Comparative Effects of 30 Antipsychotics on Risk of Catatonia:
An Analysis of the WHO Pharmacovigilance Database

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ABSTRACT

Objective: Catatonia is a life-threatening psychomotor syndrome that occurs in approximately 10% of patients with acute psychiatric illnesses. Although some case reports have argued that first generation antipsychotics (FGAs) are more likely to induce catatonia than second generation antipsychotics (SGAs), no large observational study has confirmed this hypothesis. We investigated whether FGAs were associated with an increased risk of reporting catatonia when compared with SGAs.

Methods: A pharmacovigilance study was performed within VigiBase to compare the cases of catatonia syndromes reported in patients exposed to FGAs with those reported in patients exposed to SGAs. This approach is similar in concept to case-control study, but adapted to a pharmacovigilance database, and allows the estimation of reporting odds ratios (RORs) with 95% confidence intervals.

Results: We identified 60,443 adverse effects reported in patients who received FGAs and 253,067 adverse effects reported in patients treated with SGAs. Compared with SGAs, the use of FGAs was associated with an increased risk of reporting catatonia syndromes (ROR = 2.2; 95% CI, 2.0–2.3). Consistent results were observed when the analysis was restricted to reports generated from physicians, reports from the US, and reports with the highest completeness score. The highest RORs were found for molindone (6.0; 95% CI, 3.1–10.4) and haloperidol (3.8; 95% CI, 3.5–4.0).

Conclusions: In this large pharmacovigilance study of patients exposed to antipsychotics, the use of FGAs was associated with an increased risk of reporting catatonia syndromes compared to the use of SGAs. This increased risk is consistent with the pharmacodynamic hypothesis of antipsychotic-induced catatonia. Our results warrant replication in population-based studies.

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Catatonia is a severe and life-threatening psychomotor syndrome including several symptoms such as motor, behavioral, or affective disturbances, sometimes accompanied by autonomic dysfunction and fever.[1] Several studies based on systematic screening in psychiatric and medical admissions found a prevalence of 4% to 33%.[2] Many physical or psychiatric conditions have been identified as etiologies of catatonia. Among them are mood disorders, schizophrenia, infectious illnesses, substance abuse, and autoimmune disorders such as *N*-methyl-D-aspartate receptor (NMDAR) antibody encephalitis.[3,4] Moreover, some authors argue that catatonia syndromes can be precipitated by the prescription of antipsychotic drugs,[5] which supports theories that the neuroleptic malignant syndrome (NMS) is part of the catatonia spectrum.[6,7] The incidence of NMS, which has several clinical similarities with malignant or lethal catatonia, is estimated to be around 0.01%–0.02%, with a mortality rate estimated around 10%.[8,9] Although some authors argue that first generation antipsychotics (FGAs), by their higher blockade of D_2 dopamine receptor activity, are more likely to induce catatonia syndromes than second generation antipsychotics (SGAs), catatonia syndromes have also been reported with SGAs.[3,10–12] Those recommendations are contradictory and mainly based on case reports.

Given these uncertainties, and since to date no study has had enough power to compare the risk of catatonia syndromes between antipsychotics, additional studies are necessary to determine this risk. VigiBase, the World Health Organization (WHO) global Individual Case Safety Reports (ICSRs) database, which includes more than 22 million reports (as of January 2021), can be useful for conducting studies on rare and specific clinical outcomes such as catatonia syndromes.[13] A recent study showed that relative risks obtained from meta-analyses of clinical trials and from pharmacovigilance studies are well correlated.[14] Thus, we investigated within VigiBase whether the use of FGAs was associated with an increased risk of reporting catatonia syndromes when compared with the use of SGAs. In addition, we aimed to better inform clinical practice by comparing different SGAs and FGAs for the risk of reporting catatonia syndromes.

Clinical Points

- To date, no study has had enough power to compare the risk of catatonia between antipsychotics.
- In this pharmacovigilance study, first generation antipsychotics were associated with more reporting of catatonia syndromes than second generation antipsychotics.
- Clinicians should remain careful when considering prescribing first generation antipsychotics for patients with a history of or at great risk of developing catatonia.

METHODS

Data Sources

We conducted a postmarketing study within VigiBase, which is maintained by the Uppsala Monitoring Centre. VigiBase stores ICSRs with contributions from national pharmacovigilance programs of more than 130 countries. Adverse effects are reported post marketing by physicians, patients, and pharmaceutical companies. VigiBase uses the Medical Dictionary for Regulatory Activities (MedDRA) to code adverse effects. The database also records the patient's demographics, reporter's qualification, seriousness of the adverse effect, drugs used at the time of the adverse effect, a causality assessment for each drug, and additional information relevant to the case. Moreover, each report is associated with a completeness score, which indicates the level of quality of information of a report (value ranges from 0 to 1,000).[15] This score is calculated by taking into consideration 10 dimensions, including time from treatment start to the suspected adverse effect, indication for treatment with the drug, and outcome of suspected adverse effect in the patient. If information is missing or unknown, the ICSR receives penalties that reduce the completeness score. Duplicate ICSRs are detected by individual case review or by computerized duplicate detection algorithms and are ruled out of the database. According to the French clinical research law, 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.

