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INVITED REVIEW

Drug-induced sleep: theoretical and practical considerations

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Abstract Faithful replication of normal sleep through medications—can it be achieved? Departure from normal sleep with the use of drugs—when is it desired? Answers to these questions depend on accurate understanding of sleep and on concrete criteria upon which to define it. Since these elements are evolving sciences, as yet incompletely known, one might take a nihilistic approach that we simply cannot judge whether we have successfully replicated sleep, since we do not fully grasp what sleep is or what it does. To address these potential obstacles, our article is written in two sections. The first addresses theoretical considerations for how medications might be seen in the larger framework of sleep. The purpose of this section is to inform readers about key issues in evaluating whether a drug has sufficient data to persuasively argue it is re-creating sleep. (We hope that researchers interested in conducting studies, or critical readers of the drug-study literature, might find this section particularly useful.) The second section of this article approaches exemplary, current concepts of pharmacologic manipulation of sleep, organized by disorders as articulated by the International Classification of Sleep Disorders (2005). This second section will combine practical knowledge of clinical sleep medicine, with emphasis on contemporary knowledge about molecular mechanisms that are felt to underlie some of these phenomena. We recognize that our collective knowledge about sleep will advance in the coming years. We hope that this article serves to facilitate that advance.

Keywords Sleep · Sleep disorders · Slow-wave sleep · Sleep-inducing drug · Pharmacology · Sleep apnea · Receptor

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Part 1: theoretical considerations

The obvious cannot be overstated: it is critical to clearly define sleep, when considering whether a drug induces that same biological state. While a full discussion is beyond the scope of this article, the inclined reader might consider detailed articles about the nature and purpose of sleep [20, 61].

Broadly speaking, the definition of sleep includes observed physiology (objective measures) and reported experience (subjective measures). But which objective measures, and which subjective measures? And what if objective and subjective measures dissociate, as can be observed by, for example, a mismatch between how much people report they slept and how much our observational techniques quantify their sleep? Consider four possibilities when confronted with a mismatch: (1) The person's subjective experience of sleep is inaccurate. (2) Our laboratory

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observations are inaccurate. (3) Both are inaccurate. (4) Both are measures of distinct processes. Take an example of a person who consumes drug X for a night of sleep. If a side effect of drug X includes anterograde amnesia (i.e., the inability to form new memories), then under the condition of drug X throughout the night, the person might overestimate how much he/she slept, if, having awoken for a while in the middle of the night, he/she was unable to remember the awakening event. Subjective experiences are reliant on accurate time perception and memory therein. Subjective experiences, furthermore, might be influenced by personality, mood, and other factors. They are not necessarily accurate surrogates for objective measures of sleep. Subjective reporting of sleep, accurate or not, provides useful information about the subject's experience of sleep. And that is how those data are best used.

Objective measures of sleep, particularly electroencephalography (EEG), supply outstanding contributions to quantifying sleep. But while the staging of sleep has enjoyed a long and meaningful tradition in sleep medicine and in sleep science, the objective quantification of sleep stages maintains some vagueness and capacity for human error. Furthermore, summarizing data from EEG, eye movements, and muscle tone by 30-s epochs into five discrete categories (i.e., wake, N1, N2, N3, REM) is not an objective truth so much as an agreed level of resolution with which to summarize data—a convention. Natural and man-made boundaries are often not one and the same. With improved signal-processing techniques, there is diminishing reason to preserve these standards as the singular metrics of value when objectively quantifying sleep. It should also be noted that EEG, with its outstanding objective measures, provides information about emerging properties of the brain at the cortical surface. High-density EEG, MEG, and other modalities have the potential to provide greater spatial resolution, including deep structures in the brain [53, 76]. Signal processing of EEG (e.g., fast Fourier transform) is now widely available as a technique for objective quantification of EEG energy and should complement, and possibly supplant, visual scoring. The selection of bandwidths to examine (e.g., 8–13 Hz) should be principled, however, or these techniques will be subject to some of the problems already existing in conventional, visual inspection of EEG.

