CMI Clinical Management Issues

Cognitive-Behavioral and Pharmacological Treatments for Insomnia: A Combined Approach

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Abstract

Insomnia is the most prevalent sleep disorder (10–40%). It is defined as the subjective perception of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep and that results in some form of daytime impairment. Among the typical symptoms, there are fatigue, decreased mood or irritability, general malaise, and cognitive impairment. According to the International Classification of Sleep Disorders 3rd edition, ICSD-3, it has been defined as chronic (lasting more than three months) or short-term insomnia (less than three months).

In clinical practice, the usual therapeutic approach is pharmacological (benzodiazepines, z drugs, slow wave sleep enhancers), even if the American Academy of Sleep Medicine (AASM), the American College of Physicians (ACP), and the European Sleep Research Society (ESRS) guidelines suggest that the first clinical choice should be non-pharmacological (cognitive behavioral therapy). A combined (non-pharmacological and pharmacological)approach could be considered in poor responders to manage drug dependence and to increase compliance to treatment and patients' quality of life.

Keywords: Sleep; Insomnia; Pharmacological Treatment; Non-pharmacological treatment; Cognitive-behavioral therapy for insomnia (CBT-I)

CMI 2020; 14(1): 27-38

http://dx.doi.org/10.7175/cmi.v14i1.1474

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INTRODUCTION

The sleep is one of the most complex and dynamic cerebral phenomena, resulting from the combination or alternation of multiple neurophysiological and neuro-biochemical active processes. Thanks to the application of recent discoveries and techniques and the development of sleep medicine, during the last decade, much knowledge has been acquired about the inner mechanisms that promote, induce, maintain, and interrupt the sleep itself, how its processes take place, and how anatomical sites and their neuronal systems work.

Different modes of sleep exist, based on the presence or absence of rapid eye movements, respectively, rapid eye movements—REM sleep, and non-rapid eye movements—NREM sleep. The NREM sleep is divided into three stages: N1, N2, and N3 (N3 also defined as "slow waves sleep", SWS).

To date, four main systems interacting to regulate sleep are known.

1. The circadian oscillator is responsible for the organization of the 24-hour sleep-wake cycle and is located in the supra-chiasmatic nucleus at the hypothalamic level [1].
2. The ultradian oscillator, in the brainstem (REM-off and REM-on neuronal cells), is responsible for the precise alternation NREM and REM sleep [2].
3. The sleep homeostasis controls the propensity to fall asleep and is regulated by

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Received: 13 April 2020
Accepted: 8 July 2020
Published: 30 July 2020

the concentration of adenosine in the frontobasal cortex; its quantity is directly proportional to the number of hours we are awake [3].

4. The arousal system regulates the stability of sleep (sleep and awakening). It is controlled by the ascending reticular activating system in the brainstem and by the orexinergic neurons in the lateral hypothalamus [4,5].

INSOMNIA

Definition, Epidemiology, and Symptoms

Insomnia is the most common of all sleep disorders, affecting more than 40% of the population every year, with a much higher prevalence in older age groups and women. Despite that, only 10% of affected subjects have a daytime functioning impairment and need treatment. Insomnia is defined as the subject's perception of inadequate or insufficient sleep and poorly restorative sleep due to reduced quality, duration, or efficiency of sleep itself. It is characterized by difficulty in starting or maintaining sleep or early morning awakening. Insufficient sleep must be associated with daytime symptoms such as fatigue, decreased mood or irritability, memory, and attention impairment. These symptoms can lead to a reduced quality of life and can induce physical disturbances, economic repercussions due to poor performance at work, and sometimes medical and legal problems [6]. Insomnia can, therefore, be defined as a 24-hour sleep disorder. Insomnia is defined as a subjective complaint and doesn't usually require instrumental verification. Diagnosis relies on an accurate interview that should assess bedtime habits, daily symptoms, excessive daytime sleepiness (EDS), awakenings (during night and early morning), regularity and duration of sleep, and the presence of leg movements or snoring during sleep [7]. Taking a complete sleep history will help in determining a differential diagnosis among possible sleep-waking rhythm disorders, sleep-related movement or breathing disorders such as circadian rhythm sleep-wake disorders (CRSWD), restless legs syndrome (RLS), periodic limb movement disorders (PLMD), and obstructive sleep apnea syndrome (OSAS). Difficulty initiating sleep, for example, is a common feature in both insomnia and delayed sleep-wake phase disorder (DSWPD). However, patients affected by DSWPD usually sleep a regular or even more considerable amount of time if they can maintain late-rising time. This disorder is also more common in the teenagers. Excessive daytime sleepiness (that is a significant complaint in many cases), lack of attention and concentration, irritability, and behavioral problems are shared with other sleep disorders such as RLS, PLMD, and OSAS, due to sleep fragmentation caused by apneas or leg movements. The repeated episodes of obstruction of the upper airways during sleep in OSAS patients, causing oxyhemoglobin desaturation and micro-arousals, are responsible for memory and attention impairment [8,9], a feature shared with chronic insomnia. Performing actigraphy to determine the sleep-wake rhythm and polysomnography (PSG) or out-of-center sleep testing (OCST) to assess obstructive respiratory events and leg movements would definitively help in diagnosis. Chronic auto-induced sleep restriction should also be considered.

