

REVIEW

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Treating insomnia with medications

J. F. Pagel^{1,4*} , Seithikurippu R. Pandi-Perumal² and Jaime M. Monti³

Abstract

Insomnia is a conspicuous problem in modern 24 h society. In this brief overview, medications used to treat insomnia such as hypnotics, sedatives, medications inducing sedation as a side effect, medications directed at the sleep-associated circadian neuroendocrine system, and agents utilized in treating insomnia-inducing sleep diagnoses such as restless leg syndrome are discussed. The newer GABA-effective hypnotics are the only medications with demonstrated effectiveness in treating chronic insomnia with the majority of evidence supporting treatment efficacy for cognitive-behavioral therapy and short acting GABA-receptor agonists. In patients with comorbid insomnia the use of hypnotics can improve outcomes and potentially reduce morbidity and mortality associated with the use of more toxic medications. Except in individuals whose insomnia is secondary to circadian disturbance, mood disorder/depression and/or restless leg syndrome, there is minimal evidence supporting the efficacy of other medications used to treat insomnia despite their widespread use. Sedatives and other medications used off-label for sedative side-effects are a contributing factor to drug induced hypersomnolence, a factor in more than 30% of motor accident deaths. Hypnotic medications with low toxicity, addictive potential, minimal next day sleepiness, and an otherwise benign side-effect profile can be utilized safely and effectively to treat and improve function and quality of life for patients suffering from insomnia. These are the agents that should be exclusively classified as hypnotics and utilized to induce sleep when medications are required to treat the complaint of insomnia. Other pharmacological agents producing sedation (sedatives and agents used off-label for sedative side-effects) should be used cautiously for the treatment of insomnia due to the increased risk of next day sleepiness as well as for known toxicities and adverse side effects.

Keywords: Insomnia, Medications, Hypnotics, Sedatives, Benzodiazepine

Introduction

Insomnia, defined as the subjective perception of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep, is a conspicuous problem in modern 24-h society (Sateia et al. 2017). Episodes of acute or transient insomnia each year affect >80% of adults. Chronic insomnia (>3 months in duration) includes difficulty falling asleep, insufficient sleep, or perceived nonrestorative sleep producing daytime complaints of somnolence, fatigue, irritability, or difficulty concentrating and performing everyday tasks, and has a population prevalence of approximately 14% (Hauri 2005; *NIH State of the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults Statement, Journal*

of Clinical Sleep Medicine 2005). Chronic insomnia is significantly associated with a decrease in quality of life measures, the exacerbation of co-morbid diagnoses, and an increased likelihood for developing mood disorders / depression (Sateia et al. 2017). While there are dozens of insomnia-associated sleep diagnoses, any medical or psychiatric disorder or environmental stress that produces nighttime discomfort is likely to induce insomnia. Medications for treating insomnia are classified as hypnotics, sedatives, medications inducing sedation as a side effect, medications directed at the sleep-associated circadian neuroendocrine system, and agents utilized in treating insomnia-inducing sleep diagnoses such as restless leg syndrome (RLS) (Curry et al. 2006; Bhat et al. 2008).

Sleep hygiene and cognitive behavioral therapies

Sleep behaviors must be addressed for any patient presenting with insomnia. Insomnia can be treated without medications, using sleep hygiene combined with

* Correspondence: pueo34@gmail.com

¹University of Colorado School of Medicine, Coughern Colorado Residency Program, Pueblo, CO, USA

⁴Rocky Mountain Sleep, 1306 Fortino Blvd, Pueblo, CO 81008, USA

Full list of author information is available at the end of the article



cognitive and behavioral therapies (CBT). This approach avoids potential drug side effects and toxicities and has shown long-term persistence in treating chronic insomnia that can be superior to results obtained using drug therapies (Morin 2005). Sleep hygiene refers to environmental factors, dietary approaches, drugs, and a lack of required sleep facilitating approaches that can induce insomnia. Insomnia inducing drugs include caffeine, nicotine, weight loss preparations, and activating agents of both prescription and abuse. CBT extends sleep hygiene into the use of sleep facilitating cognitive and behavioral approaches for treating insomnia (Finley and Perlis 2014). CBT has proven its usefulness in treating chronic insomnia, working best when administered by a trained provider over several extended visits (Riemann and Perlis 2009). Insomnia treatment can be limited to the use of hygiene and CBT, but such an approach has clear limitations. Behavioral approaches are rarely effective in treating acute and transient episodes of insomnia and have limited usefulness in treating comorbid insomnia. CBT requires patient interest and effort and as a clinical approach is unavailable to many affected individuals due to both cost and limitations in provider access (Lichstein et al. 2005). Even when appropriately utilized, CBT does not work for every patient (Trauer et al. 2015).

Sleep neurophysiology

From a behavioral stand-point, sleep is a complex, reversible behavioral state of perceptual disengagement from, and unresponsiveness to, the environment (Carskadon and Dement, 2011). To this point, no specific anatomical site or required neurochemical trigger has been identified. Neuroanatomical structures in the CNS are affected globally by sleep associated changes in neurochemical, electrophysiological and neuroendocrine systems.

