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CLINICAL REVIEW

Secondary insomnia: diagnostic challenges and intervention opportunities

Christina S. McCrae and Kenneth L. Lichstein

Sleep Research Project, Department of Psychology, The University of Memphis, Memphis, Tennessee, USA

KEYWORDS
insomnia, secondary insomnia, diagnosis, treatment, prevalence

Summary The assessment and treatment of secondary insomnia (SI), the most common form of insomnia, are often complicated. Establishing an accompanying disorder as causal rather than comorbid is the key to assessment, but can be difficult even for experienced clinicians. Treatment often focuses on the primary disorder. In many cases, however, there is reason to treat the insomnia directly (insomnia is partially independent, does not respond to treatment of the primary condition, or has been misdiagnosed as SI). Although hypnotic medications are frequently used, behavioral interventions may be the best treatment approach, providing better long-term management of symptoms. Older adults warrant special consideration as age-related illnesses, changes in drug absorption and metabolism, and polypharmacy make them especially susceptible to SI. Recent research suggests successful treatment of insomnia may also relieve the primary disorder and merits follow-up. Future research is also needed on the efficacy of psychological treatment for SI for specific disorders as well as for older adults.

INTRODUCTION

Secondary insomnia (SI) warrants special attention, because it is the most common form of insomnia, accounting for approximately three-quarters of cases seen in both patient and general populations. Sleep is vulnerable to disruption by a wide variety of conditions. This review begins with a general discussion of SI diagnosis and treatment. Then, the focus is narrowed, providing more detailed discussion of some of the more common primary disorders causing SI. The review concludes by introducing a new heuristic model of SI.

Correspondence should be addressed to: Christina S. McCrae, PhD, Department of Psychology, The University of Memphis, 202 Psychology Building, Memphis, TN 38152-3230. Fax: (901) 678-2579.

DIAGNOSIS

Secondary insomnia is characterised by a complaint of poor sleep that is either precipitated or aggravated by another disorder (medical or psychiatric) or substance. As SI is a common symptom of a variety of disorders, it does not typically receive separate diagnosis unless severe enough to warrant independent clinical attention [1,2]. Specific guidelines for determining severity vary, but generally agree that insomnia is severe if it results in significant subjective distress and/or social or occupational impairment. Distinguishing between primary insomnia (PI) and SI can be difficult. Insomnia is frequently accompanied by another condition, and it is not always clear whether the accompanying condition plays a causal role or is simply comorbid. Other sleep disorders (sleep apnea and periodic limb movements) can also produce insomnia-like

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symptoms and need to be ruled out [1,2]. Insomnia can also have dual etiology, such that it is partially due to the primary condition and partially independent.

Polysomnographic (PSG) evaluation is not generally recommended for the assessment of insomnia, but may be necessary to rule out other sleep disorders [3]. Self-report is the most practical means of evaluating SI. Therefore, obtaining an accurate history from the patient is the key to accurate diagnosis [4]. Information pertaining to the onset and course of the insomnia and the other disorder can help to establish the etiology of the sleep complaint. Secondary insomnia is indicated when the onset of the insomnia coincides with or shortly follows that of the other disorder. It is also indicated when the course of the insomnia mimics that of the other disorder, remitting or diminishing in severity as the primary condition remits. Frequently, SI can be directly linked to some feature of the primary disorder (i.e. joint pain due to arthritis resulting in disrupted sleep). Insomnia can also precede another disorder (i.e. a patient may develop depression following 6 months of insomnia) [5]. Whether it is causal or prodromal in such cases is unclear.

CLASSIFICATION SYSTEMS

The International Classification of Diseases (ICD-10) [8], the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) [1], and the International Classification of Sleep Disorders (ICSD) [2] all agree that insomnia is a symptom common to a variety of disorders. They disagree, however, on whether SI warrants separate classification. The ICD-10 does not distinguish SI from PI; the DSM-IV and ICSD do make this distinction. The ICD-10 categorises both SI and PI as "non-organic insomnia". For SI, this categorisation is given in addition to that of the primary disorder when the complaint of insomnia "dominates the clinical picture". The DSM-IV provides broad classification based on SI's three main causes: insomnia related to another mental disorder; sleep disorder due to a general medical condition, insomnia type; and substance-induced sleep disorder, insomnia type. The ICSD provides the most detailed classification, listing 19 psychiatric and medical disorders and substances that may result in SI.

All three systems provide some basic guidelines for diagnosing insomnia. The DSM-IV and the ICSD provide some specific guidelines for diagnosing SI, but unfortunately, these are not consistent across the two systems. These guidelines may also lack sufficient detail to be clinically useful. Across several clinical settings, Buysse *et al*. [9] found only moderate agreement (kappas ranged from .26 to .80) between sleep specialists and general clinicians using DSM-IV criteria to diagnose individuals reporting insomnia complaints. The establishment of clear, detailed guidelines that are consistent across systems would clarify assessment. The Discussion section will return to an exploration of the difficulties in distinguishing comorbidity from SI, wherein an alternative diagnostic scheme that acknowledges the ambiguity inherent in diagnosing SI is proposed.

