

POTENTIAL RISKS AND PHARMACOLOGICAL SAFETY FEATURES OF HYPNOTICS. MUSIC THERAPY AS A NON-DRUG WAY TO IMPROVE SLEEP QUALITY

*Kalko Kateryna¹, Drogovoz Svitlana¹, Dubenko Andriy²,
Soloviova Evgeniya³, Horoshko Viktoriia⁴, Voskoboinikova Viktoriia⁵
Zhurenko Dmitriy¹, Berezniakov Andriy¹

¹National University of Pharmacy, Kharkiv, Ukraine

²Institute of neurology, psychiatry and narcology of NAMS of Ukraine, MC «Neuron», Kharkiv, Ukraine

³Kharkiv National Medical University, Kharkiv, Ukraine

⁴National University of Yuri Kondratyuk Poltava Polytechnic, Poltava, Ukraine

⁵Kharkiv State Academy of Culture, Kharkiv, Ukraine

*ketrin27kalko@gmail.com

Abstract

Sleep is critical to maintaining the immune system and contributes to physical and mental health. Covid-19 crisis has affected the habits of billions of people around the world. Compliance with quarantine restrictions and self-isolation led to an increase in the occurrence of post-traumatic stress, confusion and anger among the population, while social isolation and changes in the daily routine lead to an increased level of anxiety, panic attacks, irrational fears directly negatively affect the quality of sleep. The aim of this work was to analyze the drug and non-drug approaches that are used to improve the quality of sleep in humans. Analyze the pharmaco-safety and potential risks when taking medications intended for pharmacological correction of sleep.

Materials and methods. Analysis of scientific publications on drug and non-drug approaches used to improve the quality of sleep in people over the past 10 years on the PubMed platform; analysis of pharmacological safety and potential risks of hypnotics.

Results and discussion. Therefore, unfortunately, at the present time there is no ideal hypnotic that would induce sleep without changing its normal structure and side effects. All hypnotics should not be prescribed to patients snoring during sleep, since profundosomnia (deepening sleep) can increase the manifestations of sleep apnea syndrome, myocardial and brain hypoxia. The duration of the appointment of sleeping pills – no more than 3 weeks. Music has been successfully used as a complementary therapy in various fields of medicine. Music can also improve the quality of sleep and reduce pain for the patient, given the subsequent reduction in the effects of sedatives, which will lead to faster weaning from medical ventilation and faster recovery. Therefore, music is a non-drug highly effective method for improving the quality of sleep on a subjective and objective level.

Keywords: *hypnotics, music therapy, side effects.*

Introduction

Sleep is critical to maintaining the immune system and contributes to physical and mental health [5, 16, 30, 1, 29]. Sleep deficit is linked to chronic health problems such as heart disease, kidney disease, high blood pressure, diabetes, stroke, obesity, and depression [31, 17, 14]. Healthcare professionals are increasingly focusing on sleep and its impact on health and well-being as a measure of human vitality. The impact of sleep on neurological functions and cognitive endurance affects performance throughout life [22].

Covid-19 crisis has affected the habits of billions of people around the world. Compliance with quarantine restrictions and self-isolation led to an increase in the occurrence of post-traumatic stress, confusion and anger among the population, while social isolation and changes in the daily routine lead to an increased level of anxiety, panic attacks, irrational fears directly negatively affect the quality of sleep [3, 10]. There are even some studies that looked at the effects of the Covid-19 pandemic on sleep disturbance [23]. In one of them, it was found that dreams have changed significantly after Covid-19, namely, emotions in dreams have significantly increased - fear, anger, helplessness, anxiety [27]. Pandemic dreams reflect mental anguish, fear of infection and important changes in daily habits that directly affect socialization. [25, 27].

Two large international surveys conducted during the peak of the Covid-19 pandemic showed significant increase of disorders prevalence among adults. Although the duration of sleep did not change, there were new complaints of insomnia, changes in circadian rhythm and daytime dysfunction in a third of the respondents. There has also been a significant increase in the use of hypnotics for sleep correction. It was established that the most susceptible to violations were such categories of the population as: women of 31-45 years; persons who were in quarantine and had significant restrictions on physical activity; persons who have lost their jobs or experienced material losses due to the pandemic [23, 28]. All of the studies were very consistent as the first survey was conducted with 2,500 respondents from 49 countries and the other included 1,000 US residents.

