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2023 Guidelines on the Diagnosis and Treatment of Insomnia in Adults – Brazilian Sleep Association

Luciano Ferreira Drager[1,2] Márcia Assis[1,3] Andrea Frota Rego Bacelar[1,4] Dalva Lucia Rollemberg Poyares[5,6] Silvia Gonçalves Conway[7,8,9] Gabriel Natan Pires[5,6] Alexandre Pinto de Azevedo[7] Alicia Carissimi[10,11] Allan Luiz Eckeli[12] Álvaro Pentagna[13] Carlos Maurício Oliveira Almeida[14] Clélia Maria Ribeiro Franco[15] Emmanuelle Silva Tavares Sobreira[9,16,17] Fernando Gustavo Stelzer[12] Giuliana Macedo Mendes[18] Gisele Richter Minhoto[19] Ila Marques Porto Linares[7,20] Ksdy Maiara Moura Sousa[5,21] Livia Leite Góes Gitaí[22] Lucia Sukys-Claudino[23] Manoel Alves Sobreira-Neto[16] Marcio Andrei Zanini[24] Regina Margis[25] Sandra Cristina Gonçalves Martinez[26]

[1] Associação Brasileira do Sono, São Paulo, SP, Brazil.
[2] Unidades de HipertenSão, Instituto do Coração (InCor) e Disciplina de Nefrologia, Universidade de São Paulo, São Paulo, SP, Brazil.
[3] Clínica do Sono de Curitiba, Hospital São Lucas, Curitiba, Brazil.
[4] Clínica Bacelar - Neuro e Sono, Rio de Janeiro, RJ, Brazil.
[5] Departamento de Psicobiologia, Universidade Federal de São Paulo, São Paulo, Brazil.
[6] Instituto do Sono, São Paulo, SP, Brazil.
[7] Instituto de Psiquiatria (IPq), Universidade de São Paulo, São Paulo, SP, Brazil.
[8] Departamento de Otoneurologia, Universidade de São Paulo, São Paulo, SP, Brazil.
[9] AkasA - Formação e Conhecimento, São Paulo, SP, Brazil.
[10] Faculdade Dom Bosco, Porto Alegre, RS, Brazil.
[11] Cronosul Clínica de Psicologia do Sono, Psicoterapia e Neuropsicologia, Porto Alegre, RS, Brazil.
[12] Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil.
[13] Hospital das Clínicas (HCFMUSP), Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.
[14] Departamento de Neurologia, Universidade Estadual do Amazonas, UEA, Brazil.
[15] Hospital Universitário Oswaldo Cruz (HUOC), Universidade Federal de Pernambuco, Recife, PE, Brazil.
[16] Universidade Federal do Ceará, Fortaleza, CE, Brazil.
[17] Clínica Sinapse Diagnóstico, Fortaleza, CE, Brazil.
[18] Instituto de Especialidades e Sono, Goiânia, GO, Brazil.
[19] Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, PR, Brazil.
[20] Instituto da Criança, Faculdade de Medicina, Universidade de São Paulo (FMUSP), São Paulo, SP, Brazil.
[21] SleepUp Tecnologia e Saúde LTDA, São Paulo, SP, Brazil.
[22] Faculdade de Medicina, Universidade Federal de Alagoas, AL, Brazil.
[23] Disciplina de Neurologia, Universidade Federal de Santa Catarina (UFSC), Florianópolis, SC, Brazil.
[24] Instituto de Assistência Médica ao Servidor Público Estadual (IAMPSE), São Paulo, SP, Brazil.
[25] Private clinic, Porto Alegre, RS, Brazil.
[26] Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil.

Address for correspondence Luciano F. Drager, Associação Brasileira do Sono, Rua Pamplona, 788 - Jardim Paulista, São Paulo - SP, Brazil CEP 01405-001 (e-mail: luciano.drager@incor.usp.br).

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Abstract

Chronic insomnia disorder (simplified in this document as insomnia) is an increasingly common clinical condition in society and a frequent complaint at the offices of different areas of health practice (particularly Medicine and Psychology). This scenario has been accompanied by a significant evolution in treatment, as well as challenges in approaching patients in an appropriately way. This clinical guideline, coordinated by the Brazilian Sleep Association and the Brazilian Association of Sleep Medicine and counting on the active participation of various specialists in the area, encompasses an update on the diagnosis and treatment of insomnia in adults. To this end, it followed a structured methodology. Topics of interest related to diagnosis were written based on theoretical framework, evidence in the literature, and professional experience. As for the topics related to the treatment of insomnia, a series of questions were developed based on the PICO acronym (P – Patient, problem, or population; I – Intervention; C – Comparison, control, or comparator; O – Outcome). The work groups defined the eligible options within each of these parameters. Regarding pharmacological interventions, only the ones currently available in Brazil or possibly becoming available in the upcoming years were considered eligible. Systematic reviews were conducted to help prepare the texts and define the level of evidence for each intervention. The final result is an objective and practical document providing recommendations with the best scientific support available to professionals involved in the management of insomnia.

Keywords

- adults
- diagnosis
- insomnia
- treatment

Introduction

Insomnia is characterized by a range of complaints that reflect dissatisfaction with the quality and quantity of sleep. Nighttime symptoms or types of insomnia include difficulties falling and remaining asleep and waking up too early in the morning (i.e., before the desired/planned time), which can frequently coexist. They must occur at least three times a week for at least three months to diagnose chronic insomnia disorder – which, to facilitate and standardize, this study will generically refer to as insomnia).[1] Daytime symptoms comprise this diagnosis and are consequences of insomnia, namely: fatigue; decreased energy, attention, concentration, and memory; and mood changes, such as irritability and dysphoria.[1] Sleep deprivation causes multiple consequences to the quality of life and is responsible for absenteeism and decreased productivity, risk of accidents, and predisposition to mental, cardiovascular, metabolic, and other disorders.[2,3]

In terms of physiopathology, insomnia is often associated with hyper-alertness, in which the autonomic nervous system is activated, increasing the adrenergic and hypothalamic-hypophysis-adrenal axis activity. However, it has been questioned whether such hyperarousal can be chronically sustained, whether it would be enough to cause insomnia or a combination of other factors would be necessary, and whether it would be better characterized by disinhibition or failure to inhibit wakefulness during sleep periods or a disconnection between systems that should be connected during wakefulness and connected during sleep (maladaptive conditioning).[4] (►**Fig. 1**)

Spielman's 3P model (predisposing, precipitating, and perpetuating factors) to understand chronic insomnia suggests that genetic/epigenetic aspects and early stress are predisposing factors, that affect individuals' brain functioning and personality differences.[5] The growing prevalence of mood disorders can help precipitate or worsen insomnia,[2,3] which sharply increased with the COVID-19 pandemic, as confirmed by various publications.[6–10] Precipitating and perpetuating factors encompass neurobiological sleep mechanisms, including homeostatic mechanisms, biological time controllers (circadian rhythm), and the flip-flop (switch) control model of the mechanisms in neuronal cell group centers that promote sleep and wakefulness. Thus, insomnia can be understood as a lack of control between sleep-inducing mechanisms and wake-inducing mechanisms (wakefulness), with a hyperactive alert system, hypoactive sleep system, or both simultaneously. Hence, current theoretical approaches encompass cognitive-behavioral models, neurobiological models, and models that consider both simultaneously.[5] (►**Fig. 1**).

The prevalence of insomnia varies between studies due to their different definitions, assessment methods, and study intervals. Populational studies report that 30% to 36% of individuals have nighttime symptoms of insomnia. On the other hand, when the assessment includes daytime consequences, the prevalence drops from 10% to 15%.[11] Considering diagnostic criteria in DSM-5 (Diagnostic and Statistical Manual of Mental Disorders – 5th edition) and ICSD (International Classification of Sleep Disorders – 3rd edition), such rates range from 5% to 10%. In primary healthcare, ~40% of the patients report sleep problems.[12] Insomnia is more prevalent in middle-aged and older females, shift workers, individuals with clinical and psychiatric diseases, with a low income, and who live alone (single, separated people or

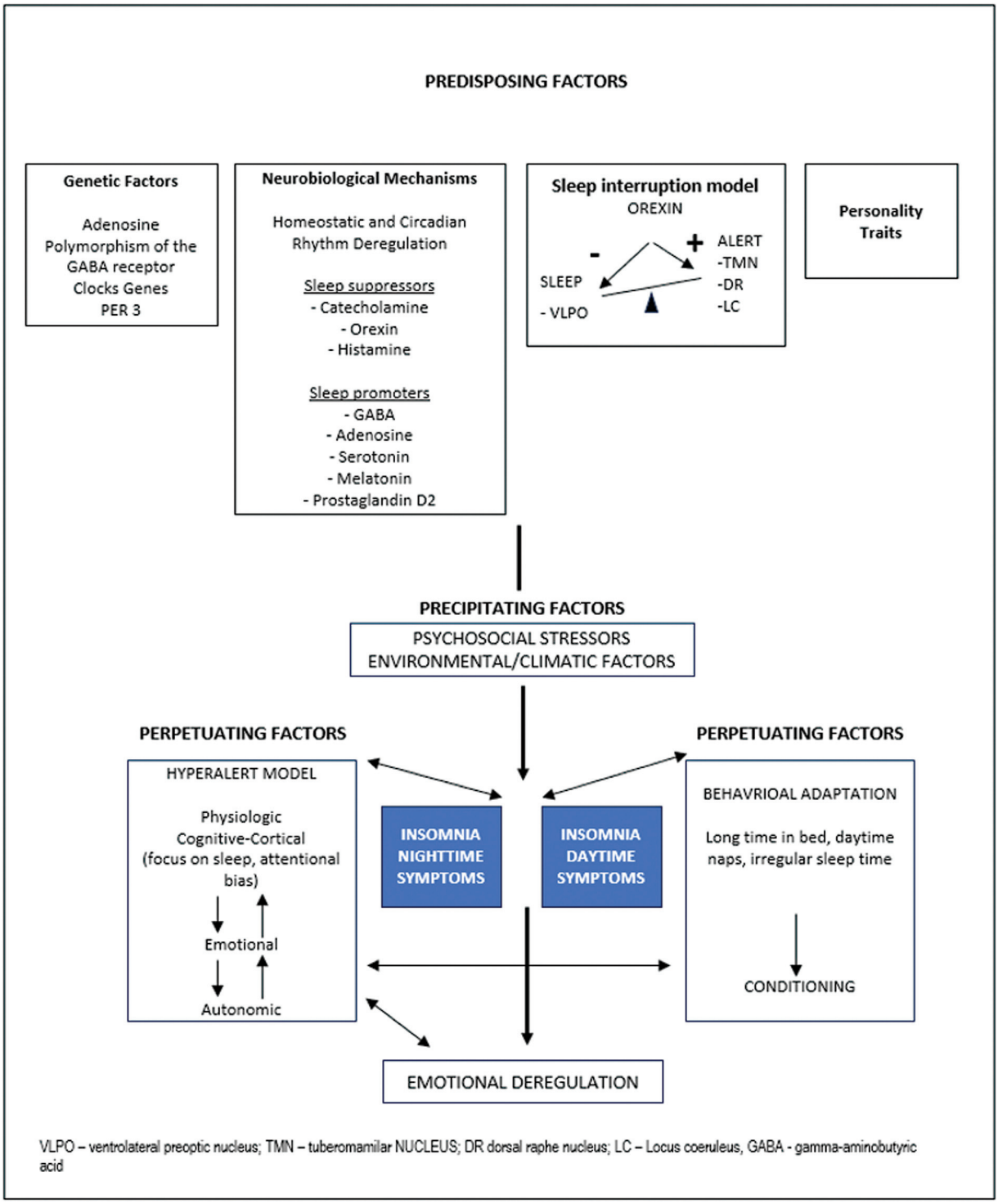

Fig. 1 Physiopathological model of insomnia (adapted from Bollu and Kaur[12] and Riemann and colleagues[5]).

widows). Being female, especially after menopause, having an advanced age (older adults), family history of insomnia, previous personal history of insomnia, and having anxious personality traits are risk factors for insomnia.[13]

Various new pharmacological and non-pharmacological treatments for insomnia have been proposed, developed, and improved in the last few years. Also, a growing number of health professionals (particularly in Medicine and Psychology) have been seeking specialized training, education, and information on the diagnosis and treatment of insomnia, which reflects its high prevalence in the population. Hence, there is an evident need for a new version of the Brazilian Consensus on Insomnia, meeting the needs of trained and specialized Sleep Medicine professionals and all other ones

whose patients have complaints and symptoms compatible with this sleep disorder. Thus, this guideline aimed to provide patient-centered clinical guidelines with a structured methodology. The final result is an objective and practical document that provides recommendations to professionals who manage insomnia with the best scientific support available.

Systematic Reviews and Levels of Evidence – Methods and Results

This paper aimed to develop the official recommendations of the Brazilian Sleep Association (*Associação Brasileira do Sono* – ABS) to diagnose and treat chronic insomnia in adults. To this end, the ABS board of directors invited a group of Brazilian professionals experienced in diagnosing and treating insomnia – hereinafter named the "steering committee," comprising four physicians (LFD, MA, AB, and DP), one psychologist (SC), and one methodologist (GNP), all accredited, qualified, or with a history of relevant research in the area. The steering committee was responsible for selecting the topics approached in this paper and inviting coordinators for each one. Lastly, other professionals were invited to make up each topic's work group.

Methods

Research Questions and Systematic Review

Even though this paper covers both the diagnosis and treatment of insomnia, structured research questions were developed only for the topics on treatment, not for the ones on insomnia diagnosis. Developing research questions for diagnostic accuracy – such as with the PI(R)T approach – requires clearly established reference tests as valid comparators.[14] Since the reference tests are analyzed in this study, the topics on diagnosis were not addressed with structured research questions – rather, these topics were written based on theoretical considerations, previous guidelines, and professional experience. The same is true about topics related to pathophysiological aspects and insomnia classification.

Hence, a series of questions were developed for the topics on insomnia treatment based on the PICO acronym, following the model, "*What is the effect of [INTERVENTION] compared with [CONTROL] on [OUTCOME] in adults with chronic insomnia without comorbidities?*." Each PICO parameter was defined by the steering committee in a synchronous online meeting. Concerning pharmacological interventions, only the ones currently available in Brazil or possibly becoming available in the upcoming years were considered eligible. Given the large number of interventions to be included in this paper, it was decided to restrict the research questions to the primary treatment of chronic insomnia in adults. Other aspects related to the use and implementation of each selected intervention (e.g., different insomnia phenotypes, comorbidities, combined treatment, etc.) were not included in the research questions, although they are discussed in the reviews prepared by each work group. The list of eligible interventions is presented in ►**Table 1**. Each PICO item is detailed in ►**Table 2** and explained in detail along with the inclusion and exclusion criteria.

The results of the systematic reviews based on the research questions were used with two main purposes: 1. Generating material to analyze the level of evidence for each intervention and 2. Providing references to each work group to help them prepare their reviews. No meta-analyses were performed.

Bibliographic Search and Eligibility Analysis

Independent search strategies were developed for each intervention (as seen in ►**Table 1**). Exceptions were made in the following three cases: 1. interventions related to cannabinoids and cognitive-behavioral therapy applied to insomnia (CBT-I), for which a general search was made for each group; 2. alternative and complementary interventions, of which it was decided not to conduct systematic reviews due to the great heterogeneity in studies using these treatments; and 3. phytotherapy interventions (*Matricaria recutita* and *Withania somnifera*), of which no systematic reviews were conducted because they were included later in this document.

The strategies combined two search domains, one for insomnia (addressing both population and outcome) and the other combining each intervention's search strategy. Regarding specifically non-pharmacological interventions, the search strategies were limited to CBT-I, acceptance and commitment therapy applied to insomnia (ACT-I), and mindfulness-based cognitive therapy applied to insomnia (MBCT-I). All search strategies are available in a supplementary file at: https://osf.io/p746g/. The searches were made in two databases (PubMed and Web of Science – full collection), last updated on June 5, 2023. No secondary search or gray literature evaluation was made. Search results were exported to Covidence and grouped in a single systematic review with all interventions. Duplicates were automatically excluded. Each non-duplicate record was analyzed by two out of six reviewers (AGB, GLRC, IPAL, MPK, VAK, and YML) in a two-stage process – the first one to analyze titles and abstracts, and the second stage to analyze full texts. Discrepancies were solved by a third reviewer (GNP). In each phase, eligibility was analyzed according to the predefined inclusion and exclusion criteria. As with the research questions, the topics of insomnia diagnosis were not addressed in the systematic reviews.

Inclusion and Exclusion Criteria

Each article was analyzed based on the following criteria, which were applied in the same order as presented below.

- *Abstract and language*
  - o *Inclusion:* Only articles with abstracts in Portuguese or English.
  - o *Exclusion:* Articles without abstracts or with abstracts in languages other than Portuguese or English.
- *Types of articles*
  - o *Inclusion:* Only original articles (including meta-analyses).

Table 1 List of eligible interventions.

Non-pharmacological interventions	
CBT-I	In-person CBT-I
	Online CBT-I
	Group CBT-I
	Digital CBT-I
	Self-help CBT-I
ACT-I	
MBCT-I	
Alternative	Acupuncture[a]
treatments	Aromatherapy[a]
	Biofeedback[a]
	Massage[a]
	Meditative practices[a,c]
	Mind-body practices[a,d]
	Physical exercises[a]
Pharmacological interventions	
BZD agonists	Zolpidem
	Zopiclone
	Eszopiclone
BZD[b]	Bromazepam
	Diazepam
	Clonazepam
	Alprazolam
	Midazolam
	Flunitrazepam
	Estazolam
	Flurazepam
DORA	Suvorexant
	Lemborexant
	Daridorexant
Antidepressants	Trazodone
	Doxepin
	Mirtazapine
	Amitriptyline
	Agomelatine
Melatonin	
Melatoninergic agonist	Ramelteon
Anticonvulsants	Gabapentin
	Pregabalin
Antipsychotics	Quetiapine
	Olanzapine
	Clozapine
	Periciazine
	Levomepromazine
	Chlorpromazine
Others	Diphenhydramine
	Promethazine
	Hydroxyzine
	Dimenhydrinate
	GABA
	Tryptophan
Phytotherapeutics	*Valeriana officinalis*
	Passiflora incarnata
	Matricaria recutita[a]
	Withania somnifera[a]
	Erythrina mulungu
Cannabinoids	*Cannabis sativa*
	Cannabidiol
	Delta-9-THC

Abbreviations: ACT-I: Acceptance and commitment therapy applied to insomnia. BZD: Benzodiazepines. DORA: Dual orexin receptor antagonists. GABA: Gamma-aminobutyric acid. MBCT-I: Mindfulness-based cognitive therapy applied to insomnia. CBT-I: cognitive-behavioral therapy applied to insomnia. THC: Tetrahydrocannabinol.
[a]Interventions not included in the systematic reviews.
[b]Recommendations voted in group for the whole class, instead of individually for each intervention.
[c]Encompassing meditation and vipassana.
[d]Encompassing qigong, tai chi, and yoga.

- o *Exclusion:* Non-original articles (including narrative reviews, systematic reviews without meta-analyses, letters to the editor, editorials, etc.).

- *Population:*
  - o *Inclusion:* Articles assessing individuals with primary chronic insomnia, evaluated or diagnosed with one of the following criteria:
    - ■ Insomnia diagnosed with standardized criteria, including ICSD-3, the International Statistical Classification of Diseases and Related Health Problems – 10th version (ICD-10), DSM-5, and previous and posterior editions of this guideline.
    - ■ Moderate to severe symptoms of insomnia, evaluated with the Insomnia Severity Index (ISI) or the Athens Insomnia Scale (AIS).
  - o *Exclusion:* Articles using any of the following criteria were excluded:
    - ■ Self-reported insomnia (as long as none of the inclusion criteria had been used).
    - ■ Insomnia symptoms were evaluated with tools other than ISI or AIS (as long as none of the inclusion criteria had been used).
    - ■ Insomnia comorbid with any other condition (regardless of the use of diagnostic methods indicated in the inclusion criteria). This refers to comorbid conditions evaluated to define the study population and does not apply to the occasional occurrence of

Table 2 Research questions according to PICO criteria.

Population	Interventions	Comparators	Outcomes
Adults diagnosed with chronic insomnia	Table 1	No treatment	Sleep latency (PSG or actigraphy)
Adults with moderate to severe insomnia symptoms		Waiting list	Total sleep time (PSG or actigraphy)
		Placebo	Sleep efficiency (PSG or actigraphy)
		Minimum intervention	WASO (PSG or actigraphy)
		Pharmacotherapy*	Sleep quality (PSQI)
		CBT-I (any format) *	Daytime sleepiness (ESS)
			Insomnia symptoms (ISI)
			Insomnia diagnosis
			Sleep diary*
			Self-reported total sleep time, sleep latency, and sleep efficiency*

Abbreviations: CBT-I, Cognitive-behavioral therapy applied to insomnia; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; PICO, Population, intervention, comparator, and outcome; PSG, Polysomnography; PSQI, Pittsburgh Sleep Quality Index; WASO, wake after sleep onset. *Items applied only to search strategies related to non-pharmacological interventions.

comorbidities not comprising the study population and not applied to all participants.
- Studies in children, adolescents, and older adults. Adults are defined as those aged 18 to 65 years. Samples with more than one age range were considered eligible, as long as most of the population were adults, and the analyses enabled conclusions regarding specifically adults.

- *Intervention:*
  - *Inclusion*: Any of the interventions presented in ►**Table 1**. Studies assessing two or more interventions were considered eligible, as long as each group received only one intervention, and the results enabled independent conclusions for each intervention. There were no limitations on the posology or treatment duration in pharmacological interventions. Likewise, there were no restrictions on the composition, number of sessions, or session duration in non-pharmacological interventions.
  - *Exclusion:* Interventions not listed in ►**Table 1** or studies in which more than one intervention is used simultaneously in the same group of individuals.
- *Comparator:*
  - *Inclusion:* Only articles with control groups were considered eligible. Crossover studies were considered eligible, as long as the order of the interventions was randomized. The following types of control groups were considered eligible:
    - No intervention, waiting list, or placebo.
    - Minimum intervention: Refers to interventions with limited effectiveness or deemed ineffective, including but not limited to sleep hygiene interventions alone, lectures, instructional leaflets, and sham therapies.
    - Pharmacotherapy (only when considered as a control group for non-pharmacological interventions).
    - CBT-I (only when considered as a control group for non-pharmacological interventions). This allows for the inclusion of studies comparing two different non-pharmacological therapies (such as two different CBT-I modalities).
  - *Exclusion:* Articles with no control groups, before-and-after designs, studies comparing two pharmacological interventions, and studies whose control group was submitted to a concomitant intervention.
- *Outcomes:*
  - *Inclusion*: Objective and subjective sleep parameters, as detailed in ►**Table 2**.
  - *Exclusion*: Studies without any of the outcomes listed in ►**Table 2**.
- *Full-text articles*:
  - *Inclusion:* Full-text articles available in Portuguese or English.
  - *Exclusion:* Full texts unavailable or available in languages other than Portuguese or English.

Level of Evidence and Critical Review

The group of articles retrieved in each intervention's systematic review was analyzed and ascribed a level of evidence, based on the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence.[15] A single author (GNP) ascribed the levels of evidence. The structure of analysis of the levels of evidence is available in ►**Table 3**.

The critical review aims to summarize practical aspects and professional procedures regarding each intervention, based on the selected references and applied clinical knowledge. An independent critical review was conducted for each topic (and for each intervention, when appropriate).

Table 3 Levels of evidence, adapted from OCEBM.

	Assessment during eligibility analysis	Increase during critical review	Decrease during critical review
Level 1	Systematic reviews of RCTs	Large or very large effect sizes.	Poor-quality, imprecise studies, lacking directionality, or with small effect sizes.
Level 2	RCTs or observational studies with dramatic effects		
Level 3	Nonrandomized cohorts/follow-up studies		
Level 4	Case series, case-control studies, controlled history studies		
Level 5	Mechanism-based assessment		

Abbreviations: OCEBM, Oxford Centre for Evidence-Based Medicine; RCT, Randomized clinical trial.

Each work group received a selection of articles resulting from the systematic reviews specifically related to the treatment of primary chronic insomnia. Additional literature, besides the selected articles, and the package inserts of the selected drugs were consulted at the discretion of the group responsible for each critical review.

Recommendations and Consensus

All interventions were voted for consensus in three standardized manners: 1. As a treatment for sleep-onset insomnia; 2. As a treatment for sleep-maintenance insomnia and early waking; and 3. As a treatment for insomnia during pregnancy and breastfeeding (only in round #2). In all cases, the interventions were voted as a primary treatment for insomnia in adults with no comorbidities. All sentences to be voted on were written in a standardized positive manner (i.e., avoiding negative sentences). No specific recommendations were made for the posology or route of administration of pharmacological interventions – except for zolpidem, for which four different presentations (oral, sublingual, controlled release, and orodispersible) were voted independently. Also, each work group formed a special list of recommendations for each intervention and diagnosis, including subtopics such as specific populations, comorbidities, characteristics, insomnia phenotypes, posology, and so forth, when relevant. Special recommendations were voted declaring their direction (in favor or against them).

These statements were used to assess the level of consensus for each possible recommendation to diagnose and treat insomnia, based on the Delphi method.[16–18] To reach a consensus, each practical recommendation was assessed by all task force members on a 5-point scale, ranging from 1 (totally agree) to 5 (totally disagree). A consensus was reached when at least 75% of the task force members voted on the two agreement options (consensus in favor) or the two disagreement options (consensus against). The items about which no consensus was reached in the first voting round were submitted to a second one, being adapted when necessary. Due to limitations and professional prerogatives, only physicians voted on recommendations related to pharmacological treatments. All participants voted on the recommendations related to non-pharmacological treatments, but the psychologists' votes had triple weight. All professionals voted on recommendations related to diagnoses.