The neurochemistry of sleep

Sleep is a global state involving multiple factors and systems, with no single neurochemical identified as necessary for modulating sleep (Brown et al. 2012). In most cases, the CNS effects of drugs can be ascribed to primary effects on specific neurotransmitters and neuromodulators. Most hypnotics affect GABA, the primary negative neurotransmitter in the CNS, or affect specific neuromodulators of GABA that include serotonin, acetylcholine, and dopamine (Pagel 2017). Other drugs, particularly those classified as sedatives, induce sedation by antagonizing one or more of the central activating neuromodulators. These activating neuromodulators include serotonin, norepinephrine, histamine, acetylcholine, dopamine, and orexin. Other substances known to affect sleep include adenosine, substance P, corticotrophin releasing factor (CRF), thyrotrophin releasing factor (TRF), vasoactive intestinal peptide (VIP),

neurotensin, muramyl peptides, endotoxins, cytokines [interleukin-1B, tumor necrosis factor-α], interleukin 1B, tumor necrosis factor-α (TNFα), prostaglandin D2 (PGD2) and melanin concentrating hormone (MCH) (García-García et al. 2009; Urade and Hayaishi 2011; Pabst et al. 1999). Sedation is among the most common effects and/or side effects of prescription medications. The list of agents inducing sedation as an effect and/or side effect is extensive and includes most medication classifications (Table 1) (Pagel 2017). Sedation is commonly induced by over the counter (OTC) preparations (particularly anti-histamines), and commonly used drugs of abuse such as cannabis and ethanol. When the use of

Table 1 Medications Not Classified As Sedative/Hypnotics Inducing Daytime Sleepiness As A Side Effect

Medication Class	Neurochemical Basis For Sleepiness
Antiparkinsonian Agents	Dopamine Receptor Agonists
Antimuscarinic/ Antispasmodic	Varied effects
Skeletal Muscle Relaxants	Varied Effects
Alpha- Adrenergic Blocking Agents	Alpha-1 Adrenergic Antagonists
Beta-Adrenergic Blocking Agents	Beta Adrenergic Antagonists
Gamma-Hydroxy-Butyrate	GABA Agonist
Opiate Agonists	Opioid Receptor Agonists (General Cns Depression)
Opiate Partial Agonists	Opioid Receptor Agonists (General Cns Depression)
Anticonvulsants	
<i>Barbiturates</i>	GABA Agonist
<i>-Benzodiazepines</i>	GABA Agonist
<i>- Hydantoins</i>	Neurotransmitter effect poorly defined - electrophysiologic?
<i>- Succinimides</i>	Neurotransmitter effect poorly defined - electrophysiologic?
Other Antidepressants	
<i>- Maoi</i>	Norepinephrine, 5ht & Dopamine
<i>- Ssri</i>	Serotonin Uptake Inhibition
<i>-Agents With Mixed Effects</i>	Serotonin, Dopamine, & Norepinephrine
Other Antipsychotics	Dopamine Receptor Blockage, Varied Effects On Histaminic, Cholinergic And Alpha Adrenergic Receptors
Other Benzodiazepines Not Used For Sedation	GABA Agonist
Anxiolytics, misc. Sedative & hypnotics	GABA Agonist, Varied Effects
Antitussives	Neurotransmitter Effect Poorly Defined
Antidiarrhea agents	Neurotransmitter Effect Poorly Defined - Opioid In Some Cases
Antiemetics	Antihistamine & Varied Effects
Genitourinary Smooth Muscle Relaxants	Neurotransmitter Effect Poorly Defined

these agents is coupled with the use of sedating prescriptions, additive sedation, toxicity, and side-effects increase the danger of life-threatening over-dose (National Institute on Drug Abuse: National Institutes of Health 2015).

The electrophysiology of sleep

In the clinical laboratory, sleep is defined by its electroencephalography (EEG) in concert with electromyography (EMG), electrooculography (EOG) and other telemetry. Using polysomnographic recordings, sleep can be classified into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. The NREM sleep is further classified into 3 sleep stages namely Stage N1 sleep, Stage N2 sleep, and stage N3 sleep (also known as slow wave sleep, delta sleep or deep sleep), based primarily on the occurrence of synchronous physiologic EEG potentials. Drowsy awake with eyes closed is defined by the presence of alpha - the frequency with the most power on spectral analysis. Sleep onset (Stage N1) is generally defined as occurring at the point in which there is a decline of alpha rhythm (9–11 Hz) to less than 50% of the recorded epoch. Stage N2 sleep is denoted by bursts of sleep spindles at sigma frequency (11–16 Hz) and K-complex events - electrophysiological down states known to negatively affect the general tendency of neurons to develop spike potential activity (Cash et al. 2009). Deep sleep (stage N3 sleep) occurs in association with delta frequency oscillations (0.5–1.5 Hz). REM sleep is characterized by bursts of intracranial theta (5–8 Hz), with alpha and gamma oscillations noted in scalp recordings, associated with conjugate eye

movements and diminished skeletal EMG activity. Medications producing CNS-related behavioral effects generally affect background EEG frequencies (Mamdema and Danhof 1992). In most cases, a consistent pattern of EEG change produced by a drug is associated with a consistent pattern of behavioral change (Hermann and Schaerer 1986). Psychoactive drugs produce alterations in physiologic EEG rhythms consistent across therapeutic classifications and utilized to predict the behavioral activity of new preparations, drug interactions and toxicities (Blume 2006) (Table 2).

