Chapter

The Pharmacology of Parasomnias and Movement Disorders of Sleep

Gregory S. Carter

Abstract

The treatment of parasomnias and sleep related movement disorders is not always pharmacologic, indeed, some of these disorders respond to behavioral approaches without the risks of pharmaceuticals. This chapter endeavors to pull forward the disorders in which pharmacologic treatment is the best choice and lay out the pharmacologic properties of the treatments. It is not the goal of this chapter to present an encyclopedic review of the parasomnias and sleep related movement disorders. It is, however, the intent of this chapter to comprehensively review pharmacologic treatments used in the management of the disorders in which drug use is most necessary. The pharmacokinetic and pharmacodynamic properties and known risks of these pharmaceuticals are presented and discussed. When more than one pharmaceutical is used clinically within a class of drugs, thorough review of selected drugs is presented. The chapter includes investigations, mostly human studies, of the drugs discussed. The author's extensive experience in pharmacology, neurology, and sleep medicine take the chapter through pharmacological information a clinician needs to guide the management of these disorders.

Keywords: Treatment of parasomnias, movement disorders of sleep, pharmacology of sleep disorders, comparison of the benzodiazepines, comparison of the dopamine receptor agonists, gabapentin and pregabalin for sleep disorders, risks of sleep medications, melatonin, restless leg syndrome, alcohol, caffeine, and opiate effects on sleep disorders

1. Introduction

Henri Roger first gave us the term "parasomnia" in 1932 [1]. Subsequently, parasomnias have been extensively described and classified into non-REM-related parasomnias and REM-related parasomnias, so designated for the sleep stage from which the parasomnia emerges [2]. Though there is overlap in treatment options for the parasomnias, treatment most often follows semiology and pathophysiology. Sleep-related movement disorders are likewise varied in their presentations [3]. The treatment of parasomnias and sleep-related movement disorders relies on removal or avoidance of precipitants, behavioral techniques, prosthetic or dental devices, as well as, medications. Multi-pronged approaches including behavioral techniques in addition to medications may be most effective. The use of medication is still a necessary component of care in illnesses with significant immediate and long-term complications. This includes serious complications to the individual suffering from these sleep disorders, as well as, their bed partners and others within their circle of family and friends. In the body of this chapter, I will review the parasomnias and sleep-related

movement disorders with behavioral and pharmaceutical approaches to treatment. Where behavioral approaches alone are much preferred, this chapter will not delve into the physiology, psychology or known pathology of the disorder. Where pharmaceutical approaches are common, the chapter will briefly discuss the pathophysiology of the disorder and the desirable treatment strategies from clinical studies and expert opinion. Drug classes will be fully addressed in individual sections. These sections will discuss the pharmacokinetics, pharmacodynamics, and adverse effect profiles of the more commonly prescribed drugs within these classes, comparing them by popularity, desirable properties, and risks of adverse events. Lastly, in the conclusion this chapter will briefly review the current controversies of pharmacologic treatment.

2. The parasomnias

The parasomnias can be divided into the non-REM parasomnias, the REM parasomnias, the overlap parasomnias, and others which defy definition by sleep stage [4]. To best understand these differences, it is necessary to have some knowledge of role sleep plays in normal physiology. The sleep stages show a cyclic pattern of light sleep (N1) proceeding to common sleep (N2), then to slow wave or deep sleep (N3) and finally rapid eye movement (REM) sleep. The cycles gradually change with more N3 sleep in the first half of the night and more REM sleep in the second half of the night. These sleep cycles have been shown to serve multiple physiologic and homeostatic functions, but for the purposes of this chapter, deep sleep (N3) has been associated with the arousal disorders (confusional arousals, sleep walking, and sleep terrors) and REM sleep has been associated with dream enactment or REM sleep behavior disorders and nightmares. Each of these disorders demand therapeutic approaches that may not work for the others, i.e., sedation may be helpful (at least temporarily) for REM sleep parasomnias, but be counter-productive in the arousal disorders.

2.1 Clinical evaluation

The clinical differentiation of the parasomnias demands a careful and complete history and physical exam. Witnesses to and video recordings of the parasomnia are invaluable. Precipitants for parasomnias include sleep-related breathing disorders, sleep deprivation and insufficient sleep for age, emotional trauma and chronic mental illness, narcolepsy, endocrine disorders including hypothyroidism, diabetes, and perimenstrual distress, degenerative brain disorders, such as Parkinsonism and dementia with Lewy bodies, head injury and stroke, epileptic and non-epileptic seizures, and medications including lithium, neuroleptics, anticholinergics, antidepressants, sedative-hypnotics, opioids, and various recreational drugs including alcohol. Very high dose caffeine consumption is another concern as is current marijuana use and the use of illegal drugs such as fentanyl and cocaine. A family history of parasomnia may or may not be present on initial evaluation. A thorough physical examination may reveal findings consistent with sleep apnea or respiratory compromise, thyroid enlargement or tenderness, neurologic deficits or psychiatric abnormalities. Given the spectrum of parasomnias and varying etiologies underlying them, if the clinician's assessment misses an important precipitant or co-morbidity, pharmacologic management will likely fail or cause adverse effects.

2.2 Arousal disorders

The arousal disorders arise out of deep sleep (N3) and are felt to represent parasomnias emerging from difficulty completely awaking from sleep.

A.	Recurrent episodes of incomplete awakening from sleep
B.	Inappropriate or absent responsiveness to efforts of others to intervene or redirect the person during the episode
C.	Limited (e.g., a single visual scene) or no associated cognition or dream imagery
D.	Partial or complete amnesia for the episode
E.	The disturbance is not better explained by another sleep disorder, mental disorder, medical condition, medication or substance use

Notes
The events usually occur during the first third of the major sleep episode
The individual may continue to appear confused and disoriented for several minutes or longer following the episode.

Table 1.
General diagnostic criteria for disorders of arousal (criteria A-E must be met) [2].

These disorders consist predominantly of confusional arousals, sleep walking and sleep terrors and effect children under 11 years of age more than adults. There is a wide variance in reports of prevalence of arousal disorders from 9–45% of children [2, 4–7]. The lifetime prevalence in individuals over 15 years of age falls to 2.9% to 4.2%. The diagnostic criteria are presented in **Table 1**. Genetic factors [8], infections, sleep deprivation, and obstructive sleep apnea [9] can all be predisposing factors, whose elimination may prevent recurrent events. With the exception of epilepsy, pharmacotherapy may not be effective and may actually worsen symptoms [10]. Reassurance and behavioral approaches such as creating a safe sleeping environment, anticipatory or scheduled awakenings, cognitive behavioral therapy [10, 11], and hypnosis [12] are among the non-pharmacologic options.

Use of drugs in the developing brain is a concern for pharmacologists due to the extreme plasticity of immature neuronal networks. Another concern for the use of pharmaceutical agents in children is the tendency of the disorders to resolve spontaneously as a child matures. Proserpio et al. [13] laid out four indications for initiation of pharmacotherapy. The first is persistence of frequent episodes despite elimination of predisposing factors. The second is high risk of injury. The third is significant functional impairment, and the fourth is potential legal consequences. In the presence of 2–4, there may not be time to pursue behavioral approaches to management.

The most frequently used drugs for arousal disorders are the benzodiazepines. Antidepressant drugs have been used less frequently. Of note, none of these drugs has an FDA indication for their use in arousal disorders or have any large-scale controlled studies of their efficacy. The very long-acting benzodiazepine, clonazepam, has been the most frequently used agent [14–16] though other benzodiazepines including alprazolam and diazepam have been used in adult sleep terrors and sleepwalking. Antidepressant drugs including sertraline, paroxetine [17], clomipramine, imipramine [18], and trazodone [19] have been used in small case series. Case reports have also shown efficacy in the treatment of arousal disorders for melatonin [20, 21], hydroxytryptophan [22, 23], and ramelteon [24].

2.2.1 Sleep-related Hypermotor epilepsy

Nocturnal frontal lobe epilepsy, otherwise known as sleep-related hypermotor epilepsy, can present as recurrent, intractable confusional arousals [25, 26]. Routine polysomnography is not as helpful in differentiating an arousal disorder from sleep-related hypermotor epilepsy as is video-electroencephalographic recording in an

inpatient epilepsy monitoring center. While this is an expensive evaluation option, home video recording via cell phone camera, stereotypical behavior of the events, frequency up to nightly, persistence into adulthood, and the presence of a brain disorder can guide a clinician's decision to proceed [27]. In the author's experience in a busy university sleep clinic, less than 5% of adult patients presenting with arousal disorders are referred for epilepsy monitoring, however, 30% of the patients who were referred for epilepsy monitoring were diagnosed with likely or definite sleep-related hypermotor epilepsy. As a side note, treatment trials with anti-seizure drugs in these patients are not helpful for differentiation, as the pharmacologic control of sleep-related hypermotor epilepsy is often challenging.

