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Diagnosis, prevalence, pathways, consequences & treatment of insomnia

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Abstract

Insomnia is a highly prevalent sleep disorder that frequently occurs in its acute form and occurs at a rate of approximately 10 per cent in its chronic form in many countries. There is a high prevalence of insomnia in a variety of medical and psychiatric conditions for which insomnia often serves as a risk factor. The aetiology and pathophysiology of insomnia is such that several factors may predispose individuals for or precipitate and/or perpetuate the condition. Both sedative-hypnotic and cognitive-behavioural interventions exist for insomnia and each type of intervention have substantial levels of empirical support for their efficacy.

Keywords

Aetiology; assessment; co-morbidity; consequences; diagnosis; insomnia; pathophysiology; prevalence; treatment

Insomnia is a sleep disorder that may occur acutely and dissipate or may become a vexing chronic disorder. Although difficulty in initiating and/or maintaining sleep is a fairly straightforward complaint, a thorough assessment of the presenting insomnia is well worth the upfront effort before formulating and delivering a specific intervention strategy. The pathophysiology of insomnia can actually be somewhat complex (or at least multi-factorial) because of the many inputs to the sleep-wake system in general and the additional specific behaviours and cognitions which an individual layers on top of the physiologic substrates. Chronic insomnia has a surprising number of individual and societal consequences, which far exceed being a nuisance. In fact, there is considerable morbidity associated with chronic insomnia and even a degree of mortality. Fortunately, there are a number of safe and effective treatments for insomnia.

Definition & diagnosis of insomnia

The definition of insomnia

The International Classification of Sleep Disorders, second edition (ICSD)[1] diagnostic criteria for primary insomnia requires: *(i)* a predominant complaint of difficulty in initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month; *(ii)* that the sleep

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disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; *(iii)* that the sleep disturbance does not occur exclusively during the course of another sleep disorder (*e.g*., narcolepsy, breathing-related sleep disorder, *etc*.); and *(iv)* that the disturbance is not due to the direct physiological effects of a substance (*e.g*., a drug of abuse, a medication) or another psychiatric or general medical condition. Within this nosology the definition of primary insomnia is further refined to include three types of primary insomnia (psychophysiological, paradoxical, and idiopathic). In addition to the above insomnia criteria, psychophysiological insomnia requires evidence of somaticized tension and learned sleep-preventing associations that contribute to insomnia. Paradoxical insomnia is reserved for a small subset of patients who have an extreme discrepancy between their subjective report of insomnia and traditional polysomnographic findings, which demonstrate normal sleep architecture. Idiopathic insomnia is a lifelong and unremitting inability to obtain adequate sleep which may commence in childhood and that may be due to abnormal neurological control of the sleep-wake system. There are also seven additional chronic insomnia classifications related to a variety of co-morbid presentations of insomnia[1].

Research diagnostic criteria have been established for the insomnias (Table I)[2]. These closely match the ICSD entities and criterion. These criteria are based on recent evidence based literature and are presented in individual, reader-friendly, reproducible tables accessible in one manuscript.

Interestingly, neither nosology specifies severity or frequency criteria. For instance, there is no benchmark for how much wakefulness or how little total sleep is considered abnormal and/or indicative of insomnia. Nor is there a standard for number of nights per week (or per month) that disturbed sleep must occur to meet insomnia criteria. Nonetheless, most clinicians and investigators consider ≥ 30 min to fall asleep and/or ≥ 30 or more min of wakefulness after sleep onset and total sleep time of ≤ 6.5 h per night to represent the threshold between normal and abnormal sleep. While a frequency complaint of ≥ 3 nights per wk is used as inclusion criteria for many insomnia trials, this is less often used clinically. Regardless of the nosology used to diagnose insomnia, however, assessment is fairly standard.

The assessment of insomnia

An insomnia assessment includes a thorough sleep, medical and psychiatric history[3]. The sleep history can begin with a chronological review of sleep starting with childhood and may also include: identifying any factors that precipitated the insomnia (and whether these factors are still present), current life stressors, factors currently thought to be contributing to insomnia, a description of a typical 24-h period in terms of sleep behaviours and schedule, how often a typical night occurs, how a bad night differs from a good night, if there are any identifiable weekly, monthly or seasonal sleep patterns, what has been tried to correct the sleep disturbance and to what extent such strategies worked. A sleep history also includes questions to rule out other possible sleep disorders. Differential diagnosis also includes distinguishing the primary insomnias from a co-morbid insomnia. Some of these conditions do warrant targeted intervention prior to treating the presenting insomnia. Typical

exclusions for initiating insomnia treatment include untreated or unstable medical, psychiatric or substance abuse conditions (*e.g*., gastroesophageal reflux disease, cardiopulmonary disorders, seizure disorders, some neuroendocrine disorders, sleep apnoea, bipolar disorder, severe mental illness, active substance dependence). It is imperative to note that co-morbid insomnia may nonetheless be treated in conjunction with the treatment of a 'primary' disorder or even as a front line intervention.

