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Review Article

REVIEW OF AVAILABLE DRUGS AND NON-PHARMACOLOGICAL STRATEGIES USED TO TREAT INSOMNIA

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ABSTRACT

Insomnia is one of the most prevalent sleep disorders occurring worldwide among the adult population. Prolonged lack of proper nightly rest can have a significant impact not only on the psychological individual well-being but also on their overall somatic health. Due to said problem's frequent occurrence it is important that every clinician has a basic knowledge of available treatment options for insomnia. Currently, both pharmacological options as well as non-pharmacological approaches can be implemented to improve sleep quality. When choosing a specific treatment method, one must consider the patient's health factors such as comorbidities, age, chronically used medications, and financial resources. Nowadays the first recommended line of treating insomnia is focused on cognitive behavioral therapy (CBT), behavioral changes, and patient education in matters of sleep hygiene. In certain cases, it may be beneficial to implement hypnotic drugs, of which non-benzodiazepine benzodiazepine receptor agonists (non-BZRA) have relatively highest numbers of studies dedicated to testing their efficacy and safety. In patients with coexisting psychiatric disorders, certain antidepressants may play a significant role in sleep disorders management. Despite the prevalence of sleep disorders in the general population there still exists a need to conduct more comprehensive studies directly comparing distinct groups of hypnotic drugs – both their safety profile as well as their efficacy in treating insomnia.

KEYWORDS: insomnia, CBT-I, hypnotics, melatonin, non-BZRA

1. Insomnia – definition, prevalence, risk factors

Sleep disorders are a vast group of conditions related to disturbance in physiological sleep patterns. Insomnia is one of the most widespread sleep disorders in the adult population – it is estimated that at least 30% of the general population have experienced symptoms of insomnia at some point during their lifetime [1].

The exact definition of insomnia (also called sleeplessness) is not precisely agreed on. General scientific consensus usually defines insomnia as an individual's subjective feeling of having trouble sleeping. This definition encapsulates problems with falling asleep (sleep latency), sleep that provides less-than-adequate rest, frequent awakenings at night, and abnormally increased tiredness and need to sleep during the day. According to one of the more in-depth studies dedicated to defining insomnia, those symptoms need to occur at least three times per week and last longer than one month to be categorized as clinical insomnia [2]. The time frame of one month was defined in both ICD-10 and DSM-IV diagnostic tools. Since the publication of DSM-5 in 2022 the minimal duration of symptoms needed to diagnose insomnia was increased to 3 months [3].

Proper sleep follows a cyclical pattern, typically comprising 4-5 cycles throughout the night. Each cycle consists of two distinct phases: the NREM (Non-rapid eye movement) sleep phase and the REM (rapid eye movement) sleep phase – both phases are needed in appropriate amounts for sleep to provide adequate rest. Physiological sleep time duration may differ between any given two individuals. The optimal amount of time spent sleeping per day depends on numerous factors, of which age is the most important. The general consensus on recommended daily sleep duration for newborns is 14 to 17 hours, infants 12 to 15 hours, toddlers 11 to 14 hours, preschoolers 10 to 13 hours, school-age children 9 to 11 hours, teenagers 8 to 10 hours, and adults (between ages 18 to 64) – 7 to 9 hours of sleep. However, 7 to 8 hours of sleep is sufficient for older people

[5] (Table 1). This data shows that the need for sleep naturally diminishes with age which is essential information to consider when diagnosing insomnia. Sleep duration smaller than the aforementioned amounts does not necessarily mean that an insomnia diagnosis can be made. One of the most important aspects is how the shortened sleep duration impacts a patient's overall well-being and functioning during the day.

Table 1. Recommended sleep duration [5].

Age	Recommended sleep duration in hours
Newborns	14 to 17
Infants	12 to 15
Toddlers	11 to 14
Preschoolers	10 to 13
School-aged children	9 to 11
Teenagers	8 to 10
Adults	7 to 9
Older adults	7 to 8

Insomnia may develop at any point during one's life. It is important to note that there are several well-documented risk factors for developing insomnia – for example, women are more likely to be affected than men, with a prevalence rate 1.7 times higher, especially in age groups above 60 years. Insomnia occurs more often in people with coexisting medical conditions, both physical (e.g., asthma, arthritis, heart disease, or chronic back pain) and mental disorders, like depressive episodes or anxiety disorder. What must be taken into consideration is that in these cases insomnia might also be a symptom of underlying conditions. Oftentimes, insomnia is transient and occurs during periods of high stress or emotional turmoil. The largest demographic of insomnia patients consists of individuals with mental or physical ailments. Because of these phenomena, it is of utmost importance to properly evaluate a patient's overall well-being before beginning to treat insomnia as a separate disorder [4]. However, there exists a subset of patients where the root causes of insomnia are unclear, termed primary insomnia.