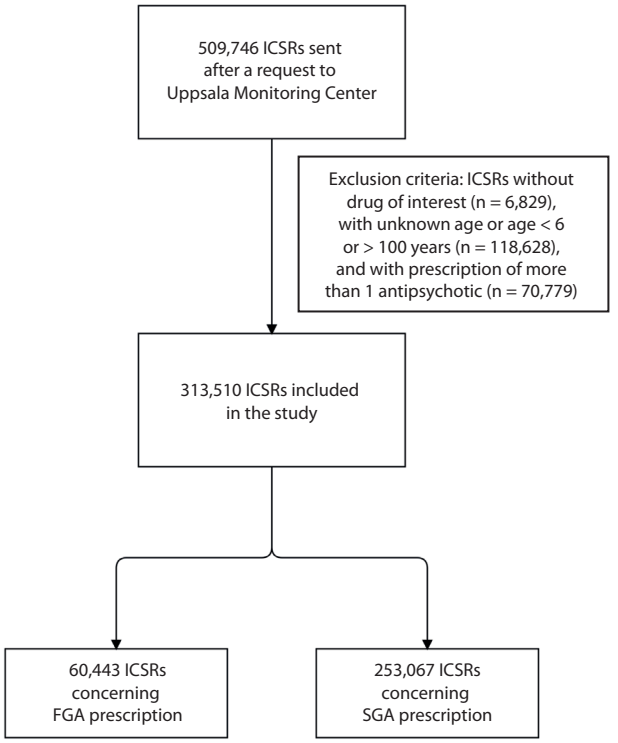
Study Population

We considered all ICSRs registered from January 1, 1967, to December 31, 2018, of all patients with known age and sex, from any country in the world. All patients 6 years or older at the date of ICSRs and with at least 1 antipsychotic prescription were included. The inclusion of children and adolescents was motivated by increasing concern in the recent literature regarding the occurrence of catatonic syndrome in this population, especially in those with autism spectrum disorder.[16,17]

Case and Non-Case Definitions

Within the selected ICSRs, we performed a disproportionality analysis using the case non-case method, which is similar to the case-control method but adapted for pharmacovigilance studies.[13] Thus, cases were ICSRs of catatonia syndromes including benign catatonia, malignant catatonia, and NMS. Cases were identified with all subterms retrieved using the MedDRA terms "Catatonia," "Malignant Catatonia," and "Neuroleptic Malignant Syndrome" (NMS).[6] Non-cases were all other ICSRs recorded in VigiBase during the same period.

Figure 1. Study Flowchart



Abbreviations: FGA = first generation antipsychotic, ICSR = Individual Case Safety Report, SGA = second generation antipsychotic.

Exposure Definition

For all cases and non-cases (controls), we identified all prescriptions of antipsychotics. For that, we used the WHO Anatomic Therapeutic Chemical (ATC) classification and included all drugs identified as "neuroleptics," which we separated into 2 categories: FGAs and SGAs. Despite their categorization as antipsychotics in the ATC classification, the following drugs were excluded from our study: lithium, because it is not prescribed for antipsychotic purposes, and oxypertine, as its prescription is very uncommon in clinical practice. For the primary analysis, we excluded ICSRs with more than 1 antipsychotic prescription to avoid confounding by disease severity. The list of 64 antipsychotics is shown in Supplementary Table 1.

Statistical Analysis

As a primary analysis, we estimated the risk of reporting catatonia syndromes by performing a disproportionality analysis allowing the calculation of the reporting odds ratios (ROR) with their 95% confidence intervals (95% CIs). The

Table 1. Characteristics of Catatonia Reports (Cases) and Other Reports (Non-Cases) With First and Second Generation Antipsychotics