Numerous self-report instruments exist for the assessment of sleep disturbance. Among the most widely used are the Pittsburgh Sleep Quality Index[4], which provides a global assessment of sleep, and the Insomnia Severity Index[5], specifically designed for insomnia. Perhaps the most useful self-report measure is a daily sleep diary, which patients are asked to complete on a daily basis for 1-2 wk. At a minimum, a sleep diary assesses time to bed, minutes to fall asleep, number and duration of awakenings, final awakening and time out of bed. From these data, averaged over the 1-2 wk period, a patients sleep continuity can be determined. This includes latency to sleep, wake time, average time in bed, total sleep time, sleep efficiency (sleep time divided by time in bed). Objective measures of sleep can be obtained via wrist-worn actigraphy. Although not as informative as a full night polysomnograhic recording, actigraphy can corroborate or replace sleep diary data. Unless paradoxical insomnia or another sleep disorder (*e.g*., sleep apnoea) is suspected, polysomnography is not indicated in the assessment of insomnia.

An important consideration for the general, family, or other primary care practitioner is that any evaluation of sleep is not the norm in standard practice. Therefore, even asking a simple question such as "how are you sleeping?" can begin to unmask chronic insomnia. Given the prevalence of insomnia, this can be a valuable conversation starter that leads to a more thorough sleep assessment or a referral based on the providers preference for managing insomnia in their practice.

Epidemiology of insomnia

Insomnia is a highly pervasive condition. Approximately one third to one fourth of the population in industrialized nations report sleep disturbance problems at some point in their lives and approximately 10 per cent suffer from persistent insomnia[6].

As stated in a 2005 US National Institutes of Health State of the Science Statement on Manifestations and Management of Chronic Insomnia in Adults[7]:

Population-based studies suggest that about 30 per cent of the general population complains of sleep disruption, while approximately 10 per cent has associated symptoms of daytime functional impairment consistent with the diagnosis of insomnia, though it is unclear what proportion of that 10 per cent suffers from chronic insomnia. Not surprisingly, higher prevalence rates are found in clinical practices, where about one-half of respondents report symptoms of sleep disruption.

Chronic insomnia does not typically resolve spontaneously, although the presenting form of insomnia (*i.e*., initial, middle, or late) can vary over time[8]. For instance, subjects in one study presented with an average chronicity of 10 yr at their initial assessment and 88 per

cent continued to report insomnia 5 yr later[9]. Insomnia is also a highly co-morbid condition and appears more frequently as a co-morbid illness than as primary insomnia[10]. The day-to-day cost of insomnia is not limited to fitful sleep. Insomnia, when chronic, tends to be unremitting, disabling, costly, and may pose a risk for additional medical and psychiatric disorders.

Aetiology & pathophysiology of insomnia

Cognitive & behavioural perspectives

There is currently no single, cognitive-behavioural model of insomnia. Instead, a number of related and overlapping models are available. All such models consider insomnia a condition that develops over time, is related to maladaptive behaviours and cognitions, and becomes chronic unless treated aggressively in its acute phase.

Spielman and colleagues[11] set forth what has become known as the '3-P Model' of insomnia, which is essentially a diathesis-stress model. The model suggests that *(i)* individuals may be primed to develop insomnia by individual predisposing characteristics, such as various forms of hyperarousal and/or tendency to worry or ruminate, *(ii)* precipitating factors, such as stressful life events and/or new illness, initiate an episode, and *(iii)* predisposing factors, such as maladaptive coping strategies like napping or extending time in bed beyond the usual sleep window despite being asleep less, result in conditioned arousal and chronic insomnia.

