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SHORT COMMUNICATION

Association between NMDAR antagonists, drug abuse and dependence: A disproportionality analysis from the WHO pharmacovigilance database

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Ketamine and dextromethorphan are widely abused psychoactive substances. Inhibition of N-methyl-d-aspartate receptors (NMDARs) results in neurobehavioural effects including hallucinations, "out of body" sensations and dissociative effects. However, little is known about a possible extended addictive class effect linked to pharmacologically-related amino-adamantane derivatives (e.g., amantadine and memantine). Using a quasi-Bayesian analytic method, we investigated the potential association between the use of approved NMDAR antagonists (i.e., dextromethorphan, ketamine, amantadine and memantine) and the reporting of drug abuse and dependence in the WHO pharmacovigilance database (VigiBase®), which includes >21 million individual case safety reports collected from >130 countries. This disproportionality analysis identified a significant association for all investigated drugs: dextromethorphan (IC = 3.03 [2.97–3.09]), ketamine (IC = 1.70 [1.57–1.83]), amantadine (IC = 0.21 [0.06–0.35]) and memantine (IC = 0.27 [0.13–0.40]), suggesting a class effect for drug abuse and dependence. This first signal requires further investigations, but health professionals need to be alert to the potential of abuse of NMDAR antagonists, especially in the current "opioid epidemic" context, due to their growing interest as non-opioid antinociceptive drugs.

KEYWORDS
addictovigilance, dependence, drug abuse, NMDA-R antagonists, VigiBase®

1 | INTRODUCTION

N-methyl-D-aspartate receptors (NMDARs) are one class of ionotropic receptors for the excitatory neurotransmitter L-glutamate. Excitotoxicity is triggered by the accumulation of L-glutamate, contributing to a large variety of acute and chronic neurological disorders. Approved NMDAR antagonists include **dextromethorphan**, **ketamine**, **amantadine** and its dimethyl-derivative, **memantine**. Over the years, NMDAR antagonists have been used in clinical anaesthesia or to treat various central nervous system (CNS) conditions including neurodegenerative diseases, drug-induced dyskinesia, traumatic brain injury, stroke, epilepsy and depression. Recently, their potential for the treatment of pain has come under investigation. Indeed, the "opioid epidemic" in the United States has revealed a pressing need to develop new non-opioid antinociceptive drugs.[1] To date, the available clinical data are consistent with

analgesic benefits of NMDAR antagonists for neuropathic pain, complex regional pain syndrome, acute pain in the emergency room, resulting in a reduced requirement for opioids.[2] Due to the growing interest in NMDAR antagonists for use as antinociceptives, studies are needed to effectively manage their adverse effects. In fact, even during the development of these drugs, dose-dependent CNS adverse effects were reported, such as hallucinations, delirium and psychosis.[3]

Ketamine and dextromethorphan are widely diverted from their medical use for dissociative effects.[4] However, only limited knowledge is available concerning addictive disorders linked to amino-adamantane derivatives (e.g., amantadine and memantine), even though their abuse potential has been suspected since the late 1980s.[5] Moreover, visual hallucinations and agitation due to memantine in individuals with Alzheimer's disease have been reported,[6] as well as psychostimulant effects in healthy volunteers with previous stimulant use[7] and recreational use.[8] To our knowledge, there is no such report of diversion with amantadine, even though this drug is commonly used as a CNS stimulant for the treatment of fatigue associated with multiple sclerosis.[9]

In order to identify a possible class effect, we performed a disproportionality analysis in VigiBase®, the WHO pharmacovigilance database. The post-marketing phase is crucial to monitor drug safety and gain insight into the risk–benefit profile, as it reflects real-life use.

What is already known about this subject

- Approved NMDAR antagonists include dextromethorphan, ketamine, amantadine and memantine.
- Ketamine and dextromethorphan are widely diverted from their medical use for dissociative effects.
- Only limited knowledge is available concerning addictive disorders linked to amantadine and memantine, even if their abuse potential has been suspected since the late 1980s.

What this study adds

- A significant disproportionality signal for drug abuse and dependence was found for all investigated NMDAR antagonists, including amantadine and memantine, suggesting a class effect.
- The risks and benefits of long-term treatment with NMDAR antagonists need to be carefully assessed, especially due to their growing interest for use as antinociceptives in the current opioid epidemic context.

2 | METHODS

VigiBase® includes more than 21 million deduplicated individual case safety reports (ICSRs) from over 130 countries. VigiBase® relies on reports made by health professionals, pharmaceutical companies and patients. ICSRs usually contain information on the reporter, the patient (age, gender and medical history), a clinical description of the adverse drug reaction (ADR) along with its seriousness and evolution, and the drug implicated with indication, date and dosage. Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) system and ADRs are coded using the Medical Dictionary for Regulatory Activities (MedDRA). If the proportion of an ADR (i.e., drug abuse and dependence in the current study) reported for a specific drug (dextromethorphan, ketamine, amantadine or memantine) is greater than the proportion of the same ADR reported for a control group of drugs (i.e., the full database), this suggests a potential safety signal called "signal of disproportionate reporting".