PREVALENCE

Epidemiological estimates of the prevalence of sleep difficulties in the general population range from 10–48% [4,5,10,11]. Although very little data specifically targets SI, the available evidence suggests it is much more common than PI, accounting for 70–90% of insomnia (variously defined) reported by the general population [4,5,10,11] and up to 73% of insomnia diagnosed (using ICSD criteria) in sleep disorders centers [12–15]. Some caution should be exercised in interpreting these data, because they may overestimate the occurrence of SI. Much of the epidemiological research on insomnia is flawed by inadequate definitions of insomnia and inadequate efforts to rule out other sleep disorders or to distinguish SI from comorbidity. Epidemiological research that takes these flaws into account is needed.

CAUSES OF SECONDARY INSOMNIA

Psychiatric secondary insomnia

Psychiatric causes of SI include anxiety, depression, panic disorder, adjustment disorders, somatoform disorders, and personality disorders [1,2,8]. Epidemiological research has found comorbidity rates of 40–50% between insomnia and psychiatric distress [4,5,10]. In one study, more than 70% of individuals with a mood disorder complained of insomnia [4]. In sleep disorders centers, psychiatric SI was the most frequent diagnosis (35–50%) among

individuals presenting for evaluation of chronic insomnia, and depression and anxiety were the most common psychiatric causes [12–15]. Some patients present with insomnia complaints, because they are easier to discuss and less stigmatising than other psychiatric symptoms. Ohayon *et al.* [4] found a high percentage of individuals with depressive symptoms had sought medical treatment for their sleep problems, raising the unsettling possibility that many cases of depression go undetected by the general medical community. In individuals already receiving treatment for a psychiatric disorder, psychotropic medication may contribute to insomnia. Psychiatric disturbance and/or its treatment should always be a consideration in individuals complaining of insomnia.

Table 1 Prescription medications with insomnia side-effects

Anti-arrhythmic
Quinidine

Anti-depressants
Fluoxetine
Imipramine
Phenelzine
Protriptylene

Anti-epileptic
Phenytoin

Anti-hypertensives
Clonidine
Methyldopa
Propranolol
Triamterene

Anti-inflammatory
Steroids

Anti-parkinsonian
Levodopa

Bronchodilator
Theophylline

Diuretic
Triamterene

Hormones
Synthroid (thyroid hormone)

Medical conditions

A wide variety of medical conditions lead to SI, including asthma, pulmonary disease, heart disease, arthritis, renal disease, obstructive airway disease, back problems, headaches, Alzheimer's disease, and seizures [16–20]. The prevalence of medical SI is difficult to estimate, but some data is available for specific disorders. Monjan and Foley found older adults with stroke or heart disease were about twice as likely to develop insomnia within 3 years than were older controls [21]. Almost half of cirrhotic and over one third of chronic renal failure patients report disturbed sleep [22]. Sleep disorders centers data (7 studies, combined $n = 2249$) found that on average medical SI accounted for 5.8% of individuals complaining of insomnia [10,13–15, 23–25]. Determining which aspect of the medical disorder is actually causing the SI is particularly important. Medical SI can arise due to pain, psychological stress, and/or concurrent medication [7]. Different medical conditions affect sleep in different ways. Based on self-report, Kaye, Kaye and Madow [26] found maintenance insomnia was typical of cancer patients; while onset and/or terminal insomnia was typical of cardiac patients.

Substances

Prescription medications, nonprescription drugs (over-the-counter), and substances of abuse can interfere with sleep, resulting in SI. Insomnia is a potential side effect of many commonly prescribed medications (Table 1). Common non-prescription substances, such as caffeine, nicotine and alcohol can also result in sleep difficulties [27,28]. Over-the-counter medications containing caffeine can effect sleep (e.g. Anacin, Excedrin) as can some nasal decongestants and pain medications. Medication response is highly individualised and whether a patient exhibits insomnia for a given medication depends on dosage level, time of administration, and age [18,29,30]. Psychoactive substances that may induce SI include: alcohol, amphetamines, caffeine, cannabis, cocaine, nicotine, opiods and sedatives. These substances can effect sleep through the direct physiological effects of ingestion (i.e. arousal) and/or by disrupting sleep patterns [31]. Withdrawal from a substance can also result in insomnia [31].

OLDER ADULTS

Secondary insomnia is more common and more severe in older adults for a multitude of reasons. Age-related changes in sleep architecture cause older adults to sleep lighter, making their sleep more vulnerable to disruption by medical and psychiatric disorders. In a Gallup poll, SI was due to medical problems in 5% of insomniacs below the age of 55 and in about 15% of those 55 or older [32]. Hoch *et al.* [33] surveyed 100 older adults and found 59% attributed their sleep disruption to nocturia, 16% to coughing or difficulty breathing and 12% to pain.

Other reasons given (less frequently) were feeling cold or hot, leg cramps and dreams. Higher rates of medical illness in older adults increase their risk of insomnia due to both the illness itself and the medication used in its treatment. There are normal age-related physiological changes that retard drug absorption, distribution, metabolism and elimination and elevate target site sensitivity [30,34]. Older adults also tend to take multiple medications. Certain neurological diseases (Alzheimer's, Huntington's and Parkinson's diseases), which are high risk factors for SI, are most prevalent in the elderly and can interfere with both the patient's and the caregiver's sleep [6]. Sundowning, a unique variation of SI, is commonly seen in patients with Alzheimer's disease. The caregivers of such patients are typically older adults themselves and often experience poor sleep as a direct consequence of their patients' disrupted sleep patterns [35].