As reviewed elsewhere, others have proposed additions to this basic model[12]. Such models incorporate other aspects of insomnia including how patients may engage in safety behaviours, have dysfunctional beliefs about sleep, engage in excessive rumination and catastrophizing, as well as being cortically primed for pre-sleep arousal and overt attention to stimuli that good sleepers easily ignore. As a whole, these models provide convincing rationale for the various aetiologic factors targeted by cognitive-behavioural treatments for insomnia.

Physiologic perspectives

Hyperarousal, circadian dysrhythmia, and homeostatic dysregulation of sleep are each thought to contribute to the occurrence of insomnia. The largest body of work exists for hyperarousal conceptualized as either elevated basal levels or as a failure to down-regulate at night and further construed along somatic/physiologic, cognitive, and cortical/neurophysiologic dimensions[12]. In terms of physiologic arousal, patients with insomnia have been shown to have elevations of heart rate, galvanic skin response, sympathetic arousal (as measured by heart rate variability), and increased hypothalamic-pituitary-adrenal (HPA) axis activity[12]. In terms of cognitive arousal, patients with insomnia are more prone to generalized worry, sleep-related worry, and selectively attend to and monitor insomnia symptoms[12]. In terms of cortical/neurophysiologic arousal patients with insomnia exhibit increased high frequency EEG activity at or around sleep onset and during non-rapid eye movement (REM) sleep[12], elevated whole brain metabolism across waking and non-REM sleep[13], and smaller metabolic declines than normals in the ascending reticular activating system, in the hippocampus, the amygdala and anterior cingulated cortex during the wake to

sleep transition[14]. Overall, there is a fairly large body of evidence that supports an association between hyperarousal and insomnia.

With respect to circadian dysregulation, research suggests that chronobiologic abnormalities, in the form of phase shifts of the core-body temperature rhythm, are related to sleep initiation or maintenance problems[12]. These shifts are similar to but smaller than those seen in full-fledged circadian rhythm disorders of sleep. These abnormalities may be partly driven or exacerbated by behaviour. Some patients change their sleep schedule and wake-time activities in ways that may dramatically alter the timing of their exposure to bright light and have been shown to attempt sleep prior to the decline in core body temperature associated with sleep onset[15]. Such behaviour may, in turn, reset the “biological clock” and result in the observed phase shifts in core body temperature. Overall there exists a small, but growing body of evidence that supports an association between circadian factors and primary insomnia.

As reviewed elsewhere[16], there is some limited evidence that altered sleep homeostasis may serve to predispose, precipitate, and/or perpetuate insomnia. Specifically, patients with Primary Insomnia, as compared to good sleepers, tend to exhibit what may be homeostatic abnormalities. First, sleep propensity is measured by the multiple sleep latency test[17] (MSLT) in which mean time to fall asleep across successive daytime napping opportunities represent the level of objective sleepiness or sleep drive. Given that patients with insomnia tend to have less total sleep time than good sleepers, they would be expected to have shorter sleep latencies on the MSLT. Most MSLT studies have shown that patients with insomnia have normal, or longer than normal sleep latencies[18]. This suggests a possible reduction in sleep drive, and by inference, a faulty sleep homeostat.

Second, patients with insomnia have less slow wave sleep (SWS) than good sleepers, although one study had null findings[16]. By itself diminished SWS does not directly implicate homeostatic dysregulation. Third, following sleep deprivation patients with insomnia show a diminished SWS, a cardinal homeostatic response to sleep loss[16]. Finally, following interventions that putatively target sleep homeostasis, patients with insomnia exhibit increases in SWS over pre-treatment levels[16].

It is important to note that some of these findings might be explained by factors other than sleep homeostasis. For example, the down regulation of body temperature at sleep onset may be critical for the initiation of SWS, such that it is thermoregulation that is dysregulated[19]. In addition, hyperarousal may account for longer than expected sleep latencies on MSLT tasks and potentially create a barrier to consistent SWS. In all likelihood, there are interactions between hyperarousal, circadian dysrhythmias and homeostatic processes that contribute to the pathophysiology of insomnia. At what point in the development of insomnia these occur remains unanswered. What is known is that regardless of how insomnia is initiated it comes with a host of consequences.