The neuroendocrinology of sleep

Sleep regulation is a complex interaction between the homeostatic and the endogenous circadian processes (Borbély et al. 2016). The circadian processes of sleep are largely controlled by the suprachiasmatic nucleus (SCN) in the hypothalamus (Dai et al. 1998; Hofman et al. 1996; Swaab et al. 1985; Vimal et al. 2009). This internal human clock responds to external factors with the greatest influence being exposure to light/dark (LD) cycle (Lewy et al. 1980; Morin 2015). The other important element to the timing of the sleep/wake cycle is the endogenously produced neural hormone melatonin, produced by the pineal gland in response to signals from the SCN. Melatonin can induce sedation, an effect sometimes utilized to assist children in tolerating medical procedures (Johnson et al. 2002). In addition to regulation of the sleep/wake cycle, body temperature and numerous other processes vary with circadian rhythm (Sack et al. 2007). Externally introduced

Table 2 Consistent quantitative alteration in physiologic EEG frequencies induced by psychoactive medications

Class of drugs	Eeg frequencies					Treatment indications
	Delta (0.5–1.5 Hz)	Theta (5.5–8.5 Hz)	Alpha (8.5–11 Hz)	Sigma (12–16 Hz)	Beta/Gamma (21–32 Hz)	
Benzodiazepines (BZDs)			Decrease	Increase	Increase	Anxiety Sedation
Barbiturates				Increase	Increase	Anxiety Sedation Epilepsy
Tricyclic Antidepressants (TCAs)	decrease	Decrease			Increase	Depression
SSRI Antidepressants	decrease		Increase			Depression Anxiety OCD
Amphetamines	decrease	Decrease			increase	Somnolence Narcolepsy AD/HD
Opiates	increase		decrease			Pain
Anticonvulsants Phenytoin, valproate, carbamazepine		increase				Epilepsy
Gamma hydroxy butyrate (GHB)	increase					Cataplexy Narcolepsy
Classic Neuroleptics		increase	decrease	decrease		Schizophrenia Psychosis

melatonin can be utilized to reset circadian rhythms of sleep and body core temperature through its actions on the SCN (Abbott et al. 2014).

The optimal hypnotic

Sleep-inducing drugs (hypnotics) are medications specifically designed to induce sleepiness directly after intake. Optimal agents affect cognitive performance during this period while inducing minimal sleepiness in the waking day after use. An optimal hypnotic would have low toxicity and addictive potential, as well a minimal side effect profile (Oswald 1970). Among the first hypnotics, and an agent still in use is chloral hydrate - the original “Mickey Finn” - slipped into the drinks of unsuspecting marks for the purposes of criminal activity. Unfortunately, this medication is difficult to use since the LD-50 (potentially fatal dose) is quite close to the therapeutic dose. In the years leading up to the 1970’s, rapidly acting barbiturates were commonly utilized for their hypnotic effects. Unfortunately, these medications, also drugs of abuse, had a significant danger of overdose and contributed to an era that was characterized in part by deaths due to overdoses of sleeping pills. These medications and similar barbiturate-like medications [Methaqualone (Quaalude, Sopor) Glutethimide (Doriden), Ethchlorvynol (Placidyl), Methyprylon (Nodudar)] have limited availability and are rarely used due to limited efficacy, cognitive effects, the potential for abuse and lethal toxicity associated with overdose (Oswald 1970). Today their primary therapeutic uses include executions and facilitated euthanasia (Lossignol 2008).

Most currently utilized hypnotics affect the widely dispersed negative neurotransmitter GABA. In the 1970’s benzodiazepines (GABA agonists) were first marketed as hypnotics. Some of these agents had an extremely short duration of action [Triazolam (Halcion)]. While this agent-induced minimal next day somnolence, use was associated with daytime memory impairment, particularly at higher dosages (Roehrs et al. 2000; Adam and Oswald

1989). In the 1990’s newer agents were developed and marketed that had selective effects on GABA receptors including Zolpidem (Ambien), Zaleplon (Sonata), Eszopiclone (Estorra) and Indiplon. While all hypnotics have abuse potential for individuals with addictive histories and personalities, these agents have been noted to have minimal additive potential (Hajak et al. 2003). These agents are less likely to have deleterious side effects than most OTC treatments for insomnia, however, with increased use, more side effects including next effects on driving have been reported. This effect as well as next day rebound insomnia has particularly been reported for higher doses of zolpidem (Verster et al. 2002). In many cases, MVA’s occurred in the period of somnolence and cognitive impairment during the first few hours after ingestion. Comparatively normal results on psychomotor tests can be obtained 3.25 h. after zaleplon ingestion and 6.25 h. after zopiclone ingestion (Paul et al. 2003). While these agents have excellent efficacy with minimal side effects, at higher doses these agents can exhibit benzodiazepine-like effects. Idiosyncratic reactions of persistent daytime somnolence and/or memory loss have been reported. Some patients will report next day sedation after the nighttime use of these agents, as well as demonstrate an increased error rate in driving tests (Verster et al. 2007). Such information was forthcoming only after these drugs became generic and widely utilized in clinical practice. Most sedating drugs if adopted into such widespread use would also be at least as likely to demonstrate epidemiological effects on MVA’s and MVA associated deaths. In the elderly, chronic use of sedating drugs (particularly those with anti-cholinergic side effects) can be associated with an increased risk for falls, and confusion (American Geriatrics Society 2015). Reported next day sleepiness and other side effects associated with hypnotic use are summarized in Table 3.

