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ORIGINAL RESEARCH ARTICLE

Signal of Gastrointestinal Congenital Malformations with Antipsychotics After Minimising Competition Bias: A Disproportionality Analysis Using Data from Vigibase®

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Abstract

Introduction Investigations have highlighted the lack of evidence regarding the likelihood of congenital malformations following exposure to antipsychotic drugs during pregnancy. To gain further knowledge regarding their safety, we evaluated signals of congenital malformations with antipsychotics using VigiBase®, the World Health Organization (WHO) Global Individual Case Safety Report (ICSR) database.

Method A case/non-case study was conducted in VigiBase® between 1967 and 2014. Signals of disproportionate reporting (SDRs) were detected using the proportional reporting ratio (PRR), which defines SDRs as drug-report associations with a PRR $\geq$2, Chi square $\geq$4, and number of cases $\geq$3. SDR detection for antipsychotics was performed for congenital malformations after removing all reports related to drug competitors and reports of movement disorders from the database.

Results After removing reports related to drug competitors (antiepileptics, antidepressants, antivirals) and movement disorders, three signals were revealed: 'palate disorders congenital' (PRR 2.1, 95 % CI 1.6–2.9, Chi square = 30; n = 41), 'oesophageal disorders congenital' (PRR 2.5, 95 % CI 1.3–4.7, Chi square = 11; n = 10) and 'anorectal disorders congenital' (PRR 3.0, 95 % CI 1.6–5.6, Chi square = 13; n = 11). Among antipsychotics, phenothiazines with a piperazine side-chain, risperidone and aripiprazole appeared to be more suspect.

Conclusion Confirming a first signal from spontaneous reporting data, three SDRs for antipsychotics and gastrointestinal congenital abnormalities were unmasked in VigiBase®. This signal should be further explored by ad hoc pharmacoepidemiologic studies in order to assess whether it is relevant for prescription and public health.

Key Points

In VigiBase®, reporting rates for antipsychotics were found to be significantly higher than the global rate of reporting when considering congenital palate disorders (twofold increase), congenital oesophageal disorders (threefold increase), and congenital anorectal disorders (threefold increase).

Among antipsychotics, phenothiazines with a piperazine side-chain, risperidone and aripiprazole were more likely reported.

No other signals of congenital malformations were found with antipsychotic drugs.

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1 Introduction

1.1 Context

Many studies have highlighted the lack of evidence regarding the association between exposure to antipsychotics during pregnancy and congenital malformations. This gap concerns both first-generation antipsychotics (FGAPs) and second-generation antipsychotics (SGAPs) [1–5]. This was highlighted by a Cochrane review focusing on the use of antipsychotic drugs during pregnancy, which concluded that prescriptions in this context pose significant clinical and ethical problems [6, 7]. Even information on the structural teratogenicity of FGAPs and SGAPs is too limited to draw definite conclusions [3], although pharmacodynamic and pharmacokinetic data on antipsychotics support the hypothesis of a potential teratogenicity. Indeed, all lipophilic antipsychotics pass through the placenta and could induce structural or functional dysgenesis of fetal organs (cardiac, kidney, liver, etc.) when exposure occurs during the first trimester [8, 9]. Moreover, all antipsychotics express antagonist dopaminergic D_2 properties, and SGAPs are relatively potent blockers of serotonin 5-HT receptors. Both may interact with fetal development [10].

Despite these doubts regarding the safety of antipsychotic use during pregnancy, recent studies have shown that the increasing use of antipsychotics in patients of all ages concerns both pregnancy age and pregnant women [11–13]. This increase mostly concerns SGAPs. Indeed, in the US between 2001 and 2007, a 2.5-fold increase was observed in the prevalence of SGAP exposure during pregnancy, while the prevalence of FGAPs remained unchanged [14].

