Real-world data on the abuse potential of medications for the treatment of insomnia

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167

Introduction

- Insomnia disorder is estimated to affect about 12% of the adult population in the United States (1).
- Although first line guidance for the treatment of insomnia disorder is cognitive-behavioral therapy (CBTi) the use of prescription medications for insomnia has become a standard of medical treatment (2,3,4).
- FDA approved medications for the treatment of insomnia include benzodiazepines, benzodiazepine receptor agonists (z-drugs), melatonin receptor agonists, low dose doxepin, and most recently the dual orexin receptor antagonists (DORAs).
- The three approved DORAs in the US (suvorexant, lemborexant, and daridorexant) demonstrated clinical safety in registrational trials with pre-clinical data showing no evidence of abuse potential or drug withdrawal and clinical trials showing no features of withdrawal or rebound insomnia.

Study objective

This analysis of the FDA Adverse Event Reporting System database was designed to interpret the real-world abuse potential of medications used for the treatment of insomnia disorder

Methods

- THE FAERS (FDA Adverse Event Reporting System) database queried for adverse events (AEs) associated with the following preferred terms (PT): drug abuse, drug withdrawal, drug dependence.
- Cases were *excluded* if in the same case (patient) the following PTs were reported: "accidental overdose" *or* "intentional overdose" *or* "overdose" *or* "prescribed overdose" *or* "toxicity to various agents" AND any events of suicidal behavior: "completed suicide" *or* "suicidal behavior" *or* "suicide attempt" *or* "suicide threat" *or* "suspected suicide" *or* "suspected suicide attempt" (done to exclude cases or overdose that would not qualify for drug abuse) – this was represented as a modified SMQ (Standardized MedDRA Query) term.
- The reporting period (Jan 1, 2014 - Mar 31, 2024) was used to capture the market presence of the DORA class and provide a decade of pharmacovigilance experience.
- Drugs of interest were those with FDA approval for insomnia. These included the 3 DORA medications, benzodiazepines (both approved and non-approved for insomnia), z-drugs and non-scheduled drugs (doxepin, ramelteon). Analysis was also performed for trazodone, increasingly the single most prescribed medication for insomnia in the US (5). The number of cases identified for each PT was divided by the total number of AEs reported.
- Disproportionality measures were applied to compare the frequency of reporting against two references: z-drugs and trazodone, the two most widely prescribed medications for the treatment of insomnia in the US. An Odds Ratio of less than 1 indicates a lower reporting rate of interest for a drug compared to a reference. If the 95% Confidence Interval includes 1 it is considered that there is no significant difference in reporting compared to the reference.

Results

FAERS Database: US cases received between Jan 1, 2014 and Mar 31, 2024

	N	Preferred SMQ Terms (n)	%	Modified SMQ terms (n)	%
BZ's approved for all indications	67584	21794	32.2	18690	27.7
BZ's approved for insomnia	2868	900	31.4	659	23.0
Z-drugs	13495	3185	23.6	2063	15.3
DORA	9963	277	2.8	262	2.6
Trazodone	9965	3103	31.1	2261	22.7
Doxepin	2358	763	32.3	525	22.3
Ramelteon	314	26	8.3	25	8.0

Discussion

- Based on disproportionality analysis, significantly lower reported cases of real-world abuse, misuse, overdose, and other safety risks for the DORA class were seen when compared to all z-drugs (Figs 1,2). Benzodiazepines, even restricted to those approved for insomnia, were associated with the highest reporting odds. This is consistent with prior findings that z-drugs are associated with significant dependence and abuse potential (6,7) and congruent with a post-marketing study wherein benzodiazepines were associated with the highest risk of abuse (8).
- Likewise, significantly lower reported cases denoting drug abuse for the DORA class were seen when directly comparing to trazodone, non-scheduled and non-approved for the treatment of insomnia (Fig 2).
- The abuse features of the DORA class are also markedly less (2.6%) than those seen for non-scheduled approved hypnotics doxepin (22.3%) and ramelteon (8.0%) as well as the non-approved medication trazodone (22.7%). (Fig 3,4).