2.3 REM parasomnias

The REM sleep related parasomnias most prominently include REM sleep behavior disorder and nightmare disorder [2]. REM sleep behavior disorder is often managed with medications, but nightmare disorder is more often treated with behavioral interventions. The prevalence of REM sleep behavioral disorder (REMSBD) is unknown but has been estimated to be 0.38% of the general population, increasing in frequency with age [28, 29]. It is more prevalent in men and usually emerges after age 50 [2]. There is a prominent association in older patients with the synucleinopathies [30]. The differential in younger patients can be quite wide. This parasomnia can be co-morbid with narcolepsy, brain tumors, antidepressant medications, and neurodevelopmental disorders [2]. Severe obstructive sleep apnea can cause dream enactment that mirrors REM sleep behavior disorder [31]. A variety of medications have been implicated in the precipitation of REM sleep behavior disorder. Antidepressants including venlafaxine, mirtazapine, and selective serotonin reuptake inhibitors, but not the dopamine reuptake inhibitor bupropion [32], can precipitate REMSBD. Medications including beta-blockers, anticholinesterase inhibitors, and selegiline have been reported to precipitate REMSBD [2]. Nightmares may occur in 60–75% of children; however, frequent nightmares are far less common occurring in only 1–5% of children [33]. Post-traumatic stress disorder is a common cause of nightmares in adults [34], but 2–8% of the general population may have troublesome nightmares. Various pharmaceuticals can precipitate nightmares. These include drugs affecting the neurotransmission of norepinephrine, serotonin, and dopamine such as antidepressants, antihypertensives, and dopamine receptor agonists. In addition, the withdrawal of a REM sleep suppressant can precipitate the complaint of nightmares. Varenicline, a nicotinic antagonist, may commonly induce nightmares [35]. The clinical management of nightmares includes removing as many predisposing factors as possible.

The chapter will not discuss parasomnias, such as exploding head syndrome and sleep related hallucinations, that are treated with reassurance and very rarely with drugs. Sleep enuresis may occur in 15–20% of five-year-old's [2]. It is more common in boys. Non-pharmacologic treatments are superior when the etiology is obstructive sleep apnea [36], ingestion of high doses of caffeine or psychosocial stressors. Nightly desmopressin is used when indicated for frequent intractable sleep enuresis. Pharmacologic management is necessary for urinary tract infections, diabetes insipidus, diabetes mellitus, or nocturnal epilepsy [2]. Fortunately, improvement occurs with age in these children.

3. Sleep related movement disorders

The sleep related movement disorders consist of restless leg syndrome, periodic limb movement disorder, sleep related leg cramps, sleep related bruxism, the sleep

related rhythmic movement disorders, sleep related myoclonus at sleep onset, propriospinal myoclonus at sleep onset [2]. Benign sleep myoclonus of infancy is different in that more than half of these infants have neonatal opioid withdrawal syndrome [37]. Sleep related rhythmic movement disorders, sleep related myoclonus at sleep onset, and propriospinal myoclonus at sleep onset, and benign sleep myoclonus of infancy are very rarely treated with pharmaceuticals once the diagnosis is made. Reassurance and building a safe bedroom environment are the treatments of choice. Likewise, sleep related bruxism (SRB) is best treated with oral devices that protect the teeth. Sleep related bruxism has its highest incidence in childhood, occurring in 14–17% of children before decreasing over the life span to 3% of older persons [38]. Sleep related breathing disorders are often co-morbid with sleep bruxism [39] though the relationship is unclear. More recently, botulinum toxin has been used for intractable sleep bruxism [40, 41]. Sleep related leg cramps are common. Almost all adults have had a leg cramp during sleep, and likely during wakefulness. Nightly leg cramps are reported in 6% of adults older than 60 [42]. The precipitants of sleep related leg cramps are as numerous as the over-the-counter dietary supplements used to treat them. The fact that no supplement has dominated the market speaks to their success. Predisposing factors include, but are not limited to, hypokalemia, hypocalcemia, hypomagnesemia, vigorous exercise, prolonged standing, oral contraceptives, diuretics, and long duration of action beta blockers [43]. Prescription medications including carisoprodol, diltiazem, gabapentin, orphenadrine, verapamil, have been used with success that likely does not significantly exceed placebo, presuming there were any controlled trials.

3.1 Periodic limb movement disorder/restless leg syndrome

The remaining sleep related movement disorders are the closely related periodic limb movement disorder and restless leg syndrome. Restless leg syndrome (RLS) is a clinical symptom complex. Periodic limb movements (PLM) are a polysomnographic finding seen very frequently with the symptom complex of restless leg syndrome. When the symptom complex of restless leg syndrome is absent, the polysomnographic finding of periodic limb movements become a disorder when there is clinically significant sleep disturbance or impairment in mental, physical, social, occupational, educational, behavioral, or other areas of functioning [2]. Periodic limb movements are seen on polysomnograms with greater frequency as patients grow older, though not all of these patients complain of sleep disturbance or nonrestorative sleep. Patients with periodic limb movement disorder can develop symptom worsening with prescription drugs including selective serotonin reuptake inhibitors, tricyclic antidepressants, lithium, and dopamine receptor antagonists. Low brain iron levels as manifested in peripheral blood by low ferritin levels and low total iron binding percentage are another precipitant. As with RLS, gene variants have been identified accounting for a fraction of affected individuals with a family history [3]. Care must be taken on polysomnograms to separate arousals secondary to limb movements from arousals due to sleep related breathing disorders. Distinction of periodic limb movements of sleep with no secondary sleep arousal versus periodic limb movement disorder with secondary arousal can be difficult. This is especially true of patients undergoing polysomnograms for another sleep pathology, such as suspected sleep related breathing disorder. The use of PLM associated cortical electroencephalographic arousals to determine clinical significance of periodic limb movements may thus be misleading. Cortical arousals as measured by an abrupt change to 3 seconds of 8 cycles per second rhythms (or higher frequencies) within 0.5 second of the limb movement [44] may be more subjective than the rule would suggest. Thus, the decision to treat or

not to treat a patient with a periodic limb movement index of greater than 15 limb movements per hour can be dependent on the treating physician's overall clinical assessment. Restless leg syndrome is an urge to move the legs usually accompanied by an uncomfortable sensation in the legs. The need to move worsens with rest, is relieved by movement, and emerges in a drug naïve patient at a specific time in their circadian cycle, usually in the evening [2]. Between 21 and 57% of patients will have arm symptoms. Sleep initiation and maintenance may be quite difficult for these patients resulting in their seeking medical care. The overall prevalence of RLS is estimated to be 5–10% in Europe and the United States but lower in Asia. Both prevalence and severity increase with age. Family history (obtained in 40–92% of cases) and the female gender confer increased risk. Pregnancy, especially the third trimester, has a risk three times greater risk than the general population. Restless leg syndrome is a clinical diagnosis that requires differentiation from the pain of leg cramps, arthralgias, myalgias, neuropathic pain, neuroleptic-induced akathisia, subtle spasticity from myelopathy, and anxiety-induced restlessness and repetitive movements. Many of these patients require prescription medications for control of symptoms. Medications for RLS and PLM disorder fall into four classes which will be discussed in depth later in this chapter. The four classes are the dopamine agonists, the alpha 2 delta subunit neuronal voltage-gated calcium channel blockers, the benzodiazepines and the opioids.

4. Implications for pharmacological management

The prescription drugs used in parasomnias and sleep related movement disorders fall into several classes. The benzodiazepines are broadly used for parasomnias and sleep related movement disorders. Melatonin is also widely used for parasomnias. Antidepressants with various pharmacodynamic properties are often used both to suppress parasomnias and treat comorbid mood disorders. Prazosin is a drug that has been widely used for nightmares. The dopamine receptor agonists are used with great frequency for both periodic limb movements and restless legs syndrome. The alpha 2 delta subunit neuronal voltage-gated calcium channel blockers are used predominantly for RLS/PLMD and other disorders. The final class of prescription drugs is the opioids.

We cannot go further into this chapter without taking into consideration the ideal properties of a drug to treat sleep disorders. These properties of oral medications include good gastro-duodenal absorption, ability to cross the blood brain barrier, a metabolic rate and duration of action that match the need for intervention, and a low potential for drug interactions. Low short-term and long-term effects on the molecular receptor target are also important. Direct and indirect adverse effects are additional determinants of patient compliance and satisfaction.

5. The Benzodiazapines

The benzodiazepines were first synthesized by Leo Sternbach in 1955 [45]. The benzodiazepines had activity on the neuronal chloride ionophore augmenting the effect of gamma aminobutyric acid (GABA) in facilitating sleep, sedation, anti-anxiety effects, and muscle relaxation. Hundreds of benzodiazepines were synthesized between 1960 and 1980 [46], but only a few have had commercial success. With the marketing of chlordiazepoxide in 1960 and diazepam in 1963 the benzodiazepines increased rapidly in prescription frequency [47]. The utility of these drugs as anti-anxiety agents and sedative hypnotics was important to this

rise, but safety characteristics were equally important. The therapeutic window of the benzodiazepines was much wider than the barbiturates and the lethal dose for 50% of animals in toxicology studies of diazepam was ten times that of secobarbital [48]. Over 50 years the growth of benzodiazepine prescribing was substantial. In 2017 there were 45.0 million alprazolam, 26.4 million lorazepam, 29.2 million clonazepam, 12.6 million diazepam, and 7.0 million temazepam prescriptions dispensed in the United States [49]. The benzodiazepines were placed in Schedule IV of the Controlled Substances Act of 1971. Alprazolam was one of the top three prescription drugs diverted to the illicit market. While the benzodiazepines were less dangerous than barbiturates due to a wider therapeutic window, there were still 14 deaths associated with benzodiazepines in 2017, most due to intentional overdose. According to the National Institute on Drug Abuse there were a total of 70,630 overdose deaths in the United States in 2019 [50]. Most of those deaths were due to opioids, mainly fentanyl. The benzodiazepines were involved in 9,711 of those deaths, usually in combination with opioids. By comparison there were 5,175 deaths in 2019 associated with antidepressants. Many dose-related adverse effects of benzodiazepines resulted from depression of the central nervous system including drowsiness, impaired judgment, diminished motor skills, and anterograde amnesia, causing falls and confusion in the elderly, breathing problems in symptomatic sleep apnea or chronic pulmonary disease, driving impairment, and worsened job performance.

