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PHARMACOLOGICAL TREATMENTS

Psychosis with use of amphetamine drugs, methylphenidate and atomoxetine in adolescent and adults

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ABSTRACT

Background Use of psychostimulants and relative drugs has increased worldwide in treatment of attention-deficit hyperactivity disorder (ADHD) in adolescents and adults. Recent studies suggest a potential association between use of psychostimulants and psychotic symptoms. The risk may not be the same between different psychostimulants.

Objective To assess whether amphetamine or atomoxetine use is associated with a higher risk of reporting symptoms of psychosis than methylphenidate use in adolescents and adults, particularly in patients with ADHD.

Methods Using VigiBase, the WHO's pharmacovigilance database, disproportionality of psychotic symptoms reporting was assessed among adverse drug reactions related to methylphenidate, atomoxetine and amphetamines, from January 2004 to December 2018, in patients aged 13–25 years. The association between psychotic symptoms and psychostimulants was estimated through the calculation of reporting OR (ROR).

Findings Among 13 863 reports with at least one drug of interest, we found 221 cases of psychosis with methylphenidate use, 115 with atomoxetine use and 169 with a prescription of an amphetamine drug. Compared with methylphenidate use, amphetamine use was associated with an increased risk of reporting psychotic symptoms (ROR 1.61 (95% CI 1.26 to 2.06)]. When we restricted the analysis to ADHD indication, we found a close estimate (ROR 1.94 (95% CI 1.43 to 2.64)). No association was found for atomoxetine.

Conclusion Our study suggests that amphetamine use is associated with a higher reporting of psychotic symptoms, compared with methylphenidate use.

Clinical implications The prescription of psychostimulants should consider this potential adverse effect when assessing the benefit–risk balance.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ International guidelines recommend psychostimulants (eg, methylphenidate, dexamfetamine, lisdexamfetamine) and non-psychostimulants (eg, atomoxetine, guanfacine) for managing attention-deficit hyperactivity disorder. Recent studies suggest that amphetamine potentially has a higher risk of inducing psychosis compared with methylphenidate.

WHAT THIS STUDY ADDS

⇒ Using the largest pharmacovigilance database VigiBase, the WHO Global Individual Case Safety Reports database, this study provides evidence that amphetamine use is linked to a higher risk of reporting psychotic symptoms compared with methylphenidate use, consistent with previous findings. Nevertheless, we were unable to exclude the possibility of confounding by disease severity as an explanation for the increased risk observed with amphetamines compared with methylphenidate uses.

⇒ No significant association between atomoxetine use and risk of reporting psychotic symptoms has been identified.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study's findings emphasise the importance of considering the potential risk of psychosis when prescribing psychostimulants in clinical practice.

⇒ Concerning atomoxetine use, it is necessary to compare our results with other observational studies to rule out the risk of such adverse events.

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by a persistent pattern of inattention and/or hyperactivity–impulsivity that interferes with functioning or development.[1 2] International guidelines[3] concerning the pharmacological treatment of ADHD suggest the use of psychostimulants (mostly methylphenidate, dexamfetamine, lisdexamfetamine) and non-psychostimulants (atomoxetine, guanfacine). No specification of preference between methylphenidate and lisdexamfetamine is made for pharmacological management of adults with ADHD. Dexamfetamine and atomoxetine are recommended respectively in second- and third-line treatment in these guidelines.

