

Causes of insomnia

In this chapter, we will discuss some of the more common factors associated with the development and maintenance of insomnia such as age, physiology, circadian rhythms, and environment.

Age

Aging is one of the most significant factors associated with changes in sleep across the lifetime [1]. Sleep consists of two physiologically distinct states: rapid eye movement (REM) and non-rapid eye movements (NREM) sleep [1]. NREM sleep is associated with minimal mental activity and is divided into three stages, with increasing depth of sleep achieved from stages N1 through N3 (Figure 2.1). REM sleep consists of electroencephalography (EEG) activation, muscle atonia, and rapid eye movements. For most adult sleepers, sleep onset occurs through NREM sleep with REM sleep occurring at least 80 minutes afterwards and NREM and REM sleep typically alternating throughout the rest of the sleeping

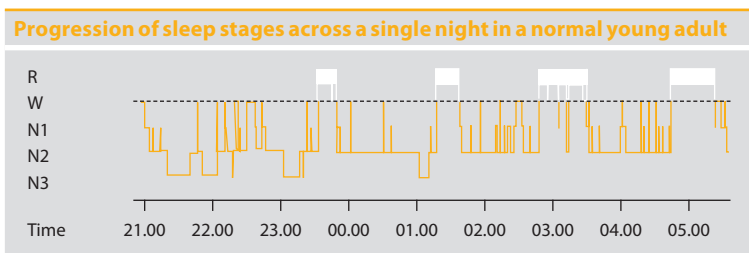


Figure 2.1 Progression of sleep stages across a single night in a normal young adult. (R) Rapid eye movement sleep; (W) Wake; (N1, N2, N3) Non-rapid eye movement sleep stages 1, 2, and 3. Reproduced with permission from Sheenan and Hirshkowitz [2] ©Elsevier.

period. REM cycles become longer over time, with a reduction of stage 3 and 4 sleep across the sleep period.

One of the biggest changes in the structure of sleep (also known as ‘sleep architecture’) is seen in newborn infants. During the first year of life, infants transition from wake to sleep through REM sleep, as opposed to the NREM to REM progression seen in older ages [1]. Infants also begin to develop consolidated nocturnal sleep during their first year of life, with slow wave sleep (also known as ‘deep sleep’) occurring with the greatest frequency in young children and then decreasing with age [1]. Other age-related changes in sleep (sometimes beginning as early as young adulthood) include an increasing amount of time spent in the lighter stages (ie, N1 and N2) of sleep, more time spent awake, and an advancing of the circadian rhythm (ie, becoming sleepier earlier in the cycle) [1]. Figure 2.2 depicts changes occurring in sleep architecture across the lifespan [3].

Although there are age-related changes in sleep architecture, the majority of changes in sleep are not due to age but rather are a result of various medical and psychiatric comorbidities that become increasingly

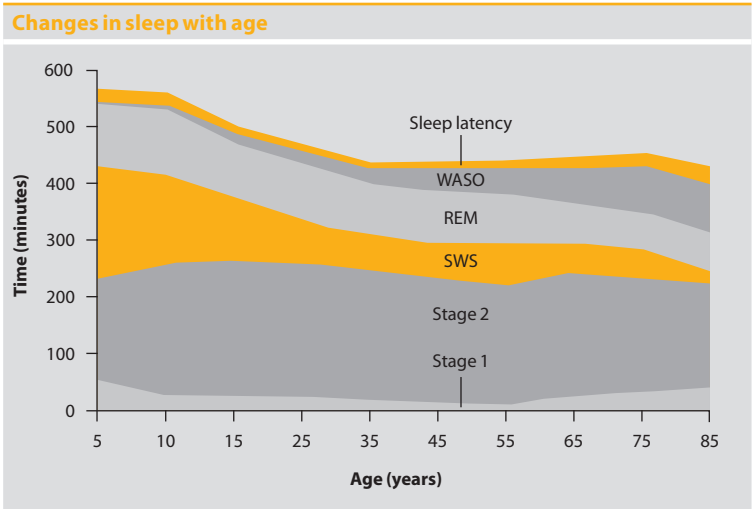


Figure 2.2 Changes in sleep with age. Time (in minutes) for sleep latency and wake time after sleep onset (WASO) and for rapid eye movement (REM) sleep and non-REM (NREM) sleep stages N1, N2, and slow wave sleep (SWS). Summary values are given for ages 5 to 85 years. Reproduced with permission from Ohayon et al [3] ©Associated Professional Sleep Societies.

prevalent with age [1]. As Figure 2.3 illustrates, in addition to factors predisposing older adults to poor sleep, there are a number of factors that can precipitate poor sleep such as the onset of an illness, loss of physical functioning, or another primary sleep disorder (eg, obstructive sleep apnea) [4,5]. Furthermore, once an older adult develops insomnia, there are a number of factors that can perpetuate poor sleep such as social isolation, caregiving, or bereavement.