The optimal therapeutic path for treating insomnia may vary, depending mostly on its etiology and coexisting individual health factors. Before beginning to treat the patient presenting with insomnia one must ensure that comorbidities which may be a reason for sleep disorders are managed adequately. Medical interventions aimed at eliminating the root cause of an individual's sleeping problems usually bring satisfactory improvement and are crucial in the effective therapy of secondary insomnia. Best results are most often observed when combining two treatment methods: pharmacotherapy and non-pharmacological interventions. Pharmacotherapy encompasses medications from diverse categories, each with distinct mechanisms of action, pharmacokinetics, indications for use, and side effects. The non-pharmacological methods include cognitive-behavioral therapy, introducing proper sleep hygiene, and distinct types of relaxation techniques [6].

After eliminating probable causes for secondary insomnia, it is important to differentiate between acute and chronic insomnia. The exact cut-off duration between those two types of sleeplessness often varies in the available literature. General consensus separates short-term insomnia from chronic insomnia at the 3-month mark of symptom duration [7]. The treatment of mild to moderate acute insomnia (often caused by psychological distress) may be limited to educating the patient and reassuring them of the plan for follow-up if the symptoms do not improve without stronger intervention. In the case of severe acute insomnia which substantially impacts a patient's functioning, there is a vast array of different medications that can be used in short-term pharmacological treatment. In the case of chronic insomnia, the pharmacological methods differ from the medications used in a short-term treatment. Moreover, psychological interventions such as cognitive-behavioral therapy play a more significant role [8].

The efficacy of those different methods of treating insomnia is the topic of this paper – each of the main groups of drugs and interventions is briefly summarized below.

2. Pharmacological methods of treating insomnia

2.1. Benzodiazepines (BZD)

One of the most established groups of drugs used in the treatment of insomnia is benzodiazepines. Benzodiazepines function by enhancing the potency of the naturally occurring neurotransmitter, γ-aminobutyric acid (GABA), which in turn lowers the excitability of neurons. This diminishes the transmission of signals between neurons, resulting in a calming influence on various brain functions. In addition to being used in treating insomnia, various BZD are implemented as anxiolytics, anticonvulsants, and sedatives [9]. The first benzodiazepine to be used as a hypnotic was flurazepam, approved by the FDA (Food and Drug Administration) in 1970. Currently (in the US) five benzodiazepines are approved and classified as hypnotic drugs: flurazepam, estazolam, triazolam, temazepam, and quazepam. In Europe, the most often cited BZD drugs used both on-label and off-label to treat insomnia are diazepam, flurazepam, flunitrazepam, lormetazepam, oxazepam, nitrazepam, temazepam and triazolam [10].

Since benzodiazepines work as central nervous system (CNS) depressants, they are quite efficient in treating insomnia. There have been many studies analyzing the efficacy and safety of any given benzodiazepines as hypnotics. One of the most comprehensive meta-analyses of such studies has shown that benzodiazepine use led to a notable increase in overall sleep duration by 61.8 minutes (with a 95% confidence interval ranging from 37.4 to 86.2) and an overall increase in patient satisfaction with their nighttime rest. What is interesting is the fact that sleep record studies indicated a lack of significant decrease in sleep latency (4.2 minutes compared to placebo, 95% confidence interval [CI] −0.7 to 9.2) while patient-reported outcomes indicated a decrease by 14.3 minutes (95% CI 10.6 to 18.0) [11].

Despite their efficacy and generally favorable safety profile, benzodiazepine use is associated with numerous downsides that cannot be ignored in clinical practice. Compared to older classes of hypnotic drugs, such as barbiturates, benzodiazepines are rather difficult to overdose on their own, yet they still may present

substantial health hazards when combined with other CNS depressants, such as alcohol or opiates [12].

Benzodiazepines are recommended to be used only in short-term treatment of acute cases of insomnia since they are prone to causing dependence in patients and later on, they may lead to the development of secondary insomnia associated with benzodiazepine withdrawal. The risk of developing benzodiazepine habituation is higher in patients who have a history of previous addictions [13]. Moreover, given the long biological half-time of many BZD drugs they also may lead to drowsiness, decreased mental performance, worsened reaction time, and motor coordination in the morning following the day of administering BZD [12, 13]. Given these factors, some authors suggest that benzodiazepines in most cases should be avoided as a first line of treatment for any kind of insomnia. Instead, one should consider a safer alternative, which pharmacologically works analogously to benzodiazepines – nonbenzodiazepine benzodiazepine receptor agonists (non-BZRA) [13].

