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Exploring New Frontiers for the Pharmacological Treatment of Insomnia

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Insomnia is the most common sleep disorder and approximately 10% of the world's population will report that they suffer from chronic or persistent insomnia [1]. Insomnia is a condition of unsatisfactory sleep, either in terms of sleep onset, sleep maintenance or early waking. Furthermore, insomnia impairs daytime well-being and subjective abilities and functioning. Insomnia must be considered a '24-hour' disorder [2].

In contrast with DSM-IV, the new Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) does not distinguish between primary insomnia and secondary insomnia. DSM-V recognizes that co-existing medical or mental conditions with sleep disorders (comorbid insomnia) are interactive and bidirectional. For this reason, the diagnosis of primary insomnia has been renamed insomnia disorder [3]. This change in the definition of insomnia will most likely change the approach to insomnia drug development.

Classically, the most used hypnotic drug target has been the positive allosteric modulation of GABA-A receptors. This mechanism is used by ethanol, classical barbiturates, benzodiazepines and their analogues, knows as "Z drugs". The effectiveness as hypnotics of these agents is obvious, but there is no improvement, and it may even worse, daytime performance. Furthermore, the ubiquitous distribution of GABA-A receptors in brain structures involves the production of a broad profile of undesirable effects. With these agents, sedation excessive and a psychomotor deficit, which may interfere with the daytime performance, is present. Moreover, respiratory depression, most frequent with barbiturates, and the emergence of tolerance, psychic and physical dependence with withdrawal syndrome are frequent adverse events [4].

The benzodiazepine hypnotic analogues "Z drugs" do not share the classical benzodiazepine structure, but they exert similar effects upon the GABA-A receptor. The potential for abuse and side effects are less but still can limit their use in some patients. Rare anaphylaxis, angioedema, complex sleep-related behaviours and their effects on memory and psychomotor performance are also of concern. It is unclear that there is any advantage to "Z drugs" hypnotics compared to the older benzodiazepines [5].

Despite the existing recommendations on the use of benzodiazepines for a limited time, the reality is that its use is in a majority of cases indefinitely. In recent years has emerged a series of worrying publications related to the prolonged exposure to benzodiazepines with a greater risk of dementia and cognitive impairment [6,7], and even an increased risk of overall mortality [8].

Other medications and alternative medicines have been used to induce sleep. For example valerian is used as hypnotic for some peoples. Although studies on valerian have yielded conflicting results, in general, the evidence shows no benefit compared with placebo when studied more stringently. Moreover, this phytotherapeutic herb can induce hepatotoxicity [9] and consensus guidelines do not recommend the uses of OTC and herbal agents in the treatment of chronic insomnia [10].

Most of the over-the-counter sleep-promoting agents contain drugs that block histamine type 1 receptors, thus decreasing arousal. These sedative drugs can increase appetite and weight gain and have anticholinergic effects that predispose to delirious in elderly. Theoretically, the selective anti-histaminic action at lower doses for mirtazapine and trazodone may provide off-label effectiveness for insomnia [11].

In this sense, the off-label use of tricyclic antidepressants with antihistaminic properties can induce sleep but can cause adverse reactions due to blockade of these and other neurotransmitter receptors, as secondary delirium, orthostatic hypotension and cardiac arrhythmias. Most of them reduced REM sleep due to its anticholinergic properties or to enhance monoaminergic neurotransmission. Recently, Food and Drug Administration (FDA) has approved doxepin at low dose (3 or 6 mg) for the treatment of insomnia. At these doses, doxepin has an exclusively antihistaminic effect [12].

The use of antipsychotic medications in elderly nurse residents for sleep induction and maintenance, especially quetiapine, olanzapine and risperidone, are often prescribed off-label. However, this practice needs to be readdressed given their potential risks of sudden death in patients with dementia and the current lack of evidence. Quetiapine even a low dose was not recommended and several adverse event, as weight gain and triglyceride elevations, or increase in periodic leg movements during sleep has also been observed [11].

Melatonin, a naturally-occurring substance released from the pineal gland, has been identified as an important modulator of the circadian rhythm. Over-the-counter melatonin immediate release has been shown to decrease sleep onset latency as well as improve subjective sleepiness upon awakening, although it did not improve scores of sleepiness, fatigue, and alertness throughout the day in more formal studies, perhaps by the inconsistency of dose and formulation and timing of administration [4].

