Dual Orexin Receptor Antagonists and Suicide Risk:

Findings From the WHO Spontaneous Reporting Database

Francesco Salvo, MD, PhD; Jean-Arthur Micoulaud-Franchi, MD, PhD; Laura Palagini, MD, PhD; and Pierre A. Geoffroy, MD, PhD

Suicide is the leading cause of death among young adults, with significant and independent associations with sleep alterations.[1] Hypnotics are commonly prescribed in patients with major depressive disorder (MDD) and have been associated with a suicidal ideation reduction in patients with insomnia disorder.[2] However, there remains a debate regarding the potential increased risk of suicidal behavior associated with the use of hypnotics.[3] Dual orexin receptor antagonists (DORA), a new class of hypnotics, were recently marketed with precautionary measures for use in patients with MDD and suicidal ideation. Nevertheless, their safety data are very limited.

Our aim was to investigate the association between DORA and suicide ideation/behavior using real-world data.

Methods

We queried the WHO pharmacovigilance database (VigiBase), which comprises more than 34 million cases of possible adverse reactions.[4] We reviewed all terms related to "Suicide/self-injury" and characterized 2 phenotypes: ideation and behavior (completed or attempted suicide), to distinguish cases of possible adverse effects related to hypnotics intake from cases in which hypnotics were possibly used to commit suicide. We used Information Component (IC), the WHO Bayesian measure, to quantify the association between DORA and suicide reporting.[5] Briefly, IC is a measure that, when significantly increased ($IC025 \geq 0$), indicates that the observed number of cases is more frequent than expected, thus suggesting a possible increased risk. We conducted the same analysis for Z-drugs and acetaminophen (paracetamol). The latter was used as a positive control for suicidal behavior and as a negative control for suicidal ideation.

Results

Suicidal ideation. Among the 80,069 cases collected in VigiBase, we found 94 cases (1.2‰) related to DORA and 781 (9.8‰) to Z-drugs. DORA were the only suspected drugs in 85 cases (90.4%), while Z-drugs were in 396 cases (50.7%). Among cases reporting a drug withdrawal, a positive dechallenge (suicidal ideation improving) was recorded in 59.3% of DORA-related and 66.0% of Z-drugs–related cases.

Suicidal ideation was 2.1 times more frequent than expected with DORA and 2.2 times more frequent with Z-drugs, with no meaningful difference among drugs; data on daridorexant, lemborexant, and zaleplon were sparse. Acetaminophen was confirmed as the negative control (Table 1).

Suicidal behavior. Among the 161,574 cases collected in VigiBase, we found 43 cases (0.7‰) related to DORA and 8,453 (52.3‰) to Z-drugs. DORA were the only suspected drugs in 7 cases (16.3%), while Z-drugs were in 1,338 cases (15.8%). Among cases reporting a drug withdrawal, a positive dechallenge was recorded in 44.8% of DORA-related and 62.7% of Z-drugs–related cases.

Suicidal behavior was 1.3 times more frequent than expected with

Table 1.

Risk of Reporting Suicidal Ideation and Suicidal Behavior With Investigated Drugs

	Suicidal ideation				Suicidal behavior			
	Cases (N)[a]		Disproportionality		Cases (N)		Disproportionality	
	Observed	Expected[b]	IC_{025}	IC	Observed	Expected	IC_{025}	IC
DORA	**94**	**21**	**1.8**	**2.1**	**109**	**43**	**1.0**	**1.3**
Suvorexant	82	19	1.7	2.1	98	39	1.0	1.3
Daridorexant	8	1	1.1	2.3	10	3	0.8	1.8
Lemborexant	4	1	−0.1	1.6	1	2	−4.5	−0.7
Z-drugs	**781**	**164**	**2.1**	**2.2**	**8,453**	**331**	**4.6**	**4.7**
Zolpidem	528	104	2.2	2.3	6,343	210	4.9	4.9
Zopiclone	169	30	2.2	2.5	1,520	61	4.5	4.6
Eszopiclone	84	28	1.3	1.6	558	56	3.2	3.3
Zaleplon	10	3	0.6	1.7	150	6	4.4	4.6
Acetaminophen	**277**	**451**	**−0.9**	**−0.7**	**13,761**	**910**	**3.9**	**3.9**

[a]More than 1 hypnotic could be reported as suspected drug in single cases.
[b]The number of expected cases is related to the total number of cases received for each drug or drug class. As an example, for suicidal ideation, it is 21 for DORA as 9,240 cases were collected, while it is 164 for Z-drugs as 70,977 cases were collected.
Abbreviations: DORA = dual orexin receptor antagonists, IC = Information Component.

DORA and 4.7 times more frequent for Z-drugs; data on lemborexant were sparse. Acetaminophen was confirmed as the positive control (Table 1).

Discussion

DORA were related to a warning concerning suicidal ideation,[3] but, to date, we found no specific pharmacovigilance signal or unexpected increase in the number of cases, in particular when compared with Z-drugs. Nevertheless, the limitations of spontaneous reporting studies (such as underreporting) and the specific pharmacologic profile of DORA, in particular the link between orexin and serotonin pathways,[6] require further pharmacovigilance attention and neurobehavioral studies.

Our findings regarding suicidal ideation were coherent between DORA and Z-drugs, with a positive dechallenge occurring in one-third of the reported cases, and that was associated with an improvement in around two-thirds of cases related to both hypnotics. These results could be at least in part related to an indication bias, as insomnia disorder is closely associated with MDD and suicidal ideation.[1] However, it is important to note that the available data on suicidal ideation and DORA are still preliminary, and further studies using real-world data are necessary to provide more comprehensive and updated information.

Concerning suicidal behavior, in comparison with Z-drugs, we found a relative paucity of cases of voluntary intoxication with DORA.

In perspective, comparative data on validated efficacy and safety outcomes are essential to clarify the role of hypnotics in suicidal risk in patients with insomnia disorder. Elucidating this role is important for thoughtful and evidence-based prescription of hypnotics to improve sleep alteration in patients with MDD and suicidal ideation.

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Corresponding Author: Prof Pierre Alexis Geoffroy, MD, PhD, University Hospital Bichat-Claude Bernard, Department of Psychiatry and Addictive Medicine, 46 rue Henri Huchard, 75018, Paris, France (pierre.a.geoffroy@gmail.com).

Author Affiliations: Department of Medical Pharmacology, Regional Pharmacovigilance Center of Bordeaux, University Hospital of Bordeaux, Inserm U1219, Université de Bordeaux, F-33000, Bordeaux, France (Salvo); University Sleep Clinic Service, University Hospital of Bordeaux, F-33076, Bordeaux, France; UMR CNRS 6033 SANPSY, University Hospital of Bordeaux, F-33076, Bordeaux, France (Micoulaud-Franchi); Psychiatric Clinic Department of Experimental Medicine, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy (Palagini); Département de Psychiatrie et d'Addictologie, AP-HP, GHU Paris Nord, DMU Neurosciences, Hopital Bichat—Claude Bernard, F-75018, Paris, France; Centre ChronoS, GHU Paris—Psychiatry & Neurosciences, Paris, France; Université Paris Cité, NeuroDiderot, Inserm, FHU I2-D2, F-75019, Paris, France (Geoffroy).

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ORCID: Pierre Alexis Geoffroy: https://orcid.org/0000-0001-9121-209X

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