Results

The search results for each intervention were integrated into a single systematic review with 24,092 articles. After excluding the duplicates, 13,422 articles were submitted to eligibility analysis, resulting in a final sample of 181 articles – of which, 133 (73.4%) were randomized clinical trials (RCTs, including crossover studies), and 44 (24.3%) were meta-analyses. The number of articles per intervention varied considerably: in-person CBT-I (k = 43), digital CBT-I (k = 43), and zolpidem (k = 28) had the most articles, whereas 21 interventions had no articles included. In general, CBT-I (considering all modalities) and the most recent hypnotic drugs (including zolpidem, dual orexin receptor antagonists [DORAs], and melatoninergic agonists) concentrated most records. A limited number of articles assessed benzodiazepines (BZDs) and drugs not primarily intended to treat insomnia (such as antidepressants and antipsychotics), and many of these interventions were not properly assessed in any study. The number of articles included in the final sample and specifically per intervention is available as supplementary material at: https://osf.io/p746g/, and the selection

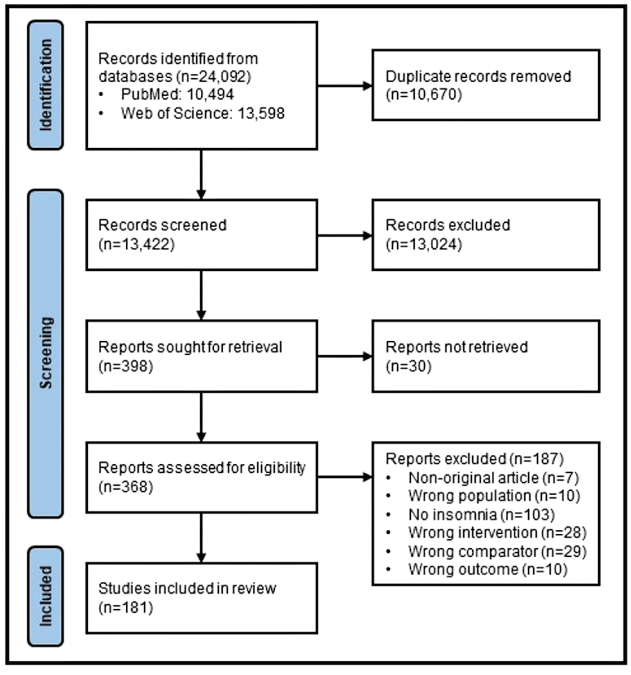

Fig. 2 Flowchart of study inclusion.

process is presented in ►**Fig. 2**. These files were used as a reference to ascribe the levels of evidence and vote on the recommendations (described in ►**Tables 4** to **9**).

The process of defining levels of evidence revealed that most interventions were not based on adequate evidence. Most of them ($n = 23$, 47.9%) were classified as level of evidence 5 (indirect evidence, based only on action mechanisms), reflecting the absence of studies assessing them appropriately to treat insomnia. Only eight interventions (16.7%) were assessed with level of evidence 1, and 11 with level of evidence 2 (22.9%). Intervention assessed with the level of evidence 1 includes two BZD agonists (zolpidem and eszopiclone), two DORAs (suvorexant and daridorexant), one melatoninergic agonist (ramelteon), and three CBT-I presentations (in person, in group, and digital). The levels of evidence for each intervention are shown in ►**Tables 5** and **7**.

In round #1, 18 non-pharmacological and 39 pharmacological interventions were voted on, each of them in two contexts (for sleep-onset insomnia and for sleep-maintenance insomnia and early waking). Also, six special recommendations were made for non-pharmacological interventions, 23 for pharmacological interventions, and 19 to insomnia diagnosis. Recommendations related to BZDs were grouped and voted as a collective class, rather than as separate drugs. Thus, 154 recommendations were voted on in round #1–of which, a consensus was reached on

Table 4 Recommendations for insomnia diagnosis.

Recommendation	Consensus rate	Voting rounds
Insomnia is very prevalent and can lead to impaired quality of life, physical health and mental health.	100.00%	1
Insomnia is often comorbid with clinical illnesses and psychiatric disorders, requiring independent treatment.	100.00%	1
The diagnosis of insomnia is essentially clinical, depending on a directed and attentive anamnesis.	100.00%	1
The most important topics to be evaluated in an anamnesis for diagnosing insomnia include:		
• Difficulties in initiating and maintaining sleep, early morning awakenings, and non-refreshing sleep.	96.88%	1
• Clinical characteristics of insomnia, such as onset and course.	100.00%	1
• Treatments carried out and responses to them.	90.63%	1
• Patient's daytime and nighttime behaviors and habits: bedtime, sleeping, waking up, and getting up.	100.00%	1
• Patient's daytime and nighttime behaviors and habits: Daytime naps, voluntary or not.	100.00%	1
• Patient's daytime and nighttime behaviors and habits: Physical exercise, activity, intake of alcoholic beverages, and those containing caffeine.	100.00%	1
• Sleeping environment and activities before bed.	100.00%	1
• Consequences of insomnia in different areas of life: cognition, mood, fatigue, drowsiness, performance, and risk of accidents.	100.00%	1
• Identification of clinical, psychiatric, and other sleep disorders comorbidities.	100.00%	1
Using a sleep diary can help with diagnosis and assessment of response to treatment.	100.00%	1
Sleep questionnaires can be used to identify and assess the severity of insomnia and identify comorbidities.	100.00%	1
PSG is not routinely indicated in the diagnosis of insomnia.	100.00%	1
PSG may be indicated in the diagnosis of insomnia in the following situations:		
• Suspected other sleep disorders and paradoxical insomnia.	100.00%	1
• Treatment failure.	90.63%	1
• Assessment and identification of insomnia with objective short sleep duration.	78.13%	1
Actigraphy can help differentiate insomnia from circadian rhythm disorder, but alone cannot diagnose insomnia.	100.00%	1

Table 5 Level of evidence and recommendations of non-pharmacological treatments of insomnia.

			Sleep-onset insomnia			Maintenance insomnia and early waking		
Category	**Intervention**	**Level of evidence**	**Recommendation**	**Consensus rate**	**Voting rounds**	**Recommendation**	**Consensus rate**	**Voting rounds**
CBT-I	In-person CBT-I	1	Recommended	100.0%	1	Recommended	100.0%	1
	Online CBT-I	2	Recommended	100.0%	1	Recommended	100.0%	1
	Group CBT-I	1	Recommended	96.9%	1	Recommended	96.9%	1
	Digital CBT-I	1	Recommended	78.1%	1	Recommended	78.1%	1
	Self-help CBT-I	3	No consensus		2	No consensus		2
ACT-I		2	Recommended	87.5%	1	Recommended	84.4%	1
MBCT-I		2	Recommended	87.5%	1	Recommended	81.3%	1
Alternative	Acupuncture[a]	N/A	NOT Recommended	80.7%	2	NOT Recommended	77.4%	2
treatments	Aromatherapy[a]	N/A	NOT Recommended	80.7%	2	NOT Recommended	78.1%	1
	Biofeedback[a]	N/A	No consensus		2	No consensus		2
	Massage[a]	N/A	No consensus		2	No consensus		2
	Meditative practices[a,b]	N/A	No consensus		2	No consensus		2
	Mind-body practices[a,c]	N/A	No consensus		2	No consensus		2
	Physical exercises[a]	N/A	No consensus		2	No consensus		2

Abbreviations: ACT-I, Acceptance and commitment therapy applied to insomnia; CBT-I, Cognitive-behavioral therapy applied to insomnia; MBCT-I, Mindfulness-based cognitive therapy applied to insomnia; N/A, Not applicable.
[a]Interventions not included in the systematic reviews.
[b]Includes meditation and vipassana.
[c]Includes qigong, tai-chi, and yoga.

Table 6 Special recommendations for non-pharmacological treatment of insomnia.

Recommendation	Consensus rate	Voting rounds
Multicomponent CBT-I is recommended as the gold standard for treating chronic insomnia, suggesting a greater number of sessions and techniques and observing the clinical caveats described in the text.	100.00%	1
CBT-I via online services is not inferior to in-person service.	93.75%	1
Sleep hygiene is not recommended as an isolated form of intervention, but should be included in the practice of CBT-I.	100.00%	1
ACT is recommended as an adjuvant treatment to CBT-I.	93.75%	1
Mindfulness practices are recommended as adjuvants to CBT-I.	96.88%	1
Patients with objectively measured TST $<$ 6h should receive multicomponent CBT-I intervention associated with mindfulness and/or ACT strategies. At clinical discretion, it can be associated with pharmacotherapy.	96.88%	1
Biofeedback therapies, although safe, show inconsistent results for the treatment of chronic insomnia disorder and, therefore, should not be recommended. There is a clear need for well-designed and adequately powered studies to understand the role of this form of therapy.	100.00%	1
Acupuncture is safe, but current literature is limited to formally recommend this therapeutic strategy for treating insomnia.	100.00%	1
Physical exercise (mainly aerobic) appears to have benefits in objective and subjective parameters in patients with chronic insomnia and can be used as an adjuvant therapy.	87.10%	1
Mind-body techniques are safe but with limited evidence as a therapeutic tool for treating insomnia. The formal approach can be adopted as an adjuvant practice.	100.00%	1
The use of aromatherapy has limited evidence for treating insomnia and should not be formally recommended.	94.77%	1

Abbreviations: ACT, Acceptance and commitment therapy; CBT-I, Cognitive-behavioral therapy applied to insomnia. TST, Total sleep time.

123 items (79.9%) – 77 in favor (50.0%) and 46 against (29.9%). No consensus was reached on the other 31 items (20.13%)

The round #2 had 89 items, encompassing the second voting round on the 31 items that had not reached a consensus in round #1, five new items related to special recommendations for alternative and complementary recommendations, 53 items on insomnia treatment during pregnancy and breastfeeding (14 non-pharmacological and 39 pharmacological treatments). Items included in round #2 were voted on only once, and a consensus was reached on 63 items (70.8%) – 11 in favor (12.36%) and 52 against (58.43%). No consensus was reached on 26 items (29.21%).

Altogether, considering both voting rounds, 214 items were voted on – 21 on insomnia diagnosis, 53 on non-pharmacological treatment (14 interventions in three different conditions – sleep-onset insomnia, sleep-maintenance insomnia and early waking, and insomnia during pregnancy and breastfeeding – and 11 special recommendations), and 140 on pharmacological treatment (39 interventions in the three different conditions and 23 special recommendations).

A consensus was reached for all 21 recommendations (100%) on insomnia diagnosis (►**Table 4**). As for non-pharmacological treatments (►**Table 5**), six interventions (42.8%) were recommended for both sleep-onset and maintenance insomnia (including four modalities of CBT-I, ACT-I, and MBCT-I), and two (14.3%) were not recommended (acupuncture and aromatherapy).

Regarding the pharmacological treatment (►**Table 7**), nine interventions (23.1%) were recommended to treat sleep-onset insomnia, including three zolpidem presentations (oral, sublingual, and orodispersible), zopiclone, eszopiclone, suvorexant, lemborexant, daridorexant, and ramelteon. Eight interventions (20.5%) were recommended to treat maintenance insomnia and early waking, including prolonged-release zolpidem, zopiclone, eszopiclone, suvorexant, lemborexant, daridorexant, trazodone, and doxepin.

Only six interventions (11.3%) were recommended for insomnia treatment during pregnancy and breastfeeding (►**Table 9**), all of them non-pharmacological. Four presentations of CBT-I, ACT-I, and MBCT-I were included.

The mean consensus rate was $88.0 \pm 13.4\%$ – $97.7 \pm 5.6\%$ for diagnosis, $82.5 \pm 14.9\%$ for non-pharmacological interventions, and $88.7 \pm 12.7\%$ for pharmacological interventions.

Considerations of the Results

This study is based on methods commonly used for evidence synthesis and guidelines development, encompassing systematic reviews, levels of evidence, and standardized methods to reach consensus. Nonetheless, some considerations must be made to properly interpret these results, especially in the case of comparisons with other guidelines to diagnose

Table 7 Level of evidence and recommendations for pharmacological treatment of insomnia.

			Sleep-onset insomnia			Maintenance insomnia and early waking		
Category	Intervention	Level of evidence	Recommendation	Consensus rate	Voting rounds	Recommendation	Consensus rate	Voting rounds
BZD agonists	Zolpidem - Oral	1	Recommended	100.00%	1	No consensus		2
	Zolpidem - Sublingual	1	Recommended	94.12%	1	NOT Recommended	87.50%	2
	Zolpidem - CR	1	No consensus		2	Recommended	100.00%	1
	Zolpidem – orodispersible	1	Recommended	100.00%	1	NOT Recommended	87.50%	2
	Zopiclone	3	Recommended	94.12%	1	Recommended	82.35%	1
	Eszopiclone	1	Recommended	94.12%	1	Recommended	100.00%	1
BZD[a]		5	NOT Recommended	82.35%	1	NOT Recommended	75.00%	2
DORAs	Suvorexant	1	Recommended	82.35%	1	Recommended	100.00%	1
	Lemborexant	2	Recommended	82.35%	1	Recommended	100.00%	1
	Daridorexant	1	Recommended	82.35%	1	Recommended	94.12%	1
Antidepressants	Trazodone	2	No consensus		2	Recommended	82.35%	1
	Doxepin	2	No consensus		2	Recommended	88.24%	1
	Mirtazapine	5	No consensus		2	No consensus		2
	Amitriptyline	5	No consensus		2	No consensus		2
	Agomelatine	5	NOT Recommended	82.35%	1	NOT Recommended	75.00%	2
Melatonin	Melatonin	2	NOT Recommended	76.47%	1	NOT Recommended	88.24%	1
Melatoninergic agonist	Ramelteon	1	Recommended	88.24%	1	NOT Recommended	76.47%	1
Antipsychotics	Quetiapine	5	NOT Recommended	93.75%	2	NOT Recommended	81.25%	2
	Olanzapine	5	NOT Recommended	82.35%	1	NOT Recommended	76.47%	1
	Clozapine	5	NOT Recommended	94.12%	1	NOT Recommended	94.12%	1
	Periciazine	5	NOT Recommended	100.00%	1	NOT Recommended	100.00%	1
	Levomepromazine	5	NOT Recommended	100.00%	1	NOT Recommended	100.00%	1
	Chlorpromazine	5	NOT Recommended	100.00%	1	NOT Recommended	94.12%	1
Anticonvulsants	Gabapentin	5	NOT Recommended	88.24%	1	NOT Recommended	82.35%	1
	Pregabalin	5	NOT Recommended	88.24%	1	NOT Recommended	82.35%	1
Others	Tienopramine	3	NOT Recommended	94.12%	1	NOT Recommended	94.12%	1
	Promethazine	5	NOT Recommended	100.00%	1	NOT Recommended	100.00%	1
	Hydroxyzine	5	NOT Recommended	100.00%	1	NOT Recommended	100.00%	1
	Dimenhydrinate	5	NOT Recommended	94.12%	1	NOT Recommended	100.00%	1

(*Continued*)

Table 7 (*Continued*)

			Sleep-onset insomnia			Maintenance insomnia and early waking		
Category	Intervention	Level of evidence	Recommendation	Consensus rate	Voting rounds	Recommendation	Consensus rate	Voting rounds
	GABA	3	NOT Recommended	94.12%	1	NOT Recommended	94.12%	1
	Tryptophane	5	NOT Recommended	100.00%	1	NOT Recommended	94.12%	1
Phytotherapeutics	Valeriana officinalis	2	NOT Recommended	82.35%	1	NOT Recommended	88.24%	1
	Passiflora incarnata	2	NOT Recommended	94.12%	1	NOT Recommended	94.12%	1
	Matricaria recutita[a]	N/A	NOT Recommended	77.78%	2	NOT Recommended	76.47%	1
	Withania somnifera[a]	N/A	NOT Recommended	77.78%	2	NOT Recommended	76.47%	1
	Erythrina Mulungu	5	NOT Recommended	76.47%	1	NOT Recommended	82.35%	1
Cannabinoids	Cannabis sativa	3	NOT Recommended	94.12%	1	NOT Recommended	100.00%	1
	Cannabidiol	3	NOT Recommended	100.00%	1	NOT Recommended	94.12%	1
	Delta-9-THC	3	NOT Recommended	100.00%	1	NOT Recommended	100.00%	1

Abbreviations: BZD, Benzodiazepines; CR, Controlled release; DORAs, Dual orexin receptor antagonists; GABA, Gamma-aminobutyric acid, N/A, Not applicable; THC, Tetrahydrocannabinol.
[a]Recommendations voted in group for the whole class, instead of individually for each intervention. All BZDs were assessed with level of evidence 5, except for flurazepam, assessed with level of evidence 4.

and treat insomnia, such as the ones issued by the American Academy of Sleep Medicine (AASM), the European Sleep Research Society (ESRS), and other societies.[19–25]

The list of pharmacological and non-pharmacological interventions to treat insomnia may differ from interventions assessed in other guidelines for two main reasons. First, due to the focus on interventions available in Brazil, which left out some interventions present in other studies (e.g., zaleplon and temazepam) and included interventions not commonly found in other guidelines (especially some phytotherapeutics). Moreover, this guideline is more recent than the ones mentioned above, thus including interventions developed more recently (e.g., cannabinoids and ACT-I).

The list of studies selected based on systematic reviews for each intervention may differ from lists included in other guidelines, mainly due to the inclusion and exclusion criteria used in this guideline. Particularly, the definition of the population (only adults with insomnia and no comorbidities), the criteria to diagnose insomnia, eligible types of control groups, and the list of outcomes may have limited the list of references, excluding from this guideline some studies that may have been included in other ones. This observation is especially valid for BZDs and other non-primarily hypnotic drugs, for which few or no references were found.

The method to ascribe levels of evidence was essentially based on the experimental design used in the selected studies. Even though the level of evidence can be raised or lowered based on other aspects (as described in ►**Table 3**), this is not done in a structured and parameterized manner. Other methodologies would have allowed the assessment of other aspects associated with the level of evidence, such as the quality of the studies or the level of the certainty of evidence (e.g., using the GRADE tool [Grading of Recommendations Assessment, Development, and Evaluation]).

Despite these observations, this guideline presents recommendations to diagnose and treat insomnia robustly and based on evidence, primarily applicable to Brazil, but certainly extensible to other countries and contexts. The following sections present the critical reviews developed for each topic included in this guideline.

Insomnia Diagnosis

The diagnosis of insomnia must be standardized, and the patient's complaints must be correctly characterized to understand the duration, frequency, and type of insomnia, lifestyle and sleep habits, and triggering factors and comorbidities (and their respective treatments). This section objectively highlights the most relevant points to correctly diagnose insomnia.

Assessing Insomnia

Medical History Survey

The diagnosis of chronic insomnia is essentially clinical, in which the medical history is greatly important. Its survey must encompass the patient's daytime and nighttime habits, precipitating and perpetuating factors, and psychiatric and

Table 8 Special recommendations for pharmacological treatment of insomnia.

Recommendation	Consensus rate	Voting rounds
The use of zolpidem should NOT exceed 4 weeks, intermittent use or "if necessary" is recommended.	100.00%	1
The initial dosage of immediate-release zolpidem for the elderly should be 5 mg.	100.00%	1
In young adults, doses greater than 10 mg of regular-release zolpidem and 12.5 mg of controlled-release zolpidem are not recommended.	94.12%	1
It is recommended that zolpidem be tapered due to the risk of rebound insomnia.	94.12%	1
Zolpidem is associated with non-REM sleep parasomnias and addiction syndrome.	100.00%	1
Zopiclone should be administered on a short-term basis, if possible intermittently or on an "as needed" basis.	82.35%	1
The initial dosage of zopiclone for the elderly should be 3.75 mg.	100.00%	1
It is recommended that the dose reduction of zopiclone be gradual due to the risk of rebound insomnia.	82.35%	1
Eszopiclone should be administered on a short-term basis, if possible intermittently or on an "as needed" basis.	88.24%	1
The dosage of eszopiclone, for the elderly population, should not exceed 2mg.	100.00%	1
Lemborexant is NOT recommended as a treatment for insomnia in patients with narcolepsy.	82.35%	1
The recommended doses of doxepin should be between 3 and 6 mg used close to bedtime, even in formulated presentations (since there are no industrialized presentations in Brazil).	100.00%	1
Doxepin is recommended at the lowest therapeutic dose in adults over 65 years of age.	94.12%	1
Trazodone doses used to treat insomnia should be lower than the doses recommended for treating major depression, at intervals between 25 and 150mg used close to bedtime.	100.00%	1
Trazodone is NOT recommended for pregnant or breastfeeding women or for use in children and adolescents.	94.12%	1
Amitriptyline may be useful for managing comorbid insomnia in patients with depressive disorders.	94.12%	1
Mirtazapine is effective in the management of insomnia comorbid with depressive disorders.	94.12%	1
The long elimination half-life of mirtazapine may cause residual drowsiness with cognitive and motor impairment.	94.12%	1
Mirtazapine should be avoided in patients with metabolic disorders due to the risk of weight gain.	100.00%	1
Melatonin can be used to treat initial insomnia in the elderly and children with autism spectrum disorder.	100.00%	1
Ramelteon is recommended as a treatment for sleep-onset insomnia comorbid with OSA (COMISA).	100.00%	1
Ramelteon is recommended as a treatment for sleep-onset insomnia comorbid with COPD.	88.24%	1
Quetiapine may be recommended for the management of insomnia in comorbidity with other psychiatric disorders that justify its prescription.	100.00%	1

Abbreviations: COMISA, Comorbid insomnia and obstructive sleep apnea; COPD, Chronic obstructive pulmonary disease.

clinical factors that may contribute to it. It must be assessed whether the complaint refers to sleep-onset insomnia, sleep-maintenance insomnia, and/or early waking, as well as its weekly frequency, the time of occurrence, daytime symptoms related to it, and its possible interference that may compromise the quality of life, functioning, and interpersonal relationships.[1] ►**Table 10** presents a suggested investigation roadmap. This detailed approach enables precise

Table 9 Recommendation for insomnia treatment during pregnancy and breastfeeding.

Category	Intervention	Recommendation	Consensus rate
BZD agonists	Zolpidem - Oral	NOT Recommended	93.75%
	Zolpidem - Sublingual	NOT Recommended	93.75%
	Zolpidem - CR	NOT Recommended	93.75%
	Zolpidem – orodispersible	NOT Recommended	93.75%
	Zopiclone	NOT Recommended	93.75%
	Eszopiclone	NOT Recommended	93.75%
BZD[a]		NOT Recommended	87.50%
DORAs	Suvorexant	NOT Recommended	87.50%
	Lemborexant	NOT Recommended	86.67%
	Daridorexant	NOT Recommended	81.25%
Antidepressants	Trazodone	NOT Recommended	81.25%
	Doxepin	NOT Recommended	81.25%
	Mirtazapine	NOT Recommended	81.25%
	Amitriptyline	NOT Recommended	75.00%
	Agomelatine	NOT Recommended	93.75%
Melatonin	Melatonin	NOT Recommended	87.50%
Melatoninergic agonists	Ramelteon	NOT Recommended	93.75%
Antipsychotics	Quetiapine	NOT Recommended	81.25%
	Olanzapine	NOT Recommended	87.50%
	Clozapine	NOT Recommended	93.75%
	Periciazine	NOT Recommended	93.75%
	Levomepromazine	NOT Recommended	81.25%
	Chlorpromazine	NOT Recommended	87.50%
Anticonvulsants	Gabapentin	NOT Recommended	87.50%
	Pregabalin	NOT Recommended	87.50%
Others	Difenhydramine	NOT Recommended	87.50%
	Promethazine	NOT Recommended	93.75%
	Hydroxyzine	NOT Recommended	93.75%
	Dimenhydrinate	NOT Recommended	87.50%
	GABA	NOT Recommended	93.75%
	Tryptophane	NOT Recommended	93.75%
Phytotherapeutics	Valeriana officinalis	NOT Recommended	93.75%
	Passiflora incarnata	NOT Recommended	87.50%
	Matricaria recutita1	NOT Recommended	93.75%
	Withania somnifera1	NOT Recommended	93.75%
	Erythrina Mulungu	NOT Recommended	93.75%
Cannabinoids	Cannabis sativa	NOT Recommended	100.00%
	Cannabidiol	NOT Recommended	100.00%
	Delta-9-THC	NOT Recommended	100.00%
CBT-I	In-person CBT-I	Recommended	100.00%
	Online CBT-I	Recommended	100.00%
	Group CBT-I	Recommended	100.00%
	Digital CBT-I	Recommended	100.00%

Table 9 (*Continued*)

Category	Intervention	Recommendation	Consensus rate
	Self-help CBT-I	No consensus	
ACT-I		Recommended	83.87%
MBCT-I		Recommended	77.42%
Alternative	Acupuncture[a]	NOT Recommended	87.10%
treatments	Aromatherapy[a]	No consensus	
	Biofeedback[a]	No consensus	
	Massage[a]	NOT Recommended	77.42%
	Meditative practices[a,b]	No consensus	
	Mind-body practices[a,c]	No consensus	
	Physical exercises[a]	No consensus	

Abbreviations: ACT-I, Acceptance and commitment therapy applied to insomnia; BZD, Benzodiazepines; CBT-I, Cognitive-behavioral therapy applied to insomnia; DORA, Dual orexin receptor antagonists; GABA, Gamma-aminobutyric acid; MBCT-I, Mindfulness-based cognitive therapy applied to insomnia; THC, Tetrahydrocannabinol.
[a]Intervention not included in the systematic reviews.
[b]Recommendations voted in group for the whole class, instead of individually for each intervention.
[c]Includes meditation and vipassana.
[d]Includes qigong, tai-chi, and yoga.

diagnoses and adequate and individualized treatment approaches.[20,21,26–28]

Sleep Diary

Sleep diaries are considered the main subjective sleep assessment method, addressing sleep patterns and distinguishing insomnia from circadian rhythm disorders.[29] The patient must be instructed to fill it out every day, preferably no more than 1 hour after waking up in the morning. The following data were considered essential in a 2012 specialist consensus: the time when the person goes to bed; the time when they begin trying to fall asleep; the time they take to fall asleep; and the number of wakes, not counting the last one; total time each wake lasts; time when they last woke up; time when they get up from bed to begin their daily activities; assessment of the quality of sleep; relevant comments on their sleep. The aforementioned consensus presented another two expanded versions of the sleep diary – one of them includes data on early waking, and the other one includes daytime information, such as naps and caffeine, alcohol, and drug intake.[29]

Questionnaires and Scales

Questionnaires and/or scales such as the following can be used to help identify and assess the severity of insomnia and associated symptoms.