Ramelteon is a selective melatonin receptor (MT1 and MT2) agonist. This drug has been approved in 2005 by the FDA and in Japan (2010) for the treatment of insomnia. It is has been known to be useful in initiating sleep with no clear effect on maintenance of sleep [13]. However, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency had given a negative opinion and did not recommend a marketing authorization for ramelteon. The CHMP was concerned that the company (Takeda) had not demonstrated the effectiveness of ramelteon, which was measured by looking at only one

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aspect of insomnia, the time to fall asleep. In addition, in only one of the three studies carried out in the natural setting was there a difference in the time taken to fall asleep between patients taking ramelteon and those taking placebo. When other aspects of sleep were considered, ramelteon did not have any effect. The Committee was also concerned that the company had not demonstrated the long-term effectiveness of ramelteon (Document Ref. EMEA/CHMP/502946/2008). In October of 2011, Takeda Pharmaceutical Company has decided to discontinue the development of ramelteon in Europe for the treatment of insomnia.

Interesting, a prolonged-release melatonin was developed in order to circumvent the fast clearance of melatonin in the body. Melatonin prolonged release (2 mg) mimics the physiological melatonin plasma profile, avoiding the peaks produced by immediate-release melatonin that could reduce the number and sensitivity of receptors available for the action of circulating melatonin. Indeed, it has been demonstrated that the administration of melatonin to supra-physiologic levels decreases the union of melatonin MT1 receptors and desensitizes them [14,15]. In fact, it has been demonstrated that supraphysiological levels of melatonin loses its effectiveness on various parameters of sleep [16]. In contrast, the administration of melatonin at physiological concentrations, mimicking endogenous nocturnal melatonin levels, does not alter the number, affinity, or the sensitivity of MT1 receptors.

Melatonin prolonged release has been licensed since 2007 in Europe, Australia, and other countries, for insomnia in patients aged 55 and older. In clinical trials, melatonin prolonged release provides significant improvements in sleep quality, sleep onset latency, and quality of life and importantly, morning alertness and psychomotor performance [17,18].

The safety and tolerability profile of melatonin prolonged release in clinical trials was comparable to placebo group, with no negative effects on memory or postural stability during the night. Based on long term efficacy and safety data, treatment with melatonin prolonged release was not limited to 2–4 weeks as with classical sedative hypnotics sleep drugs but allowed for up to 3 months without interruption [13].

Based on its benefit/risk ratio melatonin prolonged release was recommended as first-line therapy for insomnia patients aged 55 years and older in a recent British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders [2].

On the other hand, the hypocretin/orexin system is a novel area of focus in the fight against insomnia. This system promotes wakefulness mainly through excitation of tuberomammillary histaminergic, locus coeruleus noradrenergic, and midline raphe serotonergic neurons, as well as dopaminergic neurons. Orexin action is mediated by two G-protein coupled receptors (GPCRs), orexin 1 (OX1R) and orexin 2 (OX2R) receptors. Orexin receptor antagonists are currently perceived to be the most innovative and promising candidates in the late-stage insomnia pipeline [18].

Suvorexant is the first dual orexin receptor antagonist (DORA) approved by the US FDA (August 2014) for insomnia treatment. Suvorexant induces and maintains sleep by reducing arousal and wakefulness. However, there was a debate between the FDA and the promoters on the right dose of suvorexant. The final approved doses are 5, 10, 15 and 20 mg. The major issues are next-morning somnolence and safety as seen in driving tests, with possible signs of muscle weakness, weird dreams, sleep walking, other nighttime behaviors and suicidal ideation. Despite its limitations, its different mechanism of action and potentially different safety and tolerability profile compared with currently available hypnotics represents a new option for the pharmacological treatment of insomnia [19-21].

As the neurophysiolgical mechanisms of sleep and wake are better understood, treatment options for insomnia targeting these mechanisms are emerging. While the sleep-promoting effects of GABA-A enhancement and antihistaminic is well-established, newer research examining other mechanisms of action are very important. Recent results with melatonergic an orexinergic mechanism open new pathway for the insomnia treatment. Furthermore, there is growing evidence that serotonin receptors modulators, norepinephrine, neurokinin, prokineticin 2 and cannabinoid systems show promise in treating this highly prevalent condition [4,18].

Therefore, all drug treatments of insomnia should be assessed in their relationship benefits risks, with respect to its adverse effects, their influence on the state of alert morning and symptoms of withdrawal [17]. The need for treating insomnia as a primary entity or as a secondary symptom of mental or medical disorder continues, as does the need to find agents that are more specific for sleep–wake neurocircuitry with less risky adverse effects.

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