	First generation antipsychotics		Second generation antipsychotics	
	Cases[a]	Non-cases[b]	Cases[a]	Non-cases[b]
Patients, n	1,862	58,581	3,557	249,510
Age, mean ± SD, y	48.5 ± 21.02	46.5 ± 20.6	47.0 ± 18.9	43.2 ± 18.3
Age in groups, n (%)				
6–11 y	13 (0.7)	1,017 (1.7)	30 (0.8)	4,926 (2.0)
12–17 y	90 (4.8)	2,652 (4.5)	160 (4.5)	10,715 (4.3)
18–34 y	449 (24.1)	16,238 (27.7)	845 (23.7)	72,303 (29.0)
35–65 y	848 (45.5)	25,903 (44.2)	1,853 (52.1)	130,560 (52.3)
66 + y	462 (24.8)	12,771 (21.8)	669 (18.8)	31,006 (12.4)
Sex, female, n (%)	759 (40.8)	32,770 (55.9)	1,436 (40.4)	118,084 (47.3)
Reporting period, n (%)				
1968–1969	…	594 (1.0)	…	…
1970–1979	6 (0.3)	4,733 (8.1)	…	80 (-)
1980–1989	130 (7.0)	7,489 (12.8)	2 (0.1)	189 (0.1)
1990–1999	621 (33.4)	10,190 (17.4)	314 (8.8)	21,070 (8.5)
2000–2009	417 (22.4)	10,498 (17.9)	1,405 (39.5)	64,917 (26.0)
2010–2018	688 (37.0)	25,077 (42.8)	1,836 (51.6)	163,254 (65.4)
Region reporting, n (%)				
Americas	649 (34.9)	15,308 (26.1)	1,520 (42.7)	116,102 (46.5)
US	587 (31.5)	9,970 (17.0)	1,309 (36.8)	100,452 (40.3)
Europe	736 (39.5)	26,167 (44.7)	1,216 (34.2)	83,724 (33.6)
France	192 (10.3)	7,851 (13.4)	143 (4.0)	7701 (3.1)
Germany	76 (4.1)	4,363 (7.5)	140 (3.9)	11,369 (4,6)
United Kingdom	170 (9.1)	4,417 (7.5)	474 (13.3)	37,755 (15.1)
Asia	347 (18.6)	12,605 (21.5)	488 (13.7)	34,354 (13.8)
China	9 (0.5)	1,950 (3.3)	17 (0.5)	8,658 (3.5)
Japan	193 (10.4)	1,353 (2.3)	304 (8.6)	4,167 (1.7)
Singapore	71 (3.8)	1,584 (2.7)	29 (0.8)	546 (0.2)
Oceania	106 (5.7)	3,732 (6.4)	307 (8.6)	14,154 (5.7)
Africa	24 (1.3)	769 (1.3)	26 (0.7)	1,176 (0.5)
Reporter qualification, physician, n (%)	650 (34.9)	21,288 (36.3)	1,540 (43.3)	94,836 (38.0)
Serious, n (%)	718 (38.6)	13,949 (23.8)	2,157 (60.6)	107,841 (43.2)
Death, n (%)	241 (12.9)	2,680 (4.6)	310 (8.7)	23,726 (9.5)
Completeness score,[c] mean ± SD	488.5 ± 231	533.5 ± 241	471.0 ± 224	486.9 ± 234

[a]Cases were reports containing all subterms retrieved using the MedDRA terms "catatonia," "malignant catatonia," and "neuroleptic malignant syndrome."
[b]Non-cases were all other reports recorded in VigiBase.
[c]Completeness score indicates the level of quality of information of a report (value ranges from 0 to 1,000).

ROR, similar in concept to the odds ratio in case-control studies, is the ratio between the exposure odds among reported cases of catatonia and the exposure odds among reported non-cases.[13] To control for potential confounding, we adjusted ROR on the following covariates: age, sex, type of reporter, region, and number of other non-antipsychotic drugs prescribed (0, 1–2, > 2). We also stratified the primary analysis on age (6–11 years, 12–17 years, 18–34 years, 35–65 years, and over 65 years) and sex (male, female).

As a secondary analysis, we assessed the risk of reporting catatonia syndromes for the 64 FGAs and SGAs on the list of interest. In this analysis, we only considered antipsychotics on the list of interest with at least 10 ICSRs of catatonia syndromes. The RORs were adjusted on the following covariates: age, sex, type of reporter, region, and number of other non-antipsychotic drugs prescribed (0, 1–2, > 2). As a third analysis, we also estimated the risk of reporting catatonia syndromes with the use of 1 antipsychotic drug on the list of interest versus the use of 2 or more antipsychotic drugs.

Sensitivity Analyses

To assess the robustness of our study, we conducted 6 sensitivity analyses for the primary analysis. First, we restricted the study period to January 1, 2009, to December 31, 2018, to minimize variability of risk estimation over the time. Second, we included only ICSRs disclosed by physicians because the diagnoses of adverse drug effects may be more specific. Third, we repeated the primary analysis including only ICSRs from the US, as most ICSRs originate from this country. Fourth, we restricted the analysis to ICSRs with a completeness score > 600. Finally, we performed 2 analyses changing the outcome definition using only the terms "malignant catatonia" or "catatonia" and only the term "neuroleptic malignant syndrome."

RESULTS

Following a request to the Uppsala Monitoring Centre, 509,746 ICSRs were extracted from VigiBase between January 1, 1968, and December 31, 2018. At the end of the

Table 2. Reporting Odds Ratios (RORs) for the Association Between Catatonia and the Use of FGAs Versus SGAs for the Primary and Secondary Analyses

		Cases[a]	Non-cases[b]	Crude ROR (95% CI)	Adjusted ROR (95% CI)
All patients	SGA	3,557	249,510	1 (ref)	1 (ref)
	FGA	1,862	58,581	2.2 (2.1–2.4)	2.2 (2.0–2.3)[c]
6–11 years of age	SGA	30	4,926	1 (ref)	1 (ref)
	FGA	13	1,017	2.1 (1.1–4.0)	2.0 (0.9–4.3)[d]
12–17 years of age	SGA	160	10,715	1 (ref)	1 (ref)
	FGA	90	2,652	2.3 (1.8–3.0)	2.4 (1.8–3.1)[d]
18–34 years of age	SGA	845	72,303	1 (ref)	1 (ref)
	FGA	449	16,238	2.4 (2.1–2.7)	2.5 (2.2–2.4)[d]
35–65 years of age	SGA	1,853	130,560	1 (ref)	1 (ref)
	FGA	848	25,903	2.3 (2.1–2.5)	2.2 (2.1–2.4)[d]
>65 years of age	SGA	669	31,006	1 (ref)	1 (ref)
	FGA	462	12,771	1.7 (1.5–1.9)	1.7 (1.5–1.9)[d]
Male	SGA	2,121	131,426	1 (ref)	1 (ref)
	FGA	1,103	25,811	2.6 (2.5–2.9)	2.5 (2.3–2.7)[e]
Female	SGA	1,436	118,084	1 (ref)	1 (ref)
	FGA	759	32,770	1.9 (1.7–2.1)	1.7 (1.6–1.9)[e]