Among the components to evaluate, beyond the physiology that takes place during sleep, are the consequences of healthy sleep. A number of physiologic properties are influenced by sleep. A medication that induces sleep ought to, it follows, cause the same outcome as natural sleep itself. Given, for example, that sleep facilitates memory consolidation [27] and cortical plasticity [4], one would expect similar cognitive performance after sleeping with a medication purported to induce sleep. Metabolism [18], immunologic function [55], and cardiovascular function [17] are among those physiologic processes that are influenced by sleep. Drug-induced sleep should contribute similarly to these systems—as it would in normal sleep—if we are to characterize the sleep induced by the drug as equivalent to natural sleep. Trazodone and zolpidem, for instance, appear to interfere with the effects of sleep, when examining a model of cortical plasticity [3, 94]. Many more drugs have simply not been tested across a wide range of physiologic consequences of natural sleep, impeding our ability to judge them as faithfully replicating sleep.

Another area to keep in mind, when evaluating a medication's plausibility as a sleep-inducing molecule, includes the network of brain systems that generate the various aspects of sleep. Bathing the brain in a sedating molecule, for example, seems inconsistent with the complex physiology felt to underlie the dynamic processes of sleep. (For contemporary models of human sleep physiology, see [14, 90].)

It is worth noting that perfectly replicating natural sleep is not necessarily ideal. It might be that certain parts of sleep are most advantageous in certain situations, and we might benefit from maximizing these particular components. Slow-wave sleep (SWS), for instance, has been invoked in a number of cognitive processes [11, 110]. Perhaps, boosting SWS could boost cognitive performance. Similarly, as we will describe later, there might be certain disease states that take place in one physiological state of sleep or another. REM sleep behavior disorder (RBD), for instance, takes place in REM sleep. Perhaps a molecule that can reduce or eliminate REM sleep would be advantageous in that setting.

In summary, a sleep drug will look and behave like sleep, both with respect to objective and subjective measures during sleep, cognitive and physiologic outcomes as a consequence of sleep, and should have biological plausibility with known brain dynamics. And select situations might make departure from normal sleep physiology advantageous.

Part 2: drugs for diseases of sleep—clinical and molecular considerations

Insomnia

Benzodiazepines (BZDs) are pharmacologic agents commonly used for sedation. They are a class of synthetic molecules that modulate the class A gamma-aminobutyric acid receptor ($GABA_A$ receptor). When activated by GABA, the chloride ion channel of this receptor leads to membrane hyperpolarization and neuronal inhibition. BZDs do not activate the receptors themselves but potentiate the affinity of the $GABA_A$ receptor for GABA, allowing it to exert a greater effect by being bound longer and increasing the opening frequency of the chloride ion channel [8].

The $GABA_A$ receptor is a pentameric structure, each subunit of which consists of four transmembrane domains (the second from the N terminus forms the channel wall). The most abundant subunits are termed α, β, and γ, and these exist in six, three, and three isoforms, respectively. The $GABA_A$ receptor typically consists of two α, two β, and one γ subunits [85]. Junctions between α and γ subunits form the site at which BZDs exert their effect. In the central nervous system, endogenous GABA molecules bind to the junction of α and β subunits on the $GABA_A$ receptor. Simultaneous binding of BZD molecules serves to potentiate the ability of GABA to hyperpolarize the membrane to which it is bound [104].

Different α subunits are now believed to be responsible for the diverse pharmacological effects of BZDs [64, 65, 71, 85, 86]. The somnogenic effects of classical BZDs are mediated by actions at benzodiazepine sites containing α_1 subunits. This finding has led to the development of new BZDs, the "z-drugs," including zolpidem, zaleplon, zopiclone, eszopiclone, and indiplon. (They are commonly called "non-benzodiazepines" because they have a molecular structure that is distinct from benzodiazepine, but this terminology can be misleading because they still work via the benzodiazepine site of the $GABA_A$ receptor, as do traditional BZDs.)

These newer molecules primarily bind to receptors containing the α_1, β, and γ_2 subunits [56, 64, 71, 104]. Although zolpidem displays some affinity for receptors containing α_2 and α_3 subunits, its hypnotic effects are mediated primarily by the $\alpha_1\beta\gamma_2$ BZD site [23]. Zolpidem can therefore, purportedly, exploit the sedative hypnotic effects of BZDs while limiting diverse effects of classical BZDs (e.g., anxiolytic, addictive, amnestic, motor, cognitive) [97]. However, unlike zolpidem, zopiclone and its S-enantiomer, eszopiclone, bind equally to receptors containing multiple α subunit isoforms, and specific interactions of eszopiclone within the BZD binding site account for its specifically hypnotic effects [42].

