Possible Suicidal Risk With Daridorexant, a New Treatment for Insomnia

To the Editor: Recently, Quviviq (daridorexant) received its approval by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to be commercially available to treat insomnia.[1] Daridorexant significantly improves sleep outcomes such as wake time after sleep onset and latency to persistent sleep within patients with severe insomnia.[2]

Sleep disorders are highly associated with suicidal behaviors (ie, suicide attempt and suicide) and ideation (SI).[3] Indeed, a recent meta-analysis[4] confirmed that sleep disorders, especially insomnia and nightmares, were associated with increased risk of suicidal behaviors in depressed patients. Thus, the percentage of prescription of hypnotics within suicidal patients (ie, lifetime suicide attempt and/or SI) is high, with more than one-third of these patients using these medications. Yet, hypnotics have been associated with increased suicidal risk whatever the medication type, indicating that insomnia could actually be an underlying factor in this relationship.[5] Furthermore, in a recent study,[6] zolpidem intake (vs placebo) was associated with greater improvement of SI, which was positively correlated to improvement of insomnia and independent of other symptoms of depression. This reduction of SI was more pronounced within patients with more severe insomnia. Treating insomnia may thus help reduce SI and suicidal behavior. Those results raise the question concerning the use of daridorexant in suicidal depressed patients.

The instructions for use of daridorexant mention a cautious use in patients with a history of suicide attempt or SI.[7] Daridorexant has been associated with a risk of aggravation of depression and emergence and/or aggravation of SI.[2,7] This risk be explained by several factors deserving further study. First, daridorexant is an antagonist of orexin receptors 1 and 2. Low levels of orexin have been found in depressed patients with lifetime history of suicide attempt.[8] In addition, low levels of orexin have been related to higher symptoms of inertia and reduced motor activity in suicidal patients, suggesting a more severe depressive symptomatology.[9] Furthermore, the orexin system interacts closely with the hypothalamic-pituitary-adrenal (HPA) axis, which is known to be deregulated in suicidal behavior.[10] Second, suvorexant, a commercially available treatment for insomnia with a similar mechanism of action, has been associated with aggravation of depression and emergence of SI.[11] Interestingly, there was a dose-effect worsening of SI with that medication.[12] Third, suicidal depressed patients usually take psychotropic drugs such as antidepressants, anxiolytics, and antipsychotics. Daridorexant may interact with such medications through cytochromes and affects clinical response to these treatments. Indeed, daridorexant is metabolized by CYP3A4,[1] as are citalopram, mirtazapine, quetiapine, aripiprazole, and diazepam. To our knowledge, only one study reported negative results about the interaction between citalopram and daridorexant in healthy subjects,[13] but the number of participants was small (N = 24) and the clinical response to citalopram could not be assessed in healthy subjects.

To conclude, because hypnotics are commonly prescribed in suicidal and depressed patients, daridorexant should be used very cautiously due to the possible risk of symptomatic aggravation. Further studies would be needed to evaluate its safety of use for psychiatric patients.

REFERENCES

1. Markham A. Daridorexant: first approval. *Drugs*. 2022;82(5):601–607.
2. 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.
3. Lopez-Castroman J, Jaussent I. Sleep disturbances and suicidal behavior. In: Baca-Garcia E, ed. *Behavioral Neurobiology of Suicide and Self Harm*. Cham: Springer International Publishing. 2020:46:211–228.
4. Wang X, Cheng S, Xu H. Systematic review and meta-analysis of the relationship between sleep disorders and suicidal behavior in patients with depression. *BMC Psychiatry*. 2019;19(1):303.
5. Tubbs AS, Fernandez FX, Ghani SB, et al. Prescription medications for insomnia are associated with suicidal thoughts and behaviors in two nationally representative samples. *J Clin Sleep Med*. 2021;17(5):1025–1030.
6. McCall WV, Benca RM, Rosenquist PB, et al. Reducing Suicidal Ideation Through Insomnia Treatment (REST-IT): a randomized clinical trial. *Am J Psychiatry*. 2019;176(11):957–965.
7. US Foof 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. 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.
9. Brundin L, Petersén A, Björkqvist M, et al. Orexin and psychiatric symptoms in suicide attempters. *J Affect Disord*. 2007;100(1–3):259–263.
10. Alacreu-Crespo A, Olié E, Guillaume S, et al. Dexamethasone suppression test may predict more severe/violent suicidal behavior. *Front Psychiatry*. 2020;11:97.
11. Petrous J, Furmaga K. Adverse reaction with suvorexant for insomnia: acute worsening of depression with emergence of suicidal thoughts. *BMJ Case Rep*. 2017:bcr-2017-222037.
12. Sutton EL. Profile of suvorexant in the management of insomnia. *Drug Des Devel Ther*. 2015;9:6035–6042.
13. Berger B, Kornberger R, Dingemanse J. Pharmacokinetic and pharmacodynamic interactions between daridorexant, a dual orexin receptor antagonist, and citalopram in healthy subjects. *Eur Neuropsychopharmacol*. 2021;51:90–104.

Bénédicte Nobile, PharmD, PhD[a,b,*]
Emilie Olié, MD, PhD[a,b]
Philippe Courtet, MD, PhD[a,b]

[a]Department of Emergency Psychiatry and Acute Care, Lapeyronie Hospital, CHU Montpellier, Montpellier, France

[b]IGF, Univ. Montpellier, CNRS, INSERM, Montpellier, France

**Corresponding author:* Bénédicte Nobile, PharmD, PhD, IGF, La Colombiere Hospital, 39, avenue Charles Flahault, BP 34493, 34093 Montpeiller cedex 5, France (benedicte.nobile@gmail.com).

Published online: December 7, 2022.

Relevant financial relationships: None.

Funding/support: None.

J Clin Psychiatry 2023;84(1):22l14628

To cite: Nobile B, Olié E, Courtet P. Possible suicidal risk with daridorexant, a new treatment for insomnia. *J Clin Psychiatry*. 2023;84(1):22l14628.

To share: https://doi.org/10.4088/JCP.22l14628