The International Classification of Sleep Disorders (ICSD) 3rd edition (ICSD-3) [6] includes three diagnostic categories for insomnia:

1. chronic insomnia disorder;
2. short-term insomnia disorder; and
3. other insomnia disorder.

Chronic insomnia disorder should be present at least three times per week for at least three months. Short-term insomnia doesn't meet the duration criteria (<3 months).

For many years, insomnia has been classified from an etiopathogenetic point of view that distinguishes primary and secondary forms [10,11].

Primary insomnias are considered to be a distinct diagnostic entity from insomnia, that is a symptom of an underlying medical and psychiatric condition. These patients show a sort of "weakness" of the biological system that regulates sleep, even if sometimes it is possible to find a trigger. They usually begin in young-adult age and, if not treated, may have a chronic course, with potential phases of remission. On the neurophysiological level, the representation of SWS is deficient.

Secondary forms may depend on physical and environmental (e.g., pain), medical (e.g., hyperthyroidism, respiratory disorders), mental (e.g., anxiety, mood), pharmacological (e.g., caffeine, benzodiazepines, alcohol), and situational (e.g., job loss) conditions.

Over the years, several diagnostic nosologies for insomnia have been debated and

diagnostic criteria and classification have changed. The ICSD [12] and the ICSD 2nd edition [13] describe numerous primary and secondary insomnia subtypes and incorporate findings from interviews and laboratory tests. The Diagnostic and Statistical Manual of Mental Disorders IV edition (DSM-IV) [14], from 1994, also distinguishes primary and secondary insomnia. Some authors [15] highlighted that the distribution of diagnoses underlines the importance of psychiatric and behavioral factors in the assessment of insomnia and that diagnostic concordance for these diagnoses likely reflects actual clinical practice.

Some others [16] showed that the best-supported insomnia categories both from DSM-IV TR and ICSD-2 were insomnia related to another mental disorder, insomnia due to a general medical condition, breathing-related sleep disorder, circadian rhythm sleep disorder, and restless legs syndrome. The category of primary insomnia appeared to have marginal reliability and validity.

More recently, the ICSD-3 [6], as well as DSM-V [17] has made a lot of changes from the former editions [18]. All previous chronic insomnia diagnoses merge into a single *Chronic insomnia disorder* (ICSD-3) and *Insomnia Disorder* (DSM-V) diagnosis. This change in insomnia diagnostic criteria in both ICSD-3 and DSM-5 implies a paradigm shift, stresses the comorbid nature of insomnia, and calls for treatment of both insomnia and the medical disorder. That's because, first of all, overlapping primary and secondary insomnias share many symptoms and features. Second, secondary insomnia often develops an independent course over time and may remain as a clinically separate significant condition. Finally, clinical experience suggests that it is rare to encounter patients who meet the diagnostic criteria for exclusively one of the primary subtype (psychophysiological insomnia, idiopathic insomnia, inadequate sleep hygiene, and paradoxical insomnia).