5.1 Pharmacokinetics and pharmacodynamics

The GABA system is the location of the primary pharmacodynamics of the benzodiazepines [51]. This system is the major inhibitory system in the central nervous system, thus the drug effect producing central nervous system depression. The GABA-A receptors upon which the benzodiazepines produce their effect are pentameric ligand-gated chloride ion channels. There are 21 different subunit isoforms within the GABA-A chloride ionophore. These are divided into eight families which within their family share 70% of their amino acid sequences. These subunit families are classified into alpha, beta, gamma, delta, epsilon, pi, omega, and rho. The first four of these are most important for benzodiazepine action. The structure most frequently seen in the brain consists of two alpha subunits and two beta subunits and one gamma or, less frequently, one delta subunit [52]. The neurotransmitter GABA binds to the interface between the alpha and beta subunits to open the chloride ionophore. Benzodiazepines bind to the interface of the alpha and gamma subunits. The benzodiazepine binding produces an allosteric change making the GABA receptor more sensitive, producing benzodiazepine clinical effects. Of interest for future drug development, the alpha subunit family contains alpha-1 through alpha-6 subunits which vary in benzodiazepine sensitivities and specific clinical effects [53, 54]. Thus, alpha subunit composition containing alpha-1 is associated with sedation, amnesia, anti-seizure activity, and addiction propensity. Alpha-2 subunits are associated with anti-anxiety propensity, muscle relaxation, cognitive disturbance, and analgesic properties. Alpha-5 subunits are associated with learning, memory, and muscle relaxation.

While the basic 3 ring skeletal molecular structure of the benzodiazepines is the same, different additions to this molecular structure yield important differences in properties. Classification of these additions to the basic benzodiazepine nucleus use 7 groupings, five of which are important to this discussion. The triazolo group (alprazolam, triazolam, estazolam) and the imidazo group (midazolam) include drugs that are closely related structurally. Likewise, the 3-hydroxy group (lorazepam, oxazepam, and temazepam) all have similar molecular structures. The

2-keto group, including diazepam and the 7-nitro group including clonazepam are significantly different structurally from the other benzodiazepines. These molecular structure differences contribute to the pharmacologic properties of these drugs. The GABA-A receptors also change in response to exogenous factors including benzodiazepine exposure. Internalization of the receptor complex leads to degradation and altered composition of the pentameric structure, rendering the receptor complex less sensitive and less numerous.

There are two prime factors in the choice of a benzodiazepine, half-life and potency. A low potency and long half-life benzodiazepine is diazepam and a low potency and short half-life benzodiazepine is temazepam. A high potency and long half-life benzodiazepine is clonazepam and two high potency short half-life benzodiazepines are alprazolam and lorazepam. The pharmacodynamic effects of the benzodiazepines are similar. Thus, pharmacokinetic properties, potency, dosing requirements, and efficacy have determined usage. Several of the benzodiazepines have been used in the pharmacologic treatment of parasomnias and sleep related movement disorders, and as a class may be the most frequent and widely used pharmacological management. Four commonly used agents are described below in alphabetical order.

5.2 Alprazolam

This triazolo benzodiazepine was approved by the FDA in 1981 for the treatment of panic disorder. The doses of alprazolam for panic disorder were very high, up to 6–12 mg per day. It quickly became the most widely prescribed benzodiazepine shortly after marketing. The oral absorption of alprazolam after a single 1 mg dose is rapid with an oral bioavailability of 80–100% and peak plasma concentrations in young males occurring within 0.7 to 1.8 hours after administration [55]. It is a CYP3A4 substrate subject to multiple metabolic inducers and inhibitors. The metabolic products of hepatic microsomal oxidation yield alpha-hydroxy and 4-hydroxy alprazolam which have 10% of the plasma concentrations of the parent drug and lower affinity for benzodiazepine receptors. A number of drugs may impair metabolism of alprazolam, including fluoxetine [56] and propoxyphene, enhancing central nervous system effects. The elimination half-life in young men ranged from 9 to 16 hours. Healthy elderly men had significantly longer half-lives with a mean of 19 hours versus a mean of 11 hours in young men [57].

Alprazolam falls into the intermediate range among benzodiazepines in regards to lipid solubility (50% of diazepam). This characteristic determines the degree of uptake into the brain [58] as well as the speed at which alprazolam enters the brain. Several studies have demonstrated that the steady state plasma concentrations of alprazolam after multiple dosing are proportional to the daily dose and do not change the half-life [59–61].

The general binding characteristics are similar to the other benzodiazepines, however, the receptor affinity of alprazolam (K_i) of 3.4 nm is tighter than diazepam's K_i of 5.3 nm [62]. This reflects the potency enhancement from the chloride at position 8 on the phenyl ring along with the triazolo ring. This enhancement is even tighter for another triazolobenzodiazepine, triazolam, with its remarkable receptor affinity (K_i) of 0.5 nm [63]. A unique characteristic not shared by other benzodiazepines [62] was seen with low doses (0.02–0.05 mg/kg) of alprazolam in mice [64]. An increased benzodiazepine receptor number was seen compared to the decreased receptor number seen with other benzodiazepines and high dose alprazolam.

Clinical information regarding the use of alprazolam in REM sleep behavioral disorder is limited [65]. Published results [66, 67] yield varying utility, though this author's results [68, 69] have been quite positive at doses of alprazolam 0.5 mg at

bedtime. Alprazolam would appear to have good pharmacokinetic and pharmacodynamic properties for use in nocturnal parasomnias when a benzodiazepine is indicated. Currently, however, it is not frequently prescribed for that purpose. Of note, in the elderly (>65 years old) there is a significant and dramatic dose related increase in sedation and neuromotor testing decrement between alprazolam doses of 0.5 mg and 2.0 mg [60].

5.3 Clonazepam

Clonazepam is the most common drug used for parasomnias. It is limited to oral administration, but has been used widely for panic disorder and psychosis, as well as, having anti-seizure properties shared with diazepam, lorazepam, and clobazam. This 7-nitro group benzodiazepine differs structurally from other benzodiazepines resulting in high potency and tight binding affinity (Ki 2.0 nm) to benzodiazepine receptors. Clonazepam is rapidly and completely absorbed after oral administration and reaches peak plasma concentrations in 1–4 hours [70]. Absolute bioavailability is 90%. It is highly metabolized by the hepatic microsomal system with less than 2% being excreted unchanged in the urine. The remarkable property of this drug is its long half-life of 30–40 hours. The constant presence of the drug with multiple dosing results in benzodiazepine downregulation with loss of both high affinity binding and receptor number [71, 72]. Specific clonazepam binding was reduced by 24.9% with chronic administration. This likely explains the loss of efficacy and development of tolerance with multiple dosing. Clonazepam, more than lorazepam or alprazolam, produced impairment on neuromotor tasks [73, 74]. Alprazolam showed significantly faster recovery on testing performance than either clonazepam or lorazepam even though lorazepam has a similar half-life. Ellinwood et al. also found that the equivalent dose of alprazolam was half the dosage level of the other two drugs, a phenomenon that could not be explained by receptor affinity. The length of impairment with lorazepam was greater than clonazepam presumably secondary to its greater lipid solubility.

Clonazepam is currently the suggested treatment for REM sleep behavioral disorder with more published studies than other drugs that have been used in this disorder [65]. Clonazepam showed efficacy in 80% of 200 patients at the Minnesota Regional Sleep Disorders Center [66, 67]. There is concern, however, for the use of clonazepam in dementia, gait disorders, and obstructive sleep apnea due to reports of worsening of each of these with chronic clonazepam dosing. Aurora et al. [65] reviewed the adverse event profile of clonazepam and found reports of sedation, impotence, early morning loss of motor coordination, confusion, and memory dysfunction.

5.4 Diazepam

Diazepam, within six years of it being marketed, became the most prescribed drug in the United States from 1969 to 1982 [49]. Diazepam has chemical properties of lipid solubility and non-ionization at physiological pH that made absorption through the gut wall and cerebral capillaries rapid, allowing potent brain concentrations within minutes. Peak blood levels with oral dosing are achieved in 1–2 hours. The half-life varies between 20 and 80 hours making the drug a long-acting agent. Diazepam gained multiple uses including anti-anxiety, sedative, anti-seizure, anti-vertigo, and muscle relaxant effects due to its action on both central and peripheral benzodiazepine receptors. It is available in oral, rectal, and parenteral formulations. Hepatic metabolism of diazepam produces an active metabolite, desmethyldiazepam (DMD), which at steady state with repeated dosing eventually has a higher

plasma concentration than its parent drug. The elimination of DMD occurs much more slowly than diazepam with a half-life of 36–96 hours. If diazepam is discontinued, withdrawal symptoms can occur ranging from anxiety to seizures with higher doses. Diazepam remains a secondary benzodiazepine for both non-REM and REM sleep related parasomnias. It is a tertiary treatment when first and second-line treatments have failed.

5.5 Lorazepam

Lorazepam has many uses in addition to its indication for anxiety with depression. It has been used as a hypnotic and as a treatment for panic disorder, alcoholic delirium tremens, status epilepticus, and pre-procedural sedation [73]. It is available in oral and parenteral formulations. Its use for parasomnias and sleep-related movement disorders has been limited and Aurora et al. [65] did not report lorazepam being used for REM sleep behavior disorder.

Lorazepam is one of the 3-hydroxy group of benzodiazepines. This drug is available in oral and parenteral formulations and is metabolized by glucuronidation thus the absence of concern for hepatic impairment or an active metabolite. It has utility for anti- anxiety and anti-seizure applications. It is absorbed quickly after oral administration with a time to peak plasma levels of 1–5 hours [70]. Like diazepam, lorazepam is highly lipophilic and quickly crosses the blood–brain barrier. It is rapidly absorbed when administered orally and has a half-life of 10–20 hours. As discussed in Section 4.1b, lorazepam has a longer duration of action than might be expected for its elimination half-life. The ortho chloride on the ring structures of lorazepam, clonazepam, and triazolam increase receptor binding and thus potency. The tighter binding may be the reason for the longer duration of action [73].