Consequences of insomnia

Economic consequences

From the standpoint of societal cost, insomnia is estimated to have direct and indirect costs exceeding US$100 billion annually in the US alone[20]. Direct costs have been estimated at US$13 billion per annum in physician visits, prescriptions and procedures[21]. Indirect costs associated with motor vehicle and workplace accidents, reduced productivity, and absenteeism account for the majority of the economic consequences of insomnia. Patients with insomnia in particular have been found to be two and a half times more likely to report car crashes because of feeling tired as compared to those who do not report insomnia[22,23]. In an Australian study, the annual cost of work place accidents was estimated to be in excess of AUS$1.9 billion and patients with insomnia were approximately 8 times more likely to have such accidents compared to good sleepers[23]. At the individual level, work by Ozminkowski and colleagues suggests that individuals with insomnia have approximately US$1,200 more in direct health care expenses than patients without insomnia[24].

Cognitive, social and vocational consequences

Many investigations suggest individuals with chronic insomnia, as opposed to no or occasional insomnia, have more difficulty with intellectual, social and/or vocational functioning. Several studies report that patients with chronic insomnia have subjectively impaired cognitive performance[25-27]. Yet, objective evaluations of patients with chronic insomnia have not revealed any reliable evidence of cognitive deficits[28]. This discrepancy may be related to either an attentional bias for negative performance (that actually does not differ from normal deficits)[29,30] or to the patient's real appreciation of the fact that extra effort is required to maintain normal or near normal performance[28]. In terms of social functioning, chronic insomnia is associated with decreased ability to handle minor irritations and to enjoy family and social life, along with more impaired interpersonal relationships with spouses[27]. In terms of vocational functioning, chronic insomnia is associated with less job satisfaction and productivity, poorer performance scores, and increased absenteeism[31-33].

Health consequences

Mood disorders—There is a rather large body of evidence suggesting that insomnia is a risk factor for new onset and recurrent major depressive disorder (MDD)[34]. A number of cross-sectional studies at the community and epidemiologic level have been conducted to determine the prevalence of both insomnia and depression. Both disorders are highly prevalent and frequently co-occur in all age ranges and especially in older cohorts and women. While both disorders are variably defined across studies, in general the prevalence of insomnia is approximately 15 per cent and that of depression is approximately 8-9 per cent[35,36]. For example, baseline estimates of prevalence rates from a study (n=7,954) based on the National Institute of Mental Health Epidemiologic Catchment Area data were 10 per cent for insomnia and 5 per cent for depression. Among those subjects with insomnia, 23 per cent were depressed; among subjects with depression, 42 per cent had insomnia[37]. Stewart *et al*[38] applied more stringent diagnostic criteria than most prior studies to data from the Second National Survey of Psychiatric Morbidity conducted in the United Kingdom

(n=8,580). Using more stringent criteria, prevalence rate estimates were 5 per cent for insomnia and 3 per cent for depression. Among those subjects with insomnia 21 per cent were depressed, whereas among subjects with depression 40 per cent had insomnia.

Overall, in the above studies, the likelihood of having depression in the context of insomnia is approximately twice that of having insomnia in the context of depression. Such data suggest that insomnia may be considered a risk indicator for depression.

A number of longitudinal studies provide additional insight into the relationship between insomnia and depression. In one such study of patients with remitted, recurrent depression insomnia was the most prominent depressive symptom cluster leading up to a new depressive episode and reached its zenith at the week of recurrence. This suggests that insomnia is both a risk factor for and a prodromal sign of a recurrent depressive episode[39].

Other longitudinal studies have assessed whether insomnia occurring at one or two time points predicts depression at the second time point. These include several studies assessing the onset of new depression over a 1-3 yr period[37,40-46] with odds ratios (OR) of 2-4 for insomnia being associated with subsequent depression compared to no insomnia. A meta-analysis of such studies conducted in older adults found that sleep disturbance, with an odds ratio of 2.6, was second to recent bereavement (OR 3.3) as a risk factor for late-life depression[47].

Several lengthier, longitudinal studies have been undertaken. In a study of college aged men, insomnia in college conferred a relative risk of 2.0 (1.2-3.3) for developing depression during the ensuing 30 yr[48]. In another long term study, baseline insomnia was an independent predictor of depression 12 years later in women, [OR: 4.1 (2.3-7.2)], but not in men[49]. In an elegant analysis of epidemiologic dataset from Zurich, which assessed insomnia and depression at 6 time points over a 20 yr span, Buysse and colleagues[50] found that at each time point the presence of insomnia absent depression was strongly associated with the presence of co-occurring insomnia and depression at the subsequent time point.

Finally, one recent assessment of clinical trial data from a primary care-based depression intervention suggests that comorbid insomnia is a risk factor for unremitting depression[51]. Patients with insomnia that persisted across a baseline and 3 month assessment had a diminished treatment response at 6 and 12 months compared to patients with insomnia at one or neither of the baseline and 2 month time points.