Understanding the changes in sleep that occur with age is important because older adults may have lowered expectations for their sleep and assume that poor sleep is a natural consequence of aging. As a result, it may be up to the clinician to inquire about sleep complaints from older patients. Poor sleep is an important complaint to assess in older adults as it is associated with poorer overall physical and mental health status [6].

Illustration of the development of sleep complaints and associated adverse outcomes

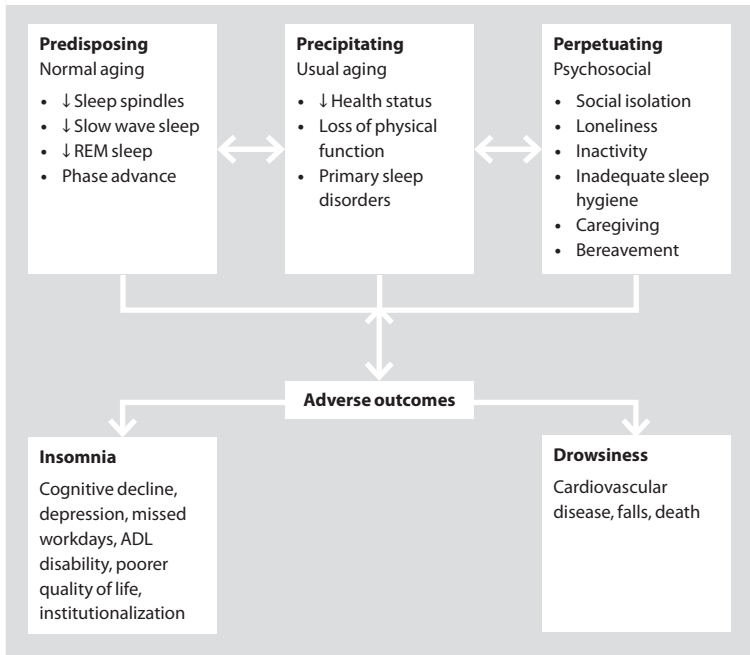


Figure 2.3 Illustration of the development of sleep complaints and associated adverse outcomes. ADL, activities of daily living; REM, rapid eye movement. Reproduced with permission from Vaz Fragoso et al [5] © John Wiley and Sons.

Specifically, poor sleep has been implicated in an increased risk for falls, impaired physical functioning, cognitive decline, and memory problems in older adults [7–11].

Another consideration for a clinician treating insomnia in older adults is the use of medication. Many medications (eg, anti-hypertensives, inhaled steroids) used in conditions commonly seen in advanced age such as hypertension and chronic obstructive pulmonary disease are known to cause sleep difficulties in older adults. Furthermore, many sedating medications (eg, long-acting benzodiazepines and muscle relaxants) can cause daytime napping that, in turn, could impair nocturnal sleep. Older adults can work with their physician to adjust the dosage or timing of their medication use to avoid impaired sleep. The effect of medication on sleep architecture will be discussed in more detail later in this chapter.

Additionally, older adults may sometimes employ alcohol as a sleep aid due to its sedating effects. Although initial consumption of alcohol can have a relaxing effect, it can result in a ‘rebound’ of insomnia, causing the older adult to wake during the night. Accordingly, greater alcohol consumption has been linked to poor sleep in older adults [12,13].

Environmental factors

Several environmental factors can contribute to the development and maintenance of insomnia, including noise, light, temperature, and presence of electronic and communication devices in the bedroom. Individuals with insomnia are often more susceptible to sleep interference and disruption related to external environmental stimuli, such as noise and temperature, than patients without insomnia [14]. Noise and light levels that may not bother other people can have a profound disruptive impact on the sleep of patients with insomnia. For example, external noise from traffic or insects, as well as indoor noises (eg, television, radio, a bed partner’s snoring, other people in the household, even a squeaky door hinge) can contribute to a restless and sleepless night for patients with insomnia. Interestingly, white noise or other repetitive noise (eg, sound of a fan) can have a soothing effect and can be conducive to promoting sleep for some patients with insomnia [15,16].

