# INSOMNIA

CHI Formulary Indication Review

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Council of Health Insurance

| INDICATION UPDATE |
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| **ADDENDUM- October 2023**<br><br>**To the CHI Original Insomnia Clinical Guidance- Issued April 2020** |

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## Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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# Abbreviations

| | |
|---|---|
| AASM | American Academy of Sleep Medicine |
| ASD | Autism Spectrum Disorder |
| BDZ | Benzodiazepine |
| CBT-I | Cognitive Behavioral Therapy for Insomnia |
| CHI | Council of Health Insurance |
| CPAP | Continuous Positive Airway Pressure |
| DORA | Dual Orexin Receptor Antagonist |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration |
| HAS | Haute Autorite de Sante |
| HTA | Health Technology Assessment |
| IQWIG | Institute for Quality and Efficiency in Health Care |
| MHT | Menopausal Hormone Therapy |
| MT1 | Melatonin Receptor Type 1 |
| MT2 | Melatonin Receptor Type 2 |
| OSA | Obstructive Sleep Apnea |
| PBAC | Pharmaceutical Benefits Advisory Committee |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PQA | Pharmacy Quality Alliance |
| SFDA | Saudi Food and Drug Authority |
| VMS | Vasomotor Symptoms |
| y/o | years old |

# Executive Summary

Insomnia is a patient-reported complaint of difficulty falling asleep or difficulty maintaining sleep, i.e., frequent awakenings, difficulty returning to sleep after awakenings, or awakening too early with inability to return to sleep[1].

A prevalent clinical condition, insomnia is characterized by difficulty falling asleep or staying asleep, accompanied by feelings of irritability or fatigue when awake. The estimated prevalence of insomnia disorder is around 10% to 20%, with approximately half of those affected experiencing a chronic course[1].

Insomnia poses a risk to overall functioning and contributes to the development of other medical and mental disorders, leading to increased healthcare expenses. Its underlying causes involve a combination of genetic, environmental, behavioral, and physiological factors, ultimately resulting in a state of hyperarousal[1].

Factors associated with persistence of insomnia are often the same as those associated with its incidence (ie, female gender, older age, and presence of medical or mental health problems), with depression and mental health problems presenting stronger associations than physical health problems. Insomnia can also be a persistent condition, independent of mental disorders[2].

Effective treatments for insomnia encompass behavioral, cognitive, and pharmacologic interventions. While simple behavioral approaches can be applied in primary care settings, their implementation is hindered by a lack of sufficient training[1].

Among pharmacologic treatments, benzodiazepine receptor agonist drugs have the most substantial evidence, although concerns persist regarding their safety compared to their relatively modest effectiveness. It is recommended to prioritize behavioral treatments whenever possible and to restrict medication usage to the lowest necessary dosage and shortest duration required[1].

According to the International Classification of Sleep Disorders, the second edition Criteria for General Insomnia Disorder is as follows[1]:

- A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early or sleep that is chronically unrestorative or poor in quality. In children, sleep difficulty is often reported by the caretaker and may consist of observed bedtime resistance or inability to sleep independently.
- The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
- At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the patient:

  a. fatigue or malaise

b. attention, concentration, or memory impairment

c. social or vocational dysfunction or poor school performance

d. mood disturbance or irritability

e. daytime sleepiness

f. motivation, energy, or initiative reduction

g. proneness for errors or accidents at work or while driving.

h. tension, headaches, or gastrointestinal symptoms in response to sleep loss

i. concerns or worries about sleep.

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[3].

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 several other conditions associated with pain, endocrine or metabolic disorders, and reduced daytime physical activity[3].

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[3].

**CHI issued Insomnia clinical guidance after thorough review of renowned international and national clinical guidelines in April 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.**

**This report functions as an addendum to the prior CHI Insomnia clinical guidance and seeks to offer guidance for the effective management of Insomnia. It provides an update on the Insomnia Guidelines for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing the most updated best available clinical and economic evidence related to drug therapies.**

**Main triggers for the update are summarized, being the addition** of new guidelines namely; Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder: Report of the Guideline Development, Dissemination and Implementation Subcommittee of the American Academy of Neurology 2020, Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical

practice guideline 2021, Italian Association of Sleep Medicine (AIMS) position statement and guideline on the treatment of menopausal sleep disorders 2019, Treatment of insomnia in older adults. Recommendations of the Polish Sleep Research Society, Polish Society of Family Medicine, and the Polish Psychiatric Association 2023, Treatment Strategy for insomnia disorder: Japanese Expert Consensus 2023, Alliance for Sleep Clinical Practice Guideline on Switching or Deprescribing Hypnotic Medications for Insomnia 2023, Department of veteran affairs for the management of chronic insomnia and obstructive sleep apnea 2019.

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include the SFDA registered drug for their off-label use for insomnia (Agomelatine, Alprazolam, Promethazine, Hydroxyzine Hydrochloride in the CHI formulary while removing Amitriptyline and Lorazepam as they are no longer registered on the SFDA Drug List of June 2023. New drug molecules that are FDA approved, non-SFDA registered, can also be considered for the treatment of insomnia's sleep onset or maintenance; daridorexant (Quviviq™) and Lemborexant (Dayvigo®).

There have been changes or updates made to the previously listed drugs in terms of drug information and prescribing edits since April 2020; amitriptyline and lorazepam are no longer SFDA registered. Prescribing edits were added and modified for diazepam, lorazepam, mirtazapine, nitrazepam and zolpidem.

**All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Insomnia therapeutic management.**

**Below is a table summarizing the major changes based on the different insomnia guidelines used to issue this report:**

**Table 1.** General Recommendations for the Management of Insomnia

| Management of Insomnia | | |
|---|---|---|
| **General Recommendations** | **Level of Evidence/Grade of Recommendation** | **Reference** |
| Clinicians should offer melatonin to children and adolescents with ASD if behavioral strategies have not been helpful and contributing coexisting conditions and use of concomitant medications have been addressed | Level B | American Academy of Neurology, 2020 |

| | | |
|---|---|---|
| Clinicians offering melatonin for sleep disturbance in children and adolescents with ASD should write a prescription for melatonin or recommend using a high-purity pharmaceutical grade of melatonin when available | Level B | American Academy of Neurology, 2020 |
| Clinicians offering melatonin for sleep dysregulation in children and adolescents with ASD should start by initiating a low dose (1–3 mg/d), 30–60 minutes before bedtime, and titrate to effect, not exceeding 10 mg/d | Level B | American Academy of Neurology, 2020 |
| Clinicians offering melatonin for sleep disturbance in children and adolescents with ASD should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents regarding potential adverse events of melatonin use and the lack of long-term safety data | Level B | American Academy of Neurology, 2020 |
| For Menopausal sleep disorders, Melatonin may stabilize circadian rhythm while helping insomnia symptoms as well as VMS | Not graded | Italian Association pf Sleep Medicine, 2019 |
| For people over 65 years, the most important requirements for insomnia treatment 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 | Not graded | Polish Society of Family Medicine and the Polish Psychiatric Association, 2023 |
| The main group of drugs used for the treatment of insomnia are nonbenzodiazepine sedative hypnotics referred to in practice as Z-drugs (zolpidem, | Not graded | Polish Society of Family Medicine and the Polish |

| | | |
|---|---|---|
| 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. | | Psychiatric Association, 2023 |
| 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 | Not graded | Polish Society of Family Medicine and the Polish Psychiatric Association, 2023 |
| 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 | Not graded | Polish Society of Family Medicine and the Polish Psychiatric Association, 2023 |
| 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. Doxepin is the only antidepressant drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of insomnia | Not graded | Polish Society of Family Medicine and the Polish Psychiatric Association, 2023 |
| The other antidepressants: 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 | Not graded | Polish Society of Family Medicine and the Polish Psychiatric Association, 2023 |
| In people aged 55 and over, melatonin | | Polish Society |

| | | |
|---|---|---|
| treatment shows higher efficacy due to a marked decrease in melatonin secretion by the pineal gland occurring after 50 years of age | Not graded | of Family Medicine and the Polish Psychiatric Association, 2023 |
| 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, 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. | Not graded | Polish Society of Family Medicine and the Polish Psychiatric Association, 2023 |
| Regarding the primary pharmacological treatment for sleep initiation in insomnia, Lemborexant was categorized as a first-line recommendation | (7.3 ± 2.0) | Japanese Expert Consensus, 2023 |
| Regarding the primary pharmacological treatment for sleep maintenance insomnia, Lemborexant and suvorexant were categorized as first-line recommendations | Lemborexant (7.3 ± 1.8)<br><br>Suvorexant (6.8 ± 1.8) | Japanese Expert Consensus, 2023 |

**Table 2.** New Non SFDA Registered Drugs

| **New Molecules (Non SFDA Registered)** | |
|---|---|
| **Drug** | **Drug Class** |
| Zopiclone | Hypnotic, Nonbenzodiazepine Benzodiazepine Receptor Agonist |
| Daridorexant | Hypnotic, Orexin Receptor Antagonist |
| Levomepromazine | Analgesic, First Generation (Typical) Antipsychotic |

| | |
|---|---|
| (Off-label use) | |
| Promazine (Off-label use) | Phenothiazine Derivative |
| Doxylamine (Off-label use) | Ethanolamine Derivative, Histamine H1 Antagonist, First Generation |

At the end of the report, a key recommendation synthesis section is added highlighting the latest updates in the clinical and therapeutic management of insomnia, and appendices are available for further information.

# Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from updated versions of guidelines mentioned in the previous CHI Insomnia report, and the second includes newly added guidelines that have helped generate this report.

## 1.1 Revised Guidelines

There are no updated versions of the guidelines mentioned in the April 2020 CHI Insomnia Report.

**Table 3.** Guidelines Requiring Revision

| **Revised Guidelines** | |
|---|---|
| **Old Versions** | **Updated versions** |
| **1.1** Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline from the American College of Physicians [2016] | N/A* |
| **1.2** Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline [2017] | N/A* |
| **1.3** European guideline for the diagnosis and treatment of insomnia [2017] | N/A* |

| | |
|---|---|
| **1.4** British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias, and circadian rhythm disorders: An update [2019] | N/A* |

*: *No updated versions available*

## 1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI Insomnia report, along with their recommendations.

**Table 4.** List of Additional Guidelines

| **Additional Guidelines** |
|---|
| **1.2.1** Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the *American Academy of Neurology* 2020[4] |
| **1.2.2** Behavioral and psychological treatments for chronic insomnia disorder in adults: an *American Academy of Sleep Medicine* clinical practice guideline 2021[5] |
| **1.2.3** *Italian Association of Sleep Medicine (AIMS)* position statement and guideline on the treatment of menopausal sleep disorders 2019[6] |
| **1.2.4** Treatment of insomnia in older adults. Recommendations of the Polish Sleep Research Society, Polish Society of Family Medicine, and the Polish Psychiatric Association 2023 (people over 65 years of age)[3] |
| **1.2.5** Treatment Strategy for insomnia disorder: Japanese Expert Consensus 2023 |
| **1.2.6** Alliance for Sleep Clinical Practice Guideline on Switching or deprescribing Hypnotic Medications for Insomnia 2023 |
| **1.2.7** Department of veteran affairs for the management of chronic insomnia and Obstructive Sleep Apnea (OSA) 2019 |

### 1.2.1 Practice Guideline: Treatment for Insomnia and Disrupted Sleep Behavior in Children and Adolescents with Autism Spectrum Disorder: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology (2020)

The American Academy of Neurology Guideline's Level of evidence and recommendation grades are outlined below[4]:

**Table 5.** Level of Recommendations

| Level of Recommendations | Definition |
|---|---|
| **Level A** | The strongest recommendation level and is denoted by use of the helping verb must. These recommendations are rare. |
| **Level B** | *Level B* corresponds to the helping verb **should**. Such recommendations are more common, as the requirements are less stringent but are still associated with confidence in the rationale and a favorable benefit–risk profile.<br>*Level B* based on feasibility and cost relative to net benefit. |
| **Level C** | *Level C* corresponds to the helping verb **may**. These recommendations represent the lowest allowable recommendation level that the American Academy of Neurology considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation. |

The American Academy of Neurology's recommendations are assigned the class of recommendations defined in the preceding table:

1. *Recommendation statements for care of children and adolescents with autism spectrum disorder (ASD) and sleep disturbance regarding coexisting medical conditions and concomitant medications:*

➢ Clinicians seeking to improve sleep in children and adolescents with ASD should perform an assessment for coexisting conditions that could be contributing to sleep disturbance (Level B)

- ➢ Clinicians seeking to improve sleep in children and adolescents with ASD should review concomitant medications that could contributing to sleep disturbance (Level B)
- ➢ Clinicians seeking to improve sleep in children and adolescents with ASD who have a coexisting condition that is contributing to their sleep disturbance should ensure they receive appropriate treatment for their coexisting condition (Level B)
- ➢ Clinicians seeking to improve sleep in children and adolescents with ASD who have medications that could be contributing to sleep disturbance should address whether the potentially contributing medications can be stopped or adjusted (Level B)
- ➢ Clinicians aiming to enhance sleep quality in youngsters and teenagers with ASD should advise parents or caregivers about methods to enhance sleep routines. Initially, they should consider behavioral techniques as the primary treatment method, either on their own or alongside medical or nutraceutical methods, based on individual situations (Level B).