[a]Cases were reports containing all subterms retrieved using the MedDRA terms "catatonia," "malignant catatonia," and "neuroleptic malignant syndrome."
[b]Non-cases were all other reports recorded in VigiBase.
[c]Results adjusted on age, gender, health care professional, US, and number of coprescriptions.
[d]Results adjusted on gender, health care professional, US, and number of coprescriptions.
[e]Results adjusted on age, health care professional, US, and number of coprescriptions.
Abbreviations: FGA = first generation antipsychotic, ref = reference, SGA = second generation antipsychotic.

selection process, 313,510 ICSRs were included in our study. We found that 60,443 ICSRs concerned an FGA prescription (19.2%) and 253,067 ICSRs an SGA prescription (80.7%) (Figure 1). For the third analysis, 384,289 ICSRs were included in our study, including 313,510 ICSRs with a prescription of only 1 antipsychotic (81.6%) and 70,779 ICSRs with prescriptions of more than 1 antipsychotic (18.4%) *(*Supplementary Figure 1*)*.

Among all reports involving one of the 64 antipsychotics of interest, we found 5,419 reports of catatonia syndromes, mainly reported with SGA prescription (n = 3,557; 66%) (Table 1). Catatonia syndromes were more frequently reported in males (n = 3,224; 59%), and the mean age was 47.5 years (± 19.6). Reports of catatonia syndromes originated mainly from the US (35.0%). Benign catatonia or malignant catatonia was reported in 522 patients (10%), including only 2 reports of malignant catatonia, and NMS was reported in 4,796 patients (90%). NMS and benign catatonia were coreported in 101 ICSRs.

Compared to the use of SGAs, the use of FGAs was significantly associated with a higher risk of reporting catatonia syndromes (ROR = 2.2; 95% CI, 2.0–2.3) (Table 2). Similar patterns were observed in each age group except for children (6 to 11 years), where the difference was not significant (ROR = 2.0; 95% CI, 0.9–4.3). The risk of reporting catatonia syndromes was also increased with the use of FGAs when we stratified on sex (female, ROR = 1.7; 95% CI, 1.6–1.9; male, ROR = 2.5; 95% CI, 2.3–2.7). In sensitivity analysis, results remained consistent (Supplementary Tables 2 and 3). When we performed analysis of reports submitted only by physicians, ROR was still significant (1.9; 95% CI, 1.7–2.1). Analyses considering only cases recorded as benign catatonia/malignant catatonia or only cases recorded as NMS found similar patterns (respectively, ROR = 1.8; 95% CI, 1.5–2.2 and ROR = 2.2; 95% CI, 2.1–2.3).

We found 30 antipsychotic drugs with at least 10 reports of catatonia syndromes. Among them, molindone produced significantly more reports of catatonia syndromes (ROR = 5.99; 95% CI, 3.11–10.44), followed by haloperidol (ROR = 3.76; 95% CI, 3.49–4.04) and loxapine (ROR = 3.47; 95% CI, 2.75–4.32) (Figure 2). Prochlorperazine was significantly less associated with the reporting of these side effects (ROR = 0.39; 95% CI, 0.28–0.53), followed by clozapine (ROR = 0.44; 95% CI, 0.41–0.48) and asenapine (ROR = 0.46; 95% CI, 0.28–0.71). When we restricted the analysis to cases recorded as benign catatonia, haloperidol was the drug most associated (Supplementary Figure 2). For the analysis considering NMS only, results were consistent with the first analysis. Molindone and haloperidol were the drugs most associated with NMS (Supplementary Figure 3).

