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Short communication

# Antipsychotics and seizures: Higher risk with atypicals?

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ABSTRACT

*Purpose:* Almost all antipsychotics have been associated with a risk of epileptic seizure provocation. Among the first-generation antipsychotics (FGA) chlorpromazine appears to be associated with the greatest risk of seizures among the second-generation antipsychotics (SGA) clozapine is thought to be most likely to cause convulsions. This information is largely based on studies that are not sufficiently controlled. Besides, information about the seizure risk associated with newer antipsychotics is scarce.
*Method:* The Pharmacovigilance Unit of the Basque Country (network of centers of the Spanish Pharmacovigilance System, SEFV) provided reporting data for adverse reactions (AR) from the whole SEFV to estimate the reporting odds ratio (ROR) for antipsychotics and seizures ("convulsions" as Single MedDra Query). Data was obtained from SEFV database from 1984 to the June 2011.
*Results:* The total number of convulsions reported for SGA was 169 (total reported AR 3.204). The number of convulsions reported for FGA was 35 (total reported AR 2.051). 94 convulsions were reported in association with clozapine (total AR 1.052). The ROR for SGA versus FGA was 3.2 (CI 95%: 2.21–4.63). The ROR for SGA excluding clozapine versus FGA was 2.08 (CI 95%: 1.39–3.12).
*Conclusion:* Our results show that SGA may pose a higher risk of seizures than FGA, mainly, but not only due to clozapine. This is line with recent studies suggesting that some SGA carried a higher average risk of electroencephalographic abnormalities than many FGA. Nonetheless, It is well known that spontaneous reports do not allow strong inferences about adverse drug effects, because differences in reporting fractions by time, drug or type of event are difficult or even impossible to distinguish from differences in the occurrence rates of adverse events. Still, we consider that the possibility of SGA carrying a higher risk of seizure induction than FGA warrants further research.


## 1. Introduction

Almost all first- and second-generation antipsychotic drugs have been implicated in increasing the risk of epileptic seizures.[1] Antipsychotics are used for a wide range of conditions and may be indicated in people with epilepsy. In fact, several cross-sectional studies have demonstrated that psychotic disorder and other psychiatric conditions for which antipsychotics may be prescribed are more common among people with epilepsy than in the general population.[2] Indeed, it has been estimated that the overall prevalence of psychiatric disorders in patients with epilepsy is as high as 25% (psychosis affects 2–9% of patients) – and even higher in pharmocoresistant cases seen in specialized centers.[3]

Low starting doses, use of minimum effective doses and avoidance of unnecessary antipsychotic polypharmacy have been described as strategies which may lower the risk of seizure provocation associated with these drugs.[4]

Previous studies demonstrate that clozapine is associated with a clear, dose-dependent risk of seizure provocation and compared to other second-generation antipsychotics, appears to have the highest risk of seizure induction.[5] Among first-generation antipsychotics, chlorpromazine seems to be associated with the greatest risk of provoking epileptic seizures. Risperidone, fluphenazine, haloperidol, molindone, pimozide and trifluoperazine seem to be the least likely antipsychotics to induce seizures.[1] Data about newer antipsychotics, such as aripiprazole, paliperidone and ziprasidone are scarce.[6–7] As it was temporally withdrawn from the market, data about sertindole are also scant.[8] Whether second-generation antipsychotics are safer than first-generation antipsychotics in terms of seizure induction is not known.

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Evidence supporting the notion that neuroleptic drugs lower the seizure threshold is based on studies that are not sufficiently controlled and typically report patients with other risk factors for seizures. Case reports, often complicated by polypharmacy and other risk factors for seizures, form a substantial portion of the available literature.

In order to find out if different antipsychotic drugs are associated with different risks of causing epileptic seizures, we studied data about antipsychotic-related epileptic seizures drawn from spontaneous reports to several Spanish and international pharmacovigilance databases.

## 2. Methods

### 2.1. Case/non-case method

The case/non-case method measures the disproportionality of combinations of a drug and a particular adverse drug report (ADR) in a pharmacovigilance database.[9] This method can be used to generate safety signals. Cases are defined as reports of the ADR of interest and non-cases as all other reports of ADR. For each drug of interest, the association with the ADR was assessed by calculating an ADR reporting odds ratio (ROR) with its 95% confidence interval (CI).