While insomnia is certainly not the sole significant risk factor for depression is it a necessary condition for its occurrence. Taken together, these data suggest that both incident and persistent insomnia predict new onset depression and recurrent depression and may serve as a barrier to fully effective antidepressant therapy.

In regard to other mood disorders and conditions, five retrospective studies have shown that patients identify sleep disturbance as a top prodromal sign of a manic episode, but not bipolar depression[52]. Five studies of varying design demonstrate an association between insomnia and suicide or suicidality[53-57]. Anxiety disorders overall are equally or more prevalent than depression among insomnia subsamples in a number of reports[38,58-60].

Epidemiologic data include that 24 per cent of respondents with insomnia had an anxiety disorder and that they were 6 times more likely to have an anxiety disorder than those without insomnia [37].

Anxiety disorders & substance abuse disorders

Sleep disturbances, particularly nightmares and insomnia, are a common feature of post-traumatic stress disorder (PTSD) in both the general population[61] and in combat veterans[62]. Rates of insomnia in trauma populations range from 60-90 per cent[61-63]. Harvey & Bryant[64] found that 72 per cent of civilians experiencing a sleep disturbance within 1 month of their trauma went on to develop PTSD. Furthermore, insomnia is a prevalent residual symptom following otherwise successful treatment of PTSD[63].While not as substantial as the evidence for insomnia as a risk factor for depression, insomnia frequently co-occurs with PTSD and it may be involved in its pathophysiology and successful resolution.

Surprisingly, sleep data in generalized anxiety disorder (GAD) populations is even more scant. There is a report of 141 patient presenting to an insomnia clinic, where GAD was the most common co-occurring psychiatric disorder[58]. In cross-sectional data of 1,007 respondents, among those with insomnia 36 per cent had at least one anxiety disorder as opposed to 19 per cent in those with no insomnia[44]. In the insomnia subsample specific anxiety disorders occurred at the following rates: GAD 8 per cent, panic disorder 6 per cent, obsessive-compulsive disorder 5 per cent and phobia 25 per cent[44]. This is clearly an area requiring additional attention.

This is also the case for substance abuse, where it has been shown that substance abuse occurs at double the rate in individuals with insomnia compared to those without insomnia[37,40,44]. Patients admitted to inpatient alcohol treatment who had insomnia were also shown to be twice as likely to report using frequent alcohol use for sleep than those without insomnia[65]. Anecdotal reports suggest that particularly in patients acutely recovering from alcoholism, problems related to sleeping lead to relapse. Insomnia and fragmented sleep have been found to predict relapse in a two samples of abstinent alcoholics[65,66]. So again, based on limited data, insomnia may be a risk indicator for the development of alcoholism as well as a risk factor for relapse in alcohol dependence.

Medical disorders and conditions

There is an intricate link between sleep and immunity[67]. Iinsomnia is associated with changes in innate immunity including decreased natural killer cell activity[68,69], higher evening levels of interleukin-6 (IL-6)[70], a shift in the circadian distribution of IL-6 and TNF-α from the night to the daytime[70], and that IL-6 secretion is negatively correlated with self-reported sleep quality and PSG-measured SWS minutes[71]. While intriguing, these data do not support a direct association between insomnia and subsequent immune-mediated disease. Similarly, limited data from an adaptive immune system studies are also suggestive[72], but again no data exist associating insomnia to the development of a specific infectious disease.

Cross-sectional studies have implicated sleep disturbance (not necessarily insomnia) in conditions such as Type II diabetes and glucose homeostasis dysregulation (pre-diabetic

syndromes), gastrointestinal distress, recovery from cardiac surgery, and a variety of chronic pain conditions[73]. Insomnia is also highly prevalent in patients with HIV infection[74]. Longitudinal epidemiologic studies have found that insomnia increases the risk of developing hypertension and cardiovascular disease. For instance, in 4,794 male Japanese telecommunication workers followed for up to four years or until they developed hypertension, insomnia was associated with a significant increased risk of hypertension [OR 1.96:(1.42-2.70)][75]. In 8,757 participants without hypertension and 11,863 without cardiovascular disease followed for up to 6 yr, insomnia predicted a slight increased risk of hypertension [OR 1.2:91.03-1.30] and cardiovascular disease [OR 1.5:(1.1-2.0)][76].