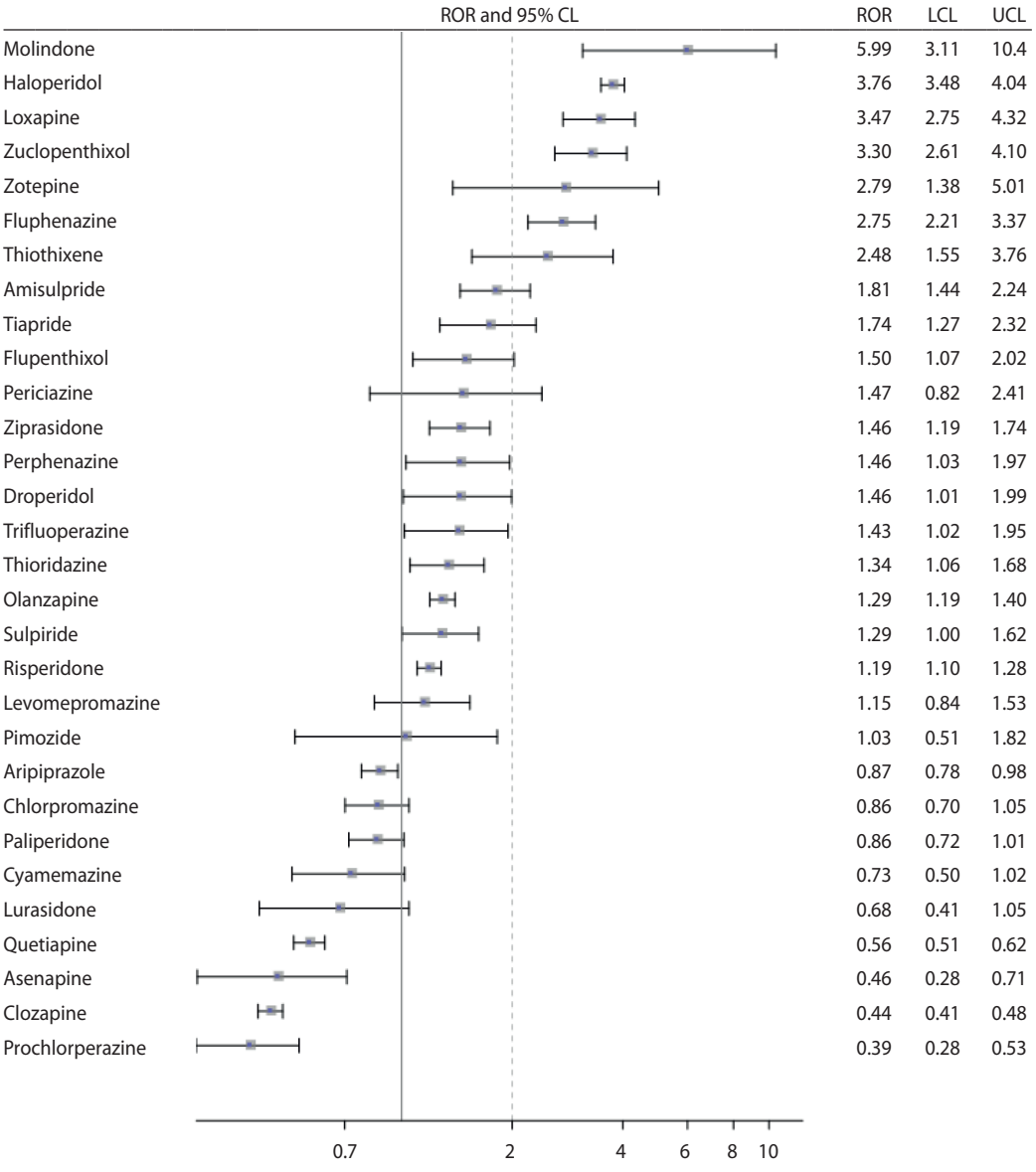
Disproportionality analyses for 1 antipsychotic prescription versus more than 1 antipsychotic prescription outlined that poly-prescription was significantly more associated with the reporting of catatonia syndromes, even when adjusted for age, sex, notifier, country, and number of coprescriptions (ROR = 2.5; 95% CI, 2.3–2.6).

DISCUSSION

In this large pharmacovigilance study, including more than 300,000 patients exposed to antipsychotics, the use of FGAs was associated with an increased risk of reporting catatonia syndromes compared to the use of SGAs. Consistent results were observed in secondary and sensitivity analyses. Highest risks were found for molindone, haloperidol, and loxapine, while the risk was lower with prochlorperazine, clozapine, and asenapine. A prescription of 2 or more antipsychotic drugs was more associated with reporting catatonia syndromes than the prescription of 1 antipsychotic drug. These results add more evidence regarding the risk of catatonia syndromes associated with antipsychotics but should be interpreted with this study's limitations and compared with other studies already published.

To date, the largest observational study of NMS in patients prescribed antipsychotics was a population-based study using data from the Hong Kong Hospital Authority's Clinical Data Analysis and Reporting System database.[18] This study showed that recent use of any antipsychotic within a 1-month window was associated with increased risk of NMS. However, this study was underpowered to evaluate the risk between each antipsychotic, and the authors highlighted the importance of performing studies with a larger sample size to investigate the risk of NMS associated with individual antipsychotic agents. Another recent study evaluated 52 NMS cases documented in

Figure 2. Adjusted RORs for the Association Between Each Antipsychotic and Catatonia Syndromes



Abbreviations: LCL = lower confidence limit, ROR = reporting odds ratio, UCL = upper confidence limit.

the drug safety program "Arzneimittelsicherheit in der Psychiatrie" from 1993 to 2015.[19] In line with our results, this observational study found that high-potency FGAs had the highest incidences of NMS while SGAs were associated with lower incidences. In fact, some authors advise clinicians to avoid FGA prescription and prefer SGA prescription for patients with a catatonic syndrome.[12] In the study, catatonia syndromes were serious in 53% of reports according to WHO definition (death, hospitalization). This result should be interpreted according to the limitation of pharmacovigilance data since the percentage could be overestimated as it reflects reporting bias. In pharmacovigilance databases, the worst cases are more frequently reported than benign cases. These data therefore do not call into question the overall benefit-harm balance of antipsychotics for the majority of patients.

