Sleep and Sleep Disorders 2

Insomnia

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Insomnia is highly prevalent in clinical practice, occurring in up to 50% of primary care patients. Insomnia can present independently or alongside other medical conditions or mental health disorders and is a risk factor for the development and exacerbation of these other disorders if not treated. In 2016, the American College of Physicians recommended that insomnia be specifically targeted for treatment. The recommended first-line treatment for insomnia, whether the underlying cause has been identified or not, is cognitive behavioural therapy for insomnia (CBT-I). Currently, there is no global consensus regarding which pharmacological treatment has the best efficacy or risk-benefit ratio. Both CBT-I and pharmacological intervention are thought to have similar acute effects, but only CBT-I has shown durable long-term effects after treatment discontinuation. Administering a combined treatment of CBT-I and medication could decrease the latency to treatment response, but might diminish the durability of the positive treatment effects of CBT-I.

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Introduction

Insomnia occurs in up to a third of the adult population worldwide.[1] Although insomnia often occurs comorbidly with other medical conditions (eg, cardiometabolic diseases) or mental health disorders (eg, depression), treatment for insomnia should be provided regardless of the presence or absence of any comorbid illnesses that could have precipitated the insomnia. Pharmacological and behavioural treatments for insomnia are available. The acute treatment effects of these two methods are similar (eg, in pretreatment to post-treatment changes in sleep continuity over 1 week or more)[2–5] but the better safety profile and durability of the behavioural approach have made it the recommended first-line treatment for insomnia.[6–8] This Series paper provides an update of the definition and diagnosis of insomnia, summarises treatment types and their absolute and relative efficacy and safety, and comments on future prospects for assessment, therapeutics, and alternative treatment regimens. The first and third papers in this Series are published in *The Lancet* and discuss excessive daytime sleepiness[9] and disorders of the timing of sleep,[10] and the fourth paper is published in *The Lancet Neurology* and discusses an evolutionary perspective of sleep function.[11]

Signs and symptoms of insomnia

Insomnia is defined as sleep continuity disturbance associated with daytime complaints related to sleepiness, fatigue, somatic symptoms (eg, head or body aches), mood disturbance, compromised cognitive or occupational function, concerns about sleep, or dissatisfaction with sleep. Sleep continuity refers to variables that represent sleep performance, including sleep latency, number of awakenings, wake after sleep onset, total sleep time, and sleep efficiency. If one or more of these variables are pathological, their occurrence can be referred to as sleep continuity disturbance.[12] The use of this term encourages a specificity that is unconfounded by the many denotations and connotations of the term insomnia. When sufficiently frequent and chronic, sleep continuity disturbance is classified as insomnia disorder. In the third edition of the *International Classification of Sleep Disorders* (ICSD-3) and the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), the primary–secondary distinction has been removed. This change implies that, regardless of any diseases that occur comorbidly with insomnia, sleep continuity disturbance itself should be targeted for treatment if it is chronic.

Severity

Neither the ICSD-3 nor the DSM-5 have quantitative severity criteria for insomnia disorder; it is up to the clinician to judge what is severe enough to treat. Although clinical researchers tend to use a 30 min rule (eg, takes 30 min or more to fall asleep, 30 min or more spent awake in the night, or continuously awake for 30 min or more before desired wake-up time), individual clinical judgement is still required when assessing whether sleep continuity disturbance lasting less than

Search strategy and selection criteria

PubMed, PsychNet, and the Cochrane Library were searched from Jan 1, 1970, to Jan 1, 2021, with the terms "insomnia", "CBT-I", "pharmacologic treatment", each indicated treatment for insomnia ("zolpidem", "temazepam", "triazolam", "zolpidem", "eszopiclone", "zaleplon", "daridorexant", "suvorexant", "lemborexant", "ramelteon", "melatonin", and "doxepin"), and "meta-analysis". Information was also extracted from relevant medication package inserts and from selected chapters from the *Principles and Practice of Sleep Medicine*. The search was restricted to studies published in English and conducted with human participants. Relevant references were also suggested by the authors and reviewers of this Series paper, which were sourced from various locations, such as journals, conferences, online databases and searches, and reference lists of relevant papers.

30 min is of a severity that warrants treatment. The ICSD-3 and the DSM-5 define illness severity in terms of problem endorsement (eg, when the patient says it's a problem). Alternatively, treatment might be warranted when total time during the night lost to sleep latency, wake after sleep onset, and early morning awakenings are greater than a threshold that is set by the clinician (eg, 30 min, 45 min, or 60 min) or when sleep efficiency is less than optimal (<85%; sleep efficiency is equal to total sleep time as a percentage of time in bed).[12] 85% is also the standard threshold value of sleep efficiency used to decide when to decrease prescribed time in bed during sleep restriction therapy.[12]

Frequency

The criterion for diagnosing insomnia disorder is 3 or more days per week of sleep continuity disturbance. This frequency criteria was first adopted in 2013 with the publication of the ICSD-3 and the DSM-5. One point of discussion regarding this criterion is the use of 3 days per week as the threshold for frequent, as opposed to less or more than this amount of time. Sleep continuity disturbance occurring fewer than 3 days per week, or occurring on an interval basis (eg, occurring periodically instead of being relatively constant), might not be considered clinically consequential or might represent a different sleep disorder (eg, delayed sleep–wake phase disorder). Also of interest is the low upper limit (3 or more days per week as opposed to 5 or more days per week). This stipulation could be an intuitive acknowledgment of the observation that the incidence of insomnia is rarely 5 or more days per week. The episodic or cyclical nature of insomnia incidence is probably due to the homoeostatic regulation of sleep.[13,14] For example, if an individual sleeps poorly on multiple successive nights, and therefore does not fulfill their sleep need, the result is an increase in so-called sleep debt. After a period of time (eg, 3–5 nights of poor sleep), an individual might have enough sleep debt (sleep pressure) to result in a better-than-average night of sleep or a good night of sleep. The proposition that insomnia does not typically occur on a nightly basis, but instead occurs episodically, has been evaluated in two studies.[15,16] These studies reported that for approximately every 3 nights of insomnia an individual has, that individual has at least 1 better-than-average night of sleep or at least 1 good night of sleep. Therefore, the consensus of using 3 or more days per week of sleep continuity disturbance is justifiable based on data regarding the rhythm of insomnia. There are at least two studies, however, investigating the night-to-night variability of insomnia symptoms that contradict these findings.[17,18] One of these studies found that night-to-night variability of insomnia symptoms could be profiled into three types, only one of which showed that insomnia occurred on an episodic basis.[17] The other study detected no discernible pattern or rhythm regarding the incidence of insomnia.[17,18]