Psychostimulants, such as amphetamine and amphetamine-like (methylphenidate), are known to block the dopamine transporter, which inhibits the reuptake of dopamine in presynaptic terminals,

and enhance the dopamine and norepinephrine releases, mainly (when they are used in normal condition of prescription) in the prefrontal cortex. According to some studies, the release of dopamine may be four times greater with amphetamine than with methylphenidate.[4] Atomoxetine also increases dopamine and norepinephrine release in the prefrontal cortex.[5]

Among the potential side effects of methylphenidate, amphetamines and atomoxetine, the risk of onset of psychosis episode was reported.[6] The occurrence of psychotic symptoms and disorders with these drugs could be explained by increased concentrations of synaptic dopamine. In a review requested by the US Food and Drug Administration in 2008, data of 49 randomised controlled clinical trials were analysed and concluded that 'patients and physicians should be aware that psychosis or mania arising during drug treatment of attention-deficit/hyperactivity disorder may represent adverse drug reactions'.[7] In 2018, a Cochrane systematic review with meta-analysis and trial sequential analysis (with 10 randomised trials (1103 participants), 17 non-randomised studies (76 237 participants) and 12 patient reports) could not confirm or refute whether methylphenidate increases the risk of psychotic symptoms.[8] More recently, a large cohort study (221 846 adolescents and young adults), using data from two US administrative claims databases, found 343 episodes of psychosis, with 106 episodes in the methylphenidate group and 237 episodes in the amphetamine group. The study concluded that amphetamine use was associated with a greater risk of psychosis than methylphenidate use (with an HR across both databases of 1.65 (95% CI 1.35 to 2.09)).[9]

Furthermore, very few recent studies have assessed the risk of developing psychotic symptoms with atomoxetine compared with methylphenidate. A 2015 study,[10] by Cortese *et al* conducted using the Italian National ADHD Registry, demonstrates a higher risk of hallucinations following the use of atomoxetine compared with methylphenidate and concluded in favour of a better safety profile of methylphenidate.

Objective

We aimed to corroborate or not results from Moran *et al* using a different method and a different source of data. In our study, we used the largest pharmacovigilance database VigiBase, the WHO Global Individual Case Safety Reports database, to assess whether amphetamine or atomoxetine use is associated with a higher risk of reporting symptoms of psychosis than methylphenidate use in adolescents and adults with ADHD.

METHODS

Data source

We conducted a pharmacovigilance analysis (with a case–non-case method) using the WHO pharmacovigilance database VigiBase. This database, which includes more than 37 million reports and covers 90% of the world population from 130 countries, includes adverse case reports since 1967.[11] Each report contains variable amounts of information depending on the submitting countries. Each report originates from different sources such as physicians, pharmacists and other healthcare professionals as well as non-healthcare professionals. Reports from clinical trials represent a small proportion of the reports found in VigiBase. Data available are information about patients (age, sex, country), drugs (indication, concomitant drugs, route of administration, dose), notifications (date, reporter qualification), adverse drug reactions and coreported reactions coded using the Medical Dictionary for Regulatory Activities (MedDRA).[12]

Study population

For primary analysis, we included all Individual Case Safety Reports registered between 1 January 2004 and 31 December 2018 (same date that Moran's study). For the sake of scientific replicability and to corroborate the results of Moran *et al* study using a different methodology, we limited our main analysis to patients between 13 and 25 years old and with at least one medication among treatments recommended for management of ADHD: psychostimulant (methylphenidate, dexamfetamine, lisdexamfetamine) and non-psychostimulant treatment (atomoxetine). Drug prescription defined as 'suspected' in the report was included, that is, the involvement of the drug in the adverse reaction has been recognised by a pharmacovigilance authority. Patients with a prescription of antipsychotic drugs, mood stabilisers, other stimulant drugs (phentermine, pemoline or methamfetamine) or glucocorticoids were excluded. We also excluded patients who took medication with a specified indication of psychotic disorder, mood disorder with psychotic features, bipolar disorder and central nervous system disorder. In secondary analyses, we extended our study to patients aged 13–65 years.

Case and non-case definition

The outcomes of interest were psychotic symptoms or psychotic disorders. Cases were identified by the standardised MedDRA queries (SMQs) 'psychosis and psychotic disorders'. Narrow criteria have been chosen for the primary analysis (online supplemental file 1). Non-cases were all other reports recorded in VigiBase during the same period. We also identified patients with the mentioned indication of ADHD among cases and non-cases. In secondary analyses, a more specific definition of psychotic disorders was identified in the 'psychosis and psychotic disorders' section of the SMQs by a psychiatrist (JH) and a psychopharmacologist (FM).