Among the various approaches used for the detection of adverse drug reactions (ADRs) in real-life settings, disproportionality analyses of spontaneous reporting databases are currently applied in most drug safety monitoring centres, in particular by the WHO Collaborating Centre for International Drug Monitoring and the US FDA [15, 16]. They are based on the identification of drug–event pairs reported more often than expected with regard to the frequency of reporting of other drug–event pairs [17–19], which results in signals of disproportionate reporting (SDRs). Several disproportionality computation techniques have been proposed for the detection of SDRs, among which the proportional reporting ratio (PRR) method has been widely used, including for consideration of competition biases [20]. The cause of these biases is that the detection of an SDR for a given drug can be hampered if the event of interest is strongly associated with another drug or class of drugs. Similarly, an event strongly associated with the drug of interest can hamper the detection of SDRs for other events that could be investigated for that drug [21, 22]. To circumvent this difficulty, one option consists of removing from the analysis set all reports involving the competing drug(s). For example, it has been demonstrated that the relatively high frequency of reporting of rhabdomyolysis associated with statins hampers the detection of any other signal for these drugs. Similarly, when trying to detect signals associating bleeding with a given drug, it might be worth removing all reports involving antiplatelet, anticoagulant or thrombolytic agents from the analysis dataset [20].

In a previous study exploring the potential masking effect of movement disorder (including parkinsonism) reports on SDRs detected for antipsychotics [20], three of the six SDRs unmasked for antipsychotics related to congenital malformations and events coded in the dataset considered as 'Cleft lip and cleft palate disorders', 'Gastrointestinal tract disorders' and 'Congenital NEC'.

1.2 Aims of the Study

As these results were obtained from a study not intending to explore this hypothesis but potential event competition biases in signal detection, we conducted a study specifically designed to research a signal, if any, between antipsychotic use and gastrointestinal congenital disorders by using data from VigiBase®, the WHO Global Individual Case Safety Reports (ICSR) database of spontaneous reporting, and taking into account competition biases.

2 Methods

2.1 Data Source

This case/non-case study was conducted using data from adverse event reports recorded in VigiBase® between 1 January 1967 and 31 December 2014. The WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden (the Uppsala Monitoring Centre [UMC]), receives ICSRs of suspected ADRs from national pharmacovigilance centres around the world, and these reports are stored in VigiBase® [23]. The size and worldwide coverage of this database makes it particularly appropriate for exploring putative signals for rare events such as teratogenic effects. Indeed, VigiBase® contains more than 12 million ICSRs from 123 countries. Each ICSR includes anonymous administrative data (country, reporter qualification), patient information (age, sex, etc.), data on medication(s) used (international nonproprietary name [INN] and coding according to the Anatomical Therapeutic Chemical [ATC] classification, date of introduction, date of

withdrawal, switch or daily dosage modification, etc.), ADR (coding according to the Medical Dictionary for Regulatory Activities [MedDRA®], date of onset, time course, seriousness) and causality assessment. All information in the ICSRs is described on the UMC website [24], and all reports entered within this 47-year period were considered for analysis.

2.2 Data Analysis

SDR detection was performed using the PRR method, which compares the rate of reporting of one event among all reports for a given drug with the rate of reporting of the same event among all drugs present in the database. In this study, an SDR was defined as a drug–event pair for which the statistical analyses led to a PRR $\geq$2 associated with a Chi square $\geq$4 and number of exposed cases $\geq$3 (see electronic supplementary material [ESM] Table 1) [25].

Exposure to antipsychotic drugs was identified according to ATC level 3; all reports mentioning a drug associated with the ATC code N05A ('antipsychotics') were considered as being exposed to these drugs, with the exception of those with an N05AN code, which corresponds to lithium salts.

Events related to congenital malformations were first considered according to the MedDRA® highest level of coding (System Organ Class [SOC]). Identification of cases using the SOC 'Congenital, familial and genetic disorder' (SOC 'Congenital') was performed to investigate potential competing effects between drugs for SDRs related to congenital malformations. In the present study, potential competitors were defined as drugs for which an SDR in the first disproportionate analyses led to a PRR $\geq$2 associated with a Chi square $\geq$4 and number of exposed cases $\geq$3. To focus on the most relevant competitors, we restricted exclusion to drugs accounting for more than 5 % of the SOC 'Congenital, familial and genetic disorder' (SOC 'Congenital') [26].

After this preliminary step, all SDR detection analyses for antipsychotics (all combined), taking into account potential drug-competition effects, were performed by considering events according to the MedDRA® higher-level term (HLT) level of coding, as used for SDR detection in several previous studies [20, 27].

