glycaemic levels and insulin resistance. On the other hand, deep sleep during the NREM phase has been shown to prevent physiological stress – increases in blood pressure and ischaemia of the brain [30]. The effects of the sleep disorders referred to above can result in the development or exacerbation of hypertension, heart failure, cardiac arrhythmias, and an increased risk of heart attacks, strokes and deaths [30, 31].

This has been confirmed by clinical studies. Just one night when a person gets 1-2 hours less sleep results in an increase in systolic blood pressure. The results of a meta-analysis of 17 studies, involving 58,924 people, with a minimum 1-year follow-up, showed an increase in the prevalence of hypertension in people sleeping < 6 hours per day [32]. The Coronary Artery Disease in Young Adults (CARDIA) study found a relationship between reduced sleep duration and increased coronary artery calcification and faster progression of atherosclerotic lesions in the arteries [33]. People > 45 years of age, who sleep less than 6 hours per night, have a 2 times higher risk of having a heart attack or stroke as compared to those sleeping 8 hours per night. This is often linked to the increasing burden of family and work life, leading to permanent stress that exacerbates sleep disturbances, which brings on more stress. The results of a meta-analysis of 11 prospective studies in more than 1,000,541 adults without cardiovascular diseases showed that both short, < 6 hours, and long, > 8 hours, sleep periods cause, respectively: 11% and 33% higher risk of cardiovascular complications or death from coronary heart disease or strokes as compared to those sleeping 6 to 8 hours [34]. These data confirmed the results of another meta-analysis involving 74 studies in 3,340,684 patients [35]. It is most desirable to aim for 7 hours of sleep per night.

Another aspect of sleep disorders are nocturnal awakenings, which are associated with long-term cardiovascular mortality, more often in women than in men [36]. Another analysis, covering the period 2000-2013 (Taiwan's Longitudinal Health Insurance Database) and a cohort of 1,685,500 people, found a significant increase in the incidence of heart failure in people with sleep disorders [37]. Equally important is the timing of falling asleep. A 6-year observational study using accelerometers (smartwatches) showed a possible link between bedtime and the incidence of cardiovascular diseases, particularly in women. The optimum time is between 10:00 and 11:00 p.m. [38].

On the other hand, the coexistence of cardiovascular diseases also affects sleep disorders. Hypertension causes sleep problems, difficulty staying asleep, frequent waking up and poor sleep quality. The effects of heart failure and coronary artery disease can include shortness of breath when lying down, frequent trips to the toilet and chest pain. The cardiac arrhythmias experienced by patients often cause stress, anxiety and difficulty falling asleep or waking up.

The same is true for respiratory diseases, especially chronic obstructive pulmonary disease (COPD) and asthma, which are among the most common causes leading to insomnia [1]. Sleep disturbances accompanying COPD have a similar mechanism to

that associated with cardiovascular diseases and obstructive sleep apnoea, i.e. they are related to the activation of the sympathetic nervous system. It leads to numerous awakenings or micro-awakenings from sleep, which ultimately reduces the quality of sleep and shortens its duration [39]. Poor sleep quality is, in turn, a risk factor for COPD exacerbations. This is suggested by the results of a multicentre study of 1,647 COPD patients, which found that those with poor sleep quality had a 25-95% higher risk of COPD exacerbations as compared to patients with good sleep quality [40].

In asthma, frequent awakenings, shortened sleep duration and reduced sleep quality are associated both with physiological changes in night-time breathing mechanics, including decreased tonic respiratory muscle activity and increased airway resistance, and with asthma exacerbations. They very often present at night in the form of persistent coughing and breathlessness, and poor sleep quality can be a significant health problem for patients [41].

Given its prevalence, gastroesophageal reflux disease (GERD) should also be considered as a possible cause of insomnia. A study by Vakil et al. [42] found that up to 64% of GERD patients suffer from sleep problems. These data were also confirmed by studies conducted in France (62%) and Canada (55%) [43, 44]. The main cause leading to deterioration of sleep quality in GERD patients is the accumulation of food content in the lower part of the oesophagus, especially in the supine position, resulting in numerous awakenings from sleep. As many as two out of three GERD patients report that heartburn is a factor negatively affecting their sleep [45]. In the senior population, due to its prevalence, attention should also be paid to chronic kidney disease (CKD), which can affect up to 10% of the general population, with a significantly higher prevalence in people over 65 years of age [46]. Sleep problems are a common health problem faced by patients, particularly in end-stage renal failure. A review of 17 studies showed that the mean prevalence of sleep disturbances associated with CKD was 44%. One mechanism leading to the development of insomnia in CKD patients is a disproportion between the sympathetic and parasympathetic nervous system activity, resulting from impaired baroreceptor functions [47]. Restless legs syndrome is also common in CKD patients. Proper identification and treatment of the cause of insomnia in CKD patients can significantly improve their quality of life and reduce morbidity and mortality from comorbidities [48].

Differentiation and co-occurrence of insomnia against other primary sleep disorders

Sleep disorders refer to diverse disorders classified into 6 major diagnostic groups: 1) insomnia, 2) sleep-disordered breathing 3) hypersomnias of central origin 4) circadian rhythm disorders of sleep and wakefulness, 5) parasomnias, 6) sleep-related movement disorders.

Given its prevalence in patients with insomnia, obstructive sleep apnoea (OSA) should be excluded. For this screening assessment, the STOP-BANG questionnaire

[49] or the Berlin questionnaire [50] can be used. OSA is a sleep disorder for which pharmacotherapy is not effective. In addition, the presence of OSA is a relative contraindication to the use of sedative hypnotics. The exception is prolonged-release melatonin.

It is also necessary to carefully exclude circadian rhythm sleep-wake disorders (CRSWD), for which sedative hypnotics are not effective and are contraindicated in older people with dementia syndromes [51]. The primary form of treatment for this group of disorders should be non-pharmacological chronobiological treatment, as discussed below, combined with the use of melatonin or melatoninergic drugs, avoidance of light or bright light therapy at designated times of the day [52, 53].

