

Lemborexant: An adjuvant in difficult-to-control diabetes?

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Abstract

Diabetes is a multi-faceted syndrome on which the brain is an etiopathogenetic factor, as well as a target organ for damage. Drugs which act on the brain, such as bromocriptine and antipsychotic drugs, are known to influence glycaemic control. This article describes lemborexant, a dual orexin receptor antagonist (DORA), and hypothesizes that it may be used as an adjuvant in difficult-to-control diabetes. Its utility should be explored in persons with insomnia and high fasting glucose, unregulated appetite, and diabetes distress.

Keywords: Appetite regulation, diabetes, DORA, metabolic syndrome, orexin, sleep apnea, sleep disorders

DOI: <https://doi.org/10.47391/JPMA.22-93>

Introduction

Diabetes is a multi-factorial syndrome with varied etiopathogenetic factors. The Ominous Octet includes the brain, along with insulin and incretin dysfunction, as one of the homeostatic processes involved in the development of diabetes.¹ Sleep disorders, including insomnia and obstructive sleep apnoea, have also been shown to have a bidirectional link with diabetes and its associated complications.²

Contemporary research continues to unravel the mechanisms that contribute to these clinical relationships. Discovery of various dopamine receptors, for example, led to the development of bromocriptine as an anti-diabetic drug.³ Scientists are also working to identify the links between Alzheimer's disease and diabetes,⁴ while on the other hand, the use of never atypical psychotropic drugs is associated with dysglycaemia and obesity.⁵

Orexin and metabolic health

Orexin, also known as hypocretin, is a neuropeptide that is involved in the homeostasis of arousal, wakefulness and appetite. Secreted from the lateral hypothalamus and perifornical area of the brain, orexin regulates not only appetite, but energy expenditure and visceral homeostasis as well. It regulates brown adipose tissue activity via the

sympathetic nervous system, thus contributing to weight balance. Orexin causes a craving for food, by suppressing inhibitory feedback after digestion. This increase in appetite may also be a part of the overall stimulatory effects of orexin.⁶

Orexin is associated with insulin resistance in persons with type 2 diabetes.⁷ Sleep deprivation, too, has been shown to increase the transmission of orexin.⁸ Keeping this link in mind, it makes sense, to explore the utility of orexin antagonists in management of diabetes and associated conditions, apart from their well-documented use in insomnia. This development is timely, as it is concordant with the overall shift towards ensuring viscera-metabolic health optimization in diabetes.

Lemborexant

The approval of a DORA (dual orexin receptor antagonist), lemborexant, for the management of insomnia, open up new horizons for metabolic management.⁹ The molecule has been studied in the landmark SUNRISE 1 and SUNRISE 2 phase 3 clinical trials. Lemborexant is administered as a 5 mg or 10 mg tablet, at bedtime. There is a low risk of tolerance and dependence, and it does not impact memory or day-time attention. Side effects include somnolence, headache, vivid dreams and fatigue. It can be used with benzodiazepines, zolpidem and GABA modulators.

Lemborexant appears to associate and dissociate rapidly from orexin receptors. This gives it a shorter duration of action (half-life 17-19 hours) as compared to other DORA like suvorexant. While its bioavailability is good (87%), its absorption and time to achieve peak levels (normally 1-3 hours) are delayed by up to 2 hours when consumed with a high-fat, high-calorie meal. The drug is excreted through the faeces (57%) and urine (29%)

Expanded spectrum of use

Lemborexant is being studied in circadian rhythm sleep disorders, sleep apnoea and chronic obstructive pulmonary disease (COPD).⁹ Its efficacy and safety suggest that it has the potential to improve metabolic health. Though we do not suggest that it be tried as primary glucose-lowering or weight-lowering therapy, its use in persons with disturbed sleep may help manage difficult-to-control diabetes. The benefits are seen in persons with relatively higher fasting

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glucose levels, those with unregulated appetite, those who are 'evening chronotropes' (having a greater caloric intake late in the day), and those with symptoms of obstructive sleep apnoea &/or diabetes distress (personal communication).

Summary

Lemborexant is a novel non-benzodiazepine drug that is approved for the management of insomnia in adults. It is also being studied in sleep apnoea and COPD. Its effects on the orexin receptor, which promotes appetite, and the association of hyperglycaemia and orexin dysfunction leads one to consider the possibility of using lemborexant as an adjuvant in difficult to-manage diabetes.

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