American College of Neuropsychopharmacology

HOT TOPICS

Sleep disturbance in substance use disorders: the orexin (hypocretin) system as an emerging pharmacological target

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Sleep disturbances are a hallmark feature of all substance use disorders (SUDs). During detoxification, persons with SUDs report difficulty falling/staying asleep as well as frequent awakenings, and the severity of these disturbances is a predictor of subsequent drug use (relapse) [1]. Improving sleep during abstinence can reduce relapse [1]; however, most conventional hypnotics are contraindicated for persons with SUDs due to their high abuse liability. Accordingly, there is significant interest in novel sleep medications that might be used as standalone treatments or as adjuncts to existing medications (e.g., buprenorphine) for the management of sleep disturbance in SUD populations [2].

The hypothalamic orexin (hypocretin) neuropeptide system has emerged as a promising target for such medications. The orexin peptides maintain wakefulness, primarily via actions at brain nuclei containing cholinergic and monoaminergic cell groups [3]. In 2014, Merck gained regulatory approval for their dual orexin receptor 1/2 antagonist suvorexant (Belsomra™) for the treatment of insomnia, and extensive clinical data now indicate that this medication improves several sleep outcomes [4]. Despite being designated a schedule IV drug, suvorexant appears to have limited abuse liability, raising the possibility that this medication could be repurposed for managing sleep disturbances in SUD [2]. This prospect is particularly appealing as the orexin peptides also play a critical role in promoting drug craving and seeking via their projections to several reward regions [3]. Thus, the potential utility of using suvorexant in SUDs might be twofold: (1) normalizing sleep, which in turn might improve "top down" executive control over drug-seeking behaviors, and (2) reducing craving by suppressing "bottom-up" craving networks [1].

In a recent landmark clinical trial, Huhn et al. examined sleep and craving outcomes in opioid use disorder (OUD) patients receiving suvorexant (0, 20, and 40 mg) during a buprenorphine/naloxone taper [5]. Suvorexant was associated with a drastic improvement in total sleep time during taper, as well as decreased subjective opioid withdrawal symptom severity scores post-taper. Ratings of subjective "high" and "liking" did not differ between suvorexant and placebo treatments, and participants assigned a low monetary value to suvorexant, indicating limited abuse liability. Although these outcomes will need to be replicated in a larger patient population (complete data were collected from $N = 26$ patients), these data provide compelling proof-of-principle support for the repurposing of suvorexant for OUD, and open the door for potential clinical use for other SUD indications. To this end, several clinical trials are currently underway in populations with cocaine (NCT03937986), nicotine (NCT03999099), and alcohol (NCT04229095) use disorders.

Moving forward, studies should determine the optimal dosing regimen (dose, duration, adjunctive vs. standalone treatment) for suvorexant and similar compounds for managing withdrawal outcomes in SUD patients and other opioid-using populations (e.g., persons with chronic pain). We note that there is also a dire need to characterize any sex differences in orexin system function in the context of sleep and SUDs, and to understand how drug-induced changes in orexin levels [6] affect sleep (and vice versa). Collectively, such efforts have the potential to drastically reshape the pharmacological management of SUDs.

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AUTHOR CONTRIBUTIONS

Both UG and MHJ drafted and edited the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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