Older adults may also be particularly vulnerable to psychiatric SI. Guerro and Crocq [36] examined an older (over age 65) and a younger (under age 55) group of depressed individuals matched for severity of mood disturbance and found more frequent and more severe insomnia in the older group. Other psychiatric threats are also more common in older adults. For example, bereavement is a risk factor for insomnia, and the elderly are more likely to experience the death of a spouse, other loved one or close friend. Other factors, such as retirement, social isolation and restricted movement resulting from disability, occur more frequently in older adults and may affect sleep by provoking anxiety or depression [37].

Clinical considerations for older patients

- Changes in drug absorption and metabolism
- Polypharmacy
- Sundowning
- Psychosocial stress (i.e. bereavement, retirement, loss of independence)

TREATMENT

Both pharmacological and behavioral interventions are used to treat PI. Secondary insomnia treatment, however, is usually directed at the primary disorder. Typically, SI receives direct treatment only when the insomnia is severe or does not respond to treatment of the primary disorder. There may be reason, however, to make direct treatment of SI a more common practice. Most notably, there has not been a single empirical demonstration of the successful resolution of SI following successful treatment of the primary condition. Conversely, clinical studies have shown that in some cases the primary condition may actually improve following successful treatment of the insomnia [16,38]. In other cases, insomnia initiated by a primary disorder becomes increasingly independent over time and as a result, may respond only partially to treatment of the primary disorder.

Pharmacological treatment

Low doses of hypnotics, particularly benzodiazepines, are commonly used. Complications can arise, however, from adding pharmacological treatment to the regimen of patients already undergoing treatment for primary illnesses. Concurrent medications should be carefully considered before instituting pharmacological treatment. Because many medications (benzodiazepines and antidepressant drugs) are metabolised by the cytochrome oxidase P450 system in the liver, patients taking several prescribed drugs utilising this system may be at an increased risk of side-effects and toxicity [39]. Older patients for whom polypharmacy is a common occurrence may be particularly susceptible. Hypnotics are recommended for short-term use only, because their effectiveness diminishes over time. Tolerance and dependence can also develop, particularly for some of the older benzodiazepines with longer half lives (i.e. clonazepam, diazepam, flurazepam). Buysse and Reynolds [39] recommend a 1-month trial followed by an attempt to taper and discontinue. When long-term maintenance is an issue (as it often is), psychological treatments are the preferred treatment [40]. It should be noted, however, that research now being conducted may demonstrate that the newer, shorter-acting hypnotics (zaleplon and zolpidem) also provide adequate long-term insomnia control.

Psychological treatments

Primary insomnia [41,42] responds well to psychological intervention. Research has just begun to examine such interventions for SI, and so far, the results have been encouraging. There are a variety of

Table 2 Psychological treatments for secondary insomnia

Cognitive	techniques intended to target beliefs and attitudes about sleep and sleeplessness that may be maladaptive for sleep (i.e. "I need 8 full hours of sleep every night in order to function") [43]
Cognitive behavioral	combines cognitive techniques intended to target sleep maladaptive beliefs and attitudes with one or a combination of the behavioral techniques (described below) intended to target sleep maladaptive behaviors
Relaxation	any of a collection of methods intended to evoke the relaxation response consisting of both experiential and physiological calm; methods of relaxation include muscular relaxation (progressive muscle relaxation), passive methods of body focusing, and soothing imagery techniques [44]
Sleep restriction	as the name implies, slep improvements are achieved primarily by limiting/restricting the time allotted for sleep each night [45]
Stimulus control	a collection of 6 instructions intended to help a patient eliminate habits that interfere with sleep (i.e. "Don't use your bed or bedroom for anything but sleep") [46]

psychological or behavioral treatments for insomnia. Table 2 contains brief descriptions of the most common treatments: cognitive, cognitive behavioral, relaxation, sleep restriction and stimulus control.

Efficacy of psychological interventions

Only a handful of case studies and a few randomised group studies have been conducted. Five case studies have shown insomnia improves following psychological treatment for SI due to cancer [47], chronic pain [48], depression and pain [38], hemophilia [49] and multiple medical problems [50]. A variety of treatments were employed in these studies (i.e. relaxation, slow deep breathing, sleep restriction, stimulus control, imagery). In a multiple baseline study, Morin *et al.* [16] had three chronic pain patients continue their usual pain care (i.e. physical therapy, nerve blocks) during 6 weeks of psychological treatment consisting of stimulus control and sleep restriction. Each patient reported improved sleep (i.e. decreased time to fall asleep, less and shorter awake times at night) following treatment and maintained these improvements at 6 months follow-up. All-night PSG sleep studies at pre and post-treatment corroborated the self-report data. Interestingly, over the course of treatment, two of the three patients also improved substantially on measures of depression and anxiety. Tan *et al.* [51] treated 20 psychiatric inpatients with severe insomnia for an average of 5 weeks using multimodal, individualised treatment, involving some combination of individual psychotherapy, group psychotherapy, marital therapy, occupational therapy, sleep medication, progressive relaxation, stimulus control and biofeedback. Rating their overall quality of sleep on a 0 to 8 scale, the patients demonstrated significant improvement from pre-treatment (mean = 1.6, SD = 0.2) to post-treatment (mean = 6, SD = 0.4) and maintained these gains at 6-month follow-up (mean = 6.9, SD = 0.4).