2. *Recommendation statements for care of children and adolescents with autism spectrum disorder (ASD) and sleep disturbance regarding melatonin use:*

- ➢ Clinicians should offer melatonin to children and adolescents with ASD if behavioral strategies have not been helpful and contributing coexisting conditions and use of concomitant medications have been addressed (Level B)
- ➢ Clinicians offering melatonin for sleep disturbance in children and adolescents with ASD should write a prescription for **melatonin** or recommend using a high-purity pharmaceutical grade of melatonin when available (Level B)
- ➢ Clinicians offering melatonin for sleep dysregulation in children and adolescents with ASD should start by initiating a low dose (1–3 mg/d), 30–60 minutes before bedtime, and titrate to effect, not exceeding 10 mg/d (Level B)
- ➢ Clinicians offering melatonin for sleep disturbance in children and adolescents with ASD should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents regarding potential adverse events of melatonin use and the lack of long-term safety data (Level B).

3. *Recommendation statements for care of children and adolescents with autism spectrum disorder (ASD) and sleep disturbance regarding complementary alternative medicine:*

- ➢ Clinicians should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents that there is currently no evidence to support the routine use of weighted blankets or specialized mattress technology for improving disrupted sleep (Level B)

➢ Although evidence of efficacy is lacking, clinicians should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents asking about *weighted blankets* that the reviewed trial reported no serious adverse events with blanket use and that blankets could be a reasonable nonpharmacologic approach to try for some individuals (Level B)

### 1.2.2 Behavioral and Psychological Treatments for Chronic Insomnia Disorder in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline (2021)

The American Academy of Sleep Medicine (AASM) guideline's level of evidence and recommendation grades are outlined below[5]:

**Table 6.** Implications of Strong and Conditional Recommendations for Users of AASM Clinical Practice Guidelines

| Level of Recommendations | Definition |
|---|---|
| **Strong Recommendation "We recommend…"** | ***Almost all patients*** should receive the recommended course of action. Adherence to this recommendation could be used as a quality criterion or performance indicator. |
| **Conditional Recommendation "We suggest…"** | ***Most patients*** should receive the suggested course of action; however, different choices may be appropriate for different patients. The clinician must help each patient determine if the suggested course of action is clinically appropriate and consistent with his or her values and preferences. |

The recommendations listed below are assigned the grades defined in the preceding table:

1. It is recommended that clinicians use multicomponent cognitive behavioral therapy for insomnia for the treatment of chronic insomnia disorder in adults. (STRONG)
2. It is suggested that clinicians use multicomponent brief therapies for insomnia for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)
3. It is suggested that clinicians use stimulus control as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)
4. It is suggested that clinicians use sleep restriction therapy as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)

5. It is suggested that clinicians use relaxation therapy as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)
6. It is suggested that clinicians not use sleep hygiene as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)

### 1.2.3 Italian Association of Sleep Medicine (AIMS) Position Statement and Guideline on the Treatment of Menopausal Sleep Disorders (2019)

The 2019 *Italian Association of Sleep Medicine (AIMS)* position statement and guideline on the treatment of menopausal sleep disorders level of evidence and recommendation grades are outlined below[6]:

**No assigned grades for the recommendations listed below**

- Menopausal sleep disorders have a wide variety of manifestations, including not only insomnia but also breathing and movement disorders. VMS (Vasomotor Symptoms) have a large effect on postmenopausal women's sleep, mood, and quality of life. Treatment needs to be individualized, taking into accounts comorbidities and preferences.
- Insomnia per se best responds to CBT-I (Cognitive Behavioral Therapy), MHT (Menopausal Hormone Therapy), and escitalopram. New drugs with different therapeutic targets are in development.
- **Melatonin** may stabilize circadian rhythm while helping insomnia symptoms as well as VMS.
- CPAP (Continuous Positive Airway Pressure) and MADs (Mandibular Advancement Device) decrease the hypertension burden of OSA (Obstructive Sleep Apnea), but without a major impact on sleep quality and mortality risk.
- There is a need for adequately powered randomized controlled trials as well as cohort studies to better understand the impact of menopausal sleep disorders and increase the evidence-base of therapeutic strategies.

### 1.2.4 Treatment of Insomnia in Older Adults. Recommendations of the Polish Sleep Research Society, Polish Society of Family Medicine, and the Polish Psychiatric Association (2023) (People Over 65 Years of Age)

The Polish Psychiatric Associations' Guidelines for the treatment of Insomnia's level of evidence and recommendation grades are outlined below[3]:

*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 specialization, 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.*

**No assigned grades for the recommendations listed below**

- The aim of this article is to present the current recommendations for the management of insomnia in people over 65 years of age.
- 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.

<u>Diagnosis</u>

- 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.
- A detailed history and psychiatric examination make it possible to differentiate between primary insomnia and sleep disorders caused by another mental disorder.

Treatment

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 behavioral therapy for insomnia.

Non-pharmacological treatment of insomnia

- Current recommendations focus on improving sleep conditions and promoting a 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 pm).
- Treatment of insomnia using cognitive behavioral therapy techniques based on a classical approach includes cognitive and behavioral interactions as shown in the table below:

**Table 7.** Cognitive Behavioral Therapy Techniques Used in the Treatment. Retrieved from Treatment of insomnia in older adults. Recommendations of the Polish Sleep Research Society Wichniak A, Bieńkowski P, Dąbrowski R, Mastalerz-Migas A, Rymaszewska J., Polish Society of Family Medicine and the Polish Psychiatric Association. Psychiatr Pol. Published online April 19, 2023:1-22. doi:10.12740/pp/onlinefirst/161597

| **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. |
| 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 behavioral techniques – sleep restriction and stimulus control – which should be used consistently by the patient for at least 6 weeks.

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.

Hypnotics

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

**Table 8.** Drugs Approved for Treatment of Insomnia in Poland

| Drug | Dose | 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** | 5-20 | 24 |
| **Temazepam** | 10-20 | 7-11 |
| ***Other medicines*** | | |
| **Prolonged-release melatonin** | 2 | 3.5-5 |
| **Daridorexant** | 25-50 | 8 |

*Adapted from Treatment of insomnia in older adults. Recommendations of the Polish Sleep Research Society, Polish Society of Family Medicine and the Polish Psychiatric Association. Psychiatr Pol, by Wichniak A, Bieńkowski P, Dąbrowski R, Mastalerz-Migas A, Rymaszewska J. Published online April 19, 2023:1-22. doi:10.12740/pp/onlinefirst/161597*

- The mechanism of action of zolpidem and other Z-drugs is similar to that of *benzodiazepines* (**diazepam**, **lorazepam**, **alprazolam**).

- 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.
- Due to their rapid onset of action, Z-drugs should be used shortly before bedtime.
- In older adults the use of hypnotics is associated with a significantly increased risk of falls and fractures.

Sedative drugs

**Table 9.** 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 |

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

*Adapted from Treatment of insomnia in older adults. Recommendations of the Polish Sleep Research Society, Polish Society of Family Medicine and the Polish Psychiatric Association. Psychiatr Pol, by Wichniak A, Bieńkowski P, Dąbrowski R, Mastalerz-Migas A, Rymaszewska J. Published online April 19, 2023:1-22. doi:10.12740/pp/onlinefirst/161597*

- 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.
- 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, urinary retention and anticholinergic side effects, which significantly limits their use for the treatment of sleep disorders in older patients.
- The other antidepressants: **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.

<u>Melatonin and melatonergic drugs</u>

- In people aged 55 and over, **melatonin** treatment shows higher efficacy due to a marked decrease in melatonin secretion by the pineal gland occurring after 50 years of age.
- 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.

[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 behavioral interventions. In the case of predominant difficulty to fall asleep, it may be advisable to administer the drug earlier, 1-2 hours before bedtime.]

- 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, 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.

### 1.2.5 Treatment Strategy for Insomnia Disorder: Japanese Expert Consensus (2023)

The Japanese Expert Consensus's analysis of recommendation is outlined below[7]:

**Table 10.** Japanese Expert Consensus's Analysis of Recommendations

| Level of Recommendations | Definition |
|---|---|
| **Analysis** | The following values were calculated for each treatment option: mean, standard deviation, 95% confidence interval (CI), and number of rating categories (i.e., not-recommended: responses 1–3; neutral: responses 4–6; and recommended: responses 7–9).<br>Pearson's chi-squared test was used to compare the numbers of these three rating categories for each treatment choice. When the responses were evenly distributed across the three categories with a p-value ≥ 0.05, "no consensus" was given for the corresponding clinical question, indicating a controversial strategy.<br>Treatment options with 95% CI **values ≥ 6.5 were regarded as "first-line recommendations,"** indicating a consensus among experts for a particular situation. Options rated as 9 by > 50% of responders were defined as "treatments of choice," indicating a particularly strong first-line recommendation. **Options with 95% CI values ≥ 3.5 were regarded as "second-line treatments,"** indicating reasonable options for patients who do not respond to or cannot tolerate first-line strategies. **Treatment options with 95% CI values < 3.5 were considered "third-line treatments**" (notrecommended) indicating that they are inappropriate options or used only when other options are ineffective. |

The recommendations listed below are assigned the grades defined in the preceding table:

➔ There is a lack of evidence regarding answers for clinical questions about treating insomnia disorder. This study aimed to answer the following clinical questions:

1. How to use each hypnotic and non-pharmacological treatment differently depending on clinical situations
2. How to reduce or stop benzodiazepine hypnotics using alternative pharmacological and nonpharmacological treatments.

➔ Expert consensus indicates that orexin receptor antagonists and sleep hygiene education are recommended as first-line treatments in most clinical situations to treat insomnia disorder.

➔ The *primary pharmacological treatment*, Lemborexant (7.3 ± 2.0), was categorized as a first-line recommendation for sleep initiation insomnia, and Lemborexant (7.3 ± 1.8) and suvorexant (6.8 ± 1.8) were categorized as the first-line recommendations for sleep maintenance insomnia.

Regarding *non-pharmacological* treatments for primary treatment, sleep hygiene education was categorized as the first-line recommendation for both sleep initiation (8.4 ± 1.1) and maintenance insomnia (8.1 ± 1.5), while multicomponent cognitive behavioral therapy for insomnia was categorized as the second-line treatment for both sleep initiation (5.6 ± 2.3) and maintenance insomnia (5.7 ± 2.4).

When reducing or discontinuing benzodiazepine hypnotics by switching to other medications, Lemborexant (7.5 ± 1.8) and suvorexant (6.9 ± 1.9) were categorized as first-line recommendations.

**Primary treatment strategy for insomnia disorder**

- Regarding the primary pharmacological treatment for **sleep initiation** in insomnia, Lemborexant (7.3 ± 2.0) was categorized as a first-line recommendation; eszopiclone (6.2 ± 1.8), suvorexant (6.0 ± 2.1), zopiclone (4.7 ± 2.0), and kampo were categorized as second-line treatments; and ramelteon (5.4 ± 2.2) and zolpidem (4.9 ± 2.2) were categorized as having “no consensus.” Other BZDs, including trazodone and quetiapine, were categorized as third-line treatments (not recommended).
- Similarly, regarding the primary pharmacological treatment for **sleep maintenance** insomnia, Lemborexant (7.3 ± 1.8) and suvorexant (6.8 ± 1.8) were categorized as first-line recommendations; eszopiclone (5.2 ± 2.0), quetiapine (4.0 ± 2.3), and kampo (3.9 ± 2.2) were categorized as second-line treatments; and ramelteon (5.2 ± 2.2) and trazodone (4.8 ± 2.3) were categorized as having “no consensus.”

- Regarding **non-pharmacological treatments for sleep initiation** in insomnia, sleep hygiene education (8.4 ± 1.1) and relaxation therapy (7.0 ± 2.0) were categorized as first-line recommendations; stimulus control (6.5 ± 2.1), sleep restriction therapy (6.4 ± 2.2), and multicomponent CBT-I (5.6 ± 2.3) were categorized as second-line treatments; and sleep hygiene education was categorized as a "treatment of choice". Similarly, **for sleep maintenance insomnia**, sleep hygiene education (8.1 ± 1.5) was categorized as a first-line recommendation; and relaxation therapy (6.6 ± 2.1), sleep restriction therapy (6.5 ± 2.3), stimulus control (6.2 ± 2.2), and multicomponent CBT-I (5.7 ± 2.4) were categorized as second-line treatments.