It has been demonstrated that aspects of the bedroom environment, such as the use (or even just the presence) of an electronic device (eg, television, phone) or a desk where finances and/or other paperwork are done, can lead to the bedroom becoming associated with arousing, non-sleep conducive behaviors [17,18]. This may be due to classical conditioning, a theory which helps to explain the importance of ‘cues’ (ie, discriminative stimuli) in either promoting or disrupting sleep. For patients with normal sleeping patterns, the bed, bedroom, and bedtime are usually strong cues for sleep; inversely, they become strong cues for wakefulness in patients with insomnia, as they adopt and perpetuate arousal-inducing behaviors (eg, worrying, watching TV, surfing the internet, paying bills) while in the bed or bedroom. Another reason for limiting the use of electronic devices in the bedroom is the light from these devices also contributes to arousal.

Another important environmental consideration is how comfortable a patient finds his/her mattress and pillow (eg, size, firmness). For example, patients with insomnia who have comorbid pain and other medical conditions can be greatly impacted by their mattress and pillow, as both impact sleeping position and aggravate pain, which can negatively impact sleep [19–22].

Physiology

Insomnia is generally considered to be a disorder of hyperarousal and the manifestations of this excessive arousal are varied [23]. Initially, investigations focused on somatic hyperarousal in patients with insomnia compared to good sleepers. In these investigations, patients with insomnia were found to have elevations in heart rate, body temperature, galvanic skin conductance, and whole body metabolic rate, all suggestive of elevated activity of the sympathetic nervous system [24,25]. These effects are paralleled by findings that there is elevated activation of the hypothalamic-pituitary-adrenal (HPA) axis in terms of higher levels of cortisol in the blood [26]. These differences seem to be strongest at night and it is as if the body is in a state of ‘fight-or-flight,’ instead of minimizing arousal in preparation for sleep.

For a number of years, an enigma in the sleep research field was the finding that patients with insomnia often did not have evidence of

disturbed sleep during overnight sleep studies when compared to good sleepers, despite feeling that they had slept poorly. One theory about this discrepancy between subjective perceptions and the objective evidence was that there is an inherent limitation in the traditional method of conducting sleep studies [27]. This is because sleep study records are visually scored and so determinations of wake and the different sleep stages rely on direct observation. An alternative approach is to use computer-based spectral analysis measures that decompose the EEG signal into different frequency bands. When this approach was applied to sleep studies of patients with insomnia, it was found that they often display elevated activity in the beta frequency range during sleep [28,29]. Beta EEG activity is usually seen while awake and actively engaged in mental processing. It is now believed that patients with insomnia can experience a state that is a mixture of waking and sleeping features. They appear to be asleep, but at the cortical level they are continuing to process information; this type of 'sleep' is thus perceived as wakefulness. This phenomenon has been referred to as cortical hyperarousal.

Another line of research has been the use of neuroimaging methods to study hyperarousal in insomnia. These studies have been difficult to apply to the study of insomnia, in part due to the loudness of functional magnetic resonance imaging (fMRI) scanners, which often does not allow the patient to undergo scanning while asleep. A few studies have utilized positron emission tomography (PET) imaging in which infusion of the radioisotope can occur during sleep and then the patient can be awoken for scanning [30,31]. These studies have found that, for patients with insomnia and without insomnia, there is a decrease in whole brain arousal in the transition from wakefulness to sleep, as is logical. However, for those with insomnia there is less of a reduction compared to those without (Figure 2.4) [28]. Certain brain regions remain more active during sleep and are another indicator of hyperarousal. One region prone to remaining more active is the reticular activating system, the brainstem region in which most of the major neurotransmitter pathways (eg, serotonin, norepinephrine, acetylcholine, histamine, dopamine, neuropeptide A and B) originate. Given that these neurotransmitters modulate levels of