6. Melatonin

Endogenous melatonin is a hormone secreted by the pineal gland in tandem with the circadian rhythm. Studies of melatonin revealed sedative properties leading to its use in sleep disorders [75–77]. Melatonin is considered a dietary supplement by the Food and Drug Administration in the United States and thus the formulations are not subject to the regulations that govern prescription medications mentioned in this chapter.

Buscemi et al. [78] did a clinical review of 14 randomized controlled trials of exogenous melatonin for sleep disorders. The meta-analysis showed a reduced sleep latency of 11.7 minutes (CI: −18.2, −5.2), but this was most significant in those patients with delayed sleep-phase syndrome. All of the patients studied carried diagnoses of either insomnia or delayed sleep-phase disorder. No doses higher than 5 mg per night were used and half the studies used no more than 3 mg per night. Of the 222 combined participants, 13 reported headaches, 10 dizziness, 3 nausea, and 3 drowsiness. In all of these there was no significant difference between melatonin and placebo.

Moroni et al. [79] conducted another systematic review looking at 19 published studies utilizing different formulations of exogenous melatonin. Most of the studies reviewed used low dose melatonin (<5 mg). The immediate-release formulations produced a decrease in sleep onset latency and the sustained release formulations had a greater effect on reducing wakefulness after sleep onset. Oral formulations of melatonin had variability in both absorption and metabolism. There were no adverse effects noted in very short-term therapy among healthy research participants.

The amount of melatonin that enters the systemic circulation is decreased by first-pass metabolism. The hepatic enzyme involved in metabolism of melatonin is CYP1A2 [80, 81]. This enzyme has higher activity in males, likely contributing to the gender differences seen in one study [82] which showed almost three times higher systemic circulation concentrations in females. An older group of research participants also showed three times the maximal concentration in their systemic circulation [83].

The Standards of Practice Committee of the American Academy of Sleep Medicine (AASM) published recommendations which included a suggestion that melatonin be used for the treatment of REM sleep behavior disorder [65]. They noted that melatonin had been shown to be effective with few adverse effects. There are actually only a few reports showing efficacy of melatonin in parasomnias [75, 84]. This author's experience in a large university sleep clinic confirms the efficacy of melatonin in some patients, but the patients with parasomnias treated successfully with melatonin comprise less than half of the patients treated successfully with benzodiazepines [68].

Dose related adverse effects were reported including headache, morning sleepiness, and delusions/hallucinations [75]. In another set of AASM recommendations for the management of circadian disorders [85] melatonin adverse effects were discussed in greater depth. There were no serious adverse effects, however, headaches, somnolence, hypotension, hypertension, gastrointestinal upset, and exacerbation of alopecia areata were all reported. An increase in depressive symptoms [86], impairment of glucose tolerance [87], and reproductive function [88] were reported. Studies beyond 3 months of melatonin use and studies in pediatrics were and remain scarce. Pediatric concerns were reported including potential effects on growth hormone regulation with high dose melatonin (10 mg) [89]. There was additional thought that the efficacy in pediatric parasomnias might be related to an indirect effect of improving sleep rather than a direct effect of melatonin [65].

In conclusion, melatonin is efficacious in some patients with REM sleep behavioral disorder and possibly other parasomnias with no serious adverse effects.

7. The antidepressants

There have been many antidepressants used in patients with a variety of parasomnias either as primary or concomitant therapy. Parasomnias can be co-morbid with mental health disorders leading to antidepressant treatment. The confounding factor is that some parasomnias and sleep-related movement disorders may be exacerbated or even elicited by antidepressant therapy [90–94]. Lam et al. [95] used a questionnaire to identify patients with parasomnias then confirmed the diagnosis via a clinical interview. Of the 1235 participants who completed the interview 22.3% had clinically confirmed somnambulism, sleep-related eating disorder, or sleep related injury. REM sleep behavior disorder (RSBD) was the cause of sleep related injury in 66.7% of the subgroup of participants with sleep related injury. The use of selective serotonin reuptake inhibitors (SSRIs) was associated with symptoms of RSBD in 5% of participants. Of the 29 participants diagnosed with somnambulism 34.5% were using sedating antidepressants [96].

Drug-induced RSBD has been further associated with the tricyclic antidepressant clomipramine and the monoamine oxidase inhibitors selegiline and phenelzine [94]. In spite of these risks co-morbid psychiatric disorders often lead to treatment with antidepressants in individuals with parasomnias. There are also a variety of case reports of the effective use of antidepressants for management of parasomnias. Imipramine was used successfully in seven children diagnosed with sleep terrors

or somnambulism [97]. Paroxetine at a dose of 40 mg in the morning was used successfully in a 46-year-old woman with a 30-year history of sleep terrors and somnambulism. REM suppressant properties of the antidepressants would appear to be a rational approach to the control of nightmares, though the evidence is not convincing [98]. Given these therapeutic uncertainties with use of the antidepressants for parasomnias and sleep related movement disorders, these drug classes are not first line treatments for these disorders and will not be discussed in depth here.

8. The alpha 2 delta subunit neuronal voltage-gated calcium channel blockers

The two drugs in this class are gabapentin and pregabalin and will be discussed separately. These drugs are not used for management of parasomnias, but have gained increasing favor for use in restless legs syndrome and periodic limb movement disorder. The current recommendations of the Scientific and Medical Advisory Board of the Restless Legs Syndrome Foundation were recently published in Mayo Clinic Proceedings. The alpha 2 delta subunit neuronal voltage-gated calcium channel blockers were recommended as first line therapy for chronic persistent restless legs syndrome (RLS) [99].

8.1 Gabapentin

Gabapentin was approved in December 1993 by the Food and Drug Administration (FDA) for the adjunctive therapy of partial seizures. After initial approval gabapentin sales increased significantly due to off-label uses for treatment of chronic pain syndromes [100]. In 2000 gabapentin was the top-selling anticonvulsant and ranked 17th in total expenditures among all drugs. In 2002 the FDA added the indication of postherpetic neuralgia, but by 2004 gabapentin sales had increased to 3 billion dollars per year [101]. In 2004 the US Department of Justice issued its largest fine to date ($430 million) to the Warner-Lambert group of pharmaceutical companies, manufacturer of gabapentin, for promoting gabapentin for uses not approved by the FDA [102]. In 2012 gabapentin enacarbil (a pro-drug with better absorption characteristics) received FDA approval for the treatment of restless legs syndrome and postherpetic neuralgia. By 2015 the use of gabapentin formulations had tripled from 2002 [103]. In 2017 gabapentin was the fifth most commonly prescribed medication in the United States [104].

Gabapentin has many desirable pharmacokinetic properties [105]. Mean maximum plasma concentrations were attained 2–3 hours after a 300–400 mg oral dose with a bioavailability of 60%, however, absorption kinetics are slowed and bioavailability decreased as the dose is increased. Gabapentin readily crosses the blood brain barrier due to its lipid solubility. It is not bound to plasma proteins. The elimination half-life is dependent on renal clearance alone in a linear fashion. The drug does not affect the metabolism of other drugs or induce hepatic enzymes. The elimination half-life of gabapentin after a single oral dose of 200–400 mg is about 5–7 hours with 80% of the dose recoverable unchanged in the urine. The most common adverse effects (significantly greater than placebo) are somnolence, dizziness, and ataxia. Happe et al. [106] reported efficacy of gabapentin given 2 hours before bedtime in restless legs syndrome in 2001. Subsequently, gabapentin enacarbil was found to be effective in a double-blind, placebo-controlled, multicenter study of 325 subjects [107]. This pro-drug (rapidly converted to gabapentin after absorption) sought to overcome the absorption deficiencies of gabapentin which was dependent upon active transport by a

low-capacity nutrient transport system expressed in a narrow region of the upper small intestine. Gabapentin enacarbil is actively transported by a high-capacity nutrient transporter located throughout the large and small intestine [108]. There was significant improvement in RLS symptoms with both the 600 mg and 1200 mg doses of gabapentin enacarbil in the 12-week study compared to placebo. The most commonly reported adverse effects were dizziness and somnolence. Gabapentin enacarbil remains a preferable drug to generic gabapentin, however, cost concerns have made generic gabapentin more widely prescribed.

8.2 Pregabalin

Pregabalin and gabapentin share the same mechanism of action, inhibiting calcium influx into neuronal terminals and thus inhibiting the release of excitatory neurotransmitters. Orally dosed pregabalin is absorbed more rapidly than gabapentin with maximal plasma concentrations achieved in 1 hour [108]. The absorption is linear with plasma concentrations increasing proportionally to dose and the bioavailability of 90% or greater. Neither drug binds to plasma proteins or inhibits hepatic enzymes, and both drugs are eliminated by renal excretion alone with elimination half-lives of less than 6 hours. At higher dose therapy (1800–4800 mg) gabapentin bioavailability can fall to 25–50% [109]. Pregabalin bioavailability remained above 90% across its entire dose range.