2.2. Nonbenzodiazepine benzodiazepine receptor agonists

Nonbenzodiazepine benzodiazepine receptor agonists (colloquially called Z-drugs) are a class of drugs whose pharmacodynamics are remarkably similar to benzodiazepines. Nonbenzodiazepines function as positive allosteric modulators of the GABA receptor by attaching to the benzodiazepine site in neuron cell walls within the receptor complex. The differentiation between BZD and nonbenzodiazepines stems from their dissimilar chemical structures. They also present a slightly different (oftentimes more beneficial) safety profile compared to traditional benzodiazepines [13].

The most commonly prescribed hypnotic nonbenzodiazepines are eszopiclone, zolpidem, and zaleplon. Similarly to benzodiazepines, many studies have proven Z-drugs efficacy in treating insomnia. One meta-analysis focused specifically on nonbenzodiazepines has proven that Z-drugs enhance both objective and subjective sleep onset compared to a placebo, especially among younger individuals and female patients [14]. Another meta-analysis which encompassed over 154 trials with over 44000 participants concluded that eszopiclone has one of the most favorable profiles (both in terms of efficacy and safety) of all hypnotic drugs in treating both acute and chronic insomnia [15]. Other studies have also proven that eszopiclone improves numerous areas in which overall sleep quality is judged, such as sleep latency, number of awakenings during the night, total sleep time, and depth of sleep [16].

Compared to benzodiazepines Z-class drugs present fewer side effects and lesser potential for abuse. Many of those differences stem from their lower biological half-time, compared to BZD. This is the primary reason nonbenzodiazepines show significantly less frequent side effects after awakening, such as somnolence, trouble with waking up, or memory impairment. The tolerance for nonbenzodiazepines does not increase as rapidly as it does for benzodiazepines, therefore decreasing the risk of substance dependence. Withdrawal symptoms and rebound insomnia are rare when stopping nonbenzodiazepines and occur less frequently compared to those experienced when discontinuing hypnotic benzodiazepines [17].

Although nonbenzodiazepines have certain advantages when compared with benzodiazepine hypnotics their use may lead to experiencing adverse effects. Most of them are similar to benzodiazepine side effects, although they occur less frequently. What is interesting is that usage of nonbenzodiazepines has been linked to infrequent, unusual central nervous system reactions, such as visual hallucinations occurring after taking nonbenzodiazepine drugs before going to sleep. These reactions however are not dangerous and do not influence the overall quality of sleep of the patients [17, 18].

When prescribing both benzodiazepines and nonbenzodiazepine BZRA drugs the initial dose should be rather low. In case that dosage will not achieve the expected therapeutic effect, it can be adjusted to the lowest effective dose. BZD and non-BZRA should be avoided in patients with a history of substance abuse. Treatment plans using these groups of hypnotics should always be adjusted individually to the patient, considering their comorbidities, long-term used medicines, and other factors. In cases of young patients with few coexisting health issues, a nonbenzodiazepine hypnotic is usually a reasonable first-line pharmacological treatment method [13].

2.3. Antihistamines

Antihistamines were initially developed with the intent of treating allergies. However, the involvement of the histaminergic system in the subcortical networks affecting wakefulness has made them a useful tool in treating insomnia. In the treatment of insomnia mostly first-generation antihistamines are used. Currently, two medications of that group are approved by the FDA for insomnia treatment: diphenhydramine and doxylamine. Despite not being approved for this indication, hydroxyzine is also frequently used.

Doxylamine is a first-generation antihistamine, a derivative of ethanolamine. Its mechanism of action is a competitive, nonspecific, and reversible antagonism of histamine H1 receptors [19]. In 1996 Shadeck et al. conducted a study with 338 patients who were divided into three groups: receiving doxylamine (15 mg), zolpidem (10 mg), and a placebo for 15 days. The said study was a double-blind, randomized, placebo-controlled study. The efficacy of doxylamine was comparable to zolpidem and significantly greater than the placebo group. At the end of the study, 65.8% of patients receiving doxylamine expressed a desire to continue the therapy, compared to 70.1% receiving zolpidem and 41% receiving placebo. Overall tolerance assessment conducted after two weeks indicated that more than 80% of patients rated the tolerance of therapy as “good” or “excellent,” with no significant difference between the groups (85.6%, 87.7%, 86.3% for doxylamine, zolpidem, and placebo, respectively). No significant differences in the incidence of side effects were found among all groups [20].

Diphenhydramine is a first-generation antihistamine, a derivative of ethanolamine [21]. In a 2005 study conducted by Molin et al. the effects of diphenhydramine were compared with a valerian-hops combination. The

study involved 184 adults with moderate insomnia, divided into three groups receiving diphenhydramine, herbal preparation, and placebo. The efficacy of the therapy was assessed using insomnia severity rating scales and polysomnography. No severe side effects or rebound insomnia were reported. Improvements were noted in sleep efficiency, sleep latency, and total sleep time, with only slight differences between the groups. The study demonstrated the effectiveness of both the valerian-hop preparation and diphenhydramine in treating moderate insomnia. Furthermore, it was established that diphenhydramine does not affect sleep architecture in adults [22].