Lastly, SDR detection was performed, taking into account potential event-competition effects. Event competition is due to a frequently reported ADR of the drug of interest. When the proportion of reports related to this ADR is higher for the drug of interest than it is for other drugs, the reporting rate for other ADRs for the drug of interest is mathematically reduced compared with that observed for other drugs present in the database. This decreases the value of the PRR for the drug–event pair. Such an effect has been demonstrated in SDR detection regarding antipsychotics as a result of the large number of reports concerning movement disorders (including parkinsonism) for these drugs [20]. The effect can be managed by removing all reports (whatever the involved drugs) of the competing event (in this case movement disorders, including Parkinsonism) from the analysis dataset. This was carried out in the last phase of the analysis. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3 Results

The total number of reports recorded in VigiBase® during the study period (i.e. 1 January 1967 to 31 December 2014) was 10,304,819. Of these, 42,502 reports (0.41 %) related to 'congenital, familial and genetic disorders'. When considering events on the basis of the MedDRA® higher-level group term (HLGT) level of coding (see ESM Table 2), the most represented were 'Cardiac and vascular disorders congenital' (n = 10,527), 'Congenital and hereditary disorders NEC' (n = 9421) and 'Musculoskeletal and connective tissue disorders congenital' (n = 8388). Exposure to antipsychotics was found in 351,028 reports (3.4 %), of which 1235 (0.35 %) related to events of 'Congenital, familial and genetic disorders'. The most represented were 'Musculoskeletal and connective tissue disorders congenital' (n = 285), 'Cardiac and vascular disorders congenital' (n = 250) and 'Neurological disorders congenital' (n = 212) (see Table 1).

3.1 Identification of Potential Drug Competitors

Drug competition analysis using SDR detection for SOC 'Congenital' revealed 20 drugs. Of these, only three (antidepressants, antiepileptics and direct-acting antivirals) accounted for more than 5 % of 'Congenital, familial and genetic disorder' notifications. In this preliminary analysis, no SDR was detected for antipsychotics (PRR 0.8; Chi square = 17; n = 1235).

3.2 Signals of Disproportionate Reporting (SDR) Detection After Excluding Reports Related to Potential Drug Competitors

Excluding reports involving antidepressants, antiepileptics and direct-acting antivirals resulted in an analysis dataset of 9,286,170 reports, including 16,508 cases of congenital malformations. No SDR associating an antipsychotic with any type of congenital malformation was unmasked after dealing with this potential drug competition bias.

Table 1 Congenital, familial and genetic disorders reported with antipsychotics in VigiBase® ($n = 1235$)

MedDRA terms	No. of reports
HLGT—musculoskeletal and connective tissue disorders congenital	285
HLGT—cardiac and vascular disorders congenital	250
HLGT—neurological disorders congenital	212
HLGT—congenital and hereditary disorders NEC	167
HLGT—gastrointestinal tract disorders congenital	172
HLGT—metabolic and nutritional disorders congenital	65
HLGT—renal and urinary tract disorders congenital	58
HLGT—reproductive tract and breast disorders congenital	52
HLGT—chromosomal abnormalities and abnormal gene carriers	50
HLGT—blood and lymphatic system disorders congenital	44
HLGT—eye disorders congenital	38
HLGT—respiratory disorders congenital	29
HLGT—ear and labyrinthine disorders congenital	23
HLGT—skin and subcutaneous tissue disorders congenital	19
HLGT—endocrine disorders congenital	13
HLGT—hepatobiliary disorders congenital	5
HLGT—cytoplasmic disorders congenital	3
HLGT—immune system disorders congenital	1
HLGT—infections and infestations congenital	0

MedDRA Medical Dictionary for Regulatory Activities, *HLGT* higher-level group term

3.3 SDR Detection After Excluding Reports Related to the Competing Event of Movement Disorders (Including Parkinsonism)

After excluding reports related to movement disorders (including parkinsonism) from the dataset, the analysis set was reduced to 9,014,653 reports, of which 16,508 cases related to congenital malformation. By using this procedure, an SDR associating antipsychotics with 'neurological disorders congenital' (MedDRA® HLGT term) was unmasked (PRR 2.1, Chi square = 89, 95 % CI 1.8–2.5; $n = 157$). However, after investigation, it was found that most cases ($n = 88$) related to events of 'Tourette Syndrome' or 'Huntington's disease' for which antipsychotics are indicated. The description of these cases confirmed that most were not related to newborns.