To date, there have been three randomised group studies of SI [52–54]. Cannici *et al.* [52] evaluated progressive relaxation (PR) with patients with various cancer diagnoses. Thirty patients (mean age of 56 years) were assigned at random to either usual medical care or usual care plus three sessions of PR. Pre and post-treatment data were collected for 3 days prior to 3 days of consecutive treatment; 3-month follow-up data were also collected. Latency to sleep improved significantly from 124 min pre-treatment to 29 min post-treatment in the PR group, but remained unchanged in a control group. The PR group maintained this improvement at the 3-month follow-up (latency to sleep was 33 min), while the comparison group remained unchanged. The improvements in this measure were large and clinically meaningful. Unfortunately, this is the only measure demonstrating statistically significant treatment gains. Most of the other sleep measures (e.g. total sleep time, number of awakenings during the night, rated sleep satisfaction) and pain ratings improved in the PR group, but the differences were not statistically significant, perhaps due to low power as a result of small sample size.

Currie *et al.* [53] evaluated cognitive behavioral

therapy (CBT) in 60 chronic pain patients (mean age of 45 years). Over two-thirds of these patients (72%) experienced chronic back pain; the remainder experienced neck pain, lower limb or pelvic region pain. Thirty-two participants were assigned to CBT, consisting of sleep restriction, stimulus control and relaxation, and 28 were assigned to a wait list control (WLC). Therapy was administered in a group format over a 7-week period. Overall, CBT participants demonstrated significant improvement on self-report measures of sleep onset latency, waketime-after-sleep onset, sleep efficiency, and sleep quality compared with WLC participants, and these improvements were maintained at 3-month follow-up. Sleep onset latencies for the CBT participants were reduced by an average of 26.6 min from pre-treatment to post-treatment (54.7 min to 28.1 min) and remained improved over pre-treatment at follow-up (27.8 min). Sleep efficiency for the CBT participants increased significantly from 72% at pre-treatment to 85% at post-treatment and maintained at 84% at follow-up. Wake-after-sleep onset was reduced by 48.7 min from baseline to post-treatment in CBT participants, and again, this improvement was maintained at follow-up (51.6 min). Both CBT and WLC participants demonstrated small, but significant improvement in self-rated sleep quality from pre-treatment to post-treatment; however, only the CBT participants maintained this improvement at follow-up. There was no significant difference between the treated and non-treated groups in total number of awakenings following treatment. Total sleep time (TST) was not increased; however, this analysis approached significance. The CBT participants also demonstrated a significant reduction in nocturnal motor activity levels from baseline to post-treatment, suggesting they were having a more restful sleep period.

Lichstein *et al.* [54] have recently conducted the only randomised study focusing specifically on older adults. The study examined 44 older adults (age 58 or older) who reported at least a 6-month history of insomnia. Subjects had to be sleep-medication free and qualified as having SI based on the following criteria: (i) a plausible causal link could be established between the psychiatric or medical disorder; (ii) insomnia onset closely followed the onset of the primary disorder; and/or (iii) variations in the severity of the insomnia closely followed variations in the primary disorder. Medical and psychiatric SI were equally represented with depression and chronic pain acting as the most common primary disorders. Participants were assigned at random to either treatment or a delayed treatment control group. Treatment consisted of four sessions of hybrid passive relaxation, stimulus control and sleep-hygiene instructions. At post-treatment and 3-month follow-up, the treated group improved significantly on three sleep measures: wake time during the night, sleep efficiency (ratio of time slept to time spent in bed $\times 100$), and rated quality of sleep (1 = very good to 5 = excellent). From baseline to follow-up, wake time for the treated group went from 87.3 to 56.4 min, sleep efficiency went from 66.7 to 77.0%, and rated quality of sleep went from 2.7 to 3.2%. The control group showed no significant improvement. There were no differences in treatment response for medical versus psychiatric SI. Because older insomniacs are typically difficult to treat, these results are highly encouraging, particularly given that the treatment was conducted briefly in only four sessions. Additional research on the efficacy of psychological treatments for SI is needed.

Pharmacological versus psychological treatment

Both treatments provide effective short-term management of insomnia. Unfortunately, hypnotic medications lose effectiveness over time. Because insomnia is often a chronic condition, behavioral therapy may be the best treatment option. In a randomised, placebo-controlled clinical trial ($n = 78$), Morin *et al.* evaluated the efficacy of behavioral and pharmacological (temazepam) therapies, singly and combined, in older (mean age, 65 years) individuals with chronic insomnia. Treatment lasted 8 weeks and follow-ups were conducted at 3, 12 and 24 months. Behavioral intervention alone was found to be more effective in sustaining sleep improvements over time than either medication alone or the two treatments combined [40]. Some caution, however, should be used in interpreting the results of this study. As medication and behavioral treatment were administered and discontinued concurrently, additional research is needed to determine whether other methods of combining behavioral and drug therapies will produce similar results. Likewise, this study used an older benzodiazepine and, therefore, does not tell us whether

the combination of a newer non-benzodiazepine hypnotic (zaleplon, zolpidem) and behavioral therapy would be effective. Finally, this study does not take into consideration individuals who experience intermittent insomnia and as a result, use medication intermittently.