The above effects of GABA and sedative–hypnotic drugs focus on phasic, synaptic effects on postsynaptic membranes. However, recent evidence suggests that tonic inhibition mediated by lower levels of GABA acting on extrasynaptic $GABA_A$ receptors may also play important roles in the regulation of neuronal excitability and the effects of hypnotic drugs [115]. It appears that the ability of tonic inhibition to effect ion conductance is partly mediated by the subunit composition of the $GABA_A$ receptor [37]. Although the above-described $\alpha_1\beta\gamma_2$ $GABA_A$ receptors contribute to this extrasynaptic tonic inhibition, the majority of this effect arises from $GABA_A$ receptors in which the δ subunit substitutes for the γ_2 subunit and α_4 substitutes for the α_1 subunit [115, 118]. Receptors that contain the δ subunit have a higher affinity for GABA [115]. Non-neuronal, glial release of GABA may be especially important in regulating extrasynaptic GABA levels involved in tonic inhibition [50], and drugs targeting these receptors such as gaboxadol (THIP) are showing promise as novel treatments for insomnia [108]. This interesting molecule has a more pronounced effect on $GABA_A$ receptors containing δ isoforms, but it will also activate γ isoforms.

In addition to the location of $GABA_A$ receptors containing different subunits on the neuron itself, the anatomical localization of diverse $GABA_A$ receptors within the brain determines both the therapeutic effects and side effects of drugs that target these receptors [104, 115]. For example, $GABA_A$ receptors in limbic areas are responsible for anxiolytic effects of BZDs, whereas those specifically localized to the hippocampus are likely to mediate the amnestic effects of classical BZDs [104]. The high expression of δ subunit-containing $GABA_A$ receptors in the thalamus may allow drugs such as gaboxadol to regulate the expression of the thalamocortical oscillations crucial to NREM sleep [108]. It should also be noted that at localized sites in the mesopontine brainstem, higher levels of GABA may actually promote wakefulness at the expense of REM and NREM sleep due to the complex circuits of inhibition and disinhibition involved in switching behavioral states [113].

Traditional benzodiazepines, such as temazepam, reduce N1 and SWS and increase N2, and they increase the rate of sleep spindles [10, 47, 48, 82]. It is not known if these spindles are physiologically identical to those produced in normal sleep. Spectral power in delta frequencies is reduced by both acute [99] and chronic [6] benzodiazepine use. The newer z-drug benzodiazepines also modestly expedite the onset and increase the duration of sleep. Unlike traditional benzodiazepines, however, these drugs do not tend to influence traditional measures of sleep stages, although zopiclone (but not eszopiclone) reduces SWS and REM at higher doses [81, 109]. [For a detailed review, see [80].

A number of other GABA-related drugs have been investigated for utility in sleep medicine. For example, the selective GABA reuptake inhibitor tiagabine has been found to enhance both sleep continuity and SWS in middle-aged [112] and elderly persons with insomnia [84, 112] as well as in cocaine users [67]. This increase in SWS—conferred by tiagabine—appears to mend the daytime, behavioral consequences of sleep deprivation [111].

Although originally developed as structural analogs of GABA, gabapentin and pregabalin target the α2-δ ($Ca_v\alpha2$-δ) protein subunit of the voltage-gated calcium channel thereby reducing the synaptic release of excitatory neurotransmitters [100] such as substance P, serotonin, norepinephrine, and dopamine [102]. Gabapentin and pregabalin are employed by sleep medicine in the context of pain-related sleep

disruption due to fibromyalgia [87] and other chronic pain syndromes [2, 98].

Antagonists of the neuropeptide, orexin (hypocretin), are under development as novel treatments for insomnia [12, 93]. Orexin is produced by neurons in the perifornical and lateral hypothalamus that project to, excite, and maintain the sustained activity of wake-promoting aminergic neurons in the posterior hypothalamus, locus coeruleus, and dorsal raphe as well as arousing cholinergic systems in the basal forebrain and mesopontine brainstem [89, 90, 93]. When this drive is attenuated in narcolepsy with cataplexy, an orexin-deficient condition, the mutually inhibitory circuit between the sleep-promoting ventrolateral preoptic area of the anterior hypothalamus and multiple brain arousal systems produces abnormally rapid shifts from waking to sleep [90].