Nevertheless, in the age of "precision medicine", the etiopathogenesis in a specific patient should be taken into account in the choice of both the therapeutic approach and prognosis; therefore, the distinction between primary and secondary forms cannot be based on comorbidity *per se*.

Etiopathogenesis of insomnia is complex and partially unknown. At different levels, genes, molecules, circuits, cognition, and behavior contribute to determining this disorder.

Conceptual Models of Insomnia

Insomnia is often considered to be a disorder of hyperarousal. The increased somatic, cognitive, and cortical activation could take part in the pathophysiology of insomnia along with other contributory factors [19,20].

Numerous sleep regulatory substances are linked to circadian rhythmicity and sleep regulation [21]. Endogenous molecules can be categorized as primarily wake-promoting/sleep-suppressing (e.g., catecholamines, orexins, and histamine) and sleep-promoting/wake-suppressing substances (e.g., γ-aminobutyric acid [GABA], adenosine, serotonin, melatonin, prostaglandin D2) and many of them are linked to insomnia. For example, blood serum melatonin levels are reduced [22], whilst cortisol evening and morning salivary levels are higher [23] in insomnias.

Besides, the activity of arousal and sleep centers is modulated by two critical physiologic processes: wake-dependent sleep drive (homeostatic or process S) and circadian rhythmicity (process C). Sleep propensity is regulated by the interaction of S-process and C-process. Accumulation of extracellular adenosine during prior wakefulness may be the primary input to these systems. One hypothesis based on the two-process model is that insomnia is caused by insufficient sleep propensity during the desired sleep period due to dysfunction in the S- or C-process [24,25]. Behavioral and cognitive mechanisms can also regulate sleep and contribute to, or exacerbate, insomnia [19].

A conceptual model of insomnia, the "Behavioral Model of Insomnia", by Spielman and colleagues in 1987 [26], regarding the etiology of chronic insomnia, put forward what factors should be targeted for treatment. This model suggests that insomnia is due to three main factors.

1. Predisposing factors:
   - biological, including hyperarousal/hyper-reactivity and weak sleep generating system;
   - psychological, including worry or the tendency to be excessively ruminative;
   - social factors, such things as the bed partner, keeping an incompatible sleep schedule or social pressures.
2. Precipitating factors are acute occurrences that interact with the patient's predisposition for insomnia to produce transient sleep initiation or maintenance problems and may be:

- biological, including medical illness and injury;
- psychological, as acute stress reactions and psychiatric illness;
- social, such as factors that change the patient's social environment, that require a significant shift in or disrupt the subject sleep phase.

3. Perpetuating factors are maladaptive coping behavior and cognitive strategies that individuals adopt in an attempt to get more sleep [27].

TREATMENTS

Interventions aimed at preventing or treating insomnia may target various aspects of the different pathophysiologic processes [28].

Treatments can be both pharmacological and non-pharmacological. Pharmacological therapies are directly active on neurotransmission systems (GABA, 5-hydroxytryptamine—5HT aka serotonin, noradrenaline—NA, orexins, melatonin), in contrast, specific non-pharmacological techniques act on specific sleep mechanisms such as the circadian oscillator, the arousal system, and the homeostatic process through educational, cognitive, behavioral, and relaxation techniques.

Pharmacological Treatment

The pharmacological approach can rely on different pharmacological classes, interacting with varying neurotransmission systems. Currently, the most used drugs in the treatment of insomnia are benzodiazepines (BDZ) and non-benzodiazepine drugs (z drugs), to which imidazopyridines (zolpidem) and cyclopyrrolones (zopiclone) belong, all of them interacting with the GABAergic system (BDZ receptor agonists, BDZ-Ra) [29].