General secondary insomnia treatment guidelines

- Aggressively treat the primary condition
- Treat the insomnia as well using psychological interventions:
  - they are effective and provide good long-term maintenance
  - unlike medication, they are not likely to cause any serious, adverse effects
  - SI can rarely be definitively diagnosed, because causality is extremely difficult to establish
  - treating the insomnia will not aggravate, and may even result in, improvement in the primary condition

SPECIFIC DISORDERS

Psychiatric

Depression

Sleep difficulties occur in 40–60% of depressed outpatients and up to 90% of depressed inpatients [1]. Polysomnographic assessment may help differentiate depressed patients [55], but is not diagnostic because approximately 50% of depressed out-patients have normal PSGs. Characteristic PSG findings in major depression include sleep fragmentation, reduction of NREM stages 3 and 4 sleep, shortened REM latency, and increased density of rapid eye movements, particularly during the first REM period. Pathology involves disturbed phase relationships of circadian rhythms. Frequent awakenings and early morning waking are hallmark complaints of depression-related insomnia. Although insomnia typically mimics the course of the depression, it can also precede onset [4,5] and persist after remission [1,2]. In Ford and Kamerow's often cited epidemiological study, complaints of insomnia during the initial interview predicted the development of depression by 1-year follow-up [5]. Whether insomnia is interpreted as a risk factor for depression or as a prodromal symptom is debatable. Individuals who suffer recurrent depression often have more pronounced sleep disturbance, which may occur several weeks prior to recurrence and proceed other depressive symptoms [56].

Anti-depressants, specifically selective serotonin reuptake inhibitors (SSRIs: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram), are commonly used to treat depression [57]. Unfortunately, SSRIs stimulate serotonin-2 (5-HT-sub-2) receptors and can cause changes in sleep architecture, resulting in insomnia. For example, research has shown disturbed sleep (prolonged REM latency and suppressed REM sleep) in fluoxetine treated depressed patients [58]. When fluoxetine was compared with nefazodone in depressed outpatients in three separate 8-week trials, both were equally effective anti-depressants, but fluoxetine disturbed sleep (decreasing sleep efficiency – SE, increasing awakenings, decreasing total REM sleep). Nefazodone, which has a pharmacological profile different from most types of anti-depressants, improved sleep (increasing SE, decreasing awakenings, increasing total REM sleep). Research demonstrating the negative effects of fluoxetine on sleep is not unequivocal. A meta-analysis of seven randomised double-blind, placebo-controlled clinical trials (2456 depressed subjects with insomnia) using fluoxetine hydrochloride to treat depression found statistically significant decreases in sleep disturbance as measured by the Hamilton Rating Scale for Depression [59].

To relieve SSRI-induced insomnia, hypnotics [60], low dose trazodone [61–63], or antidepressants with 5-HT-sub-2 blocking properties (i.e. mirtazapine) [63] can be prescribed. Zolpidem improved self-rated sleep, daytime functioning and well-being in a 5-week single-blind placebo study of 190 SSRI-treated depressed out-patients [60]. Trazodone has also been shown to be effective, both objectively and subjectively, in improving sleep in depressed patients who developed insomnia during treatment with Brofaromine, a selective and reversible monoamine oxidase (MAO) inhibitor. In a study comparing dose response to trazodone (50 mg vs 75 mg vs 100 mg), 100 mg/day was found most effective in sleep-disturbed depressed patients ($n = 33$) [64]. Psychological interventions may be particularly useful and have been shown to effectively treat insomnia [26,32] and depression [65], separately. Research investigating the *concurrent*

treatment of both conditions using behavioral techniques is definitely warranted.

Anxiety

Characteristic complaints include frequent awakenings which may be accompanied by anxiety dreams. Insomnia is often due to conditioning, and worry about inability to sleep may be present. Polysomnography generally reveals non-specific findings. A single treatment with a benzodiazepine is not generally recommended for anxiety, but may benefit patients with generalised anxiety or panic [39]. Very little research has specifically targeted anxiety. In a 5-week single-blind study of trazodone, Arriaga *et al*. [61] found improvement in both anxiety and insomnia related to improvement in sleep PSG (increased slow-wave sleep; SWS). Psychological interventions may be particularly helpful in relieving the physical tension (relaxation) and/or the disturbed thinking patterns (cognitive therapy) often seen in anxious patients.

Medical

Chronic pain

Pain frequently causes insomnia [66,67], particularly for cancer [68,69], back pain [70] and headache [71]. Approximately 50–70% of pain patients experience insomnia [16,72,73]. Morin *et al*. [16] found poor sleep coincided with or followed the onset of pain in 90% of the patients experiencing insomnia. Pain and insomnia are often reciprocal [74,75]. For example, in osteoarthritis, insomnia may worsen daytime pain by lowering pain thresholds and promoting poor sleep posture resulting in joint strain [74]. Polysomnographic findings in 25 headache patients (only seven had insomnia complaints) found instances of headache causing insomnia, insomnia causing headache, and insomnia and headache exacerbating each other [75]. Insomnia and pain associated with fibromyalgia and rheumatoid arthritis may benefit from antidepressant drugs. As previously discussed, CBT has been shown to be effective for insomnia secondary to chronic pain and in fact, is one of the few conditions for which CBT has been systematically studied [54].