Exposure definition

For all cases and non-cases, we identified patients exposed to methylphenidate (reference category), amphetamine (dexamfetamine and lisdexamfetamine) and atomoxetine. Reports with a prescription of two or more of these treatments were excluded.

Data analysis

Descriptive statistics were used to compare characteristics of the different medications for ADHD (methylphenidate, dexamfetamine, lisdexamfetamine, atomoxetine). The primary analysis estimated the risk of reporting psychotic symptoms or psychotic disorders in patients exposed to amphetamine or atomoxetine compared with those exposed to methylphenidate. We performed disproportionality analyses, using case–non-case method, which is similar to case–control study but adapted to pharmacovigilance databases.[13–15] This analysis allows the calculation of reporting ORs (RORs), with their 95% CI, of the exposure odds among reported cases of psychosis to the exposure odds among reported non-cases (online supplemental file 2).

The ROR of a combination of interest drug–adverse drug reaction was defined as the ratio between proportions of reports containing the drug of interest in the 'case' (reports containing the adverse drug reaction of interest) and in the 'non-case' (reports containing other adverse drug reactions) groups.

To control for potential confounding factors, we adjusted RORs on the following covariates: age, sex, type of reporters and countries.

In our secondary analysis, we extended our study to patients aged 13–65 years and performed subgroup analyses according to age (13–17 years old, 18–25 years old, 26–35 years old, 36–45 years old, 46–65] years old).

We performed several sensitivity analyses to assess the robustness of our study by limiting the analyses to reports reported by a health professional, restricting the study period to the last 5 years and limiting it to US reports. In order to test potential confounding bias, we performed negative control analyses. Like Moran's team, we considered that a higher risk of psychosis with amphetamine compared with methylphenidate or atomoxetine could be explained by a more severe psychiatric illness among amphetamine users. Therefore, we conducted analyses to estimate the difference between the amphetamine, methylphenidate and atomoxetine groups for the risk of reporting depression. We selected one criterion: 'major depression', aiming for greater specificity and to minimise the potential for confounding bias. For this analysis, we excluded any reports with coreported terms related to psychotic symptoms.

Ethics

According to the French law on clinical research, review from an ethics committee is not required for such observational studies. As all data from VigiBase were deidentified, patient informed consent was not necessary.

RESULTS

During the study period, out of 22 389 532 included in VigiBase, 46 350 reports contained at least one of the four drugs studied (methylphenidate, dexamfetamine, lisdexamfetamine, atomoxetine). After applying exclusion criteria, there were 31 009 reports of patients aged 13–65 years (figure 1). More than two-thirds of the reports came from the USA (70.3%), followed by Canada (4.7%), the Netherlands (4.2%) and Germany (3.1%). The highest number of reports (5453) was found in 2015. Among all the cases, 15 554 (50%) had the indication of ADHD. There were 13 863 reports of patients being between 13 and 25 years. The male/female sex ratio in the study population was 1.58 and the mean age was 17.24±3.59 years. 'Serious' cases, defined as any unintended, harmful and undesirable effect leading to hospitalisation, significant or persistent disability, life-threatening conditions, congenital abnormalities, or patient death, constituted 38% of these reports. The median completeness score, which measures the level of completeness of each report (between 0 and 1) was 0.45±0.23. Among the 13 863 reports included in our final selection, we identified 6037 reports