The Covid-19 pandemic also leads to the available evidence of the prevalence of depression, anxiety and insomnia among healthcare workers. One study found that healthcare workers were at high risk of worsening sleep quality during the COVID-19 epidemic [2].

The aim of this work was to analyze the drug and non-drug approaches that are used to improve the quality of sleep in humans. Analyze the pharmacology and potential risks when taking medications intended for pharmacological correction of sleep.

Methods

Analysis of scientific publications on drug and non-drug approaches used to improve the quality of sleep in people over the past 10 years on the PubMed platform; analysis of pharmacological safety and potential risks of hypnotics.

Results and Discussion

Music therapy is one of the non-pharmacological approaches to treatment and can be used to improve the quality of sleep in people [20]. Music has been successfully used as a complementary therapy in various fields of medicine [18, 22, 21, 6]. Improving people's sleep with music therapy will enable nurses to intervene with sleep problems and prevent insomnia [19].

Listening to music is useful to relieve stress in all areas of medicine and it tends to be a reliable and effective for treatment of critically ill patients. [26]. It can reduce stress response and anxiety during artificial lung ventilation, and induce an overall relaxation response without medication. This relaxation response can reduce stress on the heart and oxygen consumption, which will lead to more efficient ventilation. Music can also improve the quality of sleep and reduce pain for the patient, given the subsequent reduction in the effects of sedatives, which will lead to faster weaning from medical ventilation and faster recovery [26].

Throughout history, music has been used to improve healing processes, but its power to reduce stress and enhance emotional health has only recently begun to gain scientific evidence for the neurochemical changes that occur during active listening or while playing music. Based on their own

research, a team of scientists concluded that listening to relaxing music before bedtime can reduce the time spent sleeping in the N1 phase and the power of high frequency ranges. It was also established that patients had more restorative sleep after listening to music [8].

Therefore, music is a non-drug highly effective method for improving the quality of sleep on a subjective and objective level.

Prescription of hypnotics can be used to correct the quality of sleep in cases of ineffectiveness of non-drug approaches. Hypnotics are a group of medicines that are used for the purpose of pharmacokinetic correction of the qualitative and quantitative characteristics of sleep [24]. Hypnotics have the ability to restore the process of failed sleep, the depth and duration of sleep if they are disturbed. According to the ATC classification, hypnotics are classified as Hypnotics and sedatives (N 05C) Psycholeptic drugs (N 05) of the group of drugs affecting the nervous system (N) [7]. Hypnotics enhance inhibitory processes in the central nervous system: they inhibit the activity of neurons in the reticular formation. The exact mechanism of some hypnotic drugs is not fully understood [24].

According to the ATC-classification, the group Hypnotics and sedatives (N 05 C) includes:

- ✓ Barbiturates, combinations (N 05C B);
- ✓ Benzodiazepine derivatives (N05C D);
- ✓ Benzodiazepine related drugs (N05C F);
- ✓ Melatonin receptor agonists (N05C H);
- ✓ Other hypnotics and sedatives (N05C M);
- ✓ Hypnotics and sedatives in combination (N05C X) [7].

Of the large arsenal of modern hypnotics, there is not a single one that would not have side effects [24]. In particular, all drugs can cause fatigue, headache, depression, and impair memory [24, 15, 4]; disrupt the structure of physiological sleep and lengthen periods of falling asleep and severe awakening (all drugs) [24, 32]; muscle weakness, poor coordination, drowsiness (nitrazepam, triazolam); cause paralysis of the respiratory and vasomotor centers; mental and physical dependence (all barbiturates and benzodiazepines) [9]; impair vision (all benzodiazepines, cyclopyrrolones) [11, 12]; addictive, psychomotor agitation, psychosis, seizures, sweating, fear,

paradoxical effect, irritability (all barbiturates, benzodiazepines, except flunitrazepam, cyclopyrrolones) [13]; withdrawal syndrome (barbiturates, brotizolam, methaqualone); nightmares (barbiturates, imidazopyridines) [11, 13]; aftereffect syndrome (barbiturates, benzodiazepines, ethanolamines, methaqualone); increased risk of fractures and injuries [32].

The side effect of hypnotics is associated not only with inhibition of the central nervous system, but also with impaired function of the cardiovascular system and the blood system. For example, hypnotics can cause hypotension, thrombosis and tissue necrosis when administered intravenously (all benzodiazepines) [33]; tachycardia (nitrazepam, brotizolam); thrombophlebitis (flunitrazepam) [12]; megaloblastic anemia, hemorrhages, neutropenia (barbiturates, reladorm); thrombocytopenia, agranulocytosis (bromizoval).