Fibromyalgia

Sleep is often light and accompanied by physical discomfort (musculoskeletal pain, chronic fatigue). Characteristic PSG results include alpha activity during NREM, alpha-delta activity and occasional periodic limb movements. Subjective complaints of daytime sleepiness and fatigue, however, are not supported by multiple sleep latency tests (MSLT). Research suggests SWS disturbance contributes to complaints of non-restorative sleep [76]. When treating insomnia related to SI, adequate pain control and sleep habits should be achieved before medication is prescribed [77]. Tricyclic antidepressants, trazodone, and selective serotonin re-uptake inhibitors may be helpful.

Rheumatoid arthritis (RA)

Morning stiffness, unrefreshing sleep and fatigue are common complaints. Polysomnography often reveals sleep fragmentation and reduced sleep efficiency, alpha–delta sleep and K-alpha complexes [78]. Research is needed to determine if imbalances in cytokine networks are related to disturbed sleep and daytime fatigue. In a double-blind, cross-over study, Walsh *et al*. [79] found triazolam increased TST and decreased daytime sleepiness and morning stiffness in RA patients compared to placebo; objective measures of sleep fragmentation were unchanged. The results of a study by Hardo *et al.* [80] however, suggest the use of hypnotics may be questionable as arthritic patients ($n = 165$) receiving night sedation had more pain than those who did not as evidenced by greater usage of codeine (34% compared with 18%).

Dementia

Alzheimer's disease and other dementias are frequently associated with sleep disturbance, particularly sundowning [81]. Hypnotics (low doses of short-acting benzodiazepines), anti-histamines, and anti-depressants are commonly used in nursing homes as are anti-psychotic drugs such as haloperidol and resperidol. Dementia patients are particularly susceptible to the cognitive side effects of such drugs and should be carefully monitored for confusion. Despite their common use, anti-histamines have not been thoroughly researched. A few studies, however, have shown them to be sedative compared with placebo and comparable to benzodiazepines with similar cognitive effects [39]. Non-pharmacological interventions can be helpful and should focus on improving daytime activity, providing sufficient light exposure and ensuring a proper night-time sleep environment (one that minimises noise and other disruptions).

Parkinson's disease (PD)

Secondary insomnia may result from the muscle tremors and stiffness associated with neurological disease [6] and is the most common sleep problem in PD (seen in 60–90% of patients) [2]. Characteristic complaints include sleep fragmentation and daytime sleepiness. Neurochemical changes, including alterations in dopaminergic, serotonergic and norepinephrin systems, can interfere with the sleep–wake cycle, reducing REM and SWS [2]. Toxicity caused by dopamine agonists and anticholinergic medications used to treat PD can disturb sleep. Medication-induced sleep complaints are seen in up to 80–90% of patients treated with levodopa and bromocriptine [2]. Insomnia may improve when levodopa administration is restricted to earlier hours and may even disappear altogether when it is discontinued. In some cases, however, dopamine agonists improve sleep by reducing rigidity. Dementia and depression frequently accompany PD and contribute to insomnia. Limb movements, tremor and/or medication-induced myoclonus can cause arousal, while bradykinesia and rigidity can result in abnormal body shifting during the night. Sleep apnea should be ruled out as abnormal motor activity in the upper airway and chest can disrupt breathing. Complaints of sleep disturbance often increase as PD progresses. There are no distinctive PSG features in PD [2].

According to self-report data, the rate of PD amongst 153 patients and their spouses was almost double that of 103 healthy, age-matched controls [82]. Insomnia was attributed to the physiological effects of PD (pain, tremor, rigidity, excessive sweating, nocturia), medications used in treatment (e.g. levodopa, selegiline) and associated psychiatric distress (i.e. depression). Both PD patients and their spouses reported high levels of depressive symptoms. The burden of taking care of someone with a chronic illness was evident in the slightly higher rate of insomnia in the spouses than in the patients. A review of the literature revealed only one study that failed to report elevated levels of insomnia in PD patients. Comparing PD patients with age-matched controls, Factor *et al.* [83] found only a small increment in insomnia in the PD patients.

Substance

Alcohol abuse

Self-prescribed use of ethanol as a sedative is distinct from alcoholism, because it is not typically accompanied by daytime drinking or physical tolerance or dependence [2]. Alcohol appears to have a positive effect on sleep at the beginning of the night, but this is countered by worse sleep at the end of the night. Typical PSG results reveal reduced wake time and REM, and increased SWS for first 3–4 h of sleep followed by wakefulness and REM rebound during the last 2–3 h of sleep [2]. Alcohol's initial, positive effect may be the reason some patients believe very strongly that alcohol helps them sleep better. Withdrawal from alcohol also disturbs sleep, resulting in very short TST on some nights, REM rebound for the first few days and a profound reduction or even absence of SWS. Recovery of SWS occurs gradually (and occasionally not at all), taking take up to 2 years in some cases. Tolerance to withdrawal and alcohol cravings are inversely correlated with SWS. As benzodiazepines are not generally recommended for patients with addictive potential, non-pharmacological interventions may prove particularly helpful [84]. Benzodiazepines may be useful, however, for treatment of acute alcohol withdrawal. Some clinicians prefer to use sedating antidepressant drugs, but the effectiveness of this approach has yet to be demonstrated [39].

