

Toward a classification of medications for sleep and circadian rhythm disorders

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Abstract: While some systems classify medications according to therapeutic class, others are based on the mechanism of action of the drugs. The two main classifications of medications used to treat patients in the United States are those of the United States Pharmacopeia and US Food and Drug Administration, and they vary in their organization of the medication categories. Here we propose a taxonomy for medications used to treat sleep and circadian rhythm disorders based on symptoms and disorders.

Keywords: circadian, sleep, taxonomy, classification, diagnosis

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To facilitate health care decisions and clinical research, physicians, scientists, patients, insurers, hospitals, and other entities find it helpful to list drugs into classification systems. Most systems are organized around therapeutic mechanisms, organ systems, diseases, and chemical characteristics. Therapeutic classification may reflect the condition for which drugs are used – including, for example, antidepressants, antihypertensives, and antipsychotics – or the salient chemical characteristics of a drug class (eg, benzodiazepines, thiazolidinediones). Although some drugs are classified under one drug class, as the therapeutic benefit of some drugs can extend to multiple conditions, several listings are occasionally used. Basic research frequently classifies drugs based on chemical structure or binding characteristics. For example, beta-lactams comprise a diverse group of antibiotics, all of which prevent bacterial cell wall synthesis and possess a beta-lactam ring as one element of their chemical structure.¹ Similarly, nuclear receptors are a class of agents that bind DNA and affect the expression of genes.²

For drugs used clinically, the best systems are based on clinical indications since they provide the prescriber with information about the condition for which the drug is prescribed. The United States Pharmacopeia (USP)³ classification takes this approach by having clinical categories such as cardiovascular agents and anticonvulsants. Each of these broad categories is subdivided according to mechanism of action: cardiovascular agents are subdivided into α -adrenergic agonists, α -adrenergic blocking agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, antiarrhythmics, β -adrenergic blocking agents, calcium channel blocking agents, diuretics (carbonic anhydrase inhibitors, loop, potassium-sparing, and thiazide), dyslipidemics (fibrin acid derivatives, 3-hydroxy-3-methylglutaryl-coenzyme A [HMG CoA] reductase inhibitors, and other), direct-acting arterial and direct-acting arterial/

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venous vasodilators, and others, whereas anticonvulsants are subdivided into calcium channel modifying agents, gamma-aminobutyric acid augmenting agents, glutamate reducing agents, sodium channel agents, and others. Product labeling for the US Food and Drug Administration (FDA)-approved medications follows a similar philosophy, which categorizes medications primarily according to mechanism of action and/or therapeutic effect (eg, sedatives-hypnotics). Clearly, there is little consensus about what constitutes an optimal classification system for therapeutic medications.

We propose a taxonomy for drugs used to treat a group of disorders referred to by the *Diagnostic and Statistical Manual of Mental Disorders-5*,⁴ the International Classification of Sleep Disorders,⁵ and the International Classification of Diseases,⁶ as sleep-wake and sleep disorders. The classification currently used in the USP system would provide a broad framework for a more detailed and useful classification scheme. The USP classification system is particularly relevant since prescription and over-the-counter products (but not dietary supplements) sold in the United States are required to follow the standards in the USP National Formulary. Most formularies cover at least one drug in each drug class and thus rely on an accurate classification, emphasizing the importance of drug categories. Currently, the USP employs a hierarchical system that includes therapeutic categories based on diseases or symptoms – eg, analgesics, sleep disorder agents, antidepressants – for which drugs are prescribed. Most categories are subcategorized further into pharmacologic classes based primarily on mechanism of action. Prominent examples include nonsteroidal anti-inflammatory drugs and serotonin/norepinephrine reuptake inhibitors. Considering such a system, we propose a therapeutic category to be known as “Sleep and Circadian Rhythm Disorders”.