Typical side effects of the gastrointestinal tract when taking hypnotics can be nausea, vomiting, dry mouth (nitrazepam, brotizolam, imidazopyridines, cyclopyrrolones, ethanolamines, methaqualone); anorexia (triazolam); dyspepsia, urinary disorders, metallic taste in the mouth (cyclopyrrolones, methaqualone); constipation (cyclopyrrolones, ethanolamines).

Other side effects that may arise from usage of hypnotics are: allergic reactions, mainly skin reactions (all barbiturates, nitrazepam, midazolam, cyclopyrrolones, methaqualone, reladorm); cumulation, osteopathy, ataxia, nystagmus (barbiturates); violation of the menstrual cycle, teratogenic effect, respiratory inhibition of the fetus, porphyria (all benzodiazepines); "bromism" (bromizoval); blurred speech, tremors, muscle weakness (reladorm) [4].

Side effects on the central nervous system of benzodiazepine derivatives is largely associated with the inhibition of synaptic transmission in different parts of the central nervous system (in the cerebral cortex, afferent pathways, limbic system) due to the activation of GABA receptors. Withdrawal syndrome - the result of a change in the GABA-benzodiazepine receptor complex, a decrease in inhibitory mechanisms. Impaired coordination - the result of muscle relaxant activity. Hepatotoxicity of phenobarbital, apparently, is of an allergic nature, since all patients have a rash, fever, eosinophilia [9].

With prolonged use of hypnotics, the act of falling asleep and awakening is lengthened. Inhibition of the central nervous system increases with the simultaneous use of hypnotics and other drugs that inhibit the central nervous system, incl. alcohol.

Benzodiazepines, when administered intravenous, lead to thrombosis and tissue necrosis. Rapid intravenous administration of benzodiazepines may cause transient hypotension [9]. Elderly patients are more susceptible to side effects of benzodiazepines. Serious side effects of benzodiazepines are observed more often in diseases of the liver, heart, lungs and brain, when paired with the use of other drugs that reduce the functional reserves of these organs [4].

Barbiturates of pregnant and lactating women reduce androgen levels, which may in the future reduce puberty in male children and sexual activity of young men. Barbiturates should not be taken by pregnant women, as they cross the placenta, cause drowsiness during lactation, refusal of newborns from the breastfeeding, provoke bleeding.

For the prevention of syndromes of «recoil», insomnia, nightmares and withdrawal symptoms, the hypnotics should be gradually withdrawn with a dose reduction [12]

Zopiclone, zolpidem most fully meet the requirements for the «ideal» hypnotics: they practically do not cause addiction and the syndrome of «recoil», do not affect the daytime activity of patients (Table 1) [32, 4].

Zopiclone does not inhibit the paradoxical phase of sleep, which is necessary for the restoration of mental functions, memory, but somewhat lengthens the slow-wave phase, which is important for the restoration of the physical strength of the body. The bioavailability of the drug is 80%, it does not cause post-somnic disturbances, less often it causes drug dependence. Zopiclone is not recommended for use over 4 weeks [32].

Zolpidem reduces the time to fall asleep, increases the duration and quality of sleep, reduces the number of night awakenings. In contrast to zopiclone, with prolonged use, it lengthens the phase of paradoxical sleep ("refreshing sleep"), therefore, provides optimal daytime performance, has a weak amnestic effect. Its bioavailability is 70%. When zolpidem interacts with rifampicin, a decrease

in the hypnotic effect is observed; with warfarin - an increase in the prothrombin index and the development of hemorrhagic diathesis is possibility, and with antifungal drugs of the azole group (fluconazole is exception) there are psychomotor disorders.

Doxylamine shortens the time to fall asleep, increases the duration and quality of sleep, has an atropine-like and antihistamine effect, is similar to benzodiazepine derivatives, changes the sleep phase less. Doxylamine drug dependence does not occur even with prolonged use. Patients on a salt-restricted diet should take into account that each doxylamine tablet contains 484 mg of sodium bicarbonate.

Melatonin is a synthetic analogue of the neuropeptide melatonin (produced by the pineal gland), through the neurohumoral mechanisms of the central nervous system regulates the biological cycle "wakefulness-sleep", circadian rhythms regulate the change of sleep and wakefulness, affects mental and physical performance, the rhythm of gonadotropic hormones, the severity of stress. The drug is not addictive and does not cause withdrawal.