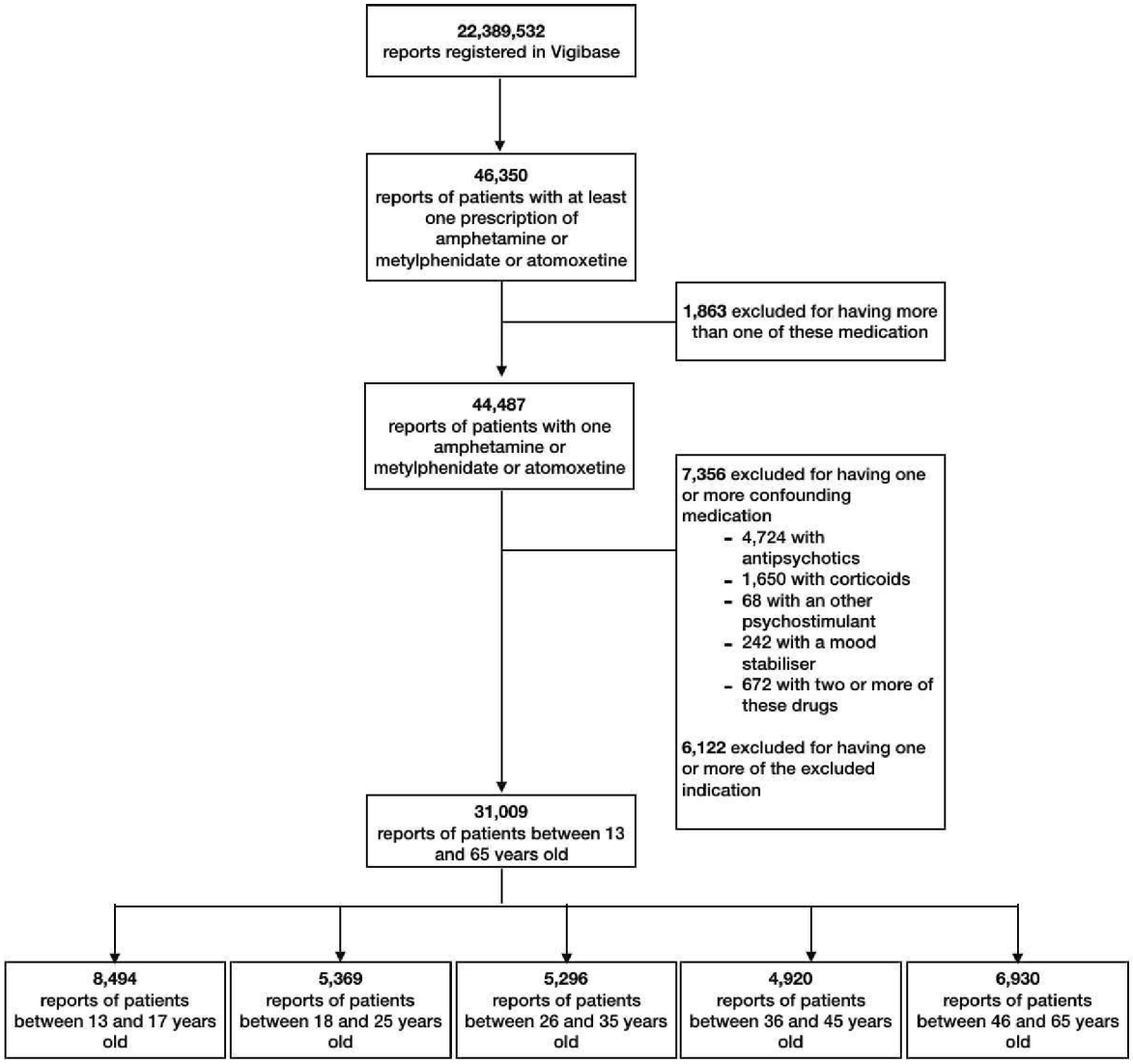

Figure 1 Flow chart of the selection of reports.