Disorders whose incidence increases significantly after the age of 50 include restless legs syndrome (RLS). Any patient with chronic insomnia should therefore be asked about the occurrence of an unpleasant feeling of restlessness in the legs when trying to rest in the evening or fall asleep at night, and which tends to disappear when the patient walks or moves the legs [54]. Pharmacological treatment is indicated in the treatment of restless legs syndrome, but it is different from that in insomnia. Pregabalin and gabapentin are currently indicated as first-choice drugs while dopamine receptor agonists ropinirole and pramipexole are second-choice drugs [55]. Before implementing pharmacotherapy for RLS, it is necessary to carefully rule out latent iron deficiency by determining ferritin and iron metabolism parameters and to exclude adverse effects of the drugs being used. RLS symptoms can be caused, for example, by antidepressants, especially mirtazapine and mianserin, and sedative antipsychotics such as chlorprothixene, levomepromazine, perazine, promethazine, quetiapine, olanzapine, which are sometimes used to treat insomnia in people over 65 years of age.

A warning sign that the patient's insomnia is caused by another sleep disorder, somatic illness or psychiatric disorder is the occurrence of excessive sleepiness with falling asleep against one's will during the day. If the patient additionally reports sleep attacks and their general health does not explain their occurrence, it should be considered referring the patient for a polysomnographic study to assess their sleep.

Treatment of insomnia

The treatment of insomnia in people over 65 focuses on two main interventions:

- treatment of comorbidities associated with insomnia using non-pharmacological and pharmacological methods when indicated, according to the treatment recommendations for the condition,
- non-pharmacological interventions, including general health-promoting interventions with an emphasis on age-appropriate physical activity and specific interventions used in cognitive behavioural therapy for insomnia.

In addition, following a careful assessment of indications and contraindications, it is possible to use drugs recommended for the pharmacotherapy of insomnia in people over 65 years of age.

Non-pharmacological treatment of insomnia

Comprehensive and personalised rehabilitation of somatic comorbidities associated with insomnia results in the improvement of the patient's overall condition. Most importantly, it increases the parasympathetic nervous system activity [56]. Current recommendations focus on improving sleep conditions and promote healthy lifestyle. The rhythm of exercise is important – aerobic exercises are recommended, with a duration of at least 30 minutes, every day, at least a few hours before bedtime. The rhythm of meals is also important: avoiding hard-to-digest foods and large quantities of liquids late in the evening, avoiding stimulants in the evening (coffee, tea, alcohol). Controlling body weight, ensuring optimal sleep duration (6-8 hours), earlier bedtime (at 10:00-11:00 p.m.) – all of these create conditions conducive to reducing sleep disturbances. These issues are clarified by the 2021 guidelines contained in the publicly available expert opinion of the Polish Cardiac Society titled 'Comprehensive cardiac rehabilitation as they keystone in the secondary prevention of cardiovascular disease' [57, 58].

Treatment of insomnia using cognitive behavioural therapy techniques based on a classical approach includes cognitive and behavioural interactions [59], as briefly characterised in Table 1.

Table 1. **Cognitive behavioural therapy techniques used in the treatment of insomnia (compiled from [59])**

Behavioural techniques	
Sleep restriction	This is the primary intervention to increase the homeostatic need for sleep as well as the most effective intervention that can be used to increase deep sleep. The patient is advised to reduce their sleep time to the average length of their sleep as assessed based on a sleep diary kept for 7-day periods; however, it should not be less than 5 hours.
Stimulus control	The intervention aims to reverse the conditioned learning mechanisms that perpetuate insomnia and are exacerbated when the patient uses bed for purposes other than sleep. The patient is advised not to use bed for activities other than sleep and sexual activity, and to leave bed when they cannot fall asleep and feel upset about it.
Sleep hygiene	It includes a number of behavioural recommendations that, if followed, help to improve sleep quality. When used as a sole intervention, it is only useful for the primary prevention of sleep problems and it is not, when not combined with other interventions, an effective treatment for insomnia.
Relaxation training	A group of psychological interventions, of which progressive muscle relaxation – Jacobson's technique – is most commonly used for the treatment of insomnia. It reduces the level of physiological arousal before sleep and makes it easier to fall asleep.
Cognitive techniques	
Psychoeducation	Education about the mechanisms regulating sleep improves patient co-operation in adherence to behavioural therapy for insomnia. It also corrects the patient's unfavourable beliefs and expectations related to sleep, e.g. regarding its necessary length and quality.

table continued on the next page

Cognitive reappraisal	Includes more complex interactions than psychoeducation, which are used to reduce the patient's fear of insomnia, e.g. its health consequences or its negative impact on daytime functioning, also shifting the patient's attention and concerns related to sleep quality to real activities performed during the day.
Paradoxical intervention	It aims to reduce the anticipatory anxiety associated with trying to fall asleep. Patients are instructed to close their eyes and remain still after going to bed, but to try to stay awake for as long as possible. The patient's failure to attempt to fall asleep results in a shorter period to fall asleep.
Cognitive control/ Worry time	A group of techniques to help the patient release emotionally charged thoughts before going to sleep, e.g. the patient is asked to sit in a comfortable chair and write down a list of tasks and worries, as well as a plan for the next day, before going to sleep. A difficulty encountered in treating many patients is that such activities, along with trying to remember tasks, are performed after they have gone to bed, which exacerbates their sleep problems.