Chronicity

The criterion for chronic insomnia, or insomnia disorder, is that sleep continuity disturbance for 3 or more days per week persists for at least 3 months. A threshold is required to distinguish between normal insomnia, acute insomnia, and chronic insomnia. This definition of chronicity is based on the consensus of experts in the field, but such consensus views are often provided without detailed rationales. For example, chronic insomnia might be defined on the basis of the amount of time that must elapse before the insomnia is unlikely to subside. Alternatively, it might also be defined on the basis of the amount of time it takes a patient to focus on the insomnia as opposed to the precipitant of the insomnia,[19] engage in behaviours that perpetuate insomnia,[20] spend enough time in bed over successive nights to promote conditioned wakefulness, or develop neurobiological changes that promote sleeplessness or states that are neither wake nor sleep—also known as hybrid states.[21–23] Ultimately, establishing what constitutes normal, acute, and chronic insomnia will require many research questions to be answered, most through longitudinal natural history studies.

Chronicity might be the least important factor regarding whether or not to engage treatment as the most conservative chronicity criterion is the most clinically useful; an assessment or an intervention is warranted after a patient has insomnia symptoms for 2 weeks or more. This criterion might represent the optimal time to engage in medical management of insomnia, such as an aggressive short-term treatment regimen to alleviate symptoms, prevent the occurrence of sleep related worry, and obviate the need for compensatory behavioural strategies.

Ultimately, the issue of chronicity might be irrelevant as most patients do not seek treatment until they have had insomnia for months, years, or decades. For chronicity to truly be relevant, patient reporting or clinician querying of behaviour will have to change. Patients should be encouraged to disclose when they are not sleeping well and clinicians should be encouraged to inquire about sleep health.[24] This change could be implemented as part of the annual physical check-up of an individual by adding a sleep inquiry to the other 14 systems identified for review by the US Centers for Medicare and Medicaid Services.[25] This inquiry could simply be asking a patient to rate their sleep quality during the last 7 days.[26] One reason to promote the use of sleep inquiries in clinical settings is that early detection of insomnia could better position medical staff to manage acute insomnia, and therefore potentially prevent development of chronic insomnia. Moreover, early diagnoses of and interventions for insomnia could positively influence the clinical course of any medical comorbidities that might occur alongside or be exacerbated by insomnia disorder (panel 1).

Treatments indicated for insomnia disorder

Approaches to the treatment of insomnia are numerous and varied, and include dietary supplements, naturopathic medications, non-evidenced-based behavioural remedies, national-agency-approved medications (eg, medications approved by the US Food and Drug Administration [FDA], the European Medicines Agency, the Australian Therapeutic Goods Administration, or the Pharmaceuticals and Medical Devices Agency of Japan), and cognitive behavioural therapy for insomnia (CBT-I). Over the past 20 years, most of the regulatory agencies and professional societies that make practice recommendations for the treatment of insomnia have recommended both agency-approved medications and CBT-I for the treatment of insomnia (with caveats related to the evidence base for each therapeutic or class of therapeutics). In 2016, the American College of Physicians[6] recommended that CBT-I be used as the first-line therapy for insomnia. This decision was based explicitly on the safety and efficacy profile of CBT-I. Although not overtly acknowledged, the decision was also potentially influenced by the finding that only CBT-I treatment has durable outcomes (clinical effects that persist after treatment discontinuation for periods measured up to 2 years).[35,36] This recommendation has since been supported by several professional societies.[7,37–39]

Cognitive behavioural approach

CBT-I is a multicomponent therapy that usually consists of four core treatments: stimulus control, sleep restriction, sleep hygiene, and cognitive therapy. Some treatment protocols do not include sleep hygiene or cognitive therapy, whereas other treatment protocols include some form of relaxation training (eg, progressive muscle relaxation, diaphragmatic breathing, or autogenic training). The technical specifications for the component therapies (eg, sleep restriction rules) vary from manual to manual.[12,40–43]

Stimulus control therapy

The administration instructions for stimulus control therapy[44,45] include restricting behaviours that occur in the bedroom to sleep and sex, limiting the amount of

***Panel 1*: Types and subtypes of insomnia**

Beyond insomnia as a general classification

- Insomnia is frequently described in terms of types and subtypes
- Insomnia types are based on the putative cause or unique clinical profile of the insomnia (eg, idiopathic insomnia, psychophysiological insomnia, or paradoxical insomnia)
- Insomnia subtypes are based on the tradition of characterising insomnia in terms of the presenting complaint of a patient (eg, initial insomnia, middle insomnia, or late insomnia)

Insomnia types

- Idiopathic insomnia, also referred to as childhood-onset insomnia, appears to be lifelong
- Psychophysiological insomnia appears to have cognitive and behavioural features, and a physiological basis
- Paradoxical insomnia considers subjective and objective measures of insomnia severity that are substantially discordant (eg, when the subjective measure of sleep latency is 60 min but the objective measure is 20 min); there is no quantitative definition for this form of insomnia (eg, how much discordance is pathological)[27]
  - These classifications have clinical value as psychophysiological insomnia is thought to respond most to treatment and idiopathic insomnia and paradoxical insomnia are thought to respond least to treatment
  - Other types of insomnia include inadequate sleep hygiene insomnia, physiological insomnia, and insomnia because of a mental health disorder, medical condition, or substance use or withdrawal
  - Arguably, diagnoses of insomnia because of a mental health disorder, medical condition, or substance use or withdrawal represent forms of acute insomnia as the precipitant is clearly identified

Insomnia subtypes

- Initial insomnia, also referred to as sleep-onset insomnia, refers to difficulty falling asleep
- Middle insomnia refers to difficulty staying asleep after having initially fallen asleep; such episodes can be protracted but are followed by additional bouts of sleep
- Late insomnia, also referred to as terminal insomnia, refers to nocturnal awakenings that persist until the end of the given sleep period has elapsed (eg, from the time of awakening until the start of the day)