When focusing on the risk of reporting catatonia syndromes for each antipsychotic, we notice that our ranking shows some similarities with other studies assessing risks of antipsychotic-induced movement disorders or extrapyramidal side effects (EPS).[20,21] Thus, the same antipsychotics associated with risk of EPS could be associated with risk of precipitating catatonia syndromes, raising the hypothesis of common pharmacologic pathways. On one hand, it has been discussed that the risk of an antipsychotic drug producing EPS could be reduced when its dopaminergic blockade activity is counterbalanced by serotonin (5-HT_2) antagonism properties.[22] On the other hand, the neurobiological mechanisms of catatonia remain poorly understood, but current theoretical models point to the involvement of dopamine and γ-aminobutyric acid (GABA) dysregulations.[23,24] Interestingly, positron emission tomography studies showed a

markedly reduced dopamine binding affinity in the putamen of patients with catatonia when compared to matched controls.[25] Thus, antipsychotic drugs could worsen a subcortical hypodopaminergic state, in a more or less severe manner depending on their 5-HT_2 properties. This hypothesis could explain why, in our study, FGAs were associated with a higher risk of reporting catatonia syndromes than SGAs, and clozapine and quetiapine were associated with the lowest risk among all antipsychotics. While haloperidol is consistently associated with risk of NMS in the literature, our results should be taken with great caution, as other studies with heterogeneous designs have shown conflicting results. Due to this lack of consistency on isolated drugs, other studies should be performed to replicate our results.

Our work suffers from the inescapable limitations of data-mining approaches in pharmacovigilance, the first being underreporting. It is considered that only 5%–10% of side effects are subject to pharmacovigilance ICSRs.[26–28] However, this might not be relevant in the present case, as it has previously been shown that underreporting is expected to be approximately similar for drugs belonging to the same therapeutic class.[29] Second, we did not take into account the doses used or the durations of exposure, this information not being systematically recorded in pharmacovigilance databases. Further analyses on these 2 parameters could lead to a more precise determination of the impact of a dose effect or a duration effect on the association between antipsychotics and the risk of catatonia. Third, even if our results have been adjusted for non-antipsychotic coprescription, confounding remains possible, especially for patients with an antipsychotic prescription associated with the prescription of other drugs suspected to induce catatonia.[30] While we considered only 30 antipsychotics for the secondary analyses, this list covered most antipsychotics used in current practice. In addition, we cannot also exclude an indication bias as we could not include this information in our estimations. For example, FGAs may have been prescribed more for schizophrenia or mania (which are associated with inherently greater risk of developing a catatonic syndrome) and SGAs for patients at lower risk for such disorders (for example in depression) or in lower dose (eg, lurasidone in depression). However, the adjusted ROR of clozapine (ROR = 0.44; 95% CI, 0.41–0.48) counterbalances this hypothesis as this drug is mainly prescribed for catatonic high-risk mental disorders, especially resistant schizophrenia. Concerning the low ROR with prochlorperazine, it seems relevant to add that this drug is mainly prescribed as an antinausea treatment, mainly in the US. This could lead to a low dosage prescription and represents a confounding factor that could explain the low risk of reporting a catatonic syndrome. Finally, as the diagnosis of catatonia syndromes (including NMS) is still complex, the use of the MedDRA dictionary may not always fit with the subtle characterization of such disorders.[31] In fact, despite the existence of approved catatonia rating scales, there is still a lack of consensus on catatonic syndrome diagnosis. Moreover, as we did not focus on how many symptoms of catatonic syndrome were present in each report, we can assume that the diagnosis was made on clinician's choice, which represents another limitation. Therefore, some clinically atypical presentations may have been misclassified. However, the persistence of statistically significant RORs in our sensibility analyses on completeness score superior to 600, corresponding to the best-informed ICSRs, adjusted this potential classification bias.

Despite these limitations, the present work has several strengths. First, we used the largest pharmacovigilance database available, VigiBase, including more than 22 million ICSRs worldwide (as of January 2020), which minimizes the risk of bias specific to a given country. Second, more than 300,000 ICSRs were included in the study, providing the required statistical power to study this poorly documented adverse drug reaction. This material represents a unique source of data for studying rare effects of drugs in real-life settings and adds to knowledge on the topic of catatonia acquired mainly from case ICSRs, scarce observational studies, and expert advice.[13] Third, it has been shown that such a pharmacovigilance approach could be used to hierarchize risk among a drug class. Indeed, a recent study[14] suggested that pharmacovigilance studies are well correlated with relative risk estimate in meta-analyses based on clinical data, in particular for risk associated with antipsychotic drugs. Finally, our study is, to our knowledge, the first large-scale study of pharmacovigilance focused on the association between a catatonic syndrome and the prescribing of antipsychotics. Our results could guide clinicians in their prescription of antipsychotics for patients with a history of catatonia syndromes but requiring reintroduction of an antipsychotic treatment.