Functional neuroimaging evidence for hyperarousal in insomnia

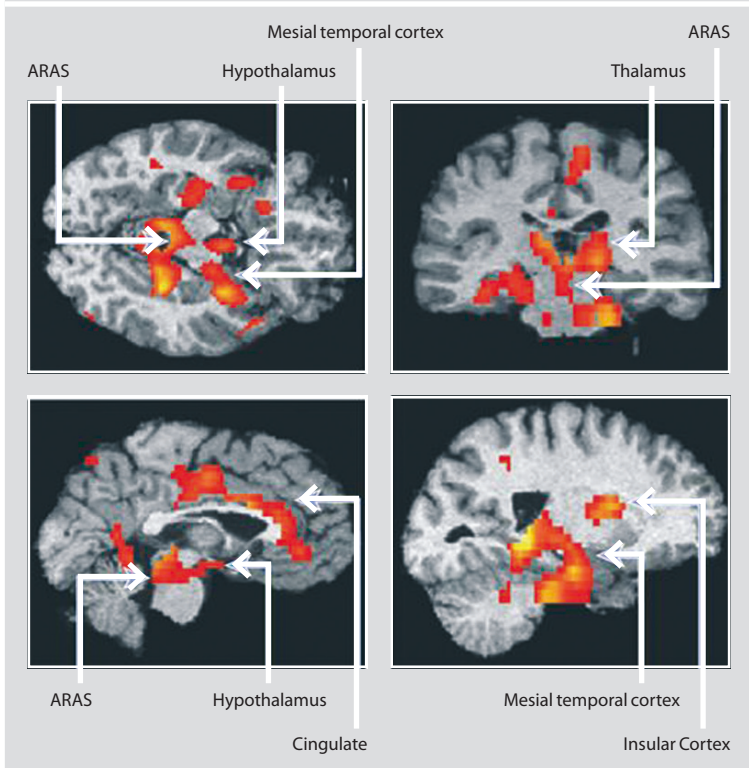


Figure 2.4 Functional neuroimaging evidence for hyperarousal in insomnia. Brain structures that do not show decreased metabolic rate from waking to sleep in patients with insomnia. All regions shown reach statistical significance ($P < 0.05$), corrected, level of significance in relation to healthy sleeper control subjects. ARAS, ascending reticular activating system. Reproduced with permission from Nofzinger et al [32] ©American Psychiatric Publishing.

brain arousal, this implies that these systems are maintaining a higher level of arousal in patients with insomnia. It is noteworthy that most sleep medications used to treat insomnia act by way of γ -aminobutyric acid (GABA) mechanisms, as GABA inhibits the activity of the neurotransmitter systems that originate in the reticular activation system. Thus, efficacy of medications used to treat insomnia appears to be due to the ability to reduce brain hyperarousal. Pharmacotherapies are discussed in more detail in Chapter 5.

Circadian rhythms

Circadian rhythms refer to patterning of biological rhythms, including sleep and wake periods, that occur across a 24-hour cycle [33]. Circadian rhythms work with sleep homeostasis to maintain discrete periods of alertness and sleepiness. The two-process model proposed by Borbely describes how the homeostatic (S process) and the circadian process (C process) work in conjunction (Figure 2.5) [34]. Sleep homeostasis refers to the pressure to sleep that accumulates as the duration of wakefulness increases. For example, the homeostatic drive to sleep decreases as the sleep need is met.

Circadian regulation of sleep is not influenced by the amount of preceding sleep, but rather is controlled by an endogenous biological clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Figure 2.6) [35,36]. These rhythms typically run longer than 24 hours but they become synchronized to the 24-hour clock via environmental cues (eg, the light–dark cycle). Sunlight is the strongest ‘zeitgeber,’ or influence, on the timing of sleep and wake. For example, sunlight impacts sleep and wakefulness through its impact on the secretion of melatonin, a hormone which promotes sleep [37]. This is due to sunlight transmitted through the retina along the optic nerve to the SCN in the hypothalamus, which regulates melatonin, body temperature, and other functions that contribute to sleep. Specifically, the pineal gland of the SCN produces melatonin at night (or in darkness), which promotes sleepiness. Thus,

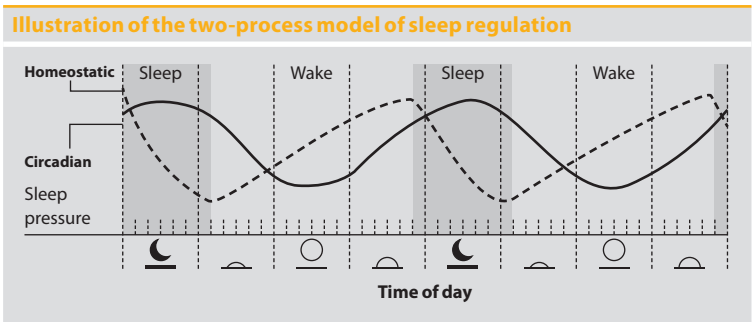


Figure 2.5 Illustration of the two-process model of sleep regulation. Including circadian (solid line) and homeostatic (dashed line) components. Adapted with permission from Borbely [34] and Glickman [35] ©Elsevier.