Diagnosing insomnia types and subtypes

- All diagnoses of insomnia types and subtypes mentioned in this panel are made based on the clinical presentation of patients
- Patients can be diagnosed on the basis of their psychological profile, physiological profile, neurophysiological profile, or genetic profile; for example:
  - Vgontzas and colleagues[28,29] and Fernandez-Mendoza and colleagues[30] have effectively subtyped patients with insomnia using polysomnography measures of total sleep time
  - Blanken and van Someren[31] and Blanken and colleagues[32] have effectively subtyped patients with insomnia using their life history and affective trait histories
  - Stein and colleagues[33] and Hammerschlag and colleagues[34] have effectively subtyped patients with insomnia using genome-wide analysis studies

time spent awake in bed or the bedroom, ensuring that the bed and bedroom environment are tightly coupled with sleep, and making sure the patient goes to bed and gets out of bed at the same time each day, regardless of sleep quality. The proposed mechanism of action for stimulus control therapy is thought to be the re-establishment of both the bed and the bedroom as discriminative stimuli for sleepiness and sleep, and the extinction of the conditioned insomnia response. Furthermore, stimulus control therapy probably allows for homoeostatic priming (increased sleep pressure) at night by preventing microsleeps during nocturnal waking intervals. The implementation of stimulus control therapy is based on a series of standardised rules regarding timing issues (eg, when to leave and return to the bedroom). Stimulus control therapy is probably most effective when implemented by a skilled therapist who can support the patient in finding solutions to anticipated problems adhering to the therapy (eg, not being able to leave the bed or bedroom while awake at night). Details of these rules from established therapist CBT-I manuals have been reported elsewhere.[43] The side-effects of stimulus control therapy, although not systematically documented, can include transient decreases in total sleep time owing to reduced opportunity for sleep, increased daytime fatigue, and increased sleepiness.

Sleep restriction therapy

Sleep restriction therapy[12,46,47] requires the patient to limit the amount of time they spend in bed to an amount equal to their average total sleep time, as assessed prospectively with high-density sampling of self-reported sleep continuity (daily sleep diaries). For example, if the average total sleep time of a patient is 6 h and their average time in bed is 8 h, the amount of time in bed prescribed under sleep restriction therapy is 6 h. This component of therapy, also referred to as sleep rescheduling, requires that the clinician matches sleep ability (total sleep time) with sleep opportunity (time in bed) by delaying the time a patient gets into bed and specifying the time they get out of bed. Once sleep is efficient (eg, sleep efficiency is ≥90%), time in bed is incrementally increased, usually by 15 min per week. The mechanism of action for sleep restriction therapy derives from the alignment of sleep opportunity and sleep ability and the enhancement of sleep drive (sleep pressure) by extending the time a patient is awake per day. Evidence-based implementation of sleep restriction therapy requires daily data that are assessed weekly with a series of standardised rules. As with stimulus control therapy, sleep restriction therapy is probably most effective when implemented by a clinician who is adept at finding solutions to patient resistances, such as issues delaying the time the patient gets into bed. Details of the rules and algorithms of sleep restriction therapy from established therapist CBT-I manuals have been published previously.[43] The side-effects of sleep restriction therapy include transient decreases in total sleep time, increased daytime fatigue, and increased sleepiness.[48,49] These side-effects can be substantial for the first 1–3 weeks of treatment and can be associated with other sequelae related to sleep loss, such as irritability, headaches, body aches, and gastrointestinal discomfort.[48,49] The primary outcome of concern for sleep restriction therapy pertains to iatrogenic sleepiness and the effects on daytime performance (eg, driving).

Sleep hygiene

Sleep hygiene[50,51] requires that the patient review a set of instructions that aim to help them maintain good sleep habits, ideally done with a clinician. These instructions are largely based on a set of common sense principles regarding sleep health (eg, go to bed and get out of bed at the same time each day), and vary widely from clinic to clinic. Often, simplified versions of stimulus control therapy instructions are included, such as instructing an individual to get out of bed when they cannot sleep. It is generally held that sleep hygiene is not effective as a monotherapy. This perception might have occurred because of the common practice of sleep hygiene being used as a control condition for CBT-I trials. It could also be an overgeneralisation from a report by the American Academy of Sleep Medicine[52,53] that concluded that there is insufficient evidence to recommend sleep hygiene as a single therapy. To our knowledge, the implementation of sleep hygiene has no known side-effects.

Cognitive therapy

Cognitive therapy[54–56] is an amalgam of techniques that aim to have patients reassess their sleep-related beliefs that are often misinformed, overvalued, and catastrophic. The strategies used in cognitive therapy focus on helping the patient to discover their implicit or explicit dysfunctional beliefs about sleep, gathering evidence for and against the validity of these beliefs, and generating responses to cope with or overcome them. The aim of this process is to decrease overall sleep-related worry and sleep-related effort. Furthermore, cognitive interventions aim to increase patient adherence with the behavioural aspects of CBT-I (eg, a required delay in time to bed with a specified time out of bed, regardless of the quality or quantity of sleep each night). Other forms of cognitive therapy can be used to address problems that are thought to exacerbate nocturnal wakefulness, including thoughts that precipitate anxious or depressed mood.

Efficacy and effectiveness of CBT-I

Changes after treatment

Sleep latency and wake after sleep onset time are typically reduced from 45–60 min before treatment to 20–35 min after treatment. These absolute changes correspond to an approximate 50% reduction in symptom severity and to pretreatment to post-treatment effect sizes of 1·0–1·2.[3,5,57,58] Early morning awakening measures are

generally combined with wake after sleep onset times. Therefore, little is known about the direct effects of CBT-I on late insomnia.