DISCUSSION

Proposed model of secondary insomnia

Conferring the diagnosis of SI rests on the ability to assert causal inference: condition A (medical, psychiatric or substance) causes condition B (sleep disturbance). Though clinicians and researchers alike may not dwell on philosophy of science issues in determining such diagnoses, the present context provides such an opportunity, and careful analysis of this matter may help illuminate ambiguity and better prepare those entrusted with diagnostic decisions. When rendering a diagnosis, it always concerns an individual patient, so that models of randomised clinical trial methodology that best protect internal validity and causal inference do not apply. Single-subject designs, particularly the A–B–A–B design [85], also justify causal inference and are salient to the present discussion. We can be confident of our diagnosis of SI in the unlikely event of a naturally occurring experimental design. Such an example might occur with a cancer patient who reports a history of *always* experiencing insomnia

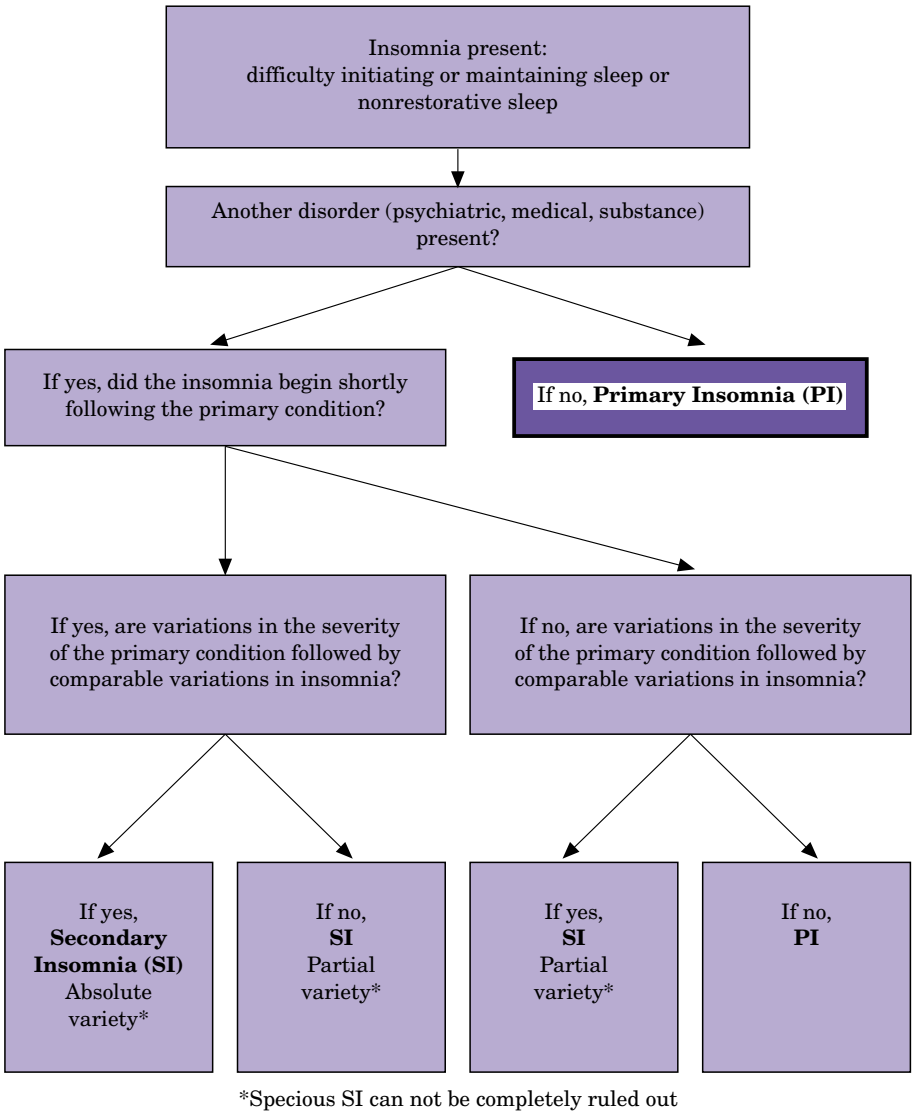

Figure 1 Decision tree for differentiating the three proposed subtypes of primary and secondary insomnia.

when the cancer is active and *never* having difficulties sleeping when the cancer is in remission.

In practice, the conditions needed to assert causal inference for SI are almost never present. It is easy to establish comorbidity, wherein, two disorders co-occur but neither necessarily owns causal influence over the other. From a philosophy of science point of view, it is usually impossible to render a definitive diagnosis of SI. Complicating this matter is the exclusive reliance on the historical report of the patient in determining the origin and course of the "primary" and "secondary" disorders. In our experience, if this history has lasted more than 6 months, most patients cannot provide a reliable accounting of the course of the two disorders and their relative sequence.

Lichstein [86] recently proposed a heuristic model that more accurately maps onto the reality of diagnosing secondary insomnia (Fig. 1). The model divides SI into three distinct types: absolute, partial and specious. Absolute SI requires the insomnia to be under the complete control of the primary condition (i.e. chronic headache pain causing insomnia). Absolute SI corresponds to the customary meaning of the term SI, and in our opinion, this is uncommon. Absolute SI is most likely to be found

in acute conditions, but as the primary condition becomes chronic, the strong causal link between it and the sleep disturbance fades.