Pathway light travels through the optic nerve to the areas of the brain that control sleep

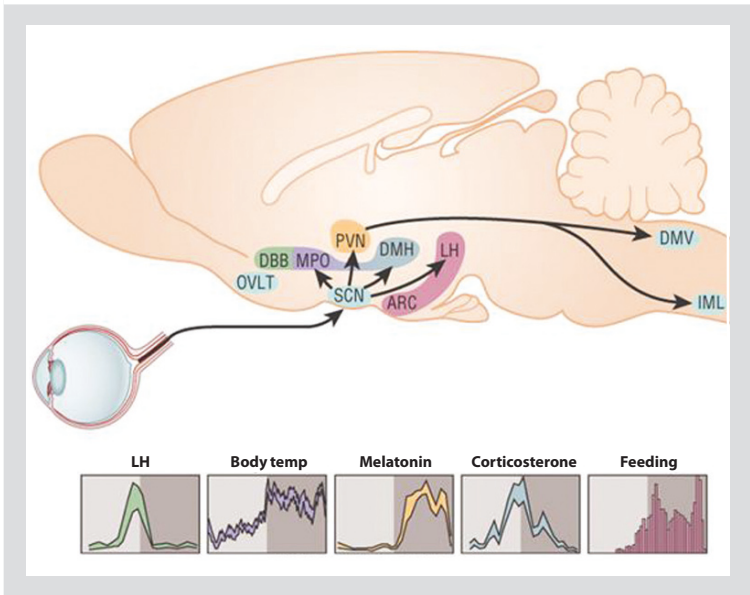


Figure 2.6 Pathway light travels through the optic nerve to the areas of the brain that control sleep. Graphs illustrating the circadian rhythms of luteinizing hormone (LH; involved in ovulation in women and production of testosterone in men), body temperature, melatonin (implicated in the sleep-wake cycle by causing drowsiness and lowering the body temperature), corticosterone (involved in the regulation of immune and stress responses), and feeding in a rat brain. ARC, arcuate nucleus; DBB, double B-box; DMH, dorsomedial hypothalamic nucleus; DMV, dorsomedial nucleus of vagus; IML, intermediolateral nucleus; MPO, medial preoptic area; OVLT, organum vasculosum lamina terminalis; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus. Reproduced with permission from Guardiola-Lemaitre and Quera-Salva [37] ©Elsevier.

melatonin production is indirectly inhibited by sunlight and stimulated by darkness. Circadian rhythms complement the homeostatic process by maintaining alertness during day and facilitating sleepiness at night.

Circadian rhythms are implicated in the development of insomnia when there is a mismatch between an individual's internal circadian rhythm and the timing of their sleep-wake cycle. For example, on Sunday night, after staying up late on Friday and Saturday nights, an individual may not experience the onset of sleepiness until midnight. However, because they have to be at work early on Monday, they may attempt to sleep earlier in the evening (eg, 10 PM), and as a result, experience sleep-onset insomnia.

In some cases, the patient may have a circadian rhythm sleep disorder resulting from a significant misalignment between the internal circadian clock and the physical social environment of the individual that is presenting as insomnia [33]. This could be caused by a change in the environment outside of the patient’s control, such as shift work or jet lag, or simply that the patient’s internal circadian clock does not match that of the ‘societal norms,’ as seen with advanced sleep phase disorder (ie, circadian rhythm causes significantly earlier sleep and wake times [eg, 8 PM and 2 AM, respectively]) or delayed sleep phase disorder (ie, delayed sleep onset and wake times [eg, 2 AM and 11 AM, respectively]).