**Treatment strategy when BZD hypnotics are ineffective**

- When BZD hypnotics do not improve the symptoms of insomnia, there was no first-line recommendation. Switching to lemborexant (6.7 ± 2.2) and suvorexant (6.1 ± 2.3), as well as combination treatment with lemborexant (6.3 ± 2.3) and suvorexant (5.9 ± 2.3), were categorized as second-line treatments. Additionally, increasing the dose of BZD hypnotics was also categorized as second-line treatment. Switching to other medications, trazodone (5.3 ± 2.4), other BZDs (4.9 ± 2.4), quetiapine (4.7 ± 2.5), and ramelteon (4.5 ± 2.3) were categorized as having "no consensus." Combination treatment with trazodone (5.4 ± 2.5), ramelteon (5.1 ± 2.4), and quetiapine (4.7 ± 2.5) were also categorized as having "no consensus." Only combination treatment with other BZDs (3.0 ± 2.2) was categorized as a third-line treatment (not-recommended)
- ***For non-pharmacological treatment***, the differential diagnosis of other psychiatric disorders (8.2 ± 1.3), sleep hygiene education (8.1 ± 1.4), differential diagnosis of other sleep disorders (8.0 ± 1.6), and relaxation therapy (7.0 ± 1.9) were categorized as first-line recommendations. Consultation with a specialist (6.8 ± 2.0), sleep restriction therapy (6.5 ± 2.2) stimulus control (6.5 ± 2.1), and multicomponent CBTI (5.9 ± 2.4) were categorized as second-line treatments. Differential diagnosis of other psychiatric disorders, sleep hygiene education, and differential diagnosis of other sleep disorders were all categorized as "treatments of choice."

**Discontinuation of BZD hypnotics**

- There was no first-line recommendation for the timing of reducing or discontinuation of BZD hypnotics following improvement in insomnia symptoms. As for timing, 1–3 months (6.4 ± 2.0), 3–6 months (5.9 ± 2.1), and immediately (4.2 ± 2.3) after improvement in symptoms were categorized as second-line treatments, while 6–12 months (5.1 ± 2.4) after improvements in symptoms were categorized as having "no consensus." Only a timing of >1 year after improvement in symptoms (3.5 ± 2.2) was categorized as a third-line treatment (not-recommended)

- Regarding the suggested excusable reasons for continuing BZD hypnotics, anticipation of physical or mental deterioration upon discontinuation (6.9 ± 1.8) was categorized as the first-line recommendation; and a history of insomnia symptom relapse when discontinuing hypnotics (6.4 ± 1.9), unstable physical or mental states or quality of life (6.1 ± 2.1), monotherapy or low dose use of hypnotics (5.8 ± 2.0), desire to continue hypnotics (5.2 ± 2.1), and no serious side effects (4.9 ± 2.1) were categorized as second-line treatments
- When reducing or discontinuing BZD hypnotics, gradual reduction (8.1 ± 1.2) and sleep hygiene education (7.9 ± 1.5) were categorized as first-line recommendations. Relaxation therapy, switching to other hypnotics, sleep restriction therapy, switching to as-needed use of hypnotics, stimulus control, and patients' self-adjustment of hypnotics were categorized as second-line treatments.
- When reducing or discontinuing BZD hypnotics while switching to other medications, lemborexant (7.5 ± 1.8) and suvorexant (6.9 ± 1.9) were categorized as first-line recommendations. Switching to ramelteon (5.7 ± 2.3) was categorized as a second-line treatment, while trazodone (5.3 ± 2.3), quetiapine (4.4 ± 2.4), and kampo (4.4 ± 2.5) categorized as having "no consensus".

### 1.2.6 Alliance for Sleep Clinical Practice Guideline on Switching or Deprescribing Hypnotic Medications for Insomnia (2023)

The Alliance for Sleep's clinical practice guideline on switching or deprescribing hypnotic medications for insomnia's grading is outlined below[8]:

**Table 11.** The Alliance for Sleep Clinical Practice Guideline Grading of Literature

| Level of Recommendation | Definition |
|---|---|
| **A** | Evidence obtained from meta-analysis, including at least one large, randomized control trial (RCT). |
| **B** | Evidence obtained from either meta-analysis, including at least one small RCT, or from at least one well-designed large RCT |
| **C** | Evidence obtained from well-designed cohort or case-controlled studies. |
| **D** | Evidence obtained from case series, case reports, or flawed clinical trials. |

| | |
|---|---|
| **E** | Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees |

The recommendations listed below are assigned the grades defined in the preceding table:

The purpose of this clinical practice guideline is to review the evidence surrounding insomnia medication transitions and deprescribing to identify the best means of discontinuing each type of medication therapy and of switching among the different treatment options as shown in table 11.

**Table 12.** Consensus recommendation for switching insomnia medications, both within-class and to a new drug class. Retrieved from Watson NF, Benca RM, Krystal AD, McCall W V., Neubauer DN. Alliance for Sleep Clinical Practice Guideline on Switching or Deprescribing Hypnotic Medications for Insomnia. J Clin Med. 2023;12(7). doi:10.3390/jcm12072493

| Initial Drug Class/Group | Consensus Recommendation for Different Class Switching | Grading of Evidence | Consensus Recommendation for Within-Class Switching | Grading of Evidence |
|---|---|---|---|---|
| BZDs | Slow taper method/cross taper | B /C | Direct switch | B |
| Zolpidem | Taper and then wait 1–2 days | B | Taper and then wait 1–2 days | B |
| Zaleplon | Direct switch | B | Direct switch | B |
| Eszopiclone | Taper and then wait 1–2 days | B | Taper and then wait 1–2 days | B |
| Suvorexant | Direct switch | B | Direct switch | B |
| Lemborexant | Direct switch | B | Direct switch | B |
| Daridorexant | Direct switch | B | Direct switch | B |
| Ramelteon | Direct switch | B | N/A | |
| Doxepin 3–6 mg | Direct switch | B | N/A | |
| Trazodone | Slow taper method /cross taper | D | Not recommended | E |
| Mirtazapine | Slow taper method /cross taper | E | Not recommended | E |
| TCAs | Slow taper method /cross taper | D | Not recommended | E |
| Quetiapine | Slow taper method /cross taper | D | Not recommended | E |

Definition of the consensus-based switching methods are as follows: *slow taper*: gradual dose reduction of insomnia drug, with lowering by increments every few days, usually over a period of 4 weeks, with the goal of discontinuing the medication. This process's duration and success depend on drug dosage, pharmacological properties, and subject response to the decreased dose. *Cross taper*: The first insomnia drug dose is reduced while a new insomnia medication is introduced at a low dose and gradually increased. This can only be safely done with medications that have no interaction. Taper and wait 1–2 days: similar to the slow taper method of gradually decreasing the dose until discontinuation, followed by a withholding period of 1–2 days before any new insomnia medication is started. This can be due to the insomnia treatment having a longer half-life and needing time to be cleared from the system prior to initiating new therapies. *Direct switch*: The first insomnia drug is stopped, and a new insomnia drug is commenced the next day at the usual

therapeutic dose. There can be a considerable risk of withdrawal symptoms and drug interactions.

FDA-approved insomnia therapies at standard doses can be deprescribed or switched safely and effectively. In many cases, except for BZDs, zolpidem, eszopiclone, and the off-label use of antidepressants and antipsychotics, medication tapering or “cross-tapering” when switching is not necessary. Among classes of medications, DORAs, selective H1 antihistamines (low-dose doxepin), and melatonin receptor agonists (ramelteon) appear to have the lowest risk of rebound insomnia or withdrawal symptoms upon discontinuation or switching when compared to other classes of FDA-approved medications.

**Best Practices for BZD Discontinuation**

Clinical data suggest that BZDs should be tapered, preferably with some kind of behavioral therapy (e.g., CBT-I) or other support in place (Table 2). No data were found to determine whether switching to a longer half-life hypnotic drug decreases withdrawal or rebound insomnia symptoms. Currently, there is no consensus in the literature as to what the tapering schedule should be, although most studies reported reducing the dose by ~10–25% increments at intervals of one to several weeks.

**Best Practices for Z-drug Discontinuation**

Most of the RCTs examining the acute sleep and daytime effects of stopping Z-drugs have not tapered the Z-drug and instead have used abrupt placebo substitution. Tapering is always medically necessary when the individual is taking excessively high doses of Z-drugs, to avoid severe withdrawal reactions, which might include seizures.

**Best Practices for DORAs, Doxepin, or Ramelteon Discontinuation**

It appears that the data do not support the need for a taper or the institution of any other measures to ensure safety in the discontinuation of any of these medications. Further, there seems to be no need for such measures when trying to switch from these agents, other than setting expectations about the possibility that in some individuals, sleep may transiently worsen.

**Best Practices for Discontinuation of Off-Label Drugs for Insomnia**

The authors state that discontinuation of TCAs and atypical antidepressants can result in sleep disturbances, nightmares, and vivid dreams, and they note an intermediate risk of antidepressant discontinuation syndrome with amitriptyline and trazodone and a low risk for mirtazapine. Indeed, discontinuation effects in serotonin and norepinephrine reuptake inhibitor (SNRI) treatment can be seen for weeks and months in some patients. A recommendation to gradually reduce the dose when discontinuing these off-label medications is consistent with each drug’s Prescribing

Information. However, whether there is a lower threshold below which tapering is unnecessary remains an open question.

### 1.2.7 Department of Veteran Affairs for the Management of Chronic Insomnia and Obstructive Sleep Apnea (OSA)

The Department of veteran affairs for the management of chronic insomnia and OSA's grading of recommendations is outlined below[9]:

**Table 13.** Department of Veteran Affairs for the Management of Chronic Insomnia and Obstructive Sleep Apnea (OSA) Levels of Recommendations

| Level of Recommendations | Definition |
|---|---|
| **Strong** | High confidence in the quality of the available scientific evidence, a clear difference in magnitude between the benefits and harms of an intervention, similarity among patient or provider values and preferences, and the apparent influence of other implications (e.g., resource use, feasibility) |
| **Weak** | Less confidence after the assessment across these domains and additional evidence may change the recommendation |
| Note: It is important to note that the GRADE terminology used to indicate the assessment across the four domains (i.e., Strong versus Weak) should not be confused with the clinical importance of the recommendation. A "Weak" recommendation may still be important to the clinical care of a patient with insomnia disorder and/or OSA | |

| **Using the previous elements, the grade of each recommendation is presented as part of a continuum** |
|---|
| • Strong for (or "We recommend offering this option …")<br>• Weak for (or "We suggest offering this option …")<br>• No recommendation for or against (or "There is insufficient evidence …")<br>• Weak against (or "We suggest not offering this option …")<br>• Strong against (or "We recommend against offering this option …") |

The recommendations listed below are assigned the grades defined in the preceding table:

**Treatment and Management of Chronic Insomnia Disorder**

Behavioral and Psychological Treatments

- We recommend offering CBT-I for the treatment of chronic insomnia disorder. Strong for Reviewed, New-added.
- We suggest offering brief behavioral therapy for insomnia (BBT-I) for the treatment of chronic insomnia disorder. Weak for Reviewed, New-added.
- There is insufficient evidence to recommend for or against group versus individual CBT-I for the treatment of chronic insomnia disorder. Neither for nor against Reviewed, New-added.
- There is insufficient evidence to recommend for or against internet-based CBT-I as an alternative to face-to-face based CBT-I for the treatment of chronic insomnia disorder. Neither for nor against Reviewed, New-added
- For patients diagnosed with chronic insomnia disorder, we suggest CBT-I over pharmacotherapy as first-line treatment. Weak for Reviewed, New-added
- We suggest offering CBT-I for the treatment of chronic insomnia disorder that is comorbid with another psychiatric disorder. Weak for Reviewed, New-added
- There is insufficient evidence to recommend for or against mindfulness meditation for the treatment of chronic insomnia disorder. Neither for nor against Reviewed, New-added
- We suggest against sleep hygiene education as a standalone treatment for chronic insomnia disorder. Weak against Reviewed, New-added

Complementary & Integrative Health Treatments

- We suggest offering auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. Weak for Reviewed, New-added
- There is insufficient evidence to recommend for or against acupuncture other than auricular acupuncture with seed and pellet for the treatment of chronic insomnia disorder. Neither for nor against Reviewed, New-added
- There is insufficient evidence to recommend for or against aerobic exercise, resistive exercise, tai chi, yoga, and qigong for the treatment of chronic insomnia disorder. Neither for nor against Reviewed, New-added

- We suggest against cranial electrical stimulation for the treatment of chronic insomnia disorder. Weak against Reviewed, New-added

Over-the-counter Treatment

- We suggest against the use of **diphenhydramine** for the treatment of chronic insomnia disorder. Weak against Reviewed, New-added
- We suggest against the use of **melatonin** for the treatment of chronic insomnia disorder. Weak against Reviewed, New-added.
- We suggest against the use of **valerian** and **chamomile** for the treatment of chronic insomnia disorder. Weak against Reviewed, New-added.
- We recommend against the use of **kava** for the treatment of chronic insomnia disorder. Strong against Reviewed, New-added.

