It is illegal to post this copyrighted PDF on any website.

Potential Aggravation of Suicide Risk With Daridorexant: Currently Not Enough Data to Show a Link

To the Editor: As sleep specialists, we wish to comment on the recent letter by Nobile et al,[1] which suggests a potential role for daridorexant, a new hypnotic, in increasing suicide risk.

Since insomnia symptoms are independent risk factors for increased suicide risk and major depression,[2–4] we suggest that it is of great clinical importance to treat insomnia in order to reduce its potential consequences on mental health in general.[5] We think it is important to develop new pharmacologic agents for insomnia treatment based on alternative pharmacologic mechanisms.

As the only newly available pharmacologic option in Europe, daridorexant, based on orexin receptor antagonism, seems to represent a new option for insomnia treatment. The statement by Nobile et al[1] that "Daridorexant has been associated with a risk of aggravation of depression and emergence and/or aggravation of suicidal ideation" was surprising to us, and we believe that this statement may not provide enough context behind this possible risk and the benefit of treating insomnia with daridorexant. Thus, their statement might be misleading for readers and prevent unbiased assessment and treatment of insomnia, depression, and/or suicidal ideation.

Daridorexant was approved in the US and Europe very recently (2022), following the rigorous benefit-risk assessments of the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory reviews of human medicines. Its prescription is approved for chronic insomnia and not for acute forms, which may be more frequently related to acute depressive symptoms and suicide risk.

The instructions for cautious use of daridorexant in patients with a history of suicide attempt or suicidal ideation are more or less generic for all approved hypnotics and not specific to daridorexant. FDA and EMA advise, "Patients with psychiatric disorders, including insomnia, are at increased risk of suicide. In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions (including completed suicides) have been reported. As with other hypnotics, daridorexant (Quviviq) should be administered with caution in patients exhibiting symptoms of depression."

Nobile and colleagues'[1] statement was based on 2 references that should be clarified regarding these adverse events.

The first reference is the Mignot et al[6] publication in *Lancet Neurology* (daridorexant phase 3 trials). In the publication, 2 adverse events of suicidal ideation were reported in the study ID-078A302 (with 614 participants exposed to daridorexant); 1 event occurred in each of the daridorexant groups (25 and 10 mg), and both were in patients with preexisting psychiatric conditions at baseline (paranoid schizophrenia/insomnia and depression/insomnia, respectively). The publication's appendix mentions 2 cases of depression that were reported as serious adverse events, both occurring in the placebo group.[6]

The second reference is the FDA risk assessment[7] for daridorexant, which is publicly available. The 2 cases of suicidal ideation mentioned are the same 2 cases already reported in the *Lancet Neurology* publication.[6]

Two additional cases were observed in the ID-078A303 study, which included 804 patients (2 reported suicidal ideation, 1 in the placebo group and 1 in the 50 mg group, both with acute extenuating circumstances [family/financial stress, illicit drug use]).[8] So, currently, in the clinical trials of daridorexant, a total of 4 cases of suicidal ideation have been reported, and they were equally distributed across treatment groups, including placebo.[9] A causal relationship to the study drug could not have been established due to significant confounding factors in all cases. Nobile et al[1] supposed that low orexin levels may be involved in suicidal risk and major depression, but they cite for this statement an experimental study conducted in mice[10] and a work[11] which showed that low orexin levels in patients who have attempted suicide were not causally correlated with suicidal risk. Instead, recent reviews of clinical and preclinical data on major depression proposed that orexin antagonists may also possess antidepressant-like properties.[12] A review of dual orexin receptor antagonists (DORAs) administered in patients with psychiatric disorders including major depression, titled "Orexin Receptor Antagonists as Emerging Treatments for Psychiatric Disorders," showed the efficacy of these compounds on mood symptoms.[13] Recent works showed an overactivation of orexins in unipolar and bipolar depression[14] and in maladaptive stress response, anxiety, and insomnia as well.[13–15] Growing evidence from preclinical and clinical studies suggests that orexins and their receptors are involved in the pathophysiology of depression. Orexin neurons are believed to be a coordination center for multiple brain regions, and it is plausible that this involves a differential signaling network. In fact, the orexinergic system regulates functions that are disturbed in depressive states, such as sleep, reward system, feeding behavior, the stress response, and monoaminergic neurotransmission.[13–15] So, currently, it seems that with the orexin system we are opening new complex windows on our understanding of mood and suicide psychopathologies, and DORAs may also potentially open new scenarios in the treatment of psychiatric disorders.

To conclude, we currently do not have enough data to show the potentiality of aggravation of suicide risk and depression of daridorexant, an important new option for the treatment of chronic insomnia, which per se predicts suicidal behaviors. Surely, further studies would be needed to evaluate its safety for patients with mood disorders and the mechanistic interaction between orexin pathways and mental disorders.

REFERENCES

1. Nobile B, Olié E, Courtet P. Possible suicidal risk with daridorexant, a new treatment for insomnia. *J Clin Psychiatry*. 2022;84(1):22l14628.
2. Hertenstein E, Feige B, Gmeiner T, et al. Insomnia as a predictor of mental disorders: A systematic review and meta-analysis. *Sleep Med Rev*. 2019;43:96–105.
3. Geoffroy PA, Oquendo MA, Courtet P, et al. Sleep complaints are associated with increased suicide risk independently of psychiatric disorders: results from a national 3-year prospective study. *Mol Psychiatry*. 2021;26(6):2126–2136.
4. Romier A, Maruani J, Lopez-Castroman J, et al. Objective sleep markers of suicidal behaviors in patients with psychiatric disorders: A systematic review and meta-analysis. *Sleep Med Rev*. 2023;68:101760.
5. Palagini L, Hertenstein E, Riemann D, et al. Sleep, insomnia and mental health. *J Sleep Res*. 2022;31(4):e13628.
6. Mignot E, Mayleben D, Fietze I, et al; investigators. Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials. *Lancet Neurol*. 2022;21(2):125–139.
7. US Food and Drug Administration. Center for Drug Evaluation and Research. Risk Assessment and Risk Mitigation Review(s). US Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214985Orig1s000RiskR.pdf. January 2022.
8. Kunz D, Dauvilliers Y, Benes H, et al. Long-term safety and tolerability of daridorexant in patients with insomnia disorder. *CNS Drugs*.