1. **Insomnia Severity Index (ISI):** A scale with seven items that assesses the severity of insomnia, its impact on the quality of life, and the patient's perception of it. Responses range from 0 to 4, indicating the intensity of the symptoms – scores higher than 15 are suggestive of significant clinical insomnia.[30]
2. **Pittsburgh Sleep Quality Index (PSQI):** It assesses the overall quality of sleep and sleep complaints; it does not specifically assess insomnia.[31,32]
3. **Epworth Sleepiness Scale (ESS):** can be used to assess sleepiness due to insomnia, approaching the likelihood of dozing in different everyday situations.[33,34]

The assessment can also use scales and inventories to investigate symptoms of depression and anxiety, fatigue, and quality of life – including the Quality-of-Life Scale (SF-36) and Fatigue Severity Scale.[20,26]

Polysomnography (PSG)

Insomnia is clinically diagnosed and, although PSG is the first-choice method to objectively assess various sleep parameters, its routine use is not recommended to diagnose chronic insomnia.[35] The following situations are indicated to perform PSG to diagnose insomnia: (a) to exclude other sleep disorders, such as obstructive sleep apnea (OSA) and periodic limb movements[27]; (b) to objectively assess sleep-onset latency, total sleep time (TST), the number of wakes, sleep efficiency, duration of the stages, and wake after sleep onset (WASO); (c) to assess cases of insomnia refractory to adequate treatment; (d) to identify inadequate perceptions of sleep, which is recurrent in patients with insomnia.[35] All these indications can be useful in the treatment with CBT-I[21,27,28] and must be considered according to the clinical judgment of each case.

PSG has been recently pointed out as an indication to distinguish insomnia with (TST $<$ 6 hour) and without (TST $>$ 6 hour) short objective sleep duration. The importance of such differentiation is based on evidence that insomnia with short objective sleep duration is a more severe insomnia phenotype. It is associated with physiological changes,

Table 10 Medical history survey roadmap suggested for patients with insomnia.

INSOMNIA SYMPTOMS
Do you have complaints related to difficulty in falling asleep, difficulty in staying asleep throughout the night, or waking up early in the morning?
How many times a week or month do you have these complaints?
When did the symptoms began? Was the course progressive, intermittent, or continuous?
Was there variation over time in terms of intensity, frequency, and severity? Were there remissions?
Have you treated for insomnia before? Did you receive any? How were the responses to treatment?
What are the predisposing, precipitating, and perpetuating factors?
NIGHTIME BEHAVIORS AND HABITS
What time do you go to bed?
Do you do any activity in bed before going to sleep, such as watching television, reading, working, or eating?
What time do you turn off the lights to go to sleep? How long do you think it takes to fall asleep?
Do you wake up during the night? What leads to awakenings (going to the bathroom, dreams, drinking water)? How many awakenings and how long do they last?
Do you frequently look at the clock at night?
How long do you think you have been sleeping? How long do you think you would need to sleep to feel better?
What activities do you do before bed? Do you use devices that emit intense light: computers, tablets, cell phones?
Do you sleep better outside or in a place other than your bed?
DAYTIME HABITS AND BEHAVIORS
What time do you normally wake up in the morning? Do you use an alarm clock, wake up spontaneously or does someone wake you up?
How do you feel when you wake up (sleepy, tired)? Do you get up as soon as you wake up?
Do you feel tired and/or sleepy during the day?
Do you have daytime and afternoon naps, whether voluntary or not?
Do you experience impaired attention, concentration, and memory complaints?
Do you consume substances with caffeine (coffee, tea, soda, *chimarrão*) and/or alcohol and/or cigarettes?
Do you consume illicit substances?
Do you practice physical activity? What time? How often?
Stress at work, personal or family life?
SLEEPING ENVIRONMENT AND ACTIVITIES BEFORE BED
Room temperature, brightness, noise level, ventilation?
Is there a television in the bedroom? Is this used when going to bed?
Do you experience tension when you see your room at nightfall, worry about sleeping during the day, fear of going to sleep?
CONSEQUENCES OF INSOMNIA
Reduced concentration, memory, attention, irritability, daytime drowsiness, fatigue, lack of energy
PRESENCE OF COMORBIDITIES
Do you have clinical illnesses, including those that involve pain?
Do you have psychiatric disorders, such as anxiety disorder, or depressive disorder?
What medications are used for sleep and/or clinical and psychiatric illnesses, as well as herbal medicines? Assess their interference with sleep.
OTHER SLEEP DISORDERS
Assess the presence of snoring, nightmares, bruxism, abnormal sleep behavior, and/or restlessness in the legs at the end of the day.

cognitive-emotional and cortical stimulation, sympathetic activation, and increased risk of systemic arterial hypertension, cardiovascular events, diabetes, significantly increased morbidity and mortality, neurocognitive impairment and seemingly responding better to treatment.[20,36]

PSG limitations to diagnose insomnia lie in the fact that a single night of sleep may be insufficient to detect its diagnosis, as some patients' sleep parameters may worsen in the first PSG night (first night effect), whereas others may have them improved for changing their usual environment, sleeping better at the laboratory. Moreover, there are variabilities between nights with insomnia.[20,26,27]

Actigraphy

Actigraphy assesses the patient's muscle activity during their prolonged use, providing more objective information than the sleep diary. Hence, AASM recommends it to diagnose circadian rhythm disorders, giving actigraphy a relevant role in distinguishing such disorders from insomnia.[37] It is indicated to diagnose insomnia in the assessment and identification of sleep onset, sleep maintenance, and early waking difficulties; the assessment of physical activities and their possible correlation with the quality of sleep; and in monitoring the response to the treatment.[37]

However, actigraphy is not a tool to diagnose insomnia. It must be used in combination with other clinical information, patient's history, and occasionally with PSG to obtain a thorough perspective of the sleep problem.[37]

Differential Diagnosis and Insomnia Comorbidities

Insomnia can be comorbid with other sleep problems such as OSA, circadian rhythm disorders, periodic limb movements, and restless leg syndrome/Willis-Ekbom disease. Careful clinical assessments provide precise diagnoses and the most adequate intervention approaches.[38] ►**Fig. 3** schematizes differential diagnoses per type of insomnia – which, however, may be insomnia comorbidities.[39]

Insomnia may be a risk factor for or a condition comorbid with clinical diseases and psychiatric disorders. Such clinical conditions include cardiovascular diseases, systemic arterial hypertension, type 2 diabetes, obesity, and chronic pain.[12,40–42] A possible explanation for such a risk is that chronic insomnia changes the levels of inflammatory mediators.[43] As for psychiatric disorders, insomnia can be comorbid and have a directional correlation with major depressive disorder, possibly preceding a depressive episode and aggravating its progress and the response to treatment. Conversely, depression also negatively affects insomnia. Moreover, it is often comorbid with post-traumatic stress disorder and anxiety disorders. Another important aspect is that insomnia increases the risk of suicide, especially in individuals with an evening chronotype.[44,45]

Non-Pharmacological Insomnia Treatment

Various authors have proposed theoretical models to explain the psychological phenomenon of insomnia and understand sleep patterns and complaints associated with insomnia disorder. They mostly explain or approach more in-depth factors involved in the etiology of insomnia described by Spielman and colleagues in the 3P model.[46] Based on this model, CBT-I explains the vicious cycle of insomnia perpetuated by the impairment of the homeostatic sleep pressure, the disorganization of the circadian rhythm, and the wakefulness conditioned by associations between the environment, cognitive and somatic excitability, and dysfunctional beliefs and thought patterns about sleep. Using techniques derived from the cognitive and behavioral approach and practices to promote relaxation,[47,48] the literature has documented well CBT-I's effectiveness in treating insomnia comorbid with medical and psychiatric conditions.[47,49] Hence, it is considered the first line of treatment to address chronic insomnia.[50–52] Other CBT-I settings and modalities have been proposed to increase its dissemination, including videoconference or phone calls, messages in virtual chat rooms or e-mail, bibliotherapy, self-guided books, and digital platforms.[52–54] Moreover, other non-pharmacological approaches have been developed and tested independently or combined with CBT-I, such as interventions based on ACT[55] and mindfulness techniques.[56,57]

This chapter aims to recommend the approaches with the highest level of scientific evidence for clinical outcomes and follow-up, considering objective parameters assessed with PSG and actigraphy and subjective ones obtained from sleep diaries and questionnaires that assess the severity of insomnia symptoms and the quality of sleep, especially ISI and PSQI, respectively.

Main Non-pharmacological Approaches and Therapeutic Planning

CBT-I

Central CBT-I components include psychoeducation and sleep hygiene, stimulus control, sleep restriction technique, cognitive therapy, cognitive restructuring, and relaxation techniques.[48,58] They generally take four to eight sessions, lasting 60 to 90 minutes on average.[57,59] The lower the intervention frequency and duration, the fewer the techniques it includes – among which sleep restriction and stimulus control are the most used. ►**Table 11** presents other CBT-I application modalities described in the literature.[54,59–66]

Acceptance and Commitment Therapy (ACT)

ACT belongs to the third wave of Behavioral Psychology and aims to develop psychological flexibility (i.e., the capacity to respond in an adapted way to life challenges with an ample awareness of and engagement in personal values) through six main processes: acceptance, defusion, being present, self as context, values, and committed action.[67]

ACT has been recently tested to treat insomnia either alone or in combination with CBT-I behavioral components, such as stimulus control and sleep restriction.[68] Both interventions approach the six processes that make up the construct of psychological flexibility.

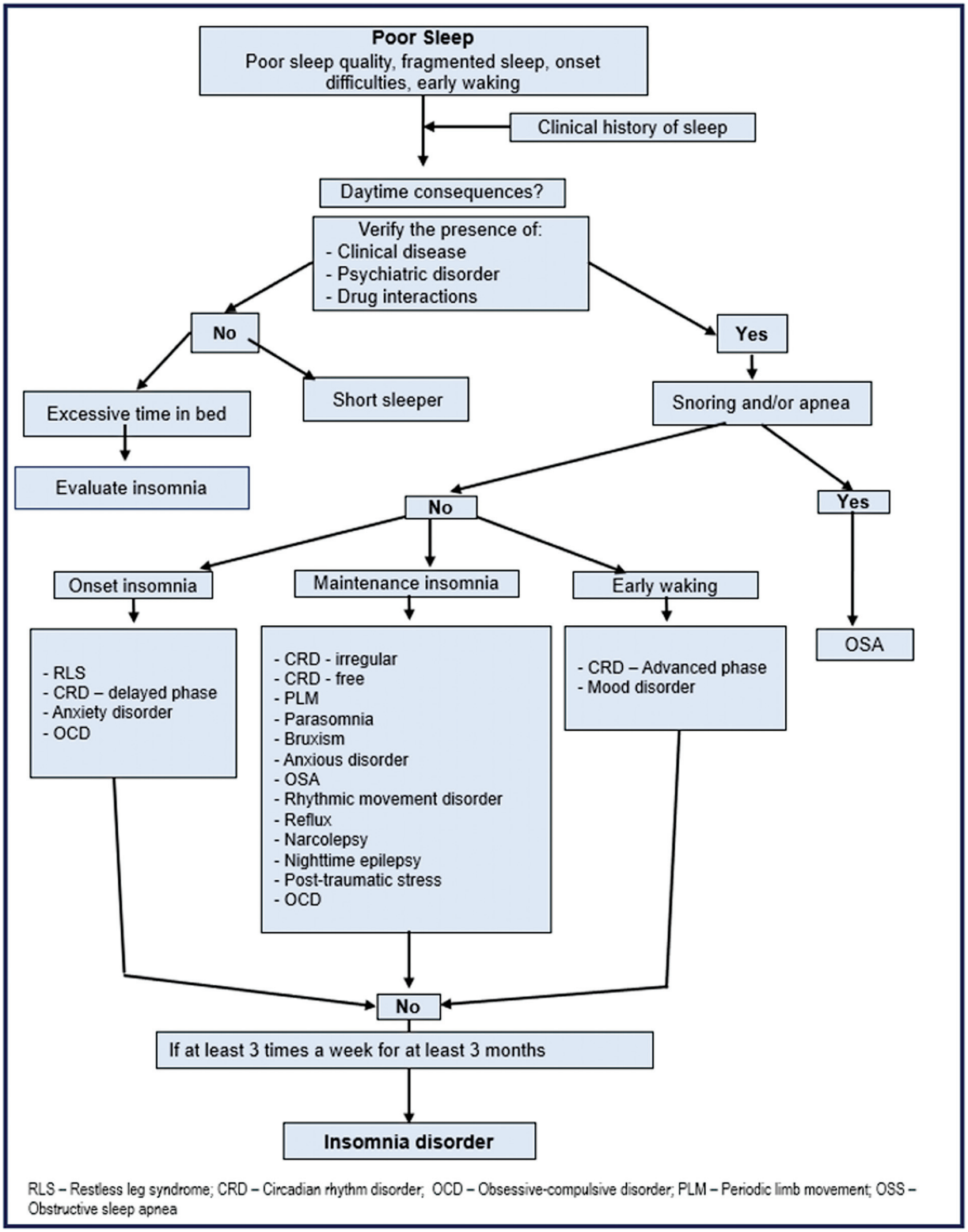

Fig. 3 Differential diagnosis of insomnia (adapted from Ferré-Maso and colleagues[39]).

Mindfulness Techniques

Mindfulness is defined as a state of full attention, deprived of judgment, capable of promoting attentional and emotional regulation, and cultivating attitudes associated with openness, acceptance, compassion, curiosity, and peace. This process is grounded on the process of widening body, mental, and environmental perception and awareness. Jon Kabat-Zinn developed a Mindfulness-based Stress Reduction Program with eight weekly encounters that include practices, discussions on applications and challenges, and guidance to individual daily practice.[69] This program has been adopted and adapted

Table 11 CBT-I modalities: application formats and settings.

Modality	Description
In-person CBT-I	Individual or group care by a trained professional.
Online CBT-I	Real-time videoconference care from a trained healthcare professional.
Digital CBT-I	Digital material organized and made available through an application for mobile devices or a web system. It can include a communication channel with a specialist professional (email or chat inserted in the application/system).
Bibliotherapy	Reading material with guidance based on the CBT-I protocol (guided or not by a health professional).
Self-help therapy for insomnia	Printed or recorded structured audio and/or video material based on CBT-I.

Abbreviations: CBT-I, Cognitive-behavioral therapy applied to insomnia.

for supplementary use in various health interventions, including insomnia.

The mindfulness-based insomnia intervention program encompasses mindfulness techniques with CBT-I components,[70,71] aiming to change the relationship with psychosomatic suffering associated with the condition and change dysfunctional thoughts and habits unfavorable to healthy sleep, thus transforming reactive responses into adaptative ones and improving emotional management.[72]

Clinical Reservations on non-pharmacological approaches to insomnia

The decision for an intervention approach must consider the therapeutic response after the treatment and follow-up, resource availability, physical and mental health conditions, and the patient's openness and readiness to adhere to the proposed therapy. Since non-pharmacological interventions depend on the patient's active participation, different managements must be aligned to ensure their greater effectiveness and efficiency.

Non-pharmacological insomnia treatments are usually well-tolerated, but they may require some precautions, and there may be some contraindications to applying them to older adults – for instance, stimulus control and sleep restriction mental changes pose a risk of falls.[73]

If there are no time or trained professionals to apply multicomponent CBT-I, the recommendation is to apply its components separately (especially the sleep restriction and stimulus control technique) or use digital CBT-I. Unwanted effects, such as excessive daytime sleepiness, fatigue, and concentration difficulties, may be associated with sleep deprivation resulting from the application of the sleep restriction technique. These are short-lasting effects, extinguished as the ideal TST is reached. This technique may be contraindicated to shift or high-risk workers, such as machine operators and drivers, and patients with psychiatric or neurological conditions, predisposed to episodes of mania/hypomania or convulsion. Older patients or those with chronic pain or depression may have difficulties filling in the time awake resulting from the sleep restriction protocol.[52,74]

Regarding insomnia phenotypes based on objective sleep duration, CBT-I is less effective among patients with TST $<$ 6 hour than in those with TST $>$ 6 hour.[75–77] The recommendation for the former is to apply multicomponent CBT-I associated with mindfulness strategies and ACT to favor the autonomic modulation promoted by somatic-cognitive hyperarousal. It can also be combined, at the clinician's discretion, with pharmacotherapy to aid its management.[78,79]

Clinical Outcomes of Non-pharmacological Intervention Approaches to Insomnia

Randomized studies and meta-analyses assessed the effect of multicomponent CBT-I on sleep parameters and mental health of patients with chronic insomnia compared with active and passive control conditions. The results of multicomponent CBT-I proved to decrease the severity of insomnia and improve the quality of life, and subjective parameters of sleep, particularly sleep latency, the number of wakes, WASO, and sleep efficiency.[47,50,53,80–83] ►**Table 12** presents these effects and the ones measured with PSG.[54,84]

The effects of CBT-I on increasing TST are evident in some studies, with sensitivity indicated by the sleep diary[50,62,64,66,83,85] and PSG,[62,84] though with no such correspondence in actigraphy analysis.[62] The effects of CBT-I are more substantial on subjective than objective sleep parameters,[54,62] suggesting greater sensitivity of subjective recordings to detect the effect of decreasing hyperarousal present in insomnia, more reliably reflecting increases in TST.[62] It is worth pointing out that clinical outcomes are maintained in follow-ups of 3 to 12 months.[47,80,83,86,87]

When compared with control conditions and isolated CBT-I techniques, multicomponent CBT-I has also been shown to improve daytime symptoms such as fatigue and sleepiness,[80,88,89] as well as symptoms of anxiety, depression, and/or stress[82,83,85,88,89] and dysfunctional beliefs and attitudes toward sleep.[63,82,85,86]

Online and digital CBT-I services compared with control conditions demonstrate improvement in subjective sleep parameters.[63,64,85,89,90] ►**Table 12** discriminates these effects per CBT-I modality. Although Soh and colleagues[90] indicate a greater effect of in-person CBT-I to reduce the severity of insomnia and WASO compared with digital CBT-I, the clinical outcomes promoted by both modalities demonstrated post-treatment and follow-up equivalence compared with in-person CBT-I.[64,89] Moreover, Arnedt and

Table 12 Effect of multicomponent CBT-I on subjective sleep parameters.

CBT-I modality (vs. control conditions)	Sleep quality (PSQI)	Insomnia severity (ISI)	Sleep latency	Number of wakes	WASO	Sleep efficiency	Total sleep time
In-person CBT-I	Increases	Decreases	Decreases*	Decreases	Decreases	Increases*	Decreases*
Online CBT-I	Increases	Decreases	Decreases	–	Decreases	Increases	Decreases
Digital CBT-I	N/A	Decreases	Decreases	Decreases	Decreases	Increases	–

Abbreviations: CBT-I, Cognitive-behavioral therapy applied to insomnia; ISI, Insomnia Severity Index; N/A, not applicable; PSQI, Pittsburgh sleep quality index; WASO, wake after sleep onset.
*Corresponding effect measured with polysomnography.

colleagues[89] found equivalence in the levels of satisfaction, credibility, and therapeutic alliance of the CBT-I modality via online care when compared with in-person CBT-I.

Given the scarce availability and accessibility of sleep psychologists and health professionals trained in CBT-I, online and digital modalities emerge as alternatives for intervention in the treatment of chronic insomnia. Concerning digital CBT-I, Zhang, and colleagues[66] demonstrated the relevance of cultural adaptation – i.e., adaptation to language, communication style (expressions), day and night life habits, and pre-sleep activities – and scientific validation of systems.

Bibliotherapy and self-help therapy as CBT-I modalities, when compared with non-intervention, demonstrate positive effects on the main subjective sleep parameters (ISI, PSQI, sleep latency, sleep efficiency, and/or WASO)[54] but with limited effectiveness when compared with other CBT-I modalities,[54] limiting their use as isolated approaches, but serving as support for interventions that demonstrate superior effectiveness.

The sleep hygiene approach alone has limited clinical outcomes in improving primary chronic insomnia when compared with control,[52,91] with no effect on comorbid insomnia or when compared with CBT-I and mindfulness approaches for treating insomnia.[91]

It is observed that the more structured and frequent the intervention with CBT-I techniques, the greater the effects on sleep parameters.[50,64,83] These effects are long-lasting and independent of comorbidity, age, and sex,[49,64,92] especially in the presence of clinical support during follow-up.[64] The adherence rate to CBT-I is higher than other active interventions.[93] The outcome of CBT-I in patients with more years of chronic insomnia and medication use is inferior to those in the opposite condition.[83]

Compared with a waiting list and a psychoeducation control group, ACT reduced the severity of insomnia[55,68] and improved sleep parameters and secondary outcomes such as dysfunctional beliefs and attitudes about sleep, acceptance of sleep problems, daytime sleepiness, and cognitive suppression.[55,68] When compared with CBT-I, ACT showed no differences in subjective sleep parameters.[55,68] Chapoutot and colleagues[94] observed reduced hypnotics, Z-drugs, and BZDs consumption in response to ACT. Although studies involving ACT suggest promising results for the intervention of chronic insomnia, they do not present the same empirical support as CBT-I, recommending its use as an adjuvant to CBT-I.

Studies involving mindfulness-based intervention protocols compared with controls demonstrate improvements in ISI,[56,95–97] PSQI,[97–99] and subjective sleep parameters: sleep latency, sleep efficiency, WASO,[97,98] with improvement in mental health parameters during follow-up.[56,86] A comparison of these approaches with CBT-I demonstrated inferior results about sleep parameters.[56,86] A meta-analysis conducted by Entrambasaguas and colleagues[95] identified inconclusive results of the mindfulness approach combined with CBT-I on clinical outcomes in the evaluation parameters of chronic insomnia due to the lack of standardization in the methodological designs that compromise the evaluation of the effectiveness of the combined therapy.

However, some studies have indicated that mindfulness practices improve dose-dependent sleep quality (PSQI) (i.e., the longer the practice, the greater the effect on sleep quality or decreased excitability),[57,86,96] suggesting preventive power for insomnia in healthy and clinical populations and adjuvant practice to CBT-I with or without comorbidity.[57]

"Alternative" treatments

Biofeedback

Biofeedback is a therapeutic tool that aims to develop the capacity for self-regulation by electronically monitoring physiological processes, such as peripheral temperature, blood pressure, heart rate, muscle tone, or brain waves. The collected signals associated with stress conditions are immediately returned to the patient through images and/or sounds to promote ess of the stress condition and promote voluntary regulation of physiological and emotional reactions, breaking the vicious cycle of stress, promoting relaxation, and improving symptoms associated with anxiety and other mood disorders, possibly acting on the reduction of sympathetic activation.[100]

Different biofeedback modalities have been described, such as neurofeedback, which aims to influence the occurrence of sleep-related brain waves, and heart rate variability biofeedback, which aims to reduce sympathetic activity by training breathing in the context of heart rate oscillations.[100]

Recent systematic reviews on the application of biofeedback to treat insomnia demonstrate inconsistent results and general limitations regarding the quality of available studies, such as small sample size and lack of control group.[101–103] Few randomized studies have tested biofeedback techniques alone or in combination for insomnia. One of the first studies,

conducted by Nicasio and colleagues,[104] tested progressive relaxation and neurobiofeedback with electrodes in the frontal region, versus simulated neurobiofeedback (placebo) in 40 adult patients. Relaxation and neurobiofeedback led to significant reductions in both self-reported sleep latency and depressive symptomatology. However, this result did not show significant differences when compared with the control group, suggesting a potential placebo effect.[104] A similar result of a potential placebo effect was observed in a double-blind study in patients with primary insomnia.[105] A recent randomized study by Kwan and colleagues[106] suggested that a neurofeedback protocol was comparable in efficacy to CBT-I, but the small sample size precludes any conclusions in this regard.

Acupuncture

Acupuncture has been used in clinical practice as an alternative to the treatment of insomnia in some countries such as China. Systematic reviews and meta-analyses[107–114] from the past 4 years evaluating different acupuncture techniques suggest that acupuncture is safe compared with no treatment or *sham* procedures and has produced reduced PSQI scores, increased TST, and sleep efficiency. However, in practically all analyses, there are criticisms about the quality of the available studies, suggesting the need for studies with more consistent protocols in this context.[107–114]

Physical Exercises

Physical exercise, with emphasis on aerobic practice, is cited as an adjuvant therapy in the treatment of insomnia, especially as it is associated with increased energy expenditure, promoting well-being, facilitating weight loss, and improving mood and cognition. However, to date, few randomized studies have tested the effect of physical exercise on insomnia.[115–117] One of the studies tested a monitored program of at least 150 minutes of physical exercise per week, of moderate intensity (brisk walking, in the chosen environment for at least 30 minutes per day, on at least 5 days of the week), for 6 months. At the end of the follow-up, the physical exercise group showed an average reduction of 4 points in the ISI.[115] More recently, Baron and colleagues showed that moderate to vigorous aerobic training for 12 weeks also improved the severity of insomnia symptoms.[116] In another investigation, Zhang and colleagues compared aerobic exercise three to five times a week with implementing a balanced diet and with non-treatment for 6 months in 72 patients with insomnia.[117] Both physical exercise and diet improved sleep quality and reduced objective sleep latency and sleep efficiency in relation to the baseline period.[117] However, no significant differences were shown compared with the control group.[117]

Evidence on resistance exercise or strength exercise is even scarcer, although it suggests a benefit in objective and subjective parameters in patients with chronic insomnia.[118] Meta-analyses point to safety and some favorable effects on insomnia symptomatology; however, they also report inconsistencies and significant quantity and quality limitations of the studies.[119,120]

Mind-body techniques

Mind-body techniques include meditative practices, yoga, Tai Chi, qigong, and so forth. These are ancestral practices that aim to train the mind, especially attention, through contemplation, body movement, and/or posture, focused on breathing to integrate mind and body. In general, studies on the effect of these techniques involve practices with a frequency of one to three times a week (60–120 minutes per session) for 12 or more weeks.[57]

Although some studies evaluating the effect of practicing Yoga and Tai-chi point to improvements in sleep quality, some parameters of sleep architecture,[57,121–124] and psychiatric symptoms,[124] the evidence is very limited due to studies with small samples, relatively short follow-up, high response heterogeneity, and the lack of standardized techniques.