Pharmacotherapy

- In patients who are offered a short-course of pharmacotherapy for the treatment of chronic insomnia disorder, we suggest use of low-dose (i.e., 3 mg or 6 mg) **doxepin**. Weak for Reviewed, New-added
- In patients who are offered a short-course of pharmacotherapy for the treatment of chronic insomnia disorder, we suggest the use of a non-benzodiazepine benzodiazepine receptor agonist. Weak for Reviewed, New-added
- There is insufficient evidence to recommend for or against the use of **ramelteon** for the treatment of chronic insomnia disorder. Neither for nor against Reviewed, New-added
- There is insufficient evidence to recommend for or against the use of **suvorexant** for the treatment of chronic insomnia disorder. Neither for nor against Reviewed, New-added
- We suggest against the use of antipsychotic drugs for the treatment of chronic insomnia disorder. Weak against Reviewed, New-added
- We suggest against the use of benzodiazepines for the treatment of chronic insomnia disorder. Weak against Reviewed, New-added
- We suggest against the use of trazodone for the treatment of chronic insomnia disorder. Weak against Reviewed, New-added

# Section 2.0 Drug Therapy in Insomnia

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details new drugs that have been approved by the FDA and/or EMA, but are not currently SFDA registered.

## 2.1 Additions

Several drugs that are SFDA list have an off-label use for insomnia. Hence, relevant information pertaining to these drugs can be found below.

### 2.1.1 Agomelatine

This section includes pertinent information regarding the use of Agomelatine (in Insomnia)[10]:

**Table 14.** Drug Therapy with Agomelatine

| **SCIENTIFIC NAME**<br>**Agomelatine** | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | NO |
| **EMA** | Yes, for MDD |
| **MHRA** | Yes, for depression |
| **PMDA** | NO |
| **Indication (ICD-10)** | G47. 00 |
| **Drug Class** | Antidepressant |
| **Drug Sub-class** | 5-ht2c receptor antagonist, melatonergic agonist |
| **ATC Code** | n06ax22 |
| **Pharmacological Class (ASHP)** | Antidepressant |
| **DRUG INFORMATION** | |
| **Dosage Form** | Film-coated tablet |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | Major depressive disorder: Oral: Initial: 25 mg once daily at bedtime. If symptoms do not improve after 2 weeks, may increase to 50 mg once daily at bedtime (maximum dose). Note: |

| | |
|---|---|
| | Consider hepatic risks if dose is increased to 50 mg.<br>Discontinuation of therapy: Dose tapering is not required upon abrupt discontinuation; agomelatine is not associated with withdrawal symptoms (Fasipe 2019; Levitan 2015).<br>Switching from an SSRI/SNRI to agomelatine: May immediately start agomelatine while appropriately tapering the dosage of the SSRI/SNRI. |
| **Maximum Daily Dose Adults*** | 50 mg |
| **Dose (pediatrics)** | N/A |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Adjustment** | ***For Altered Kidney Function:***<br>There are no dosage adjustments provided in manufacturer's labeling; use caution in moderate-to-severe renal impairment (limited data).<br>***For Hepatic Impairment:***<br>Preexisting hepatic impairment: Use is contraindicated in patients with active liver disease, cirrhosis, or transaminases >3 x ULN.<br>Onset of hepatic impairment during treatment:<br>Transaminases elevated ≤3 x ULN: If signs/symptoms of hepatotoxicity, discontinue therapy. If no signs/symptoms of hepatotoxicity, repeat monitoring within 48 hours. If transaminases remain ≤3 x ULN, may continue therapy and resume regular monitoring schedule.<br>Transaminases elevated >3 x ULN during therapy or signs/symptoms of hepatotoxicity: Discontinue therapy |
| **Prescribing edits*** | AGE, MD |
| **AGE (Age Edit):** The use of agomelatine in older adults aged ≥75 years is not recommended (lack of efficacy) | |
| **CU (Concurrent Use Edit):** N/A | |

| | |
|---|---|
| **G (Gender Edit):** N/A | |
| **MD (Physician Specialty Edit):** To be used after psychiatrist or neurologist assessment of mental status for depression, suicidal ideation (especially at therapy initiation or dose titration). Monitor hepatic enzymes at baseline and weeks 3, 6, 12, 24, and then when clinically required; restart monitoring cycle if dosage is increased. Repeat liver function testing within 48 hours for any patient in whom serum transaminases have increased. | |
| **PA (Prior Authorization):** N/A | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** N/A | |
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | **Most common:**<br>• Endocrine & metabolic: Weight gain<br>• Gastrointestinal: Abdominal pain, constipation, diarrhea, nausea, vomiting<br>• Hepatic: Increased serum alanine aminotransferase (>3x ULN: ≤3), increased serum aspartate aminotransferase (>3 x ULN: ≤3%)<br>• Musculoskeletal: Back pain<br>• Nervous system: Abnormal dreams, anxiety, dizziness, drowsiness, fatigue, insomnia<br>**Most serious:**<br>• Allergic reactions (symptoms include difficulty breathing, swelling of the face or throat, and itching skin lumps)<br>• Damage to the liver (dark urine, light-coloured poo, yellowing of the skin and eyes, pain in the upper-right belly, and sudden and unexplained tiredness). |
| **Drug Interactions** | **X** Alcohol (Ethyl)<br>**X** Ciprofloxacin (Systemic)<br>**X** FluvoxaMINE<br>**X** Viloxazine<br>**C** Capmatinib |

| | |
|---|---|
| | CDeferasirox<br>CEnoxacin<br>CFexinidazole<br>CGivosiran<br>CMethoxsalen (Systemic)<br>CMexiletine<br>CRifAMPin<br>CRucaparib<br>CStiripentol<br>CThiabendazole<br>CTobacco (Smoked)<br>CVemurafenib |
| **Special Population** | **Older Adult Considerations**<br>Older adult: Avoid use in older adult patients ≥75 years old (due to lack of efficacy) or in patients with dementia (lack of data).<br>Smokers: Smoking (particularly ≥15 cigarettes/day) induces agomelatine metabolism and decreases its bioavailability; may decrease efficacy. |
| **Pregnancy** | Adverse effects have not been observed in animal reproduction studies. Due to limited data, the manufacturer recommends avoiding use during pregnancy. |
| **Lactation** | It is not known if agomelatine is present in breast milk. According to the manufacturer, a decision to either discontinue breastfeeding or discontinue therapy should be made, taking into account the benefits of breastfeeding for the child and the benefit of therapy for the mother |
| **Contraindications** | Hypersensitivity to agomelatine or any component of the formulation; hepatic impairment (ie, active liver disease or cirrhosis) or transaminases >3 times ULN; concomitant use of strong CYP1A2 inhibitors (eg, fluvoxamine, ciprofloxacin) |

| | |
|---|---|
| **Monitoring Requirements** | Mental status for depression, suicidal ideation (especially at therapy initiation or dose titration).<br>Monitor hepatic enzymes at baseline and weeks 3, 6, 12, 24, and then when clinically required; restart monitoring cycle if dosage is increased. Repeat liver function testing within 48 hours for any patient in whom serum transaminases have increased. |
| **Precautions** | **Suicidal thinking/behavior**:<br>Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders; consider risk prior to prescribing. Short-term studies did not show an increased risk in patients ≥25 to <65 years of age and showed a decreased risk in patients ≥65 years (Stone 2009). Patients with a history of suicidal activity or ideation are at higher risk. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during early treatment or following dosage changes; the patient's family or caregiver should be instructed to closely observe the patient and immediately communicate condition with healthcare provider. *AGOMELATINE IS NOT APPROVED FOR USE IN CHILDREN <18 YEARS OF AGE*<br>**Concerns related to adverse effects:**<br>CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).<br>Hepatic impairment/injury: Severe |

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|---|---|
| | hepatic injury, including hepatic failure and death (rare), increases in hepatic enzymes >10 x upper limit of normal (ULN), hepatitis, and jaundice have been reported, most often during the first few months of treatment. If symptoms of hepatic injury occur (eg, dark urine, light colored stool, yellow skin/eyes, upper abdominal pain, fatigue) or if transaminases are >3 x ULN, discontinue therapy.<br>Disease-related concerns:<br>*Hepatic impairment:* Use caution when initiating therapy in patients with mild transaminase elevations ≤3 x ULN or with risk factors for hepatic injury (eg, obesity, nonalcoholic fatty liver disease, diabetes, heavy alcohol consumption, or use of concomitant hepatotoxic medications). Concentrations, bioavailability, and half-life are increased in patients with mild and moderate hepatic impairment. Initiation of therapy is contraindicated in patients with preexisting hepatic injury, cirrhosis, or transaminases >3 x ULN (Mauri 2014).<br>Mania/hypomania: May precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Combination therapy with an antidepressant and a mood stabilizer may be effective for acute treatment of bipolar major depressive episodes but should be avoided in acute mania or mixed episodes as well as maintenance treatment in bipolar disorder due to the mood-destabilizing effects of antidepressants. Patients presenting with depressive symptoms should be screened for bipolar disorder.<br>Renal impairment: Relevant pharmacokinetic changes were not |

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| | observed with severe renal impairment; however, data are limited in patients with depression and caution is recommended with moderate-to-severe renal impairment when used for treating depression. |
| **Black Box Warning** | N/A |
| **REMS** | N/A |

**Clinical Trials – Agomelatine**

According to an article published in Frontiers in Psychiatry (2021) regarding the effects of agomelatine on insomnia; It is recommended that initial insomnia may benefit from the use of agomelatine. Furthermore, agomelatine is shown to extend sleep duration, improve performance, and decrease daytime drowsiness. However, its impact on sleep architecture in patients with depression appears to be negligible. In a randomized double-blind controlled trial, agomelatine demonstrated significantly greater improvements in insomnia among depressed patients compared to venlafaxine. Another double-blinded study by Quera-Salva et al. revealed that agomelatine effectively reduced sleep latency to a greater extent than escitalopram. In randomized clinical trials contrasting agomelatine with selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, agomelatine exhibited enhancements across various aspects of the sleep-wake cycle, particularly during the initial sleep stages and sleep quality, while also promoting daytime alertness. Agomelatine has additionally proven effective in alleviating circadian rhythm disruptions commonly reported in patients with Major Depressive Disorder (MDD)[11].

For menopausal insomnia, melatonin treatment has been proposed as a means to alleviate sleep disturbances during this phase. While no direct comparison between melatonin and agomelatine exists in insomnia treatment, there is promising evidence that agomelatine holds potential for effectively treating insomnia in menopausal women[11].

**Health Technology Assessment (HTA)**

**Table 15.** Agomelatine HTA Analysis

| Medication | Agency | Date – HTA Recommendation |
|---|---|---|
| Agomelatine | CADTH[12] | Not available |
| | HAS[13] | October 2015 - No clinical benefit demonstrated in the treatment of major depressive episodes in adults. VALDOXAN has Marketing Authorization in the treatment of major (i.e. clear) depressive episodes in adults.<br>Its efficacy is modest and has been demonstrated only in the short term (6-12 weeks) versus placebo. It has not been shown to have any impact on the remission rates for depressive episodes, the primary efficacy endpoint. Its use necessitates strict monitoring of liver function before the initiation of and throughout the treatment. |
| | PBAC[14] | Not available |
| | NICE[15] | 27 July 2011 - Agomelatine for the treatment of major depressive episodes; NICE is unable to recommend the use in the NHS of agomelatine for the treatment of major depressive episodes because no evidence submission was received from the manufacturer or sponsor of the technology. |
| | IQWIG[16] | Not available |

**Conclusion Statement – Agomelatine**

No HTA recommendations about the use of Agomelatine in patients with major depressive episodes or insomnia.

