# PHARMACOLOGICAL TREATMENT OF SLEEP DISORDERS

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The Anatomy, Physiology, and Neurotransmitters of Sleep

Sleep is a rich set of physiology that is by convention divided into rapid eye movement (REM) and three non-REM sub-stages. Sleep circuitry consists of a balance between sleep promoting and wake promoting nuclei (Table 1). The sleep- and wake-promoting centers reciprocally inhibit each other in a "flip-flop" arrangement. The main sleep promoting center, VLPO, inhibits the multiple wake promoting nuclei in the brainstem, while the brainstem wake promoting nuclei project widely to both hemispheres (in addition to inhibiting the VLPO).

*Table 1. Sleep circuits and transmitters*

| Nucleus | Transmitter | Actions |
|---|---|---|
| Locus Ceruleus (LC) | Norepinephrine | Wake promoting |
| Dorsal Raphe (DR) | Serotonin | Wake promoting |
| Tuberomammillary Nuc. (TMN) | Histamine | Wake promoting |
| LDT/PPT[a] | Acetylcholine | Wake and REM promoting |
| Brainstem dopaminergic Nuc.[b] | Dopamine | Wake promoting (lesser role) |
| Basal Forebrain (BF) | Acetylcholine | Wake and REM promoting; adenosine inhibits, → sleep |
| Lateral hypothalamus (LH) | Orexin | Wake promoting |
| Ventrolateral pre-optic Nuc. (VLPO) | GABA | Sleep-promoting |

[a]Lateral dorsal tegmentum, pedunculopontine tegmentum
[b]Substantia nigra and periaqueductal gray

Insomnia and Hypnotic Pharmacology

Insomnia is defined by reported difficulty in sleep onset or sleep maintenance, associated with daytime symptoms or impairment. There is no requirement for objective testing, although there are several reasons to do so. For example, co-morbid sleep apnea or periodic limb movements of sleep may impact management. Some chronic insomnia patients have misperception: that they are sleeping more than they perceive.

Insomnia is an umbrella term with many sub-types, each with potentially distinct therapies. Pharmacological therapy for insomnia is not to be undertaken lightly, as the risks associated with hypnotic medications may outweigh the benefits, especially with long-term use. Recent data suggests that the previously documented medical impact of chronic insomnia is mainly associated with objective insomnia (i.e., understanding misperception is important). It is arguable whether hypnotic-assisted sleep is normal: many drugs change the sleep stage distribution (suppressing REM and/or slow wave sleep) and EEG characteristics such as spindle and higher frequencies. Reported risks include parasomnia, sleep-eating, hangover, morning driving risk, cognitive changes, falls, and even malignancy and all-cause mortality in some epidemiology studies. Finally, in head-to-head comparative trials, cognitive behavioral therapy for insomnia (CBT-I) is at least as effective as hypnotic therapy.

If hypnotics are used, after careful consideration of the risk-benefit balance, there are several classes of FDA approved and off-label agents used in practice.

GABA-A enhancement is the most common mechanism. Benzodiazepines (lorazepam, clonazepam, etc) showing broad activation of multiple receptor subtypes for hypnotic, anxiolytic, and anti-convulsant effects. The new generation "z-drugs" (e.g., zolpidem) act on a subset of benzodiazepine-sensitive GABA-A receptor, and thus have mainly hypnotic effects. They are sometimes called "non-benzodiazepines" because of their distinct chemical structure. Z-drugs tend to have shorter half life, but some traditional benzos also are short acting. Even the Z-drugs, however, have FDA warnings regarding hangover effect the next morning (especially in women; dose reduction is advised), including regarding motor vehicle accident risk.

Drugs with anti-histamine activity are sedating. Centrally acting anti-histamines such as diphenhydramine are used in various over-the-counter agents (e.g., “PM” formulations of pain medications). Hydroxyzine is a prescription anti-histamine that may have additional serotonergic and adrenergic activity.

Other over-the-counter agents include melatonin, and various supplements - many of which are not well studied (valerian, chamomile, 5-hydroxytrypophan). Melatonin has both chrono-therapeutic (below) and hypnotic potential. Of note, melatonin can raise INR values in those taking warfarin. A prescription synthetic melatonin analog, ramelteon, is also available for insomnia.

Several groups of drugs have been used, generally off-label, for insomnia because of sedation as a side effect. This may be due to anti-histamine or anti-cholinergic activity, among other possibilities. Such drugs include antidepressants (trazedone, mirtazapine, doxepin) and anticonvulants (gabapentin).

Most recently, the FDA approved a novel orexin antagonist, suvorexant, for insomnia. Orexin is a wake promoting peptide, among many other functions, and partial inhibition causes sleepiness (and can cause other symptoms of narcolepsy, which is associated with orexin deficiency in animals, and in humans with combined narcolepsy and cataplexy).

Hypersomnia and Stimulant Pharmacology

Excessive sleepiness can be difficult to differentiate from mimics ranging from chronic fatigue to depression. The most common cause of sleepiness is behavioral: insufficient sleep duration. However, it can occur because of underlying sleep disorders such as sleep apnea, narcolepsy, and idiopathic hypersomnia. Even some patients with treated sleep apnea continue to have sleepiness. We quantify the degree of sleepiness by performing a multiple sleep latency test (MSLT). This consists of a series of naps during the day, usually after an overnight sleep study to rule out sleep apnea or periodic limb movements of sleep. Interestingly, chronic insomnia patients are often not sleepy during the day, and do not show abnormal sleep pressure on MSLT. For narcolepsy patients, in addition to fast latencies, early entry into REM sleep occurs in two or more of the 5 nap test (and thus, REM suppressing agents should be discontinued, if possible, for several weeks beforehand).