The newer GABA-effective hypnotics are the only medications with demonstrated effectiveness in treating chronic insomnia (*NIH State of the Science Conference*

Table 3 Hypnotics - Agents Utilized To Induce Sleep With Minimal Next Day Sleepiness After Used Based On Pharmacodynamics, Clinical Trials, And/Or Performance Testing

Drug & Class	1/2 Life	Next Day Sleepiness [Clinical Trials]	Toxicity And/Or Significant Side Effects
Short acting gaba agonist - triazolam	1–2 HR.	Anecdotal and per survey [placebo Equivalent]	Antegrade Amnesia, Confusion At Higher Dose
GABA selective agents - zaleplon	1 HR.	[Placebo Equivalent]	No consistent reports [not in widespread use]
Zolpidem	1.5 HR.	Anecdotal [placebo Equivalent] Per survey when dosed outside pharmacodynamic profile and in the elderly	Symptomatic Parasomnias, Next night rebound insomnia
Eszopiclone	6 HR.	Anecdotal [placebo Equivalent]	Possible Parasomnia Associations [Agent Not In Widespread Generic Use]

Statement on Manifestations and Management of Chronic Insomnia in Adults Statement, Journal of Clinical Sleep Medicine 2005). According to the NIH, the majority of evidence supports the efficacy of cognitive-behavioral therapy and short acting benzodiazepine receptor agonists in the treatment of chronic insomnia, at least in the short term. Chronic insomnia is often, however, a lifelong illness, and the longest clinical trials for these agents have been one year in duration. These agents can be safely utilized chronically or in an “as needed” (prn) basis in individuals with both short and long term insomnia (Morin and Espie 2003; Schutte-Rodin et al. 2008). Except in individuals whose insomnia is secondary to circadian disturbance, mood disorder/depression and/or restless leg syndrome, there is minimal evidence supporting the efficacy of other medications used to treat insomnia despite their widespread use (*NIH State of the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults Statement, Journal of Clinical Sleep Medicine* 2005; Morin, Medalie and Cifu 2017).

Sedatives

Sedatives induce calming and reduce arousal during waking. At the extreme end of the spectrum of use, sedative agents are utilized in anesthesia. The sedative category included the opiates, a drug class developed from the domesticated poppy with evidenced utilization from neolithic archeologic sites (5000–7000 B. C.) (Heinrich 2013). At the dawn of medicine as a specialty, among the few agents useful as a medication was laudanum - a tincture of opium that mixed with water or wine was used as a soporific even for crying infants. Most sedative drugs selectively affect specific neurotransmitters and neuromodulators in the CNS (Schwartz 2000). Multiple factors and systems are involved. Sedative drugs can exert primary effects either at the inhibitory neurotransmitter gamma-Aminobutyric acid (GABA), or on sedating neuromodulators. Others potentiate sedation by antagonizing one of the widely dispersed central activating neuromodulators: serotonin, norepinephrine, dopamine, histamine, and orexin.

Many patients suffering from chronic insomnia are hyperaroused, unable to fall asleep even after minimal sleep the night before. Treatment of this hyperarousal presenting clinically as agitation and sometimes anxiety can produce improved sleep. Unfortunately, sedation and reduced arousal are variants of the same cognitive calming effect. Because of this, sedatives induce daytime sleepiness in many users. The ideal sedative agent, like the ideal hypnotic, should have low toxicity, low addiction potential, and a benign side effect profile.

Fifty years ago, longer acting benzodiazepines, particularly Diazepam (Valium) preempted the role of opiates

in sedation. Some of these agents had active breakdown products that produced an extraordinarily long active half-life (11 days) (Oswald 1970). The prolonged effect is one of waking calming and sedation, associated with increased auto accidents and falls with hip fractures. Medium 1/2 life agents including alprazolam, temazepam, and lorazepam affect next day performance tests (Ray et al. 1989). The use of these agents may be associated with an increased level of next day MVA's (Ceutel 1995; Buysse 1991).

Other sedating agents affect the GABA neuromodulators - acetylcholine, dopamine, and serotonin. Most of these agents are classified as sedating antidepressants. Sedating antidepressants include the tricyclics (amitriptyline, imipramine, nortriptyline, etc.), and atypical antidepressants: Trazodone (Deseryl), and Mirtazapine (Remeron). Trazodone is among the most widely prescribed agents for inducing sleep. There are few studies addressing the efficacy this off-label approach to treating insomnia, but there are more describing trazadone's significant side-effects including next day sleepiness and psychomotor impairment in the elderly (Mendelson 2005). Among the SSRI's, Paroxetine (Paxil) can induce mild sedation. Use of sedating antidepressants has been associated with declines in daytime performance, driving test performance, and an increased potential for involvement in motor vehicular accidents (Volz and Sturm 1995). Both tricyclic and atypical antidepressants are widely used as a hypnotics despite significant next day sedation (Settle 1998).

Many of the sedating medications treat hyperarousal by antagonizing the wake-producing neuromodulating systems: serotonin, norepinephrine, dopamine, histamine, and orexin. Both prescription and over the counter (OTC) agents are marketed for sedative effects produced pharmacologically by antagonizing orexin, histamine, and norepinephrine.