### 2.1.2 Alprazolam

This section includes pertinent information regarding the use of Alprazolam (in Insomnia)[10]:

**Table 16.** Drug Therapy with Alprazolam

| **SCIENTIFIC NAME**<br>**Alprazolam** | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes, for the treatment of anxiety and panic disorders |
| **EMA** | Yes, for anxiety disorders |
| **MHRA** | Yes, short-term symptomatic treatment of anxiety in adults. |
| **PMDA** | Yes |
| **Indication (ICD-10)** | G47. 00 |
| **Drug Class** | Hypnotics and sedatives |
| **Drug Sub-class** | Benzodiazepine |
| **ATC Code** | N05BA12 |
| **Pharmacological Class (ASHP)** | Bone Anabolic Agents |
| **DRUG INFORMATION** | |
| **Dosage Form** | Tablet |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | **Anxiety**:<br>Anxiety disorders (adjunctive therapy or monotherapy) (alternative agent):<br>Note: Generally used short term for symptom relief until preferred therapy (eg, serotonin reuptake inhibitor) is effective (eg, 4 to 6 weeks, followed by tapering). Long-term, low-dose therapy (eg, 2 mg/day) may be considered in select patients when other treatments are ineffective or poorly tolerated. Use with caution in patients with posttraumatic stress disorder; benzodiazepines may worsen symptoms.<br>Immediate release: Oral: Initial: 0.25 mg 3 to 4 times daily; may increase dose based on response and tolerability in increments ≤1 mg/day at intervals ≥3 days up to a usual dose of 2 to 6 mg/day in 3 to 4 divided doses. Some patients |

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| | may require up to 8 mg/day for optimal response; manufacturer's labeling maximum: 10 mg/day. With doses >4 mg/day, increase more gradually to minimize adverse effects; periodically reassess and consider dosage reduction.<br>Extended release (panic disorder labeled use): Oral: Initial: 0.5 to 1 mg once daily; may increase dose based on response and tolerability in increments ≤1 mg/day at intervals ≥3 days up to a usual dose of 2 to 6 mg/day. Some patients may require up to 8 mg/day for optimal response; manufacturer's labeling maximum: 10 mg/day. With doses >4 mg/day, increase more gradually to minimize adverse effects; periodically reassess and consider dosage reduction. Administration in 2 divided doses may be considered to maximize efficacy. |
| **Maximum Daily Dose Adults*** | 10 mg per day |
| **Dose (pediatrics)** | Anxiety: Children ≥7 years and Adolescents <18 years: Limited data available: Oral: Initial: 0.005 to 0.02 mg/kg/dose 3 times daily; in trials, doses were rounded to nearest available tablet size (lowest available dose is 0.125 mg [1/2 of 0.25 mg tablet]). May titrate at 2- to 3-day intervals in 0.125 to 0.25 mg/dose increments up to a maximum 0.06 mg/kg/day or 4 mg/day, whichever is less |
| **Maximum Daily Dose Pediatrics*** | 0.06 mg/kg/day or 4 mg/day, whichever is less |
| **Adjustment** | ***For Altered Kidney Function:***<br>CrCl ≥10 mL/minute: No dosage adjustment necessary (Ref).<br>CrCl <10 mL/minute: No dosage adjustment necessary; use with caution as enhanced pharmacodynamic effects (eg, psychomotor and memory |

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| | impairment) may be observed in patients with end-stage kidney disease.<br>***For Hepatic Impairment:***<br>Advanced liver disease:<br>IR tablet, oral concentrate, orally disintegrating tablet: 0.25 mg 2 to 3 times daily.<br>Extended release: 0.5 mg once daily |
| **Prescribing edits*** | AGE, MD, PA |
| **AGE (Age Edit):** Safety and effectiveness of alprazolam in individuals below 18 years of age have not been established. | |
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit):** N/A | |
| **MD (Physician Specialty Edit):** To be used after psychiatrist or neurologist assessment | |
| **PA (Prior Authorization):**<br>Alprazolam should be given to adults at a dose of 0.25 mg 3 to 4 times daily and to children ≥7 years and adolescents <18 years at a dose of 0.005 to 0.02 mg/kg/dose 3 times daily by a psychiatrist or neurologist. Alprazolam should be prior authorized because the dose should be reduced or the use avoided in patients receiving opioids, with significant chronic disease (eg, respiratory compromise), or at increased risk for accumulation (eg, advanced cirrhosis) and the use should be avoided in patients with a history of substance use, misuse of medications, or depression | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** N/A | |
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | <u>Most common:</u><br>• Dermatologic: Skin rash<br>• Endocrine & metabolic: Decreased libido<br>• Gastrointestinal: Constipation (IR: 26%; ER: 8%), decreased appetite (IR: 28%), increased appetite (IR: 33%; ER: 7%), xerostomia (IR: 15%)<br>• Genitourinary: Difficulty in micturition (IR: 12%; ER: ≥1%)<br>• Nervous system: *Ataxia (IR: 40%; ER:* |

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| | *7% to 9%) (See Table 1), cognitive dysfunction (IR: 29%; ER: Bradyphrenia: <1%), depression (ER: 12%; depressed mood: 1%), dizziness (IR: 2% to 21%; ER: ≥1%), drowsiness (IR: 41% to 77%; ER: 23%) (See Table 2), dysarthria (IR: 23%; ER: 11%), fatigue (IR: 49%; ER: 14%) (See Table 3), irritability (IR: 33%; ER: ≥1%), memory impairment (IR: 33%; ER: 15%), sedated state (ER: 45%)*<br>Most serious:<br>• shortness of breath.<br>• seizures.<br>• severe skin rash.<br>• yellowing of the skin or eyes.<br>• confusion.<br>• problems with speech.<br>• Problems with coordination or balance. |
| **Drug Interactions** | XAdagrasib<br>XAtazanavir<br>XAzelastine (Nasal)<br>XBromperidol<br>XCeritinib<br>XClarithromycin<br>XCobicistat<br>XDarunavir<br>XDelavirdine<br>XErdafitinib<br>XFexinidazole<br>XFlunarizine<br>XFusidic Acid (Systemic)<br>XIdelalisib<br>XIndinavir<br>XItraconazole<br>XKetoconazole (Systemic)<br>XKratom<br>XLevoketoconazole<br>XLonafarnib<br>XLopinavir |

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| | XMiFEPRIStone<br>XNelfinavir<br>XOlopatadine (Nasal)<br>XOrphenadrine<br>XOxomemazine<br>XOxybate Salts (Calcium, Magnesium, Potassium, and Sodium)<br>XPacritinib<br>XParaldehyde<br>XPimozide<br>XPosaconazole<br>XSaquinavir<br>XSodium Oxybate<br>XTelithromycin<br>XThalidomide<br>XTreosulfan<br>XTucatinib<br>XVoriconazole |
| **Special Population** | • Debilitated patients: Use with caution in debilitated patients; use lower starting dose.<br>• Older adult patients: older adults may be at an increased risk of death with use; risk has been found highest within the first 4 months of use in elderly dementia patients.<br>• Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.<br>• Obese patients: Use with caution in obese patients; may have prolonged action when discontinued.<br>• Smokers: Cigarette smoking may decrease alprazolam concentrations up to 50%. |
| **Pregnancy** | Alprazolam and its metabolites cross the human placenta. |
| **Lactation** | Alprazolam is present in breast milk. Breastfeeding during benzodiazepine therapy is not recommended due to the |

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| | potential for drowsiness in the breastfeeding infant; breastfeeding during alprazolam therapy is not recommended by the manufacturer. If a benzodiazepine is needed in breastfeeding patients, use of a short-acting agent is preferred. |
| **Contraindications** | Hypersensitivity to alprazolam, any component of the formulation, or other benzodiazepines (cross-sensitivity with other benzodiazepines may exist); concurrent therapy with strong cytochrome P-450 3A (CYP3A) inhibitors (eg, itraconazole, ketoconazole), except ritonavir; acute narrow angle glaucoma. |
| **Monitoring Requirements** | Respiratory and cardiovascular status; mental alertness; assess risk for abuse, misuse, and substance use disorder. |
| **Precautions** | Concerns related to adverse effects:<br>*Sleep-related activities:*<br>Hazardous sleep-related activities such as sleep-driving, cooking and eating food, and making phone calls while asleep have been noted with benzodiazepines.<br>*Disease-related concerns:*<br>• Depression: Avoid use in patients with depression because of concerns about worsening mood symptoms, particularly if suicidal risk may be present, except for acute or emergency situations (eg, acute agitation, status epilepticus) (Craske 2022).<br>• Hepatic impairment: Use with caution in patients with hepatic impairment.<br>• Renal impairment: Use with caution in patients with renal impairment or predisposition to urate nephropathy; has weak uricosuric properties. |

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| | • Respiratory disease: Reduce dose or avoid use in patients with respiratory disease, including chronic obstructive pulmonary disease or sleep apnea. Benzodiazepines may cause significant respiratory depression.<br>*Concurrent drug therapy issues:*<br>• Flumazenil: Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy. |
| **Black Box Warning** | • Risks from concomitant use with opioids<br>• Abuse, misuse, and addiction<br>• Dependence and withdrawal reactions |
| **REMS** | N/A |

**Health Technology Assessment (HTA)**

**Table 17.** Alprazolam HTA Analysis

| Medication | Agency | Date – HTA Recommendation |
|---|---|---|
| Alprazolam | CADTH[12] | Not available |
| | HAS[13] | Not available |
| | PBAC[14] | Alprazolam is recommended for panic disorder under clinical criteria:<br>• The treatment must be for use when other treatments have failed, **OR**<br>• The treatment must be for use when other treatments are inappropriate. |
| | NICE[15] | Not available |
| | IQWIG[16] | Not available |

**Conclusion Statement – Alprazolam**

No HTA recommendations about the use of Alprazolam in patients with insomnia. Recommendations are for the use of Alprazolam in patients with panic disorder as per PBS.

### 2.1.3 Hydroxyzine

This section includes pertinent information regarding the use of Hydroxyzine (in Insomnia)[10]:

**Table 18.** Drug Therapy with Hydroxyzine

| **SCIENTIFIC NAME Hydroxyzine** | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes, provides relief from anxiety symptoms. provide sedation (a relaxed state, for relief of tension and anxiety) before surgery or another medical procedure |
| **EMA** | Yes, for the treatment of anxiety disorders, sleep disorders and pruritus |
| **MHRA** | Yes, for anxiety in adults |
| **PMDA** | NO |
| **Indication (ICD-10)** | G47. 00 |
| **Drug Class** | Histamine h1 antagonist, first generation |
| **Drug Sub-class** | Piperazine derivative |
| **ATC Code** | N05BB01 |
| **Pharmacological Class (ASHP)** | Antihistamines |
| **DRUG INFORMATION** | |
| **Dosage Form** | Tablet |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | Anxiety, monotherapy, or adjunctive therapy (alternative agent):<br>Note: May be useful for insomnia associated with anxiety or for short-term immediate control of symptoms until maintenance therapy is effective.<br>Oral: Usual dosage range: 25 to 50 mg |

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| | up to 4 times daily, as needed; may increase based on response and tolerability up to 400 mg/day; maximum single dose: 100 mg. For insomnia associated with anxiety, administer at bedtime. |
| **Maximum Daily Dose Adults*** | 100 mg per day for adults. 50 mg for elderly people |
| **Dose (pediatrics)** | **Anxiety:** Children and Adolescents: Oral: 0.5 mg/kg/dose every 6 hours; maximum dose is age-dependent: Age <6 years: 12.5 mg/dose; age ≥6 years: 25 mg/dose (Ref). Note: In pediatric patients, some experts have recommended lower initial doses, although reported experience is lacking. In adults, experts suggest a lower daily dosing regimen of 37.5 to 75 mg/day in divided doses. |
| **Maximum Daily Dose Pediatrics*** | 0.06 mg/kg/day or 4 mg/day, whichever is less |
| **Adjustment** | ***For Altered Kidney Function:***<br>CrCl ≥50 mL/minute: No dosage adjustment necessary.<br>CrCl 10 to <50 mL/minute: Administer ~50% of usual dose.<br>CrCl <10 mL/minute: Administer ~25% to 50% of usual dose.<br>***For Hepatic Impairment:***<br>There are no dosage adjustments provided in the manufacturer's labeling. In patients with primary biliary cirrhosis, change dosing interval to every 24 hours |
| **Prescribing edits*** | AGE, MD, PA |
| **AGE (Age Edit):** Hydroxyzine, a first-generation antihistamine, is identified in the beers criteria as a potentially inappropriate medication to be avoided in patients 65 years and older | |
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit):** N/A | |
| **MD (Physician Specialty Edit):** Available only with the doctor's prescription | |

**PA (Prior Authorization):**
Hydroxyzine should be given to adults with anxiety as a monotherapy or adjunctive therapy at a usual dose of 25 to 50 mg up to 4 times daily only with the doctor's prescription. Hydroxyzine, a first-generation antihistamine, is identified in the beers criteria as a potentially inappropriate medication to be avoided in patients 65 years and older (independent of diagnosis or condition) due to its potent anticholinergic properties resulting in increased risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity; use should also be avoided due to reduced clearance with advanced age and tolerance associated with use as a hypnotic.