The orexin protein exists in two forms, A and B, that bind to two G-protein-coupled receptors, OR-1 and OR-2, that both induce membrane depolarization [34]. As orexin is a key player in the normal sleep–wake transition [90], antagonists of orexin receptors have become targets for investigational drugs to treat insomnia. A number of orexin antagonists are under development as potential insomnia treatments including almorexant [69] and suvorexant [114], both of which antagonize both OR1 and OR2 receptors. Clinical studies in rats, dogs, and humans demonstrate reduced alertness when using this class of medications, leading to a faster onset of sleep, greater ability to maintain sleep throughout the night, and increased energy in delta and theta bands [12].

A number of psychoactive drugs developed to treat neuropsychiatric disorders have come to be used as medications for sleep. These include the atypical antipsychotic quetiapine as well as the antidepressants trazadone, mirtazepine, and older tricyclic antidepressants such as amitriptyline and doxepin. The somnogenic mechanism of quetiapine is believed to be due to its H1 antihistaminergic properties [22] although its D1 antidopaminergic effects, alpha-1 noradrenergic antagonism, and serotonergic effects (see below) may also contribute to its sleep promotion [22]. Blockade of serotonin 5HT-2A and 5HT-2C receptors is known to augment SWS [24, 54], and 5HT-2A/C antagonism may account for the somnogenic effects of trazadone and mirtazepine as well as the atypical antipsychotics quetiapine [35] and olanzapine [95]. Similarly, sedating effects of tricyclic antidepressants such as trimipramine, amitriptyline, and doxepin are linked to antihistaminergic as well as 5HT-2 antagonist effects [52, 79]. [For a review of this topic, see citation [59].

Hypersomnias of central origin

This set of disorders is grouped by a state of sleepiness during the daytime that cannot be accounted for by sleep disruption alone. The brain seems to be driving toward a state of sleep within waking hours. Normal control mechanisms that stabilize and initiate sleep are felt to be unbridled in this disorder, and as such, there is instability of the system to maintain wake and sleep as two distinct, stable systems [25, 92]. None of the disorders in this category are common, but the most prevalent among them is narcolepsy.

Treating narcolepsy requires attention to three levels: cataplexy, daytime sleepiness, and difficulty sleeping. (For a detailed discussion, see [25].) At its core, narcolepsy is felt to be a disorder in which elements of REM sleep, in particular, intrude into wakefulness [25, 92]. As such, the signs and symptoms of narcolepsy are felt to be fragments of REM sleep impinging on wakefulness. These include cataplexy and sleep paralysis (impaired motor tone in wakefulness and in transitions between wake and sleep, respectively), sleepiness, and hypnogogic hallucinations (i.e., dream-like mentation at the interface of sleep and wakefulness). Pharmacologic approaches include inhibiting REM sleep, as seems to be achieved through certain antidepressant medications such as venlafaxine or through an entirely different compound: gamma-hydroxy butyrate (GHB), which targets the $GABA_B$ receptor [62].

The $GABA_B$ receptor is a heterodimer consisting of a pair of G-protein linked receptors ($GABA_{B2}$ and $GABA_{B1}$) that exist as two distinct subtypes defined by the two isoforms of $GABA_{B1}$ termed $GABA_{B1a}$ and $GABA_{B1b}$ [30, 103]. The $GABA_B$ receptor exists as both presynaptic auto- and heteroreceptors as well as postsynaptic receptors, the latter of which induce inhibitory postsynaptic potentials [103]. $GABA_B$ receptors also exist on glia.

At physiological levels, GHB is an endogenous neurotransmitter with specific receptors [74]. During treatment of narcolepsy, using its sodium salt (sodium oxybate), GHB acts as a $GABA_B$ receptor agonist. This agent has the capacity to increase SWS and to reduce the symptoms of narcolepsy [9].

Although not typically used in sleep medicine, baclofen has also been shown, like GHB, to exert somnogenic effects, increase SWS, and improve sleep continuity through the $GABA_B$ pathway [13, 45]. Experiments with $GABA_B$ receptor sub-unit knock-out mice demonstrate the role of the $GABA_B$ receptor in the effects of both GHB and baclofen on sleep physiology [106]. However, because GHB, but not baclofen, improved excessive daytime sleepiness and cataplexy in narcoleptics, $GABA_B$ agonism cannot be the only clinically significant pharmacological action of GHB [45]. Therefore, the endogenous GHB receptor system may also be involved in its therapeutic effects. The endogenous GHB receptor system operates at physiological levels of GHB insufficient to activate $GABA_B$ receptors. It is characterized by calcium-dependent

release in response to presynaptic membrane depolarization, G-protein-linked binding sites, brain regional differences in both release and binding sites, as well as an active reuptake mechanism [74].