However, some studies have indicated that mind-body approaches, including mindfulness practices, improve dose-dependent sleep quality (PSQI) (i.e., the longer the practice, the greater the effect on sleep quality or decreased excitability).[57,86,96] These results indicate that such approaches can be adopted as preventive practices for insomnia in healthy and clinical populations,[57,124] and can be adjuvants to CBT-I with or without comorbidity.

Aromatherapy

Aromatherapy is a therapeutic approach based on the principle that substances that make up the aroma of essential oils release particles capable of generating favorable stimuli to brain areas related to emotions, helping to treat symptoms of anxiety, depression, and insomnia, among other medical and psychological conditions. Preliminary studies limited to a few patients and short follow-up suggest that aromatherapy (mainly using lavender) may have benefits on sleep quality in patients with mild forms of insomnia.[125–127]

Pharmacological Insomnia Treatment

The pharmacological treatment of insomnia today consists of several classes of medications with different mechanisms of action, sometimes specific to a certain type of insomnia. As detailed below, some classes have greater scientific support for safety and efficacy while others lack greater scientific evidence and are often used "off-label." In this guideline, we will divide the classes into the items presented below.

Selective Benzodiazepine Receptor Agonists and Benzodiazepines

Selective Benzodiazepine Receptor Agonists (Z-drugs)

Selective BZD receptor agonists marketed so far in Brazil – zolpidem, zopiclone, and eszopiclone – constitute a class approved for the treatment of insomnia, acting as hypnotics.

Zolpidem

Mechanism of action: hypnotic agent of the imidazopyridine class, acts on the α1 subunit of type A gamma-aminobutyric acid (GABA) receptors.[128,129] Immediate-release presentations have a short half-life (0.5–3.5 hours), with peak plasma

concentrations of 45 to 60 minutes. Controlled-release presentations have biphasic absorption, with rapid initial absorption and prolonged plasma concentration, lasting more than 3 hours.[128]

Available presentations: in Brazil, available presentations include immediate-release tablets, 10 mg; sublingual, 5 mg and 10 mg; 5 mg and 10 mg orodispersible; controlled-release tablets of 6.25 mg and 12.5 mg; oral solution 10 mg/mL (0.5 mg/drop).[128]

Patient assessment: it is indicated for acute night sleep-onset insomnia (immediate release – dose of 5 to 10 mg) and for sleep maintenance (prolonged release – dose of 6.25 mg), in adults. For older adults, it is recommended to start with half this dose.[1] The initial dose should be lower for women. Use for children, adolescents, pregnant women, or during breastfeeding is not recommended.

Therapeutic planning: should be administered at bedtime, over no more than 4 weeks.[129]

Expected outcomes: In a meta-analysis ($n = 1{,}068$), zolpidem resulted in increased TST, reduced sleep latency, and improved sleep quality, with no difference in WASO.[129] Evaluating different doses of zolpidem (5; 7.5; 10; 15; and 20mg), it was shown that doses of 7.5 and 10 mg decreased sleep-onset latency and the number of nighttime wakes and increased TST, without impact on psychomotor performance.[130]

Comparing sublingual and oral zolpidem, 10 mg, the sublingual presentation reduced sleep onset latency by 8.6 minutes, with no differences in TST and WASO, compared with oral zolpidem.[131] In individuals with chronic insomnia, oral (10mg) and sublingual (5mg) zolpidem led to a similar reduction in the number of wakes and an increase in TST, but with a greater reduction in sleep latency with sublingual zolpidem.[132]

For maintenance insomnia, with nighttime wakes, sublingual zolpidem (5 mg) increased TST, without significant changes in sleep latency, WASO, or sleep quality, and with sleepiness and reduced alertness in the morning.[133]

Extended-release zolpidem (12.5 mg), in individuals with chronic insomnia, increased TST and sleep efficiency, while reducing latency to persistent sleep, wakes, and WASO. The following morning, there was no impairment of psychomotor performance.[134,135]

Drug interactions, contraindications, and side effects: zolpidem is metabolized by cytochrome p450 (CYP). Use with CYP3A4 inhibitors (fluvoxamine, ciprofloxacin, and ketoconazole) is not recommended due to the potential increase in the sedative effect. Use with CYP3A4 inducers (rifampicin and St. John's wort) may decrease zolpidem levels.

Side effects of zolpidem include sleepiness (5%), dizziness (5%), headache (3%), gastrointestinal symptoms (4%), sleepwalking (1%), nightmares (1–2%), and mental confusion (1–2%).[128,131,132,135] The risk of falls and fractures is increased, especially among older people.[128] Non-REM (NREM) sleep parasomnias, and behavioral changes (disinhibition, aggressiveness, impulsivity, visual and auditory hallucinations, driving) are possible effects, more prevalent in association with alcohol.[128] There is an increased risk of suicide, especially with high doses and psychiatric comorbidities.[128] The prevalence of rebound insomnia with discontinuation of zolpidem was not greater than that observed with placebo after daily use for one year,[136] but it may be observed with abrupt discontinuation of higher doses.[128]

Zolpidem can cause dependence syndrome. Abrupt interruption is associated with headache, myalgia, irritability, anxiety, mental confusion, and, in more serious cases, derealization, depersonalization, hyperacusis, hypersensitivity to light, noise, and tactile stimuli, hallucinations, and epileptic seizures. There has been a recent increase in zolpidem abuse and the use of high doses, with tolerance, particularly in individuals with reported dependence and abuse of other drugs.[137] In Brazil, between 2018 and 2022, there was a 161% growth in zolpidem sales, reaching, almost 22 million boxes sold in 2022, according to data provided by the National Controlled Products Management System, managed by the National Health Surveillance Agency (ANVISA). In this same period, comparatively, the sale of clonazepam increased by just over 9%. Therefore, measures to combat indiscriminate use, as well as the correct assessment and reassessment of patients during the use of zolpidem, are priorities in the treatment of patients.

Zopiclone

Mechanism of action: It is a non-benzodiazepine hypnotic agent from the cyclopyrrolone family. It has a high affinity for the α-1 and α-2 subunits of the GABA-A receptor.[128] After oral administration, zopiclone is rapidly absorbed, with maximum plasma concentrations of 30 and 60 ng/mL reached within 1.5 to 2 hours, after administration of 3.75 and 7.5 mg, respectively. Its terminal elimination half-life (t1/2) is ∼5 hour.

Available presentations: Zopiclone is available in Brazil in the form of 7.5 mg coated tablets.[128]

Patient assessment: Due to its mechanism of action, zopiclone is indicated for adult patients with acute, onset, and/or maintenance insomnia. Older people should start with half the dosage (3.75 mg).

Therapeutic planning: The recommended administration is 1 tablet, orally, only at bedtime (considering that the patient must adopt a regular pattern in the times they go to bed and get up). Treatment should be short-term, trying not to exceed 4 weeks.

Expected outcomes: A systematic review evaluated the use of zopiclone in 12 double-blind, placebo-controlled RCTs, two open studies, and two observational reports, and concluded that it can be an effective and relatively safe treatment to treat insomnia in adults and older people, with and without comorbidities.[138] Zopiclone reduced sleep latency, nighttime wakes, and WASO, increasing TST, with probable effects on sleep architecture, at dosages of 3.75 mg, 5 mg, 7.5 mg, and 10 mg. It was compared with placebo or BZDs in different populations (older people living in the community, residents of long-term care institutions, and those admitted to hospitals). Zopiclone was well tolerated, with a low rate of adverse events and low impact on psychomotor or cognitive

performance, as long as the dosages and guidelines established for its use were respected. However, the quality of most studies was low or unclear.[138] There are two RCTs – one compared the effectiveness of zopiclone with zolpidem and the other, with eszopiclone, demonstrating that both substances were effective in decreasing sleep latency and increasing TST and sleep efficiency, respectively.[139,140]

Drug interactions, contraindications, and side effects: The binding of zopiclone to plasma proteins is weak and nonsaturable; therefore, the risk of drug interactions is very small. Reducing the dose of zopiclone is necessary when used concomitantly with potent CYP3A4 inhibitors, such as erythromycin and ketoconazole. The opposite was also observed with rifampicin, carbamazepine, phenobarbital, phenytoin, and St. John's wort, drugs that induce CYP3A4, decreasing the action of racemic zopiclone by 80%. Ethanol should not be consumed concomitantly with zopiclone due to the risk of parasomnia such as sleepwalking, food intake, telephone calls, and amnesia, in addition to increasing the sedative effect of zopiclone.

This medicine should not be used by pregnant women as there are no adequate and well-controlled studies in these conditions. The use of this medication in women who are breastfeeding is also not recommended. Likewise, the use of zopiclone in children and adolescents is not recommended.

Very common adverse events ($>$ 10%): bitter taste; common ones ($>$ 1% and $\leq$ 10%): dizziness, headache, residual sleepiness, dry mouth, dyspepsia, nausea. Nightmares or inappropriate behaviors such as sleepwalking were rarely recorded.

Other considerations: 1) Withdrawal syndrome has been reported upon discontinuation of zopiclone and may cause rebound insomnia, anxiety, tremors, sweating, agitation, confusion, palpitations, and tachycardia; 2) The risk of dependence or abuse increases with the dose and duration of treatment, history of abuse with alcohol or other drugs and concomitant use of alcohol or other psychotropic drugs. 3) Continued use of zopiclone can reduce its effectiveness, generating tolerance. 4) Anterograde amnesia may occur, especially when sleep is interrupted or when the time to lie down is delayed after taking the zopiclone tablet.

Eszopiclone

Mechanism of action: Eszopiclone, an S-enantiomer of racemic zopiclone, is a nonbenzodiazepine hypnotic agent from the cyclopyrrolone family.[1,128] After oral administration, it is rapidly absorbed and reaches maximum concentration (Tmax) in ~1 hour. It has a high affinity for the α-1, α-3 and α-5 subunits of the GABA-A receptor.[142,143]

Available presentations: Eszopiclone is available in Brazil as 2 and 3 mg coated tablets. The 1mg presentation is expected to arrive soon, which could be attractive for older patients.

Patient assessment: Due to its mechanism of action, eszopiclone is indicated for adult patients with acute, onset, and/or maintenance insomnia.[1]

Therapeutic planning: The recommended administration is one tablet only when going to bed (considering that the patient must adopt a regular pattern in the times they go to bed and get up). Always try to start with the lowest dosage. Intermittent dosing or "treatment as needed" may be an alternative to the treatment.[143]

Expected outcomes: There are already numerous RCT studies and two meta-analyses. The first reviewed 14 RCTs with 4,732 participants and demonstrated that eszopiclone reduced sleep latency by 12 minutes and WASO by 17 minutes, helping increase TST by at least 30 minute, increasing sleep efficiency and improving functioning the next day when compared with placebo.[142,143] This effect was observed in different age groups (3 mg being administered to adults and 2 mg to older adults) and in different types of insomnia, including comorbid conditions. Two 6-month studies indicated that therapeutic benefits can be maintained for prolonged periods.[145,146]

A dosage of 1mg of eszopiclone is enough to reduce sleep latency and increase sleep efficiency. However, only with 3 mg was there a significant difference in WASO, number of wakes, and wake-up time (with PSG) when compared with placebo.[147] A study in a Japanese population observed a statistical difference with a dosage of 2 mg.[148]

The most recent meta-analysis, from 2019, brought together 6 RCTs involving 2,809 patients with insomnia disorder and concluded that eszopiclone is an effective and safe therapeutic option, especially for older patients. Eszopiclone was associated with significant improvements in subjective sleep latency, WASO, number of wakes, TST, increasing sleep quality, ability to function, daytime alertness, and sense of physical well-being in studies with follow-ups of 1 week, 2 weeks, 1 month, 3 months, and 6 months.[146] Roth and Walsh described the same results, but with follow-ups of 12 months, the last 6 months being an open study.[149]

Drug interactions, contraindications, side effects: Eszopiclone is weakly bound to plasma proteins. The high fraction of free drugs in plasma suggests that its distribution is not affected by interactions with other medications related to binding to these proteins. Eszopiclone did not show any inhibitory potential on CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, or 3A4A.

Reducing the dosage of eszopiclone is necessary when used concomitantly with potent CYP3A4 inhibitors, such as ketoconazole. The opposite was also observed with rifampicin, a drug that induces CYP3A4, decreasing the action of racemic zopiclone by 80%. Ethanol should not be consumed concomitantly with eszopiclone due to a potentiation of the effect on psychomotor performance up to 4 hours after use.[143]

This drug should not be used by pregnant women as there are no adequate and well-controlled studies in these conditions. Its use in women who are breastfeeding is also not recommended. Likewise, the use of eszopiclone in children and adolescents is not recommended.

Very common adverse events ($>$ 10%): Headache, and unpleasant taste; common ones ($>$ 1% and $\leq$ 10%): sleepiness, dry mouth, viral infection, dyspepsia, and nausea.[143]

Other considerations: 1) Discontinuation of eszopiclone after several weeks and months of treatment did not result in withdrawal symptoms; 2) Rebound effect was reported in a minority of studies; 3) The efficacy of eszopiclone has been proven in patients with insomnia comorbid with severe depression, generalized anxiety, rheumatoid arthritis, and OSA, with improvement in sleep parameters.[145,150] 4) Eszopiclone provided significant improvements in sleep, mood, and menopause-related symptoms in perimenopausal and early postmenopausal women.[151]

Benzodiazepines (BZDs)

BZDs' history began in 1955 with the discovery of chlordiazepoxide and in 1963 with the launch of diazepam. The expectation of a new variety of drugs with more effective and safer psychic effects than the predominant barbiturates and opioids meant that BZDs dominated the neuropsychopharmacology market from the 1960s and 1970s onwards. The perception of medical society about these drugs began to change after the second half of the 1970s and into the following decade due to side effects, mainly abuse, addiction, and accidents.[152] Although there has been a decline in prescription in the past 20 years,[153] BZDs remain popular[153–155] with new formulations emerging as recreational drugs, the so-called designer BZDs.[156]

***Mechanism of action*:** They act as allosteric agonists of GABA-A type A receptors – i.e., they bind to the same receptor, but in different GABA sites, facilitating the effect of the agonist neurotransmitter. This effect is predominantly in postsynaptic neurons, where there is a cellular influx of chloride leading to neuronal hyperpolarization. BZDs demonstrate different effects depending on the α subunits that make up the GABA-A receptor and their locations in the different GABAergic pathways of the central nervous system (CNS): anxiolytic, hypnotic, myorelaxant, amnesic, antiepileptic, and respiratory depressant.[157] In the mesolimbic dopaminergic system, GABA inhibition in the ventral tegmental area leads to an increase in the dopaminergic signal, resulting in a reward effect, which is related to the mechanism of abuse and dependence.[158]

***Available presentations*:** Several BZDs are sold in Brazil. This study will evaluate those for outpatient use and aiming to treat insomnia – thus, only oral and sublingual tablet presentations and drop bottles will be mentioned. Those for injectable hospital use, intravenously and intramuscularly, will not be listed, as well as the presentations absent in our country, nasal spray and rectal gel. The BZDs analyzed were bromazepam (3 mg, 6 mg oral tablets and 2.5 mg/mL solution), diazepam (5 mg and 10 mg oral tablets), clonazepam (0.25 mg sublingual tablets, 0.5 mg oral tablets, 2 mg and 2.5 mg/mL solution), alprazolam (0.25 mg, 0.5 mg, 1 mg and 2 mg oral tablets), midazolam (7.5 mg and 15 mg oral tablets), flunitrazepam (1 mg oral tablets), estazolam (oral tablets 2 mg), flurazepam (30 mg oral tablets), nitrazepam (5 mg oral tablets), clobazam (10 mg and 20 mg oral tablets) and lorazepam (1 mg and 2 mg oral tablets). It is noteworthy that temazepam is the only BZD indicated for the treatment of insomnia according to the AASM guidelines,[19] not available in Brazil and for this reason not included in this Brazilian guideline.

***Patient assessment*:** Due to their mechanism of action, BZDs have hypnotic potential for onset, maintenance, and early morning awakening insomnia. However, the risks of abuse, dependence and withdrawal, intoxication, enhancement of other substances with a hypnotic effect, accidents, and death mean that they are not drugs of choice for the treatment of insomnia.[105–107]

Therapeutic planning: Only in cases of insomnia comorbid with diseases of which BZDs are treatment options (e.g., epilepsy, some psychiatric and sleep disorders) is it possible to seek their therapeutic hypnotic effect according to the clinical standard. It is not recommended to use a benzodiazepine for more than 4 weeks as almost half of patients using it daily for more than a month can develop dependence.[161] In early-night insomnia, BZDs with a short and intermediate half-life (alprazolam, flunitrazepam, estazolam, midazolam, and bromazepam) are usually more used, with those with prolonged effect duration (clonazepam, diazepam, and flurazepam) being options for cases of maintenance and early-morning insomnia. Sublingual administration presentations can be an option for early-night insomnia as it is a faster absorption route than oral. One difficulty regarding the duration of the drug's effect is that some of them have active metabolites, such as alprazolam and diazepam.[159,160,162,163] Furthermore, short-acting BZDs present a greater risk of abuse by users.[159,160,162,163] It is noteworthy that the option is also linked to the disease that primarily requires the use of benzodiazepine.

Expected outcomes: There are no recent studies with a sufficient level of evidence for BZDs marketed in Brazil to be recommended for the treatment of insomnia.

Drug interactions, contraindications, and side effects: Drugs that interfere with CYP3A4 may influence the metabolism of BZDs. The main pharmacological interactions are with phenothiazines, opioids, barbiturates, monoamine oxidase inhibitors, antidepressants with hypnotic effects, and alcohol and illicit drugs. Interaction may also occur with some foods, grapefruit, St. John's wort, and Kava.[164]

BZDs can exacerbate symptoms such as respiratory depression, incoordination and imbalance, behavioral changes, and sleepiness. Therefore, the use of this pharmacological class is not recommended in patients with myasthenia gravis, ataxic syndrome, OSA, chronic respiratory failure, CNS depressant intoxication, angle-closure glaucoma, older people presenting agitation, or patients in delirium. The use of BZDs by pregnant and breastfeeding women is also not recommended.[164] Populations with psychiatric comorbidities are those at greatest risk of abuse and dependence.[160,161]

The most common side effects are sleepiness, lethargy, fatigue, daytime sleepiness, impaired attention and concentration, amnesia, abuse, dependence and withdrawal, hypotonia, and ataxia. Falls, fractures, accidents, memory impairment, and a greater risk of paradoxical reactions can occur in older people.[162,163]

Dual Orexin Receptor Antagonists (DORA)

Orexins or hypocretins are hypothalamic neuropeptides that have a role in regulating the sleep-wake cycle and maintaining wakefulness.[165] The orexin/hypocretin system is considered a target for the treatment of insomnia.

Suvorexant

Suvorexant was the first DORA approved for the treatment of insomnia.[166]

Mechanism of action: Suvorexant is DORA that promotes sleep through selective antagonism of the OX1R and OX2R orexin receptors. Its half-life is ~12 hours and the time to reach the maximum concentration (Tmax) is ~1 to 2 hours (if ingested on an empty stomach) and ~3 hours (with food).

Available presentations: Suvorexant is available in the following doses: 5, 10, 15, and 20 mg oral tablets.

Patient assessment: It is indicated to treat sleep-onset and maintenance insomnia in adults and older adults.

Therapeutic planning: According to the American Food and Drug Administration (FDA), the recommended dose is 10 mg taken once at night, 30 minutes before going to bed, and at least 7 hours before the planned time to get up the next morning. The dose can be increased to up to 20 mg if the 10 mg dose is not effective, although well tolerated. The total daily dose should not exceed 20 mg per day. In patients using moderate CYP3A4 inhibitors, the maximum recommended dose is 10 mg per day (starting with 5 mg).

Expected outcomes: As this was the first DORA approved, more studies and systematic reviews exist on this medication.[167,168] Outcomes such as sleep onset latency, TST, WASO reduction, maintenance of sleep architecture, as well as global and patient clinical impression, have been systematically evaluated with suvorexant in placebo-controlled trials involving more than 1,000 patients.[168] A review that included 1,824 patients using suvorexant revealed significant improvement in sleep, as assessed with ISI when compared with the placebo group. Improvement in sleep (onset/maintenance), as well as a reduction in the impact of sleep problems on daytime function, contributed to the overall improvement observed in the ISI total score.[169] A double-blind RCT conducted in 522 patients aged $\geq$ 18 years (322 used suvorexant versus 162 placebo) for 1 year showed that patients who received suvorexant had subjective improvement in sleep latency and maintenance when compared with the placebo group. The perception of improved sleep was evident in the first week of sleep and was maintained after 1 year at the end of it. According to this study, suvorexant improves the perception of sleep quality and the feeling of morning well-being, with no effect on mood, and there were no marked differences between the groups in the occurrence of adverse events.[170] Suvorexant was also evaluated in patients with insomnia and probable Alzheimer's disease, maintaining the same efficacy and safety profile observed in studies in patients with primary insomnia.[170]

Suvorexant significantly reduces sleep-onset latency, increases TST, and decreases WASO,[167] being effective and safe compared with placebo.

***Drug interactions, contraindications, and side effects*:** According to the FDA, the most common adverse effects include sleepiness, fatigue, and headache. Other less common adverse effects are dry mouth, coughing, increased incidence of respiratory tract infections, and changes in dream patterns. The risk of adverse effects is dose-dependent and appears to occur more frequently in women. There is no significant difference between young people and older adults in relation to the risk of adverse effects.

When evaluating this drug in patients with insomnia, no significant differences were observed in the occurrence of narcolepsy symptoms, such as hypnagogic or hypnopompic hallucinations or sleep paralysis. No events suggestive of cataplexy were observed.[167]

Daridorexant

Mechanism of action: Daridorexant binds to G protein-coupled orexin (hypocretin) receptors A and B to promote wakefulness – like the other DORAs mentioned in this section. Hence, daridorexant suppresses excessive vigilance during the sleep period by selectively targeting and blocking the binding of orexin neuropeptides to the two receptors.[171] Its half-life is ~8 hour, and Tmax is ~1 to 2 hour. The rapid absorption of daridorexant associated with its rapid elimination allows a rapid onset of action and maintenance of nighttime sleep, avoiding sleepiness the next morning.

Available presentations: Daridorexant is available as 25 and 50mg oral tablets.

Patient assessment: It is indicated for the treatment of insomnia, sleep-onset, or maintenance difficulties in adults and older adults.

Therapeutic planning: Daridorexant was approved by the FDA for the treatment of insomnia in adults aged $\geq$ 18 years in doses of 25 to 50 mg, with a recommendation for use 30 minutes before bedtime, with this medication taking at least 7 hours before the planned time to wake up.

Expected outcomes: The main randomized, placebo-controlled study, lasting 52 weeks, showed that daridorexant was generally safe and well tolerated, without inducing residual morning sleepiness at the doses studied. One of the study results showed that daridorexant improved sleepiness the next morning. Reports of adverse events were rare in all groups studied (active and placebo). Narcolepsy symptoms were not reported by study participants, as monitored for all DORAs already approved for insomnia. Finally, there were no signs of rebound insomnia upon withdrawal.[172] In summary, it was concluded that in patients with insomnia, daridorexant administered for up to 1 year was generally safe, with no signs of tolerance, physical dependence, or rebound after withdrawal.

A secondary analysis of the study evaluated the efficacy and safety in a subpopulation of older people with insomnia, demonstrating that, as in younger patients, the efficacy of daridorexant is maximum in nighttime and daytime variables at the highest dose of 50 mg. Older patients particularly required this dose to improve daytime functioning. They did not present an increased risk of adverse events or residual effects the following morning after the evening administration of 50 mg.[173]

A systematic review with meta-analysis gathered data from 2,271 patients from 4 RCTs, showing that 50 mg of daridorexant was superior to placebo for the four efficacy outcomes, including WASO, sleep latency, subjective TST and Insomnia Daytime Symptoms and Impacts Questionnaire domain score. Furthermore, there were no significant differences in adverse events between daridorexant and placebo.[174] Daridorexant is effective and safe for the treatment of insomnia when compared with placebo.

Drug interactions, contraindications, and side effects: The most common side effects are sleepiness, fatigue, headache, and nasopharyngitis.

Lemborexant

Lemborexant is a new DORA used for the treatment of adults and older people with insomnia, characterized by sleep-onset and/or maintenance difficulties. Lemborexant was approved in 2019 for use in the United States, Japan, and Canada.

Mechanism of action: It acts as a reversible competitive antagonist at both orexin 1 and 2 receptors (OX1R and OX2R). Compared with suvorexant, it has a greater affinity for the orexin 2 receptor and, therefore, has a more potent inhibition effect for this receptor in addition to faster dissociation of both receptors, providing a shorter duration of action and faster elimination in initial phases. These differences corroborate the lower risk of residual sleepiness the next day.[175]

Available presentations: Lemborexant is available as 5 and 10 mg oral tablets.[175]

Patient assessment: It is indicated for the treatment of sleep-onset and sleep-maintenance insomnia in adults and older people. Use for children, adolescents, pregnant women, or during breastfeeding is not recommended.[175]

Therapeutic planning: The recommended dose is 5 mg administered at bedtime, at least 7 hours before the planned wake-up time. The dosage may be increased to 10 mg based on clinical response and tolerability.