A highly effective treatment of insomnia is achieved first and foremost by the introduction of behavioural techniques – sleep restriction and stimulus control – which should be used consistently by the patient for at least 6 weeks. It is most advisable to follow the treatment protocol in full during the treatment period. If this is not possible due to health contraindications, e.g. when using a sleep restriction technique or due to patient-specific needs, a transdiagnostic treatment model is beneficial [60]. It includes interventions provided on a case-by-case basis (transdiagnostic interventions), including e.g. case formulation, education on sleep and circadian rhythm, setting treatment goals, establishing recommended behavioural changes and assessing motivation to implement them. The core modules used in the treatment of most patients include establishing regular bedtimes and getting up in the morning, promoting activity and improving daily functioning, working on misconceptions about sleep, and maintaining recommended behavioural changes. Optional modules used according to the patient's individual needs and health status include: improving sleep efficiency by reducing time in bed, improving the management of worry and alertness, treating sleep apnoea and treating delayed or advanced circadian sleep rhythm. Although both conditions can occur in people over 65 years of age, delayed sleep rhythm is more typical of teenagers and young adults, while older people are more likely to complain of advanced sleep phases. The patient then reports to the doctor with complaints of waking up from sleep at least two hours earlier than the desired time and asks for sleep-prolonging medication. However, he/she does not convey the information that the time of sleep onset is very early and therefore the total sleep time is not significantly reduced. For those with an advanced sleep rhythm, it is advisable to maintain family or social activities in the evening, to have evening exposure to light and exercise, and to avoid light and intense activity after waking up too early in the morning [52].

In order to generalise the use of CBT techniques in the treatment of insomnia, given the limited availability of therapists, mobile apps based on CBT techniques are being intensively developed. Among them, it is worth mentioning:

- CBT-I Coach, an app developed by a Stanford team, commissioned by the Department of Veterans Affairs,
- Sleepio, created by an Oxford team,
- Go!to Sleep, developed at Cleveland Clinic,
- Goodsleeper, a programme in Polish and Ukrainian with professional therapeutic tools and a complete sleep improvement programme for self-use.

Pharmacological treatment of insomnia

Drugs used to treat insomnia must meet a wide range of requirements. The most important requirements are as follows: 1) rapid action, 2) effective induction and maintenance of sleep, 3) natural sleep profile, 4) no impact on daytime performance, 5) no side effects or interactions, 6) no development of tolerance, 7) no risk of dependence, 8) no withdrawal symptoms, 9) use regardless of age, 10) wide therapeutic window. Many medicines come close to meeting these requirements, but none fully addresses the needs of people over 65 years of age with regard to treatment efficacy and safety. Consequently, other groups of psychotropic drugs are used off-label in this patient group in addition to drugs approved in Europe for the treatment of insomnia, which include specific benzodiazepine and nonbenzodiazepine sedative hypnotics. Melatonin in a prolonged-release form is also recommended for the treatment of insomnia in people over 55 years of age due to its high safety profile.

Hypnotics

The main group of drugs used for the treatment of insomnia are nonbenzodiazepine sedative hypnotics (Table 2) referred to in practice as Z-drugs (zolpidem, zopiclone, eszopiclone, zaleplon).

Table 2. **Drugs approved for treatment of insomnia in Poland**

Drug	Dose (mg)	Half-life interval (hours)
Nonbenzodiazepine hypnotics*		
Eszopiclone	1-3	6
Zaleplon	10	1-1.5
Zolpidem	5-10	2-3
Zopiclone	3.75-7.5	5-8
Benzodiazepine derivatives #		
Estazolam	1-2	10-24
Lormetazepam	0.5-1	10-12
Nitrazepam	5-10	24

table continued on the next page

Temazepam	10-20	7-11
Other medicines		
Prolonged-release melatonin	2	3.5-5
Daridorexant	25-50	8

* For older patients, 1/2 of the recommended dose should be used, and the use of this group of drugs, due to the increased risk of falls, should be limited to cases where the severity of insomnia prevents daily functioning or causes acute suffering.

Another drug in this group, which is approved for short-term treatment of insomnia, is midazolam. Midazolam should be avoided in the treatment of insomnia due to its potent effects, rapid development of tolerance and high risk of developing severe dependence. The other drugs in this group are also relatively contraindicated in older adults; if they need to be administered, 1/2 of the recommended dose should be used.

These drugs have an inhibitory effect on brain regions associated with wakefulness mechanisms by stimulating GABA-A receptors for ɣ-aminobutyric acid. The mechanism of action of zolpidem and other Z-drugs is similar to that of benzodiazepines (diazepam, lorazepam, alprazolam); however, Z-drugs are more selective. Z-drugs stimulate only certain subtypes of GABA-A receptors, and therefore, at recommended doses, they produce no pronounced anti-anxiety or myorelaxant effects which are typical of benzodiazepines [61].

The pharmacokinetic features of Z-drugs as well as their rapid onset and short duration of action are beneficial from the point of view of insomnia patients. The use of Z-drugs is associated with a lower risk of morning drowsiness than most benzodiazepines. In contrast, the introduction of Z-drugs into treatment has not brought a breakthrough in terms of the risk of developing tolerance and addiction. In practice, the use of Z-drugs should follow the same principles for preventing the development of dependence as those used for benzodiazepines [61, 62].

The significant differences between Z-drugs result from their pharmacokinetic characteristics, most notably their duration of action [63]. Zopiclone has a significantly longer duration of action (T1/2 = 5-8 h). Zaleplon is a drug with a very short duration of action (T1/2 = 1-1.5 h). Zolpidem is a drug with a T1/2 ranking between zaleplon and zopiclone (T1/2 = 2-3 h). A patient suffering primarily from sleep initiation problems will be eligible for zaleplon or zolpidem therapy. A patient reporting nocturnal awakenings or waking prematurely can be treated with zopiclone; however, they should not receive zaleplon. Due to their rapid onset of action, Z-drugs should be used shortly before bedtime [64].