Hydroxyzine is a first-generation antihistamine, a derivative of piperazine. Hydroxyzine's primary indication for use is the treatment of generalized anxiety disorder in which it is both a safe and effective medication [23]. Hydroxyzine's use in treating insomnia is quite debatable. In 2022, Burgazli et al. conducted a systematic review which included five studies of which four were randomized, covering a total of 207 adult patients receiving hydroxyzine at doses of 25 mg, 50 mg, and 100 mg before sleep. No severe side effects were reported. Sleep onset and overall sleep quality improved, while sleep maintenance either did not change or worsened. The study indicated the potential use of hydroxyzine for short-term treatment of insomnia in adults, although not in those with sleep maintenance impairment [24].

The most common side effects of first-generation antihistamines include dry mouth, tachycardia, gastrointestinal disorders, and dementia [25]. This group of drugs should not be used in older patients due to the exacerbation of side effects and anticholinergic activity which may lead to hazardous complications [26]. There is a limited amount of research regarding the use of antihistamines in the treatment of insomnia. Currently, the evidence for the efficacy of hydroxyzine is insufficient to justify its use in the treatment of insomnia [27].

2.4. Melatonin

Melatonin, also known as N-acetyl-5-methoxytryptamine, is a hormone produced by the pineal gland during the night. Secretion of melatonin is dependent on the biological clock and is strictly associated with suprachiasmatic nuclei (SCN). Melatonin aids in promoting sleep in humans, likely by suppressing circadian wakefulness mechanisms and influencing the function of brain networks conducive to inducing sleep. Melatonin acts as a sleep regulator and signal of darkness in humans [28].

Exogenous melatonin is currently available as an over-the-counter medication, with an indication to be used to manage insomnia, by activating melatonin receptors MT1 and MT2 in SCN. Exogenous melatonin's affinity to these receptors is weaker than melatonin agonists such as e.g. Ramelteon. Half-time of melatonin's bonding with aforementioned receptors is approximately 30 minutes. Melatonin is a relatively safe and well-tolerated medication with the most frequently reported side effects being headaches, somnolence, dizziness, and nausea. When prescribing patients melatonin, it is crucial to assess each patient's circadian rhythm individually to avoid phase shifts in the circadian clock. According to the review of clinical guidelines and case reports from 2023, melatonin use is weakly recommended for insomnia due to limited proof of effectiveness, flawed research methods, worries regarding purity or contaminants in over-the-counter medications, and potential adverse effects regarding destabilizing circadian rhythm if not administered properly [29]. Nevertheless, some studies have been performed to research melatonin effectiveness in specific disorders or populations.

It has been observed that due to calcification of the pineal gland or age-related decline in SCN circadian rhythmic functions endogenous melatonin levels may decrease with age. It can lead to sleep disorders and disturbance in the sleep-wake cycle. Therefore, the effectiveness of melatonin in insomnia among older persons has been the subject of numerous studies. Wade et al. conducted a randomized, double-blind, parallel-group clinical trial, which examined 791 adult outpatients. The results indicated that patients aged 65 years and over with primary insomnia are likely to have a good response to melatonin therapy and the response will increase and be sustained over a period of 6 months. Moreover, no rebound or withdrawal effects were observed after long-term use of melatonin in that specific population [30].

Additionally, some authors focused on melatonin use in the pediatric population. Although it is not officially recommended by the FDA, melatonin is being used to manage sleep onset insomnia or delayed sleep phase syndrome within otherwise healthy pediatric patients and children suffering from some neurodevelopmental disorders. A meta-analysis from 2020 has proven that melatonin treatment significantly advanced sleep onset time by 0.62 h compared to a placebo. Additionally, compared to the placebo group, melatonin treatment led to a significant advancement in dim light melatonin onset by −0.82 h and sleep onset time by −0.36 h [31]. Van Geijlswijk et al. in 2010 showed that melatonin administration in both adolescents and adults with delayed sleep phase syndrome average advancement of endogenous melatonin secretion by 1.18 h, coupled with a notable reduction in average sleep latency by 23 min and a decrease in sleep onset latency by 23.27 min, reflecting enhanced sleep initiation in adolescents [32]. Gringras et al. in 2027 performed a double-blind clinical trial on subjects with autism spectrum disorder. Results showed that those who received melatonin treatment presented with an increased average of 57.5 min of additional sleep, while those who received a placebo experienced only a minor increase of 9.14 min in their sleep duration [33].