Total sleep time is minimally affected during six to eight sessions of CBT-I, with only about 45% of patients exceeding baseline total sleep time at acute treatment end.[3,5,58,59] These total sleep time outcomes correspond to mean changes in sleep continuity of less than 30 min and less than a 10% change in sleep duration. Within-patient effect sizes are 0·15–0·46.[3,5,58] When insomnia severity is assessed before and after treatment (eg, by using the Insomnia Severity Index [ISI]),[60] within-patient effect sizes and between-patient effect sizes are consistently larger than single measures of sleep continuity, with a within-patient effect size of around 2·0.[58] The ISI assesses illness severity (magnitude of sleep continuity disturbance), but also allows for multiple measures of insomnia-related daytime impairments. When evaluating the percentage of patients exhibiting treatment responses (eg, pretreatment to post-treatment scores of more than –8 on the ISI), 60–80% of patients have a therapeutic response during acute treatment.[61,62]

Durability

Long-term randomised controlled trials (RCTs) of CBT-I found that sleep latency effects and wake after sleep onset effects are stable for up to 24 months,[35,63,64] indicating that clinical gains are maintained for months or years after treatment is discontinued. Total sleep time effects, which are initially marginal, appear to increase over time. When followed up longitudinally, patients exhibit an average increase in total sleep time of around 50 min.[59,63] These improvements in total sleep time do not appear to be related to additional improvements in sleep latency or wake after sleep onset, but instead are likely to be related to increased time in bed while maintaining good sleep efficiency. When evaluating the percentage of patients who exhibit remission, 50–60% of treatment responders have remission in the 6–12 months after CBT-I (ISI scores ≤8). These durability findings have been corroborated in a large-scale clinical case series study[36] that found that mean ISI values from the end of CBT-I (T1) to follow-up (T2, 4–10 years later) were stable (baseline ISI=17·1 [SD=4·5], T1=9·7 [SD=4·6], T2=9·9 [SD=6·3]). In 2019, a meta-analysis showed that CBT-I continues to be effective at month 3, month 6, and month 12 when compared with no active treatment, but that clinical gains in the active treatment group appear to decline over time.[64] The results of this meta-analysis might differ from results reported in other single studies because of differences in the administration of CBT-I across studies. If differences in the administration of CBT-I provide different long-term outcomes, and the individual studies used robust methodologies, then durability outcomes of the meta-analysis could be the result of the inclusion of studies with small magnitude outcomes and greater variability in the effect size estimates.

Trial settings and safety issues

The conclusions drawn from RCTs are often subject to scepticism; RCT outcomes are widely believed to represent the best-case scenario. This perspective is a result of the belief that RCTs are populated by healthy patients—individuals that have the illness of interest but do not have comorbid disorders—whereas patients in clinics or hospitals often have complex medical, psychiatric, and psychosocial profiles, and therefore might be less responsive to targeted treatments than patients in RCTs. In perhaps the first evaluation of this idea, a clinical case series of 47 patients[65] found that they had an average 23 min decrease in sleep latency (d=1·00), an average 39 min decrease in wake after sleep onset (d=1·09), and an average 20 min increase in total sleep time (d=0·36).[65] These data are similar to those seen in meta-analyses, which suggests that patients in clinics or hospitals might benefit from CBT-I to the same extent as patients in clinical trials. This result could be due to a variety of factors, including better treatment outcomes because of professional therapists, tailoring clinical treatment to individual cases, or to other factors, such as patients in clinics or hospitals paying for treatment versus patients in RCTs being paid to be treated.

The in-clinic data also give credence to the concept that CBT-I can be effective in treating insomnia even when it is comorbid with other medical and behavioural disorders. This concept has been evaluated across a wide array of single-disorder RCTs (eg, insomnia comorbid with depression;[66,67] bipolar disorder;[68,69] post-traumatic stress disorder;[70,71] generalised anxiety disorder;[72,73] schizophrenia or psychosis;[74,75,76] cancer;[77,78,79] heart failure;[80,81] chronic pain;[82,83,84] multiple sclerosis;[85,86] addiction to alcohol;[87,88] chronic obstructive pulmonary disease;[89,90] and obstructive sleep apnea).[91,92] All these RCTs found that CBT-I was effective in treating insomnia with comorbid disorders. Most studies found that treatment outcomes in patients with insomnia comorbid with other disorders were similar to those observed in patients with primary insomnia.

CBT-I is widely assumed to be free from side-effects and drug interactions. Both assumptions are untrue. Sleep restriction therapy, and to a lesser extent stimulus control therapy, have the side-effect of increased daytime sleepiness.[49,93,94] Although this side-effect is usually transient (1–3 weeks in duration), special precautions should be taken. These precautions include making sure the patient is aware of potential adverse effects and developing a plan to manage behaviours that might result in accidents or injuries because of increased daytime sleepiness (eg, driving or operating heavy machinery). With regard to drug interactions, sleepiness as a result of CBT-I might be augmented by medications that produce similar effects (eg, antihistamines, β blockers, or sedative antidepressants).

Pharmacological approaches

There are four agency-approved approaches regarding pharmacological treatment of insomnia. Each approach has a different mechanism of action, one or more compounds within its class, and multiple RCTs assessing its safety and efficacy. Of note, most pharmacological RCTs are conducted for 1–3 months, with some studies having longer assessment periods or open-label extensions of 6–12 months. Information about off-label approaches is not provided in this Series paper (eg, trazodone, mirtazapine, and quetiapine). The first pharmacological approach to the treatment of insomnia