A randomized, double-blind, 6-week study of pregabalin in 137 patients with restless legs syndrome showed an effective daily dose for 50% of patients at 37.3 mg and for 90% of patients at 123.9 mg per day [110]. A higher proportion of responders to the Clinical Global Impressions-Improvement Scale (CGI-I) was seen at the two highest doses of pregabalin 300 and 450 mg per day. Dizziness and somnolence were the most common adverse effects, though dry mouth complaints also exceeded placebo. A second double-blind, placebo-controlled study [111] was performed almost simultaneously with the Allen et al. [110] study. This second study randomized 58 patients in a 12-week flexible-dose trial. The mean effective dose at the end of treatment was 322.5 mg per day. There was a significant improvement in the International Restless Legs Scale (IRLS) and Clinical Global Impression (CGI). Polysomnography measured a reduction in mean periodic limb movement index, improvement in sleep architecture, and decrease in wakefulness after sleep onset. Adverse effects were reported to be mild and included unsteadiness, somnolence, and headache.

From the earliest studies of pregabalin there has been a concern about cognitive effects of this drug. Salinsky et al. [112] looked at this potential adverse effect in 32 healthy volunteers. The participants were randomized in a double-blind, parallel study receiving either pregabalin or placebo. Pregabalin was titrated over 8 weeks to 600 mg per day. At baseline and after 12 weeks of treatment all subjects underwent cognitive testing. A battery of 14 tests were used including finger tapping, grooved pegboard, digit symbol, Stroop color-word, selective reminding, name learning, story recall, Wonderlic personnel, visual reaction time, controlled oral word association, divided attention, letter-number sequencing, profile of mood states and Portland neurotoxicity scale. Thirty subjects completed the trial. There was significant ($p < 0.01$) worsening in the treatment group on the objective Stroop-color-word test and controlled oral word association test, as well as, the subjective Portland neurotoxicity scale. While the study demonstrated cognitive effects, both the speed of the titration and the final dose were greater than this author's current practice and the methodology of the treatment studies described here. This study, however, does demonstrate concerns over rapid dose increases and high dose therapy.

9. The dopamine receptor agonists

The dopamine agonists have been the first line treatment of periodic limb movement disorder and restless legs syndrome for many years. It is only recently that the alpha 2 delta subunit neuronal voltage-gated calcium channel blockers have advanced to preferred therapy [99]. It has, however, been long appreciated that the dopamine receptor agonists have adverse effects [113]. Impulse control disorders such as pathological gambling, hypersexuality, compulsive shopping, or an irresistible urge to wander have been identified in surveys [114]. The D3 dopamine receptor has been implicated in these behaviors [115], however, no dose response curve or dose related risk assessment has been established for these phenomena. A more pervasive and widespread adverse effect is the phenomena of augmentation. Augmentation manifests as earlier onset of RLS symptoms with decreased duration of benefit from medications and symptoms involving other parts of the body. Though the highest risk of augmentation occurs with short acting agents such as levodopa, current expert opinion is that augmentation will occur with all the currently available dopamine agonists over time [99].

9.1 Pramipexole

Pramipexole is a non-ergot dopamine agonist with higher affinity to D3 than D2 or D4 receptor subtypes. It has FDA indications for Parkinson's disease and restless leg syndrome [116]. It is rapidly absorbed and reaches peak plasma concentrations in 2 hours. If taken with a meal the absorption is delayed by about an hour. The bioavailability of pramipexole is greater than 90%. Renal excretion is the primary route of elimination with 90% of the dose recovered unchanged in the urine. The half-life of pramipexole is 8 hours in young adults and 12 hours in the elderly. The most common adverse effect (in excess of placebo) was somnolence. The recommended final treatment dose after up-titration was 0.5 mg given 2–3 hours before bedtime. Though higher doses are used in practice, the risk of increasing augmentation with high dose therapy leads to concern about high dosing [68].

9.2 Rotigotine

Rotigotine is dispensed as a transdermal delivery system [117]. It is a non-ergoline dopamine agonist for the D3, D2, and D1 dopamine receptors approved by the FDA for use in RLS as well as Parkinson's disease. When a patch is applied there is a 3-hour delay before the drug is detected in plasma and the time to maximal plasm levels is 15–18 hours. Approximately 45% of the dose is released from the patch in 24 hours. After removal of the patch the elimination half-life is 5–7 hours. Most rotigotine is eliminated in the urine as inactive conjugates. The highest recommended dose (for RLS) of rotigotine is 3 mg per 24 hours. The most common adverse effect was a skin reaction at the site of the patch, though nausea also exceeded placebo. The constant delivery system suppresses RLS augmentation temporarily though other medications may ultimately be needed for breakthrough symptoms [68].

9.3 Ropinirole

Ropinirole is a selective non-ergoline dopamine D3 much greater than D2 receptor agonist [118]. It is rapidly absorbed but its bioavailability is only 50%. The maximal plasma concentrations are achieved in 0.5 to 4 hours (mean 1.5 hours). The drug is metabolized in the liver to inactive metabolites by the P450 iso-enzyme CYP1A2. The elimination half-life is 3 hours, though this can be variable and elderly

patients have 15% slower clearance. The drug is FDA approved for use in restless legs syndrome, as well as, Parkinson's disease. The short half-life and duration of action of this drug can lead to tachyphylaxis and doses higher than recommended producing a high rate of augmentation in the author's experience.

10. Prazosin

The American Academy of Sleep Medicine published a position paper on the treatment of nightmare disorder in 2018 [119]. The position paper divided nightmares into those associated with post-traumatic stress disorder (PTSD) and those not associated with PTSD. Nightmares associated with PTSD are more difficult to suppress and thus a wide variety of behavioral and drug combinations have been used, beyond the capability of this chapter. The drugs that may be used in nightmare disorder in the absence of PTSD are benzodiazepines, not including clonazepam, and prazosin.

Prazosin is a quinazoline derivative and peripheral vasodilator [120]. Its vasodilator properties are due to postsynaptic alpha adrenergic receptor blockade. Prazosin is extensively metabolized in the liver producing high first pass elimination and resultant low oral bioavailability after oral dosing. With an oral dose of 1 mg in normal subjects the bioavailability of prazosin ranged from 43.5 to 69.3% [121]. The mean elimination half-life is about 2.5 hours. Prazosin shows initial dose postural hypotension which disappears with continued administration.

On acute administration of prazosin, only very low levels crossed the blood–brain barrier [122]. On chronic administration of high dose prazosin, however, prazosin apparently crossed the blood–brain barrier in adequate concentrations to affect the central alpha adrenergic receptor density in the cerebral cortex [123]. This effect would not have occurred without significant penetration of prazosin into the brain. There were a number of studies showing efficacy of prazosin in veterans with PTSD induced nightmares [119]. In contrast, however, there was a recent large randomized, placebo-controlled study with negative results [124], leading to uncertainty about this treatment.

11. The opioids

Various opioids have been used for intractable restless legs syndrome. These include propoxyphene [125]. tramadol [126], oxycodone [127], hydrocodone [128], and methadone [129]. Most of these have been used as adjunctive therapy, but methadone has been used in monotherapy. The mechanism of action of the opioids in RLS is unclear, however, it appears to work through a central dopaminergic neurotransmission as dopamine receptor antagonists will block the therapeutic effect. The current opioid crisis has lent a stigma to chronic use of methadone that has discouraged its use by many patients suffering with intractable restless legs syndrome. This is unfortunate as opioid therapy with management directed towards restless legs syndrome rather than chronic pain syndromes can be quite helpful [130]. The concern with long-term opioid therapy is the occult development or exacerbation of a sleep related breathing disorder. For this reason, all patients on chronic opioids should be clinically monitored for evidence of sleep apnea [131].

11.1 Methadone

Methadone is a synthetic opioid that is nearly equipotent with morphine, but with dramatically different pharmacokinetic characteristics [132]. Methadone

is a racemic mixture of R and S-methadone with the R isomer being 8–50 times more potent. Methadone may prevent or attenuate opioid tolerance via its weak antagonist properties on the N-methyl-D-aspartate (NMDA) receptor. Methadone is rapidly absorbed with maximal plasma concentrations 2.5 to 4 hours after oral administration. The bioavailability of methadone is 70–80%, though this can vary depending on the degree of first pass metabolism. Methadone is hepatically metabolized to inactive metabolites by the cytochrome P450 enzymes, CYP3A4 and CYP2B6. The elimination half-life of methadone ranges from 5 to 130 hours with a mean of 20–35 hours. The elimination half-life of the R isomer is approximately 25% longer than the S isomer. Methadone shows apparent autoinduction of its own metabolism. The half-life during chronic therapy is only 40% of the half-life with acute administration. A number of medications can either decrease or increase methadone levels via induction or inhibition of CYP3A4. Quantitative plasma levels may be necessary. Of note, there have been unintentional deaths with methadone. Many of these deaths occurred on the fifth day of regular dosing [133]. Prescribers need to be aware of methadone's peculiar pharmacokinetics.

In practice doses of methadone from 5–40 mg daily have been used. Given the pharmacokinetics starting therapy at a small dose of 2.5–5 mg is appropriate with up-titration of the dose as needed for symptoms. Methadone in patients with intractable RLS can produce remarkable improvement [68, 129].

11.2 Oxycodone-naloxone

Constipation and bowel dysfunction is the prime adverse effect of long-term opiate therapy. The combination of an opioid with a competitive mu receptor antagonist in a sustained release formulation is a unique answer to opioid adverse effects. The combination is also a tool against abuse of oxycodone since dissolution and injection results in naloxone having a much greater effect blocking mu receptors. A double-blind, randomized, placebo-controlled trial with this formulation was performed with 276 RLS patients [134]. The study started participants on a dose of oxycodone 5.0 mg and naloxone 2.5 mg twice a day increasing per each study site's investigator to a maximal dose of oxycodone 40 mg and naloxone 20 mg. Adverse effects more than twice as frequent as placebo included fatigue, constipation, somnolence, dry mouth and pruritis. There was clear efficacy of the combination over placebo.

