

Orexin might Predict Status of Alcohol Dependence

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To the Editor: Alcohol dependence is a severe mental disorder that can have devastating physical and psychological impacts on patients. Alcohol dependence is reported to be one of the leading causes of death among people aged between 15 and 49 years.^[1] Thus, comprehensive interventions are important for reducing mortality and disability among patients with alcohol dependence.^[2]

Currently, comprehensive intervention strategies for patients with alcohol dependence include inpatient treatment of alcohol withdrawal syndromes, inpatient group therapy, outpatient department or community interventions, and participation in alcoholics anonymous meetings led by psychiatrists or psychologists. However, although many studies have reported that these intervention strategies are effective for reducing the quantity and frequency of drinking in patients with alcohol dependence, relapse following treatment in alcohol-dependent patients remains common.^[3] It is difficult to determine whether patients are still drinking or not after they are discharged from hospital, because of the lack of an effective objective indicator. Alcohol is metabolized very rapidly by the human body, and it typically takes approximately 6 h for alcohol to be fully eliminated from the blood after drinking. Thus, blood alcohol level cannot be used as an indicator for monitoring patients' drinking after discharge. This creates a barrier for doctors seeking to accurately evaluate the abstinence status of patients with alcohol dependence. Abstinence duration is a critical factor that strongly influences the outcomes of patients with alcohol dependence, and long abstinence duration is closely related to better patient outcomes. Hence, there is an important need to explore other objective biomarkers to help doctors objectively evaluate patients' abstinence status, enabling accurate personalized comprehensive intervention strategies for patients to maintain abstinence for long periods of time.

Orexins are peptides that are synthesized in neurons or nuclei – orexinergic neurons send projections to the ventral tegmental area and nucleus accumbens. These regions play key roles in the reward system in the brain and are associated

with addiction-related behaviors. Many previous studies^[4,5] have suggested that orexins play a key role in some brain functional activity, including feeding behavior, regulation of the sleep-wake cycle, and reward system functional activity. Simultaneously, functional disturbances in the reward system also influence the secretion of orexins. Some previous studies reported that the alteration of plasma concentrations of orexins was associated with psychological symptoms in alcohol-dependent patients. During acute alcohol withdrawal, plasma concentrations of orexins were highest among alcohol-dependent patients and were more than three times greater than those of healthy controls. Simultaneously, plasma concentrations of orexins were significantly positively related to the severity of withdrawal symptoms after acute alcohol withdrawal. Another study^[6] also reported that decreases in the plasma concentrations of orexins were accompanied by the alleviation of withdrawal syndromes. Several previous studies reported that plasma concentrations of orexins were also related to relapse in alcohol drinking.^[4-6] Exposure to cue-induced status was found to cause elevated orexin levels and enhanced alcohol-seeking behavior. Taken together, these findings suggest that plasma concentrations of orexins could potentially be used as an indicator for monitoring the abstinence status of patients with alcohol dependence. Thus, if patients were able to maintain abstinence, plasma concentrations of orexin would be expected to be close to normal levels, whereas plasma concentrations of orexin would be expected to be greatly increased if patients did not maintain abstinence.

Moreover, a recent review reported that orexins may be considered a treatment target for the abuse of alcohol

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and other substances, such as cocaine. A large number of animal studies have reported that SB-334867, an orexin-1 receptor and orexin-2 receptor antagonist, can selectively block orexins.^[7] In addition, SB-334867 is reported to be involved in the regulation of the functional activity of the reward system and can simultaneously block functional activity in the circuit and motivational processes.^[7] Thus, SB-334867 can reduce the effect of origins on the reward circuit, decreasing alcohol-seeking behavior. Studies using animal models have confirmed that SB-334867 can enhance alcohol administration in animals and reduce the rate of relapse in alcohol drinking. Another study^[8] reported that SB-334867 can abolish the cue-induced reinstatement of alcohol-seeking behavior not only immediately after extinction but also after an extended period of abstinence following extinction. Taken together, these studies suggest that orexins provide a potential treatment target for reducing alcohol relapse drinking and improving long-term prognosis in patients with alcohol dependence.^[5,7]

Although the above-mentioned studies confirmed the relationship between alcohol dependence symptoms and abnormally increased plasma concentrations of orexins, further studies are needed to clarify this finding. A long-term (e.g., 2 years) cohort study would be helpful for exploring the dynamic relationship between the symptoms of alcohol dependence and alterations of plasma concentrations of orexins in hospitalized patients with alcohol dependence. Such a study would enable characterization of the evolutionary trajectories of the plasma concentrations of orexins in patients during the stages from withdrawal to absolute abstinence. In addition, this type of study would enable comprehensive and accurate objective indicators to help doctors treat patients with alcohol dependence. We hope that orexin receptor antagonists will be used as therapeutic drugs in clinical practice as soon as possible.

In summary, although previous studies have involved some limitations, convergent evidence from both animal models and human studies suggests that orexins can be used as objective indicators and potential treatment targets for alcohol dependence. These methods could enable dynamic monitoring of the status of alcohol relapse drinking after patients are discharged from hospital, helping doctors assess

abstinence status among patients with alcohol dependence. Simultaneously, orexin receptor antagonists such as SB-334867 have also been developed, potentially enabling new anti-alcohol abuse therapeutic drugs to help doctors improve long-term prognoses and improve quality of life, while reducing mortality in patients with alcohol dependence.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Roerecke M, Rehm J. Alcohol use disorders and mortality: A systematic review and meta-analysis. *Addiction* 2013;108:1562-78. doi: 10.1111/add.12231.
2. Cherpitel CJ, Ye Y, Bond J, Borges G, Chou P, Nilsen P, *et al.* Multi-level analysis of alcohol-related injury and drinking pattern: Emergency department data from 19 countries. *Addiction* 2012;107:1263-72. doi: 10.1111/j.1360-0443.2012.03793.x.
3. Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: When are these medications most helpful? *Addiction* 2013;108:275-93. doi: 10.1111/j.1360-0443.2012.04054.x.
4. James MH, Mahler SV, Moorman DE, Aston-Jones G. A decade of orexin/Hypocretin and addiction: Where are we now? *Curr Top Behav Neurosci* 2017;33:247-81. doi: 10.1007/7854_2016_57.
5. Ubaldi M, Giordano A, Severi I, Li H, Kallupi M, de Guglielmo G, *et al.* Activation of hypocretin-1/Orexin-A neurons projecting to the bed nucleus of the stria terminalis and paraventricular nucleus is critical for reinstatement of alcohol seeking by neuropeptide S. *Biol Psychiatry* 2016;79:452-62. doi: 10.1016/j.biopsych.2015.04.021.
6. Ziolkowski M, Czarniecki D, Budzyński J, Rosińska Z, Żekanowska E, Góralczyk B, *et al.* Orexin in patients with alcohol dependence treated for relapse prevention: A pilot study. *Alcohol Alcohol* 2016;51:416-21. doi: 10.1093/alc/alz129.
7. Vanderhaven MW, Cornish JL, Staples LG. The orexin-1 receptor antagonist SB-334867 decreases anxiety-like behavior and c-Fos expression in the hypothalamus of rats exposed to cat odor. *Behav Brain Res* 2015;278:563-8. doi: 10.1016/j.bbr.2014.10.028.
8. Brown RM, Kim AK, Khoo SY, Kim JH, Jupp B, Lawrence AJ, *et al.* Orexin-1 receptor signalling in the prelimbic cortex and ventral tegmental area regulates cue-induced reinstatement of ethanol-seeking in iP rats. *Addict Biol* 2016;21:603-12. doi: 10.1111/adb.12251.