Expected outcomes: In randomized, double-blind, placebo-controlled studies and objective and subjective assessments, lemborexant 5 mg and 10 mg provided efficacy with minimal residual sleepiness the following morning in adult and older participants with insomnia. Individuals treated with lemborexant experience improvement in all sleep parameters - i.e., reduced sleep-onset latency, increased sleep efficiency, and increased TST when compared with placebo. The benefits are observed at dosages of 5 mg and 10 mg from the first week of use and maintained for 12 continuous months of treatment.[176,177]

Roth and colleagues evaluated changes in insomnia severity in 949 individuals with moderate to severe insomnia (ISI score >15) treated for 12 months with both dosages of lemborexant. It reduced the severity of insomnia (reduction >7 points in ISI), which was maintained at the end of the analysis for 12 months, versus placebo.[178]

There is no evidence of rebound insomnia or withdrawal after stopping 12 months of treatment. Furthermore, no deaths or falls were recorded. No suicidal tendencies, suicidal ideation, suicidal behavior, or self-injurious behavior are reported with up to 12 months of treatment.[179]

In a randomized, double-blind study of 1,006 participants aged $\geq$ 55 years or older with insomnia, Rosenberg and colleagues found that lemborexant therapy significantly improved both sleep latency and maintenance compared objectively via PSG with placebo and extended-release zolpidem treatment (6.25mg). Therapy with 5 mg and 10 mg lemborexant was well tolerated in older adults and proved to be effective, especially in the last half of the night, compared with placebo. Benefits for sleep onset and maintenance were also observed from the beginning of treatment and maintained throughout treatment for 30 days.[180] Also in older people, the use of lemborexant led to significant increases in the percentage of rapid eye movement (REM) sleep and significant reductions in baseline latency to REM sleep compared with placebo and zolpidem.[180] These findings suggest that Lemborexant may modify some of the changes in sleep architecture normally observed in older people with insomnia.[181]

Drug interactions, contraindications, side effects: The effective half-life is 17–19 hour and reaches peak concentration in $\sim$1 to 3 hour. It is predominantly eliminated via CYP3A-mediated metabolism and the major metabolites are physiologically inactive.[175,182] Concomitant use with CYP3A inhibitors (itraconazole, clarithromycin, fluconazole, verapamil, and ranitidine) increases bioavailability and maximum concentration and risk of adverse reactions. Concomitant use with a CYP3A inducer (rifampin, carbamazepine, modafinil) decreases lemborexant exposure, which may reduce efficacy. The association with alcohol increases the maximum concentration and bioavailability of lemborexant, increasing the sedative effect and adverse reactions. Sleep onset may be delayed if administered concomitantly with or after a meal. The 5 mg dosage is recommended in cases of mild and moderate hepatic insufficiency and is contraindicated in severe hepatic insufficiency.

Doses of 5 mg and especially 10 mg lemborexant were beneficial for the treatment of patients with insomnia, being well tolerated. Adverse effects are considered mild and moderate, the most common being sleepiness, nasopharyngitis, and headache.[176] Sleepiness is the most common adverse reaction reported in 5% or more of patients (10% for 10 mg lemborexant versus 7% for 5 mg lemborexant and 1% for placebo).[182]

Adverse reactions considered uncommon (incidence $<2\%$) were sleep paralysis (1.6% and 1.3% for 10 mg and 5 mg, respectively), hypnagogic hallucinations (0.7% and 0.1% of patients who received 10 mg and 5 mg, respectively), compared with no reports of patients receiving placebo. Although rare, complex behaviors during sleep have been reported with the use of lemborexant at a dose of 10 mg.[182]

Observations

1) DORAs are not available in Brazil, sofar, but are expected to be launched. 2) Like most data and studies presented in this guideline, very rare studies evaluated patients with comorbid insomnia. Therefore, caution should be taken in

extending these results to this population. 3) Drug interactions between DORAs and antidepressants may occur, and suicide risk in serious patients has not been well evaluated. 4) This class of hypnotic is contraindicated for the treatment of insomnia in patients with narcolepsy.

Melatoninergic Agonists

Melatoninergic receptor agonists, represented in Brazil by Ramelteon, are an approved class for the treatment of insomnia, acting as a chronohypnotic.

Mechanism of action: They are sleep promoters acting on the sleep-wake cycle by stimulating melatonin receptor (MT) MT1 (attenuating the alert signal in the suprachiasmatic nucleus) and the MT2 receptor (synchronizing the circadian clock).[183] Although there are no direct comparison studies, there is evidence from experimental data that ramelteon is 3 to 16 times more powerful than melatonin.[184]

Available presentations: Ramelteon is available in 8 mg doses. Ramelteon is absorbed rapidly; therefore, its low bioavailability is due to the extensive first-pass metabolism, with cytochrome p450 being the largest isoenzyme involved in the liver metabolism of Ramelteon – which is highly lipophilic and allegedly spread quickly to tissues including CNS. Its half-life is 1 to 2.6 hour.

Patient assessment: Ramelteon can be indicated for adult patients with sleep-onset insomnia.

Therapeutic planning: The recommended administration is one tablet a day, 30 minutes before bedtime (considering that the patient should adopt a regular sleep pattern). The tablet should not be broken, and there is no evidence of the need to adjust doses for specific cases.

Expected outcomes: To date, there are two systematic reviews[185,186] (one of them with meta-analysis [185]) and several randomized studies lasting up to 12 months of treatment that evaluated the effect of ramelteon on insomnia.[187–198] In that meta-analysis, Kuriyama and colleagues[185] reported 13 studies involving > 5,800 patients with insomnia or insomnia symptoms with an average follow-up duration of 38 days. Ramelteon was associated with reduced sleep latency (a weighted average difference of 4.30 minute [95% CI, 7.01 to 1.58]) and improved sleep quality, but was not associated with subjective TST increase. Ramelteon has also been associated with improving persistent sleep latency (time from lights off to the first sleep lasting at least 10 minutes), improving sleep efficiency, and objective TST.

Drug interactions, contraindications, and side effects: When co-administered with ramelteon, fluvoxamine (strong CYP1A2 inhibitor) significantly increased the concentration and half-life when compared with ramelteon administered alone. Thus, ramelteon and fluvoxamine should not be co-administered. Ramelteon should be administered with caution in patients taking other CYP1A2 inhibitors (such as ciprofloxacin), as well as CYP3A4 inhibitors (such as ketoconazole), and CYP2C9 inhibitors (such as fluconazole).

This medicine should not be used by pregnant women as there are no adequate and well-controlled studies under these conditions. The use of this medicine in women who are breastfeeding is also not recommended. Similarly, the use of ramelteon is not recommended in children and adolescents due to the lack of studies focused on these populations.

The most common adverse events seen with ramelteon, with at least one difference in incidence with 2% placebo, were sleepiness (5% versus 3% placebo); dizziness (5% versus 3% placebo), and fatigue (4% versus 2% placebo). Although very rare, there are reports of serious allergic reactions such as angioedema with the use of ramelteon.

Other considerations: 1) Toxicity and relatively low abuse potential compared with other hypnotic agents[199]; 2) Evidence of safety with more prolonged use and no evidence of rebound insomnia in 12-month-use studies[189]; 3) Safety in older patients and patients with comorbidities such as chronic obstructive pulmonary disease (COPD)[200,201] and mild to moderate OSA,[202] without worsening their severities (including hypoxemia).

Melatonin

Endogenous melatonin (N-Acetyl-5-metoxytryptamine) is a neurohormone synthesized mainly in the pineal gland and known for its chronobiotic effects. Melatonin biosynthesis has a circadian rhythm, being synchronized by the light/dark cycle by the suprachiasmatic nuclei. During the night, the absence of light allows the activation of noradrenergic neurons that stimulate the production of melatonin in the pineal gland. During the day, the luminous stimulus activates the retinal-hypothalamic tract that projects an inhibitory signal for these noradrenergic neurons, limiting the production of the molecule. Thus, endogenous melatonin acts as a marker of the dark phase, synchronizing biological functions to the day/night cycle.[203,204]

Exogenous melatonin has been marketed for ~30 years, being a chronobiotic suitable for circadian rhythm disorders.[205] However, melatonin has erroneously become one of the most used substances in the world to induce sleep.[206]

Mechanism of action: Endogenous melatonin and exogenous melatonin act on the sleep-wake cycle by stimulating the MT1 receptor (attenuating the alert signal in the suprachiasmatic nucleus) and the MT2 receptor (synchronizing the circadian clock).[203,204]

Available presentations: Exogenous melatonin is marketed in various presentations in the forms of immediate-release tablets (2 mg, 3 mg, 5 mg, and 10 mg), sublingual use tablets (0.21 mg) and drops (0.21 mg/drop), and the molecule is available for formulation in compounding pharmacy. marketing in the form of drops (0.21 mg/drop and 0.20 mg/6 drops) has been approved in Brazil.

In oral immediate-release formulations, exogenous melatonin reaches maximum plasma concentration in ~50 minutes and bioavailability is low and variable. Metabolism is hepatic by the p450 system and excretion is urinary. The half-life is ~60 minutes (40 minutes - 2 hours).[207,208]

Patient assessment: There is no consistent evidence supporting melatonin use to treat insomnia in healthy young adults. Although evidence is not robust, melatonin can be indicated in the management of insomnia in older adults and children with autistic spectrum disorder. Melatonin has

proven effective in the management of circadian rhythm disorders.

Therapeutic planning: There is no recommended therapeutic planning for the use of melatonin in chronic insomnia in adults since there is no proven effectiveness.

Expected outcomes: There are three systematic reviews[186,209,210] and some recent randomized studies that evaluated the effect of melatonin on insomnia in adults.[211–213] The results are heterogeneous, encompassing effects on reduced sleep latency,[209] reduced sleep latency only in older people,[212] increased TST in comorbid insomnia,[186] reduced early waking,[213] and even the absence of effectiveness.[213,214]

There is evidence suggesting that melatonin can effectively treat chronic insomnia in children with neurological diseases, especially autism and attention-deficit/hyperactivity disorder (ADHD), as well as older adults. However, a broader assessment of possible long-term consequences is still needed.[213–217]

Drug interactions, contraindications, side effects: Exogenous melatonin administration is considered quite safe in relation to potential drug interactions, risk of intoxication, abuse potential, and significant short and medium-term side effects.[206] The most common adverse events reported are headaches and sleepiness.[207]

Exogenous melatonin should not be used by pregnant women as it crosses the placental barrier, and there are no adequate and well-controlled studies under these conditions. The use of this medicine in women who are breastfeeding is likewise not recommended.

Clinical observations: As a chronobiotic, exogenous melatonin delays or advances phases in the sleep-wake cycle, depending on the time when it is administered. Delayed phases can occur if it is ingested around the end of the usual sleep period, and advanced phases when ingested 3 to 5 hours before the usual sleep onset.[218,219]

Other considerations: In some countries, including in Brazil, exogenous melatonin has been released by regulatory agencies as a food supplement and is therefore not subject to the same quality rules of drugs. In 2017, after testing 30 different types of exogenous melatonin sold in Canada, Erland and Saxena reported disagreements between label specifications and formulation content – large differences in the actual amount of melatonin, presence of serotonin in 26% of formulations, addition of herbal extracts and variations between lots of the same manufacturer.[220]

Antidepressants

The use of sedative antidepressants to treat chronic insomnia is widespread, but none is approved for insomnia by ANVISA. Hence, its prescription is considered off-label and based on scientific evidence of non-systematized trials, which limits the power of generalizing their effectiveness.[221,222] This unlicensed medicine use can be motivated by concern for the prolonged use of hypnotics and the limited availability of psychological treatments. Although few studies evaluate the effect of antidepressants on insomnia symptoms, with limited sampling, short-term follow-up, and design limitations, the long-term safety profile of antidepressants makes them empirically chosen, instead of other medications, for the treatment of chronic insomnia.[221,222] High-quality antidepressants for insomnia treatment are required. It is important to clarify that indicating the use of sedative antidepressants to treat insomnia is independent of the presence of psychiatric comorbidity and that the doses used for this purpose are significantly lower than those originally recommended to treat depression.[20,223]

Doxepin

Mechanism of action: Tricyclic antidepressant, whose mechanism of action as an antidepressant is to block the reuptake of monoaminergic neurotransmitters for pre-synaptic terminals, having anticholinergic activity and modulating the antagonism of histamine (H) H1 and H2[221] receptors. Due to the very high affinity of doxepin by the H1 receiver, its effect as a selective antagonist of the H1 receiver can be ensured when used at low doses and promoting its hypnotic action (1 to 6 mg of doxepin as a hypnotic, compared with 150 to 300 mg of doxepin as an antidepressant).[221] In addition, doxepin is actually a mixture of two chemical forms, one of which (and its active metabolites) has a shorter half-life (8 to 15 hour) than the other, which has the traditionally long half-life tricyclic antidepressants (24 hour). From a functional point of view, the mix of the two agents means that their night administration produces substantially lower residual drug plasma levels in the morning, thus reducing possible residual daytime effects.

Available presentations: Doxepin is available in Brazil only for compounding in registered pharmacies upon specific prescription. As it is an FDA-approved drug for insomnia treatment, the usually recommended dose should be that of the same industrialized presentation in the United States – i.e., 3 and 6 mg.[19,20]

Patient assessment: Due to pharmacokinetic characteristics, doxepin can be indicated for different clinical insomnia phenotypes in adults and can, therefore, be used in sleep-onset and maintenance insomnia and early waking.[19,20,221] There are no specific contraindications for different age groups and can also be used in adults over 65 years.[222,223]

Therapeutic planning: The recommended initial dose is 3 mg used ~30 minutes before the planned sleep onset time.[19,20,221] In the absence of response in the first weeks, the dose should be raised to 6 mg.[221] The recommended therapeutic dose for adults over 65 is 3 mg.[221] Patients should be suggested to allow for ~7 hours of sleep to avoid residual morning sleepiness, at least in the first nights of treatment. Unfortunately, there is no evidence in studies or guidelines recommending the time of use to treat chronic insomnia. Due to its exclusively compounding presentation in Brazil, pharmacokinetic characteristics will be potentially different from those found in the industrialized presentation[222] (doxepin Tmax occurs 3.5 hours after oral administration; it has liver metabolization with renal elimination of inactive metabolites; apparent terminal half-life (t½) of doxepin is 15.3 hours).

Expected outcomes: Five studies have compared doxepin with placebo,[224–228] using doses between 1 and 6 mg, revealing a moderate improvement in the subjective quality of sleep compared with placebo, improved sleep efficiency, increased TST, and discreet impact on sleep latency, with better responses in the 6 mg dose.[224–228] The systematic review published in 2015 with RCTs comparing doxepin with placebo[229] concluded that doxepin had a mean effect size compared with placebo for sleep maintenance and sleep duration, without significant residue the next day, being considered safe and effective, particularly for maintenance insomnia, to improve sleep in short-term evaluations.[229]

Drug interactions, contraindications, side effects, and observations: In adults over 65 years old, side effects were similar to those of placebo and included sleepiness (8–9%), nausea (4–5%) and dizziness (2%).[223] There are no association reports with complex sleep behaviors or memory impairment in older patients treated with doxepin.[223] Drug interactions may occur with cytochrome inductors and inhibitors, considering that it is metabolized by CYP2C19 and CYP2D6. Patients with decreased renal function may have delayed doxepin clearance, leading to prolonged sedation.[223] Its use in the third trimester of pregnancy may increase the risk of neonate poor adaptation symptoms (respiratory discomfort, temperature instability, diet difficulties, hypotonia, tremor, irritability); use during breastfeeding is not recommended; use in children is not recommended, as safety and effectiveness have not been evaluated.[221,223] Attention must be paid to the dose scaling in patients with liver failure or a tendency to urinary retention.[221,223] Unlike other tricyclic antidepressants, doxepin does not pose a risk of worsening symptoms of restless leg syndrome or periodic limb movement disorder.[230]

Other considerations: 1) no evidence supports long-term effectiveness (up to 5 weeks); 2) Safe, low-toxicity medicine, without evidence of abuse behaviors; 3) Considering doxepin tests as an antidepressant, it is a usually safe medication in clinical comorbidities; 4) Doxepin is not recommended for pregnant or breastfeeding women, as well as children and adolescents.

Agomelatine

Mechanism of action: It is an antidepressant whose mechanism of action is its performance as an agonist in MT1 and MT2 receptors and antagonist actions in histaminergic (H) receptors 5H2c.

Available presentations: It is available in Brazil in 25 mg coated tablets.

Patient assessment: There are no RCTs with any methodology assessing agomelatine specifically in the treatment of insomnia without comorbidities. Some publications evaluate the outcomes of sleep quality in patients with depression treated with agomelatine.[221,231,232] Thus, there are no specific recommendations for the evaluation of patients with insomnia treated with agomelatine.

Therapeutic planning: The 25 mg initial dose to treat depression with agomelatine should be recommended when going to bed, planning to increase doses to 50 mg when going to bed after 4 weeks, in the persistence of depressive symptoms.

Expected outcomes: A 24-week, double-blind, controlled randomized study evaluated the efficacy of agomelatine and escitalopram in depression and subjective sleep perceptions in patients with major depression. It reported a subjective improvement in sleep-onset latency but did not find differences between escitalopram and agomelatine in relation to sleep latency in 12 and 24 weeks.[232] A review that brought together the results of three randomized studies comparing agomelatine with selective serotonin reuptake inhibitor antidepressants or venlafaxine established that agomelatine increases slow-wave sleep, improves sleep efficiency in patients with major depressive disorder while not changing REM sleep amount or latency.[233]

Drug interactions, contraindications, side effects, and observations: Agomelatine is metabolized by cytochrome p450 1a2 (CYP1A2) (90%) and CYP2C9/19 (10%). Other medications that interact with these isoenzymes may decrease or increase the bioavailability of agomelatine. It should not be used in association with other medicines such as fluvoxamine, estrogens, and ciprofloxacin, as they can modify their serum level, as well as propranolol, and exaggerated smoking.[223] At the 25 mg dose, the average maximum concentration was $\sim$4 to 13 times higher for patients aged $\geq$ 75 years compared with patients aged $<$ 75 years. This medicine is contraindicated in the presence of liver failure with transaminases greater than three times the upper limit of the normal interval, as well as in children and adolescents. It should be avoided in pregnancy and breastfeeding.

Other considerations: When used in the treatment of major depression, agomelatine can improve subjective and objective sleep parameters when compared with other antidepressants.

Trazodone

Mechanism of action: The effect of trazodone as a hypnotic is due to its moderate antihistamine activity in the H1 receptor, and its partial agonism in the hydroxytryptamine receptor (HT) 5HT1a.[233] As an antidepressant, it promotes 5HT1C and 5HT2 receptor antagonism and post-synaptic a1-adrenergic receptor antagonism.[221,233] It also exerts relatively weak, although specific reuptake inhibition, acting on the 5-HT carrier. Thus, trazodone is classified as serotonin antagonist 2A/2C and serotonin reuptake inhibitor. Trazodone doses lower than those effective for antidepressive action are often used for the effective treatment of insomnia. Low doses explore powerful trazodone action as 5HT2a antagonist, as well as its properties as an antagonist of H1 and α1-adrenergic histamine receptors, but do not adequately explore their properties of serotonin carrier inhibition or 5HT2C receptors, which are weaker.[221,231]

Available presentations: Trazodone is available in 50 mg and 100 mg immediate-release and 150 mg and 300 mg extended-release presentations. Importantly, extended-release presentations minimize the known sedative effect of the drug.[221,231]

Patient assessment: Considering the pharmacokinetic characteristic of immediate-release trazodone, it can be recommended to treat different clinical presentations of chronic insomnia: sleep-onset and maintenance insomnia and early waking.[79,221,234,235] It is not recommended for use in children under 18, as safety and effectiveness have not been determined. It can be used in adults over 65 but with lower doses.[221,231]

Therapeutic planning: Recommended therapeutic doses of trazodone to treat insomnia are in the interval between 50 and 100 mg taken near going to bed, with an expanded interval of doses between 25 and 150 mg when lying down.[221,231,234,235] The time to take trazodone for sleep-onset insomnia should be individualized, usually between 30 and 90 minutes before bedtime. Trazodone half-life is ~7 hour after oral administration and has linear pharmacokinetics within the dosage range of 50–150 mg/day.[231] Its absorption is irregular in fasting individuals, but improves when taken after meals, although no differences were found in the total amount of trazodone absorbed with and without food: its bioavailability values.[231] It is metabolized mainly by the hepatic enzyme CYP3A4 and inhibition of this enzyme by other drugs leads to high blood levels of trazodone.[231]

Expected outcomes: A relevant number of RCTs are available evaluating trazodone in the treatment of insomnia, compared with placebo or other hypnotic medications, as well as CBT-I.[79,234,235] A meta-analysis published in 2018[234] specifically evaluated the role of trazodone in the treatment of insomnia in placebo-controlled randomized studies and included seven studies involving 429 patients. Patients receiving trazodone perceived better subjective quality of sleep than those who received a placebo,[234] as well as a significantly reduced number of wakes throughout the night with trazodone, compared with placebo. No important differences were found for sleep latency or TST between trazodone and placebo.[234] A systematic review and meta-analysis published in 2022 evaluated the effect of trazodone on PSG objective findings in insomnia patients. It included 11 studies, evaluating a total of 466 patients.[235] Compared with the control group, trazodone significantly increased TST and stage 3 (NREM sleep), significantly reducing sleep-onset latency, stage 1 time (NREM sleep), the number of wakes, and WASO.[235]

Drug interactions, contraindications, side effects, and observations: There are reports of changes in coagulation exams in patients receiving warfarin and trazodone.[231,236] Concomitant use of antihypertensive can cause an important drop in blood pressure. There are reports of increased concentrations of digoxin and phenytoin in the blood of patients who received trazodone along with one of these medications.[231,236] It is not recommended for patients recovering from a myocardial infarction.[231,236] Trazodone is associated with the occurrence of priapism (prolonged or inadequately lasting erections),[221,231,236] with a risk of occurrence in 1 per 6,000 patients treated with trazodone.[231,236]

Other considerations: 1) Trazodone should be considered in the treatment of the comorbidity between insomnia and OSA, due to its safety profile.[235] 2) Trazodone is not recommended for pregnant or breastfeeding women, as well as children and adolescents.

Amitriptyline

Mechanism of action: Amitriptyline is commonly used off-label for insomnia because of its sedative properties. Like other tricyclic antidepressants, its antidepressant action mechanism is to block reuptake bombs of serotonin and norepinephrine neurotransmitters. Sedative properties are caused by antagonism on muscarinic-cholinergic receptors, α1-adrenergic, and histaminergic, being present in low doses such as 10 mg. The antidepressant effect requires doses greater than 75 mg/day to recruit serotonergic and noradrenergic receptors.[237]

Available presentations: Amitriptyline is available in 10 mg, 25 mg, and 75 mg tablets.

Patient assessment: No RCT has assessed amitriptyline to treat specifically insomnia with no comorbidities. Therefore, there are no specific recommendations for the evaluation of patients with insomnia in treatment with amitriptyline.

Expected outcomes: There are no systematic reviews, meta-analyses, or randomized studies that specifically evaluated the effect of amitriptyline on insomnia without psychiatric comorbidities. Studies with objective research with PSG conducted in patients with major depression undergoing amitriptyline treatment had reduced sleep latency, fewer night wakes, and increased sleep efficiency.[238–240] It is important to emphasize that tricyclic antidepressants suppress REM sleep and are associated with the triggering or aggravation of periodic limb movements, restless leg syndrome, and REM sleep behavioral disorder.[237] Considering its pharmacokinetic and pharmacodynamic characteristics, the sedative effect of amitriptyline occurs with doses considered subtherapeutic for depression, around 25 and 25 mg used near the intended time for sleep.

Drug interactions, contraindications, and side effects: Amitriptyline is metabolized in the liver by cytochrome p450 2D6 enzymes. Combined use of amitriptyline with other nervous system depressors increases the risk of sedation to ataxia. Oral contraceptives, selective serotonin inhibitors, antipsychotics, and acetylsalicylic acid reuptake increase the serum levels of amitriptyline. Use with medications that extend the QT interval should be avoided due to the synergistic effect of amitriptyline in this condition. The main side effects of amitriptyline are dry mouth, constipation, increased appetite, postural hypotension, sedation, dizziness, blurred vision, reduced sexual drive, cognitive deficit, heart conduction abnormalities, reduced seizure threshold, and blurred vision. Amitriptyline is contraindicated for patients with acute myocardial infarction, cardiac conduction disorders, prostatism or urinary retention, paralytic ileum, closed-angle glaucoma, and concomitant use of monoaminoxidase inhibitors. Use in pregnancy should be avoided in the first trimester, and the risk-benefit must be assessed in cases of severe depression. Use during breastfeeding is safe.

Other considerations: 1) Due to the evidence that antidepressant amitriptyline treatment reduces sleep latency and night waking and increases sleep efficiency, it may also be useful to treat insomnia, in off-label conditions, if no other pharmacological options with robust scientific evidence are available.

Mirtazapine

Mechanism of action: Mirtazapine is an antidepressant antagonist of presynaptic α2-noradrenergic self-receptors and α2-serotoninergic hetero-receptors, acting on the disinhibition of synaptic release of noradrenaline and serotonin. In addition to stimulating the release of serotonin and noradrenaline, mirtazapine is an antagonist of the 5HT2A and H1 postsynaptic receptors, with effects associated with increased slow-wave sleep and sedation, respectively.[241] Antidepressant doses range from 30 to 60 mg/day, and the sedative effect is more pronounced with lower doses (7.5–15 mg); doses greater than 30 mg are less sedative due to the largest noradrenergic effect. Its half-life ranges from 20 to 40 hours and may cause residual sedation.[241,242]

Available presentations: 15, 30, and 45 mg orodispersible and coated tablets.