Our results support a higher risk of reporting catatonia syndromes when using FGAs versus SGAs. Among the antipsychotics most used in current practice, molindone, haloperidol, and loxapine are associated with a greater risk of reporting catatonia syndromes, while prochlorperazine, clozapine, and asenapine present very low risk. Being potentially useful for clinicians in making their therapeutic choices, our results need to be confirmed by population-based studies. Pending other studies, clinicians should remain careful when considering prescribing FGA drugs for patients with a history of or at great risk of developing catatonia.

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Supplementary material: Available at Psychiatrist.com.

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Supplementary Material

Article Title: Comparative Effects of 30 Antipsychotics on Risk of Catatonia: An Analysis of the WHO Pharmacovigilance Database

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Supplementary Table 1: List of antipsychotics

FGA	SGA
Chlorpromazine, Levomepromazine, Promazine, Acepromazine, Triflupromazine, Cyamemazine, Chlorproethazine, Dixyrazine, Fluphenazine, Perphenazine, Prochlorperazine, Thiopropazate, Trifluoperazine, Acetophenazine, Thioproperazine, Butaperazine, Perazine, Periciazine, Thioridazine, Mesoridazine, Pipotiazine, Haloperidol, Trifluperidol, Melperone, Moperone, pipamperone, Bromperidol, Benperidol, Droperidole, Fluanisone, Molindone, Sertindole, Flupentixol, Clopenthixol, Chlorprothixene, Tiotixene, Zuclopenthixol, Fluspirilene, Pimozide, Penfluridol, Loxapine, Clotiapine, Sulpiride, Sultopride, Tiapride, Remoxipride, Veralipride, Levosulpiride, Prothipendyl, Mosapramine	Ziprasidone, Lurasidone, Clozapine, Olanzapine, Quetiapine, Asenapine, Amisulpride, Risperidone, Zotepine, Aripiprazole, Paliperidone, Iloperidone, Cariprazine, Brexiprazole

Abbreviations: FGA, First Generation of Antipsychotics; SGA, Second Generation of Antipsychotics

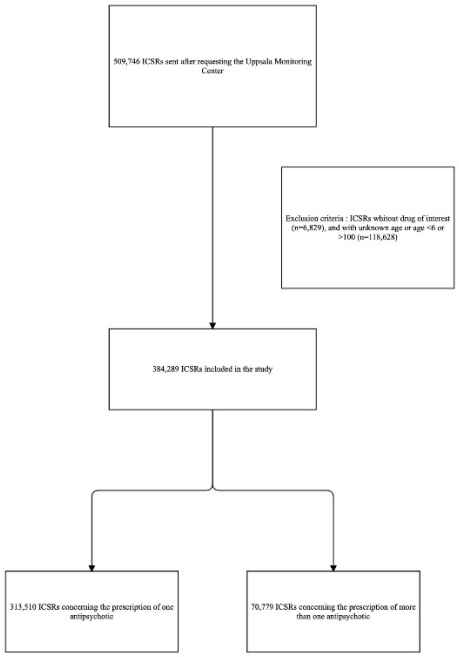
Supplementary Table 2: Number of ICSRs for each antipsychotic included in the secondary analysis

	Number of ICSRs (all adverse effects included)	Number of catatonic syndromes[a] reported	Number of catatonia OR malignant catatonia reported	Number of NMS reported
Amisulpride	2 822	85	1	82
Aripiprazole	22 944	323	37	284
Asenapine	2 480	18	.	17
Chlorpromazine	6 299	100	5	93
Clozapine	89 351	808	116	662
Cyamemazine	1 944	32	1	31
Droperidol	1 357	35	6	29
Flupentixol	1 606	40	2	38
Fluphenazine	2 073	92	10	80
Haloperidol	15 799	915	82	818
Levomepromazine	1 890	45	1	44
Loxapine	1 277	83	4	78
Lurasidone	1 638	18	2	15
Molindone	127	12	.	12
Olanzapine	32 800	737	59	664
Paliperidone	10 092	136	29	103
Periciazine	447	14	.	14
Perphenazine	1 578	38	3	35
Pimozide	564	10	1	8
Prochlorperazine	5 853	38	10	27
Quetiapine	41 756	475	48	423
Risperidone	42 598	827	82	733
Sulpiride	3 014	70	1	68
Thioridazine	2 996	75	3	71
Tiapride	1 054	46	1	45
Tiotixene	522	21	1	20
Trifluoperazine	1 599	38	1	37
Ziprasidone	4 835	113	4	104
Zotepine	213	10	1	9
Zuclopenthixol	1 468	83	3	79
TOTAL	302 996	5 337	514	4 723

Abbreviations: ICSRs: Individual Case Safety Reports NMS: Neuroleptic Malignant Syndrome

[a] By catatonic syndromes we included all ICSRs of catatonia OR malignant catatonia OR neuroleptic malignant syndrome

Supplementary Figure 1: Flowchart for the third analysis (one antipsychotic prescription versus more than one antipsychotic prescription)



Supplementary Table 3: Sensitivity analyses for the association between catatonia syndromes and the use of FGAs versus SGAs for the primary and secondary analyses