Caffeine is the most widely used stimulant, and self-medication via coffee or other sources is common. Among those who require prescription stimulants, the two major classes are the amphetamine-derivatives, and modafinil and its sister armodafinil.

Amphetamines and there derivatives differ in their pharmacokinetics, and thus therapy can be guided by the timing of greatest symptom, but individual variability in response (and in adverse effects) may occur, and some trial and error may result. Cardiovascular and psychiatric adverse effects figure most prominently, as well as the abuse potential. A rapid resumption of sleepiness can occur in some, especially with short acting agents. The risks are thought to be lesser with modafinil and armodafinil, but caution is still advised (in addition, the latter can lower blood levels of oral contraceptives, and have been associated in rare cases with Stevens-Johnson reaction).

Cataplexy and anti-cataplectics

Half of patients with narcolepsy also have cataplexy, a transient loss of muscle tone in part or all of the voluntary musculature, most often triggered by laughter, with preserved consciousness. When cataplexy requires treatment, the first line of therapy includes REM suppressing anti-depressants, as the etiology of cataplexy involves intrusion of REM-atonia into wakefulness. Sodium oxybate may also be used, which improves the sleepiness and the cataplexy symptoms, although the mechanisms remain debated.

Pharmacology of Restless Legs Syndrome (RLS) and Periodic Limb Movements of Sleep (PLMS)

RLS is an uncomfortable sensation in the legs, worse at night or at rest, and better with movement. It is defined by clinical history, and does not require objective testing. It is genetically and pathophysiologically linked to PLMS, which occurs within sleep and can involve a range of movement amplitudes and patterns (generally toe/ankle dorsiflexion). At least 80% of patients with clinical RLS also have PLMS when measured in the sleep lab overnight, but only a small fraction of people with PLMS have any RLS symptoms (and thus the latter is often incidentally found on overnight sleep study recordings done for other reasons).

Iron deficiency has been linked to both RLS and PLMS. Oral (and rarely, parenteral) iron supplementation is pursued when ferritin is <50 as the first line of therapy. Oral iron should be taken between meals with vitamin C to aid absorption.

Dopaminergic agents are the first line prescription choice for patients requiring therapy. Pramipexole, ropinirole, and the patch rotigotine, are available treatments. Carbodopa-levodopa has also been used, but may be associated with increased incidence of augmentation (which can occur with other dopaminergics as well). Augmentation is an idiosyncratic worsening of RLS symptoms, and occurrence earlier in the day, during the course of chronic dopaminergic therapy.

Gabapentin enacarbil was recently approved for RLS, and pregabalin has been shown effective and with reduced augmentation risk but is not yet approved. Other agents are also discussed off label, including benzodiazepines, amantadine, and clonidine). Opiates are the last resort for refractory and severe cases.

Drugs to avoid in, if possible, due to potential worsening of the RLS or PLMS, include antidepressants (SSRI, TCA), caffeine, and alcohol.

REM Behavior Disorder (RBD)

RBD is related to pathological loss of normal atonia during REM sleep, resulting in dream enactment. RBD has been linked to later development of Parkinson's disease or related disorders; it can also occur concurrently with a variety of other neurological disorders. For some, the dream enactment can be violent and result in self-injury or injury to the bed partner. In addition to routine bedroom safety measures, drug therapy may be indicated to suppress these events. However, risk-benefit discussions are, as usual, important in this setting, as the most commonly used drug, clonazepam, itself carries some risks, especially in older populations in whom RBD is more common. Melatonin can be used in combination with clonazepam, and in some cases may be effective in isolation. Higher doses (6-12mg) of melatonin are often used, compared to the lower doses typically used for sleep and circadian purposes. Although the diagnosis can be made by history in most cases, an overnight in-lab sleep study may be helpful in uncertain cases, as REM without atonia can be observed even if the patient does not have a clinical event on that night. Also, some prefer formal testing if benzodiazepines are to be used, to rule out sleep apnea (which could be worsened by benzos).

Certain drugs can theoretically worsen RBD, due to interference with REM atonia pathways, such as antidepressants (SSRI and TCA). However, it is uncertain what portion of RBD patients can be treated simply by removing such contributors.

Circadian Disorders and Chronotherapy

Circadian rhythm disorders are treated with a combination of light, melatonin, and scheduling. The timing of these chronotherapies is important, relative to the endogenous rhythm. In the lab, the rhythm is measured by core body temperature or other invasive measures. Clinically, one can often surmise the endogenous rhythm by diary, or actigraphy monitoring as a surrogate. Melatonin given before the circadian nadir (typically about 4 hours after habitual sleep onset time) tends to move the clock earlier, while light during this time tends to push the endogenous clock later. Light in the morning tends to anchor the clock to early rising.

The most common circadian problem in adolescents and young adults is delayed sleep phase, or the "night owl" phenotype. When treatment is required, one begins with melatonin about 2-3 hrs before their habitual bed time (often far after midnight), ensuring darkness until rise time, at which point bright light is used. Every 2-3 nights the schedule (and the timing of melatonin and light) is moved 30 minutes earlier, until the desired timing of sleep is reached.

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