Three supplementary SDRs were unmasked when considering events at the HLT level of the MedDRA® classification and after reviewing reports by a clinical pharmacologist trained in pharmacovigilance. All related to gastrointestinal tract congenital disorders and included the following: 'Palate disorders congenital' (PRR 2.1, 95 % CI 1.6–2.9, Chi square = 30; $n = 41$), 'Oesophageal disorders congenital' (PRR 2.5, 95 % CI 1.3–4.7, Chi square = 11; $n = 10$) and 'Anorectal disorders congenital' (PRR 3.0, 95 % CI 1.6–5.6, Chi square = 13; $n = 11$) (see Fig. 1). An SDR was found for 'Tongue disorders congenital' ($n = 25$) but, after reviewing, 20 reports were excluded because most of the notifications related to events of anaphylactic reactions with macroglossia.

For congenital palate disorders, more reports related to FGAPs ($n = 27$) than SGAPs ($n = 16$) (see Table 2). Among the FGAPs, phenothiazine antipsychotics were mainly represented ($n = 19$, 70 %), especially phenothiazine with a piperazine side-chain (prochlorperazine, $n = 6$; fluphenazine, $n = 4$; trifluoperazine, $n = 2$). For SGAPs, olanzapine ($n = 5$), risperidone ($n = 4$) and quetiapine ($n = 4$) were mostly represented. Co-prescriptions of other drugs were found in only 14 reports, including benzodiazepines in four reports. Among the 41 congenital palate disorder reports, 13 were an association of cleft palate and cleft lip, whereas 28 were cleft palate alone. Other congenital malformations were described in 16 cases, mainly other facial malformations ($n = 4$; hypertelorism of orbit or jaw malformations).

For congenital oesophageal disorders (oesophageal atresia, $n = 10$), seven were associated with FGAPs, mainly phenothiazine antipsychotics (with aliphatic chain, $n = 4$; or piperazine side-chain, $n = 3$), and nine were associated with SGAPs, mainly risperidone or its metabolite paliperidone ($n = 4$). A co-prescription of atropinic drugs was found in only one report. Other types of malformations were reported in seven cases.

For congenital anorectal disorders (anus imperforate or anal atresia, $n = 11$), all reports with FGAPs involved phenothiazine antipsychotics with a piperazine side-chain

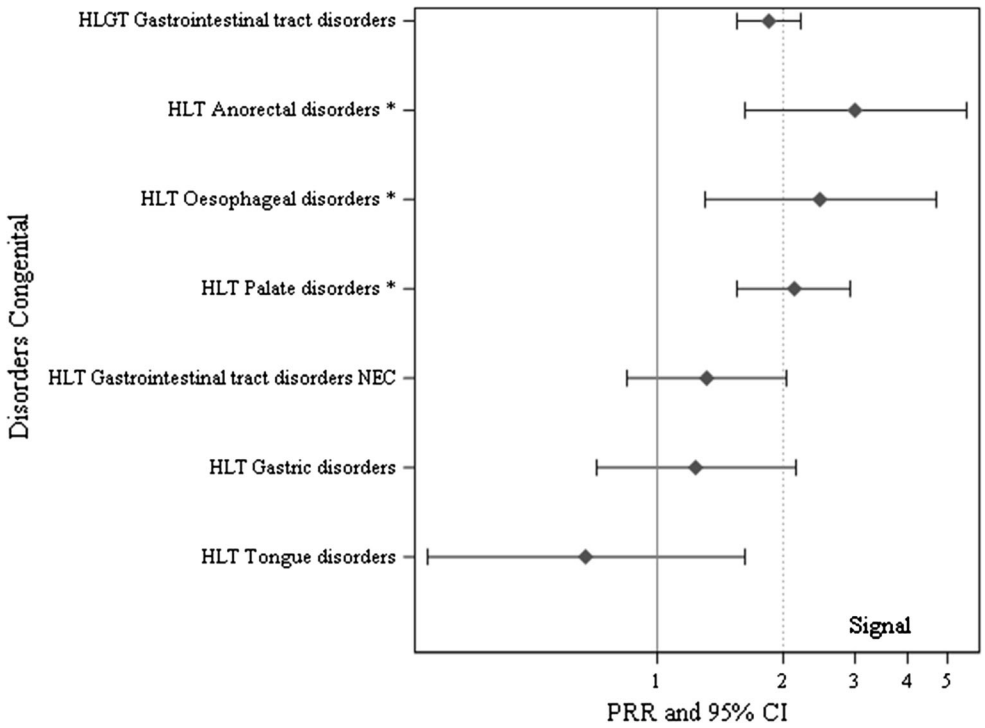

Fig. 1 SDR detection for HLGT Gastrointestinal tract disorders Congenital and antipsychotics in VigiBase®. *Significant SDR. *PPR* proportional reporting ratio, *CI* confidence interval, *SDR* signal of disproportionate reporting, *HLT* higher-level term, *HLGT* higher-level group term

($n = 5$). We also found four reports with aripiprazole and two with risperidone. Each report of anorectal disorder was associated with another: congenital malformation, mainly cardiac ($n = 4$) or gastrointestinal disorders ($n = 4$).