**QL (Quantity Limit):** N/A

**ST (Step Therapy):** N/A

**EU (Emergency Use Only):** N/A

**PE (Protocol Edit):** N/A

**SAFETY**

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| **Main Adverse Drug Reactions (Most common and most serious)** | **Most common:**<br>**Frequency not defined:**<br>• **Gastrointestinal:** Xerostomia<br>• **Nervous system:** Drowsiness (transient)<br>• **Respiratory:** Respiratory depression (high doses)<br>**Postmarketing:**<br>• **Cardiovascular:** Prolonged QT interval on ECG (rare: <1%) (Schlit 2017; Vigne 2015), torsades de pointes (rare: <1%) (Ali 2021; Schlit 2017)<br>• **Dermatologic:** Acute generalized exanthematous pustulosis (rare: <1%) (O'Toole 2014), pruritus, skin rash, urticaria<br>• **Hypersensitivity:** Fixed drug eruption (Bhari 2017)<br>• **Nervous system:** Cognitive dysfunction (Church 2010; Conen 2011), hallucination, headache, involuntary body movements, seizure (high doses)<br>• **Neuromuscular & skeletal: Tremor (high doses)** |

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| | **Most serious:**<br>• Seizures<br>• Fast/irregular heartbeat<br>• Severe dizziness<br>• Fainting |
| **Drug Interactions** | XAclidinium<br>XAzelastine (Nasal)<br>XBromperidol<br>XCimetropium<br>XEluxadoline<br>XFlunarizine<br>XGlycopyrrolate (Oral Inhalation)<br>XGlycopyrronium (Topical)<br>XIpratropium (Oral Inhalation)<br>XKratom<br>XLevosulpiride<br>XOlopatadine (Nasal)<br>XOrphenadrine<br>XOxatomide<br>XOxomemazine<br>XParaldehyde<br>XPitolisant *Depends on International labeling*<br>XPotassium Chloride *Depends on Dosage Form*<br>XPotassium Citrate *Depends on Dosage Form*<br>XPramlintide<br>XRevefenacin<br>XThalidomide<br>XTiotropium<br>XUmeclidinium |
| **Special Population** | Older adult: May cause over sedation in older adults; avoid use. |
| **Pregnancy** | Hydroxyzine crosses the placenta. |
| **Lactation** | It is not known if hydroxyzine is present in breast milk.<br>Drowsiness and irritability have been reported in breastfed infants exposed to antihistamines). Sedation has been |

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| | reported in breastfed infants exposed to hydroxyzine. In general, if a breastfed infant is exposed to a first-generation antihistamine via breast milk, they should be monitored for irritability or drowsiness. |
| **Contraindications** | Hypersensitivity to hydroxyzine or any component of the formulation; early pregnancy; prolonged QT interval. |
| **Monitoring Requirements** | Relief of symptoms, mental status and alertness, BP, rash (including worsening of pre-existing skin reactions), signs/symptoms of hypersensitivity reaction. |
| **Precautions** | <u>Concerns related to adverse effects:</u><br>• QT prolongation/torsades de pointes: Oral hydroxyzine is contraindicated in patients with a prolonged QT interval.<br><u>Disease-related concerns:</u><br>• Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.<br>• Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.<br>• Respiratory disease: Use with caution in patients with asthma or chronic obstructive pulmonary disease (COPD). |
| **Black Box Warning** | N/A |
| **REMS** | N/A |

**Health Technology Assessment (HTA)**

**Table 19.** Hydroxyzine HTA Analysis

| Medication | Agency | Date – HTA Recommendation |
|---|---|---|
| Hydroxyzine | CADTH[12] | Not available |
| | HAS[13] | Not available |
| | PBAC[14] | Not available |
| | NICE[15] | Not available |
| | IQWIG[16] | 3 March 2022 – There is one recommendation on the IQWIG website that mentions; antihistamines come in the form of tablets or drops. Some of them, like diphenhydramine and doxylamine, are available over the counter. Others, such as promethazine and hydroxyzine, have to be prescribed by a doctor. It is important to talk to the doctor before deciding whether to use antihistamines for the treatment of insomnia. It is also important to be careful if someone has already certain other medical problems. For example, antihistamines aren't suitable for men with prostate problems because they can make it difficult to pass urine. |

**Conclusion Statement – Hydroxyzine**

There is only one recommendation on the IQWIG website that hydroxyzine should be prescribed by a doctor for the treatment of insomnia. Although most people tolerate antihistamines well, they do have some side effects. The most common ones are headaches, restlessness, concentration problems, dizziness, a dry mouth and blurred or double vision. It is also not suitable for men with prostate problems making it difficult to pass urine.

### 2.1.4 Promethazine

This section includes pertinent information regarding the use of Promethazine (in Insomnia)[10]:

**Table 20.** Drug Therapy with Promethazine

| **SCIENTIFIC NAME**<br>**Promethazine** | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | Yes |
| **US FDA** | Yes |
| **EMA** | Yes |
| **MHRA** | Yes, short term use to treat adults with difficulty sleeping (insomnia) |
| **PMDA** | NO |
| **Indication (ICD-10)** | G47. 00 |
| **Drug Class** | Histamine h1 antagonist, first generation |
| **Drug Sub-class** | Phenothiazine Derivative |
| **ATC Code** | R06AD02 |
| **Pharmacological Class (ASHP)** | Phenothiazines |
| **DRUG INFORMATION** | |
| **Dosage Form** | Film-coated Tablet |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | Nausea and/or vomiting, acute:<br>Note: May use short-term (eg, up to 48 to 72 hours) for self-limiting nausea/vomiting (eg, postoperative rescue therapy, acute vertigo).<br>Oral, rectal: 12.5 to 25 mg every 4 to 6 hours as needed. To avoid intolerable adverse effects, some experts recommend a maximum dose of 50 mg/day. |
| **Maximum Daily Dose Adults*** | 50 mg |
| **Dose (pediatrics)** | **Preprocedure sedation, adjunct:**<br>Children ≥2 years and Adolescents: Oral, IM, IV: 0.5 to 1.1 mg/kg once 30 minutes prior to procedure as part of an appropriate combination regimen; maximum dose: 12.5 to 25 mg/dose; manufacturer recommends in combination with a reduced dose of opioid or barbiturate and an appropriate dosage of an atropine-like |

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| | drug if appropriate; however, other combination regimens have been described |
| **Maximum Daily Dose Pediatrics*** | **12.5 to 25 mg/dose** |
| **Adjustment** | **For Altered Kidney Function:**<br>No dosage adjustment necessary for any degree of kidney dysfunction (only 0.6% of an administered dose excreted in the urine unchanged)<br>**For Hepatic Impairment:**<br>There are no dosage adjustments provided in the manufacturer's labeling; use with caution (cholestatic jaundice has been reported with use). |
| **Prescribing edits*** | AGE |
| **AGE (Age Edit):** Promethazine should not be used in pediatric patients younger than 2 years because of the potential for fatal respiratory depression. | |
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit):** N/A | |
| **MD (Physician Specialty Edit):** N/A | |
| **PA (Prior Authorization):** N/A | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** N/A | |
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |
| **Main Adverse Drug Reactions (Most common and most serious)** | **Most common:**<br>**Frequency not defined:**<br>• **Gastrointestinal:** Xerostomia<br>• **Nervous system:** Drowsiness (transient)<br>• **Respiratory:** Respiratory depression (high doses)<br>**Postmarketing:**<br>• **Cardiovascular:** Prolonged QT interval on ECG (rare: <1%) (Schlit 2017; Vigne 2015), torsades de pointes (rare: <1%) (Ali 2021; Schlit 2017)<br>• **Dermatologic:** Acute generalized |

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| | exanthematous pustulosis (rare: <1%) (O'Toole 2014), pruritus, skin rash, urticaria<br>• **Hypersensitivity:** Fixed drug eruption (Bhari 2017)<br>• **Nervous system:** Cognitive dysfunction (Church 2010; Conen 2011), hallucination, headache, involuntary body movements, seizure (high doses)<br>• **Neuromuscular & skeletal: Tremor (high doses)**<br>**Most serious:**<br>• Seizures<br>• Fast/irregular heartbeat<br>• Severe dizziness<br>• Fainting |
| **Drug Interactions** | XAclidinium<br>XAzelastine (Nasal)<br>XBromperidol<br>XCimetropium<br>XEluxadoline<br>XFlunarizine<br>XGlycopyrrolate (Oral Inhalation)<br>XGlycopyrronium (Topical)<br>XIpratropium (Oral Inhalation)<br>XKratom<br>XLevosulpiride<br>XOlopatadine (Nasal)<br>XOrphenadrine<br>XOxatomide<br>XOxomemazine<br>XParaldehyde<br>XPitolisant *Depends on International labeling*<br>XPotassium Chloride *Depends on Dosage Form*<br>XPotassium Citrate *Depends on Dosage Form*<br>XPramlintide<br>XRevefenacin |

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| | XThalidomide<br>XTiotropium<br>XUmeclidinium |
| **Special Population** | Older adult: May cause over sedation in older adults; avoid use. |
| **Pregnancy** | Hydroxyzine crosses the placenta. |
| **Lactation** | It is not known if hydroxyzine is present in breast milk.<br>Drowsiness and irritability have been reported in breastfed infants exposed to antihistamines). Sedation has been reported in breastfed infants exposed to hydroxyzine. In general, if a breastfed infant is exposed to a first-generation antihistamine via breast milk, they should be monitored for irritability or drowsiness. |
| **Contraindications** | Hypersensitivity to hydroxyzine or any component of the formulation; early pregnancy; prolonged QT interval. |
| **Monitoring Requirements** | Relief of symptoms; mental status and CNS effects (including sedation, akathisia, delirium, extrapyramidal symptoms); signs and symptoms of tissue injury (burning or pain at injection site, phlebitis, edema) with parenteral administration. |
| **Precautions** | Concerns related to adverse effects:<br>• Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).<br>• Photosensitivity: May cause photosensitivity; avoid prolonged sun exposure.<br>• Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant |

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| | medication possessing anticholinergic effects.<br>Disease-related concerns:<br>• Hepatic impairment: Use with caution in patients with hepatic impairment; cholestatic jaundice has been reported with use. Avoid use in pediatric patients with signs and symptoms of hepatic disease (extrapyramidal symptoms caused by promethazine may be confused with CNS signs of hepatic disease).<br>• Cardiovascular disease: Use with caution in patients with cardiovascular disease.<br>• Respiratory disease: Avoid use in patients with compromised respiratory function or in patients at risk for respiratory failure (eg, COPD, sleep apnea). |
| **Black Box Warning** | - Respiratory depression – Pediatrics<br>- Severe tissue injury, including gangrene (injection) |
| **REMS** | N/A |

**Health Technology Assessment (HTA)**

**Table 21.** Promethazine HTA Analysis

| Medication | Agency | Date – HTA Recommendation |
|---|---|---|
| Promethazine | CADTH[12] | Not available |
| | HAS[13] | Not available |
| | PBAC[14] | Not available |
| | NICE[15] | Not available |

| | | |
|---|---|---|
| | IQWIG[16] | 3 March 2022 – There is one recommendation on the IQWIG website that mentions; antihistamines come in the form of tablets or drops. Some of them, like diphenhydramine and doxylamine, are available over the counter. Others, such as promethazine and hydroxyzine, have to be prescribed by a doctor. It is important to talk to the doctor before deciding whether to use antihistamines for the treatment of insomnia. It is also important to be careful if someone has already certain other medical problems. For example, antihistamines aren't suitable for men with benign prostatic hyperplasia as they may cause difficulty in urination. |

**Conclusion Statement – Promethazine**

There is only one recommendation on the IQWIG website that promethazine should be prescribed by a doctor for the treatment of insomnia. Although most people tolerate antihistamines well, they do have some side effects. The most common ones are headaches, restlessness, concentration problems, dizziness, a dry mouth and blurred or double vision. It is also not suitable for men with prostate problems making it difficult to pass urine.

## 2.2. Modifications

*Modifications have been made since April 2020.*

Prescribing edits were modified to Diazepam, Lorazepam, Mirtazapine, Nitrazepam, Zolpidem:

➔ ***Diazepam***:

AGE: According to guidelines benzodiazepines not to be used for children less than 18 years old in insomnia treatment. Diazepam should not be used in infants <6 months of age.

MD: To be prescribed by a psychiatrist or neurologist.

CU: Concomitant use of benzodiazepines (Diazepam) with opioids may result in profound sedation, respiratory depression, coma, and death; concomitant prescribing of these drugs should be reserved for use in patients for whom alternative treatment options are inadequate, dosages and durations should be limited to the minimum required. Patients should be followed for signs and symptoms of respiratory depression and sedation.

PA: Diazepam should be prior authorized because of its several contraindications and US black box warnings in addition to the risk of dependence, abuse, addiction, and withdrawal.

➔ ***Lorazepam***

AGE**:** According to guidelines benzodiazepines not to be used for children less than 18 years old in insomnia treatment.md: to be prescribed by a psychiatrist or neurologist.

PA: Lorazepam should be prior authorized because of its several contraindications and black box warnings in addition to the risk of dependence, abuse, addiction, and withdrawal.

CU: Benzodiazepines should not be used concomitantly with opioids may result in profound sedation, respiratory depression, coma, and death; reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate, and limit dosages and durations to the minimum required. follow patients for signs and symptoms of respiratory depression and sedation.

➔ ***Mirtazapine***

ST: Use after trying diazepam, lorazepam, and zolpidem.

MD: A specialist (neurologist) should make sure that insomnia is associated with comorbid depression/anxiety.

AGE: According to beers criteria, mirtazapine is identified in the beers criteria as a potentially inappropriate medication to be used with caution in patients 65 years and older due to the potential to cause or exacerbate syndrome of inappropriate antidiuretic hormone secretion (siadh) or hyponatremia; monitor sodium concentration closely when initiating or adjusting the dose in older adults.

➔ **Nitrazepam**:

QL: Treatment should typically not exceed 7 to 10 consecutive days. Reevaluation of the patient is required if treatment continues for >2 to 3 consecutive weeks. Prescriptions should be written for short-term use (7 to 10 days) and limited to ≤1 month supply.

AGE: According to guidelines, benzodiazepines should not be used for children less than 18 years old in insomnia treatment.

MD: To be prescribed by a psychiatrist or neurologist.

➔ **Zolpidem**:

MD: To be used after psychiatrist or neurologist consultation due to its complex sleep disorder ADR alert.

AGE: Not to be used for children less than 18 years of age in insomnia treatment. zolpidem, a nonbenzodiazepine benzodiazepine-receptor agonist hypnotic, is

identified in the beers criteria as a potentially inappropriate medication to be avoided in patients 65 years and older.

QL: (When cumulative day supply is > 90 days) is identified as a high-risk medication in patients 65 years and older on the PQA'S (PHARMACY QUALITY ALLIANCE).