Antihistamines and antipsychotics induce sedation based on their antihistaminic effects (Monti et al. 2016). Over the counter sleeping pills contain sedating H-1 antihistamines, usually diphenhydramine, hydroxyzine or triprolidine (Monti and Monti 2000). These agents induce sedation with acute use, and often induce increased daytime sleepiness and cognitive impairment persisting into the day following nighttime use (O'Hanlon and Ramaekers 1995). In comparative studies, driving performance at 2.5 h. after administration of 50 mg. of diphenhydramine is worse than in individuals with a blood alcohol concentration (BAC) of 0.1% - the level of legal intoxication in most states (Wiler et al. 2000). Nighttime drug use can produce drowsiness severe enough to affect next day performance and driving tests (Gango et al. 1989). Sedation is infrequent with H2 antagonists (e.g. cimetidine, ranitidine, famotidine, and nizatidine), but

somnolence as a side effect is reproducible in susceptible individuals (White and Rumbold 1988). Sedation is a common side effect of the traditional antipsychotics, with chlorpromazine and thioridazine somewhat more sedating than haloperidol. Clinical studies have shown a high incidence of persistent sedation with clozapine (46%) with less frequent reports of sedation with risperidone, olanzapine, sertindole and quetiapine (Monti et al. 2016). The sedation associated with these agents is most likely associated with their known effects on histaminic receptors.

Doxepin, a sedating psychotropic agent with pronounced histamine (H-1) receptor antagonism exerts at least part of its effects by antagonizing orexin (Krystal et al. 2013). Suvorexant, is an orexin antagonist designed to lower waking arousal (Norman and Anderson 2016). Currently, it is being heavily marketed as a hypnotic (Rhyne and Anderson 2015). As based on performance and driving tests, this agent is known to produce a dose-related next day increase in somnolence for all age groupings tested (Farkus 2013). Sedative drug effects on daytime sleepiness are summarized in Table 4.

Other agents inducing sedation

Many other agents induce significant sedation as part of their clinical effect or as an untoward side-effect.

Clinically these agents are sometimes used off-label for their sedative effects. Among antihypertensives in wide use, the complaints of tiredness, fatigue and daytime sleepiness are commonly associated with drugs having antagonistic effects at the norepinephrine neuroreceptor (Dimsdale 1992). The complaints of tiredness, fatigue and daytime sleepiness (2–4.3%) associated with beta-blocker use may occur secondary to disturbed sleep or direct action of the drug. Beta-blocking drugs with vasodilating properties (e.g. carvedilol, labetalol) are also associated with reported fatigue and somnolence (3–11%). Sedation is among the most common side effects reported for the alpha-2 agonists clonidine and methyldopa (30–75%) (AHFS 2003). Alpha-1 antagonists (e.g. terazosin, prazosin) are sometimes associated with transient sedation. Prazosin, a norepinephrine antagonist, has demonstrated value in treating insomnia associated with PTSD nightmares (Raskind et al. 2003). Clonidine is sometimes utilized to treat the agitation and insomnia that result from using amphetamines to treat AD/HD in pediatric patients (Ming et al. 2011).

Sedation is a common side effect induced by anti-epileptic drugs, reported at levels of 70% with phenobarbital, 42% with carbamazepine and valproate, and in 33% of patients using phenytoin and primidone

Table 4 Sedatives - Agents Used To Induce Sleep And Sedation With Significant Next Day Sleepiness After Used Based On Pharmacodynamics, Clinical Trials, And/OR Performance Testing

CLASS (DRUG) [Neuromodulator Effected]	1/2 LIFE	Next Day Sleepiness [Clinical Trials]	Next Day Effects On Performance & Driving Tests	Toxicity And/OR Significant Side Effects
Antidepressants - tricyclics (amitriptyline etc.) [serotonin]	10–20 HR.	Significant	Significant With Minimal Study	Anticholinergic, Respiratory suppression in overdose
- Atypicals (trazadone, mirtazapine) [serotonin]	traza- done (8 h) mirtaza-pin 20–40 HR.	Significant	Significant With Minimal Study	Respiratory Suppression In Overdose
H1 antihistamine Diphenhydramine, hydroxyzine, triprolidine) [histamine]	2–12 HR.	Significant	Significant - Multiple studies	Confusion [Black Boxed For The Elderly]
Antipsychotic - Olanzapine [histamine]	6–8 HR.	Significant	Significant with minimal study	Potentially persistent extra-pyramidal Side effects
- Doxepin [histamine, orexin]	1/2–15 h. (dose based) active metabolite	Significant	Significant With Minimal Study	Potentially persistent extrapyramidal Side effects
Gaba agonists - medium 1/2 life benzodiazepi-nes (estazolam, clonazepam, temezepam, etc.) [GABA]	7–10 HR.	Significant	Significant Multiple studies	Disinhibition
- Long 1/2 life benzodiazepi- nes (flurezepam, diazepam, etc.) [GABA]	Up To 11 Days	Significant	Significant Multiple studies	Disinhibition Falls in the elderly
Orexin antagonists (suvorexant) [orexin]	10–22 HR.	Significant	Significant	Unknown New agent

Key: the term "Significant" indicates comparison to placebo or hypnotics

(Schweitzer et al. 2003). In clinical trials sedation is reported as a side effect to treatment with topiramate (15–27%) at levels of 5–10% for gabapentin, lamotrigine, vigabatrin, and zonisamide (AHFS 2003). The neurochemical basis for the sedation induced by many of these agents remains poorly defined except for those agents known to have GABA agonist effects (e.g. gabapentin, phenobarbital) (Westbrook 2000). Some drugs may act by glutamate antagonism and others by having direct effects on CNS electrophysiology (Pagel 1996). In individuals being treated with such medications for seizure disorders, the clinical differential between medication effects and sedation secondary to recurrent seizures can be difficult to determine (Manni and Tartara 2000).