4 Discussion

4.1 Main Results

In this large pharmacovigilance database study, and after taking into account putative competition biases for the drugs and events considered, antipsychotics were found to be associated with reports of gastrointestinal congenital abnormalities. Compared with what was observed for all other drugs, reporting rates were significantly higher for congenital palate disorders (twofold increase), congenital oesophageal disorders (threefold increase) and congenital anorectal disorders (threefold increase). The antipsychotics relating to these three events were mostly phenothiazine antipsychotics with a piperazine side-chain ($n = 20$, 32 %) and risperidone ($n = 8$, 13 %). Four of 11 reports of congenital anorectal disorders have been reported with aripiprazole.

Although these results do not imply a causal association, they highlight a potential risk of gastrointestinal congenital disorders associated with these drugs and plead for dedicated pharmacoepidemiologic studies on this issue.

4.2 Relationship with Previous Findings

Our findings are consistent with some experimental studies in animals. Exposure to FGAPs (especially phenothiazine antipsychotics with a piperazine side-chain [28]) during pregnancy was associated with the occurrence of cleft palate in mouse, rat and rabbit [29–31]. Cases of such malformations have been reported in the literature in human newborns after in utero exposure to prochlorperazine [32] and ziprasidone [33]. In the case–control study (cases, $n = 601$/controls, $n = 38{,}151$), Puhó et al. found a possible association between thiethylperazine (an antipsychotic with a piperazine side-chain) and cleft lip with or without cleft palate [34]. In addition, cases of oesophageal atresia and alimentary tract malformation have also been reported with olanzapine [3, 35]. A case of anal atresia in a newborn whose mother had been using risperidone during pregnancy has also been reported [35]. While these case reports (or studies) seem to support our results, those of case–control and cohort studies appear less congruent. Indeed, they provide discrepant results regarding the risk of congenital malformation related to in utero exposure to antipsychotics, probably owing to differences in the

Table 2 Reports of cleft palate after taking into account competition bias in VigiBase® ($n = 41$)

Antipsychotics	No. of reports	Countries	Mother's age [mean ± SD] (n)	Top year of reporting	Co-prescription of benzodiazepines (n)	Co-prescription of other drugs
FGAP[a]	27	UK (9), Germany (5), US (4), Australia (2), France (2), Denmark/Finland/Ireland/New Zealand/Thailand (1)	29 ± 6.1 (10) MD (17)	2011	Yes (2)	Pyridoxine (4) Paracetamol (1) Fenfluramine (1) Levothyroxine (1) Doxylamine (1) Ampicillin (1)
Aripiprazole	0					
Clozapine	2	Australia (1), US (1)	31 (1) MD (1)	1996/1999	NS	Benzatropine (2)
Olanzapine	5	Germany (2), Canada/UK/US (1)	MD (5)	2003/2010	Yes (1)	NS
Risperidone	4	Australia/Denmark/Italy/Norway (1)	MD (4)	2007/2010/2011	Yes (1)	Tropatepine (1)
Quetiapine	4	Germany (2) Norway/UK (1)	MD (4)	2003/2008/2010/2012	NS	NS
Ziprasidone	1	Croatia (1)	MD (1)	2011	NS	NS

We found 41 reports of cleft palate with at least one antipsychotic drug (two reports contained at least one FGAP and at least one SGAP)

SD standard deviation, *MD* missing data, *NS* not specified, *FGAP* first-generation antipsychotic, *SGAP* second-generation antipsychotic

[a] FGAPs reported in the 41 notifications of cleft palate ($n = 31$): prochlorperazine ($n = 6$), flupentixol ($n = 6$), haloperidol ($n = 4$), fluphenazine ($n = 4$), chlorpromazine ($n = 3$), trifluoperazine ($n = 2$), perazine ($n = 1$), flupirilene ($n = 1$), promazine ($n = 1$), cyamemazine ($n = 1$), thioridazine ($n = 1$), droperidol ($n = 1$); four reports included more than one FGAP

definition of the studied outcomes and their limited statistical power [36–40]. Indeed, although the results of a recent meta-analysis concluded in favour of our results regarding an increased risk of major malformations associated with in utero exposure to antipsychotics, the relative lack of power of this study did not make it possible to perform more detailed analyses, considering the specific types of events (except heart defects) [41].

