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Daridorexant: Caution Is Needed About Suicidal Risk in Depressed Patients With Insomnia—Reply to Palagini et al

To the Editor: In our recent letter,[1] we wrote that "Daridorexant has been associated with a risk of aggravation of depression and emergence and/or aggravation of suicidal ideation." Palagini and colleagues[2] stipulate that this statement "may not provide enough context behind this possible risk" (ie, possible suicide risk). Our statement is based on, among others, the warnings issued by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA), and it seems surprising that the authors consider a warning from medical authorities to be "more or less generic."

We think that it is of primary importance to consider these warnings for different reasons. First, insomnia is an important risk factor for suicidal behaviors, and a large proportion of prescriptions to treat insomnia are from general practitioners (GPs) who do not systematically assess suicidal risk.[3,4] Indeed, when having sleep disturbances, patients first consult their GP, and it has been shown in numerous studies that assessment of suicidal behaviors by GPs is suboptimal and not systematically assessed even in patients with current major depressive disorder (MDD).[3] Few randomized controlled trials (RCTs) on daridorexant currently exist, and thus this treatment has been assessed in a relatively small number of patients (about 3,000 patients included in all RCTs) among the large numbers of patients with insomnia. Moreover, data on psychiatric comorbidities of patients included in these RCTs are lacking and generally not specified in published reports.[5–7] This kind of data should have been interesting since insomnia is commonly associated with psychiatric disorders. In addition, as in most RCTs,[8] suicidal patients have been excluded from these studies (examples of terms found in exclusion criteria: "suicidality," "suicidal ideation," "suicide attempt"),[5,6] thus limiting data on the effects of this new treatment in suicidal patients.

The authors wrote that dual orexin receptor antagonists (DORAs) may also possess antidepressant-like properties. Yet, the authors of a recent review of the literature concluded that evidence from preclinical and clinical studies is still conflicting and that, of the 4 existing RCTs in patients with MDD comparing DORAs vs placebo, only 1 demonstrated a superior effect of DORA.[9] Furthermore, it is important to note that even if suicidal behaviors share common pathways with depression, these two disorders are distinct, and we thank the authors for allowing us to again remind readers of this. Indeed, as insomnia is not depression, suicidal behaviors are not depression. Numerous studies showed that suicidal behaviors have their own physiopathology and that patients suffering from these disorders have their own specific clinical and genetic characteristics.[10–13] Thus, treatments that are efficient in MDD may not be efficient in suicidal behaviors, as seen with antidepressants,[14] and could also be deleterious for suicidal patients.

Finally, as we wrote in our previous letter,[1] daridorexant is metabolized by cytochrome P450 (CYP)3A4[15] as citalopram, mirtazapine, quetiapine, aripiprazole, diazepam, or clomipramine, common treatments used in suicidal patients. Only 1 study reported negative results about the interaction between citalopram and daridorexant in a small number of healthy subjects (N = 24),[16] and the clinical response to citalopram could not be assessed in healthy subjects. Thus, possible pharmacokinetic and pharmacodynamic interactions between daridorexant and common treatments used in suicidal patients are currently unknown.

To conclude, we are pleased to note that Palagini et al[2] reached the same conclusion as us regarding the need for further studies in patients with psychiatric disorders, especially suicidal patients. While waiting for these studies, caution in the use of daridorexant in suicidal patients is required.

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Bénédicte Nobile, PharmD, PhD
Philippe Courtet, MD, PhD

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Author Affiliations: Department of Emergency Psychiatry and Post-Acute Care, CHU Montpellier, France; IGF, Univ. Montpellier, CNRS, INSERM, Montpellier, France; FondaMental Foundation, Créteil, France.

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

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