Almost all drugs with CNS activity induce sleepiness as a side effect in some patients (Bittencourt et al. 2005; Guilleminault and Brooks 2001). The sedative side effects of some of these agents are clinically utilized in specific situations. However, sleepiness is a common and often-unwanted side effect for many types of prescription medications including commonly used antitussives, skeletal muscle relaxants, antiemetics, antidiarrheal agents, genitourinary smooth muscle relaxants, and others (Table 1). These sedative side effects can limit the use of these agents in patients in which the level of persistent daytime sleepiness affects waking. All sedating agents can contribute to an increased risk for motor vehicular accidents.

Drug induced Hypersomnolence

Drug induced hypersomnolence is a significant problem in today's society. Approximately 30% of traffic deaths in the United States can be attributed at least in part to the use of ethanol - the most commonly abused sedating medication (Department of Transportation (US), National Highway Traffic Safety Administration (NHTSA) 2015). Sedating drugs other than ethanol are contributing factors in 16% of motor vehicular accidents (Berning et al. 2015). While not nearly as great a risk factor for driving as alcohol, marijuana may nearly double the risk of having a vehicle collision (Sewell et al. 2009). In the United States, marijuana users are about 25% more likely to be involved in an MVA than drivers with no evidence of marijuana use (Compton and Berning 2015).

The prescription and OTC medications known to increase the risk of sleepiness-related crashes include longer acting benzodiazepine anxiolytics, sedating antihistamines (H1 class), and tricyclic antidepressants (TCAs). The risks are higher with higher drug doses and for people taking more than one sedating drug simultaneously (Ceutel 1995; Gengo and Manning 1990; Van Laar et al. 1995). Since a high percentage of the population uses drugs of abuse as well as medications for underlying illness, the use of multiple sedating drugs use

has increasingly become a problem. In 1993, about one in eight drivers were using more than one drug, but by 2010, it was closer to one in five. The number of drivers dying in MVA's with three or more sedating drugs in their system increased from 11.5 to 21.5% during this period. Among drivers who tested positive for any drug, 48% also tested positive for alcohol (Disney et al. 2011).

Comorbid insomnia

The term secondary insomnia has historically been applied to patients with insomnia associated with either a medical or psychiatric condition or a primary sleep disorder. Until 2005 the NIH guidelines regarded such insomnia as being a consequence of the primary diagnosis. This led to recommendations that indicated the key was treating the primary or underlying condition with the assumption that this would, in turn, lead to resolution of insomnia. In 2005 the NIH convened another "State of the Science" conference to review the manifestations and management of chronic insomnia (*NIH State of the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults Statement, Journal of Clinical Sleep Medicine* 2005). The committee concluded that most cases of insomnia are comorbid with other conditions. The concern over continuing to use the term "secondary" insomnia is that in many cases we do not have clear proof of cause and effect and, of greater concern; the use of the term may lead to under-treatment of insomnia. This recommendation to view insomnia as comorbid has led to a shift in treatment paradigms. While identification and treatment of the "primary" condition remain a priority, concurrent treatment of insomnia is now viewed as desirable. In general treatment of comorbid insomnia is now essentially the same as treating primary insomnia with a growing number of studies confirming that this approach is effective (Morin and Benca 2012; Sateia and Nowell 2004; Winkelman 2015). Treatment of insomnia can often improve the symptoms of the "primary" or a comorbid condition.

Circadian system disturbances

Sleep disorders related to circadian rhythm are caused by a misalignment of the approximately 24-h endogenous circadian rhythm and the "normal" 24 h day/night cycle (Melatonin can act as a hypnotic and is a useful adjunct to treatment in individuals with circadian disturbance (Pandi-Perumal et al. 2008). Prescription synthetic analogs of melatonin such as ramelteon are available. Sleep tendency and reduced sleep latency are affected from 1 3/4–4 3/4 h post ingestion (Stone et al. 2000). Melatonin has been used as a hypnotic with inconsistent results (Monti et al. 2013). The impact of this agent on next day performance is generally considered

to be minimal. Next day psychomotor test results may not be affected, although one study has demonstrated significant effects on next day deviation of lateral position in driving tests (Mets et al. 2011).

Melatonin and light exposure have proven especially effective when used to treat Delayed Sleep Phase Syndrome most prevalent in adolescents and young adults (Pandi-Perumal et al. 2008). Patients with this syndrome have difficulty falling asleep at the desired bedtime, often falling asleep between 2 and 6 AM and then, if their lifestyle permits, sleeping approximately a normal 8 h, awakening at between 10 AM and 2 PM. Individuals with this common disorder often suffer from chronic insufficient sleep time with all its daytime consequences. Treatment involves exposure to bright light at the proper time in the circadian phase response curve. In the case of delayed phase syndrome, this is after the nadir of body temperature. Treatment with 10,000 lx for 30 min on awakening and timed melatonin administration in the early evening 3–6 h before sleep time (before the Dim Light Melatonin Onset (DLMO) or 12+ hours before the temper nadir are effective. Since melatonin can be soporific so caution needs to be exercised if used when the patient has wakeful activities to perform. Advanced Sleep Phase Syndrome (ASPS) is the mirror image of DSPS with patients sleep onset and awakening both several hours earlier than desired with the total sleep period remaining fairly normal. This is less common than DSPS and tends to occur more in middle-aged to elderly adults. Treatment options are similar to those for delayed phase syndrome with the timing of treatment designed to delay rather than advance the circadian rhythm. In shift workers, melatonin can be used to help shift the worker's circadian rhythm as required. When taken before bedtime in the early morning it can improve sleep quality. For individuals suffering from Jet Lag Disorder melatonin can be used to speed the adjustment to the new time zone (Brown et al. 2009; Srinivasan et al. 2010). Visually blind and incarcerated individuals can have non-24 h. and free-running circadian patterns that can be responsive to melatonin agonists such as tasimelteon (Neubauer et al. 2015).