In any case, our findings are congruent with the first SDR identified by our previous study on competition effects performed using French Pharmacovigilance reports prior to the year 2000 [20].

4.3 Limitations

Our results were obtained from pharmacovigilance data and are thus subject to the inherent limitations of analyses conducted on spontaneous reports. The main limitation is obviously underreporting [42], which may be differential between drugs and events, especially at the early stage of drug marketing or when a safety concern receives special attention from the media [43, 44]. However, in the present case, such a differential reporting bias seems unlikely or of limited consequences. Another limitation when working on spontaneously reported data is that it is not possible to control for potential confounders such as risk factors for congenital malformations related to family history, behavioural habits or potential viral infection that could have occurred during pregnancy [45]. For example, family history of congenital malformations and/or behavioural habits such as smoking or drinking alcohol and/or viral infection (such as cytomegalovirus) could increase the risk of congenital malformation independently of drug exposure. Although not specific to our study, this is a clear limitation for causal inference and one of the major reasons why such findings can only be considered as safety signals. However, reports recorded in VigiBase® had a minimal causal assessment based on exposure time. Nevertheless, the relative consistency of literature [38, 40, 41] and animal data [32, 33, 46] appears sufficiently supportive of the association to call for a more specific investigation of the risk in dedicated observational studies. To our knowledge, no registry focusing on congenital malformation related to drugs, specifically to antipsychotics, exists. Conversely, several databases make it possible to perform a pharmacoepidemiological investigation of the potential teratogenic

effects of drugs. These, such as Rumeau-Rouqette [37] or EFEMERIS [47] for instance, could provide complementary information to that herein obtained using spontaneous reporting data. In particular, these pharmacoepidemiological analyses would not be affected by underreporting; however, it is not certain that they would provide sufficient power for the analysis of gastrointestinal tract malformations and antipsychotics, an association regarding both a rare event and rare exposure in pregnant women.

4.4 Strengths and Originality

The database used (WHO VigiBase®) is a clear strength of our study since it is the largest pharmacovigilance database in the world and allows the evaluation of infrequently reported ADRs, such as unexpected pregnancy outcomes. Its wide geographic coverage, i.e. 123 countries, also allows for the detection of outcomes associated with particular patterns of drug use that are specific to a given area. One should note that, according to VigiBase®, only 16 countries have reported cleft palate congenital disorders to date.

Disproportionality analyses have been shown to be effective for the identification of potential safety signals. Indeed, as a complement to large electronic healthcare databases, spontaneous reporting databases may provide additional valuable information, mainly to explore rare outcomes such as congenital malformations [48]. Indeed, the valid identification of a potential teratogenic risk requires the use of specific approaches [49]. To our knowledge, the present study is the first to examine congenital risks in a pharmacovigilance database.

5 Conclusions

By using an original approach and considering potential competition biases, the present study confirms the existence of a signal for gastrointestinal congenital disorders, i.e. cleft palate and oesophageal or anal malformations associated with the use of antipsychotics. Among these, phenothiazines with a piperazine side-chain, risperidone and aripiprazole appeared to be more suspect. This signal should be further explored by ad hoc pharmacoepidemiologic studies in order to assess whether it is relevant for prescription and public health.

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Authors' contributions François Montastruc, Bernard Bégaud and Antoine Pariente participated in the study design and planning; François Montastruc, Francesco Salvo, Mickaël Arnaud, Bernard Bégaud and Antoine Pariente took part in the acquisition, analysis and interpretation of the data; François Montastruc, Bernard Bégaud and Antoine Pariente drafted the manuscript; and Francesco Salvo, Mickaël Arnaud, Bernard Bégaud and Antoine Pariente critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Compliance with Ethics Standards

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Conflicts of interest François Montastruc, Francesco Salvo, Mickaël Arnaud, Bernard Bégaud and Antoine Pariente have no conflicts of interest that are directly relevant to the content of this study.

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