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2023 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

2023;37(1):93–106.
9. European Medicines Agency. Assessment report on Quviviq. EMA/187589/2022. Published February 24, 2022. https://www.ema.europa.eu/en/documents/assessment-report/quviviq-epar-public-assessment-report_en.pdf >
10. Feng P, Hu Y, Vurbic D, et al. Chromosome 1 replacement increases brain orexins and antidepressive measures without increasing locomotor activity. *J Psychiatr Res*. 2014;59:140–147.
11. Brundin L, Petersén A, Björkqvist M, et al. Orexin and psychiatric symptoms in suicide attempters. *J Affect Disord*. 2007;100(1-3):259–263.
12. Fagan H, Jones E, Baldwin DS. Orexin receptor antagonists in the treatment of depression: a leading article summarising pre-clinical and clinical studies. *CNS Drugs*. 2023;37(1):1–12.
13. Han Y, Yuan K, Zheng Y, et al. Orexin receptor antagonists as emerging treatments for psychiatric disorders. *Neurosci Bull*. 2020;36(4):432–448.
14. Li H, Lu J, Li S, et al. Increased hypocretin (orexin) plasma level in depression, bipolar disorder patients. *Front Psychiatry*. 2021;12:676336.
15. Palagini L, Geoffroy PA, Balestrieri M, et al. Current models of insomnia disorder: a theoretical review on the potential role of the orexinergic pathway with implications for insomnia treatment. *J Sleep Res*. 2023;14:e13825.

Laura Palagini, MD, PhD
Pierre A. Geoffroy, MD, PhD
Jean Arthur Micoulaud-Franchi, MD, PhD
Angelo Gemignani, MD, PhD
Dieter Riemann, PhD

Article Information

Published Online: July 3, 2023. https://doi.org/10.4088/JCP.23lr14892

© 2023 Physicians Postgraduate Press, Inc.

To Cite: Palagini L, Geoffroy PA, Micoulaud-Franchi JA, et al. Potential aggravation of suicidal risk with daridorexant: currently not enough data to show a link. *J Clin Psychiatry*. 2023;84(4):23lr14892.

Author Affiliations: Department of Clinical and Experimental Medicine, Unit of Psychiatry, Azienda Ospedaliero Universitaria Pisana AUOP, Pisa, Italy (Palagini); Département de Psychiatrie et d'Addictologie, AP-HP, GHU Paris Nord, DMU Neurosciences, Hopital Bichat—Claude Bernard, Paris, France; GHU Paris—Psychiatry & Neurosciences, Paris, Université de Paris, NeuroDiderot, Inserm, FHU I2-D2, F-75019 Paris (Geoffroy); Sleep Clinic, University Hospital of Bordeaux, Bordeaux, France (Micoulaud-Franchi); Unit of Psychology, Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa; Azienda Ospedaliero Universitaria Pisana AUOP, Pisa, Italy (Gemignani); Department of Psychiatry and Psychotherapy, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany (Riemann), Center for Basics in NeuroModulation (NeuroModulBasics), Faculty of Medicine, University of Freiburg, Freiburg, Germany (Riemann).

Corresponding Author: Laura Palagini, MD, PhD, Insomnia Clinic Department of Clinical and Experimental Medicine, Unit of Psychiatry, Azienda Ospedaliero Universitaria Pisana AUOP, Pisa, Italy (lpalagini@gmail.com).

Relevant Financial Relationships: Dr Palagini has been involved with consultancy activity for Bruno SPA, Fidia, Idorsia Pharmaceuticals, and Pfizer. **Dr Geoffroy** reports the following relationships. Communications: Biocodex, Bioprojet, Idorsia Pharmaceuticals, Janssen-Cilag, Jazz Pharmaceuticals, Lundbeck, MySommeil, and Withings. Expertise: Apneal, Biocodex, Dayvia, Idorsia Pharmaceuticals, Janssen-Cilag, Jazz Pharmaceuticals, Myndblue, Posos, ResilEyes, and Withings. Advisory board: Apneal, Idorsia Pharmaceuticals, Mindblue, and Mysommeil. **Dr Riemann** receives royalties for authored books and book chapters from several publishing companies for material related mainly to insomnia (Elsevier, Hogrefe, Kohlhammer, Wiley and Sons, etc). Dr Riemann is Editor-in-Chief of *Journal of Sleep Research,* which is owned by the European Sleep Research Society (nonprofit organization); he receives monthly payments for this task. Dr Riemann frequently lectures at conferences, meetings, and seminars, mostly invited by the organizing bodies. Most of his talks deal with aspects of insomnia. In the last 12 months, Dr Riemann received lecturing honoraria from Novartis and Idorsia. Dr Riemann receives honoraria from GAIA group (Germany), Meinstresscoach (Switzerland), and HelloBetter (Germany) for advising on the development of Internet-based approaches to insomnia treatment. **Drs Micoulaud-Franchi** and **Gemignani** report no financial relationships relevant to this letter.

Funding/Support: None.

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2023 Copyright Physicians Postgraduate Press, Inc.