Medical conditions and medications

A number of medical conditions (and/or medications that are used to treat them) can impair sleep. As seen in Table 2.1, a variety of medical problems are commonly comorbid with insomnia and may, at least partly, cause difficulty sleeping [38]. For example, hyperthyroidism can result in significant insomnia, and patients should generally be tested for this when being evaluated for insomnia. As mentioned earlier, although insomnia is often precipitated by a medical disorder, the insomnia often decouples and evolves into an independent, self-sustaining problem that can have a reciprocal exacerbation of the medical disorder.

Rates of insomnia in common medical conditions	
Disease	Patients with insomnia (%)
Heart disease	44.1
Cancer	41.4
High blood pressure	44.0
Neurological disease	66.7
Breathing problems	59.6
Urinary problems	41.5
Diabetes	47.4
Chronic pain	48.6
Gastrointestinal problems	55.4
Any medical problem	37.8

Table 2.1 Rates of insomnia in common medical conditions. Reproduced with permission from Taylor et al [38] ©Associated Professional Sleep Societies.

Several classes of medications can also cause insomnia. Table 2.2 shows the medications and stimulants that may cause insomnia, with percentage of patients reporting insomnia as a side-effect, when available. The wide variety of insomnia-causing medications indicates that it is always a good idea to review all medications a patient is taking, what the side-effects of those medications are, and when they are taking them (ie, late afternoon administration of stimulating medications is more likely to disrupt sleep than an early morning administration).

Drugs and medications associated with insomnia	
Medication	Insomnia incidence (If available)
Central nervous system stimulants	
Amphetamine	
Benzphetamine	
Dextroamphetamine	
Methamphetamine	
Methyphenidate	
Dexmethyphenidate	
Modafinil	
Pemoline	
Phentermine	
Caffeine	
Nicotine	
Psychiatric	
Selective serotonin reuptake inhibitors:	
Fluoxetine	5–9%
Paroxetine	8–14%
Sertraline	7–16%
Citalopram	10%
Escitalopram	9%
Fluvoxamine	15–19%
Other drugs:	
Bupropion	5–19%
Venlafaxine	8%

Table 2.2 Drugs and medications associated with insomnia (continues overleaf).

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Drugs and medications associated with insomnia (continued)	
Medication	Insomnia incidence (if available)
Respiratory	
Theophylline	1–2%
Aminophylline	
Beta agonists:	
Albuterol	
Metaproterenol	
Terbutaline	
Epinephrine	
Salmeterol	1–2%
Formoterol	
Corticosteroids:	
Prednisone	
Methylprednisolone	
Dexamethasone	
Inhaled corticosteroids	Rare
Antihistamines:	
Bropheniramine	Variable
Diphenhydramine	Rare
Diphenhydramine	Rare
Cardiac	
Reserpine	
Diltiazem	
Diuretics:	
Furosemide	
Hydrochlorothiazide	
Bumetanide	
Statins:	
Simvastatin	<1%
Antiarrhythmic agents:	
Amiodarone	1–3%
Beta blockers:	
Propranolol	Variable
Metoprolol	
Antimicrobial	
Atovaquone	
Isoniazid	
Meropenem	
Pentamidine	

Table 2.2 Drugs and medications associated with insomnia (continues opposite)

Drugs and medications associated with insomnia (continued)	
Medication	Insomnia incidence (if available)
Spectinomycin	
Sulfamethizole	
Sulfasalazine	
Cephalosporins:	
Cefaclor	
Cefpodoxime	
Cefprozil	
Fluoroquinolones:	
Ciprofloxacin	1%
Cinoxacin	<1%
Gatifloxacin	2%
Grepafloxacin	>1%
Levofloxacin	0.3%
Ofloxacin	up to 13%
Sparfloxacin	5.7%
Antimalarials:	
Mefloquine	
Antiviral	
Abacavir	12%
Amantadine	14%
Didanosine	22%
Efavirenz	16%
Ganciclovir	5%
Lamivudine	11%
Lopinavir	2%
Ribavirin	
Rimantadine	1–3%
Ritonavir	<2%
Zidovudine	7%
Neurological	
Lamotrigine	6.4%
Felbamate	
Clobazam	
Zonisamide	
Donepezil	6–14%
Baclofen	2–7%

Table 2.2 Drugs and medications associated with insomnia (continues overleaf)

