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LETTERS TO EDITOR

Dual orexin receptor antagonists: a new therapeutic class for the treatment of insomnia

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Insomnia is a complaint frequently reported by patients in clinical practice. The prevalence of insomnia varies considerably according to the population studied; it can range between 10% and 40% in the case of intermittent insomnia [1] . Sleep disturbances are often associated with psychiatric disorders, with approximately 50-80% of such patients reporting sleep disturbances at some point in the development of their disorder [2] . In addition, a two-way relationship may be established between psychopathology and disturbed sleep. Insomnia may precede the appearance of certain psychiatric disorders; remain after the acute phase as a residual symptom and complicate remission of symptoms [3] . In view of the high prevalence of sleep disorders and comorbidity with various psychiatric diseases, effective treatment of insomnia is a current and relevant topic in clinical practice.

Benzodiazepines (Bzs), discovered in 1955 by the chemist Leo Sternbach (1908-2005), are the drugs most widely used for the treatment of insomnia. They act by binding to the $GABA_A$ [4] receptor. However, although they have good tolerance and effectiveness, generalized and overly prolonged use of these drugs increase the risk of abuse and dependence [5] .

More recently, in 1980 other drugs emerged that, because of their more selective pharmacological characteristics, were dubbed "Z-drugs". Like the benzodiazepines, Z-drugs are positive allosteric modulators of $GABA_A$ receptors, but because of their greater selectivity for its α1 receptors they have been regarded as more effective (for example, they preserve normal sleep architecture to a greater degree, compared with Bzs) and with a lower profile of side effects [6, 7] . Currently, although we have available various benzodiazepines with different half-lives (short, medium and long duration), zolpidem is the only representative of the Z-drugs marketed in Portugal.

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In August 2014, in the USA, the Food and Drug Administration approved suvorexant for the treatment of insomnia. Suvorexant is a dual orexin receptor antagonist (DORA). As this is a drug with an innovative mechanism of action, it is worth getting to know more about this new class of medicinal products for the treatment of insomnia.

Orexin (also known as hypocretin) was discovered relatively recently. In 1998 *Sakurai et al.* and *De Lecea et al*, [8, 9] simultaneously discovered, in different experiments, a pair of peptides produced in the hypothalamus, which they named orexin-A and orexin-B. Since then these neuropeptides have been the subject of intense research; they have been implicated in narcolepsy due to deficient orexin production [10] . Studies have advanced and data has emerged showing orexin's role in regulating the sleep-wake cycle, and in anxiety, depression, post-traumatic stress, etc. [11-16] . The antagonistic effect on orexin receptors (OX1R and OX2R) causes drowsiness in mice, dogs and humans [16] . The possibility of using this mechanism of action in the treatment of insomnia has aroused huge interest within the pharmaceutical industry. As a result, several molecules with this pharmacological action have been studied for the treatment of insomnia, although to date only suvorexant has been approved.

As mentioned above, suvorexant has an antagonistic effect on orexin receptors. Although it has been studied at higher doses (10-80 mg), the recommended dose is 10 to 20 mg, taken approximately 30 minutes before the patient wishes to fall asleep. Half-life is approximately 12 hours and metabolism is essentially via cytochrome P450 (CYP-450). The first metabolite (hydroxy-suvorexant) is not active [17] .

Polysomnographic data have shown that, compared to placebo, suvorexant reduces sleep latency (SL) and total wake time after sleep onset (TWASO), improves sleep maintenance (SM) and increases total sleep time (TST) [18-20] .

The most common adverse effect, with an incidence >5%, was dose-dependent drowsiness. Effectiveness and tolerance were similar in both the age groups studied (>65 and <65 years). Other adverse effects reported less frequently include headache (7%), dizziness (3%) and also abnormal dreams, cough, diarrhea, dry mouth and respiratory tract infections (all <2%). Very rare cases of sleep paralysis, hypnopompic/hypnagogic hallucinations and mild cataplexy have also been reported [17] .

But ultimately what are the advantages of this new therapeutic class over the Bzs? The biggest problems associated with the use of Bzs in insomnia therapy have to do with the risk of rebound insomnia (worsening of insomnia after withdrawal of the drug), discontinuation symptoms and changes in cognitive function. Use of suvorexant was not associated with rebound insomnia or other abstinence effects when the drug was withdrawn after 3 or 12 months of daily night administration [19, 21] . Another advantage over Bzs is that this drug apparently does not disturb cognitive function, a phenomenon that may be related to the characteristic of having a more specific sleep-directed mechanism of action and, unlike Bzs, not being a direct global CNS depressant [22, 23] . Lastly, one significant advantage that medicinal products of this class have brought to the treatment of insomnia lies in the fact that they do not significantly alter the electroencephalogram (EEG) during sleep; that is to say, they maintain normal sleep neurophysiology [18-20] .

And what are the main disadvantages of this drug? Unfortunately, suvorexant relatively long half-life (approximately 12 hours) may contribute to the drug›s potential negative effect during the wake period and also to an increase in drug interactions. Longitudinal studies are required to enable us better to assess the risks and impact of this class of drug in individuals with comorbidity of physical and psychiatric illness. In the case of psychiatric illnesses, more research is required, as the orexigenic system appears to influence many areas of the CNS and to have an impact on mental health [24] .

To summarize, suvorexant, as a pioneering drug in the new class of drugs with a dual antagonistic effect on orexin receptors (DORAs), has shown to be effective in reducing SL, increasing TST, TWASO and SM. It does not significantly affect cognitive function, maintains the neurophysiological architecture of sleep and does not cause rebound insomnia or significant withdrawal symptoms. This drug stands as one more therapeutic option to consider in the treatment of insomnia. However, as is the case with all recent, innovative medicinal products, studies are still limited; large-scale use will help us to gain a better knowledge of this new therapeutic class, and in particular its role in the treatment of insomnia associated with psychiatric disorders.

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