2.5. Antipsychotics

Antipsychotics are another group of medications that are being prescribed for patients with insomnia. This use of antipsychotics is usually an off-label approach. Among drugs of this class being oftentimes used in treating insomnia are olanzapine, quetiapine, risperidone, chlorprothixene, levomepromazine, melperone, pipamperone, and prothipendyl. The evidence for their use is weak, and these medications should be used only if the patient has certain psychiatric comorbidities warranting antipsychotics' use. Melperone and pipamperone are the only antipsychotics listed in drug information for treating insomnia. However, there are no randomized controlled

clinical trials on these substances for insomnia disorder, with or without comorbidities. Thus, current scientific evidence does not support the use of antipsychotics for treating insomnia without comorbidities, either in the short or long term [34, 35].

2.6. Antidepressants

Currently, antidepressants are among one of the most popular drug groups prescribed for insomnia. This is mainly due to their relatively mild effect, no potential for developing physical dependency, and high efficacy in relation to their doses. Typical dosages for those drugs in the treatment of insomnia are significantly lower than their dosages when treating depression, therefore usually little to no side effects occur. Trazodone, mianserin, mirtazapine, and doxepin are among the most common antidepressants used in treating insomnia [36, 37].

Trazodone is a SARI (serotonin antagonist and reuptake inhibitor) class antidepressant. It works by blocking 5-HT2 receptors and increasing serotonin concentration in 5-HT1A receptors. Additionally, it blocks a1-adrenergic and H1-histaminergic receptors. In higher doses (≥150 mg/d) trazodone acts as an anxiolytic and antidepressant. In smaller doses (50-150 mg/d) it also shows a mild sedating effect [38]. The positive effects of trazodone on sleep quality in patients with coexisting depression are well-established and documented [39, 40, 41]. Trazodone has also proven to be a useful medication in normalizing sleep patterns in patients concurrently treated with stimulating antidepressants and in patients suffering from post-traumatic stress disorder (PTSD) [42]. Although there is a limited number of conducted studies testing trazodone's efficacy in non-depressed insomnia patients, few available studies have shown positive results. In 2011 a randomized double-blind study was conducted by Roth et al. [43]. 16 adult patients with insomnia were divided into two groups - a study group in which patients were receiving 50 mg of trazodone daily and a control group receiving a placebo. After 7 days of intervention, polysomnography revealed a statistically significant increase in the duration of stage 1 sleep and slow wave sleep as well as a lowered number of total awakenings during the night. Moreover, subjects in the study group performed better in the Multi Sleep Latency Test and reported less difficulty sleeping in the Visual Analog Scale. Another study conducted by Montgomery et al. tested the effects of trazodone (150 mg/d) on 9 otherwise healthy volunteers suffering from insomnia [44].

Trazodone was administered once daily for 2 weeks, then switched to placebo for 1 week. Polysomnographic (PSG) findings after 2 weeks included prolonged slow-wave sleep time, shortened total REM sleep time, and fewer night awakenings with no change to total sleep duration or sleep latency time. Subjective increase in sleep quality was also reported. Subjects suffered from rebound insomnia on the second night after switching to a placebo with withdrawal effects lessening over time. In 2018 a meta-analysis by Xiao-yan Yi et al. compared data from seven trials (cumulatively n=429 subjects) regarding the effectiveness of trazodone in insomnia. No improvement in sleep efficiency was reported, however, perceived sleep quality compared to placebo was recorded. Trazodone also reduced the number of night awakenings compared to placebo and had no significant effect on sleep latency, total sleep time, and waking time after sleep onset. The tolerability of trazodone was comparable to placebo [45]. Considering significant clinical experience and the beneficial safety profile of trazodone in low doses it can be considered a safe choice in the treatment of insomnia. Further studies on larger groups of subjects are warranted, as the data on its effects on sleep in otherwise healthy patients is limited.

Mirtazapine is a tetracyclic antidepressant primarily used in treating major depressive disorder. It acts as a 5HT2, 5HT3, a2-adrenergic antagonist and H1 reverse agonist. Mitrazepine use leads to an increase in serotonin and noradrenaline release in neurons. It also shows mild sedative, anxiolytic, and appetite-stimulating effects [46]. Although no randomized, double-blinded studies regarding mirtazapine's effects on sleep in healthy subjects with insomnia were conducted, it is widely used as a sedating agent with a mechanism of action similar to other sedating antidepressants. Additionally, it's one of the fastest-acting antidepressants and was proven to improve sleep quality after the first dose [47].

In 2002 Aslan and associates conducted a double-blind placebo controlled study with 20 healthy volunteers. Subjects were divided into a placebo group (n=10) and mirtazapine, 30 mg daily group (n=10). They spent 3 nights in the laboratory. On the third night, they received either a placebo or mirtazapine. Polysomnographic findings included reduced sleep latency and an increase in slow-wave sleep duration in the mirtazapine group [48]. Mirtazapine was also proven to increase sleep quality in post-menopausal age women suffering from hot flashes-induced sleep issues [49]. Available clinical experience and scarce data suggest that mirtazapine is effective in improving sleep quality more studies are needed to make definitive clinical choices regarding the use of mirtazapine in the treatment of insomnia. Clinicians need to be wary of the transient, acute negative effect mirtazapine has on psychomotor function, attention, and driving performance [50].