12. Conclusions

This chapter did not attempt to be all inclusive, as a full description of the pharmacological interventions into sleep related movement disorders and parasomnias would fill the entire book. The chapter does attempt to provide pharmacological basis for treatment of the most challenging areas for pharmaceutical intervention, notably the REM sleep parasomnias and restless legs syndrome.

A challenge of REM sleep parasomnia management is the continuing use of clonazepam as first line therapy. This potent drug is effective, but due to its extremely long half-life, is prone to adverse effects in many patients. Unfortunately, the even more potent drug, triazolam, is too short acting and the two drugs (alprazolam and lorazepam) with duration of actions that are reasonable for the goal of suppressing dream enactment are less potent than either triazolam or clonazepam, thus appearing to need higher doses. Unexpectedly, the observational experience of the University of Texas Southwestern Medical Center at Dallas Clinical Center for Sleep and Breathing Disorders has been that the efficacy of alprazolam is half the expected dose that was used in trials in Minneapolis. Retrospective review is in progress.

The other pharmacological challenge is the management of severe persistent and intractable restless leg syndrome. In recent decades the algorithms for management have become clearer pointing to the early use of gabapentin and pregabalin and the use of opioids in intractable patients, however, there is a lag of that knowledge reaching the medical community that is faced with these patients and their demands for treatment. This is another area where the growth of medical knowledge is exceeding our educational capabilities.

Author details

Gregory S. Carter
The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, United States of America

*Address all correspondence to: gregory.carter@utsouthwestern.edu

References

[1] Roger H. Les Troubles du Sommeil. Paris: Masson; 1932 p. 275-283

[2] American Academy of Sleep Medicine. Parasomnias. In: AASM, ed. International Classification of Sleep Disorders, 3rd Edition. Darien: American Academy of Sleep Medicine; 2014. p. 225-280

[3] American Academy of Sleep Medicine. Sleep-related movement disorders. In: AASM, ed. International Classification of Sleep Disorders, 3rd Ed. Darien: American Academy of Sleep Medicine; 2014. p. 281-337

[4] Ohayon MM. Epidemiology of parasomnias. In: Thorpy MJ and Plazzi G, editors. Parasomnias and Other Sleep-Related Movement Disorders. New York: Cambridge University Press; 2010. p. 301-311

[5] Gulyani S, Salas RE, and Gamaldo CE. Sleep medicine pharmacotherapeutics overview: Today, tomorrow, and the future (Part 2: hypersomnia, parasomnia, and movement disorders). Chest. 2013. 143(1): 242-251

[6] Klackenberg G. Somnambulism in childhood-prevalence, course and behavioral correlations: a prospective longitudinal study (3-16 years). Acta Paediatr Scand. 1982; 71:495-499

[7] Simonds J and Parraga H. Prevalence of sleep disorders and sleep behaviors in children and adolescents. J Am Acad Child Adolesc Psychiatry. 1982; 21:383-388

[8] Hublin C, Kaprio J, Partinen M, Heikkila K, Koskenvuo M. Parasomnias:co-occurrence and genetics. Psychiatr Genet. 2001; 11:65-70

[9] Lateef O, Wyatt J, and Cartwright R. A case of violent non-REM parasomnias that resolved with treatment of obstructive sleep apnea. Chest. 2005; 128(4 Meeting abstracts):461S

[10] Drakatos P, Marples L, Muza R, Higgins S, Gildeh N, Macavei R, Dongol EM, Nesbitt A, Rosenweig I, Lyons E, d'Ancona G, Steier J, Williams AJ and Kent BD. NREM parasomnis: a treatment approach based upon a retrospective case series of 512 patients. Sleep Med. 2018; 53(1):181-188

[11] Attarian H and Zhu L. Treatment options for disorders of arousal: a case series. Int J Neurosci. 2013;123(9):623-625

[12] Hauri PJ, Silber M, and Boeve BF. The treatment of parasomnias with hypnosis: a 5-year follow-up study. J Clin Sleep Med. 2007; 3(4):369-373.

[13] Proserpio P, Teraghi M, Manni R, and Nobili L. Drugs used in parasomnia. Sleep Medicine Clinics. 2020; 15(2):289-300

[14] Schenck CH, Milner TD, Hurwitz et.al. A polysomnographic and clinical report on sleep-related injury in 100 adult patients. Am J Psychiatry. 1989;146(9):1166-1173

[15] Schenk CH and Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. Am J Med. 1996;100(3):333-337

[16] Goldbloom D and Chouinard G. Clonazepam in the treatment of neuroleptic-induced somnambulism. Am J Psychiatry. 1984;141(11):1486

[17] Nutt DH, Wilson SJ, Lillywhite AR, Potokar JP, and Bell CJ. Adult night terrors and paroxetine. Lancet. 1997;350(9072):185

[18] Cooper AJ. Treatment of coexistent night-terrors and somnambulism in adults with imipramine and diazepam. J Clin Psychiatry. 1987; 48(5):209-210

[19] Balon R. Sleep terror disorder and insomnia treated with trazodone: a case report. Ann Clin Psychiatry. 1994;6(3):161-163

[20] Jan JE, Freeman RD, Wasdell MB, and Bomben MM. A child with severe night terrors and sleep-walking responds to melatonin therapy. Dev Med Child Neurol. 2004;46(11):789

[21] Ozcan O and Donmez YE. Melatonin treatment for childhood sleep terror. J Child Adolesc Psychopharmacol. 2014;24(9):528-529

[22] van Zyl LT, Chung S., Shahid A, and Shapiro CM. L-Tryptophan as treatment for pediatric non-rapid eye movement parasomnia. J Child Adolesc Psychopharmacol. 2018; 28(6):395-401

[23] Bruni O, Ferri R, Miano S, et.al. L-5-hydroxytryptophan treatment of sleep terrors in children. Eur J Pediatr. 2004; 163(7):402-407

[24] Sasayma D, Washizuka S, and Honda H. Effective treatment of night terrors and sleep walking with ramelteon. J Child Adolesc Psychopharmacol. 2016;26(10):948

[25] Guilleminault C and Silvestri JM. Disorders of arousal and epilepsy during sleep. In: Sterman M, Shouse M, Passouant P, editors. Sleep and Epilepsy. New York: Academic Press; 1983. p. 513-531

[26] Tung L and Carter G. Differentiating confusional parasomnias from nocturnal frontal lobe epilepsy. Sleep 2019; 42(Abstract Suppl): A425-A426

[27] Montini A, Loddo G, Balelli L, Cilea R, and Provini F. Sleep-related hypermotor epilepsy vs disorders of arousal in adults. A step-wise approach to diagnosis. Chest. 2021; 160(1):319-329

[28] Fleetham JA, Jonathan AE, and Fleming MB. Parasomnias. Canadian Medical Association Journal. 2014;186(8): E273-E280

[29] Haba-Rubio J, Frauscher B, Marques-Vidal P, Toriel J, Tobback N, Andries D, Preisig M, Vollenweider P, Postuma R, and Heinzer R. Prevalence and determinants of REM sleep behavior disorder in the general population. Sleep. 2018; 41(2):1-8

[30] McKenna and Peever J. REM sleep behavior disorder: The link between synucleinopathies and REM sleep circuits. In: Rapid-Eye-Movement Sleep Behavior Disorder, Schenck CH, Högl B, and Videnovic A, editors. Cham: Springer Nature Switzerland AG; 2019. p. 625-637

[31] Iranzo A and Santamaria J. Severe obstructive sleep apnea/hypopnea mimicking REM sleep behavior disorder. Sleep. 2005; 28:203-206

[32] Olson E, Boeve B, and Silber M. Rapid eye movement sleep behavior disorder: demographic, clinical, and laboratory findings in 93 cases. Brain. 2000; 123:331-339

[33] Levin R and Fireman G. Nightmare prevalence, nightmare distress, and self-reported psychological disturbance. Sleep. 2002; 25:205-212

[34] Germain A and Nielsen T. Sleep pathophysiology in posttraumatic stress disorder and idiopathic nightmare suffers. Biol. Psychiatry. 2003; 54:1092-1098

[35] Pagel J and Helfter P. Drug induced nightmares-an etiology-based review. Hum Psychopharmacol. 2003; 18:59-67

[36] Brooks LJ and Topol HI. Enuresis in children with sleep apnea. J Pediatr. 2003; 142:515-518

[37] Held-Egli K, Ruegger C, Das-Kundu S, Schmitt B, Bucher HU. Benign neonatal sleep myoclonus in new born infants of opioid dependent mothers. Acta Paediatr. 2009; 98:69-73

[38] Lavigne G, Guitard F, Rompre P, Montplaisir J. Variability in sleep bruxism activity over time. J Sleep Res. 2001; 10:237-244

[39] Ohayon M, Li K, and Guilleminault C, Risk factors for sleep bruxism in the general population. Chest. 2001; 119:53-61

[40] Ondo WG, Simmons JH, Shahid MH, Hashem V, Hunter C, and Jankovic J. Onabotulinum toxin-A injections for sleep bruxism: A double-blind, placebo-controlled study. Neurology. 2018; 90(7): e559-e564

[41] Shim YJ, Lee HJ, Park KJ, Kim HT, Hong IH, and Kim ST. Botulinum toxin therapy for managing sleep bruxism: A randomized and placebo-controlled trial. Toxins. 2020;12(3):168-177

[42] Butler J, Mulkerrin E, and O'Keefe S. Nocturnal leg cramps in older people. Postgrad Med J 2002; 78:596-598

[43] Weiner I and Weiner H. Nocturnal leg muscle cramps. JAMA. 1980; 244:2332-2333

[44] Iber C, Ancoli-Israel S, Chesson AL Jr., and Quan SF for the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, First Edition: Westchester, Illinois: American Academy of Sleep Medicine, 2007