Finally, there are a series of studies that suggest that poor sleep and insomnia and/or short sleep duration are associated with increased mortality[73].

While definitive causal links remain to be shown for insomnia and a variety of psychiatric and medical conditions, the weight of the evidence to date makes this a reasonable hypothesis. Given the enormous individual and societal consequences of insomnia, this disorder merits aggressive treatment. Fortunately, there are a variety of efficacious and effective interventions available for insomnia.

Treatment of insomnia

Historical backdrop

Beginning in the 1970's, the conventional clinical wisdom with respect to insomnia was that it was a symptom not a disorder and that it would resolve either when the precipitating event passed or when a co-occurring medical and/or psychiatric disorder was resolved. This point of view has largely passed as clinicians and researchers in the field argued for the recognition of insomnia as a disorder (not a symptom), as insomnia was found to persist following treatment of the primary condition, as interventions for insomnia were developed, refined and found to be efficacious, as these efficacious treatments were found to improve self-reported health, mood, concentration/alertness, daytime functioning, and quality of life[77].

Based on several meta-analyses and other findings summarizing the extant literatures for benzodiazepines (BZs), benzodiazepine receptor agonists (BZRAs), and cognitive-behavioural therapy for insomnia (CBT-I), the NIH State of the Science Conference[7], concluded that BZRAs and CBT-I are effective to treat insomnia in the short-term with relatively benign side effect profiles and that CBT-I has more durable effects when active treatment is discontinued. It has also been shown that insomnia may be treated in the context of co-occurring disorders[78-86] and that this not only improves insomnia but the co-occurring disorder as well[87-93].

The treatment of acute insomnia

For the majority of patients with acute insomnia spontaneous recovery does indeed occur. Acute episodes that last between 2-4 wk, however, may develop into chronic insomnia. For this reason, and the many consequences of chronic insomnia, early intervention is warranted. This may be accomplished with acute short-term prescription of current generation

hypnotics. In choosing the hypnotic, consideration should be given to matching the half-life of the medication prescribed to the specific insomnia complaint. In addition, a limited number of behavioural strategies should be discussed with the patient to avoid any counter-productive, and potentially perpetuating, behaviours. These include avoiding: *(i)* extending sleep opportunity/and/or time in bed (napping, sleepingin, or retiring to bed early or before feeling sleepy) *(ii)* spending more than 15-20 min awake in bed, and *(iii)* using alcohol to induce sleep. A planned follow up appointment to assess treatment response is also good practice.

The treatment of chronic insomnia with pharmacotherapy

Historically, first barbiturates and then benzodiazepines were indicated as sedative-hypnotics. While both classes have demonstrated efficacy for insomnia, barbiturates were shown to have unacceptable levels of tolerance and dose escalation, abuse potential, lethal dose threshold, and alterations to SWS and/or REM sleep. Similar attributions were made for the benzodiazepines, albeit with far less evidence. More recently the benzodiazepine receptor agonists (BZRAs) class of compounds was developed and garnered widespread acceptance as the standard of practice[7]. This was primarily due to the fact that they did not possess the negative attributes of the other sedative-hypnotic classes, though concerns about tolerance and dose escalation remain to a lesser extent. All of these agents (zolpidem, zolpiclone, zaleplon, and eszopiclone) bind at benzodiazepine receptor sites, do so more selectively than other exogenous ligands, and inhibit cortical neurotransmission. Ramelteon is a more recent non-BZRA sedative-hypnotic; it is a melatonin receptor agonist, has no tolerance or dose escalation features, and an even more benign side effect profile than the BZRAs[7].

Notwithstanding the availability and efficacy of these newer hypnotics, the off-label use of sedating antidepressants and anti-psychotics for the treatment of insomnia is an extremely common practice. This can be attributed to several reasons including the abundant data on the long-term safety of particularly the sedating antidepressants (compared to minimal long term safety and efficacy data of BZRAs), their lack of scheduling, the cost of BZRAs, and the belief that insomnia is a symptom of depression. This practice is based on little efficacy data of these agents with respect to insomnia. Ramelteon and the BZRAs (after consideration of CBT-I) are considered the accepted front line treatment for chronic insomnia[7].

As described above, selection of the appropriate hypnotic is best tailored to the individual presentation. Similarly, the discussion of basic behavioural principles of insomnia can be useful in chronic insomnia. In addition, the guidelines in Table II may be considered.