Table 1 Characteristics of psychotic symptoms reported in patients between 13 and 25 years old

	Methylphenidate		Atomoxetine		Amphetamine drugs	
	Reports	%	Reports	%	Reports	%
Total	221	100.0	115	100	169	100
Age (years)						
13–17	147	66.5	66	57.4	73	43.2
18–25	74	33.5	49	42.6	96	56.8
Sex						
Female	75	34.0	30	26.1	59	34.9
Male	146	66.0	85	73.9	110	65.1
ADHD indication	119	53.8	66	57.4	105	62.1
Continent						
Africa	4	1.8	2	1.7	0	0.0
Americas	75	34.0	74	64.3	150	88.8
Asia	15	6.8	3	2.6	0	0.0
Europe	124	56.0	31	27.0	16	9.4
Oceania	3	1.4	5	4.3	3	1.8
USA	59	26.7	66	57.4	138	81.7
Cases reported by healthcare professional						
Physician	108	48.9	57	49.6	43	25.4
Pharmacist	10	4.5	2	1.7	11	6.5
Serious adverse effect	172	77.8	66	57.4	140	82.8

ADHD, attention-deficit hyperactivity disorder.

with a prescription of methylphenidate, 4014 with atomoxetine and 3812 with an amphetamine medication (dexamfetamine or lisdexamfetamine). Among all these reports, there were 7741 reports of patients with the mentioned indication of ADHD (online supplemental file 3).

Concerning psychotics symptoms, when the narrow criteria of the SMQs 'psychosis and psychotic disorders' were applied, we found 221 reports with methylphenidate use, 115 with atomoxetine use and 169 with a prescription of medication of the amphetamine group (table 1). The adjusted ROR (95% CI) of any psychotic symptoms associated with use of amphetamine (dexamfetamine, lisdexamfetamine) was 1.61 (1.26 to 2.06) relative to methylphenidate (figure 2). We found a non-significant adjusted ROR (95% CI) of psychotic symptoms associated with atomoxetine use of 0.89 (0.70 to 1.13) compared with methylphenidate (figure 3). When reports were restricted to cases with a notified indication of ADHD, we found adjusted ROR for psychotic symptoms associated with amphetamine use of 1.94 (1.43 to 2.64) and associated with atomoxetine use of 0.85 (0.61 to 1.17), as compared with methylphenidate.

Secondary analyses showed overall persistent association between amphetamine use and psychotic symptoms compared with methylphenidate use for subgroups of reports between 13 and 35 years old. However, we did not find any risk of reporting