Partial SI occurs when only one of the conditions required for absolute SI is met. Two versions of partial SI are possible: (i) a pre-existing PI may be exacerbated by a primary condition; or (ii) insomnia created by a primary condition may acquire some degree of functional independence over time. Partial SI takes into account that PI and SI are not mutually exclusive conditions. For example, a patient may have a 10-year history of difficulty falling asleep 3 or 4 nights a week, but may now be experiencing difficulty every night due to the onset of a major depressive episode. The third variety, specious SI, refers to situations in which absolute or partial SI are wrongly diagnosed. Comorbid insomnia is mistaken for SI. Unfortunately, the diagnostician is in the precarious state of never being able to verify any one of these varieties, and no matter which SI type is asserted, neither of the other two can be ruled out. Treatment response of the sleep disturbance provides post hoc clues as to which SI diagnosis was the best. When the primary condition is resolved, we should expect comparable improvement in absolute SI. Under the same circumstances, partial SI will respond moderately well, and specious SI not at all. Conversely, when attempting to treat the sleep disturbance in SI directly, (as several well-controlled studies have shown can effectively be done [52–54]), absolute SI should respond poorly because as the insomnia improves, it is replenished by the primary condition. Partial SI should respond moderately well, and specious SI should respond as well as PI.

Which brings us to our final point. If our diagnostic tools do not permit reliable differentiation between absolute, partial and specious SI, then withholding or delaying direct insomnia treatment while the "primary" condition is treated is ill advised. This may inadvertently constitute denying effective sleep treatment to the patient and in some cases, residual benefits to the "primary" condition accruing to sleep improvement are also denied. We recommend aggressive direct treatment of SI.

SUMMARY AND CONCLUSIONS

Because SI is an extremely common condition, it's accurate diagnosis and successful treatment has the potential to benefit significant numbers of patients. Unfortunately, SI is a complex disorder and assessing and treating it is often challenging. Detailed guidelines that are consistent across the three main classification systems (ICD-10, DSM-IV and ICSD) would go a long way to help clarify diagnosis. The proposed model of SI was introduced not to replace but to supplement these systems and to provide a basis for more theoretically-oriented discussion of SI. Treatment is typically directed at the primary disorder, but does not always improve the insomnia. As a result, direct SI treatment is often necessary and according to recent evidence, may even improve the primary condition. Behavioral interventions offer promise as a primary treatment for SI and may in fact be the best approach to treating SI. They provide good long-term symptom management and unlike medications, are not likely to interfere with treatment of the primary condition, contribute to polypharmacy, or cause other serious, adverse effects.

Practice Points

Basic secondary insomnia (SI) diagnostic guidelines.

Accurate SI diagnosis requires:

- onset of the insomnia shortly follows that of the primary condition and/or
- variations in severity of the primary condition over time are shortly followed by comparable variations in the insomnia and/or
- a clear causal mechanism (i.e. back pain resulting in disrupted sleep).

SI is often multifactorial, and primary disorders can cause insomnia through:

- physiological mechanisms (particularly true for neurological disorders).
- secondary symptoms (pain or nocturia).
- alerting medications used in treatment and/or associated stress [6, 7].

Research Agenda

In the future we need to:

1. establish consistent and clear diagnostic criteria.
2. further explore the effect of direct secondary insomnia treatment on the primary disorder.

3. continue to examine the efficacy of behavioral interventions, particularly in older adults.
4. investigate the efficacy of combining behavioral insomnia treatment with behavioral interventions known to be effective for specific primary disorders, such as depression.
5. investigate the efficacy of various methods of combining psychological and pharmacological treatments.
6. determine whether the newer non-benzodiazepine hypnotics (zaleplon, zolpidem) provide effective long-term insomnia maintenance.

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APPENDIX

Glossary of terms

Absolute secondary insomnia (Absolute SI): one of the three distinct varieties of SI introduced by Lichstein [86]; refers to insomnia that mimics the course of the primary condition in terms of both origin and variation in severity.

Cognitive Therapy: a psychological technique used to treat insomnia by changing thought patterns that interfere with sleep (e.g. "I must have 8 hours of sleep each night") [44].

Cognitive behavioral therapy: a psychological intervention combining cognitive (to change sleep maladaptive thought patterns) and behavioral (to change sleep maladaptive behaviors) techniques.

Insomnia: poor sleep.

Kappa: a measure of interjudge agreement.

Partial secondary insomnia (Partial SI): one of the three distinct varieties of SI introduced by Lichstein [86]; refers to insomnia that occurs when only one of the conditions required for absolute SI is met, meaning the insomnia mimics the course of the primary condition in terms of either origin or variation in severity.

Primary insomnia (PI): poor sleep that is not the result of another disease, disorder, or substance.

Relaxation: a behavioral technique used to treat insomnia; includes any of a collection of methods intended to evoke the relaxation response consisting of both experiential and physiological calm [45].

Secondary insomnia (SI): poor sleep that results from another disease, disorder, or substance.

Sleep efficiency (SE): ratio of total time slept to the total time spent in bed multiplied by 100.

Sleep restriction: a behavioral technique used to treat insomnia in which sleep improvements are achieved primarily by limiting/restricting the time allotted for sleep each night [46].

Specious secondary insomnia (Specious SI): one of the three distinct varieties of SI introduced by Lichstein [86]; refers to insomnia that is mistakenly diagnosed as absolute or partial SI; the insomnia appears to be causally related to another disorder when in fact the two disorders are actually comorbid.

Stimulus control: a behavioral technique used to treat insomnia through the application of six instructions intended to help a patient eliminate habits that interfere with sleep (i.e. "Don't use your bed or bedroom for anything but sleep") [47].

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