The profound sleepiness experienced by disorders such as narcolepsy often requires introduction of compounds that protect the waking state from sleep during desired waking hours. Traditional psychostimulant drugs, such as dextroamphetamine, serve to oppose sleep onset, thereby providing some relief to people with excessive sleepiness such as those with narcolepsy. These drugs also appear to suppress REM sleep [19, 70]. Modafinil, however, does not appear to alter normal sleep architecture [83]. In fact, when cocaine users attempt abstinence protocols, their sleep tends to deteriorate in the ensuing days. Providing these people modafinil during the daytime appears to normalize their sleep at night [68].

The most commonly available and widely used molecule for stimulant effect is caffeine. Caffeine is a non-selective antagonist of adenosine receptors which are G-protein-coupled metabotropic receptors existing in four forms (A1, A2A, A2B, and A3) of which A1 and A2A mediate most CNS effects related to sleep and waking. Activation of the A1 receptor by extracellular adenosine that has accumulated as a product of waking metabolism is believed to constitute an important endogenous somnogen and the basis for the homeostatic control of sleep propensity [77]. The primary site of action for the sleep-promoting effects of adenosine that are proportional to preceding time awake (homeostatic sleep pressure) is believed to be A1 receptors on wake-promoting basal forebrain cholinergic cells that project to and activate the cortex and desynchronize the EEG [5, 77], although a role for A2A receptors in the hypothalamus has also been proposed [31]. Although sleep homeostatic effects of adenosine occur at the A1 receptor, the site of caffeine's arousal and psychomotor stimulant effects occurs at post-synaptic A2A receptors on medium spiny neurons in the basal ganglia [33, 46] and specifically in the shell of the nucleus accumbens [57]. Lazarus and colleagues [57] propose that blockade of nucleus accumbens shell A2A receptors prevents adenosine from maintaining these neurons' tonic GABAergic restraint of wake-promoting noradrenergic, orexinergic, and histaminergic neurons of the hypothalamus and brainstem, thereby shifting the balance of a putative hypothalamic sleep–wake flip–flop switch [90] in favor of a stable waking state. Caffeine may also effect psychomotor stimulation by increasing the ability of dopamine to stimulate indirect-pathway D2 receptors that are components of mutually antagonistic A2A/D2 receptor–receptor heterodimers [32, 33] (an arousal-promoting effect of caffeine that shares the mechanism of enhancing of striatal dopaminergic neurotransmission with the classical psychostimulants).

A largely unexplored area of research is the effect of caffeine on "local" sleep (i.e., expression of sleep-like electrophysiology along restricted areas of the brain's cortex). This has been suggested to reflect local, prior-waking activity [51]. Astrocytic release of adenosine that then inhibits local neurons by binding to A1 receptors may allow localized emergence of sleep oscillations such as the slow oscillation (i.e., <1 Hz) oscillation [38]. Since caffeine is a non-selective adenosine receptor antagonist, it may also affect the A1-mediated physiology subserving sleep-like dynamics in localized neural networks in addition to its psychostimulant action at striatal A2A receptors.

For disorders such as narcolepsy, prescription-grade stimulant medication is often needed. In addition to drugs for sleep promotion, drugs to prevent sleep at undesired times are employed in sleep medicine to treat excessive daytime sleepiness due to narcolepsy, obstructive sleep apnea, and other conditions. Among prescription drugs, modafinil has been used as an alternative to traditional amphetamine and amphetamine-like stimulants, such as methylphenidate, that are potent reuptake inhibitors at monoaminergic transporters as well as inducers of monoamine reverse transport [49].