	Dose range (mg)*	Maximum dose (mg)†	Time to maximum concentration (h)	Half-life (h)	Mechanism of action	Metabolism	Contraindications	Common side-effects
Benzodiazepines								
Temazepam	7·5–30	15	1·5	3·5–18·4	Indirect GABA agonism of BZ1 and BZ2 receptors	Glucuronidation	Hypersensitivity to benzodiazepines; respiratory failure (eg, chronic obstructive airways disease)	Drowsiness, dizziness, lightheadedness, difficulty with coordination
Triazolam	0·25–0·5	0·25	2	1·5–5·5	Indirect GABA agonism of BZ1 and BZ2 receptors	*CYP3A*	Hypersensitivity to triazolam; concomitant use with strong *CYP3A* inhibitors	Drowsiness, headache, dizziness, lightheadedness, paresthesias, difficulty with coordination‡
Non-benzodiazepine benzodiazepine receptor agonists								
Zolpidem§	5–10	10	1·5	2·5–2·6	Indirect GABA agonism of BZ1 receptor	*CYP3A4*; *CYP1A2*; *CYP2D6*	Hypersensitivity to zolpidem; complex sleep behaviours after taking benzodiazepines or benzodiazepine receptor agonists	Dizziness, drugged state, allergic reaction, diarrhoea, nausea, headache, somnolence, visual disturbance, fatigue
Eszopiclone	1–3	3	1	6	Indirect GABA agonism of BZ1 receptor	*CYP3A4*; *CYP2E1*	Hypersensitivity to eszopiclone; complex sleep behaviours after taking benzodiazepines or benzodiazepine receptor agonists	Taste disturbance, vomiting, dizziness, headache, migraine, respiratory tract infection
Zaleplon	10–20	10	1	1	Indirect GABA agonism of BZ1 receptor	*CYP3A4*	Hypersensitity to zaleplon; complex sleep behaviours after taking benzodiazepines or benzodiazepine receptor agonists	Abdominal pain, dizziness, headache, paresthesias, eye pain, dysmenorrhea
Dual orexin receptor antagonists								
Daridorexant	25–50	50	1–2	8	Orexin antagonism of OX1 and OX2 receptors	*CYP3A4*	Diagnosis of narcolepsy	Headache, somnolence, fatigue, dizziness, nausea
Suvorexant¶	10–20	20	2	12	Orexin antagonism of OX1 and OX2 receptors	*CYP3A*; *CYP2C19*	Diagnosis of narcolepsy	Dizziness, headache, somnolence, diarrhoea, xerostomia
Lemborexant	5–10	10§	1–3	17	Orexin antagonism of OX1 and OX2 receptors	*CYP3A4*; *CYP3A5*	Diagnosis of narcolepsy	Palpitations, abnormal sleep behaviour, sleep paralysis, headache, lethargy
Melatonin agonists								
Ramelteon	8	8	0·75	1–2·6	Melatonin agonism of MT1 and MT2 receptors	*CYP1A2*; *CYP2C*; *CYP3A4*	Angioedema with previous exposure; concomitant use with fluvoxamine	Nausea, amnesia, dizziness, headache, insomnia, somnolence
Melatonin								
Melatonin	1–3	2	1·6	3·5–4	Melatonin agonism of MT1, MT2, and MT3 receptors	*CYP1A1*; *CYP1A2*; *CYP2C19*	Hypersensitivity to melatonin or other component of the product (eg, excipents)	Back pain, arthralgia, weakness
Sedative antidepressants								
Doxepin	3–6	6	3·5	15	Histamine antagonism of H1 receptor	Oxidation; demethylation; glucuronidation	Hypersensitivity to doxepin; co-administration with monoamine oxidase inhibitors; glaucoma; urinary retention	Somnolence, sedation, nausea, upper respiratory tract infection

GABA=γ-aminobutyric-acid. *Lower doses might be indicated for older adults (eg, individuals older than 65 years), women, or individuals with compromised liver or kidney function. †Maximum prescribed dose, based on dose ranges provided by the American Academy of Sleep Medicine clinical practice guidelines.[34] ‡There are also concerns about the potential for anterograde amnesia and disinhibition when using triazolam. §Different dosage forms of zolpidem are not included (eg, sublingual formulation or nasal mist). ¶Suvorexant phase 3 clinical trials evaluated 15 mg, 20 mg, and 40 mg formulations.

Table: **Medication with an indication for the treatment of insomnia**

is the use of GABAergic sedative hypnotic drugs. These sedative hypnotics include barbiturates (eg, amobarbital), benzodiazepines (eg, temazepam), and benzodiazepine receptor agonists (eg, zolpidem; table). The benzodiazepine—and later the benzodiazepine receptor agonist—class of sedative hypnotics replaced barbiturates and other first-generation sleeping pills (eg, chloral hydrate) because of their more favourable safety profiles. The putative mechanism of action of sedative hypnotics is the facilitation of GABA activity in the cortex, hippocampus, thalamus, hypothalamus, basal ganglia, and brainstem, where sleep is thought to be promoted by the inhibition of glutamatergic and monoaminergic arousal. Thus, benzodiazepines and benzodiazepine receptor agonists (GABAergic sedative hypnotics) are thought to directly induce sleep, at least in terms of electroencephalogram (EEG) cortical synchronisation. In addition to eliciting sleep EEG activity (θ and Δ frequencies), benzodiazepines and benzodiazepine receptor agonists also produce an EEG anomaly referred to as a benzodiazepine artifact (EEG activity during sleep at 12–20 Hz). Little is known about the functional consequences of this EEG anomaly, how much medication use is associated with the occurrence of this anomaly, or how long this anomaly persists after discontinuation of pharmacological treatment.[95] Side-effects of this class of medication include headaches, drowsiness, dizziness, diarrhoea, dry mouth, palpitations, and grogginess.[96–100] Specific package insert warnings are provided with regard to parasomniaogenesis—partial awakening behaviours, such as walking, talking, eating, or driving while asleep. Furthermore, there are concerns about the development of psychological or physiological tolerance and dependence on benzodiazepines and benzodiazepine receptor agonists when they are used for extended periods of time (eg, months or years).[101,102]

The second approach is the use of melatonin agonists, which are not the same as naturally formulated melatonin. Although melatonin is frequently used as a naturopathic remedy for insomnia, whether or not it is efficacious is controversial. Melatonin is better thought of as a chronobiotic than a sedative hypnotic drug, and the primary indication is for circadian rhythm disorders (eg, patients with delayed or advanced sleep–wake phase disorders) or for insomnia disorder with a strong circadian rhythm disorder component.[103–105] There are two drug compounds with indications for the treatment of sleep disorders within the melatonin agonist class; ramelteon has an indication for the treatment of insomnia and tasimelteon has an indication for the treatment of non-24 h syndrome (a circadian rhythm disorder that affects blind people). The putative mechanism of action for melatonin agonists is the manipulation of the biological clock. Exogenous ligands, which bind to melatonin receptors, enhance brain concentrations of melatonin. Melatonin onset signals the beginning, and melatonin offset signals the end, of the dark period of the 24 h day. Thus, it can serve as a cue for when sleep should be initiated or terminated. Such an approach might be most helpful for the facilitation of sleep during light periods (eg, sunrise to sunset) or for individuals that have reduced exposure to light or no exposure to light. Side-effects of these agonists include elevated liver enzymes (eg, alanine aminotransferase), headache, nightmares or abnormal dreams, drowsiness, upper respiratory tract infections, and urinary tract infections.[106,107] Melatonin agonism might also influence reproductive function in women through increased prolactin secretion, which is mild and transient,[108] or through its oxygen-scavenging properties (effects as an anti-oxidant).[109]