Drugs and medications associated with insomnia (continued)	
Medication	Insomnia incidence (if available)
Dopaminergic:	
Levodopa	20%
Entacapone	30%
Amantadine	up to 14%
Endocrine drugs:	
Thyroxine	
Corticosteroids	
Adenocorticotrophic hormone (ACTH)	
Gasorelin (in women only)	11%
Tamoxifen	up to 55%
Antineoplastic drugs:	
Vincristine	
Trastuzumab (herceptin, anti-human epidermal growth factor receptor-2)	24–29%
Beta-interferon	>1%
Pamidronate	<1%
Zoledronic acid	>10%
Natural or alternative	
Caffeinated drinks	
• Coffee	
• Black tea	
• Green tea	
Chromium	
Copaiba balsam	
Country mallow	
Cowhage	
Deanol	
Dehydroepiandrosterone (DHEA)	
Ephedra	
Eyebright	
Feverfew	
Ginseng	
• American	
• Panax	
• Panax pseudoginseng	
• Siberian	

Table 2.2 Drugs and medications associated with insomnia (continues opposite)

Drugs and medications associated with insomnia (continued)	
Medication	Insomnia incidence (if available)
Guarana	
Khat	
Khella	
Marsh blazing star	
Mate	
Niacin	
Phosphatidylserine	
Policosanol	
SAMe	
St. John's wort	
Sweet vernal grass	
Tiratricol	
Tonka bean	
Valerian	
Vitamin C (ascorbic acid)	
Acerola	
Cherokee rosehip	
Rose hip	
Wormwood (above ground parts)	
Yohimbe	
Withdrawal is associated with rebound insomnia	
Opiates, narcotics	
Barbituates	
Benzodiazepines	
Alcohol	
Gamma-hydroxybutyrate	
Androgenic anabolic steroids	

Table 2.2 Drugs and medications associated with insomnia.

References

- 1 Carskadon MA, Dement WC. Normal human sleep: an overview. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. Fifth edn. St. Louis, MO: Elsevier Saunders; 2011:16-26.
- 2 Keenan S, Hirshkowitz M. Monitoring and Staging Human Sleep. In: Kryger MH RT, Dement WC, ed. *Principles and Practice of Sleep Medicine*. 5th edn. St. Louis, MO: Elsevier Saunders; 2011.
- 3 Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep*. 2004;27:1255-1273.
- 4 Spielman AJ, Caruso LS, Glovinsky PB. A behavioral perspective on insomnia treatment. *Psychiatr Clin N Am*. 1987;10:541-553.
- 5 Vaz Fragoso CA, Gill TM. Sleep complaints in community-living older persons: A multifactorial geriatric syndrome. *J Am Geriatr Soc*. 2007;55:1853-1866.
- 6 Reid KJ, Martinovich Z, Finkel S, et al. Sleep: a marker of physical and mental health in the elderly. *Am J Geriatr Psych*. 2006;14:860-866.
- 7 St George RJ, Delbaere K, Williams P, Lord SR. Sleep quality and falls in older people living in self- and assisted-care villages. *Gerontology*. 2008;55:162-168.
- 8 Blackwell T, Yaffe K, Ancoli-Israel S, et al. Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci*. 2006;61:405-410.
- 9 Dam TTL, Ewing S, Ancoli-Israel S, Ensrud K, Redline S, Stone K. Association between sleep and physical function in older men: the osteoporotic fractures in men sleep study. *J Am Geriatr Soc*. 2008;56:1665-1673.
- 10 Goldman SE, Stone KL, Ancoli-Israel S, et al. Poor sleep is associated with poorer physical performance and greater functional limitations in older women. *Sleep*. 2007;30:1317.
- 11 Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation Sleep in America Survey. *J Psychosom Res*. 2004;56:497-502.
- 12 Dufour MC, Archer L, Gordis E. Alcohol and the elderly. *Clin Geriatr Med*. 1992;8:127.
- 13 Yao K-W, Yu S, Cheng S-P, Chen I-J. Relationships between personal, depression and social network factors and sleep quality in community-dwelling older adults. *J Nurs Res*. 2008;16:131-139.
- 14 Jones BT, Macphee LM, Broomfield NM, Jones BC, Espie CA. Sleep-related attentional bias in good, moderate, and poor (primary insomnia) sleepers. *J Abnorm Psychol*. 2005;114:249-258.
- 15 Richards K, Nagel C, Markie M, Elwell J, Barone C. Use of complementary and alternative therapies to promote sleep in critically ill patients. *Crit Care Nurs Clin North Am*. 2003;15:329-340.
- 16 Stanchina ML, Abu-Hijleh M, Chaudhry BK, Carlisle CC, Millman RP. The influence of white noise on sleep in subjects exposed to ICU noise. *Sleep Medicine*. 2005;6:423-428.
- 17 Robertson JA, Broomfield NM, Espie CA. Prospective comparison of subjective arousal during the pre-sleep period in primary sleep-onset insomnia and normal sleepers. *J Sleep Res*. 2007;16:230-238.
- 18 Brunborg GS, Mentzoni RA, Molde H, et al. The relationship between media use in the bedroom, sleep habits and symptoms of insomnia. *J Sleep Res*. 2011;20:569-575.
- 19 Colbert AP, Markov MS, Banerji M, Pilla AA. Magnetic mattress pad use in patients with fibromyalgia: a randomized double-blind pilot study. *J Back Musculoskeletal Rehab*. 1999;13:19-31.
- 20 Kovacs FM, Abraira V, Peña A, et al. Effect of firmness of mattress on chronic non-specific low-back pain: randomised, double-blind, controlled, multicentre trial. *Lancet*. 2003;362:1599-1604.
- 21 Lavin RA, Pappagallo M, Kuhlmeier KV. Cervical pain: a comparison of three pillows. *Arch Phys Med Rehabil*. 1997;78:193-198.
- 22 Young G, Jewell D. Interventions for preventing and treating pelvic and back pain in pregnancy. *Cochrane Database Syst Rev*. 2002;(1):CD001139.