Mianserin is a tetracyclic antidepressant classified as NaSSA (Noradrenergic and specific serotonergic antidepressant). In larger doses, it blocks a1-adrenergic and a2-adrenergic receptors, H1-histaminergic receptors, and moderately blocks 5-HT2A, 5-HT2C, and 5-HT3 receptors. In small doses mianserin acts mainly as an antihistamine sedative [51]. Despite the wide clinical use of small doses of mianserin in patients suffering from insomnia, there are no high-quality studies regarding mianserin's influence on sleep architecture and sleep quality. In 2006 Sobańska et al. published the results of a study. Of 100 patients diagnosed with primary insomnia 64 completed the evaluation. 34 patients (n=34) were prescribed mianserin in monotherapy and 30 patients were prescribed mianserin in polytherapy (combined with either zolpidem, zopiclone, citalopram, nitrazepam, or phototherapy). They self-evaluated the improvement of their sleep on a 5-degree scale: worsening, lack of improvement, slight improvement, big improvement, and completely satisfactory sleep. Collectively 69% of subjects reported improvement, 7.8% reported worsening, and 9.3% reported no change. 14.1% of patients did not come for the follow-up visit. 14.1% of the patients required drug change due to the adverse effects [16]. A small study conducted by Ramaekers et al. in 1992 has proven that

mianserin use may directly lead to the occurrence of negative effects related to psychomotor function, driving ability, and sleepiness/drowsiness [52]. A small dose of mianserin (5-10 mg, compared to 90-120 mg used in depression) is commonly prescribed for insomnia. Clinical experience suggests the effectiveness and high safety profile of this treatment. The lack of solid data warrants extensive studies to prove or disprove the safety and efficacy of this approach.

Doxepin, a tricyclic antidepressant, inhibits serotonin and noradrenaline reuptake. Additionally, it blocks cholinergic, histaminergic, and a1-adrenergic receptors. In small doses (≤10 mg/d) doxepin mainly acts as an antihistamine sedating agent [53]. Doxepin 3 mg and 6 mg is an FDA-approved medication for the treatment of insomnia. In a study conducted by Roth et al. 66 adults with primary insomnia were tested. Subjects were randomized and divided into four groups. Each group received a placebo, 1 mg, 3 mg, and 6 mg doxepin daily in varying order. Participants were subjected to polysomnographic testing on days 5 and 12 and were tested on their subjective perception of their sleep quality throughout the trial. 3 mg doxepin and 6 mg doxepin statistically improved parameters related to sleep quality such as wake time after sleep onset (WASO) and wake time during sleep (WLDS). Doxepin in all doses improved sleep efficiency and slightly increased total sleep time. Patients also reported overall improvement in sleep quality on doxepin. Adverse effects reported in study groups did not statistically differ from placebo groups [54].

In 2011 Krystal et al. conducted a similar study. 229 adults with primary insomnia were randomized into a 3 mg doxepin group (n=75), a 6 mg doxepin group (73), and a placebo group (n=73). The study lasted for 35 days with a discontinuation rate below 12% across all groups. Polysomnographic studies revealed improved wake time after sleep onset in 3 mg and 6 mg doxepin groups, improved total sleep time in 3 mg and 5 mg doxepin groups, and improved sleep efficiency in both doxepin groups [55]. Both studies mentioned above confirmed doxepin's beneficial effect on polysomnographic and subjective sleep quality. Considering little to no reports of adverse effects and the high safety profile of doxepin in low doses it can be considered a safe choice in the treatment of primary insomnia.

2.7. Herbal medicines

Nowadays there are numerous herbal medicines available on the market that are advertised as treatments for insomnia. The precise frequency of use of these products in the general population is difficult to determine, but it is known that they are among some of the most commonly used over-the-counter medications.

One of the most comprehensive meta-analyses on the subject of the efficacy of herbal medicines in the treatment of insomnia was conducted in 2015 by Leach and Page. In the article fourteen randomized controlled trials with over 1600 participants suffering from insomnia were reviewed and analyzed. In the said trials four herbal-based preparations were used: valerian, kava, chamomile, and wuling. Measured sleep parameters included e.g. sleep onset latency, wake duration, nocturnal awakenings, sleep efficiency, and overall sleep duration. The results of this meta-analysis have shown that in all of the included studies, no significant difference in efficacy of treating insomnia was found between any of the herbal medicines and placebo groups. Some of the studies, however, have shown an increased number of adverse effects in patient groups receiving valerian-based medications compared to the placebo group. The authors conclude that at the time of publishing the article, there was insufficient evidence to support the clinical benefits of using herbal medicines to treat insomnia [56].