Overall, the current class of hypnotics is relatively safe and effective. Newer agents being investigated have the possibility of continuing to have a limited side effect profile while potentially more directly modulating the sleep-wake systems and potentially improving sleep architecture. Combining pharmacotherapy and CBT-I, where a hypnotic is initiated to stabilize sleep, delivered for a brief period and withdrawn as CBT-I progresses may also hold some promise.

The treatment of chronic insomnia with CBT-I

While individual CBT-I interventions may be delivered as mono-therapies, it is widely accepted that multi-component CBT-I is the best approach to treatment. Such a program includes three behavioural strategies as well as cognitive therapy, relaxation therapy and phototherapy, when indicated. Such a combined strategy addresses the multiple putative causes and perpetuators of insomnia.

Stimulus control therapy

Stimulus control therapy is considered to be the first line behavioural treatment for chronic primary insomnia and therefore should be prioritized accordingly[94]. Stimulus control instructions limit the amount of time patients spend awake in bed or the bedroom and are designed to decondition pre-sleep arousal. Typical instructions include: *(i)* keep a fixed wake time 7 days/wk, irrespective of how much sleep you get during the night; *(ii)* avoid any behaviour in the bed or bedroom other than sleep or sexual activity; *(iii)* sleep only in the bedroom; *(iv)* leave the bedroom when awake for approximately 10 to 15 min; and *(v)* return to bed only when sleepy. The combination of these instructions re-establishes the bed and bedroom as strong cues for sleep and entrains the circadian sleep-wake cycle to the desired phase.

Sleep restriction

Sleep restriction therapy (SRT) requires patients to limit the amount of time they spend in bed to an amount equal to their average total sleep time and proceeds as outlined in Table III. Sleep restriction is contraindicated in patients with histories of bipolar disorder, seizures, or untreated hypersomnolence as it may aggravate these conditions.

Sleep hygiene

This requires that the clinician and patient review a set of instructions which are geared toward helping the patient maintain good sleep habits such as keeping an environment and routine conducive to sleep, maintaining a regular bed and wake time, and avoiding tobacco, alcohol, large meals and vigorous exercise for several hours prior to bed. It should be noted that sleep hygiene instructions are not helpful when provided as a monotherapy[95]. Simply providing patients with a “handout” is likely to lead to noncompliance, a loss of confidence in the provider, and a sense that there may be nothing other than these ‘sleep tips’ to help with insomnia.

Cognitive therapy

Several forms of cognitive therapy for insomnia have been developed and often overlap. Some have a more didactic focus[96], others use paradoxical intention[97], cognitive restructuring[98] and focus on safety behaviours[99] and attentional biases[30]. While the approaches differ in procedure, all are based on the observation that patients with insomnia have negative thoughts and beliefs about their condition and its consequences. Helping patients to challenge the veracity and usefulness of these beliefs is the basis of cognitive therapy and is thought to decrease the anxiety and arousal associated with insomnia.

Relaxation training

A variety of relaxation techniques are available and any of these may be used as part of the CBT-I package. These include progressive muscle relaxation, diaphragmatic breathing, biofeedback, and more formal meditative techniques. The optimal relaxation method for insomnia may be the technique which is the most acceptable to and/or easiest to learn for the patient. Some techniques may be contraindicated by medical conditions (*e.g*., progressive muscle relaxation might not be an ideal choice for patients with certain neuromuscular disorders) or psychiatric disorders (techniques states are often difficult to tolerate by patients with untreated PTSD as these can precipitate re-experiencing symptoms).

Phototherapy

Bright light has antidepressant and sleep-promoting effects and may be useful for patients who have pronounced shifts in their circadian rhythms. If the patient's insomnia has a phase delay component (*i.e*., the patient prefers to go to bed late and wake up late), waking early by alarm and exposure to morning bright light is indicated. If the patient's insomnia has a phase advance component (*i.e*., the patient prefers to go to bed early and wakes up early), exposure to evening bright light is indicated. There are unwanted side effects of phototherapy including insomnia, hypomania, agitation, visual blurring, eye strain and headaches. Patients with or at risk for eye-related problems, such as patients with diabetes, should consult an eye care specialist prior to initiating light therapy. Bright light can also trigger mania in patients not previously diagnosed with bipolar mood disorder and is contraindicated in anyone known to have a bipolar disorder.