The choice among different BDZ molecules mainly depends on the desired duration of the hypnotic effect. As hypnotic, an ultra-short half-life (2-4 hours) medication such as triazolam, or short half-life (3-8 hours) medication such as brotizolam is usually used, while those with an intermediate or long half-life (over 10 hours) are less indicated due to the risk of residual drowsiness after awakening. An important aspect to be evaluated in the choice of the molecule is the different affinity of BDZ for the GABA receptor complex to which they bind. The higher the receptor affinity, the more probably the drug induces tolerance and withdrawal symptoms. This phenomenon is likely due to a variation in the gene expression of the different subunits forming the GABA receptor. To reduce these effects and to avoid abuse conditions, primarily when short- or ultra-short half-life BDZs are used (usually with high receptor affinity), care should be taken not to prolong therapy far beyond four weeks, and discontinuation should also be slow (15-20 days) [30]. The most common side effects of BDZ are cognitive and attentive disorders [31,32], especially for long half-life compounds, anterograde amnesia [33], and ataxia mainly for short half-life compounds [34]. Particular caution is needed in the case of elderly patients [35], due to the slower drug elimination (risk of accumulation) or in subjects with respiratory disease due to the risk of onset or increase of sleep apnea [36]. Insomnia, anxiety, irritability, and depression are the side effects that can occur most frequently at the time of withdrawal [37]. From a neurophysiological point of view, a reduction/suppression of slow-wave sleep has been highlighted [38].

Imidazopyridines and cyclopyrrolones are ultra-short (zolpidem) and short (zopiclone) duration drugs, respectively. They can be used as BDZ substitutes, especially in occasional or transient forms of insomnia. Compared to BDZs, they have less both muscle-relaxing and anxiolytic effects and reduced influence on the sleep structure (slow-wave sleep reduction). The most common side effects after suspension are insomnia and anxiety [39]. Moreover, caution should be used in the elderly, given the possibility of confusional events and high risk of falls and fractures [40,41].

Due to tolerance, inhibition of slow-wave sleep, and risk of residual morning drowsiness from these agents, the attention of sleep specialists has recently shifted towards drugs able to enhance slow-wave sleep, to better "take care" of the neurophysiological characteristics of primary insomnia (characterized by a deficit of this type of sleep). This kind of drug is heterogeneous both in terms of the type of use (antidepressants, neuroleptics, antihistamines, antiepileptics) [42-47] and pharmacodynamics (5HT2a and 5HT2c receptor silent antagonists, α2δCa blockers, melatonin receptor blockers, orexin receptor antagonists). Some of these molecules (e.g., trazodone, agomelatine, mirtazapine, pre-

gabalin, quetiapine, ramelteon) have been marketed for some years and are used off label. Some others still require study or authorization in some countries (suvorexant) [48,49]. Due to the reduced blood levels of melatonin in the elderly, the administration of control release melatonin should be considered in older patients [50].

Recently, American Academy of Sleep Medicine (AASM) and European Sleep Research Society (ESRS) guidelines evaluated hypnotic drug efficacy and safety [47,48].

Unfortunately, even though some data do exist, the overall quality of evidence of recommendations is relatively low for most drugs. As a result, many commonly used drugs, including some approved by Food and Drug Administration (FDA) for the treatment of insomnia, are not recommended. Keeping in mind the weak strength of recommendation, these guidelines suggest (benefits outweigh harms) the use of GABA receptor agonists in insomnia with low/very low (eszopiclone, zaleplon, zolpidem), moderate (temazepam), and high (triazolam) quality of evidence. Some evidence (low) emerge about the use of drugs with different pharmacodynamics, as suvorexant (orexin receptor agonist), ramelteon (melatonin receptor agonist), doxepin (serotonin–norepinephrine reuptake inhibitor), but the use of other drugs (tiagabine, trazodone, melatonin) is uncertain. This evidence, reflecting a low degree of certainty in the outcome and appropriateness of care strategy, should not be considered as an indication of ineffectiveness, but suggests clinicians to use their clinical knowledge and experience and refer to the individual patients' values and preferences to determine the best course of action.

Non-Pharmacological Treatment

Although the treatment of insomnia has traditionally been pharmacological, many non-pharmacological therapies have been developed over the years. There is consensus in the scientific and professional sleep community that cognitive-behavioral therapy should be the treatment of choice for chronic insomnia [47,48,51]. The cognitive-behavioral therapy for insomnia (CBT-I) includes a complex of techniques such as relaxation techniques, stimulus control, sleep hygiene, cognitive therapy, biofeedback, chronotherapy, sleep restriction, multi-component treatment, and self-help treatments. To date, CBT-I is considered the first therapeutic choice and ideally must be implemented before hypnotics are prescribed [47,52-57].