Bromizoval has a moderate hypnotic and sedative effect, is rarely used, metabolizes very slowly, can cumulate. It can be administered to children. Methaqualone has a strong hypnotic effect, less disrupts the structure of sleep, but the development of addiction is possible. Reladorm is a combined drug that has a muscle relaxant effect and should not be taken with anticoagulants, corticosteroids, doxycycline, griseofulvin, oral contraceptives. After taking vita-melatonin, it is not recommended to work with potentially dangerous mechanisms. Vita-melatonin is prescribed prophylactically for 2 months with a week break.

Chloral hydrate (rarely used), meprobamate, clomethiazole, antipsychotics and antidepressants with sedation can also be used as hypnotics.

The hypnotic drugs of the 3rd generation include the precursor of serotonin - L-tryptophan. It accelerates falling asleep, does not disturb the structure of sleep, has a wide range of therapeutic action, without notable undesirable effects. However, as a hypnotic, it has not yet found widespread use.

All hypnotics should not be prescribed to patients snoring during sleep, since profundosomnia (deepening sleep) can increase the manifestations of sleep apnea syndrome, myocardial and brain hypoxia. The duration of the appointment of sleeping pills – no more than 3 weeks.

With the simultaneous use of hypnotics and other drugs that suppress the central nervous system, as well as alcohol, the inhibitory effect on the central nervous system is enhanced. Hypnotics are incompatible with tricyclic antidepressants, muscle relaxants, atropine sulfate, opioid analgesics, antitussives and antipsychotics. Care should be taken when prescribing hypnotics to elderly patients with heart or respiratory failure, as well as patients who abuse drugs or have a history of drug dependence [24]. Hypnotics should be taken half an hour before bedtime in the minimum effective dose with intervals between doses of 2-3 days. Glucose interacts with hypnotics to reduce sleep duration. If pain is the cause of insomnia, hypnotics must be used with analgesics. The combination of hypnotics with narcotic analgesics can reduce immunity. For insomnia at the background of an agitated state and negative emotions, it is necessary to use tranquilizers.

Therefore, unfortunately, at the present time there is no ideal hypnotic that would induce sleep without changing its normal structure and side effects.

References:

1. Acosta MT. Sueño, memoria y aprendizaje [Sleep, memory and learning]. *Medicina (B Aires)*. 2019;79 Suppl 3:29-32. Spanish. PMID: 31603840.
2. Alnofaiey YH, Alshehri HA, Alosaimi MM, Alswat SH, Alswat RH, Alhulayfi RM, Alghamdi MA, Alsubaie RM. Sleep disturbances among physicians during COVID-19 pandemic. *BMC Res Notes*. 2020 Oct 21;13(1):493. doi: 10.1186/s13104-020-05341-6. PMID: 33087166; PMCID: PMC7576978.
3. Beck F, Léger D, Fressard L, Peretti-Watel P, Verger P; Coconel Group. Covid-19 health crisis and lockdown associated with high level of sleep complaints and hypnotic uptake at the population level. *J Sleep Res*. 2021 Feb;30(1):e13119. doi: 10.1111/jsr.13119. Epub 2020 Jun 28. PMID: 32596936; PMCID: PMC7361195.
4. Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. *Drugs R D*. 2017 Dec;17(4):493-507. doi: 10.1007/s40268-017-0207-7. PMID: 28865038; PMCID: PMC5694420.
5. Capezuti EA. The power and importance of sleep. *Geriatr Nurs*. 2016 Nov-Dec;37(6):487-488. doi: 10.1016/j.gerinurse.2016.10.005. Epub 2016 Nov 4. PMID: 27823857.
6. Chen CT, Tung HH, Fang CJ, Wang JL, Ko NY, Chang YJ, Chen YC. Effect of music therapy on improving sleep quality in older adults: A systematic review and meta-analysis. *J Am Geriatr Soc*. 2021 Jul;69(7):1925-1932. doi: 10.1111/jgs.17149. Epub 2021 Apr 20. PMID: 33880759.
7. Compendium online. Access mode: <https://compendium.com.ua/atc/n05c/>
8. Cordi MJ, Ackermann S, Rasch B. Effects of Relaxing Music on Healthy Sleep. *Sci Rep*. 2019 Jun 24;9(1):9079. doi: 10.1038/s41598-019-45608-y. PMID: 31235748; PMCID: PMC6591240.
9. Coteur K, Van Nuland M, Vanmeerbeek M, Henrard G, Anthierens S, Van den Broeck K, De Sutter A, Creupelandt H, Devroey D, Van Overmeire R, Offermans AM, Kacenenbogen N, Laenen A, Mathei C. Effectiveness of a blended care programme for the discontinuation of benzodiazepine use for sleeping problems in primary care: study protocol of a cluster randomised trial, the Big Bird trial. *BMJ Open*. 2020 Feb 18;10(2):e033688. doi: 10.1136/bmjopen-2019-033688. PMID: 32075832; PMCID: PMC7045121.
10. Doraiswamy S, Cheema S, Al Mulla A and Mamtani R. COVID-19 lockdown and lifestyles: A narrative review *F1000Research* 2021, 10:363 (<https://doi.org/10.12688/f1000research.52535.1>)
11. Drogovoz S.M., Lukyanchuk V.D., Sheiman B.S. *Medicinal toxicology: a handbook / Kh.: Title*, 2015: 592 p.
12. Drogovoz S.M., Shtrigol S.Yu., Shchokina E.G. et al. *Pharmacology to aid the student, pharmacist and doctor: textbook-reference book / - 2nd ed., Revised. and add. Kh.: Title*, 2018: 640 p.