Typical side effects of Z-drugs include dizziness and headaches, morning drowsiness (especially after taking zopiclone) and memory impairment. Z-drugs can cause somnambulism and sudden awakenings with disorientation, as well as incomplete awakenings accompanied by behaviours covered by amnesia. In sensitive individuals, they can cause paradoxical reactions associated with agitation, anxiety, hallucinations. Z-drugs are contraindicated in patients with myasthenia gravis, sleep apnoea and those

with severe respiratory failure. Their chronic use in older people, especially with sleep-related breathing disorders, can lead to serious negative health consequences, e.g. increase the risk of stroke [65]. Like benzodiazepines, Z-drugs can have additive interactions with alcohol. The use of Z-drugs and benzodiazepines in the older adults always requires great caution [66]. Hypnotics (with the exception of lorazepam, oxazepam and temazepam) are metabolised in the liver by cytochrome P450 3A4. To diminish the risk of interaction with cytochrome P450 inhibitors and increased plasma concentrations of the drug, in patients > 65 years of age, in women and in patients with liver failure, the dose of Z-drugs should be halved, i.e. from a typical single dose of 10 mg to 5 mg for zolpidem and zaleplon and from a typical dose of 7.5 mg to 3.75 mg for zopiclone [67].

In older adults the use of hypnotics is associated with a significantly increased risk of falls and fractures. Falls with fractures of the femoral neck in people aged 65 and older occur with an incidence of about 11 per 1,000 person-years and are about twice as common (IRR 2.08) than in people of this age not taking hypnotics [68]. Meta-analyses evaluating how hypnotics increase the risk of falls in the elderly indicate that in the case of long-acting benzodiazepines (e.g. estazolam, which is often used in Poland), it is higher (OR 1.81) than in the case of short-acting benzodiazepines (OR 1.27) [69]. For Z-drugs, the highest increase of the risk of falls with head injury or hip fracture was found for zolpidem (OR 1.87 for head injury, 1.59 for hip fracture). In contrast, eszopiclone use was not associated with a significantly increased risk (OR 0.67 for head injury, 1.12 for hip fracture) [70].

Sedative drugs

In addition to sedative hypnotics, antidepressants with sedative effects (in doses far lower than for other indications) and other psychotropic drugs with anti-anxiety and sleep-inducing effects are used to treat sleep disorders.

Antidepressants that facilitate falling asleep are effective to a degree comparable to benzodiazepine receptor agonists, and their use does not present the risk of dependency. A drug with additional antihistamine and alpha-1 blocker effects, doxepin at a dose of 3 mg (the lowest dose available in Poland is 10 mg), has been shown to be effective in treating insomnia in older patients without daytime side effects. It should be taken 3 hours after a meal and about 30 minutes before bedtime. There are no 'rebound' or residual effects. In polysomnographic studies, doxepin has been shown to increase total sleep time, reduce the time and number of awakenings after falling sleep, and improve sleep efficiency [71]. The meta-analysis by Yeung et al. [72] showed that doxepin improves sleep efficiency and prolongs total sleep time; however, it does not significantly affect sleep latency. Doxepin is the only antidepressant drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of insomnia. Potential side effects of other sedative tricyclic antidepressants (e.g. amitriptyline), which include doxepin, include sedation, weight gain, postural hypotension, cardiac arrhythmias (QTc interval

prolongation), urinary retention and anticholinergic side effects, which significantly limits their use for the treatment of sleep disorders in older patients.

The other antidepressants listed in Table 3, such as agomelatine, mianserin, mirtazapine or trazodone, can promote sleep, especially in people with depressive symptoms, and they can be expected to take effect no sooner than about 30 minutes after their use. The time of administration should be determined on the basis of pharmacokinetic parameters (Cmax, T1/2) of the drug in question. In practice, some of these drugs are administered up to 3-4 hours before the scheduled bedtime.

Table 3. **Drugs for the treatment of mental disorders that, in addition to their on-label use, are also used off-label to treat insomnia**

Drug	Hypnotic dose (mg)	Half-life interval (hours)
Antidepressants		
Agomelatine	25	1-2
Amitriptyline	10-150	10-50
Doxepin*	10-25	8-24
Mianserin	5-30	6-39
Mirtazapine	7.5-15	13-40
Trazodone	25-150	3-14
Antipsychotics		
Chlorprothixen	7.5 – 30	8-12
Levomepromazine	2.5 – 25	15-30
Olanzapine	2.5	34
Promethazine	6.25 – 25	7-14
Promazine	12.5-25	10-24
Quetiapine	12.5-100	6-8
Other psychotropic drugs		
Hydroxyzine	10-50	7-20 (29 in the older patients)
Pregabalin	50-150	6
Gabapentin	600	5-7
Tiagabine	5-8	7-9
OTCs		
Melatonin	0.5 – 5	0.8-0.9
L-tryptophan	1000	N/A
Diphenhydramine	25-50	4-6

table continued on the next page

Doxylamine	12.5-25	10-13
Valerian	225-1215	N/A

*Doxepin is approved for the treatment of insomnia in the United States, the recommended dose is 3 mg for people over 65 and 6 mg for other patients.

Potential side effects of trazodone, important for the older population, include sedation, dizziness, cardiac arrhythmias and orthostatic hypotension. Another rare side effect, typical of trazodone, is priapism [13].

Mirtazapine blocks 5-HT2 receptors, the stimulation of which may be one of the causes of sleep problems in people with depression. In a review of studies, Dolder et al. [73] showed that mirtazapine improves sleep efficiency, length and quality; however, it is necessary to monitor daytime sleepiness and weight gain.

On the other hand, among antipsychotics, quetiapine, due to its strong action on histamine receptors, can be used at doses of 12.5-100 mg as a sedative drug [74]. It improves sleep architecture, lengthens sleep, facilitates falling asleep and reduces night-time awakenings in people with depressive episodes [75] as well as in addicts in treatment [76]. It is considered to be one of the safer drugs with a sleep-inducing effect in older people, including those with dementia.