[45] Baenninger A. Good Chemistry: The Life and Legacy of Valium Inventor Leo Sternbach. New York: McGraw-Hill; 2003. 256 p

[46] Ciraulo DA and Oldham M. Sedative hypnotics. In: The Effects of Drug Abuse on the Human Nervous System. Madras B and Kuhar M, editors. 2014. Boston: Elsevier BV; 2011. p. 499-532

[47] Jick H, Miettinen OS, Shapiro S, Lewis GP. Comprehensive drug surveillance. JAMA. 1970; 213:1455-1460

[48] Gable RS. Toward a comparative overview of dependance potential and acute toxicity of psychoactive substances used nonmedically. Am J Drug Alcohol Abuse. 1993; 19:263-281

[49] Drug Enforcement Administration. Benzodiazepines (Street Names: Benzos, Downers, Nerve Pills, Tranks). December 2019. Drug and Chemical Evaluation Section https://www.deadiversion.usdoj.gov/drug_chem_info/benzo.pdf [Accessed 2021-08-16]

[50] National Institute on Drug Abuse. Trends and Statistics. https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates [Accessed 2021-08-16]

[51] DeVane CL. Clinical pharmacokinetics and pharmacodynamics of anxiolytics and sedative/hypnotics. In: Jann M, Penzak S, and Cohen L, editors. Applied Clinical Pharmacokinetics and Pharmacodynamics of Psychopharmacological Agents. Adis, Cham: Springer. 2016. p. 1-39. https:// doi.org/10.1007/978-3-319-27883-4_10

[52] Bergman R, Kongsbak K, Sorensen PL, Sander T, and Balle T. A unified model of the GABA-A receptor comprising agonist and benzodiazepine binding sites. PLos One. 2013;8(1): e52323. doi: 10.1371/journal.pone.0052323

[53] Collinson N, Kuenzi EM, Jarolimek W, Maubach KA, Cothliff R, Sur C, Smith A, Otu FM, Howell O, Atack JR, McKernan RM, Seabrook GR, Dawson GR, Whiting PJ, and Rosahl TW. Enhanced learning and memory and altered GABAergic synaptic transmission in mice lacking the alpha 5 subunit of the $GABA_A$ receptor. J Neurosci. 2002; 22(13):5572-5580

[54] Kralic JE, Korpi ER, O'Buckley TK, Homanics GE, and Morrow AL. Molecular and pharmacological characterization of GABA(A) receptor alpha1 subunit knockout mice. J Pharmacol Exp Ther. 2002; 302(3):1037-1045

[55] Greenblatt DJ and Wright CW. Clinical pharmacokinetics of alprazolam. Therapeutic implications. Clin Pharmacokinet, 1993;24(6): 453-471

[56] Lasher TA, Fleishaker JC, Steenwyk RC, and Antal EJ. Pharmacokinetic pharmacodynamic evaluation of the combined administration of alprazolam and fluoxetine. Psychopharmacol. 1991; 104:323-327

[57] Greenblatt DJ, Divoli M, Abernathy DR, Moschitto LJ, Smith RB, et.al. Alprazolam kinetics in the elderly. Relation to antipyrine disposition. Arch Gen Psychiatry. 1983; 40:287-290

[58] Arendt RM, Greenblatt DJ, Liebisch DC, Luu MD, and Paul SM. Determinants of benzodiazepine brain uptake: lipophilicity versus binding affinity. Psychopharmacol. 1987; 93:7276

[59] Dehlin O, Kullingsjö H, Lidén A, Agrell B, Moser G, Olsen I. Pharmacokinetics of alprazolam in geriatric patients with neurotic depression. Basic Clin Pharmacol Toxicol. 1991; 68:121-124

[60] Ktoboth PD, McAuley JW, and Smith RB. Alprazolam in the elderly: pharmacokinetics and pharmacodynamics during multiple dosing. Psychopharmacol. 1990; 100:477-484

[61] Wright CE and Chambers JH. Influence of alprazolam input rate and steady-state pharmacokinetics on psychomotor performance in healthy subjects. Pharm Res. 1991; 8:250

[62] Garzone PD and Kroboth PD. Pharmacokinetics of the newer benzodiazepines. Clin Pharmacokinet. 1989; 16:337-364

[63] Dobbs FR, Banks W, Fleishaker JC, Valentine AD, Kinsey BM, Franceschini MP, Digenis GA, and Tewson TJ. Studies with [11C] alprazolam: an agonist for the benzodiazepine receptor. Nucl Med Biol 1995; 22(4): 459-466

[64] Miller LG, Greenblatt DJ, Barnhill JG, Deutsch SL, Shader RI, and Paul SM. Benzodiazepine receptor binding of triazolobenzodiazepines in vivo: increased receptor number with low-dose alprazolam. J Neurochem. 1987; 49:1595-1601

[65] Aurora RN, Zak RS, Maganti RK, Auerbach SH, Casey KR, Chowdhuri S, Karippot A, Ramar K, Kristo DA, and Morgenthaler TI. Best Practice Guide for the Treatment of REM Sleep Behavior Disorder (RBD). J Clin Sleep Med. 2010; 6(1): 85-95

[66] Schenck CH, Boyd JL, and Mahowald MW. A parasomnia overlap disorder involving sleepwalking, sleep terrors, and REM sleep behavior disorder in 33 polysomnographically confirmed cases. Sleep 1997; 20:972-981

[67] Schenck CH and Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal

sleep in 170 adults. Am J Med. 1996; 100:333-337

[68] Carter GS. Unpublished data. UT Southwestern. 2021. Dallas Texas

[69] Patel A and Carter, G. Electrocution as a rare cause of REM sleep behavior disorder. Sleep. 2019; 42(Abstract Suppl): A417

[70] Altamura AC, M. D., Paletta S, Maffini M, Mauri MC, and Bareggi S. Understanding the pharmacokinetics of anxiolytic drugs. Expert Opin Drug Metab Toxicol. 2013; 9(4):423-440.

[71] Sher PK and Machen VL. Benzodiazepine receptor affinity alterations at physiologic temperature after chronic clonazepam exposure. Brain Dev 1987; 9:33-36

[72] Galpern WR, Lumpkin M, Greenblatt DJ, Shader RI, and Miller LG. Chronic benzodiazepine administration. VII. Behavioral tolerance and withdrawal and receptor alterations associated with clonazepam administration. Psychopharmacol. 1991; 104:225-230

[73] Ellinwood EH, Nikaido AM, Gupta SK, Heatherly DG, and Hege S. Comparison of the relationship between structure and CNS effects for lorazepam, clonazepam and alprazolam. J Psychopharm. 1993; 7(1):24-32

[74] Ciraulo DA and Oldham M (2014). Sedative hypnotics. In: The Effects of Drug Abuse on the Human Nervous System. Madras B and Kuhar M, editors, New York: Elsevier; 2014. p. 499-532.

[75] Boeve BF, Silber MH, and Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med. 2003; 4:281-284

[76] Antón-Tay F, Días JL, and Fernández-Guardiola A. On the effect of melatonin upon the human brain. Its possible therapeutic implications. Life Sci-Part I-Physiol Pharmacol 1971; 10:841-850

[77] Lieberman HR, Waldhauser F, Garfield G, Lynch HJ, and Wurtman RJ. Effects of melatonin on human mood and performance. Brain Res. 1984; 323:201-207

[78] Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, Baker G, Klassen TP, and Vohra S. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. J Gen Intern Med. 2005; 20:1151-1158

[79] Moroni I, Garcia-Bennett A, Chapman J, Grunstein RR, Gordon CJ, and Comas M. Pharmacokinetics of exogenous melatonin in relation to formulation, and effects on sleep: A systematic review. Sleep Med Rev. 2021; 57:101431 https://doi.org/10.1016/j.smrv.2021.101431

[80] Facciolá G, Hidestrand M, von Bahr C, and Tybring G. Cytochrome P-450 isoforms involved in melatonin metabolism in human liver microsomes. Eur J Clin Pharmacol. 2001; 56(12):881-888

[81] Ma X, Idle JR, Krausz KW, and Gonzalez FJ. Metabolism of melatonin by human cytochromes P450. Drug Metabol Dispos. 2005; 33(4):489-494

[82] Fourtillan JB, Brisson AM, Gobin P, Ingrand I, Decourt JP and Girault J. Bioavailability of melatonin in humans after day-time administration of D(7) melatonin. Biopharm Drug Dispos. 2000; 21(1):15-22

[83] Zhdanova IV, Wurtman RJ, Balcioglu A, Kartashov AI, and Lynch HJ. Endogenous melatonin levels and the fate of exogenous melatonin: age effects. J Gerontol Series A, Biol Sci Med Sci. 1998; 53(4):8293-8298

[84] Proserpio P, Terzaghi M, Manni R, and Nobili L. Drugs used in parasomnia. Sleep Med Clin. 2020;15(2):289-300

[85] Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). An update for 2015. J Clin Sleep Med. 2015; 11(10):1199-1236

[86] Werneke U, Turner T, and Priebe S. Complementary medicines in psychiatry: review of effectiveness and safety. Br J Psychiatry; 2006; 188:109-121

[87] Rubio-Sastre P, Scheer FA, Gómez-Abellán P, Madrid JA, Garaulet M. Acute melatonin administration in humans impairs glucose tolerance in both the morning and evening. Sleep; 2014; 37:1715-1719

[88] Luboshitzky R, Shen-Orr Z, Nave R, Lavi S, and Lavie P. Melatonin administration alters semen quality in healthy men. J Androl; 2002; 23:572-578

[89] Valcavi R, Zini M, Maestroni GJ, Conti A, and Portioli I. Melatonin stimulates growth hormone secretion through pathways other than the growth hormone-releasing hormone. Clin Endocrinol; 1993; 39:193-199.