Restless legs syndrome and periodic leg movement disorder

Restless Legs Syndrome (RLS) is a common neurologic condition marked by the urge to move, particularly the legs, which occurs primarily at rest in the evening or bedtime. The essential criteria for making the diagnosis include: 1) The urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; 2) The urge to move or unpleasant sensations begin or worsen with rest or inactivity; 3) The urge to move or unpleasant sensations are partially or totally relieved by movement; 4) The urge to move or

unpleasant sensations are worse in the evening (Verma and Kushida 2014). Sleep disruption and complaints of decreased quality of life is present in 3/4 of the patients with the syndrome (Allen and Earley 2001). A majority of RLS patients will have repetitive periodic limb movements (PLMS) on polysomnogram. The RLS/PLMD has a genetic basis and increases with age so that in the geriatric population (> 80 years) over 30% of individuals may meet criteria for the diagnosis. RLS/PLMD is also more common in children with AD/HD, patients in renal failure, individuals with low serum ferritin levels (< 50), and in patients taking some medications such including antidepressants, antiemetics and antihistamines (Phillips et al. 2006).

The treatment of the sleep disruption, primarily sleep onset, relies predominately on the treatment of the RLS rather than the treatment of resultant insomnia. Dopaminergic agonists have become the primary initial treatment for RLS. Pramipexole and ropinirole have both received FDA approval for this indication and are used in doses low relative to their use for Parkinson's Disease. Pramipexole is used in a range of 0.125 to 2 mg and ropinirole at 0.25 to 4 mg. Dopaminergic agents, especially pramipexole, can induce significant somnolence as well as sleep attacks in some individuals (Micalief et al. 2009). Benzodiazepines have been used, historically clonazepam but also temazepam. There are no recent studies of the efficacy of these but historically they have been useful and still have a role when side effects limit the use of the dopaminergic agents or in combination in refractory cases. When lack of response or side effects are still present opioids with significant addictive potential in this situation such as codeine or oxycodone are sometimes utilized (Comella 2014). Gabapentin, and pregabalin used off-label to treat RLS/PLMD induce significant hypersomnolence, interact with opiates, and have been described as drugs of abuse (Schifarno 2014). A variant of these agents, the alpha-2-delta ligand gabapentin enacarbil recently approved as a treatment for RLS is known to induce significant sedation and dizziness (Lee et al. 2011).

Insomnia associated with sleep apnea and its treatment

Obstructive sleep apnea (OSA) induces daytime sleepiness in a significant percentage of affected individuals. Both apnea severity and the level of daytime sleepiness affecting waking function can be negatively affected by the concomitant use of sedatives - particularly opiates and ethanol (Pagel 2017). In a subset of individuals with OSA, breathing disruption contributes to disordered sleep and insomnia. The treatment of OSA with positive airway pressure (PAP) can improve sleep quality for such individuals (Nigram et al. 2017). However for others, PAP therapy can exacerbate insomnia (particularly in those patients with co-morbid PTSD) (Nigram et al. 2016). At altitude and in patients with concomitant

heart failure, PAP therapy can induce the development of complex / central apnea - a diagnosis associated with significant complaints of insomnia (Pagel et al. 2011).

Comorbid psychiatric disorders

Psychiatric disorders commonly comorbid with insomnia include major depression, bipolar mood disorder, anxiety disorders, psychotic disorders, and amnesic disorders such as Alzheimer's disease. Estimates of the incidence of insomnia with these diagnoses are in the 50–75% range (Grandner and Perlis 2015). The most common psychiatric association is with the diagnosis of depression in which insomnia and depression have a circular or bidirectional relationship (Sateia and Nowell 2004). There are several studies that show that insomnia patients are at risk to develop depression. In a large study of young adults over a period of 20 years, 2 weeks of insomnia or longer predicted major depressive episodes and major depressive disorders (Buysse et al. 2008). Recurrent insomnia can also be the earliest sign that a patient in remission from their depression is at risk of a relapse (Breslau et al. 1996). Chronic insomnia problems may contribute to the persistence of depression. This issue is of particular importance in light of the significant rate of residual sleep disturbance in persons who have been otherwise successfully treated for depression (Ohayon and Roth 2003). Insomnia persisting after treatment of depression can be the most refractory symptom of depression. Drawing on data from a large interventional study of enhanced care for depressed elderly persons, the investigators found that persistent insomnia was associated with a 1.8 to 3.5 times greater likelihood of remaining depressed, compared with the population without continued sleep disturbance (Perlis et al. 1997). The relationship between insomnia and depression is further complicated by the fact that many common anti-depressants, especially the selective serotonin reuptake inhibitors (SSRI's), can induce disturbed sleep (McCrae and Lichstein 2001). In patients with insomnia and a psychiatric diagnosis treatment options include those also used for primary insomnia, either pharmacologic treatment, cognitive behavior treatment (psychological and behavioral) or a combination of both. Eszopiclone has been studied in patients with major depression along with the simultaneous use of fluoxetine (Fava et al. 2006). The combination was well tolerated and resulted in a rapid improvement in sleep. Of note, there was also a more rapid and larger antidepressant response. This does not suggest an antidepressant effect of eszopiclone but rather suggests that improved sleep has a beneficial effect on depression. This makes a strong case for the comorbid approach to treatment, simultaneous treatment of the two entities rather than the traditional approach of waiting for insomnia to improve as a

result of treating depression. Combining treatment with antidepressants with cognitive-behavioral therapy for insomnia also demonstrated that the combined treatment was superior to the antidepressants alone both in terms of depression outcome (61.5% vs 33.3% remission, respectively) and insomnia outcome (50% vs 7.7% remission, respectively) (Manber et al. 2008). A similar result occurred with the use of eszopiclone with escitalopram for generalized anxiety disorder compared to the escitalopram alone (Pollack et al. 2008).