NMDAR antagonists included were dextromethorphan (pIC_{50} 6.3),[10] ketamine (pIC_{50} 6.2),[10] amantadine (pIC_{50} 4.7)[10] and memantine (pIC_{50} 6.3),[10] first approved in 1953, 1970, 1966 and 2002, respectively. Drugs with only secondary effects on NMDARs (e.g., methadone, carbamazepine, valproic acid and phenytoin) were excluded from the present study, as well as illegal drugs (e.g., phencyclidine). We extracted all ICSRs associated with the four drugs of interest from VigiBase®, considered either as suspect or concomitant medication and recorded from December 1970 to April 2020, using the broad Standardised MedDRA Query (SMQ) for drug abuse and dependence. SMQs are groupings of MedDRA terms related to a defined medical condition. SMQs are validated after extensive review, testing, analysis and expert discussion by the MedDRA Maintenance and Support Services Organization. The first cases were reported in the mid-1980s for dextromethorphan (1986), ketamine (1986), amantadine (1985) and, more recently, for memantine (2005). The relationship between the use of the drug and the occurrence of the ADR was assessed by calculating the Information Component (IC) and its 95% confidence interval (CI) [IC025; IC975], using a Bayesian confidence propagation neural network (BCPNN). A positive IC025 value is the threshold used for statistical signal detection.

3 | RESULTS

Of the 21 719 830 ICSRs reported to VigiBase® between December 1970 and April 2020, 421 874 were related to drug abuse and dependence, including 2246 for dextromethorphan, 468 for ketamine, 400 for amantadine and 455 for memantine. The ICs were significant for dextromethorphan (IC = 3.03 [2.97–3.09]), ketamine (IC = 1.70 [1.57–1.83]), amantadine (IC = 0.21 [0.06–0.35]) and memantine (IC = 0.27 [0.13–0.40]) (Figure 1). Even if drug abuse and dependence are reported at a disproportionately higher level with dextromethorphan and ketamine, a significant association is also clear for amantadine and memantine, thus favouring a class effect.

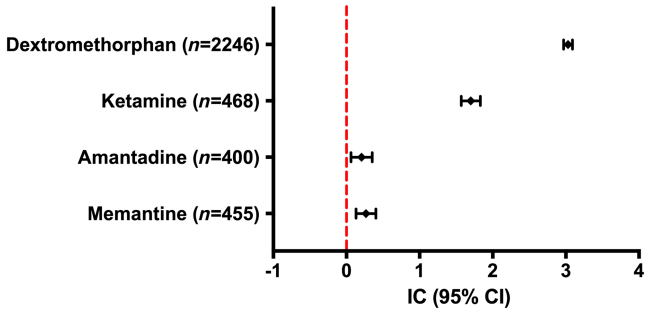

FIGURE 1 Disproportionality signal emerging from the WHO pharmacovigilance database for commercially available NMDAR antagonists. Information component (IC) of drug abuse and dependence (a broad Standardised MedDRA Query (SMQ)) associated with dextromethorphan, ketamine, amantadine and memantine (with 95% CI)

4 | DISCUSSION

Our analysis in the context of real-life data highlights a signal of disproportionate reporting of drug abuse and dependence for ketamine and dextromethorphan, but also for amantadine and memantine, suggesting a possible class effect for all NMDAR antagonist drugs. The BCPNN model, a quasi-Bayesian approach, has demonstrated robustness in identifying disproportionality signals from the data recorded in pharmacovigilance databases.[11] In addition, a deduplicated dataset was used to minimize information bias. However, several limitations should be acknowledged. The results obtained from disproportionality analysis depend upon the drug-related adverse events recorded in pharmacovigilance databases and are limited by underreporting. In our study, reporting is also influenced by a notoriety bias: abuse/dependence is more likely to be considered as being related to ketamine or dextromethorphan than to the other NMDAR antagonists. Moreover, disproportionality analysis is a hypothesis-generating approach that does not allow risk quantification. Thus, the weak signals observed for the amino-adamantane derivatives, amantadine and memantine, should not be considered as alarms but are intended to stimulate active vigilance and further research to establish actual event rates and identify risk factors that might lead to proper patient management.

For years addiction research focused on mechanisms involving dopamine and endogenous opioids. Over the last two decades, increasing attention has been paid to the role of L-glutamate and thus the abuse potential of NMDAR antagonists, which is consistent with the strong signal of disproportionate reporting observed for dextromethorphan in our study. Interestingly, clinical studies report that memantine decreased the positive subjective effects of cigarette smoking and intravenous heroin in humans.[12,13] In contrast, high doses of memantine increased the subjective effects of cocaine.[14] In studies of methamphetamine dependence, it has been demonstrated that memantine–methamphetamine combinations produce novel stimulant effects, and that memantine alone can produce some stimulant-like subjective effects.[7] Memantine and ketamine inhibit NMDARs with similar affinity and kinetics, but memantine preferentially occupies a shallower region of the channel pore.[15] This superficial binding site may, by causal partial trapping, contribute to explain the differences in the potential for abuse between drugs of the same class, although other explanations are possible.[16]

Interest in the role of NMDAR antagonists has recently increased for the treatment of opioid-resistant and neuropathic pain. A recent meta-analysis of controlled trials examined the analgesic effects of NMDAR antagonists.[2] The incidence of adverse effects was computed from 37 studies. The main ADRs were sedation, feeling of drunkenness, dizziness, drowsiness, out-of-body sensations, paraesthesia and nausea. Specific complications have also been reported with long-term ketamine abuse, including cognitive, mental, gastrointestinal and lower urinary tract symptoms. Although only affecting those who take high doses for a prolonged time, the side effects of bladder toxicity from chronic ketamine misuse are very serious.[17] Given the potential for abuse, the risks and benefits of long-term NMDAR antagonist treatment needs to be carefully assessed, especially in the current opioid epidemic context.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[18]

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COMPETING INTERESTS

The authors declare they have no conflicts of interest.

CONTRIBUTORS

B.R. and E.J. contributed to the study design, analysis of the data, and drafting the manuscript. M.L.-M. and N.F.S.-L. were responsible for acquisition of data, supervised the study and critically revised the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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