The third approach is the use of dual orexin receptor antagonists (DORAs). There are three drug compounds with indications for the treatment of insomnia within the DORA class: suvorexant, lemborexant, and daridorexant. The putative mechanism of action for these medications is the inhibition of the orexin-alerting system. Orexin is thought to be the neuronal system that promotes continuous wakefulness and consolidates wake and sleep into two distinct periods. Thus, orexin antagonists can serve to promote sleep under conditions where there is hyperarousal, hyperactivation, or conditioned wakefulness. Whether such states are, however, attributable to hyperorexinemia is unclear. Side-effects of DORAs include headache, dizziness, abnormal dreams, cough, diarrhoea, dry mouth, upper respiratory tract infections, palpitations, psychomotor hyperactivity, and anxiety.[110,111] Because abnormally low concentrations of orexin are associated with narcolepsy symptoms,[112,113] there is the concern that DORAs could be narcoleptogenic. To our knowledge, no DORAs have been shown to elicit any of the narcoleptic symptoms, which include sleep attacks; sudden urges to sleep; cataplexy; partial paralysis or generalised paralysis precipitated by anticipatory excitement, laughter, anger, or surprise; hypnagogic hallucinations or hypnopompic hallucinations (frightening or menacing hallucinations that occur at sleep onset or offset); and sleep paralysis (generalised paralysis at the time of falling asleep or on awakening).

The final approach is the use of sedative antidepressants. There is one drug compound that has an indication for the treatment of insomnia in the sedating antidepressant class (low-dose doxepin), despite the common clinical practice of prescribing low-dose tricyclic antidepressants (eg, amitriptyline) or trazodone for insomnia. The putative mechanism of action for low-dose doxepin is histamine (H1 receptor) antagonism. Thus, doxepin can facilitate sleep by counteracting histaminergic activation (which causes vigilant and attentive wakefulness) and by modulating other wake-promoting neurotransmitters (eg, acetylcholine, norepinephrine, and serotonin). Side-effects of low-dose doxepin appear to be minimal, although specific warnings are provided with regard to parasomniaogenesis.[114]

Alongside type of medication, dosing regimen is a crucial issue for the pharmacological management of insomnia, particularly for patients who are treated for long periods of time. The options available to prescribing clinicians include nightly dosing, intermittent dosing, and as-needed dosing. Although there are no comparative studies regarding these three dosing regimens, the general consensus is that it is best to start treatment with the lowest dose available, and upwardly titrate as needed to achieve treatment response. The primary advantage of the low-dose regimen is that it is thought to have a longer efficacy half-life and to result in fewer side-effects than other dose regimens. Although this standard of practice is reasonable for therapeutic trials that last for months, the application of this practice to acute medical treatment (eg, lasting days or weeks) could be misguided. Aggressive, short-term treatment for acute insomnia might be productive, particularly as it could prevent behaviours that maintain insomnia, although this is yet to be established.

Patients taking hypnotics for months or years can develop tolerance, whereby medication is no longer as effective as it was during the early phases of treatment. Many of these patients continue to use the medication because they believe that their sleep quality will decline without medication or because they have had poor-quality sleep when medication was abruptly discontinued. Patients are likely to be resistant to the recommendation to discontinue medication for insomnia whether they are physiologically dependent on hypnotics or not. These patients are best managed by implementing a titration regimen, which can also be implemented before CBT-I, during the first week of CBT-I, or after CBT-I.

Practice recommendations

Since 2016, five professional societies have provided guidelines or recommendations for the medical management of insomnia disorder in adults.[6–8,37,39] Key points in these documents include that a shared decision-making approach to prescription and treatment (where the clinician reviews the benefits, risks, and costs of each medication with the patient) should be used and that when CBT-I is not effective or available, the best treatment options are benzodiazepines, benzodiazepine receptor agonists, and sedative antidepressants (low-dose doxepin). Some recommendation documents also specify, largely on the basis of polysomnographic data, that the best treatment options for sleep onset insomnia are zaleplon, triazolam, and ramelteon; for sleep maintenance insomnia are doxepin, suvorexant, and ramelteon; and for both conditions presenting comorbidly are eszopiclone, zolpidem, and temazepam.

In 2019, the British Association of Psychopharmacology[37] published a comprehensive overview of the pharmacological treatment of insomnia. The overview included diagnostic criteria information, a synopsis of what would make for an ideal hypnotic, a summary of the various mechanisms of action for each pharmacological approach, and statements regarding the efficacy and safety of each therapeutic method. Although the four pharmacological approaches were not evaluated quantitatively for their relative efficacy and safety, a useful summary of the current state of pharmacological treatment for insomnia was provided. This summary reported that GABA modulators (benzodiazepines and benzodiazepine receptor agonists), suvorexant, and low-dose doxepin are efficacious for treating insomnia, that prolonged-release melatonin improves sleep onset latency and sleep quality in patients older than 55 years, and that side-effects and residual sedation effects are less frequent and less serious in medications with short half-lives.

Comparative efficacy and safety of pharmacological treatments

Although many studies claim to provide comparative efficacy or safety data for the various treatments for insomnia, most of these studies simply summarise and appraise the strength of the evidence base by drug class or by specific medication. Quantitative data are rarely used to form inferences about efficacy and safety, and comparative data are rarely provided for standard measures or effect size measures of treatment outcome or for adverse event or side-effect profiles. The absence of these data might be because there are few published comparative efficacy studies (investigations comparing two or more medications with one another) and because there was no precedent for a meta-analysis of treatment outcomes across single-treatment placebo-controlled trials until the early 2000s (eg, network meta-analysis).[115,116] To our knowledge, only two network meta-analyses have been done to assess the comparative efficacy of sedative hypnotics; both were limited to older adults.[117,118]