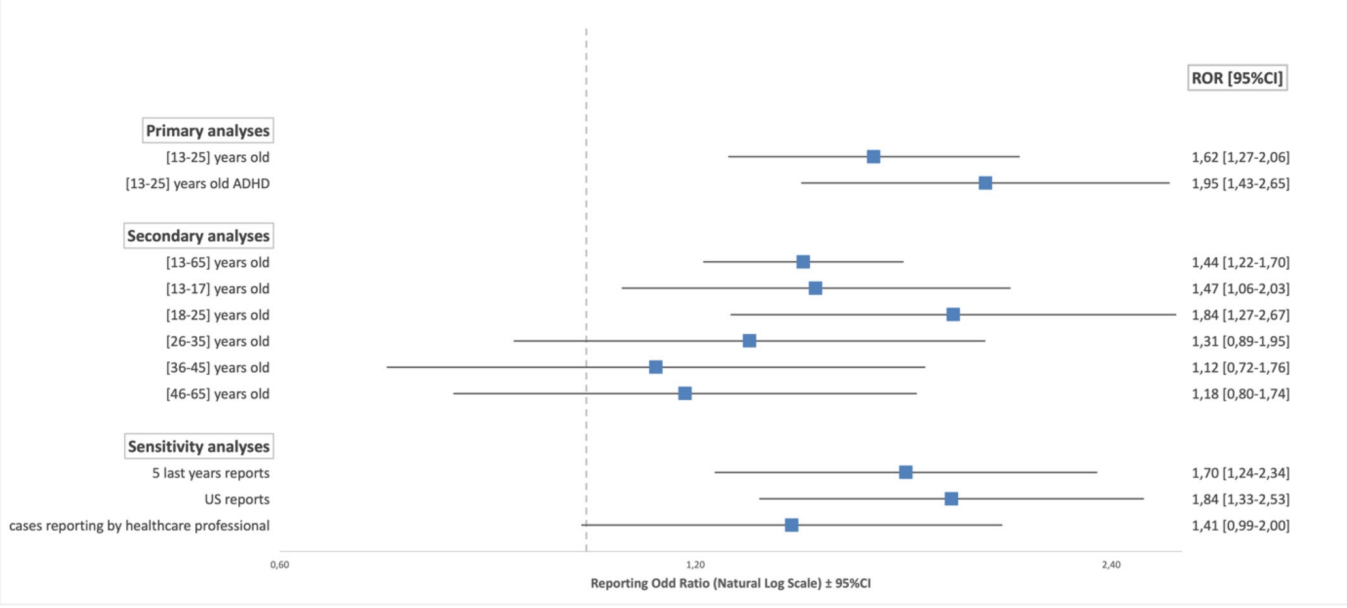

Figure 2 Forest plot of the association between the risk of reporting psychotic symptoms with amphetamine use compared with methylphenidate use. ROR, reporting odds.

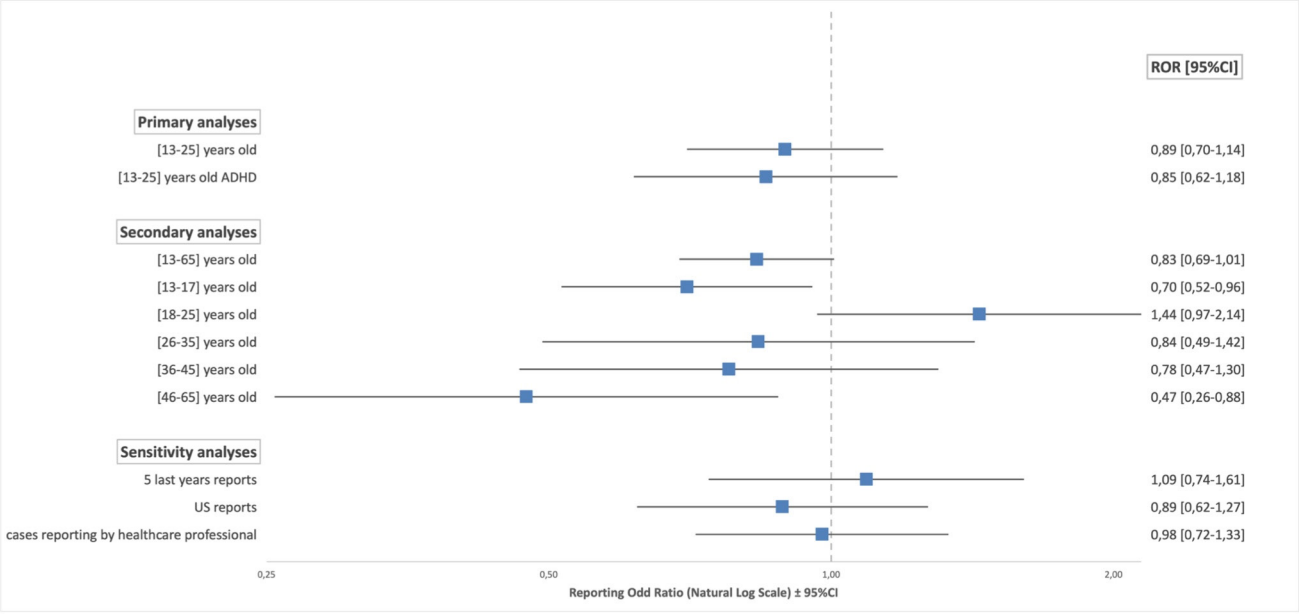

Figure 3 Forest plot of the association between the risk of reporting psychotic symptoms with atomoxetine use compared with methylphenidate use. ROR, reporting odds.