Different CBT-I techniques work on various factors to restore appropriate sleep hygiene, re-establish a proper sleep-wake rhythm, lower hyperarousal, and adequate homeostatic pressure. Psychological and behavioral interventions are considered to be effective in the treatment of both chronic primary insomnia (AASM-Standard) and secondary insomnia (AASM-Guideline) [58].

Sleep Hygiene

Proper sleep hygiene is an essential prerequisite for the treatment of insomnia regardless of other therapeutic approaches. Its benefit is maximized when provided as part of a comprehensive plan. The term "sleep hygiene" (SH) refers to all those behaviors that are considered as promoters of an adequate quantity and quality of sleep. Generally speaking, sleep hygiene can be conceived as a guide to "lifestyles" and behaviors that contribute to the creation of a healthy and regular sleep pattern [59,60]. Avoiding to extend the time of bed, exercising to promote good quality sleep, making sure that the sleep environment is pleasant, avoiding food that can be disruptive right before sleep, and avoiding stimulating substances (caffeine and nicotine) and alcohol in the evening are some of the rules. Therefore, the main objective of a sleep interview is to verify patients' habits and if the environment in which they sleep is following the rules of sleep hygiene. More recent adaptations, often included as part of therapeutic programs, contain more information about the role of food and the place for sleep. The American Academy of Sleep Medicine highlights insufficient evidence to recommend sleep hygiene education as a single therapy, but it should be associate with other insomnia treatments [53,56,58].

Sleep Restriction

The restriction of sleep (Sleep Restriction Therapy, SRT) has been conceived by Spielman, Saskin, and Thorpy in the '80 [61].

Most people suffering from insomnia think that spending time in bed, trying to sleep, can more easily shorten sleep latency; this incorrect behavior is considered one of the perpetuating factors of insomnia and is targeted by sleep restriction therapy.

SRT forces patients to limit the amount of time they spend in bed to an amount equal to their average total sleep time as obtained by baseline sleep diary measures. The clini-

cian establishes a fixed wake time according to the patient's needs. Once a target amount of time in bed is set, the patient's bedtime is delayed to later in the night so that the time in bed (TIB) and average total sleep time (TST) are the same. As sleep efficiency (TST/TIB*100) increases (at least 90%), patients are instructed to gradually increase the amount of time they spend in bed (15-minute). The treatment usually lasts eight weeks. The patient is also given additional advice not to take afternoon naps or to stick to prescribed bedtime.

The reduction of time spent in bed, although it may seem paradoxical for those patients who try to sleep more, necessarily influences the homeostatic and circadian regulation of sleep [62]. This method creates a mild sleep deprivation, which decreases sleep latency, reduces the wake after sleep onset, and promotes a more reliable and efficient sleep and a lower variability among nights. SRT appears to have a comparable risk profile for excessive sleepiness as CBT-I, and thus may be considered a less time-consuming alternative to CBT- I [63]. SRT is regarded as individually effective therapy (AASM-Guideline) and meets the criteria for empirically-supported psychological treatments for insomnia [58,56].

Stimulus Control

Often, it happens that people suffering from insomnia are frustrated when lying in bed trying to fall asleep, so they engage in behaviors other than sleep (e.g., reading, eating, watching TV). This behavior creates a negative association between bedtime routine and sleepiness/sleep, with the consequent inability to sleep. The Stimulus Control Therapy (SCT) [52,64] is focused on re-establishing a "positive connection" between the bed/bedroom/bedtime and a rapid-onset, well-consolidated sleep. Instructions limit the amount of time one may spend in the bedroom while awake and the kind of behaviors one may engage in while in the bed/bedroom and consequently discourages the association between bedtime and inability to sleep. Typical instructions include:

1. lie down only when sleepy;
2. avoid any behavior in the bed or bedroom other than sleep or sexual activity;
3. leave the bedroom if awake for more than 15 minutes; and
4. return to the bed only when sleepy.

This technique has the dual purpose of avoiding behaviors against sleep hygiene rules and, as in case of sleep restriction, influencing the sleep homeostat. SCT is considered an individually effective therapy (AASM-Standard) and meets the criteria for empirically-supported psychological treatments for insomnia [56,58].