There is a certain shortage of well-conducted, objective, and comprehensive scientific papers regarding the use of herbal medicine in treating insomnia. However, there can be found articles that address this issue in particular populations. For example, in 2018 there was conducted a systematic review and meta-analysis which focused on randomized trials assessing the effect of soy in treating sleep disorders in peri- and postmenopausal women. Two of the six studies included in the said article have shown that the standardized mean difference of issues with sleeping was lower in the patients group receiving soy compared to the placebo group. Three of the remaining studies have shown no difference between the two groups while one study indicated that taking soy medications may increase problems with sleep. The authors of the mentioned meta-analysis conclude that it is difficult to definitively conclude about soy's safety and efficacy in treating insomnia [57].

Some other studies address using herbal medicines for insomnia when treating patients with bipolar disorder [58], and patients suffering from anxiety [59]. The conclusions however fail to provide definitive recommendations for clinical practice regarding that group of medicines. When compared to given medicine groups herbal medicines show no more benefit than benzodiazepines in treating insomnia although they may less frequently lead to the occurrence of side effects [60].

Given the current state of scientific literature, it is safe to conclude that although some herbal medicines show promising results in treating insomnia no definitive recommendation can be given on regular usage of the said plant-based products in the general population.

3. Non-pharmacological methods of treating insomnia

CBT-I (Cognitive Behavioral Therapy for Insomnia) and other behavioral approaches are highly effective therapy methods used in treating insomnia. Their goal is to eliminate incorrect habits in everyday life and sleep-related behaviors that make it difficult to fall asleep and stay asleep. During CBT-I, the patient acquires knowledge and skills that allow them to reduce conditioned arousal, which is one of the main causes of insomnia. The therapy also involves actions to restore and maintain the natural circadian rhythm. According to the guidelines of the American Academy of Sleep Medicine, CBT-I is the first-line treatment for chronic insomnia [61]. The implementation of this form of therapy does not carry the risk of side effects [62] which is a main feature that distinguishes it from pharmacological methods of treating insomnia as each group of drugs used to treat insomnia is characterized by the potential for side effects. A noticeable disadvantage of CBT-I is its time consumption and price. The best results

Table 2. CBT-I basic components [64].

Component	Description
Cognitive Restructuring	Altering sleep patterns requires altering negative thoughts and beliefs developed by individuals with insomnia due to past negative experiences. Common beliefs regarding sleep disorders are e.g. "I'm afraid I won't fall asleep when I go to bed" or "This is terrible. I will not be able to sleep, and tomorrow I will be exhausted". Restructuring cognitive processes involves replacing these negative beliefs with more constructive ones, such as "Even if it takes me some time to fall asleep, everything will be fine tomorrow" or "I can trust my body's natural ability to sleep" [65].
Sleep Consolidation	The duration of time allowed in bed is initially limited to the average perceived sleep time per night, then adjusted to maintain sleep efficiency above 85%. Thanks to the shortening of sleep duration, there is an increased sleep pressure, which facilitates falling asleep and reduces wakefulness during the night. This is largely a result of the body's homeostatic regulatory mechanisms. (Calculation of sleep efficiency is conducted by dividing the time spent sleeping by the total time spent in bed)
Stimulus Control	Behavioral instructions for the patient, the aim of which is to associate the bed only with sleep and sex. The patient is instructed not to work in bed, watch TV series, or lie in bed during the day. If his living conditions allow it, he is informed about the need to allocate a separate room just for sleeping. Only going to bed when you are sleepy - and leaving the bedroom when one cannot fall asleep sleep for 15-20 minutes, and only going back to bed when one is feeling the need to fall asleep.
Sleep hygiene	Sleep hygiene encompasses a set of guidelines promoting healthy sleep habits, including: 1. Establishing consistent bedtime and wake-up times every evening and morning. 2. Refraining from eating 2–3 hours before bedtime. 3. Minimizing exposure to bright light 2 hours before bedtime. 4. Limiting caffeine intake in the afternoon and evening. 5. Engaging in a relaxing evening routine. 6. Exposing oneself to natural bright light in the morning or early afternoon. 7. Reducing screen time on computers and mobile phones 1–2 hours before bedtime.
Relaxation	Relaxation techniques alleviate muscle tension and quiet racing thoughts, facilitating the faster onset of sleep. These methods include progressive muscle relaxation, deep breathing exercises, and visualization techniques.

are achieved after several months of weekly cooperation with a qualified therapist. One way to reduce the costs of CBT-I is participating in group therapies. Group sessions spread expenses among members, making them more affordable than individual therapy. Additionally, group therapy fosters a sense of community and reduces isolation, which can be especially beneficial for mental health issues. In a study conducted by Verbeek et al. effectiveness of group therapy was compared to individual therapy. It was found that both approaches were effective in treating insomnia with similar effect sizes. However, a higher percentage of individuals in the individual therapy group showed improvement compared to those in the group therapy [63].