psychosis in the age ranges of 36–45 years old and 46–65 years old (figure 2). Concerning association between atomoxetine use and the risk of reporting psychotic symptoms, we did not find any association compared with methylphenidate use. In order to refine our results, we performed analyses with chosen restricted criteria from the SMQs 'psychosis and psychotic disorders'. We found a similar association between amphetamine use with psychotic symptoms with an ROR of 1.57 (95% CI 1.19 to 2.07) relative to methylphenidate use. Concerning risk of psychotic symptoms with atomoxetine use relative to methylphenidate use, we found a non-significant ROR of 0.96 (95% CI 0.73 to 1.27). Sensitivity analyses restricted to reports declared by a healthcare professional, restricted to the last 5 years of study period and restricted to US reports showed consistent results with our main analyses (figure 2). In negative control analyses, we found an adjusted ROR of 1.57 (95% CI (1.20 to 2.07)) when we compared amphetamine with methylphenidate groups and 1.74 (95% CI (1.36 to 2.22)) when we compared atomoxetine with methylphenidate groups.

DISCUSSION

Our comparative study included more than 30 000 reports of patients between 13 and 65 years old exposed to one of the studied medications. Our results suggest that amphetamine use was associated with a higher reporting of psychotic symptoms, compared with methylphenidate use. This association remained consistent when we performed analyses on reports that specifically contained the indication of ADHD. These findings for amphetamine and risk of psychotic symptoms were similar in sensitivity analyses. In our study, we did not find any significant association between atomoxetine use and any higher risk of reporting psychotic symptoms, compared with methylphenidate use.

These results add more evidence regarding the risk of developing psychotic symptoms after using amphetamines compared with other psychostimulants. Indeed, with the data from the worldwide pharmacovigilance database, VigiBase, we found an estimate close to the HR in Moran's study (ROR=1.61 (95% CI 1.26 to 2.06) and HR=1.65 (95% CI 1.31 to 2.09), respectively). Moreover, it is interesting to note the replicability of results from patient cohorts through the analysis of pharmacovigilance data. This was the subject of a recent study by Khouri *et al*,[16] which aimed testing if there is a correlation between adverse drug reaction relative risks estimated from meta-analyses and disproportionality analyses calculated from pharmacovigilance databases. They found that the relative risks obtained from meta-analyses and disproportionality analyses correlate in most cases. This study was realised on a panel of 13 adverse drug reaction drugs, with several from antipsychotic drugs.

One of the leading hypotheses for schizophrenia and psychotic disorder is based on dysfunction of dopamine neurotransmission. At synaptic level, this dysfunction would be mainly presynaptic, which would affect the capacity of dopaminergic synthesis, causing an increase in intrasynaptic dopamine concentrations.[17] This dysfunction could be more severe in mesolimbic area and hyperactivity of the dopamine pathway hypothetically accounts for positive psychotic symptoms.[18]

Our findings are consistent with this hypothesis and with the pharmacodynamic properties of psychostimulants and their modulation of the dopaminergic system. Methylphenidate and amphetamines are structurally related and have similar effects on the central nervous system. Both block dopamine active transporter (DAT) and norepinephrine transporter (NET), stopping the reuptake of dopamine via DAT and norepinephrine via NET. The crucial pharmacodynamical difference between these medications is that methylphenidate binds NET and DAT at sites distinct from where monoamines bind NET and DAT allosterically. Inhibition of monoamine reuptake enhances dopamine and norepinephrine release and increases concentrations of synaptic dopamine and norepinephrine.[19 20]

This pharmacovigilance study supports a consistent literature of clinical cases that first alerted practitioners to this potential adverse effect of psychostimulants.[21 22] Nevertheless, it should be noted that the literature has shown controversial findings about the potential link between methylphenidate, psychostimulants and the development of psychotic symptoms.[23] In a recent

study, Hollis *et al* used population-based observational data from three population-based registers containing data on all individuals in Sweden to identify individuals receiving methylphenidate treatment. Then Hollis *et al* used a within-individual design to compare the incidence of psychotic events in these individuals during the 12-week periods immediately before and after methylphenidate initiation to identify the emergence of psychotic symptoms. In this study, they found no evidence that initiation of methylphenidate treatment increases the risk of psychotic events in adolescents and young adults.[24]