Autogenic Training and Relaxation Techniques

Autogenic training is a combination of muscular relaxation and imaginative techniques. This method implies learning self-inducted relaxation and imaginative techniques to reduce hyperarousal, which is frequently associated with increased sleep latency. Progressive muscle relaxation is used to diminish skeletal muscle tension [65-68]. Autogenic training involves thinking to some neutral and/or pleasant images to focus purely on their descriptive properties. Imagery training involves the patient in selecting a relaxing image or memory and evoking the image and engaging with it from a multisensory perspective. Progressive muscle relaxation is considered an individually effective therapy (AASM-Standard) and meets the criteria for empirically-supported psychological treatments for insomnia [56,58].

Cognitive Techniques

Cognitive therapy is based on the assumption that negative emotions, maladaptive behaviors, and physiological symptoms associated with specific disorders are mostly the effects of dysfunctional cognitions. As a result, a person may develop a sleep disorder caused by stressful events. Still, the disorder itself can be exacerbated by the personal concept of insomnia and its consequences, and by one's perception and interpretation of such events. Cognitive therapy is a structured psychoeducational intervention that is based on a wide variety of techniques.

It consists in guiding the patient in considering insomnia and its consequences from a more realistic and rational perspective. The most crucial point is to explain that personal interpretation of a given situation can modulate the type of emotional reaction to situation itself. Therapy begins by identifying the patient's dysfunctional thoughts about sleep. Then, it is important to encourage the patient to consider his concepts only as one of the many possible interpretations instead of absolute truth.

Different cognitive restructuring techniques (paradoxical intention, "distraction and imagery", revaluation, realignment, attention deviation, and hypothesis exami-

nation) can be used to change maladaptive cognitions [51,69]. The AASM stated insufficient evidence to recommend cognitive therapy as single therapy. Positive outcomes have been highlighted if part of a multifaceted intervention, even if the specific contribution of cognitive therapy remains unclear [53,56,58].

Although the American College of Physicians (ACP) recommends that all adult patients receive cognitive behavioral therapy as the initial treatment for chronic insomnia disorder (Grade of recommendations: strong; quality of evidence: moderate) [51], CBT-I is currently underused in clinical practice.

There are still many reasons that prevent CBT from being prescribed as a first therapeutic choice. First of all, if and when professional treatment is sought, it is typically from a primary care physician, and medication is often the first and only treatment provided. Second, many individuals don't want to be misunderstood and considered to have a psychological problem. Third, both individuals and physicians are often unaware of non-pharmacological therapies. Fourth, CBT is more time-consuming than prescribing medications. Finally, there are few providers with adequate training to provide CBT for insomnia [70]. For that reason, a system of standardized CBT-I training and training center accreditation should be implemented to increase the number of sleep medicine centers offering this treatment option [71,72].

CBT is sometimes associated with medications to strengthen their power or in case you need to discontinue therapy because of either physical or psychological addiction [59]. Non-pharmacological treatments are also used for those who are reluctant to use medications, although they may benefit from an occasional pharmacological treatment. On the contrary, the pharmacological approach is introduced when the subjects would not be able to follow therapy properly or when more immediate and short-term symptomatic treatment is required [73].

Numerous meta-analyses [47,55,57,74-76] demonstrated good efficacy for CBT-I, or its components, in patients with primary insomnia on sleep-related outcome parameters, and good stability of the results at follow-up assessments. On the other side, also pharmacotherapy has been widely studied [51,77-80] and, as previously discussed, variable benefits/harms ratio has been found. Generally, drugs are able to obtain fast effects and are widely available, but have the risk to produce adverse events, such as daytime sedation, and to generate tolerance and dependence. In addition, their effect may disappear after discontinuation. Conversely, psychological/behavioral therapy showed only minimal side effects, is preferred by several patients, and produces long-lasting benefits [81].

According to ACP recommendations, physicians should share a decision-making approach, which includes a proper discussion on benefits, harms, and costs of short term use of drugs, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful (grade: weak; evidence: low quality) [51].

On the other side, treating insomnia with CBT-I, instead of medications, has several potential advantages, such as fewer known side effects, and an explicit focus on treating the factors that may be responsible for perpetuating chronic insomnia, aiming at producing long-lasting results.