Other antihistamines such as promethazine have little addictive potential. Some of them, e.g. doxylamine and diphenhydramine, are available in many countries without prescription. Due to their cholinolytic effects, these drugs may cause cognitive impairment, qualitative disorders of consciousness and deterioration of the general health status of the older adults. In this age group, they should only be used in low doses.

Medicines classified as derivatives of γ-aminobutyric acid, gabapentin and pregabalin, have not been studied for the treatment of insomnia in older patients; nevertheless, they can be used for comorbid anxiety, alcohol withdrawal, neuropathic pain or restless legs syndrome. Adverse effects may occur in the form of cognitive decline, dizziness, hypotonia and even symptoms of psychiatric disorders, including suicidal thoughts.

A Cochrane review [77] of the pharmacotherapy of sleep problems in dementia showed no sufficient evidence, including in particular randomised clinical trials, to develop recommendations for pharmacological treatment of sleep disorders in dementia. There is some evidence to support the use of low-dose trazodone in this group of patients [78].

Cholinesterase inhibitors (such as donepezil), used in dementia, increase the duration of REM sleep and sleep continuity in patients with dementia with Lewy bodies [79].

Patients also commonly use over-the-counter medicines and dietary supplements to alleviate insomnia symptoms. Tryptophan may be effective after a few days of use at a dose of more than 1 g, but there are no studies that would evaluate its efficacy and safety in older patients. Nausea, lethargy, slowness and fatigue have been observed in adults. Valerian, due to its modulating effect on GABA-A receptors, shows some efficacy and is safe for older people [13], but it is not a recommended treatment for insomnia [80].

Sedative antidepressants and antipsychotics, like hypnotics, increase the risk of falls in older adults (OR 1.54 for antipsychotics, 1.57 for antidepressants) [69]. Therefore, it is important to administer these drugs in the lowest dose. It is possible when they are used as a therapy added to non-pharmacological treatment. The use of antipsychotics only in low doses is also necessary due to the reported increased risk of stroke with these drugs [81].

Melatonin and melatonergic drugs

Melatonin is the synthetic equivalent of the natural human hormone secreted by the pineal gland in response to nightfall. Its synthesis decreases with age, and therefore, as a chronobiotic, it can be used to improve sleep induction and quality in older adults. Melatonin is not a drug generally recommended for treatment of insomnia if insomnia is not attributable to a disruption of the circadian rhythm of sleep and wakefulness [1, 80]. These recommendations do not include people aged 55 and over [6]. In this patient group, melatonin treatment shows higher efficacy due to a marked decrease in melatonin secretion by the pineal gland occurring after 50 years of age [50]. In the older patients, prolonged-release melatonin is the safest form of therapy in terms of the risk of falls or exacerbation of somatic disorders, e.g. cardiac or respiratory disorders [83]. This is due to the fact that prolonged-release melatonin does not have a strong sedative effect, and does not display anticholinergic, adrenolytic and antihistamine activity. The last one is related not only to sedation, but also to the risk of weight gain, which is not observed during treatment with melatonin. The risk of a negative impact on psychomotor performance in the morning is the lowest for prolonged-release melatonin among all the drugs that can be used in the treatment of insomnia. Moreover, prolonged-release melatonin is not an addictive drug and no development of tolerance was observed even with long-term use. It should be taken in a 2 mg dose, approximately 1 hour before the scheduled bedtime for up to 13 weeks in combination with behavioural interventions [84]. In the case of predominant difficulty to fall asleep, it may be advisable to administer the drug earlier, 1-2 hours before bedtime.

Circadian rhythm is most strongly influenced by proper exposure to daylight. Older people should go outside for a long walk every day and avoid strong light and blue light at night after taking melatonin. Other factors that shape the sleep rhythm are the rhythm of meals, social activities and physical exercise. Changes in the rhythms of daily life associated with the cessation of work activities, reduced social contact as well as ocular abnormalities increase the role of the circadian sleep rhythm disturbances in the pathogenesis of insomnia.

Drugs with melatonergic effects from the MT1 and MT2 melatonin receptor agonist group have also been introduced for the treatment of insomnia. Ramelteon, a drug recommended for the treatment of insomnia associated with sleep initiation difficulties [80], is not available in Europe. Agomelatine, which in addition to its melatonergic

action is also a serotonin 5-HT2c receptor antagonist, is approved for the treatment of depressive episodes.

Summary and conclusions

The treatment of insomnia in people over 65 years of age is a challenging task, given the need to seek compromise between treatment efficacy and safety. The treatment plan also has to take into account comorbidities as well as the drugs used to treat them.

Of primary importance is the correct diagnosis and effective treatment of comorbidities that exacerbate insomnia as well as non-pharmacological treatment of insomnia. Based on this approach, pharmacological treatment of insomnia, if still necessary, can use less potent drugs and at lower doses, which is associated with greater safety of pharmacotherapy. Due to the significant decrease in melatonin secretion occurring from 55 years of age onwards and its high safety of use, prolonged-release melatonin may be considered as first-line treatment, especially in older patients with somatic diseases.