- 23 Riemann D, Spiegelhalder K, Feige B, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev.* 2010;14:19.
- 24 Bonnet MH, Arand DL. Heart rate variability in insomniacs and matched normal sleepers. *Psychosom Med.* 1998;60:610-615.
- 25 Bonnet MH, Arand DL. Situational insomnia: consistency, predictors, and outcomes. *Sleep.* 2003;26:1029-1036.
- 26 Vgontzas AN, Bixler EO, Lin H-M, et al. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab.* 2001;86:3787-3794.
- 27 Carskadon MA, Dement WC, Mitler MM, Guilleminault C, Zarcone VP, Spiegel R. Self-reports versus sleep laboratory findings in 122 drug-free subjects with complaints of chronic insomnia. *Am J Psychiatry.* 1976;133:1382-1388.
- 28 Buysse DJ, Germain A, Hall ML, et al. EEG spectral analysis in primary insomnia: NREM period effects and sex differences. *Sleep.* 2008;31:1673.
- 29 Perlis ML, Merica H, Smith MT, Giles DE. Beta EEG activity and insomnia. *Sleep Med Rev.* 2001;5:365-376.
- 30 Nofzinger EA, Nissen C, Germain A, et al. Regional cerebral metabolic correlates of WASO during NREM sleep in insomnia. *J Clin Sleep Med.* 2006;2:316-322.
- 31 Smith MT, Perlis ML, Chengazi VU, Soeffing J, McCann U. NREM sleep cerebral blood flow before and after behavior therapy for chronic primary insomnia: preliminary single photon emission computed tomography (SPECT) data. *Sleep Medicine.* 2005;6:93-94.
- 32 Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. *Am J Psychiatry.* 2004;161:2126-2128.
- 33 Reid KJ, Zee PC. Circadian disorders of the sleep-wake cycle. In: Kryger MH, Roth T, Dement WC., eds. *Principles and Practice of Sleep Medicine.* 5th edn. St. Louis, MO: Elsevier/Saunders; 2011:470-482.
- 34 Borbely AA. A two process model of sleep regulation. *Hum Neurobiol.* 1982;1:195-204.
- 35 Glickman G. Circadian rhythms and sleep in children with autism. *Neurosci Biobehav Rev.* 2010;34:755-768.
- 36 Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. *Science.* 2002;295:1070-1073.
- 37 Guardiola-Lemaitre B, Quera-Salva MA. Melatonin and the regulation of sleep and circadian rhythms. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine.* 5th edn. St. Louis, MO: Elsevier Saunders; 2011.
- 38 Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems. *Sleep.* 2007;30:213-218.
- 39 Welsh CH, Fugit RV. Medications that can cause insomnia. In: Teofilo LC, ed. *Sleep: A Comprehensive Handbook.* New York, NY: Wiley-Liss; 2005:103-109.

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