More recently, modafinil's R-enantiomer, armodafinil, is also available. Determining the mode of action of these substances has lagged far behind their clinical use [36]. Modafinil shows activity at multiple sites, including evidence for a weak blockade of transporters of norepinephrine (NET) and dopamine (DAT) [36]. Although some antagonist studies have suggested the relatively greater importance of DAT [116], other studies suggest that noradrenergic stimulation of dopaminergic neurons also makes NET blockade important to wake promotion by modafinil [63]. Both D1 and D2 receptors are involved in the wake-promoting effect of modafinil [78], and a recent PET study using (^{11}C)raclopride and (^{11}C)cocaine showed that modafinil can block dopamine transporters and elevate dopamine levels in the human brain [107]. Most recently, it has been suggested that modafinil augments electrical coupling among cells of the ascending reticular activating system such as those of the pedunculopontine tegmental nucleus [7].

Sleep-related breathing disorders

Second to insomnia, one of the most common sleep disorders is sleep apnea, particularly obstructive sleep apnea (OSA). Given that the underlying pathology of this disorder centers around a mechanically obstructive process of the upper airway, the mainstay of treatment in OSA focuses on physical interventions that splint the airway open while asleep. Continuous, positive airway pressure is the most common treatment. Dental devices and surgical procedures remain alternatives in certain situations.

OSA is often most severe during REM sleep physiology and is sometimes exclusively a problem during this sleep

stage. This is likely due to the fact that, in REM sleep, somatic muscles are most relaxed (due to an active inhibitory process in the brainstem and spinal cord), and these include muscles in the upper airway, leading to increased likelihood of impeded airflow in this sleep state. From a pharmacologic perspective, it is tantalizing to consider that the reduction of REM sleep via certain antidepressant medications might reduce the burden of OSA simply by removing the state of sleep in which the upper airway is most vulnerable to collapse. This is an area of ongoing investigation along with other potential pharmacologic approaches to aspects of sleep apnea [88].

It is also worth noting that narcotic pain medications can induce central sleep apnea (CSA) events by suppressing respiratory centers in the brain. Other causes of CSA include congestive heart failure, severe kidney disease, or high altitude. Given that bicarbonate is a major driver for the impulse of breathing during sleep, attempts have been made to employ acetazolamide in order to stimulate breathing. (For a full discussion of CSA, see [29, 58].)

Sleep-related movement disorders

The disorder of restless leg syndrome (RLS), diagnostically speaking, is a disorder of wakefulness. But it has two key features that involve sleep. First, there is a circadian element to the symptoms of discomfort: the urge to move is worse in the evening and therefore can hinder the initiation of sleep. Furthermore, 90% of people with RLS have periodic limb movements during sleep (PLMS), which can awaken people at night. (It should be noted that while most people with RLS have PLMS, most people with PLMS do not have RLS.)

Currently, the first line of medications for this disorder is dopaminergic agents. These drugs exert presynaptic influence on spinal cord interneurons regulating afferent inputs and their sensory projections in the dorsal horn [75]. Because dopaminergic influence serves to inhibit rostral transmission of sensory input, its impairment may disinhibit these circuits leading to the sensory symptoms of RLS [21]. Such dopaminergic modulation originates in descending inputs from dopaminergic neurons in the A11 region of the posterior hypothalamus, the sole endogenous source of spinal cord dopamine [21]. Periodic leg movements that frequently accompany RLS [101] are also treated via dopaminergic drugs. This is accomplished by added suppression of spinal early flexor reflexes triggered by baseline peripheral sensory inputs (e.g., mechanoreceptive, nociceptive, joint) that, under normal circumstances, are tonically inhibited by endogenous dopaminergic input from A11 [75]. Studies showing increased flexor reflexes in D3 receptor knock-out mice suggest that abnormalities of this receptor may be involved in RLS symptomatology [75]. Alternatively, degeneration of hypothalamic A11 dopaminergic neurons may contribute to RLS pathology [21, 101].

Circadian rhythm sleep disorders

Melatonin is a hormone that is released from the pineal gland, under the control of the suprachiasmatic nucleus (SCN) in the anterior portion of the hypothalamus. This naturally occurring molecule has peak levels at night and is inhibited from release by light. Melatonin has been widely used to treat a variety of sleep conditions, including endogenous circadian misalignment (e.g., delayed sleep phase syndrome), insomnia, and RBD [105] as well as jet lag, shift work, and other environmental misalignments of circadian rhythm with the timing of sleep [96] and circadian rhythm disturbances associated with the dementias [26]. Melatonin secretion is controlled by the SCN, the master circadian pacemaker, via a multisynaptic pathway through the hypothalamic paraventricular nucleus and sympathetic ganglia of the upper spinal cord [16]. Melatonin targets melatonin MT1 and MT2 receptors—G-protein-linked receptors present in many brain structures, including the SCN itself [72].