References

1. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG et al. *European guideline for the diagnosis and treatment of insomnia.* J. Sleep Res. 2017; 26(6): 675–700.
2. Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. *Insomnia and risk of cardiovascular disease: A meta-analysis.* Eur. J. Prev. Cardiol. 2014; 21(1): 57–64.
3. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U et al. *Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies.* J. Affect. Disord. 2011; 135(1–3): 10–19.
4. Kyle SD, Morgan K, Espie CA. *Insomnia and health-related quality of life.* Sleep Med. Rev. 2010; 14(1): 69–82.
5. Daley M, Morin CM, LeBlanc M, Grégoire JP, Savard J, Baillargeon L. *Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents.* Sleep Med. 2009; 10(4): 427–438.
6. Wilson S, Anderson K, Baldwin D, Dijk D-J, Espie A, Espie C et al. *British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update.* J. Psychopharmacol. 2019; 33(8): 923–947.
7. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. *Management of chronic insomnia disorder in adults: A Clinical Practice Guideline from the American College of Physicians.* Ann. Intern. Med. 2016; 165(2): 125–133.
8. Borbély AA, Daan S, Wirz-Justice A, Deboer T. *The two-process model of sleep regulation: A reappraisal.* J. Sleep Res. 2016; 25(2): 131–143.
9. Altena E, Baglioni C, Espie CA, Ellis J, Gavriloff D, Holzinger B et al. *Dealing with sleep problems during home confinement due to the COVID-19 outbreak: Practical recommendations from a task force of the European CBT-I Academy.* J. Sleep Res. 2020; 29(4): e13052.
10. Espiritu JRD. *Aging-related sleep changes.* Clin. Geriatr. Med. 2008; 24(1): 1–14.

11. Patel D, Steinberg J, Patel P. *Insomnia in the elderly: A review.* J. Clin. Sleep Med. 2018; 14(6): 1017–1024.
12. Crowley K. *Sleep and sleep disorders in older adults.* Neuropsychol. Rev. 2011; 21(1): 41–53.
13. Abad VC, Guilleminault C. *Insomnia in elderly patients: Recommendations for pharmacological management.* Drugs Aging 2018; 35(9): 791–817.
14. Wolff JL, Starfield B, Anderson G. *Prevalence, expenditures, and complications of multiple chronic conditions in the elderly.* Arch. Intern. Med. 2002; 162(20): 2269–2276.
15. Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. *Sedative hypnotics in older people with insomnia: Meta-analysis of risks and benefits.* BMJ 2005; 331(7526): 1169–1173.
16. Neutel CI. *The epidemiology of long-term benzodiazepine use.* Int. Rev. Psychiatry 2005; 17(3): 189–197.
17. Neutel CI, Skurtveit S, Berg C. *What is the point of guidelines? Benzodiazepine and z-hypnotic use by an elderly population.* Sleep Med. 2012; 13(7): 893–897.
18. Kay DB, Dzierzewski JM. *Sleep in the context of healthy aging and psychiatric syndromes.* Sleep Med. Clin. 2015; 10(1): 11–15.
19. Ohayon MM. *Epidemiology of insomnia: What we know and what we still need to learn.* Sleep Med. Rev. 2002; 6(2): 97–111.
20. Thase M. *Depression, sleep, and antidepressants.* J. Clin. Psychiatry 1998; 59(Suppl 4): 55–65.
21. Franzen PL, Buysse DJ. *Sleep disturbances and depression: Risk relationships for subsequent depression and therapeutic implications.* Dialogues Clin. Neurosci. 2008; 10(4): 473–481.
22. AGS Panel on Persistent Pain in Older Persons. *The management of persistent pain in older persons.* J. Am. Geriatr. Soc. 2002; 50(6 Suppl): 205–224.
23. Tandberg E, Larsen JP, Karlsen K. *A community-based study of sleep disorders in patients with Parkinson's disease.* Mov. Disord. 1998; 13(6): 895–899.
24. Stewart R, Besset A, Bebbington P, Brugha T, Lindesay J, Jenkins R et al. *Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74 years.* Sleep 2006; 29(11): 1391–1397.
25. Zin-Sędek M. *Prevalence and patterns of alcohol drinking among the elderly based on the results of the Standardized European Alcohol Survey (RARHA SEAS).* Alcoholism and Drug Addiction 2019; 32(1): 1–24.
26. Fedorowicz J. *Nałóg w starości.* Na Temat – Zeszyt Dla Profesjonalnie Pomagających 2004; 4: 32–35.
27. Żółtańska JH, Łukieńczuk T. *Alkohol jako czynnik ryzyka złamań kości kończyn u osób starszych.* Piel. Zdr. Publ. 2015; 5(3): 265–274.
28. Ziółkowski J. *Zaburzenia snu w chorobach tarczycy.* Sen 2008; 8: 40–46.
29. Frøjd LA, Munkhaugen J, Moum T, Sverre E, Nordhus IH, Papageorgiou C et al. *Insomnia in patients with coronary heart disease: Prevalence and correlates.* J. Clin. Sleep Med. 2021; 17(5): 931–938.
30. Javaheri S, Redline S. *Insomnia and risk of cardiovascular disease.* Chest 2017; 152(2): 435–444.
31. Gangwisch JE. *A review of evidence for the link between sleep duration and hypertension.* Am. J. Hypertens. 2014; 27(10): 1235–1242.
32. Meng L, Zheng Y, Hui R. *The relationship of sleep duration and insomnia to risk of hypertension incidence: A meta-analysis of prospective cohort studies.* Hypertens. Res. 2013; 36(11): 985–995.