The proposed Sleep and Circadian Rhythm Disorders category would comprise four pharmacologic classes: “sedative hypnotics,” “stimulants,” “chronobiotics,” and “other”. Each proposed class has a unique (or undefined in the case of other) therapeutic effect. The first class, sedative hypnotics, consists of drugs that are sedating and as such provide symptomatic treatment of insomnia by inducing and/or maintaining sleep.⁷ The safety and efficacy of these drugs vary as a function of dose, half-life, and rate of metabolism. Drug types to be considered under this category include benzodiazepine receptor agonists (eg, estazolam, flurazepam, quazepam, temazepam, triazolam) and nonbenzodiazepines (eg, zolpidem, zaleplon, eszopiclone), which act primarily via gamma-aminobutyric acidergic signaling pathways; histamine-1 receptor antagonists such as doxepin and diphenhydramine; and

melatonin receptor agonists, including ramelteon which is FDA-approved for sleep-onset insomnia. Ramelteon may have chronobiotic properties; however, this has not been validated in registration quality, placebo-controlled clinical studies of circadian rhythm disorders.

Stimulants, the second class, primarily increase wakefulness and alertness. As such, they are effective in symptomatically treating a variety of disorders of excessive sleepiness.⁸ Like hypnotics, stimulants have a safety and efficacy profile that depends on dose, half-life, and rate of metabolism.⁸ Commonly used stimulants to control excessive sleepiness-related symptoms include amphetamine-like compounds (L/D-amphetamine and methamphetamine, methylphenidate), modafinil and armodafinil, and caffeine. The wake-promoting effects of most of these agents are primarily mediated through inhibition of dopamine reuptake/transport, and in some cases, through increased dopamine release.⁹ An exception is caffeine, which has adenosine receptor antagonistic effects.¹⁰

Chronobiotics, the third therapeutic class, include circadian regulators capable of entraining desynchronized or misaligned circadian rhythms as one might observe in patients with delayed sleep phase disorder or non-24 hour sleep-wake disorder. Drugs in this class can reset the circadian clock in the suprachiasmatic nucleus of the hypothalamus, resulting in alignment of circadian rhythms with the day/night cycle.¹¹ While drugs in this class can increase alertness or promote sleep, they can do so only to the extent that these symptoms are caused by a mismatch between the circadian cycle and 24-hour day. Unlike sedative-hypnotics, chronobiotics primarily function via activation of melatonin receptors, directly targeting underlying disease mechanisms by delaying, advancing, or locking circadian rhythms. Circadian phase is not a clinical endpoint, so chronobiotics would be further classified according to the circadian rhythm disorder for which each drug has been clinically evaluated (eg, non-24 hour sleep-wake disorder), as well as by relevant clinical endpoints (eg, nighttime sleep, daytime alertness, overall patient function). Currently, there are no chronobiotic medications available for the treatment of circadian rhythm disorders. The dietary supplement melatonin is a melatonin receptor agonist with chronobiotic properties, although no such data have been submitted for review to the FDA or other regulatory agencies. Various agents are in different stages of clinical development and/or FDA review for consideration as chronobiotics. Recent clinical and benchtop research supports the proposed chronobiotic class as a potentially important advancement in the management of circadian rhythm

disorders,¹¹ the prevalence and burden of which underscore the need for mechanism-based pharmacotherapy.

The final class of agents, other, consists of drugs that do not fit into any of the first three classes. These medications lessen the severity of one or more of the sleep and/or sleep-related disorders. In general, these medications alleviate sleep disturbances, excessive sleepiness, or such sleep-related symptoms as abnormal movements in sleep and cataplexy. Like the chronobiotic class, the other class will specify each drug by a select disorder and relevant endpoints. Sodium oxybate, which reduces excessive sleepiness and cataplexy in narcoleptics, would fall into this subclass; the exact mechanism by which sodium oxybate works is unclear. Medications for restless legs syndrome would also fall into this subclass, owing to their ability to alleviate associated symptoms. FDA-approved medications indicated for restless legs syndrome are believed to work through altered dopamine signaling.¹²

We believe that the proposed classification will help clinicians differentiate between symptomatic drugs and disease-modifying agents that can address the physiologic cause of a disease. The framework would, we think, facilitate the selection of drugs or drug combinations based on available pharmacologic and clinical data, an important consideration for the care of patients with circadian rhythm disorders.

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Disclosure

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