13. Drogovoz SM, Butko Ya. A. Side effects of drugs: a textbook. - Kh.: «SIM», 2011: 480 p.
14. Dutil C, Chaput JP. Inadequate sleep as a contributor to type 2 diabetes in children and adolescents. *Nutr Diabetes*. 2017 May 8;7(5):e266. doi: 10.1038/nutd.2017.19. PMID: 28481337; PMCID: PMC5518801.
15. Faludi B, Rozgonyi R. Az insomniák kezelésének helye az alvásmedicinában: gyógyszeres és nem gyógyszeres eljárások [Pharmacological and nonpharmacological treatment of insomnias with regard to sleep medicine]. *Ideggyogy Sz*. 2018 May 30;71(5-06):149-159. Hungarian. doi: 10.18071/isz.71.0149. PMID: 29889457.
16. Golem DL, Martin-Biggers JT, Koenigs MM, Davis KF, Byrd-Bredbenner C. An integrative review of sleep for nutrition professionals. *Adv Nutr*. 2014 Nov 14;5(6):742-59. doi: 10.3945/an.114.006809. PMID: 25398735; PMCID: PMC4224209.
17. Hanson JA, Huecker MR. Sleep Deprivation. 2021 Jun 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. PMID: 31613456.
18. Hedge S. Music-based cognitive remediation therapy for patients with traumatic brain injury. *Front Neurol* 2014; 5: 1-7.
19. Innes KE, Selfe TK, Khalsa DS, Kandati S. Effects of Meditation versus Music Listening on Perceived Stress, Mood, Sleep, and Quality of Life in Adults with Early Memory Loss: A Pilot Randomized Controlled Trial. *J Alzheimers Dis*. 2016 Apr 8;52(4):1277-98. doi: 10.3233/JAD-151106. PMID: 27079708; PMCID: PMC5649740.
20. Kavurmaci M, Dayapoğlu N, Tan M. Effect of Music Therapy on Sleep Quality. *Altern Ther Health Med*. 2020 Jul;26(4):22-26. PMID: 31221932.
21. Lin ZW, Liu JF, Xie WP, Chen Q, Cao H. The effect of music therapy on chronic pain, quality of life and quality of sleep in adolescents after transthoracic occlusion of ventricular septal defect. *Heart Surg Forum*. 2021 Mar 26;24(2):E305-E310. doi: 10.1532/hfs.3513. PMID: 33798055.
22. Loewy J. Music Therapy as a Potential Intervention for Sleep Improvement. *Nat Sci Sleep*. 2020 Jan 7; 12:1-9. doi: 10.2147/NSS.S194938. PMID: 32021519; PMCID: PMC6954684.
23. Mandelkom U, Genzer S, Choshen-Hillel S, Reiter J, Meira E Cruz M, Hochner H, Kheirandish-Gozal L, Gozal D, Gileles-Hillel A. Escalation of sleep disturbances amid the COVID-19 pandemic: a cross-sectional international study. *J Clin Sleep Med*. 2021 Jan 1;17(1):45-53. doi: 10.5664/jcsm.8800. PMID: 32900428; PMCID: PMC7849644.
24. Mansfield D, Grima NA, Bei B. Insomnia management. *Aust J Gen Pract*. 2019 Apr;48(4):198-202. PMID: 31256489.
25. Miller KE, Brownlow JA, Woodward S, Gehrman PR. Sleep and Dreaming in Posttraumatic Stress Disorder. *Curr Psychiatry Rep*. 2017;19: 71. pmid:28828641.
26. Mofredj A, Alaya S, Tassaïoust K, Bahloul H, Mrabet A. Music therapy, a review of the potential therapeutic benefits for the critically ill. *J Crit Care*. 2016 Oct;35:195-9. doi: 10.1016/j.jcrc.2016.05.021. Epub 2016 May 28. PMID: 27481759.
27. Mota NB, Weissheimer J, Ribeiro M, de Paiva M, Avilla-Souza J, Simabucuru G, Chaves MF, Cecchi L, Cime J, Cecchi G, Rodrigues C, Copelli M, Ribeiro S. Dreaming during the Covid-19 pandemic: Computational assessment of dream reports reveals mental suffering related to fear of contagion. *PLoS One*. 2020 Nov 30;15(11):e0242903. doi: 10.1371/journal.pone.0242903. PMID: 33253274; PMCID: PMC7703999.
28. Robillard R, Dion K, Pennestri MH, Solomonova E, Lee E, Saad M, Murkar A, Godbout R, Edwards JD, Quilty L, Daros AR, Bhatla R, Kendzerska T. Profiles of sleep changes during the COVID-19 pandemic: Demographic, behavioural and psychological factors. *J Sleep Res*. 2021 Feb;30(1):e13231. doi: 10.1111/jsr.13231. Epub 2020 Nov 17. PMID: 33200477; PMCID: PMC7744844.
29. Scammell TE. Overview of sleep: the neurologic processes of the sleep-wake cycle. *J Clin Psychiatry*. 2015 May;76(5):e13. doi: 10.4088/JCP.14046tx1c. PMID: 26035194.
30. Tarokh L, Saletin JM, Carskadon MA. Sleep in adolescence: Physiology, cognition and mental health. *Neurosci Biobehav Rev*. 2016 Nov;70:182-188. doi: 10.1016/j.neubiorev.2016.08.008. Epub