Patient assessment: No RCT has assessed mirtazapine specifically to treat insomnia with no comorbidities, Hence, there are no specific recommendations for the evaluation of patients with insomnia in treatment with mirtazapine.

Expected outcomes: In a double-blind, placebo-controlled RCT with healthy volunteers, the effects of 7.5 mg mirtazapine and 50 mg quetiapine were comparatively evaluated, both in normal sleep and sleep disturbed by acoustic stress (traffic noise) as a model for transient insomnia.[243] Under acoustic stress, both mirtazapine and quetiapine increased TST by half an hour and reduced the number of wakes by 35–40% compared with placebo. While quetiapine specifically increased the duration of stage N2, mirtazapine mainly increased stage N3. Individuals reported that both mirtazapine and quetiapine facilitated sleeping and improved sleep quality. Both drugs caused daytime sleepiness and diminished sustained attention.[243] Studies with clinical samples of depressed patients using mirtazapine show increased sleep, reduced latency, increased TST, reduced waking, increased efficiency, and increased slow-wave sleep.[244–246]

Drug interactions, contraindications, side effects: Mirtazapine is a substrate of cytochrome enzymes p450 1 A2, 2 D6, and 3 A4 and weakly inhibits 1A 2 and 3A4. Sedation is increased when mirtazapine is used in association with other CNS depressors. The combination of mirtazapine with other antidepressants such as selective serotonin reuptake inhibitors should be avoided due to the risk of serotonergic syndrome. Mirtazapine may increase the appetite, raise triglyceride cholesterol levels and liver enzymes, and cause dry mouth, constipation, excessive sedation, dizziness, nightmares, vivid dreams, and restless leg syndrome.

Other considerations: 1) Considering small studies, particularly with evidence that antidepressant treatment with mirtazapine improves different sleep parameters in patients with comorbid insomnia, it may also be useful to treat insomnia in off-label conditions, if no other pharmacological options with robust scientific evidence are available. Long-elimination half-life can cause residual sleepiness with cognitive and motor deficits. Avoid using it in patients with metabolic disorders due to the potential risk of weight gain.

Antipsychotics

Both typical and atypical antipsychotics differ regarding the affinity in receptors and the predominance of action in different pathways, such as the nigra-striatal, mesolimbic, mesocortical, and tuberoinfundibular ones. Thus, one can understand the various profiles of adverse effects such as sedation, hypotension, extrapyramidal symptoms, dystonia, hyperprolactinemia, and so on, which should be considered when prescribing medications of this class. Phenothiazines, such as chlorpromazine and levomepromazine, tend to cause sedation as an adverse effect, but this is not sufficient to indicate them to treat insomnia, in the absence of scientific evidence that promotes this support.[19,20,247] Considering atypical antipsychotics, a 2023 meta-analysis evaluated eight controlled RCTs on the impact of the use of this class of sleep drugs during the treatment of schizophrenia.[247] The findings indicate that among the antipsychotics, olanzapine, quetiapine, risperidone, and ziprasidone were associated with a significant increase in insomnia symptoms, concluding that clozapine is less associated with insomnia compared with other antipsychotics.[247] In guidelines for the treatment of insomnia without psychiatric comorbidities, few studies are available assessing the use of antipsychotics, limiting orientations due to the scarcity of data.[19,20,128] In recent years, there has been an increase in studies assessing the effect of quetiapine on sleep and its possible role in the treatment of insomnia,[243,248–250] which is why we will discuss this medication and its role in the treatment of insomnia below.

Quetiapine

Mechanism of action: It has a high affinity with 5-HT2a receptors. Regarding dopamine receptors, it has a relatively lower affinity with D2 and D receptors compared with antipsychotic-standard agents and a high affinity with D4 receptors. It has affinity with histaminergic and α-1adrenergic receptors and lower affinity for adrenergic α-2 receptors and 5-HT1a serotonin receptors. Quetiapine resembles other second-generation antipsychotics but has particular affinity by different CNS receptors in a dose-dependent way. Low doses have a predominance of action in H1, α-1adrenergic, and α-2 receptors by mediating sedative action. In intermediate and high doses, affinity is added by serotonergic receptors (5-HT1a, 5-HT2a, 5-HT2b, 5-HT2c) and dopamine D2 receptors providing mood stabilization, anxiety and psychosis improvement.[251]

Available presentations: Quetiapine is available in the form of immediate-release 25 mg, 100 mg, 200 mg, and 300 mg tablets and extended-release 50 mg, 200 mg, and 300 mg tablets.

Patient assessment: Due to pharmacokinetic characteristics, quetiapine could be indicated for different forms of

insomnia presentation in adults and can, therefore, be used in sleep-onset and maintenance insomnia and early waking.[19,128,248,250] Given its adverse effects profile, its prescription to adults over 65 years should be avoided or performed more carefully.[128,250] However, there is an evident need for further studies using it as a treatment of insomnia without psychiatric comorbidities[249,252] and assessing the safety profile of adverse effects using long-term low quetiapine doses.[252]

Therapeutic planning: The possibly recommended administration for the treatment of insomnia is once a day, close to bedtime, between 25 and 100 mg/day.[243,248–250] After oral administration, rapid absorption occurs, reaching peak serum concentration in 1.2 to 1.8 hour, and its bioavailability is not significantly affected by food intake. It is metabolized in the liver by CYP 3 A 4, and its elimination half-life is ~6–7 hour. The elimination occurs through renal (73%) and fecal (27%) routes.

Expected outcomes: Quetiapine has been approved by the FDA for the treatment of schizophrenia and manic episodes and as an adjuvant treatment for major depressive episodes. Quetiapine has been used, in off-label prescription, to treat insomnia, and studies have evaluated the effectiveness of treatment and sleep impact.[243,248,249] In 2010, an RCT evaluated the use of 25 mg quetiapine at night for the treatment of primary insomnia.[250] In this study, there was no statistically significant difference in sleep parameters such as TST and sleep latency in relation to the placebo group.[250] Since then, other studies have been developed. A review published in 2009 suggested that quetiapine could reduce sleep-onset latency and improve TST and sleep efficiency in patients with psychiatric disorders, but findings are still insufficient to propose it as a pharmacological option in the treatment of insomnia without psychiatric comorbidities.[248] Meta-analysis results published in 2023 point out that quetiapine, in doses lower than those used in the treatment of schizophrenia or acute manic episodes, effectively managed insomnia.[249] However, the authors point out that long-term effectiveness and safety need to be investigated, especially in groups of patients without psychiatric disorders.[249] According to a meta-analysis, doses ranging from 50–150 mg/day are recommended, particularly for symptoms of insomnia in comorbidity with generalized anxiety disorder and major depressive episodes.[249]

Drug interactions, contraindications, and side effects: Compared with other medications of the same class of antipsychotics, quetiapine is less associated with dystonia and extrapyramidal symptoms, but may promote weight gain, metabolic syndrome, and QT interval prolongation.[252] The body mass index, weight, blood pressure, fasting blood glucose, and lipid profile before starting treatment should be monitored in patients who use it, following control regularly.[251] During concomitant administration of potential CYP3A4 inhibitor drugs (such as blue antifungals, macrolide antibiotics, and protease inhibitors), their plasma concentrations may be significantly increased as observed in patients in clinical studies.[252] Long-term safety data on quetiapine treatment are not available for children and adolescents.[252]

Other considerations: 1) Despite the further cited and recently developed studies, other ones are needed with more individuals, evaluating the effect of continuous treatment and response profile in insomnia without comorbidity; 2) it is always necessary to consider risks associated with adverse effects when prescribing antipsychotic for other purposes; 3) the safety and effectiveness of quetiapine were not established for children and adolescents (10 to 17 years old); 4) the safety and effectiveness of quetiapine during human pregnancy were not established; 5) there are reports on the excretion of quetiapine in breast milk during breastfeeding. However, the level of excretion was not consistently detectable at low doses such as those used to treat insomnia. According to records in the package leaflet of manufacturing industries, women who are breastfeeding should be advised to prevent breastfeeding while using quetiapine. Still, the Center for Programmatic and Strategic Actions of the Department of Healthcare of the Brazilian Ministry of Health, in its publication on breastfeeding and the use of medicines and other substances,[253] states that the use of quetiapine is compatible with lactation, at the discretion of the prescribing physician, given the risk-benefit assessment.

Anti-epileptic Drugs

The anti-epileptic drugs, previously named anticonvulsants, included in this manuscript are: gabapentin and pregabalin.

Gabapentin

Gabapentin is an anti-crisis medication discovered in the 1970s and approved by ANVISA for the treatment of neuropathic pain in adults and as monotherapy or adjuvant therapy for epilepsy with focal seizures, with and without secondary generalization, in pediatric patients from 12 years and adults. In addition to the above indications, the FDA includes the treatment of post-herpetic neuralgia and moderate to severe restless leg syndrome.

Mechanism of action: Gabapentin has a structure analogous to the inhibitory neurotransmitter (GABA) and, although its mechanism of action is not fully understood, it inhibits the action of α-2delta subunits of the voltage-dependent calcium channels, inhibiting calcium currents and decreasing neuronal excitability.

Expected outcomes: Two studies on the efficacy of gabapentin have been included in this review, both with low-quality evidence. An open clinical study, without a control group, studied 18 patients with chronic insomnia who used gabapentin at a dose of 200 to 900 mg at night (average of 540 mg, most patients taking 600 mg) for 28 days. In this study, improved sleep efficiency, decreased WASO, increased N3, and decreased awakening rate, were reported, as measured with PSG, when compared with pre-treatment data. However, the changes were not statistically significant. There was a significant improvement in PSQI after starting the treatment.[254]

Another double-blind randomized study evaluated 237 adults (placebo: $n = 115$; gabapentin: $n = 122$) with transient

insomnia, defined as at least one night with sleep-onset or maintenance difficulties in the preceding month. This study, with a dose of 250 mg of gabapentin for 28 days at 5 PM (~5 hour on average before the usual time of sleep), showed with PSG on days 1 and 28 a significantly decreased WASO and increased TST. Residual effects during the day after use were not statistically significant. The authors concluded that 250 mg of gabapentin taken on average 5 hour before the usual time of sleep can improve the maintenance and quality of sleep in patients with transient insomnia.[255]

Pregabalin

Pregabalin is approved by ANVISA for the treatment of neuropathic pain, as an adjuvant in the control of focal-onset epileptic seizures with or without secondary generalization, generalized anxiety disorder, and adult fibromyalgia.

Mechanism of action: Pregabalin is an enantiomer analogous to GABA with a mechanism of action similar to gabapentin. No RCT so far has assessed this medication focused on the specific study of chronic insomnia.

Expected outcomes: There are no controlled pregabalin studies for chronic insomnia. A systematic review of gabapentin and pregabalin, also called α-delta ligands or gabapentinoids, for bipolar disorder, generalized anxiety, and insomnia showed inconclusive results in relation to outcomes for insomnia. This review shows that α-delta ligands appear to improve sleep in patients with insomnia associated with clinical conditions such as anxiety and neuropathic pain. However, it is unclear whether improvement occurs by direct or indirect sleep effects. There is moderate evidence of gabapentinoid efficacy in anxiety states and minimal evidence in bipolar disorder and insomnia.[256]

Cannabinoids

Cannabinoids are compounds found in *Cannabis sp*. Since 2019, ANVISA has allowed the registration, importation, marketing, and prescription in the national territory of products derived from cannabis.

Mechanism of action: There are ~100 phytocannabinoids in *Cannabis sp*. Preclinical and clinical studies were done only with Cannabidiol (CBD) and Delta-9-tetrahydrocannabinol (THC). Therefore, we do not know the action of other cannabinoids on human sleep, besides the two described above. CBD has a biphasic action – it promotes alertness in lower doses and sedation in higher ones. Acute THC administration reduces sleep latency, and chronic administration increases sleep fragmentation, WASO, and probably reduced REM sleep.

Available presentations: 18 cannabinoids have been currently approved (ANVISA's Joint Board decisions no. 327/2019 and no. 335/2020). Cannabinoids in Brazil have several presentations: CBD alone (20 mg/mL to 200 mg/ml); extracts containing CBD/THC (0.2% or 0.24% THC); or cannabis extracts containing medicinal cannabinoids without specifications.

Patient assessment: There are no scientific guidelines, even though cannabinoids have been used for the treatment of insomnia with or without comorbidities.

Therapeutic planning: No quality study so far has addressed their effectiveness and safety to guide the posology.

Expected outcomes: To date, there are three systematic reviews with meta-analysis and some randomized studies lasting up to 8 weeks of treatment that evaluated the effect of cannabinoids on insomnia.[257–260] A meta-analysis with 219 adult patients with insomnia, evaluating objective (PSG or actigraphy) and subjective outcomes, showed that the use of cannabinoid, CBD, and THC-analogous extracts, improved PSQI sleep quality by up to 8 weeks.[259] Another meta-analysis, with more than 5,000 patients, evaluated the impact of different cannabinoids on patients with sleep complaints under various medical conditions. It found that a discreet proportion of patients reported an improvement in sleep complaints compared with placebo after the use of cannabinoids, especially in the "cancer" patient subgroup.[257] In the studies described above, it is not known whether the improvement of insomnia stems from anxiolytic effects (CBD), painkillers (Δ 9-TC), or a direct effect on CNS pathways that help regulate sleep. There are also other ongoing studies (for example NCT0534170, NCT05041647, NCT05237037 - https://clinicaltrials.gov/) that can help improve evidence in the upcoming years.[261]

Drug interactions, contraindications, and side effects: Small clinical safety studies were performed only with CBD and CBD/THC extracts.[262] CBD and Δ 9-TC are metabolized in the liver and use the cytochrome p450 pathway and may interact with various drugs that use the same pathway, as well as patients with liver failure. Concomitant use of CBD with valproate increases transaminase levels and the risk of hepatotoxicity, as well as clobazam (with reciprocal interaction). CBD inhibits the enzyme responsible for its degradation by increasing its half-life by 2 times. CBD use is associated with frequent though mild to moderate and self-limited adverse events, such as sedation, epigastralgia, diarrhea, and increased transaminases. THC use, in turn, induces known pleiotropic effects, such as sedation in small doses, euphoria, and even psychotic outbreaks with high doses, which can lead to abuse and abstinence. Regarding other phytocannabinoids and synthetic cannabinoids, their mechanisms of action are still not well understood, as well as their drug interactions, contraindications, and side effects.

Phytotherapeutics

Valeriana (*Valeriana officinalis*)

Mechanism of action: Valerian's most likely mechanism of action involves an agonist role of GABA-A receptors, probably due to GABA's relatively high content in valerian extracts.[263] Recent research also points to adenosine receptor activity as the main contributor to its relaxing and sleep-inducing effects.

Available presentations: It can be found in capsules or tablets or compounding presentations containing valerian extracts (50 to 100 mg).

Patient assessment: There are no scientific guidelines, even though valerian is used to treat insomnia symptoms.

Therapeutic planning: Package inserts suggest 50 to 300 mg standardized Valerian extract administrations, 30 to 60 minutes before going to bed. The tablet should not be broken and there is no evidence of the need to adjust doses for specific cases.

Expected outcomes: A systematic review with meta-analysis demonstrated inconsistent valerian effects, possibly due to the irregularity and variability in the quality of the extracts used. Nonetheless, no significant adverse events were observed in the evaluated populations.[264,265]

Drug interactions, contraindications, and side effects: No residual effects and significant serious adverse events were observed with valerian. Rebound insomnia after its discontinuation was not observed. Herbal or herbal products should not be used by pregnant or breastfeeding women, as there are no adequate and well-controlled safety and toxicity studies in these conditions.

Passiflora (*Passiflora incarnata Linnaeus*)

Mechanism of action: Passiflora extract probably exerts its sedative effect modulating the GABAergic activity.

Available presentations: It can be found in capsules or tablets or compounding presentations containing dry passiflora extracts in variable quantities and with different flavonoid concentrations. It is also available in different liquid formulations.

Patient assessment: There are no scientific guidelines, even though passiflora has also been used to alleviate insomnia symptoms.

Therapeutic planning: No scientific guidelines instruct therapeutic planning.

Expected outcomes: A placebo-controlled, double-blind RCT demonstrated increased TST with PSG in patients with insomnia taking passiflora extracts for 2 weeks.[266]

Drug interactions, contraindications, and side effects: Passiflora possibly enhances the effect of barbiturates, and concomitant use is not recommended. Studies, which are still inconclusive, suggest an interaction with coumarin medications, such as warfarin, and concomitant use is not recommended.

Chamomile (*Matricaria recutita)*

Mechanism of action: Chamomile extract possibly exerts its sedative effects by modulating GABAergic activity.

Available presentations: No formulations are available in capsules, tablets, or liquids in Brazil.

Patient assessment: No scientific guidelines so far indicate the use of chamomile to treat insomnia or comorbid insomnia.

Therapeutic planning: No scientific guidelines instruct therapeutic planning with chamomile.

Expected outcomes: A placebo-controlled RCT used chamomile but did not find significant effects in comparison with the placebo group.[267]

Drug interactions, contraindications, and side effects: chamomile did not have more adverse effects than the placebo group in the abovementioned RCT.

Ashwagandha (*Withania somnifera L. Dunal*)

Mechanism of action: Ashwagandha possibly exerts its sedative effects by modulating GABAergic activity.

Available presentations: Compounding presentations can be found in capsules with 300 mg ashwagandha root extract.

Patient assessment: No scientific guidelines so far indicate the use of ashwagandha to treat insomnia disorders or comorbid insomnia.

Therapeutic planning: No scientific guidelines instruct therapeutic planning.

Expected outcomes: A placebo-controlled, double-blind RCT demonstrated the effects of ashwagandha to treat insomnia. There were improvements in actigraphy parameters (TST, sleep latency, sleep efficiency, and WASO), sleep quality, and anxiety scores.[268]

Drug interactions, contraindications, and side effects: No significant adverse effects have been described from using ashwagandha extract.

Mulungu (Erythrina mulungu)

Mechanism of action: The mechanism of action of mulungu has not been described yet.

Available presentations: Compounding presentations can be found in capsules with various doses (200 mg is the most common) of mulungu bark extract.

Patient assessment: No scientific guidelines so far indicate the use of mulungu to treat insomnia or comorbid insomnia.

Therapeutic planning: No study has suggested therapeutic planning.

Expected outcomes: No study has assessed the effect of mulungu on any sleep-related outcome.

Drug interactions, contraindications, and side effects: No significant adverse effects have been described by using mulungu extract.

5.10. Others

Various other medications and dietary supplements are used as treatments for insomnia symptoms, some of which are common in popular use and without a prescription. Medications in this category generally induce sleepiness as a side effect parallel to their primary use and are not formally indicated for the treatment of insomnia by any international guideline. This condition includes antihistamines (including diphenhydramine, promethazine, and hydroxyzine) and antiemetics (such as dimenhydrinate). Supplements are often based on pharmacological assumptions, including precursors of related hormones or analogs of sleep-related neurotransmitters (such as tryptophan and GABA). Specific information on antihistamines is described below, as they are the most representative medications in this category.

Antihistamines

Antihistamines, designed to treat allergies, were developed from anticholinergic medications more than 70 years ago. Over the years and with the emergence of new classes of

antihistamines, they have been divided into first and second generations according to their pharmacokinetic properties, structural characteristics, and adverse effects. First-generation antihistamines are known to have sedation and anticholinergic effects. Second-generation drugs have few adverse effects due to their high affinity for H1 receptors, low passage through the blood-brain barrier, and little or no anticholinergic effect.[269,270] The sedative effect of first-generation antihistamines led to popular dissemination as over-the-counter drugs for the treatment of insomnia despite the lack of scientific evidence of efficacy and safety. The antihistamines selected for this article were diphenhydramine, promethazine, hydroxyzine, and dimenhydrinate, which are first-generation drugs.

Mechanism of action: They act as inverse agonists rather than H1 (histamine) receptor antagonists. The effects on the CNS are basically determined by its ability to cross the blood-brain barrier and bind to central H1 receptors. The ability to cross the blood-brain barrier will depend on the lipophilic quality of the molecule and affinity with P-glycoprotein. Furthermore, it has anticholinergic, α-adrenergic, and serotonergic actions.[269]

Most antihistamines available for oral administration in Brazil have a long half-life, such as hydroxyzine (20–25 hours) and promethazine (16–19 hours). Compared with the previous ones, oral diphenhydramine (not available) has a shorter half-life (6–9 hours).

Expected outcomes: Due to the lack of well-designed studies, expected outcomes for insomnia are not adequately quantified.[271,272] Off-label use of this class can generate residual symptoms the next day and compromise everyday situations (reflexes, ability to drive, etc.).

Drug interactions, contraindications, side effects: Common adverse effects (1 to 10%) include daytime sleepiness, fatigue, impaired attention, vigilance, working and sensory memory, motor performance, and anticholinergic symptoms (insomnia, tremors, nervousness, irritability, palpitation, blurred vision, constipation, retention urinary tract, tachycardia, xerostomia, and dry throat and nose).

CNS-damaging effects of first-generation antihistamines cause impaired performance in children and impaired ability in adults to work, drive, and pilot aircraft. The association with alcohol or CNS depressants such as hypnotics causes additive sedation effects. Concomitant use with MAO inhibitors prolongs and intensifies the anticholinergic effects of antihistamines. Antihistamines may increase the arrhythmogenic effect of psychotic agents and should be used with caution in patients with narrow-angle glaucoma. Smaller doses in addition to cautious use are recommended in the elderly due to the greater potential for anticholinergic effects and sedation. Dosages should be reduced in liver failure.

Final Considerations

In recent years, ABS has been very active in implementing guidelines and recommendations for a multidisciplinary approach to sleep disorders.[273] This document presented the current evidence for the diagnosis and treatment of insomnia in adults after carrying out standardized research processes and discussions and voting sessions. The relevance of an appropriate diagnosis that will guide correct and comprehensive treatment is clear. We highlight CBT-I as the therapy of choice for most patients in this document. We also highlight the evidence for each pharmacological class that is frequently used in the treatment of insomnia disorder or insomnia symptoms. Highlighting selective benzodiazepine receptor agonists (treatment of sleep-onset and maintenance insomnia depending on the presentation), DORAs (treatment of sleep-onset and maintenance insomnia), and melatoninergic agonists (treatment of sleep-onset insomnia) due to a greater number of evidence in favor of their respective uses. We also showed the possibility of treatment with antidepressants in specific situation of insomniacomorbid with mood disorders (although more evidence is still needed).

However, it is important to emphasize that, in clinical practice, we observe little emphasis on non-pharmacological measures offered to patients with insomnia. In fact, CBT-I is often not used, and the health professional/patient binomial ends up placing much of the success on pharmacological treatment, often without a defined plan for the duration of use and/or withdrawal attempts. Furthermore, there is frequent use of off-label substances and non-treatment of comorbid conditions that are clearly influencing the course and severity of insomnia. All these factors have contributed to repeated cases of dependence and abuse of some of the available pharmacological treatments. Thus, we hope that this document can be of great use so that health professionals can improve the care of insomnia, a clinical condition that has multiple individual and societal consequences.