Beyond the use of melatonin to adjust the position of the circadian clock, to align it with sleep–wake cycles in circumstances such as jet lag or delayed circadian phase syndrome, melatonin also can modestly expedite sleep onset and increase total sleep time. When using relatively high doses (e.g., 5 mg), melatonin can increase REM sleep and alter non-REM sleep by reducing energy in delta and theta bands, but increasing sigma power [15, 28, 117].

Drugs acting as melatonin agonists, including ramelteon and tasimelteon, target both melatonin receptors and have greater receptor affinity and longer duration of action than melatonin itself [43, 66]. These medications are not used for circadian disorders but for insomnia. Like melatonin, they show modest increases in the total amount of sleep and no obvious overall change in sleep architecture, when examining traditional measures. For a thorough review of ramelteon trials, see [91].

Parasomnias

Behavior during the night can manifest during what otherwise appears to be sleep. These events can become problematic enough to be considered a medical disorder. The disorders are as diverse in character and severity as the people who are affected by them. Events range from simple and common sleepwalking or talking to more complex surges of panic or dream enactment. Fundamentally, these phenomena might offer a window into our understanding of the mechanisms of sleep by exposing activities of the brain when only partially awake.

The decision of whether or not to use medications for these disorders can be complex. Once that decision is reached, though, one of the most common approaches is to use a benzodiazepine as a sedative. The idea includes the notion that the brain, during parasomnia events, is partially awoken, and the sedative medication helps prevent that partial disruption of sleep.

Interestingly, one parasomnia disorder, RBD, is paradoxically made worse by the use of REM-suppressing medications such as antidepressants [44]. This raises fundamental issues about whether antidepressants do, in fact, suppress REM sleep or whether, instead, they suppress elements of REM sleep. It is possible, for instance, that antidepressants preferentially suppress the motor-inhibiting elements of REM sleep and, as such, unleash RBD events among those that have the disorder.

Novel concepts

Sleep is a complex, dynamic set of physiologic processes. As such, consuming a molecule at the beginning of the night, intended to exert a stable influence on sleep, would only seem to work effectively if it were exerting its influence through the naturally occurring systems in the brain. Current medications, however, might not afford the complex fluctuations of natural sleep systems to be manifest. We find it tantalizing to consider a drug-delivery system that more fully engages natural sleep physiology. Further, future medication might optimize its effect by strategically timed delivery during key moments of sleep that are more vulnerable than others. For instance, tracking alpha power could provide instantaneous information about moments of sleep that are more stable than others [60].

Another challenge for any existing sleep medication is that there is, at times, the need to interrupt sleep unexpectedly. An on-call physician, fireman, ship captain, and many other professions require on-demand disruption of sleep. This adaptive mechanism could take the form of a medication that is either quickly reversible or a medication delivery system that can be arrested based on measures of the environment (e.g., a smoke alarm in a building would interrupt the online delivery of a sleep medication). In the future, for instance, one might optically drive sleep spindles [41]—a sleep-inducing process that might be instantaneously interrupted, if the need arose.

Finally, we find it important to continue to update ourselves, periodically, regarding developing concepts within brain science and sleep dynamics, such that novel opportunities for therapeutic targets can be leveraged. For instance, novel concepts in neuromodulation include molecules such as neuropeptide S [73] and glial cells [39, 40]. These might play key roles in the modulation of neurons that govern sleep systems and therefore become enticing targets for modulation of sleep.

Summary

Through this article, we attempted to articulate a set of principles to consider when evaluating whether a drug has faithfully reconstructed sleep and when a departure from that ideal is desired. We suggest considering a broad set of objective and subjective measures, and their potential disparity, as well as embracing signal-processing technology for objective measurements. When assessing whether a drug accurately mimics sleep, we described the need for evaluating not only what happens during sleep, objectively and subjectively, but also to evaluate the consequences of sleep resulting from use of that drug. We have described some current clinical concepts and available knowledge of their underlying molecular actions. We presented exemplary novel concepts to consider in advancing the topic of drug-induced sleep to include novel systems and novel delivery methods. Finally, the concept of drug-induced sleep is an area of active ongoing investigation and will evolve in the coming years.

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