Comorbid pain

Chronic pain leads to poor sleep in a majority of patients (Cheatle et al. 2016). Pain can be an acute or chronic part of a broad range of medical ailments but most commonly cancer, rheumatologic disorders and headache. Chronic pain and sleep disruption produce a cycle of pain causing poor sleep and poor sleep leading to greater pain (Abad et al. 2008). Management is suggested as follows: diagnosis of the sleep problem, emphasis on sleep hygiene and then CBT techniques followed by pharmacologic interventions including medications for both pain and insomnia (Riemann and Perlis 2009). In rheumatologic disorders treatment of sleep with hypnotics or sedating antidepressants improves sleep but also improves pain tolerance. It should be noted that the United States is currently in the midst of an epidemic of opiate use that is resulting in a large number of deaths. Hypnotics have reduced side-effects, less addiction potential, and much lower toxicity than the opiates often used to treat chronic pain.

Other comorbid medical conditions

Patients with respiratory problems often have disruption of their sleep. COPD patients frequently have fragmented sleep (Criminon and McNicholas 2014). This can improve with oxygen if hypoxia is part of the problem. While Obstructive Sleep Apnea commonly induces daytime sleepiness, it can induce disturbed sleep as well (Talib et al. 2017). About a 1/3 of asthma patients who are poorly controlled have nocturnal asthma attacks that interfere with their sleep and may lead to daytime symptoms. Patients with gastroesophageal reflux often have sleep disruption for the reflux. In addition, reflux can trigger asthma attacks in vulnerable patients. Patients with end-stage renal disease suffer from a variety of sleep disorders with a very high prevalence (Parish 2009). These can include insomnia, sleep apnea and a high incidence of secondary RLS. Menopause is associated with insomnia which can respond to treatment with hormones but also with treatment using a hypnotic (Soares et al. 2006). Chronic neurological conditions including Parkinsons disease are associated with significant insomnia, as are gastrointestinal disorders inducing

pain and/or reflux, nocturia and enuresis, and other sleep associated disorders such as narcolepsy (Sateia et al. 2017).

The appropriate use of hypnotic and sedative medications

Sedative/hypnotic agents were among the first known pharmaceutical therapies. Many have had significant toxicities and side effects. Some with addictive potential have developed into major drugs of abuse that continue to negatively affect our modern society. For the physician addressing the patient complaint of insomnia, these agents can be difficult to appropriately utilize. This brief overview argues that today there are medications with very low toxicity, addictive potential, minimal next day sleepiness, and an otherwise benign side-effect profile that can be utilized safely and effectively to treat and improve function and quality of life for patients suffering from insomnia. These are the agents that should be exclusively classified as hypnotics and utilized as the first line of agents to induce sleep when medications are required to treat the complaint of insomnia (Table 3). The other pharmacological agents producing sedation (sedatives and others used off-label for sedative side-effects) should be used cautiously for the treatment of insomnia due to the increased risk of next day sleepiness as well as for known toxicities and adverse side effects (Tables 1 & 4).

Abbreviations

24h: twenty-four hour; AD/HD: attention deficit hyperactivity disorder; ASPS: Advanced sleep phase syndrome; BAC: Blood alcohol concentration; CBT: cognitive and behavioral therapies; CNS: Central nervous system; COPD: chronic obstructive pulmonary disease; CRF: corticotrophin releasing factor; DLMO: Dim light melatonin onset; DSPS: Delayed sleep phase syndrome; EEG: electroencephalography; EMG: electromyography; EOG: electrooculography; FDA: Federal drug administration; GABA: gamma amino-butyric acid; Hz: hertz; LD: Light dark; LD-50: lethal dose 50%; MCH: melanin concentrating hormone; MVA's: Motor vehicular accidents; NIH: National Institute of Health; NREM: non-rapid eye movement; OSA: Obstructive sleep apnea; OTC: over the counter; PAP: positive airway pressure; PGD2: prostaglandin D2; PLMD: Periodic limb movement disorder; PLMS: periodic limb movements; PTSD: Post traumatic Stress Disorder; REM: Rapid eye movement; RLS: Restless Leg Syndrome; SCN: suprachiasmatic nucleus; SSRI's: Selective serotonin reuptake inhibitors; TCAs: Tricyclic antidepressants; TNF α : tumor necrosis factor- α ; TRF: thyrotrophin releasing factor; VIP: vasoactive intestinal peptide

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Author details

¹University of Colorado School of Medicine, Couthern Colorado Residency Program, Pueblo, CO, USA. ²Somnogen Canada Inc, College Street, Toronto, ON, Canada. ³School of Medicine Clinics Hospital, University of the Republic, Montevideo, Uruguay. ⁴Rocky Mountain Sleep, 1306 Fortino Blvd, Pueblo, CO 81008, USA.

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