LIST OF ABBREVIATIONS

AASM	American Academy of Sleep Medicine
ABS	Brazilian Sleep Association (*Associação Brasileira do Sono*)
ACT	Acceptance and Commitment Therapy
ACT-I	ACT applied to insomnia
ADHD	Attention-deficit/hyperactivity disorder
AIS	Athens Insomnia Scale
ANVISA	Brazilian National Health Surveillance Agency
BZD	Benzodiazepines
CBD	Cannabidiol
CBT-I	Cognitive-behavioral therapy applied to insomnia
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CYP	Cytochrome p450
DORA	Dual orexin receptor antagonists
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – 5th edition
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
H	Histamine
HT	Hydroxytryptamine

ICD	International Statistical Classification of Diseases and Related Health Problems
ICSD-3	International Classification of Sleep Disorders – 3rd edition
ISI	Insomnia Severity Index
MBCT	Mindfulness-based cognitive therapy
MBCT-I	MBCT applied to insomnia
MT	Melatonin
NREM	Non-REM
OSA	Obstructive sleep apnea
PICO	Population, Intervention, Comparator, and Outcome
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomized clinical trial
REM	Rapid eye movement
THC	Delta-9-tetrahydrocannabinol
Tmax	Maximum concentration time
TST	Total sleep time
UA	Upper airway
WASO	Wake after sleep onset

Conflict of interest
Luciano F. Drager Lectures: Biolab, EMS, Eurofarma, ResMed, and Takeda.
Educational material: EMS and Eurofarma.
Scientific consultancy: ResMed.
Participation in scientific study: ResMed (real-world studies).
Marcia Assis Educational material: EMS, Eurofarma, Mantecorp, Takeda, and Apsen.
Andrea Bacelar Lectures: Eurofarma, Sanofi-Medley, EMS, Apsen, Aché, Resmed, Sandoz, Biolab, Torrent, Momenta.
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References

1 AASM. International Classification of Sleep Disorders. Darien, IL: American Academy of Sleep Medicine; 2014
2 Perlis ML, Posner D, Riemann D, Bastien CH, Teel J, Thase M. Insomnia. Lancet 2022;400(10357):1047–1060
3 Léger D, Bayon V. Societal costs of insomnia. Sleep Med Rev 2010;14(06):379–389
4 Vargas I, Nguyen AM, Muench A, Bastien CH, Ellis JG, Perlis ML. Acute and Chronic Insomnia: What Has Time and/or Hyperarousal Got to Do with It? Brain Sci 2020;10(02):71
5 Riemann D, Benz F, Dressle RJ, et al. Insomnia disorder: State of the science and challenges for the future. J Sleep Res 2022;31 (04):e13604
6 Bacelar A, Conway SG, Assis M, et al. Insomnia symptoms during the covid-19 pandemic: a case-control study. Rev Saude Publica 2023;57(Suppl 1):8s
7 Drager LF, Pachito DV, Moreno CRC, et al. Insomnia episodes, new-onset pharmacological treatments, and other sleep disturbances during the COVID-19 pandemic: a nationwide cross-sectional study in Brazilian health care professionals. J Clin Sleep Med 2022;18(02):373–382
8 Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2023;401(10393):e21–e33
9 Linh TTD, Ho DKN, Nguyen NN, Hu CJ, Yang CH, Wu D. Global prevalence of post-COVID-19 sleep disturbances in adults at different follow-up time points: A systematic review and meta-analysis. Sleep Med Rev 2023;71:101833
10 AlRasheed MM, Fekih-Romdhane F, Jahrami H, et al; COMITY investigators. The prevalence and severity of insomnia symptoms during COVID-19: A global systematic review and individual participant data meta-analysis. Sleep Med 2022; 100:7–23
11 Castro LS, Poyares D, Leger D, Bittencourt L, Tufik S. Objective prevalence of insomnia in the São Paulo, Brazil epidemiologic sleep study. Ann Neurol 2013;74(04):537–546
12 Bollu PC, Kaur H. Sleep Medicine: Insomnia and Sleep. Mo Med 2019;116(01):68–75
13 Morin CM, Jarrin DC. Epidemiology of insomnia - Prevalence, course, risk factors and public health burden. Sleep Med Clin 2013;8:16
14 Leeflang MM, Davenport C, Bossuyt P. Chapter 6: Defining the review question. Draft version (14 January 2022). In: Deeks JJ, Bossuyt PM, Leeflang MM, Takwoingi Y, editors. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. 2 ed. London: Cochrane; 2022
15 Howick J, Chalmers I, Glasziou P et al. The 2011 Oxford CEBM Evidence Levels of Evidence (Introductory Document): Oxford Centre for Evidence-Based Medicine; 2011
16 McPherson S, Reese C, Wendler MC. Methodology Update: Delphi Studies. Nurs Res 2018;67(05):404–410
17 Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for

reporting of Delphi studies. J Clin Epidemiol 2014;67(04): 401–409
18 Humphrey-Murto S, Wood TJ, Gonsalves C, Mascioli K, Varpio L. The Delphi Method. Acad Med 2020;95(01):168
19 Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2017;13(02):307–349
20 Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res 2017;26 (06):675–700
21 Chesson A Jr, Hartse K, Anderson WM, et al; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the evaluation of chronic insomnia. An American Academy of Sleep Medicine report. Sleep 2000;23(02):237–241
22 Baglioni C, Altena E, Bjorvatn B, et al. The European Academy for Cognitive Behavioural Therapy for Insomnia: An initiative of the European Insomnia Network to promote implementation and dissemination of treatment. J Sleep Res 2020;29(02):e12967
23 Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TDClinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med 2016;165(02):125–133
24 Ree M, Junge M, Cunnington D. Australasian Sleep Association position statement regarding the use of psychological/ behavioral treatments in the management of insomnia in adults. Sleep Med 2017;36(Suppl 1):S43–S47
25 Wilson S, Anderson K, Baldwin D, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update. J Psychopharmacol 2019;33(08):923–947
26 Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4(05):487–504
27 Littner M, Hirshkowitz M, Kramer M, et al; American Academy of Sleep Medicine Standards of Practice Committe. Practice parameters for using polysomnography to evaluate insomnia: an update. Sleep 2003;26(06):754–760
28 US Department of Health and Human Services N. NIH state-of-the-science conference statement on manifestations and management of chronic insomnia in adults. 2005. p. 30.
29 Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep 2012;35(02):287–302
30 Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2(04):297–307
31 Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(02):193–213
32 Bertolazi AN, Fagondes SC, Hoff LS, et al. Validation of the Brazilian Portuguese version of the Pittsburgh Sleep Quality Index. Sleep Med 2011;12(01):70–75
33 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(06):540–545
34 Bertolazi AN, Fagondes SC, Hoff LS, Pedro VD, Menna Barreto SS, Johns MW. Portuguese-language version of the Epworth sleepiness scale: validation for use in Brazil. J Bras Pneumol 2009;35 (09):877–883
35 Morin CM, Inoue Y, Kushida C, Poyares D, Winkelman JGuidelines Committee Members Governing Council of the World Sleep Society. Endorsement of European guideline for the diagnosis and treatment of insomnia by the World Sleep Society. Sleep Med 2021;81:124–126
36 Vgontzas AN, Fernandez-Mendoza J. Insomnia with Short Sleep Duration: Nosological, Diagnostic, and Treatment Implications. Sleep Med Clin 2013;8(03):309–322
37 Smith MT, McCrae CS, Cheung J, et al. Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2018;14(07): 1231–1237
38 Ree MJ, Richardson C. Insomnia disorder update: the benefits of screening and treatment for this common presentation. Intern Med J 2021;51(11):1798–1805
39 Ferré-Masó A, Rodriguez-Ulecia I, García-Gurtubay I. [Differential diagnosis of insomnia from other comorbid primary sleep disorders]. Aten Primaria 2020;52(05):345–354
40 Van Someren EJW. Brain mechanisms of insomnia: new perspectives on causes and consequences. Physiol Rev 2021;101 (03):995–1046
41 Dong Y, Yang FM. Insomnia symptoms predict both future hypertension and depression. Prev Med 2019;123:41–47
42 Ostovar-Kermani T, Arnaud D, Almaguer A, et al. Painful Sleep: Insomnia in Patients with Chronic Pain Syndrome and its Consequences. Folia Med (Plovdiv) 2020;62(04): 645–654
43 Xia L, Zhang P, Niu JW, et al. Relationships Between a Range of Inflammatory Biomarkers and Subjective Sleep Quality in Chronic Insomnia Patients: A Clinical Study. Nat Sci Sleep 2021;13:1419–1428
44 Lancel M, Boersma GJ, Kamphuis J. Insomnia disorder and its reciprocal relation with psychopathology. Curr Opin Psychol 2021;41:34–39
45 Bradford DRR, Biello SM, Russell K. Insomnia symptoms mediate the association between eveningness and suicidal ideation, defeat, entrapment, and psychological distress in students. Chronobiol Int 2021;38(10):1397–1408
46 Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. Psychiatr Clin North Am 1987;10(04): 541–553
47 van der Zweerde T, Bisdounis L, Kyle SD, Lancee J, van Straten A. Cognitive behavioral therapy for insomnia: A meta-analysis of long-term effects in controlled studies. Sleep Med Rev 2019; 48:101208
48 Morin CM. Cognitive-behavioral Therapy of Insomnia. Sleep Med Clin 2006;1(03):12
49 Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-analysis. Ann Intern Med 2015;163(03): 191–204
50 van Straten A, van der Zweerde T, Kleiboer A, Cuijpers P, Morin CM, Lancee J. Cognitive and behavioral therapies in the treatment of insomnia: A meta-analysis. Sleep Med Rev 2018; 38:3–16
51 Krieger T, Urech A, Duss SB, et al. A randomized controlled trial comparing guided internet-based multi-component treatment and internet-based guided sleep restriction treatment to care as usual in insomnia. Sleep Med 2019;62:43–52
52 Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2021;17(02):255–262
53 Gao Y, Ge L, Liu M, et al. Comparative efficacy and acceptability of cognitive behavioral therapy delivery formats for insomnia in adults: A systematic review and network meta-analysis. Sleep Med Rev 2022;64:101648
54 Simon L, Steinmetz L, Feige B, Benz F, Spiegelhalder K, Baumeister H. Comparative efficacy of onsite, digital, and other settings for cognitive behavioral therapy for insomnia: a systematic review and network meta-analysis. Sci Rep 2023;13 (01):1929
55 Ruan J, Chen S, Liang J, et al. Acceptance and commitment therapy for insomnia and sleep quality: A systematic review and meta-analysis. J Contextual Behav Sci 2022;26:16

56 Chen TL, Chang SC, Hsieh HF, Huang CY, Chuang JH, Wang HH. Effects of mindfulness-based stress reduction on sleep quality and mental health for insomnia patients: A meta-analysis. J Psychosom Res 2020;135:110144
57 Wang X, Li P, Pan C, Dai L, Wu Y, Deng Y. The Effect of Mind-Body Therapies on Insomnia: A Systematic Review and Meta-Analysis. Evid Based Complement Alternat Med 2019;2019:9359807
58 Perlis M, Aloia M, Kuhn B Behavioral treatments for sleep disorders: A comprehensive primer of behavioral sleep medicine intervention: Academic Press; 2010
59 Yu H, Zhang Y, Liu Q, Yan R. Efficacy of online and face-to-face cognitive behavioral therapy in the treatment of neurological insomnia: a systematic review and meta-analysis. Ann Palliat Med 2021;10(10):10684–10696
60 Horsch CHG, Lancee J, Griffioen-Both F, et al. Mobile Phone-Delivered Cognitive Behavioral Therapy for Insomnia: A Randomized Waitlist Controlled Trial. J Med Internet Res 2017;19 (04):e70
61 Seyffert M, Lagisetty P, Landgraf J, et al. Internet-Delivered Cognitive Behavioral Therapy to Treat Insomnia: A Systematic Review and Meta-Analysis. PLoS One 2016;11(02):e0149139
62 Chan NY, Lam SP, Zhang J, et al. Efficacy of Email-delivered Versus Face-to-face Group Cognitive Behavioral Therapy for Insomnia in Youths: A Randomized Controlled Trial. J Adolesc Health 2022; 70(05):763–773
63 Sharafkhaneh A, Salari N, Khazaie S, et al. Telemedicine and insomnia: a comprehensive systematic review and meta-analysis. Sleep Med 2022;90:117–130
64 Zachariae R, Lyby MS, Ritterband LM, O'Toole MS. Efficacy of internet-delivered cognitive-behavioral therapy for insomnia - A systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2016;30:1–10
65 van Straten A, Cuijpers P, Smit F, Spermon M, Verbeek I. Self-help treatment for insomnia through television and book: a randomized trial. Patient Educ Couns 2009;74(01):29–34
66 Zhang C, Liu Y, Guo X, Liu Y, Shen Y, Ma J. Digital Cognitive Behavioral Therapy for Insomnia Using a Smartphone Application in China: A Pilot Randomized Clinical Trial. JAMA Netw Open 2023;6(03):e234866
67 Hayes SC, Strosahl KD, Wilson KG. Acceptance and commitment therapy: An experiential approach to behaviour change. New York: The Guiford Press; 1999
68 Paulos-Guarnieri L, Linares IMP, El Rafihi-Ferreira R. Evidence and characteristics of Acceptance and Commitment Therapy (ACT)-based interventions for insomnia: A systematic review of randomized and non-randomized trials. J Contextual Behav Sci 2022;23:14
69 Kabat-Zinn J. Catastrophe Living: Using the Wisdom of your Body and Mind to Face Stress, Pain, and Illness. New York: Delacorte Press; 1990
70 Ong JC, Ulmer CS, Manber R. Improving sleep with mindfulness and acceptance: a metacognitive model of insomnia. Behav Res Ther 2012;50(11):651–660
71 Ong JC, Shapiro SL, Manber R. Combining mindfulness meditation with cognitive-behavior therapy for insomnia: a treatment-development study. Behav Ther 2008;39(02):171–182
72 Ong JC, Manber R, Segal Z, Xia Y, Shapiro S, Wyatt JK. A randomized controlled trial of mindfulness meditation for chronic insomnia. Sleep 2014;37(09):1553–1563
73 Morin CM, Bei B, Bjorvatn B, Poyares D, Spiegelhalder K, Wing YKGoverning Council of the World Sleep Society. World sleep society international sleep medicine guidelines position statement endorsement of "behavioral and psychological treatments for chronic insomnia disorder in adults: An American Academy of sleep medicine clinical practice guidelines". Sleep Med 2023; 109:164–169
74 Smith MT, Perlis ML. Who is a candidate for cognitive-behavioral therapy for insomnia? Health Psychol 2006;25(01):15–19
75 Bathgate CJ, Edinger JD, Krystal AD. Insomnia Patients With Objective Short Sleep Duration Have a Blunted Response to Cognitive Behavioral Therapy for Insomnia. Sleep 2017;40(01):zsw012
76 Rochefort A, Jarrin DC, Bélanger L, Ivers H, Morin CM. Insomnia treatment response as a function of objectively measured sleep duration. Sleep Med 2019;56:135–144
77 Miller CB, Espie CA, Bartlett DJ, Marshall NS, Gordon CJ, Grunstein RR. Acceptability, tolerability, and potential efficacy of cognitive behavioural therapy for Insomnia Disorder subtypes defined by polysomnography: A retrospective cohort study. Sci Rep 2018;8(01):6664
78 He D, Guo Z, Mcclure MA, Mu Q, Jiang B. Cognitive-behavioral therapy for insomnia with objective short sleep duration phenotype: A systematic review with meta-analysis. Sleep Med Rev 2023;67:101736
79 Vgontzas AN, Puzino K, Fernandez-Mendoza J, Krishnamurthy VB, Basta M, Bixler EO. Effects of trazodone versus cognitive behavioral therapy in the insomnia with short sleep duration phenotype: a preliminary study. J Clin Sleep Med 2020;16(12): 2009–2019
80 Arnedt JT, Cuddihy L, Swanson LM, Pickett S, Aikens J, Chervin RD. Randomized controlled trial of telephone-delivered cognitive behavioral therapy for chronic insomnia. Sleep 2013;36(03): 353–362
81 Ye YY, Chen NK, Chen J, et al. Internet-based cognitive-behavioural therapy for insomnia (ICBT-i): a meta-analysis of randomised controlled trials. BMJ Open 2016;6(11):e010707
82 Ho FY, Chung KF, Yeung WF, et al. Self-help cognitive-behavioral therapy for insomnia: a meta-analysis of randomized controlled trials. Sleep Med Rev 2015;19:17–28
83 Koffel EA, Koffel JB, Gehrman PR. A meta-analysis of group cognitive behavioral therapy for insomnia. Sleep Med Rev 2015;19:6–16
84 Edinger JD, Wohlgemuth WK, Radtke RA, Marsh GR, Quillian RE. Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. JAMA 2001;285(14): 1856–1864
85 Seyffert M, Lagisetty P, Landgraf J, et al. Internet-Delivered Cognitive Behavioral Therapy to Treat Insomnia: A Systematic Review and Meta-Analysis. PLoS One 2016;11(02):e0149139
86 Garland SN, Carlson LE, Stephens AJ, Antle MC, Samuels C, Campbell TS. Mindfulness-based stress reduction compared with cognitive behavioral therapy for the treatment of insomnia comorbid with cancer: a randomized, partially blinded, noninferiority trial. J Clin Oncol 2014;32(05):449–457
87 Zhang Y, Ren R, Yang L, et al. Comparative efficacy and acceptability of psychotherapies, pharmacotherapies, and their combination for the treatment of adult insomnia: A systematic review and network meta-analysis. Sleep Med Rev 2022; 65:101687
88 Luik AI, Marsden A, Emsley R, et al. Long-term benefits of digital cognitive behavioural therapy for insomnia: Follow-up report from a randomized clinical trial. J Sleep Res 2020;29(04):e13018
89 Arnedt JT, Conroy DA, Mooney A, Furgal A, Sen A, Eisenberg D. Telemedicine versus face-to-face delivery of cognitive behavioral therapy for insomnia: a randomized controlled noninferiority trial. Sleep 2021;44(01):zsaa136
90 Soh HL, Ho RC, Ho CS, Tam WW. Efficacy of digital cognitive behavioural therapy for insomnia: a meta-analysis of randomised controlled trials. Sleep Med 2020;75:315–325
91 Chung KF, Lee CT, Yeung WF, Chan MS, Chung EW, Lin WL. Sleep hygiene education as a treatment of insomnia: a systematic review and meta-analysis. Fam Pract 2018;35(04):365–375
92 Forma F, Pratiwadi R, El-Moustaid F, Smith N, Thorndike F, Velez F. Network meta-analysis comparing the effectiveness of a prescription digital therapeutic for chronic insomnia to medications and face-to-face cognitive behavioral therapy in adults. Curr Med Res Opin 2022;38(10):1727–1738

93 Wang ML, Wang C, Tuo M, et al. Cognitive Effects of Treating Obstructive Sleep Apnea: A Meta-Analysis of Randomized Controlled Trials. J Alzheimers Dis 2020;75(03):705–715
94 Chapoutot M, Peter-Derex L, Schoendorff B, Faivre T, Bastuji H, Putois B. Telehealth-delivered CBT-I programme enhanced by acceptance and commitment therapy for insomnia and hypnotic dependence: A pilot randomized controlled trial. J Sleep Res 2021;30(01):e13199
95 de Entrambasaguas M, Díaz-Silveira C, Burgos-Julián FA, Santed MA. Can mindfulness-based interventions improve outcomes in cognitive-behavioural therapy for chronic insomnia disorder in the general population? Systematic review and meta-analysis. Clin Psychol Psychother 2023
96 Kennett L, Bei B, Jackson ML. A Randomized Controlled Trial to Examine the Feasibility and Preliminary Efficacy of a Digital Mindfulness-Based Therapy for Improving Insomnia Symptoms. Mindfulness 2021;12(10):2460–2472
97 Gross CR, Kreitzer MJ, Reilly-Spong M, et al. Mindfulness-based stress reduction versus pharmacotherapy for chronic primary insomnia: a randomized controlled clinical trial. Explore (NY) 2011;7(02):76–87
98 Gong H, Ni CX, Liu YZ, et al. Mindfulness meditation for insomnia: A meta-analysis of randomized controlled trials. J Psychosom Res 2016;89:1–6
99 Wang YY, Wang F, Zheng W, et al. Mindfulness-Based Interventions for Insomnia: A Meta-Analysis of Randomized Controlled Trials. Behav Sleep Med 2020;18(01):1–9
100 Kremer S, Blue T. Biofeedback as an Adjunct or Alternative Intervention to Cognitive Behavioral Therapy for Insomnia. Sleep Med Clin 2023;18(01):85–93
101 Lovato N, Miller CB, Gordon CJ, Grunstein RR, Lack L. The efficacy of biofeedback for the treatment of insomnia: a critical review. Sleep Med 2019;56:192–200
102 Melo DLM, Carvalho LBC, Prado LBF, Prado GF. Biofeedback Therapies for Chronic Insomnia: A Systematic Review. Appl Psychophysiol Biofeedback 2019;44(04):259–269
103 Lambert-Beaudet F, Journault WG, Rudziavic Provençal A, Bastien CH. Neurofeedback for insomnia: Current state of research. World J Psychiatry 2021;11(10):897–914
104 Nicassio PM, Boylan MB, McCabe TG. Progressive relaxation, EMG biofeedback and biofeedback placebo in the treatment of sleep-onset insomnia. Br J Med Psychol 1982;55(Pt 2):159–166
105 Schabus M, Griessenberger H, Gnjezda MT, Heib DPJ, Wislowska M, Hoedlmoser K. Better than sham? A double-blind placebo-controlled neurofeedback study in primary insomnia. Brain 2017;140(04):1041–1052
106 Kwan Y, Yoon S, Suh S, Choi S. A Randomized Controlled Trial Comparing Neurofeedback and Cognitive-Behavioral Therapy for Insomnia Patients: Pilot Study. Appl Psychophysiol Biofeedback 2022;47(02):95–106
107 Cao HJ, Yu ML, Wang LQ, Fei YT, Xu H, Liu JP. Acupuncture for Primary Insomnia: An Updated Systematic Review of Randomized Controlled Trials. J Altern Complement Med 2019;25(05):451–474
108 Fang QQ, Wang XQ, Liu CY, et al. The efficacy of acupuncture on the sleep structure of patients with insomnia: A systematic review and meta-analysis. Anat Rec (Hoboken) 2021;304(11):2412–2425
109 Ji H, Zhang K, Lu Y, Kong X, Ma X. The efficacy of acupuncture with Lingguibafa acupoint selection in the treatment of insomnia: A PRISMA-compliant meta-analysis. Medicine (Baltimore) 2022;101(43):e31515
110 Kim SH, Jeong JH, Lim JH, Kim BK. Acupuncture using pattern-identification for the treatment of insomnia disorder: a systematic review and meta-analysis of randomized controlled trials. Integr Med Res 2019;8(03):216–226
111 Liu FG, Tan AH, Peng CQ, Tan YX, Yao MC. Efficacy and Safety of Scalp Acupuncture for Insomnia: A Systematic Review and Meta-Analysis. Evid Based Complement Alternat Med 2021;2021:6621993
112 Lu Y, Zhu H, Wang Q, et al. Comparative effectiveness of multiple acupuncture therapies for primary insomnia: a systematic review and network meta-analysis of randomized trial. Sleep Med 2022;93:39–48
113 Zhang J, He Y, Huang X, Liu Y, Yu H. The effects of acupuncture versus sham/placebo acupuncture for insomnia: A systematic review and meta-analysis of randomized controlled trials. Complement Ther Clin Pract 2020;41:101253
114 Zhao FY, Fu QQ, Kennedy GA, et al. Can acupuncture improve objective sleep indices in patients with primary insomnia? A systematic review and meta-analysis. Sleep Med 2021;80:244–259
115 Hartescu I, Morgan K, Stevinson CD. Increased physical activity improves sleep and mood outcomes in inactive people with insomnia: a randomized controlled trial. J Sleep Res 2015;24(05):526–534
116 Baron P, Hermand É, Bourlois V, et al. Effect of Aerobic Exercise Training on Sleep and Core Temperature in Middle-Aged Women with Chronic Insomnia: A Randomized Controlled Trial. Int J Environ Res Public Health 2023;20(08):5452
117 Zhang X, Wang X, Le S, et al. Effects of exercise and dietary interventions on serum metabolites in men with insomnia symptoms: A 6-month randomized controlled trial. Sports Med Health Sci 2020;2(02):95–101
118 D'Aurea CVR, Poyares D, Passos GS, et al. Effects of resistance exercise training and stretching on chronic insomnia. Br J Psychiatry 2019;41(01):51–57
119 D'Aurea CVR, Frange C, Poyares D, Souza AAL, Lenza M. Physical exercise as a therapeutic approach for adults with insomnia: systematic review and meta-analysis. Einstein (Sao Paulo) 2022;20:eAO8058
120 Xie Y, Liu S, Chen XJ, Yu HH, Yang Y, Wang W. Effects of Exercise on Sleep Quality and Insomnia in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front Psychiatry 2021;12:664499
121 Datta K, Tripathi M, Verma M, Masiwal D, Mallick HN. Yoga nidra practice shows improvement in sleep in patients with chronic insomnia: A randomized controlled trial. Natl Med J India 2021;34(03):143–150
122 Khalsa SBS, Goldstein MR. Treatment of chronic primary sleep onset insomnia with Kundalini yoga: a randomized controlled trial with active sleep hygiene comparison. J Clin Sleep Med 2021;17(09):1841–1852
123 Wang WL, Chen KH, Pan YC, Yang SN, Chan YY. The effect of yoga on sleep quality and insomnia in women with sleep problems: a systematic review and meta-analysis. BMC Psychiatry 2020;20(01):195
124 Yang M, Yang J, Gong M, Luo R, Lin Q, Wang B. Effects of Tai Chi on Sleep Quality as Well as Depression and Anxiety in Insomnia Patients: A Meta-Analysis of Randomized Controlled Trials. Int J Environ Res Public Health 2023;20(04):3074
125 Lewith GT, Godfrey AD, Prescott P. A single-blinded, randomized pilot study evaluating the aroma of Lavandula augustifolia as a treatment for mild insomnia. J Altern Complement Med 2005;11(04):631–637
126 Tang Y, Gong M, Qin X, Su H, Wang Z, Dong H. The Therapeutic Effect of Aromatherapy on Insomnia: a Meta-Analysis. J Affect Disord 2021;288:1–9
127 Lucena L, Santos-Junior JG, Tufik S, Hachul H. Effect of a lavender essential oil and sleep hygiene protocol on insomnia in postmenopausal women: A pilot randomized clinical trial. Explore (NY) 2023:S1550-8307(23)00163-5
128 Bacelar A, Pinto LR Jr. Insônia - Do diagnóstico ao tratamento. São Caetano do Sul; 2019 172 p.
129 Xiang T, Cai Y, Hong Z, Pan J. Efficacy and safety of Zolpidem in the treatment of insomnia disorder for one month: a meta-