PA: Zolpidem should be prior authorized for patients older than 65 years and for patients with cumulative therapy greater than 90 days.

## 2.3 Delisting

The medications below are no longer SFDA registered[17], therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to Drugs in the disease - section 2 of CHI Insomnia original clinical guidance.*

- Amitriptyline Hydrochloride
- Lorazepam

## 2.4 Other Drugs

After April 2020, there have been an insomnia drug that has received FDA and EMA approval but was not registered in the SFDA list and submitted to the CHI for evaluation.

**Daridorexant** (Quviviq)

- In January 2022, the FDA approved Daridorexant (Quviviq) to treat insomnia in adults. It's available since May 2022.
- Daridorexant is recommended to be taken once per day, orally within 30 minutes before going to bed, with at least seven hours remaining prior to planned awakening.
- Daridorexant has very few common side effects, but it has several possible interactions. Discuss this with your healthcare provider and pharmacist before starting daridorexant.
- On April 29, 2022, Daridorexant was authorized for use in the European Union. It was the first orexin receptor antagonist to become available for use in the European Union.

In addition, there is an insomnia drug that has received FDA but not EMA approval and was not registered in the SFDA list and submitted to the CHI for evaluation.

**Lemborexant** (Dayvigo)

- In December 23, 2019, the U.S. Food and Drug Administration (FDA) approved a new treatment for people with insomnia, Dayvigo (lemborexant).

- The Food and Drug Administration has approved Dayvigo (lemborexant) for the treatment of insomnia in adults. The agency approved the drug for the treatment of insomnia characterized by difficulties with sleep onset or sleep maintenance.
- Lemborexant is not approved by the European Medicines Agency (EMA) for use in the European Union.

## Section 3.0 Key Recommendations Synthesis

➢ 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: mental health, somatic diseases and general health, medications and psychoactive substances taken, lifestyle, environmental factors, primary sleep disorders[3]. (Not graded)

*Recommendation statements for care of children and adolescents with autism spectrum disorder (ASD) and sleep disturbance regarding coexisting medical conditions and concomitant medications:*

- Clinicians seeking to improve sleep in children and adolescents with ASD should perform an assessment for coexisting conditions that could be contributing to sleep disturbance (Level B)[4]
- Clinicians seeking to improve sleep in children and adolescents with ASD should review concomitant medications that could contributing to sleep disturbance (Level B)[4]
- Clinicians seeking to improve sleep in children and adolescents with ASD who have a coexisting condition that is contributing to their sleep disturbance should ensure they receive appropriate treatment for their coexisting condition (Level B)[4]
- Clinicians seeking to improve sleep in children and adolescents with ASD who have medications that could be contributing to sleep disturbance should address whether the potentially contributing medications can be stopped or adjusted (Level B)[4]

*Recommendation statements for care of children and adolescents with autism spectrum disorder (ASD) and sleep disturbance regarding <u>complementary alternative medicine:</u>*

- Clinicians should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents that there is currently no evidence to support the routine use of weighted blankets or specialized mattress technology for improving disrupted sleep (Level B)[4]

- Although evidence of efficacy is lacking, clinicians should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents asking about *weighted blankets* that the reviewed trial reported no serious adverse events with blanket use and that blankets could be a reasonable nonpharmacologic approach to try for some individuals (Level B)[4]

*Behavioral and psychological treatments for chronic insomnia disorder in adults:*

- It is recommended that clinicians use multicomponent cognitive behavioral therapy for insomnia for the treatment of chronic insomnia disorder in adults. (STRONG)[5]
- It is suggested that clinicians use multicomponent brief therapies for insomnia for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)[5]
- It is suggested that clinicians use the following: stimulus control, sleep restriction therapy, relaxation therapy, sleep hygiene as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)[5]

*Recommendations for insomnia treatment in older adults:*

- Treatment options for insomnia in adults older than 65 years of age generally follow similar principles to those for younger adults, but there are some considerations and precautions due to potential age-related changes in health, medication sensitivity and sleep patterns.
- For **people over 65 years**, the treatment 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. (Not graded)[3]
  - Non-pharmacological interventions, including general health-promoting interventions with an emphasis on age-appropriate physical activity and specific interventions used in cognitive behavioral therapy for insomnia. (Not graded)[3]
- Healthcare providers should conduct a personalized evaluation and treatment plan as appropriate.
- Medications should be used with caution in older adults due to increased risk of falls, cognitive impairment, and dependency. Lower doses approach is preferred.
- For the discontinuation of BZD hypnotics, there was no first-line recommendation for the timing of reducing or discontinuation of BZD hypnotics following improvement in insomnia symptoms. As for timing, 1–3 months (6.4 ± 2.0), 3–6 months (5.9 ± 2.1), and immediately (4.2 ± 2.3) after improvement in

symptoms were categorized as second-line treatments, while 6–12 months (5.1 ± 2.4) after improvements in symptoms were categorized as having "no consensus." Only a timing of >1 year after improvement in symptoms (3.5 ± 2.2) was categorized as a third-line treatment (not-recommended)[7]

- For the treatment strategy when BZD hypnotics are ineffective, when BZD hypnotics do not improve the symptoms of insomnia, there was no first-line recommendation. Switching to lemborexant (6.7 ± 2.2) and suvorexant (6.1 ± 2.3), as well as combination treatment with lemborexant (6.3 ± 2.3) and suvorexant (5.9 ± 2.3), were categorized as second-line treatments. Additionally, increasing the dose of BZD hypnotics was also categorized as second-line treatment. Switching to other medications, trazodone (5.3 ± 2.4), other BZDs (4.9 ± 2.4), quetiapine (4.7 ± 2.5), and ramelteon (4.5 ± 2.3) were categorized as having "no consensus."[7]
- FDA-approved treatments for insomnia can be safely and effectively reduced or changed at their standard doses. In most situations, except for BZDs, zolpidem, eszopiclone, and the use of antidepressants and antipsychotics for purposes other than their approved ones, there's usually no need to gradually reduce or transition between medications when making a switch. Among different medication categories, DORAs, selective H1 antihistamines like low-dose doxepin, and melatonin receptor agonists such as ramelteon seem to carry the lowest risk of causing rebound insomnia or withdrawal symptoms when discontinuing or changing from other FDA-approved medications[8].

*Complementary and Integrative Health treatments*

- Insufficient evidence to recommend auricular acupuncture with seed and pellet, aerobic exercise, resistive exercise, tai chi, yoga, and qigong for the treatment of chronic insomnia disorder.
- Weak evidence to recommend cranial electrical stimulation for the treatment of chronic insomnia disorder.
- Weak evidence to recommend melatonin, kava, valerian, chamomile for the treatment of chronic insomnia disorder.
- Social support
- Diet
- Light exposure

## Section 4.0 Conclusion

This report serves as an annex to the previous CHI Insomnia report and aims to provide recommendations to aid in the management of Insomnia. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Insomnia. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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# Section 6.0 Appendices

## Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

| Prescribing edits Tools | Description |
|---|---|
| **AGE (Age):** | Coverage may depend on patient age |
| **CU (Concurrent Use):** | Coverage may depend upon concurrent use of another drug |
| **G (Gender):** | Coverage may depend on patient gender |
| **MD (Physician Specialty):** | Coverage may depend on prescribing physician's specialty or board certification |
| **PA (Prior Authorization):** | Requires specific physician request process |
| **QL (Quantity Limits):** | Coverage may be limited to specific quantities per prescription and/or time period |
| **ST (Step Therapy):** | Coverage may depend on previous use of another drug |
| **EU (Emergency Use only):** | This drug status on Formulary is only for emergency use |
| **PE (Protocol Edit):** | Use of drug is dependent on protocol combination, doses, and sequence of therapy |

## Appendix B. Insomnia Scope

**Table 21.** Insomnia Scope

| Added Sections | Rationale/Updates |
|---|---|
| **1.5** Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the *American Academy of Neurology* 2020[4] | Recommendation statements for care of *children and adolescents with autism spectrum disorder (ASD) and sleep disturbance* regarding coexisting medical conditions and concomitant medications<br>➢ Clinicians seeking to improve sleep in children and adolescents with ASD should perform an assessment for coexisting conditions that could be contributing to sleep disturbance (Level B)<br>➢ Clinicians seeking to improve sleep in children and adolescents with ASD should review concomitant medications that could be contributing to sleep disturbance (Level B)<br>➢ Clinicians seeking to improve sleep in children and adolescents with ASD who have a coexisting condition that is contributing to their sleep disturbance should ensure they receive appropriate treatment for their coexisting condition (Level B)<br>➢ Clinicians seeking to improve sleep in children and adolescents with ASD who have medications that could be contributing to sleep disturbance should address whether the potentially contributing medications can be stopped or adjusted (Level B)<br>Recommendation statements for care of children and adolescents with autism spectrum disorder (ASD) and sleep disturbance regarding melatonin use<br>➢ Clinicians should offer melatonin to children and adolescents with ASD if behavioral strategies have not been helpful and contributing coexisting conditions and use of concomitant medications have been addressed (Level B) |

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|---|---|
| | ➢ Clinicians offering melatonin for sleep disturbance in children and adolescents with ASD should write a prescription for **melatonin** or recommend using a high-purity pharmaceutical grade of melatonin when available (Level B)<br><br>➢ Clinicians offering melatonin for sleep dysregulation in children and adolescents with ASD should start by initiating a low dose (1–3 mg/d), 30–60 minutes before bedtime, and titrate to effect, not exceeding 10 mg/d (Level B)<br><br>➢ Clinicians offering melatonin for sleep disturbance in children and adolescents with ASD should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents regarding potential adverse events of melatonin use and the lack of long-term safety data (Level B).<br><br>Recommendation statements for care of children and adolescents with autism spectrum disorder (ASD) and sleep disturbance regarding complementary alternative medicine<br><br>➢ Clinicians should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents that there is currently no evidence to support the routine use of weighted blankets or specialized mattress technology for improving disrupted sleep (Level B)<br><br>➢ Although evidence of efficacy is lacking, clinicians should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents asking about *weighted blankets* that the reviewed trial reported no serious adverse events with blanket use and that blankets could be a reasonable nonpharmacologic approach to try for some individuals (Level B) |

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| **1.6** Behavioral and psychological treatments for chronic insomnia disorder in adults: an *American Academy of Sleep Medicine* clinical practice guideline 2021[5]<br><br>(Non-pharmacological) | - It is recommended that clinicians use multicomponent cognitive behavioral therapy for insomnia for the treatment of chronic insomnia disorder in adults. (STRONG)<br><br>- It is suggested that clinicians use multicomponent brief therapies for insomnia for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)<br><br>- It is suggested that clinicians use stimulus control as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)<br><br>- It is suggested that clinicians use sleep restriction therapy as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)<br><br>- It is suggested that clinicians use relaxation therapy as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL)<br><br>It is suggested that clinicians not use sleep hygiene as a single-component therapy for the treatment of chronic insomnia disorder in adults. (CONDITIONAL) |

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| **1.7** *Italian Association of Sleep Medicine (AIMS)* position statement and guideline on the treatment of menopausal sleep disorders 2019[6] | ➢ Menopausal sleep disorders have a wide variety of manifestations, including not only insomnia but also breathing and movement disorders. VMS (Vasomotor Symptoms) have a large effect on postmenopausal women's sleep, mood, and quality of life. Treatment needs to be individualized, taking into account comorbidities and preferences.<br><br>➢ Insomnia per se best responds to CBT-I (Cognitive Behavioral Therapy), MHT (Menopausal Hormone Therapy), and escitalopram. New drugs with different therapeutic targets are in development.<br><br>➢ **Melatonin** may stabilize circadian rhythm while helping insomnia symptoms as well as VMS.<br>➢ CPAP and MADs (Mandibular Advancement Device) decrease the hypertension burden of OSA, but without a major impact on sleep quality and mortality risk.<br><br>- There is a need for adequately powered randomized controlled trials as well as cohort studies to better understand the impact of menopausal sleep disorders and increase the evidence-base of therapeutic strategies. |

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| **1.8** Treatment of insomnia in older adults. Recommendations of the Polish Sleep Research Society, Polish Society of Family Medicine and the Polish Psychiatric Association 2023 [3]{people over 65 years of age) | • **The aim of this article is to present the current recommendations for the management of insomnia in people over 65 years of age.**<br><br>• **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.**<br><br>• **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.**<br><br>**The diagnosis of insomnia**<br>▪ 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.<br><br>▪ A detailed history and psychiatric examination make it possible to differentiate between primary insomnia and sleep disorders caused by another mental disorder.<br><br>**Treatment**<br>▪ The treatment of insomnia in people over 65 focuses on two main interventions. |

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| | ➔ Treatment of comorbidities associated with insomnia using non-pharmacological and pharmacological methods when indicated, according to the treatment recommendations for the condition.<br><br>➔ Non-pharmacological interventions, including general health-promoting interventions with an emphasis on age-appropriate physical activity and specific interventions used in cognitive behavioral therapy for insomnia.<br><br>▪ Non-pharmacological treatment of insomnia<br><br>• Current recommendations focus on improving sleep conditions and promote healthy lifestyle.<br><br>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.<br><br>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).<br><br>Controlling body weight, ensuring optimal sleep duration (6-8 hours), earlier bedtime (at 10:00- 11:00 p.m.).<br><br>• Treatment of insomnia using cognitive behavioral therapy techniques based on a classical approach includes cognitive and behavioral interactions. (Add Table 1)<br><br>• 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. |

- 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.