Chiu and colleagues[117] undertook a formal network meta-analysis in older adults (mean age ≥60 years). Evaluated medications included benzodiazepines (flurazepam, quazepam, triazolam, estazolam, and temazepam), benzodiazepine receptor agonists (zolpidem, zaleplon, and eszopiclone), melatonin receptor agonists (ramelteon and tasimelteon), DORAs (suvorexant), and sedative antidepressants (doxepin). Treatment outcome data included objective and subjective measures of sleep continuity (sleep latency, wake after sleep onset, total sleep time, and sleep efficiency), and overall adverse event ratios. Regarding efficacy (placebo adjusted): zaleplon was found to be the most effective pharmacological treatment for reducing objective and subjective sleep latency, conferring approximately 15–20 min decreases in time to fall asleep. Temazepam was the most effective pharmacological treatment for reducing objective and subjective wake after sleep onset time, with about 20–25 min decreases in wake time. Eszopiclone and low-dose doxepin were the most effective pharmacological treatments for extending objective and subjective total

sleep time, conferring approximately 25–30 min increases in sleep duration. Low-dose doxepin appeared to be the most effective pharmacological treatment for increasing objective sleep efficiency, with roughly a 5–7% decrease in total wake time. Adverse events odds ratios (relative to placebo) were highest for triazolam (1·65) and lowest for zaleplon (0·84) and low-dose doxepin (0·85). Low-dose doxepin was established as the best overall pharmacological treatment for insomnia. Samara and colleagues'[118] analysis assessed a broad range of pharmacological treatments for insomnia in older adults (≥65 years). The meta-analysis evaluated both on-label (US FDA approved) and off-label pharmacological therapies including benzodiazepines (eg, nitrazepam), benzodiazepine receptor agonists (eg, zolpidem), melatonin, melatonin receptor agonists (eg, ramelteon), DORAs (eg, suvorexant), sedative antidepressants (eg, doxepin), and antipsychotics (eg, propiomazine). The primary outcomes were total sleep time and sleep quality. The meta-analysis, which also included sleep latency and wake after sleep onset as secondary outcome measures, did not appear to differentiate between objective and subjective measures of sleep continuity and allowed a variety of sleep-quality measures to be used as common metrics of a single latent construct (eg, the Pittsburgh Sleep Quality Index, the ISI, and the Epworth Sleepiness Scale). Adverse events data were tabulated in terms of number of patients lost to follow-up (ascribed to intolerable side-effects) and number of adverse events per treatment per included study. The following pharmacological treatments are listed from most to least effective. Decreased sleep latency was shown for diazepam, propiomazine, promethazine, doxepin, eszopiclone, temazepam, clomethiazole, ramelteon, and suvorexant, with mean decreases in time to fall asleep of 7–25 min. Decreased wake after sleep onset times were shown for suvorexant, melatonin, esmirtazapine, doxepin, zolpidem, and eszopiclone, with mean decreases in wake time of 12–24 min. Increased sleep durations were shown for diazepam, promethazine, propiomazine, temazepam, doxepin, and eszopiclone, with mean increases in sleep duration of 24–50 min. The largest improvements in sleep efficiency were shown for propiomazine, melatonin, temazepam, eszopiclone, and doxepin, with mean effect sizes of 0·35–1·77 (Hedges' g). Specific safety outcomes were not presented in the meta-analysis. The authors stated that there were no clear differences in safety profiles, possibly owing to variability in sample size, method of assessment (eg, spontaneous reports *vs* symptom checklists), and reporting convention (total counts of adverse events or number or percentage of insomnia-affected individuals).

Relative efficacy of behavioural and pharmacological treatments

The mean acute effects of behavioural and pharmacological treatments are approximately the same in pretreatment to post-treatment effects for assessment intervals of up to 4 weeks.[3,5] The primary differences between the two treatment modalities are in durability of outcomes after acute treatment; CBT-I treatment responses are maintained after treatment discontinuation, but this is not the case for medical interventions. Given these considerations (acute effects and durability) and the safety profile of CBT-I, the recommended first-line treatment for insomnia disorder is CBT-I.[6–8,37,39] This recommendation, however, still requires clinical judgement to decide which form of CBT-I to use, including in-house formulation, online or app-based therapy, or referral to specialists. Regardless of the form of CBT-I, ongoing monitoring for treatment response, treatment non-response, and treatment acceptability is crucial.

Future research

There is a variety of new forms of assessment, therapeutics, and alternative treatments that are currently in development (panel 2).

Assessment

There are two aspects to this issue, one related to the initial assessment of sleep health and one related to the prospective assessment of insomnia for treatment purposes (eg, CBT-I).

Regarding assessment of sleep health (in primary care or in other non-sleep medicine specialty care practices), there should be regular inquiries about sleep health. An inquiry could be as simple as asking the patient if they have difficulty falling asleep, staying asleep, and if their daytime function is impaired because of low-quality sleep. These enquiries can be done in a standardised way using the Single-Item Sleep Quality Scale. Dedicated brief but comprehensive screening measures could also be used to assess sleep health.[119] Several measures have been developed for this purpose, including the Global Sleep Assessment Questionnaire, which screens for four possible diagnoses with 11 questions,[120] the Holland Sleep Disorders Questionnaire, which screens for five possible diagnoses with 32 questions,[121] and the Sleep Disorders Symptom Checklist-25, which screens for the symptoms of 13 sleep disorders with 25 questions.[122] If the patient reports sleep continuity disturbance (insomnia), screening measures could be followed by the seven-item ISI.[60,123,124] Another measure is the eight-item Patient-Reported Outcomes Measurement Information System for Sleep Disturbance Short Form (PROMIS SD-SF).[125] Positive screens on either the ISI or the PROMIS SD-SF might prompt the clinician to offer treatment or to refer the patient to a specialist.

Regarding the prospective assessment of insomnia for treatment purposes, there has been an increase in demand to move from paper-based sleep diaries to digital sleep diaries as a result of the importance of prospective high-density sampling of sleep continuity for CBT-I.

For more on **Sleep Coach** see https://mobile.va.gov/app/insomnia-coach

For more on **Circady Pro** see https://circady.com/pro/

For more on **Consensus Sleep Diary** see https://consensussleepdiary.com

For more on **Hypknowledge** see https://www.hypknowledge.com

***Panel 2*: New approaches for assessing and treating insomnia currently under consideration or in development**

New forms of assessment

- Sleep Health Screeners, such as the Global Sleep Assessment Questionnaire, the Holland Sleep Disorders Questionnaire, and the Sleep Disorders Symptom Checklist-25
- Digital tracking of sleep continuity, such as online or phone app sleep diaries or wrist worn sleep–wake detectors

New behavioural therapeutic approaches

- Bright light therapy administered alone or in combination with cognitive behavioural therapy for insomnia (CBT-I)
- Mindfulness training administered in combination with CBT-I
- Acceptance and commitment therapy administered in combination with CBT-I
- In-laboratory treatment that utilises polysomnography or device-based treatment, such as intensive sleep retraining
- Sleep centre or hospital-based inpatient CBT-I
- Brief behavioural treatment for insomnia (BBTI), an alternative to traditional 6–8 session CBT-I treatment
- Single session CBT-I treatment of acute insomnia