33. King CR, Knutson KL, Rathouz PJ, Sidney S, Liu K, Lauderdale DS. *Short sleep duration and incident coronary artery calcification.* JAMA 2008; 300(24): 2859–2866.
34. Fountas E, Stratinaki M, Kyrzopoulos S, Tsiapras D, Iakovou I, Athanasopoulos G et al. *Relationship between sleep duration and cardiovascular disease: A meta-analysis.* Eur. Heart J. 2018; 39(Suppl 1): ehy565.P2540.
35. Kwok CS, Kontopantelis E, Kuligowski G, Gray M, Muhyaldeen A, Gale CP et al. *Self-reported sleep duration and quality and cardiovascular disease and mortality: A dose-response meta-analysis.* J. Am. Heart Assoc. 2018; 7 (15): e008552.
36. Shahrbabaki SS, Linz D, Hartmann S, Redline S, Baumert M. *Sleep arousal burden is associated with long-term all-cause and cardiovascular mortality in 8001 community-dwelling older men and women.* Eur. Heart J. 2021; 42(21): 2088–2099.
37. Wang ID, Chien WC, Chung CH, Tsai PY, Chang SY, Meng FC et al. *Non-apnea sleep disorder associates with increased risk of incident heart failure – A nationwide population-based cohort study.* PLoS One 2019; 14(1): e0209673.
38. Nikbakhtian S, Reed AB, Obika BD, Morelli D, Cunningham AC, Aral M et al. *Accelerometer-derived sleep onset timing and cardiovascular disease incidence: A UK Biobank cohort study.* Eur. Heart J. Digit. Health 2021; 2(4): 658–666.
39. Jen R, Li Y, Owens RL, Malhotra A. *Sleep in chronic obstructive pulmonary disease: Evidence gaps and challenges.* Can. Respir. J. 2016; 2016: 7947198.
40. Baugh A, Buhr RG, Quibrera P, Barjaktarevic I, Barr RG, Bowler R et al. *Risk of COPD exacerbation is increased by poor sleep quality and modified by social adversity.* Sleep 2022; 45(8): zsac107.
41. Cukic V, Lovre V, Dragisic D. *Sleep disorders in patients with bronchial asthma.* Mater. Sociomed. 2011; 23(4): 235–237.
42. Vakil N, Wernersson B, Wissmar J, Dent J. *Sleep disturbance due to heartburn and regurgitation is common in patients with functional dyspepsia.* United European Gastroenterol J. 2016; 4(2): 191–198.
43. Moayyedi P, Hunt R, Armstrong D, Lei Y, Bukoski M, White R. *The impact of intensifying acid suppression on sleep disturbance related to gastro-oesophageal reflux disease in primary care.* Aliment. Pharmacol. Ther. 2013; 37(7): 730–737.
44. Cadiot G, Delaage PH, Fabry C, Soufflet C, Barthélemy P. *Sleep disturbances associated with gastro-oesophageal reflux disease: Prevalence and impact of treatment in French primary care patients.* Dig. Liver Dis. 2011; 43(10): 784–787.
45. Shaker R, Castell DO, Schoenfeld PS, Spechler SJ. *Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: The results of a Gallup survey conducted on behalf of the American Gastroenterological Association.* Am. J. Gastroenterol. 2003; 98(7): 1487–1493.
46. Kovesdy CP. *Epidemiology of chronic kidney disease: An update 2022.* Kidney Int. Suppl. (2011). 2022; 12(1): 7–11.
47. Hildreth CM. *Prognostic indicators of cardiovascular risk in renal disease.* Front. Physiol. 2012; 2: 121.
48. Pierratos A, Hanly PJ. *Sleep disorders over the full range of chronic kidney disease.* Blood Purif. 2011; 31(1–3): 146–150.
49. Chung F, Abdullah HR, Liao P. *STOP-Bang Questionnaire: A practical approach to screen for obstructive sleep apnea.* Chest 2016; 149(3): 631–638.
50. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. *Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome.* Ann. Intern. Med. 1999; 131(7): 485–491.

51. Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. *Clinical Practice Guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: Advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). An update for 2015: An American Academy of Sleep Medicine Clinical Practice Guideline.* J. Clin. Sleep Med. 2015; 11(10): 1199–1236.
52. Wichniak A, Jankowski K, Skalski M, Skwarło-Sońta K, Zawilska J, Żarowski M et al. *Treatment guidelines for Circadian Rhythm Sleep – Wake Disorders of the Polish Sleep Research Society and the Section of Biological Psychiatry of the Polish Psychiatric Association. Part II. Diagnosis and treatment.* Psychiatr. Pol. 2017; 51(5): 815–832.
53. Wichniak A, Jankowski KS, Skalski M, Skwarło-Sońta K, Zawilska JB, Zarowski M et al. *Treatment guidelines for Circadian Rhythm Sleep-Wake Disorders of the Polish Sleep Research Society and the Section of Biological Psychiatry of the Polish Psychiatric Association. Part I. Physiology, assessment and therapeutic methods.* Psychiatr. Pol. 2017; 51(5): 793–814.
54. Ferri R, Lanuzza B, Cosentino FII, Iero I, Tripodi M, Spada RS et al. *A single question for the rapid screening of restless legs syndrome in the neurological clinical practice.* Eur. J. Neurol. 2007; 14(9): 1016–1021.
55. Garcia-Borreguero D, Silber MH, Winkelman JW, Högl B, Bainbridge J, Buchfuhrer M et al. *Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: A combined task force of the IRLSSG, EURLSSG, and the RLS-foundation.* Sleep Med. 2016; 21: 1–11.
56. Horsley KJ, Rouleau CR, Garland SN, Samuels C, Aggarwal SG, Stone JA et al. *Insomnia symptoms and heart rate recovery among patients in cardiac rehabilitation.* J. Behav. Med. 2016; 39(4): 642–651.
57. Jegier A, Szalewska D, Mawlichanów A, Bednarczyk T, Eysymontt Z, Gałaszek M et al. *Comprehensive cardiac rehabilitation as the keystone in the secondary prevention of cardiovascular disease. Expert Opinion of the Cardiac Rehabilitation and Exercise Physiology Section of the Polish Cardiac Society.* Kardiol. Pol. 2021; 79(7–8): 901–916.
58. Piotrowicz R, Jegier A, Szalewska D, Wolszakiewicz J, Piotrowicz E, Smolis-Bąk E et al. *Rekomendacje w zakresie realizacji kompleksowej rehabilitacji kardiologicznej.* Gdańsk: AsteriaMed; 2017.
59. Baglioni C, Altena E, Bjorvatn B, Blom K, Bothelius K, Devoto A et al. *The European Academy for Cognitive Behavioural Therapy for Insomnia: An initiative of the European Insomnia Network to promote implementation and dissemination of treatment.* J. Sleep Res. 2020; 29(2): e12967.
60. Harvey AG, Dong L, Hein K, Yu SH, Martinez AJ, Gumport NB et al. *A randomized controlled trial of the Transdiagnostic Intervention for Sleep and Circadian Dysfunction (TranS-C) to improve serious mental illness outcomes in a community setting.* J. Consult. Clin. Psychol. 2021; 89(6): 537–550.
61. Becker PM, Somiah M. *Non-benzodiazepine receptor agonists for insomnia.* Sleep Med. Clin. 2015; 10(1): 57–76.
62. MacFarlane J, Morin CM, Montplaisir J. *Hypnotics in insomnia: The experience of zolpidem.* Clin. Ther. 2014; 36(11): 1676–1701.
63. Drover DR. *Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: Zaleplon, zolpidem and zopiclone.* Clin. Pharmacokinet. 2004; 43(4): 227–238.
64. National Institute for Health and Care Excellence. *Quick reference guide Zaleplon, zolpidem and zopiclone for the short-term management of insomnia.* 2007: 1–2.