*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 the treatment of insomnia.
- The mechanism of action of zolpidem and other Z-drugs is similar to that of benzodiazepines (**diazepam**, **lorazepam**, **alprazolam**).
- 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.
- Due to their rapid onset of action, Z-drugs should be used shortly before bedtime.
- In older adults the use of hypnotics is associated with a significantly increased risk of falls and fractures.

*Sedative drugs*

- (**Table 3**); Drugs for the treatment of mental

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| | disorders that, in addition to their on-label use, are also used off-label to treat insomnia<br><br>▪ 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.<br><br>▪ 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.<br><br>▪ 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.<br><br>▪ 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, urinary retention and anticholinergic side effects, which significantly limits their use for the treatment of sleep disorders in older patients.<br><br>▪ The other antidepressants: **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.

*Melatonin and melatonergic drugs*

- In people aged 55 and over, melatonin treatment shows higher efficacy due to a marked decrease in melatonin secretion by the pineal gland occurring after 50 years of age.

- 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.

  [*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. In the case of predominant difficulty to fall asleep, it may be advisable to administer the drug earlier, 1-2 hours before bedtime.]

- 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, is not available in Europe. Agomelatine, which in addition to its melatonergic action is also a serotonin 5-HT2c receptor antagonist, is approved for

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| | the treatment of depressive episodes.<br><br>*Non-SFDA registered:*<br><br>Estazolam, Lormetazepam, Temazepam, Daridorexant, Doxepin, Mianserin, Trazodone, Levomepromazine, Tiagabine, L-tryptophan, Diphenhydramine, Doxylamine, Zaleplon, Ramelteon, Doxylamine<br><br>*SFDA-registered:*<br><br>Agomelatine |

## Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Insomnia

| Query | Filters | Search Details | Results |
|---|---|---|---|
| ((((((((((((((((((((((((((Sleep Initiation and Maintenance Disorders[MeSH Terms]) OR (Sleep Initiation[Title/Abstract] AND Maintenance Disorders[Title/Abstract])) OR (Disorders of Initiating[Title/Abstract] AND Maintaining Sleep[Title/Abstract])) OR (DIMS (Disorders of Initiating[Title/Abstract] AND Maintaining Sleep[Title/Abstract]))) OR (Early Awakening[Title/Abstract])) OR (Awakening, Early[Title/Abstract])) OR (Nonorganic Insomnia[Title/Abstract])) OR (Insomnia, Nonorganic[Title/Abstract])) OR (Primary Insomnia[Title/Abstract])) OR | Guideline, in the last 5 years | ("sleep initiation and maintenance disorders"[MeSH Terms] OR ("sleep initiation"[Title/Abstract] AND "maintenance disorders"[Title/Abstract]) OR ("disorders of initiating"[Title/Abstract] AND "maintaining sleep"[Title/Abstract]) OR ("DIMS"[All Fields] AND ("disorders of initiating"[Title/Abstract] AND "maintaining sleep"[Title/Abstract])) OR "early awakening"[Title/Abstract] OR "awakening early"[Title/Abstract] OR "nonorganic insomnia"[Title/Abstract] OR (("insomnia s"[All Fields] OR "sleep initiation and maintenance disorders"[MeSH Terms] OR ("Sleep"[All Fields] AND "Initiation"[All Fields] AND "Maintenance"[All Fields] AND "Disorders"[All Fields]) OR "sleep initiation and maintenance disorders"[All Fields] OR "Insomnia"[All Fields] OR "Insomnias"[All Fields]) AND "Nonorganic"[Title/Abstract]) OR "primary insomnia"[Title/Abstract] OR "insomnia | ((((((((((((((((((((((((((((((Sleep Initiation and Maintenance Disorders[MeSH Terms]) OR (Sleep Initiation[Title/Abstract] AND Maintenance Disorders[Title/Abstract])) OR (Disorders of Initiating[Title/Abstract] AND Maintaining Sleep[Title/Abstract])) OR (DIMS (Disorders of Initiating[Title/Abstract] AND Maintaining Sleep[Title/Abstract]))) OR (Early Awakening[Title/Abstract])) OR (Awakening, Early[Title/Abstract])) OR (Nonorganic Insomnia[Title/Abstract])) OR (Insomnia, Nonorganic[Title/Abstract])) OR |

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|---|---|---|---|
| (Insomnia, Primary[Title/Abstract])) OR (Transient Insomnia[Title/Abstract])) OR (Insomnia, Transient[Title/Abstract])) OR (Rebound Insomnia[Title/Abstract])) OR (Insomnia, Rebound[Title/Abstract])) OR (Secondary Insomnia[Title/Abstract])) OR (Insomnia, Secondary[Title/Abstract])) OR (Sleep Initiation Dysfunction[Title/Abstract])) OR (Dysfunction, Sleep Initiation[Title/Abstract])) OR (Dysfunctions, Sleep Initiation[Title/Abstract])) OR (Sleep Initiation Dysfunctions[Title/Abstract])) OR (Sleeplessness[Title/Abstract])) OR (Insomnia Disorder[Title/Abstract])) OR (Insomnia Disorders[Title/Abstract])) OR (Insomnia[Title/Abstract])) OR | | primary"[Title/Abstract] OR "transient insomnia"[Title/Abstract] OR "insomnia transient"[Title/Abstract] OR "rebound insomnia"[Title/Abstract] OR "insomnia rebound"[Title/Abstract] OR "secondary insomnia"[Title/Abstract] OR "insomnia secondary"[Title/Abstract] OR "sleep initiation dysfunction"[Title/Abstract] OR (("dysfunctional"[All Fields] OR "dysfunctionals"[All Fields] OR "dysfunctioning"[All Fields] OR "Dysfunctions"[All Fields] OR "physiopathology"[MeSH Subheading] OR "physiopathology"[All Fields] OR "Dysfunction"[All Fields]) AND "sleep initiation"[Title/Abstract]) OR (("dysfunctional"[All Fields] OR "dysfunctionals"[All Fields] OR "dysfunctioning"[All Fields] OR "Dysfunctions"[All Fields] OR "physiopathology"[MeSH Subheading] OR "physiopathology"[All Fields] OR "Dysfunction"[All Fields]) AND "sleep initiation"[Title/Abstract]) OR ((("Sleep"[MeSH Terms] OR "Sleep"[All Fields] OR "sleeping"[All Fields] OR "sleeps"[All Fields] OR "sleeps"[All Fields]) AND ("initial"[All Fields] OR "initially"[All Fields] OR "initials"[All Fields] OR | (Primary Insomnia[Title/Abstract])) OR (Insomnia, Primary[Title/Abstract])) OR (Transient Insomnia[Title/Abstract])) OR (Insomnia, Transient[Title/Abstract])) OR (Rebound Insomnia[Title/Abstract])) OR (Insomnia, Rebound[Title/Abstract])) OR (Secondary Insomnia[Title/Abstract])) OR (Insomnia, Secondary[Title/Abstract])) OR (Sleep Initiation Dysfunction[Title/Abstract])) OR (Dysfunction, Sleep Initiation[Title/Abstract])) OR (Dysfunctions, Sleep Initiation[Title/Abstract])) OR (Sleep Initiation Dysfunctions[Title/Abstract])) OR (Sleeplessness[Title/Abstract])) OR (Insomnia Disorder[Title/A |

| | | | |
|---|---|---|---|
| (Insomnias[Title/Abstract])) OR (Chronic Insomnia[Title/Abstract])) OR (Insomnia, Chronic[Title/Abstract])) OR (Psychophysiological Insomnia[Title/Abstract])) OR (Insomnia, Psychophysiological[Title/Abstract]) | | "initiate"[All Fields] OR "initiated"[All Fields] OR "initiates"[All Fields] OR "Initiating"[All Fields] OR "Initiation"[All Fields] OR "initiations"[All Fields] OR "initiator"[All Fields] OR "initiators"[All Fields])) AND "Dysfunctions"[Title/Abstract]) OR "Sleeplessness"[Title/Abstract] OR "insomnia disorder"[Title/Abstract] OR "insomnia disorders"[Title/Abstract] OR "Insomnia"[Title/Abstract] OR "Insomnias"[Title/Abstract] OR "chronic insomnia"[Title/Abstract] OR "insomnia chronic"[Title/Abstract] OR "psychophysiological insomnia"[Title/Abstract] OR "insomnia psychophysiological"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter])) | bstract])) OR (Insomnia Disorders[Title/Abstract])) OR (Insomnia[Title/Abstract])) OR (Insomnias[Title/Abstract])) OR (Chronic Insomnia[Title/Abstract])) OR (Insomnia, Chronic[Title/Abstract])) OR (Psychophysiological Insomnia[Title/Abstract])) OR (Insomnia, Psychophysiological[Title/Abstract]) |

## Appendix D. Treatment Algorithm

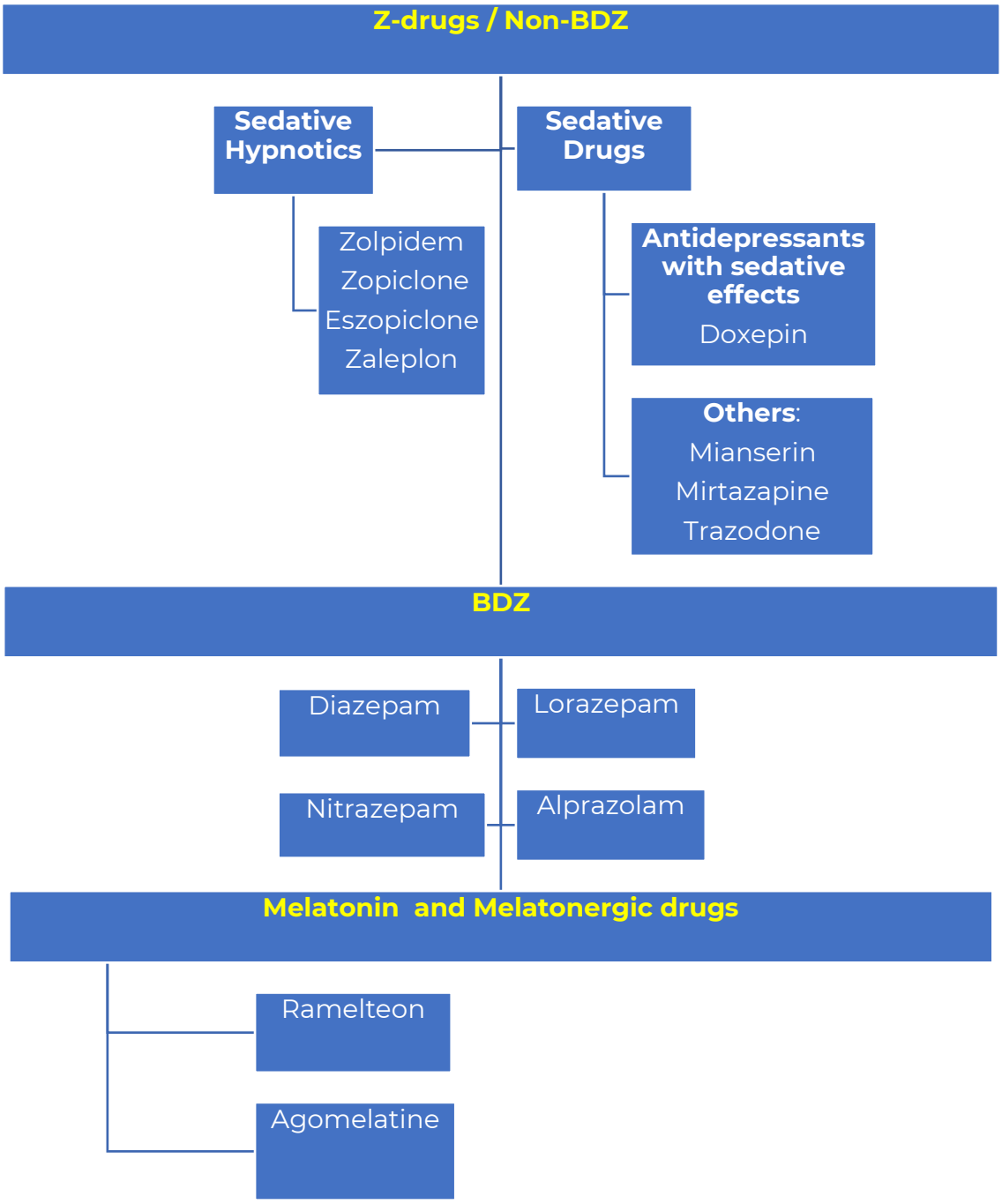


***Figure 1.*** *Treatment Algorithm for the Management of Insomnia*