A 2015 population-based study conducted on 12 856 young people who received a stimulant prescription and were subsequently hospitalised for psychosis or mania, using data from the Ontario Drug Benefit Database and the Canadian Institute for Health Information, concluded that initiation of prescription stimulants was associated with an increased risk of hospitalisation for psychosis or mania.[25]

In our study, we did not find any significant association between atomoxetine use and risk of reporting psychotic symptoms. However, regarding results of the negative control analyses, the significant differences between the amphetamine and atomoxetine groups compared with the methylphenidate group could be explained by an indication bias. Indeed, atomoxetine can be prescribed for treating depression. Moreover, despite our efforts to limit bias, it is possible that reports of patients using amphetamine could have a more severe psychiatric illness than those using methylphenidate.

This study presents several limitations. First, despite the important work of the Uppsala Monitoring Center in terms of collection and checking of reports, the completeness of information collected in VigiBase is not always guaranteed, and even basic information such as age or sex can be missing. To avoid this bias, we excluded reports in which these data were missing in the adjusted analyses. Other information potentially useful is sometimes missing such as patient's medical history or certain parameters linked to the drug of interest or comedications (doses, duration of treatment, etc). Second, the bias of underreporting is an important limitation to this type of pharmacovigilance study.[15] Indeed, the rate of reports can vary according to many factors such as the severity of adverse drug reactions or the time of the first occurrence of the adverse drug reaction. This also explains why this type of study can only provide an imprecise estimation of adverse drug reaction frequencies. However, there is no reason to think that there are some differences in reporting rates between 'cases' and 'non-cases'. Third, we used the MedDRA dictionary for the identification of psychotic symptoms, which can lack precision, especially with complex clinical entities such as psychotic symptoms and disorders. Fourth, one limitation concerns the results of the negative analysis. These would imply an over-reporting of major depressions following atomoxetine and amphetamine use compared with methylphenidate use. These findings differ from those of Moran *et al*.

Our study has several strengths. First, the study was performed using the world's largest pharmacovigilance database, including >40 000 patients treated with psychostimulants from 130 countries. These results from a large database increase the external validity of our findings. Second, unlike clinical trials, reports from VigiBase are based on real-life data and prescriptions. Third, we used reports recorded over 15 years, which also makes it possible to identify certain adverse drug reactions occurring at a distance from the treatment. For the risk of reporting psychotic symptoms, the sensitivity analyses for recent years were consistent with the primary analyses. Finally, act of reporting to an official system of pharmacovigilance assumes a potential link between drug exposure and the occurrence of the event, if the drug is recognised as 'suspect' after case assessment by a pharmacovigilance team.

Clinical implications

Our study suggests that amphetamine use is associated with a higher reporting of psychotic symptoms, compared with methylphenidate use. Nevertheless, with the lack of precise data regarding the medical records associated with the reports, it is unclear whether the increased association of amphetamine with psychosis may be attributed to greater psychiatric severity in individuals treated with amphetamines versus methylphenidate. These results corroborate results found by Moran *et al*. We did not find any significant association between atomoxetine use and risk of reporting psychotic symptoms. To our knowledge, this is the first study trying to bring to light this kind of association with atomoxetine. In clinical practice, the prescription of psychostimulants should consider this potential adverse effect when assessing the benefit–risk balance. Concerning atomoxetine use, it is necessary to compare our results with other observational studies to rule out the risk of such adverse events.

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Contributors JH: conceptualisation, methodology and writing. FM: conceptualisation and methodology. VR: data curation and formal analysis. AR and AY: methodology, validation and writing (review). GD, PG and AS: methodology and validation. FM as chief investigator had overall responsibility for the management of the study and was responsible for the overall content as a guarantor, had access to the data, controlled the decision to publish, and accepts full responsibility for the work and/or the conduct of the study.

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