Figure 1

Figure 2

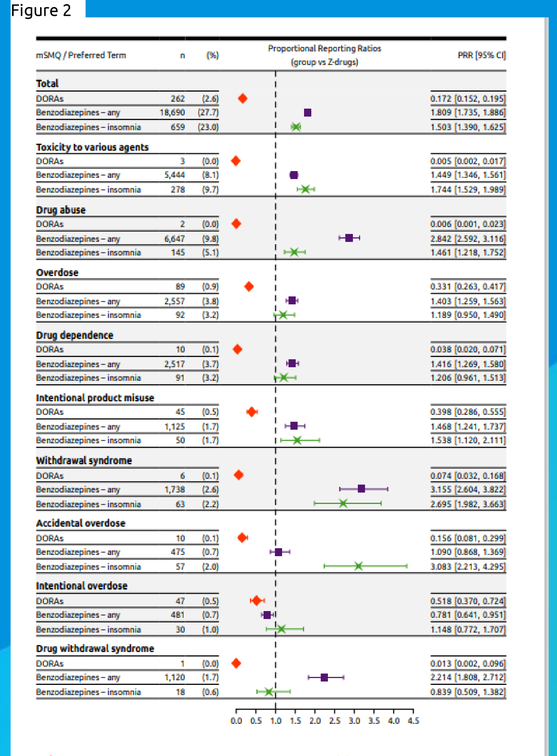


Figure 3

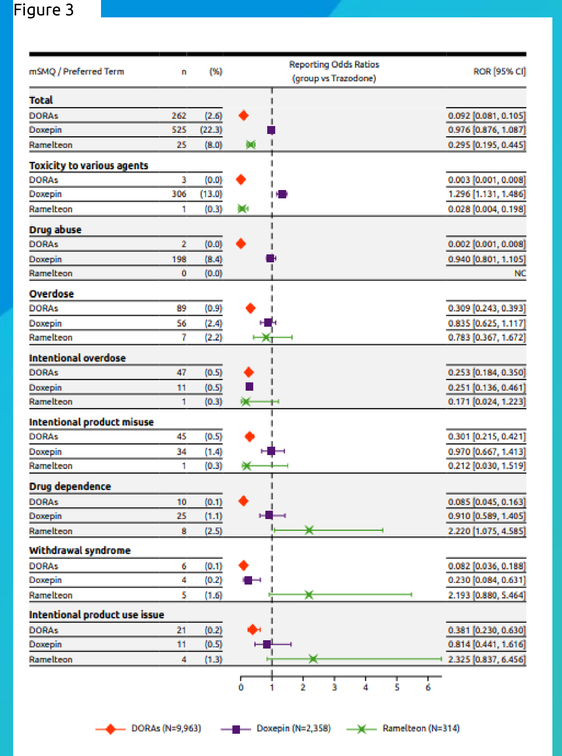
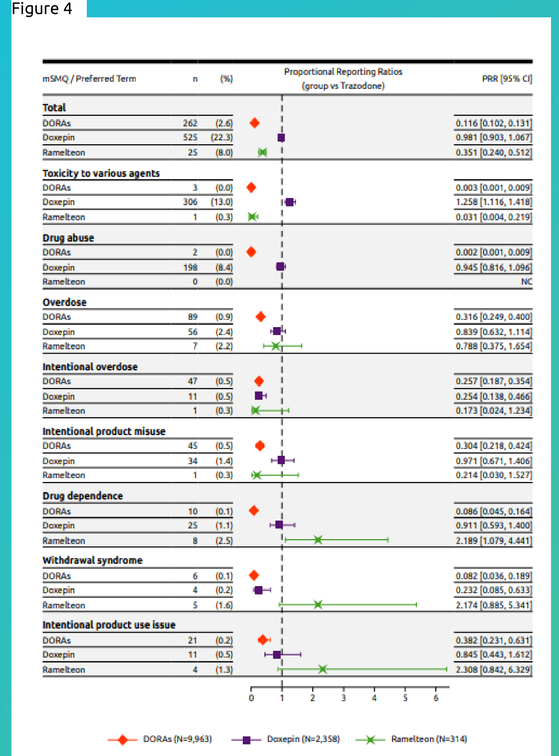


Figure 4



Conclusion

- **Abuse related features associated with real world use of DORA medications are consistent with and in some cases less than non-scheduled medications.**
- **The case reports for these key measures are far less than approved BZ and Z-drugs as well as the non-approved and unscheduled drug, trazodone.**
- **None of the DORA medications approved in the US contain warnings about drug dependence suggesting that they do not pose meaningful abuse potential or safety risks.**

Disclosures

PS, AC, and CV are current employees of Idorsia Pharmaceuticals. **BP and RJ** are former employees of Idorsia, currently with Viatris. **PPL** is a former employee of Idorsia, currently with Ironwood Pharmaceuticals. **WVM and DN** are scientific advisors to Idorsia Pharmaceuticals

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Limitations

- FAERS data are based on spontaneous reports; the presence of duplicate reports, reporting errors, and high variability in the general quality and completeness of reported data should be considered. Effort was made in the statistical analysis plan to minimize duplicate reporting.
- Most DORA related adverse event drug reports are attributed to suvorexant, which has been commercially available in the US for 10 years. The three marketed DORAs, however, all share similar mechanisms of action with minimal differences in their pharmacologic and safety profiles; the collective sum of the post-marketing surveillance data can be used to assess the abuse potential of DORAs as a class.

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