New pharmacological therapeutic approaches

- Orexin receptor antagonists with different receptor affinities (eg, those that bind specifically to OX1 or OX2 *vs* those that bind to both)
- Different pharmacokinetics, such as altered time to maximum concentration or half-life values
- Different formulations to allow for different onsets and offsets of therapeutic effects (eg, modified or extended release formulations)
- Non-racemic mixtures of compounds of which the original forms have stereoisomers (eg, zopiclone and eszopiclone)

New pharmacological treatment regimens

- Partial reinforcement of conditioned therapeutic effects versus standard intermittent dosing with sedating hypnotic drugs
- Different prescriptive strategies, such as recommending duration of time in bed
- CBT-I administered alongside sedatives
- CBT-I administered alongside stimulants

Digital diaries can be monitored for adherence, can provide reminders by email or text, and can automatically query out-range responses (eg, when an individual provides an atypical response or a response that is incompatible with previous answers). There is now a variety of free-standing trackers that are intended to be used with in-person CBT-I (therapist driven *vs* online unattended CBT-I). These apps typically contain digital sleep diaries, and sometimes contain digital versions of questionnaires that are routinely used with CBT-I (eg, ISI). Examples of these free-standing sleep trackers are Sleep Coach, Circady Pro, Consensus Sleep Diary, and Hypknowledge. Some of these apps are also able to integrate data from other sources, such as wrist-worn sleep–wake detectors or smartphones. Although wrist-worn detectors are high-precision and low-cost,[126] and might provide more reliable data collection than sleep diaries, there are no studies that show that wrist-worn detectors can be successfully used for CBT-I or to guide medical treatment.

Behavioural therapeutic approaches

Several behavioural therapeutic approaches have been suggested, are in development, or have proof-of-concept data for the treatment of insomnia. These approaches include the use of bright light therapy as a standalone or adjuvant to CBT-I (especially for initial insomnia or late insomnia),[127,128] mindfulness,[129,130] acceptance and commitment therapy (a potential alternative to traditional cognitive therapies and relaxation therapies),[131] therapy given in a sleep laboratory or led by devices for intensive forms of exposure and counter conditioning (eg, intensive sleep retraining),[132,133] inpatient-based CBT-I (in which staff ensure sleep scheduling and stimulus control),[134–136] brief behavioural treatment for insomnia (BBTI) as an alternative to standard six-to-eight session treatment,[137,138] and single-session CBT-I for the management of acute insomnia.[139,140]

Medical therapeutic approaches

Although there are national agency-approved formulations for melatonin agonists, sedative antidepressants, and DORAs, these pharmacological treatments are first-generation interventions. Therefore, the development of compounds that have different receptor affinity profiles (eg, single orexin receptor antagonists *vs* DORAs), different pharmacokinetics (eg, altered time to maximum concentration or half-life values), modified release formulations (eg, immediate release *vs* sustained release *vs* delayed release or multiphasic release versions of established compounds), or non-racemic mixtures of existing compounds (eg, zopiclone *vs* eszopiclone) should all be developed and assessed for their safety and efficacy. These refinements could improve the efficacy and safety profiles of existing pharmacological treatments (panel 2).

Not only are the medications themselves important, but also how they are used. There are two issues that require further consideration: which of the existing treatment regimens and prescriptive strategies are most effective, and whether combined approaches could produce better, quicker, and more durable outcomes or improved safety profiles than one approach administered alone.

To evaluate which treatment regimens and prescriptive strategies are most effective and safest, studies are required to establish the optimal regimen for long-term therapy or maintenance therapy with sedative hypnotics. Head-to-head trials are needed to evaluate the relative

efficacy of nightly dosing, intermittent dosing, and as-needed dosing both overall and for specific medications. An alternative to these three dosing options is the behavioural-pharmacotherapeutic approach,[141] where treatment responses can be maintained with a form of intermittent dosing in which the patient takes a placebo on nights when they do not take the medication. Prescriptive strategies have historically focused on the type of medication, the dose, the route of administration, the time medication is administered, and the number of times per day medication is administered. In other contexts, no instruction or guidance about the timing or duration of sleep that should be sought is provided with the prescription. A patient could be instructed to keep their current sleep schedule or to adapt it to optimise the effects of medication. Although it is easy to imagine that optimisation is possible, studies are required to establish if extending the period of sleep or restricting it is most effective.

There are multiple studies that suggest the combination of benzodiazepine or benzodiazepine receptor agonist hypnotics with CBT-I could provide quicker treatment responses than CBT-I alone.[142] The combination approach does not, however, result in improved acute outcomes (eg, additive effects) and could undermine the long-term durability of CBT-I.[63] Whether such findings apply to combining DORAs, sedative antidepressants, or melatonin agonists has yet to be evaluated. There is one other approach to combined therapy, the use of wake-promoting medications during acute CBT-I therapy.[49] This combined approach is thought to be useful because it prevents iatrogenic sleepiness (as a result of sleep restriction therapy) and make it easier for patients to adhere to the prescriptive elements of CBT-I. Acute treatment with stimulants could also have therapeutic value by enabling the patient to extend wakefulness and increase how active they are during the day. The use of stimulants could increase sleep pressure and positively affect sleep continuity. Although there is a proof-of-concept study,[49] the viability of this strategy has not yet been empirically validated.

Conclusion

"Insomnia, when chronic, tends to be unremitting, disabling, costly, pervasive, and pernicious."[1] The treatment of insomnia is highly effective (60–80% of patients have a therapeutic response).[61] Treatment can also provide health benefits beyond the positive clinical gains made with sleep continuity disturbance. For example, restoration of good sleep continuity and longer sleep duration can improve sleep-related functions, including mood, memory, cognition, weight, blood pressure, glucose regulation, amyloid β clearance, and immune function. As insomnia is probably easier to treat when it is less chronic, and as treatment can have multiple positive health outcomes, early detection and treatment (initiation within 4–12 weeks of new onset insomnia) should be implemented. Implementing early treatment will require a cultural change that promotes regular monitoring of sleep health. Inquiries at annual physical check-ups and new, brief, comprehensive sleep symptom screeners could help with the implementation of this practice.

Contributors

MLP wrote the first draft of the manuscript and was responsible for the first literature search. All authors reviewed subsequent drafts of the manuscript and provided conceptual and editorial feedback, and contributed to the identification of appropriate references.

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