CBT-I consists of five basic components, which are described in Table 2 [64].

In a study conducted in 2018 involving 292 insomnia patients, 123 participants (82 (66.7%) women and 41 (33.3%) men, with a mean age of 40.59 ± 11.89 years) were examined for the long-term effects of CBT-I over an average observation period of 7.8 ± 1.6 years (range: 4-10 years). The main treatment indicator was the insomnia severity index (ISI). ISI is composed of seven questions. The answers given by the patient are summed up to a total score. A score of 0-7 indicates clinically significant insomnia, while a score of 8-28 indicates insomnia, with severity classified as mild or severe depending on the number of points earned. All 258 patients who completed the treatment showed an improvement in the ISI index, indicating a reduction in insomnia and demonstrating the effectiveness of this therapy [66].

Due to the prohibitive costs of individual CBT-I, many people decide on Digital Cognitive Behavioral Therapy (dCBT). This allows the patient to reduce costs with simultaneous clinical effectiveness in treating insomnia. A meta-analysis of randomized controlled trials conducted in 2020 evaluated how well the therapy worked by examining changes in insomnia severity, as indicated by the Insomnia Severity Index (ISI), following the intervention [67].

Table 3 shows the number of participants in each group, the mean difference in post-intervention ISI scores for the dCBT-I group, the confidence interval (95%), and the p-value for each analysis. Additionally, results for the short-term study and after 1 year are presented.

This meta-analysis provides straightforward evidence for the effectiveness of the digital form of CBT-I therapy in the treatment of insomnia. Therefore, this form of therapy can be safely recommended to patients who are unable or unwilling to attend therapy in a traditional, face-to-face form. After the dCBT-I intervention, patients reported consistent improvement in sleep quality indicators such as SOL – sleep onset latency, WASO – wake after sleep onset, NWAK – number of awakenings, TST – total sleep time, and SE – sleep efficiency.

The face-to-face CBT-I yielded greater improvement in ISI scores, 3.07 (95% CI 1.18 to 4.95, p = 0.001) (I2 = 46%),

Table 3. Meta-analysis outcomes for dCBT-I intervention[67].

Outcome	Number of Studies	Number of Participants (dCBT-I)	Number of Participants (Control)	Mean Difference in ISI (95% CI)
Post-intervention	25	2545	2995	-5.00 (-5.68 to -4.33)
Short-term follow-up	11	3451	-3.99 (-4.82 to -3.16)	<0.0001
1-year follow-up	3	772	-3.48 (-4.21 to -2.76)	< 0.0001
Outcome	Number of Studies	Number of Participants (dCBT-I)	Number of Participants (Control)	Mean Difference in ISI (95% CI)

compared to dCBT-I [67]. Despite the superiority of face-to-face therapy, this meta-analysis provides strong evidence for the effectiveness of a more affordable and accessible online therapy option for insomnia. This may facilitate access to treatment for individuals who are unwilling or unable to engage in traditional in-person therapy.

4. End discussion

Insomnia is one of the most prevalent problems in modern society. It can be said with a high degree of probability that almost every clinician at some point in their medical career will treat a patient suffering from this type of sleep disorder. Luckily, many available treatment methods have a beneficial safety profile as well as high effectiveness.

While planning the treatment of insomnia it is important to remember that the first line should consist of non-pharmacological methods. In certain cases, simple patient education on sleep hygiene and maintaining a healthy sleep regimen may be sufficient to eliminate burdensome symptoms. In other cases, the patient may require the assistance of a psychology professional in the form of CBT-I. Both digital and analog forms of such therapy have well-documented positive results.

As a second line of treatment, multiple substances may be used in a pharmacological approach to treating insomnia. When choosing a specific drug, it is of utmost importance to base one's choice on evidence-based medicine (EBM). Some substances, despite being marketed as efficient hypnotic medicine, lack the proper scientific data to support its use in clinical practice. In addition to choosing an effective drug, it also should have acceptable side effects. This aspect is especially significant when treating a senior patient – in that case, side effects of certain hypnotics may lead to serious detrimental consequences regarding their somatic well-being.

Despite being such a popular topic there are still many angles of insomnia and its treatment that may benefit from conducting further studies. Given the age of some of the studies on sleep disorders, thorough research of modern causes of insomnia may be of great benefit to the clinical community. Contemporary comparisons of certain hypnotics' effectiveness with other drugs in healthy patients are also called for as high-quality data in this field also appears scarce.

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