	Cases[a]	Non-Cases[b]	Crude RORs (95% CI)	Adjusted RORs (95% CI)
Restricting to 2009-2018 period				
SGA	2,015	174,533	1 (reference)	1 (reference)
FGA	745	26,767	2·4 (2·2–2·6)	2·1 (1·9–2·3)[1]
Restricting to reports from physicians				
SGA	1,540	94,836	1 (reference)	1 (reference)
FGA	650	21,288	1·9 (1·7–2·1)	1·9 (1·7–2·1)[2]
Restricting to reports from USA				
SGA	1,309	100,452	1 (reference)	1 (reference)
FGA	587	9,970	4·5 (4·1–5·0)	4·5 (4·0–4·9)[3]
Restricting to reports with a completeness score[c] > 600				
SGA	868	68,245	1 (reference)	1 (reference)
FGA	533	22,144	1·9 (1·7–2·1)	1·8 (1·6–2·0)[1]
Considering only cases of catatonia				
SGA	381	252,686	1 (reference)	1 (reference)
FGA	141	60,302	1·6 (1·3–1·9)	1·8 (1·5–2·2)[1]
Considering only cases of neuroleptic malignant syndrome				
SGA	3,100	249,967	1 (reference)	1 (reference)
FGA	1,696	58,747	2·3 (2·2–2·5)	2·2 (2·1–2·3)[1]

Abbreviations: FGA, First Generation of Antipsychotics; SGA, Second Generation of Antipsychotics

[a]: cases were reports containing all sub-terms retrieved using the MedDRA terms "Catatonia", "Malignant Catatonia" and "Neuroleptic Malignant Syndrome"

[b]: non-cases were all other reports recorded in VigiBase®

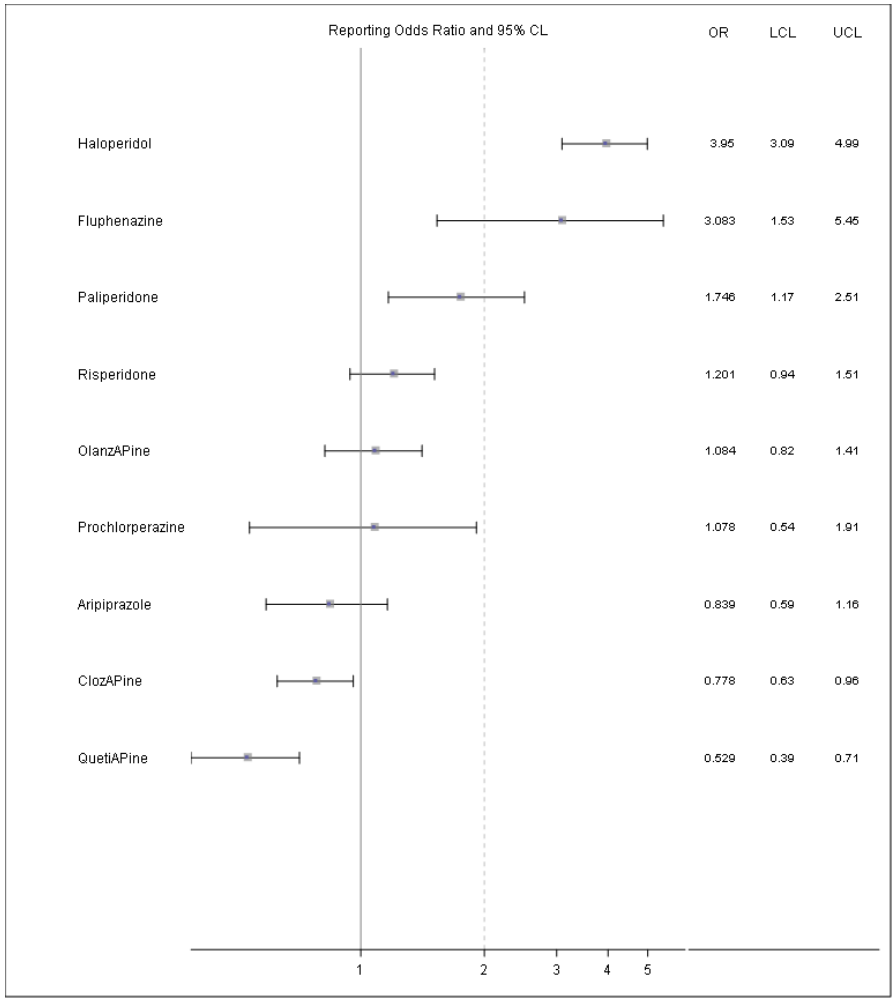
[c]: Completeness score allows to know about the level of quality of information of a report (Value ranges from 0 to 1,000)

[1]: results adjusted on age, gender, healthcare professional, USA, and number of co-prescriptions

[2]: results adjusted on age, gender, USA, and number of co-prescriptions

[3]: results adjusted on age, gender, healthcare professional and number of co-prescription

Supplementary Figure 2: Forest Plot showing adjusted RORs for the association between each antipsychotics and benign catatonia or malignant catatonia



Supplementary Figure 3: Forest Plot showing adjusted RORs for the association between each antipsychotics and Neuroleptic Malignant Syndrome