analysis of a randomized controlled trial. Sleep Med 2021; 87:250–256
130 Roth T, Roehrs T, Vogel G. Zolpidem in the treatment of transient insomnia: a double-blind, randomized comparison with placebo. Sleep 1995;18(04):246–251
131 Staner C, Joly F, Jacquot N, et al. Sublingual zolpidem in early onset of sleep compared to oral zolpidem: polysomnographic study in patients with primary insomnia. Curr Med Res Opin 2010;26(06):1423–1431
132 Castro LS, Otuyama LJ, Fumo-Dos-Santos C, Tufik S, Poyares D. Sublingual and oral zolpidem for insomnia disorder: a 3-month randomized trial. Br J Psychiatry 2020;42(02):175–184
133 Roth T, Krystal A, Steinberg FJ, Singh NN, Moline M. Novel sublingual low-dose zolpidem tablet reduces latency to sleep onset following spontaneous middle-of-the-night awakening in insomnia in a randomized, double-blind, placebo-controlled, outpatient study. Sleep 2013;36(02):189–196
134 Roth T, Soubrane C, Titeux L, Walsh JK, Group ZSZoladult Study Group. Efficacy and safety of zolpidem-MR: a double-blind, placebo-controlled study in adults with primary insomnia. Sleep Med 2006;7(05):397–406
135 Krystal AD, Erman M, Zammit GK, Soubrane C, Roth T, Group ZSZOLONG Study Group. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Sleep 2008;31(01):79–90
136 Roehrs TA, Randall S, Harris E, Maan R, Roth T. Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study. J Psychopharmacol 2012;26(08):1088–1095
137 Chiaro G, Castelnovo A, Bianco G, Maffei P, Manconi M. Severe Chronic Abuse of Zolpidem in Refractory Insomnia. J Clin Sleep Med 2018;14(07):1257–1259
138 Louzada LL, Machado FV, Quintas JL, et al. The efficacy and safety of zolpidem and zopiclone to treat insomnia in Alzheimer's disease: a randomized, triple-blind, placebo-controlled trial. Neuropsychopharmacology 2022;47(02):570–579
139 Tsutsui S, Group ZSZolipidem Study Group. A double-blind comparative study of zolpidem versus zopiclone in the treatment of chronic primary insomnia. J Int Med Res 2001;29(03): 163–177
140 Pinto LR Jr, Bittencourt LR, Treptow EC, Braga LR, Tufik S. Eszopiclone versus zopiclone in the treatment of insomnia. Clinics (São Paulo) 2016;71(01):5–9
141 Greenblatt DJ, Roth T. Zolpidem for insomnia. Expert Opin Pharmacother 2012;13(06):879–893
142 Rösner S, Englbrecht C, Wehrle R, Hajak G, Soyka M. Eszopiclone for insomnia. Cochrane Database Syst Rev 2018;10(10): CD010703
143 Greenblatt DJ, Zammit GK. Pharmacokinetic evaluation of eszopiclone: clinical and therapeutic implications. Expert Opin Drug Metab Toxicol 2012;8(12):1609–1618
144 Ancoli-Israel S, Krystal AD, McCall WV, et al. A 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia. Sleep 2010;33(02): 225–234
145 Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. Sleep 2003;26(07):793–799
146 Liang L, Huang Y, Xu R, Wei Y, Xiao L, Wang G. Eszopiclone for the treatment of primary insomnia: a systematic review and meta-analysis of double-blind, randomized, placebo-controlled trials. Sleep Med 2019;62:6–13
147 Erman MK, Zammit G, Rubens R, et al. A polysomnographic placebo-controlled evaluation of the efficacy and safety of eszopiclone relative to placebo and zolpidem in the treatment of primary insomnia. J Clin Sleep Med 2008;4(03):229–234
148 Uchimura N, Kamijo A, Kuwahara H, et al. A randomized placebo-controlled polysomnographic study of eszopiclone in Japanese patients with primary insomnia. Sleep Med 2012;13(10): 1247–1253
149 Roth T, Walsh JK, Krystal A, Wessel T, Roehrs TA. An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. Sleep Med 2005;6(06):487–495
150 Zammit GK, McNabb LJ, Caron J, Amato DA, Roth T. Efficacy and safety of eszopiclone across 6-weeks of treatment for primary insomnia. Curr Med Res Opin 2004;20(12):1979–1991
151 Soares CN, Joffe H, Rubens R, Caron J, Roth T, Cohen L. Eszopiclone in patients with insomnia during perimenopause and early postmenopause: a randomized controlled trial. Obstet Gynecol 2006;108(06):1402–1410
152 Wick JY. The history of benzodiazepines. Consult Pharm 2013;28 (09):538–548
153 Madruga CS, Paim TL, Palhares HN, et al. Prevalence of and pathways to benzodiazepine use in Brazil: the role of depression, sleep, and sedentary lifestyle. Br J Psychiatry 2019;41(01):44–50
154 Campanha AM, Ravagnani B, Milhorança IA, et al. Benzodiazepine use in Sao Paulo, Brazil. Clinics (São Paulo) 2020;75:e1610
155 Freire MBO, Da Silva BGC, Bertoldi AD, et al. Benzodiazepines utilization in Brazilian older adults: a population-based study. Rev Saude Publica 2022;56:10
156 El Balkhi S, Abbara C. Designer Benzodiazepines: Effects, Toxicity, and Interactions. Ther Drug Monit 2023;45(04):494–507
157 Sigel E, Ernst M. The Benzodiazepine Binding Sites of $GABA_A$ Receptors. Trends Pharmacol Sci 2018;39(07):659–671
158 Czeisler CA. Duration, timing and quality of sleep are each vital for health, performance and safety. Sleep Health 2015;1(01):5–8
159 Engin E. $GABA_A$ receptor subtypes and benzodiazepine use, misuse, and abuse. Front Psychiatry 2023;13:1060949
160 Soyka M. Treatment of Benzodiazepine Dependence. N Engl J Med 2017;376(24):2399–2400
161 de las Cuevas C, Sanz E, de la Fuente J. Benzodiazepines: more "behavioural" addiction than dependence. Psychopharmacology (Berl) 2003;167(03):297–303
162 Lader M. Benzodiazepines revisited–will we ever learn? Addiction 2011;106(12):2086–2109
163 Peng L, Morford KL, Levander XA. Benzodiazepines and Related Sedatives. Med Clin North Am 2022;106(01):113–129
164 Wishart DS, Feunang YD, Guo AC, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res 2018;46(D1):D1074–D1082
165 Equihua AC, De La Herrán-Arita AK, Drucker-Colin R. Orexin receptor antagonists as therapeutic agents for insomnia. Front Pharmacol 2013;4:163
166 Dubey AK, Handu SS, Mediratta PK. Suvorexant: The first orexin receptor antagonist to treat insomnia. J Pharmacol Pharmacother 2015;6(02):118–121
167 Khazaie H, Sadeghi M, Khazaie S, Hirshkowitz M, Sharafkhaneh A. Dual orexin receptor antagonists for treatment of insomnia: A systematic review and meta-analysis on randomized, double-blind, placebo-controlled trials of suvorexant and lemborexant. Front Psychiatry 2022;13:1070522
168 Snyder E, Ma J, Svetnik V, et al. Effects of suvorexant on sleep architecture and power spectral profile in patients with insomnia: analysis of pooled phase 3 data. Sleep Med 2016;19:93–100
169 Herring WJ, Connor KM, Snyder E, et al. Effects of suvorexant on the Insomnia Severity Index in patients with insomnia: analysis of pooled phase 3 data. Sleep Med 2019;56:219–223
170 Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol 2014;13 (05):461–471

171 Scammell TE, Winrow CJ. Orexin receptors: pharmacology and therapeutic opportunities. Annu Rev Pharmacol Toxicol 2011; 51:243–266
172 Kunz D, Dauvilliers Y, Benes H, et al. Long-Term Safety and Tolerability of Daridorexant in Patients with Insomnia Disorder. CNS Drugs 2023;37(01):93–106
173 Fietze I, Bassetti CLA, Mayleben DW, Pain S, Seboek Kinter D, McCall WV. Efficacy and Safety of Daridorexant in Older and Younger Adults with Insomnia Disorder: A Secondary Analysis of a Randomised Placebo-Controlled Trial. Drugs Aging 2022;39 (10):795–810
174 Jiang F, Li H, Chen Y, Lu H, Ni J, Chen G. Daridorexant for the treatment of insomnia disorder: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2023;102(07):e32754
175 Beuckmann CT, Suzuki M, Ueno T, Nagaoka K, Arai T, Higashiyama H. In Vitro and In Silico Characterization of Lemborexant (E2006), a Novel Dual Orexin Receptor Antagonist. J Pharmacol Exp Ther 2017;362(02):287–295
176 Kärppä M, Yardley J, Pinner K, et al. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. Sleep 2020;43(09):zsaa123
177 Dash A, Pinner K, Inoue Y, et al. Efficacy and safety of lemborexant over 12 months in Asian adults with insomnia disorder. Sleep Med X 2022;4:100044
178 Roth T, Rosenberg R, Morin CM, et al. Impact of lemborexant treatment on insomnia severity: analyses from a 12-month study of adults with insomnia disorder. Sleep Med 2022; 90:249–257
179 Yardley J, Kärppä M, Inoue Y, et al. Long-term effectiveness and safety of lemborexant in adults with insomnia disorder: results from a phase 3 randomized clinical trial. Sleep Med 2021; 80:333–342
180 Rosenberg R, Murphy P, Zammit G, et al. Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial. JAMA Netw Open 2019;2(12): e1918254
181 Moline M, Zammit G, Cheng JY, Perdomo C, Kumar D, Mayleben D. Comparison of the effect of lemborexant with placebo and zolpidem tartrate extended release on sleep architecture in older adults with insomnia disorder. J Clin Sleep Med 2021;17 (06):1167–1174
182 Wang C, Wang Q, Ji B, et al. The Orexin/Receptor System: Molecular Mechanism and Therapeutic Potential for Neurological Diseases. Front Mol Neurosci 2018;11:220
183 Dubocovich ML, Rivera-Bermudez MA, Gerdin MJ, Masana MI. Molecular pharmacology, regulation and function of mammalian melatonin receptors. Front Biosci 2003;8:d1093–d1108
184 Kato K, Hirai K, Nishiyama K, et al. Neurochemical properties of ramelteon (TAK-375), a selective MT1/MT2 receptor agonist. Neuropharmacology 2005;48(02):301–310
185 Kuriyama A, Honda M, Hayashino Y. Ramelteon for the treatment of insomnia in adults: a systematic review and meta-analysis. Sleep Med 2014;15(04):385–392
186 Low TL, Choo FN, Tan SM. The efficacy of melatonin and melatonin agonists in insomnia - An umbrella review. J Psychiatr Res 2020;121:10–23
187 Roth T, Seiden D, Sainati S, Wang-Weigand S, Zhang J, Zee P. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. Sleep Med 2006;7(04): 312–318
188 Erman M, Seiden D, Zammit G, Sainati S, Zhang J. An efficacy, safety, and dose-response study of Ramelteon in patients with chronic primary insomnia. Sleep Med 2006;7(01):17–24
189 Mini L, Wang-Weigand S, Zhang J. Ramelteon 8 mg/d versus placebo in patients with chronic insomnia: post hoc analysis of a 5-week trial using 50% or greater reduction in latency to persistent sleep as a measure of treatment effect. Clin Ther 2008; 30(07):1316–1323
190 Gooneratne NS, Gehrman P, Gurubhagavatula I, Al-Shehabi E, Marie E, Schwab R. Effectiveness of ramelteon for insomnia symptoms in older adults with obstructive sleep apnea: a randomized placebo-controlled pilot study. J Clin Sleep Med 2010;6(06):572–580
191 Mayer G, Wang-Weigand S, Roth-Schechter B, Lehmann R, Staner C, Partinen M. Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. Sleep 2009;32(03):351–360
192 Zammit G, Erman M, Wang-Weigand S, Sainati S, Zhang J, Roth T. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. J Clin Sleep Med 2007;3(05):495–504
193 Zammit G, Wang-Weigand S, Rosenthal M, Peng X. Effect of ramelteon on middle-of-the-night balance in older adults with chronic insomnia. J Clin Sleep Med 2009;5(01):34–40
194 Uchimura N, Ogawa A, Hamamura M, Hashimoto T, Nagata H, Uchiyama M. Efficacy and safety of ramelteon in Japanese adults with chronic insomnia: a randomized, double-blind, placebo-controlled study. Expert Rev Neurother 2011;11(02):215–224
195 Uchiyama M, Hamamura M, Kuwano T, Nishiyama H, Nagata H, Uchimura N. Evaluation of subjective efficacy and safety of ramelteon in Japanese subjects with chronic insomnia. Sleep Med 2011;12(02):119–126
196 Uchiyama M, Hamamura M, Kuwano T, et al. Long-term safety and efficacy of ramelteon in Japanese patients with chronic insomnia. Sleep Med 2011;12(02):127–133
197 Wang-Weigand S, Watissée M, Roth T. Use of a post-sleep questionnaire-interactive voice response system (PSQ-IVRS) to evaluate the subjective sleep effects of ramelteon in adults with chronic insomnia. Sleep Med 2011;12(09):920–923
198 Kohsaka M, Kanemura T, Taniguchi M, et al. Efficacy and tolerability of ramelteon in a double-blind, placebo-controlled, crossover study in Japanese patients with chronic primary insomnia. Expert Rev Neurother 2011;11(10):1389–1397
199 Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds. J Clin Psychiatry 2005;66(Suppl 9):31–41
200 Kryger M, Wang-Weigand S, Zhang J, Roth T. Effect of ramelteon, a selective MT(1)/MT (2)-receptor agonist, on respiration during sleep in mild to moderate COPD. Sleep Breath 2008;12(03): 243–250
201 Kryger M, Roth T, Wang-Weigand S, Zhang J. The effects of ramelteon on respiration during sleep in subjects with moderate to severe chronic obstructive pulmonary disease. Sleep Breath 2009;13(01):79–84
202 Kryger M, Wang-Weigand S, Roth T. Safety of ramelteon in individuals with mild to moderate obstructive sleep apnea. Sleep Breath 2007;11(03):159–164
203 Biggio G, Biggio F, Talani G, et al. Melatonin: From Neurobiology to Treatment. Brain Sci 2021;11(09):1121
204 Cipolla-Neto J, Amaral FGD. Melatonin as a Hormone: New Physiological and Clinical Insights. Endocr Rev 2018;39(06): 990–1028
205 Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An Update for 2015: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2015;11(10):1199–1236
206 Besag FMC, Vasey MJ, Lao KSJ, Wong ICK. Adverse Events Associated with Melatonin for the Treatment of Primary or Secondary Sleep Disorders: A Systematic Review. CNS Drugs 2019;33(12):1167–1186

207 DeMuro RL, Nafziger AN, Blask DE, Menhinick AM, Bertino JS Jr. The absolute bioavailability of oral melatonin. J Clin Pharmacol 2000;40(07):781–784
208 Harpsøe NG, Andersen LP, Gögenur I, Rosenberg J. Clinical pharmacokinetics of melatonin: a systematic review. Eur J Clin Pharmacol 2015;71(08):901–909
209 Baglioni C, Bostanova Z, Bacaro V, et al. A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials Evaluating the Evidence Base of Melatonin, Light Exposure, Exercise, and Complementary and Alternative Medicine for Patients with Insomnia Disorder. J Clin Med 2020;9(06):1949
210 Choi K, Lee YJ, Park S, Je NK, Suh HS. Efficacy of melatonin for chronic insomnia: Systematic reviews and meta-analyses. Sleep Med Rev 2022;66:101692
211 Almeida Montes LG, Ontiveros Uribe MP, Cortés Sotres J, Heinze Martin G. Treatment of primary insomnia with melatonin: a double-blind, placebo-controlled, crossover study. J Psychiatry Neurosci 2003;28(03):191–196
212 Wade AG, Ford I, Crawford G, et al. Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: a randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety. BMC Med 2010;8:51
213 Xu H, Zhang C, Qian Y, et al. Efficacy of melatonin for sleep disturbance in middle-aged primary insomnia: a double-blind, randomised clinical trial. Sleep Med 2020;76:113–119
214 Edemann-Callesen H, Andersen HK, Ussing A, et al. Use of melatonin in children and adolescents with idiopathic chronic insomnia: a systematic review, meta-analysis, and clinical recommendation. EClinicalMedicine 2023;61:102048
215 Xiong M, Li F, Liu Z, et al. Efficacy of Melatonin for Insomnia in Children with Autism Spectrum Disorder: A Meta-analysis. Neuropediatrics 2023;54(03):167–173
216 Larsson I, Aili K, Lönn M, et al. Sleep interventions for children with attention deficit hyperactivity disorder (ADHD): A systematic literature review. Sleep Med 2023;102:64–75
217 Marupuru S, Arku D, Campbell AM, Slack MK, Lee JK. Use of Melatonin and/on Ramelteon for the Treatment of Insomnia in Older Adults: A Systematic Review and Meta-Analysis. J Clin Med 2022;11(17):5138
218 Burgess HJ, Revell VL, Molina TA, Eastman CI. Human phase response curves to three days of daily melatonin: 0.5 mg versus 3.0 mg. J Clin Endocrinol Metab 2010;95(07):3325–3331
219 Lewy AJ, Bauer VK, Ahmed S, et al. The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. Chronobiol Int 1998;15(01):71–83
220 Erland LA, Saxena PK. Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content. J Clin Sleep Med 2017;13(02):275–281
221 Everitt H, Baldwin DS, Stuart B, et al. Antidepressants for insomnia in adults. Cochrane Database Syst Rev 2018;5(05): CD010753
222 Lou BX, Oks M. Insomnia: Pharmacologic Treatment. Clin Geriatr Med 2021;37(03):401–415
223 Abad VC, Guilleminault C. Insomnia in Elderly Patients: Recommendations for Pharmacological Management. Drugs Aging 2018;35(09):791–817
224 Hajak G, Rodenbeck A, Voderholzer U, et al. Doxepin in the treatment of primary insomnia: a placebo-controlled, double-blind, polysomnographic study. J Clin Psychiatry 2001;62(06): 453–463
225 Krystal AD, Durrence HH, Scharf M, et al. Efficacy and Safety of Doxepin 1 mg and 3 mg in a 12-week Sleep Laboratory and Outpatient Trial of Elderly Subjects with Chronic Primary Insomnia. Sleep 2010;33(11):1553–1561
226 Krystal AD, Lankford A, Durrence HH, et al. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. Sleep 2011;34(10):1433–1442
227 Lankford A, Rogowski R, Essink B, Ludington E, Heith Durrence H, Roth T. Efficacy and safety of doxepin 6 mg in a four-week outpatient trial of elderly adults with chronic primary insomnia. Sleep Med 2012;13(02):133–138
228 Rios Romenets S, Creti L, Fichten C, et al. Doxepin and cognitive behavioural therapy for insomnia in patients with Parkinson's disease – a randomized study. Parkinsonism Relat Disord 2013; 19(07):670–675
229 Yeung WF, Chung KF, Yung KP, Ng TH. Doxepin for insomnia: a systematic review of randomized placebo-controlled trials. Sleep Med Rev 2015;19:75–83
230 Kolla BP, Mansukhani MP, Bostwick JM. The influence of antidepressants on restless legs syndrome and periodic limb movements: A systematic review. Sleep Med Rev 2018;38:131–140
231 Atkin T, Comai S, Gobbi G. Drugs for Insomnia beyond Benzodiazepines: Pharmacology, Clinical Applications, and Discovery. Pharmacol Rev 2018;70(02):197–245
232 Corruble E, de Bodinat C, Belaïdi C, Goodwin GMagomelatine study group. Efficacy of agomelatine and escitalopram on depression, subjective sleep and emotional experiences in patients with major depressive disorder: a 24-wk randomized, controlled, double-blind trial. Int J Neuropsychopharmacol 2013; 16(10):2219–2234
233 Quera-Salva MA, Lemoine P, Guilleminault C. Impact of the novel antidepressant agomelatine on disturbed sleep-wake cycles in depressed patients. Hum Psychopharmacol 2010;25(03): 222–229
234 Yi XY, Ni SF, Ghadami MR, et al. Trazodone for the treatment of insomnia: a meta-analysis of randomized placebo-controlled trials. Sleep Med 2018;45:25–32
235 Zheng Y, Lv T, Wu J, Lyu Y. Trazodone changed the polysomnographic sleep architecture in insomnia disorder: a systematic review and meta-analysis. Sci Rep 2022;12(01):14453
236 StatPearls. 2023
237 Wilson S, Argyropoulos S. Antidepressants and sleep: a qualitative review of the literature. Drugs 2005;65(07):927–947
238 Kupfer DJ, Spiker DG, Coble P, McPartland RJ. Amitriptyline and EEG sleep in depressed patients: I. Drug effect. Sleep 1978;1(02): 149–159
239 Shipley JE, Kupfer DJ, Griffin SJ, et al. Comparison of effects of desipramine and amitriptyline on EEG sleep of depressed patients. Psychopharmacology (Berl) 1985;85(01):14–22
240 Dunleavy DL, Brezinova V, Oswald I, Maclean AW, Tinker M. Changes during weeks in effects of tricyclic drugs on the human sleeping brain. Br J Psychiatry 1972;120(559):663–672
241 A review of the pharmacological and clinical profile of mirtazapine [press release]. US: Neva Press; 2001
242 Krystal AD. Antidepressant and Antipsychotic Drugs. Sleep Med Clin 2010;5(04):571–589
243 Karsten J, Hagenauw LA, Kamphuis J, Lancel M. Low doses of mirtazapine or quetiapine for transient insomnia: A randomised, double-blind, cross-over, placebo-controlled trial. J Psychopharmacol 2017;31(03):327–337
244 Schittecatte M, Dumont F, Machowski R, Cornil C, Lavergne F, Wilmotte J. Effects of mirtazapine on sleep polygraphic variables in major depression. Neuropsychobiology 2002;46(04): 197–201
245 Winokur A, Sateia MJ, Hayes JB, Bayles-Dazet W, MacDonald MM, Gary KA. Acute effects of mirtazapine on sleep continuity and sleep architecture in depressed patients: a pilot study. Biol Psychiatry 2000;48(01):75–78
246 Winokur A, DeMartinis NA III, McNally DP, Gary EM, Cormier JL, Gary KA. Comparative effects of mirtazapine and fluoxetine on sleep physiology measures in patients with major depression and insomnia. J Clin Psychiatry 2003;64(10):1224–1229
247 Miller BJ, McEvoy JP, McCall WV. Meta-analysis of clozapine and insomnia in schizophrenia. Schizophr Res 2023;252:208–215

248 Wine JN, Sanda C, Caballero J. Effects of quetiapine on sleep in nonpsychiatric and psychiatric conditions. Ann Pharmacother 2009;43(04):707–713
249 Lin CY, Chiang CH, Tseng MM, Tam KW, Loh EW. Effects of quetiapine on sleep: A systematic review and meta-analysis of clinical trials. Eur Neuropsychopharmacol 2023;67:22–36
250 Tassniyom K, Paholpak S, Tassniyom S, Kiewyoo J. Quetiapine for primary insomnia: a double blind, randomized controlled trial. J Med Assoc Thai 2010;93(06):729–734
251 Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors focus on newer generation compounds. Life Sci 2000;68(01):29–39
252 Modesto-Lowe V, Harabasz AK, Walker SA. Quetiapine for primary insomnia: Consider the risks. Cleve Clin J Med 2021;88 (05):286–294
253 Brasil. Amamentação e uso de medicamentos e outras substâncias - Ministério da Saúde, Secretaria da Atenção à Saúde, Departamento de Ações Programáticas e Estratégicas. 2 ed. Brasília 2016
254 Lo HS, Yang CM, Lo HG, Lee CY, Ting H, Tzang BS. Treatment effects of gabapentin for primary insomnia. Clin Neuropharmacol 2010;33(02):84–90
255 Furey SA, Hull SG, Leibowitz MT, Jayawardena S, Roth T. A randomized, double-blind, placebo-controlled, multicenter, 28-day, polysomnographic study of gabapentin in transient insomnia induced by sleep phase advance. J Clin Sleep Med 2014;10(10):1101–1109
256 Hong JSW, Atkinson LZ, Al-Juffali N, et al. Gabapentin and pregabalin in bipolar disorder, anxiety states, and insomnia: Systematic review, meta-analysis, and rationale. Mol Psychiatry 2022;27(03):1339–1349
257 AminiLari M, Wang L, Neumark S, Adli T, Couban RJ, Giangregorio A, et al. Medical cannabis and cannabinoids for impaired sleep: a systematic review and meta-analysis of randomized clinical trials. Sleep (Basel) 2022;45(02):
258 Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA 2015;313(24):2456–2473
259 Bhagavan C, Kung S, Doppen M, et al. Cannabinoids in the Treatment of Insomnia Disorder: A Systematic Review and Meta-Analysis. CNS Drugs 2020;34(12):1217–1228
260 Walsh JH, Maddison KJ, Rankin T, et al. Treating insomnia symptoms with medicinal cannabis: a randomized, crossover trial of the efficacy of a cannabinoid medicine compared with placebo. Sleep 2021;44(11):zsab149
261 Suraev A, Grunstein RR, Marshall NS, et al. Cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC) for chronic insomnia disorder ('CANSLEEP' trial): protocol for a randomised, placebo-controlled, double-blinded, proof-of-concept trial. BMJ Open 2020;10(05):e034421
262 Dos Santos RG, Guimarães FS, Crippa JAS, et al. Serious adverse effects of cannabidiol (CBD): a review of randomized controlled trials. Expert Opin Drug Metab Toxicol 2020;16(06):517–526
263 Shinomiya K, Fujimura K, Kim Y, Kamei C. Effects of valerian extract on the sleep-wake cycle in sleep-disturbed rats. Acta Med Okayama 2005;59(03):89–92
264 Stevinson C, Ernst E. Valerian for insomnia: a systematic review of randomized clinical trials. Sleep Med 2000;1(02):91–99
265 Fernández-San-Martín MI, Masa-Font R, Palacios-Soler L, Sancho-Gómez P, Calbó-Caldentey C, Flores-Mateo G. Effectiveness of Valerian on insomnia: a meta-analysis of randomized placebo-controlled trials. Sleep Med 2010;11(06):505–511
266 Lee J, Jung HY, Lee SI, Choi JH, Kim SG. Effects of Passiflora incarnata Linnaeus on polysomnographic sleep parameters in subjects with insomnia disorder: a double-blind randomized placebo-controlled study. Int Clin Psychopharmacol 2020;35 (01):29–35
267 Zick SM, Wright BD, Sen A, Arnedt JT. Preliminary examination of the efficacy and safety of a standardized chamomile extract for chronic primary insomnia: a randomized placebo-controlled pilot study. BMC Complement Altern Med 2011;11:78
268 Langade D, Thakare V, Kanchi S, Kelgane S. Clinical evaluation of the pharmacological impact of ashwagandha root extract on sleep in healthy volunteers and insomnia patients: A double-blind, randomized, parallel-group, placebo-controlled study. J Ethnopharmacol 2021;264:113276
269 Church MK, Maurer M, Simons FE, et al; Global Allergy and Asthma European Network. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. Allergy 2010;65(04): 459–466
270 Slater JW, Zechnich AD, Haxby DG. Second-generation antihistamines: a comparative review. Drugs 1999;57(01):31–47
271 Morin CM, Koetter U, Bastien C, Ware JC, Wooten V. Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. Sleep 2005;28 (11):1465–1471
272 Glass JR, Sproule BA, Herrmann N, Busto UE. Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. J Clin Psychopharmacol 2008;28(02):182–188
273 Frange C, Franco AM, Brasil E, et al. Practice recommendations for the role of physiotherapy in the management of sleep disorders: the 2022 Brazilian Sleep Association Guidelines. Sleep Sci 2022; 15(04):515–573