- 2016 Aug 13. PMID: 27531236; PMCID: PMC5074885.
31. Tobaldini E, Costantino G, Solbiati M, Cogliati C, Kara T, Nobili L, Montano N. Sleep, sleep deprivation, autonomic nervous system and cardiovascular diseases. *Neurosci Biobehav Rev*. 2017 Mar;74(Pt B):321-329. doi: 10.1016/j.neubiorev.2016.07.004. Epub 2016 Jul 7. PMID: 27397854.
32. Treves N, Perlman A, Kolenberg Geron L, Asaly A, Matok I. Z-drugs and risk for falls and fractures in older adults-a systematic review and meta-analysis. *Age Ageing*. 2018 Mar 1;47(2):201-208. doi: 10.1093/ageing/afx167. PMID: 29077902.
33. Wilt TJ, MacDonald R, Brasure M, Olson CM, Carlyle M, Fuchs E, Khawaja IS, Diem S, Koffel E, Ouellette J, Butler M, Kane RL. Pharmacologic Treatment of Insomnia Disorder: An Evidence Report for a Clinical Practice Guideline by the American College of Physicians. *Ann Intern Med*. 2016 Jul 19;165(2):103-12. doi: 10.7326/M15-1781. Epub 2016 May 3. PMID: 27136278.

Table 1. Comparative characteristics of hypnotics

Drugs	Sleep duration	Effective for sleep disturbances		Sleep phase disorder	Syndrome		Cumulation	Addiction
		falling asleep	sleep duration		after effect	recoil		
Phenobarbital	8-10	-	+	++ +	+++	+++	++	++/+
Cyclobarbital	4	+		++ +	++	+++	+	++/+
Nitrazepam	6-8	+	+	++	++	++	±	+/+
Flunitrazepam	6-8	+	+	++	++	++	±	+/+
Triazolam	6	+	+	++	+	+	±	+/+
Midazolam	6-8	+	+	++	++	+	-	+/+
Brotizolam	6	+	+	++	+	+	±	+/+
Zolpidem	6	+	+	+	±			+/-
Zopiclon	8	+	+	±	±			±
Bromizoval	5-7	+		±	++	+	+	+/+
Methaqualone	6-8	+	+	±	±		-	-/+
Doxylamine	8-10	+	+	-	±		-	-/+
Reladorm	8	+	+	+	++	+++	+	++/+