65. Lee CC, Tsai KY, Hung YT, Chou FHC, Huang YS. *Association of hypnotics with stroke risk: A population-based case-control study.* Prim. Care Companion CNS Disord. 2014; 16(2): 26670.

66. Zammit G. *Comparative tolerability of newer agents for insomnia.* Drug Saf. 2009; 32(9): 735–748.

67. Wichniak A. *Standardy leczenia farmakologicznego wybranych zaburzeń snu.* In: Jarema M, ed. *Standardy leczenia farmakologicznego niektórych zaburzeń psychicznych,* 2nd ed. Gdańsk: Via Medica; 2015. pp. 224–249.

68. Lin FY, Chen PC, Liao CH, Hsieh YW, Sung FC. *Retrospective population cohort study on hip fracture risk associated with zolpidem medication.* Sleep 2014; 37(4): 673–679.

69. Seppala LJ, Glind van de EMM, Daams JG, Ploegmakers KJ, Vries de M, Wermelink AMAT et al. *Fall-risk-increasing drugs: A systematic review and meta-analysis: III. Others.* J. Am. Med. Dir. Assoc. 2018; 19(4): 372.e1–372.e8.

70. Tom SE, Wickwire EM, Park Y, Albrecht JS. *Nonbenzodiazepine sedative hypnotics and risk of fall-related injury.* Sleep 2016; 39(5): 1009–1014.

71. Lankford A, Rogowski R, Essink B, Ludington E, Heith Durrence H, Roth T. *Efficacy and safety of doxepin 6mg in a four-week outpatient trial of elderly adults with chronic primary insomnia.* Sleep Med. 2012; 13(2): 133–138.

72. Yeung WF, Chung KF, Yung KP, Ng THY. *Doxepin for insomnia: A systematic review of randomized placebo-controlled trials.* Sleep Med. Rev. 2015; 19: 75–83.

73. Dolder CR, Nelson MH, Iler CA. *The effects of mirtazapine on sleep in patients with major depressive disorder.* Ann. Clin. Psychiatry 2012; 24(3): 215–224.

74. Coe HV, Hong IS. *Safety of low doses of quetiapine when used for insomnia.* Ann. Pharmacother. 2012; 46(5): 718–722.

75. Karsten J, Hagenauw LA, Kamphuis J, Lancel M. *Low doses of mirtazapine or quetiapine for transient insomnia: A randomised, double-blind, cross-over, placebo-controlled trial.* J. Psychopharmacol. 2017; 31(3): 327–337.

76. Chakravorty S, Hanlon AL, Kuna ST, Ross RJ, Kampman KM, Witte LM et al. *The effects of quetiapine on sleep in recovering alcohol-dependent subjects: A pilot study.* J. Clin. Psychopharmacol. 2014; 34(3): 350–354.

77. Quinn TJ, McCleery J, Noel-Storr AH, Marcus S, Flicker L. *Cochrane Dementia Group Turns 21-Older and (Slightly) Wiser.* J. Am. Med. Dir. Assoc. 2017; 18(2): 96–98.

78. Camargos EF, Louzada LL, Quintas JL, Naves JOS, Louzada FM, Nóbrega OT. *Trazodone improves sleep parameters in Alzheimer disease patients: A randomized, double-blind, and placebo-controlled study.* Am. J. Geriatr. Psychiatry 2014; 22(12): 1565–1574.

79. Kazui H, Adachi H, Kanemoto H, Yoshiyama K, Wada T, Tokumasu Nomura K et al. *Effects of donepezil on sleep disturbances in patients with dementia with Lewy bodies: An open-label study with actigraphy.* Psychiatry Res. 2017; 251: 312–318.

80. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. *Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline.* J. Clin. Sleep Med. 2017; 13(2): 307–349.

81. Koponen M, Rajamaki B, Lavikainen P, Bell JS, Taipale H, Tanskanen A et al. *Antipsychotic use and risk of stroke among community-dwelling people with Alzheimer's disease.* J. Am. Med. Dir. Assoc. 2022; 23(6): 1059–1065.e4.

82. Pandi-Perumal SR, Zisapel N, Srinivasan V, Cardinali DP. *Melatonin and sleep in aging population.* Exp. Gerontol. 2005; 40(12): 911–925.

83. Wichniak A, Kania A, Siemiński M, Cubała WJ. *Melatonin as a potential adjuvant treatment for COVID-19 beyond sleep disorders.* Int. J. Mol. Sci. 2021; 22(16): 8623.

84. Wade AG, Crawford G, Ford I, McConnachie A, Nir T, Laudon M et al. *Prolonged release melatonin in the treatment of primary insomnia: Evaluation of the age cut-off for short – and long-term response.* Curr. Med. Res. Opin. 2011; 27(1): 87–98.

Address: Adam Wichniak
Third Department of Psychiatry
Institute of Psychiatry and Neurology
02-957 Warszawa, Sobieskiego Street 9
email: wichniak@ipin.edu.pl