[90] Kierlin L and Littner MR. Parasomnias and antidepressant therapy: a review of the literature. Frontiers in Psychiatry. 2011; 2:71,1-71,8

[91] Winkelman J and James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep. 2004; 27:317-321

[92] Teman PT, Tippmann-Peikert M, Silber M, Slocumb NL, and Auger RR. Idiopathic rapid-eye-movement sleep disorder: associations with antidepressants, psychiatric diagnoses, and other factors, in relation to the age of onset. Sleep Med. 2009; 10:60-65

[93] Yeh Y, Chen C, Feng H, Wang SC, Kuo SC, and Chen CK. New onset somnambulism associated with different dosage of mirtazapine: a case report. Clin Neuropharmacol. 2009; 32:232-233

[94] Hoque R and Chesson AL. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: literature review, qualitative scoring, and comparative analysis. J Clin Sleep Med. 2010; 6:79-83

[95] Lam SP, Fong SY, Ho CK, Yu MW, and Wing YK. Parasomnia among psychiatric outpatients: clinical, epidemiologic, cross-sectional study. J Clin Psychiatry 2008; 69:1374-1382

[96] Pesikoff RB and Davis PC. Treatment of pavor nocturnus and somnambulism in children. Am J Psychiatry. 1971; 136: 1087-1088

[97] Lillywhite AR, Wilson SJ, and Nutt DJ. Successful treatment of night terrors and somnambulism with paroxetine. Br J Psychiatry. 1994; 164:551-554

[98] van Liempt S, Vermetten E, Geuze E, and Westenberg H. Pharmacotherapeutic treatment of nightmares and insomnia in posttraumatic stress disorder: an overview of the literature. Ann NY Acad Sci. 2006; 1071: 502-507

[99] Silber MH, Buchfuhrer MJ, Earley CJ, Koo BB, Manconi M, and Winkelman JW. The management of restless legs syndrome: an updated

algorithm. Mayo Clin Proc. 2021; 96(7):1921-1937

[100] Wallach JD and Ross JS. Gabapentin approvals, off-label use, and lessons for postmarketing evaluation efforts. JAMA. 2018; 319(8):776-778

[101] Landefeld CS and Steinman MA. The Neurontin legacy-marketing through misinformation and manipulation. N Engl J Med. 2009; 360(2):103-106

[102] Department of Justice. Warner-Lambert to pay $430 million to resolve criminal and civil health care liability related to off-label promotion. 2004 [press release]. https://www.justice.gov/archive/opa/pr/2004/May/04_civ_322.htm [Accessed 2021-08-15]

[103] Johansen ME. Gabapentinoid use in the United States 2002 through 2015. JAMA Intern Med.2018; doi:10.1001/jamainternmed.2017.7856

[104] GoodRx. The GoodRx top 10: July 2017. https://www.beckershospitalreview.com/supply-chain/10-most-popular-prescription-drugs-for-2017.html [Accessed 2021-08-16]

[105] Goa KL and Sorkin EM. Gabapentin. A review of its pharmacological properties and clinical potential in epilepsy. Drugs. 1993; 46(3):409-427

[106] Happe S, Klösch G, Saletu B, and Zeitlhofer J. Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. Neurology. 2001; 57:1717-1719

[107] Lee DO, Ziman RB, Perkins T, Poceta JS, Walters AS, Barrett RW and the XP053 Study Group. A randomized, double-blind, placebo-controlled study to assess the efficacy and tolerability of gabapentin enacarbil in subjects with restless legs syndrome. J Clin Sleep Med. 2011; 7(3):282-292

[108] Cundy KC, Branch R, Chernov-Rogan T, Dias T, Estrada T, Hold K, Koller K, Liu X, Mann A, Panuwat M, Raillard SP, Upadhyay S, Wu QQ, Xiang Jia-Ning, Yan Hui, Zerangue N, Zhou CX, Barrett RW, and Gallop MA. XP13512, a novel gabapentin prodrug: I. Design, synthesis, enzymatic conversion to gabapentin, and transport by intestinal solute transporters. J Pharmacol Exp Ther. 2004; 311:315-323

[109] Wilson EA, Sills GJ, Forrest G, Brodie MJ. High dose gabapentin in refractory partial epilepsy: clinical observations in 50 patients. Epilepsy Res. 1998; 29(2): 161-166

[110] Allen R, Chen C, Soaita A, Wohlberg C, Knapp L, Peterson BT, García-Borreguero D, and Miceli J. A randomized, double-blind, 6-week, dose-ranging study of pregabalin in patients with restless legs syndrome. Sleep Med. 2010; 11:512-519

[111] García-Borreguero D, Larrosa O, Williams A-M, Albares J, Pascual M, Palacios JC, and Fernandez C. Treatment of restless legs syndrome with pregabalin. A double-blind, placebo-controlled study. Neurology. 2010; 74:1897-1904

[112] Salinsky M, Storzbach D, and Munoz S. Cognitive effects of pregabalin in healthy volunteers. A double-blind, placebo-controlled trial. Neurology. 2010; 74:755-761

[113] Silber MH and Allen RP. Dopaminergic therapy of restless leg syndrome. In: Hening WA, Chokroverty S, Allen RP, and Earley CJ. Editors. Restless Legs Syndrome. Philadelphia: Saunders Elsevier; 2009. p. 238-254

[114] Moore TJ, Glenmullen J, and Mattison DR. Reports of pathological

gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. JAMA Intern Med. 2014; 174(12):1930-1933

[115] Kelley BJ, Duker AP, and Chiu P. Dopamine agonists and pathological behaviors. Parkinson's Disease. 2012; doi:10.1155/2012/603631

[116] Boehringer Ingelheim. Mirapex (pramipexole dihydrochloride) Prescribing information. 2007. http://us.boehringer-ingelheim.com [Accessed 2021-08-13]

[117] Schwartz Pharma, LLC. Neupro (Rotigotine transdermal system) 2012 https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021829s001lbl.pdf [Accessed 2021-08-13]

[118] Kaye CM and Nicholls B. Clinical pharmacokinetics of ropinirole. Clin Pharmacokinet. 2000; 39(4):243-254

[119] Morgenthaler TI, Auerbach S, Casey KR, Kristo D, Maganti R, Ramar K, Zak R, and Kartje R. Position paper for the treatment of nightmare disorder in adults: an American Academy of Sleep Medicine Position Paper. J Clin Sleep Med. 2018;14(6):1041-1055

[120] Jaillon P. Clinical pharmacokinetics of prazosin. Clin Pharmacokinet. 1980; 5:365-376

[121] Bateman DN, Hobbs DC, Twomey TM, Stevens EA and Rawlins MD. Prazosin pharmacokinetics and concentration effect. Eur J Clin Pharmacol. 1979; 16:177-181

[122] Taylor JA, Twomey TM and Schach von Wittenau M. The metabolic fate of prazosin. Xenobiotica.1977; 7(6):357-364

[123] Takita M, Taniguchi T, Zhu J, and Muramatsu I. Chronic treatment with prazosin causes a subtype-specific increase in the alpha-1-adenoceptor density of the stressed rat cerebral cortex. J Pharm Pharmacol. 1997; 49:802-805

[124] Raskind MA, Peskind ER, Chow B, Harris C, Davis-Karim A, Holmes HA, Hart KL, McFall M, Mellman, TA, Reist C, Romesser J, Rosenheck R, Shih M-C, Stein MB, Swift R, Gleason T, Lu Y, and Huang GD. Trial of prazosin for post-traumatic stress disorder in military veterans. N Eng J Med. 2018; 378(6):507-517

[125] Kaplan PW, Allen RP, Buchholz DW, and Walters JK. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. Sleep. 1993; 16:717-723

[126] Lauerma H and Markkula J. Treatment of restless legs syndrome with tramadol: An open study. J Clin Psychiatry. 1999; 60:241-244

[127] Walters AS, Wagner ML, Hening WA, Grasing K, Mills R, Chokoverty S and Kavey N. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. Sleep. 1993; 16:327-332

[128] Kavey N, Walters AS, Hening W, and Gidro-Frank S. Opioid treatment of periodic movements in sleep in patients without restless legs. Neuropeptides. 1988; 11:181-184

[129] Ondo WC. Methadone for refractory restless legs syndrome. Mov Disord. 2005; 20:345-348

[130] Becker PM. Opioid agents in the treatment of restless legs syndrome. In: Hening WA, Chokroverty S, Allen RP, and Earley CJ. Editors. Restless Legs Syndrome. Philadelphia: Saunders Elsevier; 2009. p. 255-261

[131] Walters AS, Winkelman J, Trenkwalder C, Fry JM, Kataria V, Wagner M, Sharma R, Hening W, and Li L. Long-term follow-up on restless legs syndrome patients treated with opioids. Mov Disord. 2001; 16:1105-1109

[132] Lugo RA, Satterfield KL, and Kern SE. Pharmacokinetics of methadone. Journal of Pain & Palliative Care Pharmacotherapy. 2005;19(4):13-24

[133] Caravati EM, Grey T, Nangle B, Rolfs RT, and Peterson-Porucznik. Increase in poisoning deaths caused by illicit drugs-Utah, 1991-2003. MMWR Morb Mortal Wkly Rep. 2005; 54(2):33-36

[134] Trenkwalder C, Benes H, Grote L, Garcia-Borreguero D, Hogl B, Bosse, B, Oksche A, Reimer K, Winkelmann J, Allen RP, and Kohnen R. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomized, placebo-controlled trial with an open-label extension. Lancet Neurol. 2013; 12:1141-1150