Standard delivery of CBT-I and recent alternatives

CBT-I is typically structured to allow for weekly sessions over 6-8 wk. Detailed treatment manuals exist for this duration of treatment[100,101] and much of the efficacy data are based on studies of this length. A 6-8 session structure allows the patient and clinician to monitor progress, maintain compliance, and arrive at treatment end with what is usually an acceptable level of total sleep time.

In the clinical setting, the number of sessions can be altered based on treatment progress, the patient's ability to self-administer (and monitor) the interventions. There is preliminary evidence that brief behavioural therapy for insomnia delivered in 3-4 sessions has good efficacy[102].

CBT-I is indicated for chronic insomnia and in acute insomnia where pharmacotherapy is contraindicated. It can be employed with both primary insomnia and insomnia co-morbid with some medical or psychiatric condition[103].

Summary

Insomnia is one of the most ubiquitous forms of sleep disturbance and with it come a host of negative consequences. These extend beyond the immediate sequelae experienced by the individual such as fatigue, irritability, and perceived performance decrements. Beyond these lie the substantial societal costs associated with insomnia and the equally large degree of

morbidity (medical and psychiatric) that comes with chronic insomnia. Perhaps because of the multi-factorial causes or inputs to insomnia, multi-component CBT-I is the treatment of choice for insomnia that has become chronic. The newer classes of sedative-hypnotic have a valuable role to play in the aggressive treatment of acute insomnia that is not resolving on its own. While several pharmacotherapeutic approaches have good efficacy for chronic insomnia, it remains the case that CBT-I is the superior of the two approaches once treatment has been discontinued. That is, treatment gains achieved with CBT-I are more resilient than those achieved by hypnotics once these are discontinued. When CBT-I is not available, or palatable to the patient, then pharmacotherapy is certainly preferred to watchful waiting, as once chronic insomnia tends to persist. A combination of CBT and hypnotic therapies is a reasonable approach requiring additional empirical support. Finally, when insomnia presents following the development or exacerbation of a medical or psychiatric condition, it is often appropriate to address the insomnia in the context of the primary treatment, rather than waiting for the primary condition to abate. Overall insomnia is a disorder that can and should be addressed when it presents, irregardless of the many faces with which it may present.

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Table I

Research diagnostic criteria for insomnia

To meet research diagnostic criteria for general insomnia the individual must meet each of the three criteria below[2]:	
1	Reports at least one of the following sleep related complaints:
	(a) difficulty initiating sleep
	(b) difficulty maintaining sleep
	(c) waking up too early, or
	(d) sleep that is chronically nonrestorative or poor in quality.
2	The sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
3	Experience at least one of the following forms of daytime impairment related to the nighttime sleep difficulty:
	(a) fatigue/malaise
	(b) attention, concentration, or memory impairment
	(c) social/vocational dysfunction or poor school performance
	(d) mood disturbance/irritability
	(e) daytime sleepiness
	(f) motivation/energy/initiative reduction
	(g) proneness for errors/accidents at work or while driving
	(h) tension headaches, and/or GI symptoms in response to sleep loss; or
	(i) concerns or worries about sleep.

Table II

Basic behavioural principles in chronic insomnia

1	Assess, identify (and potentially treat) any comorbid medical or psychiatric condition potentially contributing to insomnia.
2	It is not necessary, and perhaps not advantageous, to delay the targeted treatment of the insomnia regardless of identified comorbidities.
3	Scheduled follow-ups to assess efficacy, dose escalation, and side effects.
4	When insomnia has improved to an acceptable level, develop and implement a taper/withdrawal schedule.
5	Include behavioural instructions for relapse prevention to assist in discontinuation.

Table III

Instructions for sleep restriction therapy

1	Establish an average total sleep time (TST) from 1-2 wk of daily sleep diaries.
2	Establish a fixed wake time.
3	Establish a sleep window by setting bedtime to allow for total sleep opportunity equal to TST from prior diaries (do not set sleep window < 4.5 h even if TST is shorter than this amount).
4	Continue to keep weekly sleep diaries.
5	Adjust the sleep window based on weekly sleep efficiency derived from the prior weeks sleep diaries
	(a) If sleep efficiency (TST/sleep window) is ≥ 90%, increase sleep window by 15 min
	(b) If sleep efficiency is < 90% and ≥ 85%, keep the sleep window unchanged.
	(c) If sleep efficiency is < 85% decrease sleep window by 15 min.
6	Continue daily sleep diaries and adjustments on a weekly basis until treatment completion.
7	Patients may continue this on their own following treatment.