Some patients also prefer non-medication treatments [82,83]. Long-term studies consistently favor CBT-I over both benzodiazepines and non-benzodiazepines for improving sleep efficiency [84,85].

CBT-I is at least as effective for treating insomnia when compared with sleep medications. Its effects may be more durable than medications with potentially no side effects [86]. Some techniques cannot be used if patients are also affected by epilepsy or bipolar disorders [62] and, of course, CBT requires a high level of compliance, more extensive provider contact, and has a slower therapeutic action than medications. Although significant clinical gains can be made in a relatively short number of treatment sessions, CBT has a longer latency of action than BDZ or BDZ agonists.

CONCLUSION

Both CBT techniques and medications can be used in the treatment of insomnia. They should be modulated and used according to the clinical situation, and treatment effectiveness could be influenced by patient characteristics, such as age or comorbid diagnoses. Both pharmacological and non-pharmacological approaches should be used in everyday clinics to manage insomnia and

improve patients' quality of life, combining, if possible, sleep hygiene, a simplified version of sleep restriction (sleep compression), and tailored medications [83]. Typically, short-term insomnia may benefit from brief (<10 weeks) hypnotic treatments with imidazopyridines or benzodiazepines, monitoring potential abuse and side effects, together with a non-pharmacological approach (relaxation techniques, stimulus control, sleep hygiene).

In the case of chronic insomnia, often primary insomnia associated with chronic benzodiazepine treatments or abuse, the treatment should include the progressive suspension of GABAergic drugs and the simultaneous use of non-pharmacological therapies (e.g., sleep hygiene rules combined with sleep restriction and stimulus control). Pharmacological treatment with slow-wave sleep enhancers (currently off label) could also be considered in non-responders and to avoid tolerance or in case of psychiatric comorbidity (mood depression, anxiety).

The benefit of the pharmacological therapy, in the case of primary forms, usually takes 2-6 weeks and is significantly affected by adherence to behavioral therapies; treatment is generally maintained for prolonged periods (8-12 months). In the event of recurrence, non-pharmacological techniques may be used as early as possible, with good chances of restoring a correct sleep-wake cycle without the need for pharmacological treatments.

Only a few studies [84,87,88] included a combination of CBT-I and medication treatment. Outcomes were generally comparable to those receiving CBT-I alone. In contrast, a sequential treatment strategy that commenced with six weeks of combined therapy (CBI + drug, mainly BDZ, and non-BDZ) followed by an extended 6 months of CBT alone proved superior to the continued long-term combined therapy or CBT provided in the absence of any medication [89]. Future studies should examine additional strategies for combination treatment that capitalize on the relative advantages of medications (rapid onset on the therapeutic response) and CBT-I (long-term durability of treatment gains) also in the comorbid patient.

Key points

- *Insomnia should be considered a 24-hour sleep disorder*
- *Etiopathogenesis of insomnia should be considered in managing the treatment*
- *Short-term insomnia may benefit (in term of benefits vs. harms) from brief hypnotic treatments with different quality of evidence between imidazopyridines, cyclopyrrolones (low), and benzodiazepine (moderate-high), but weak strength of recommendation in both cases (AASM and ESRS Guidelines)*
- *Hypnotics might be associated with a non-pharmacological approach (ACP: weak grade of recommendation)*
- *Chronic insomnia should be treated with non-pharmacological therapies (while GABAergic drugs should be tapered progressively off) as follow:*
  - *sleep hygiene should be added as part of a comprehensive plan (AASM);*
  - *sleep restriction is considered individually effective therapy (AASM Guideline);*
  - *stimulus control and progressive muscle relaxation are considered individually effective therapy (AASM Standard);*
  - *cognitive therapy is not recommended as single therapy but leads to positive outcomes if part of a multifaceted intervention (AASM)*
- *Treatment with slow-wave sleep enhancers should be added to CBT techniques only if needed*
- *Pharmacological and non-pharmacological therapy should be tailored to manage insomnia and improve patients' quality of life*

Funding

This article has been published without the support of sponsors.

Conflicts of interests

The authors declare he has no competing financial interests concerning the topics of this article.

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