### 2.2. Selection of cases and non-cases

Since 1984, all ADR reports sent spontaneously by health professionals have been entered into the Spanish Pharmacovigilance FEDRA database. The Pharmacovigilance Unit of the Basque Country (network of centers of the Spanish Pharmacovigilance System, SEFV) provided reporting data from the whole SEFV between 1984 and June 23rd, 2011 to estimate the reporting odds ratio (ROR). To identify cases of epileptic seizures we utilized the Standardized MedDRA Query (SMQ) "Convulsions". SMQs are groupings of MedDRA terms, ordinarily at the preferred term level that relate to a defined medical condition or area of interest. This study relies on MedDRA version 14.1. Non-cases, used as controls, were all the remaining ADR reports recorded in the database during the same period. Drug exposition was defined by the presence in the report of the drug checked "suspect" according to the WHO (World Health Organization) criteria whatever the level of causality assessment. Subsequently, data from the European Pharmacovigilance database (Eudravigilance) and WHO Pharmacovigilance database (VigiBase) were also consulted for a confirmatory analysis.

### 2.3. Statistical analysis

Collected data were compared between reports defined as convulsions (cases) and all other reports in the database (non-cases). We calculated a reporting odds ratio (ROR) to compare risk of exposure to different drugs in cases and non-cases. RORs were given with their 95% confidence interval.

## 3. Results

Reports of suspected drug-related seizures and total number of adverse reports in FEDRA database are shown in Table 1.

Reporting odds ratio calculated from the data of Table 1 are shown in Table 2.

### 3.1. Data analysis from Eudravigilance and VigiBase: confirmatory analysis

Reporting odds ratio for antipsychotics and seizures in Eudravigilance (from 1984 to June 2011) are shown in Table 3.

**Table 1**
Reports of suspected drug-related seizures in FEDRA database, 1984–June 2011.

| First generation antipsychotics (FGA) | Total number of adverse reports | Total number of convulsions |
|---|---|---|
| Chlorpromazine | 101 | 4 |
| Clotiapine | 96 | 5 |
| Fluphenazine | 82 | 4 |
| Haloperidol | 465 | 5 |
| Levomepromazine | 186 | 4 |
| Loxapin | 3 | 0 |
| Periciazine | 20 | 0 |
| Perphenazine | 72 | 3 |
| Pimozide | 29 | 1 |
| Pipothiazine | 4 | 0 |
| Sulpiride | 668 | 4 |
| Thioridazine | 145 | 3 |
| Tiapride | 55 | 0 |
| Tioproperazine | 6 | 1 |
| Trifluoperazine | 39 | 1 |
| Zuclopentixole | 80 | 0 |
| Total | 2051 | 35 |
| **Second generation antipsychotics (SGA)** | **Total number of adverse reports** | **Total number of convulsions** |
| Amisulpride | 51 | 0 |
| Aripiprazole | 168 | 6 |
| Clozapine | 1052 | 94 |
| Olanzapine | 471 | 21 |
| Paliperidone | 77 | 1 |
| Quetiapine | 276 | 19 |
| Risperidone | 962 | 18 |
| Sertindole | 18 | 0 |
| Ziprasidone | 129 | 10 |
| Total | 3204 | 169 |

**Table 2**
Reporting odds ratio (ROR) for antipsychotics and seizures in FEDRA.

| | ROR | CI 95% |
|---|---|---|
| SGA[a] vs. FGA[b] | 3.2 | 2.21–4.63 |
| SGA excluding clozapine vs. FGA | 2.08 | 1.39–3.12 |
| Clozapine + olanzapine + quetiapine vs. other SGA | 4.65 | 3.19–6.80 |

[a] Second generation antipsychotic.
[b] First generation antipsychotic.

**Table 3**
Reporting odds ratio (ROR) for antipsychotics and seizures in Eudravigilance.

| | Reported convulsions | Total reported adverse reactions |
|---|---|---|
| Second generation antipsychotics (SGA) | 3.009 | 50.615 |
| First generation antipsychotics (FGA) | 402 | 9.025 |
| ROR for SGA vs. FGA: 1.33 (1.20–1.48) | | |

**Table 4**
Reporting odds ratio (ROR) for antipsychotics and seizures in VigiBase.

| | Reported convulsions | Total reported adverse reactions |
|---|---|---|
| Second generation antipsychotics (SGA) | 5.412 | 80.300 |
| First generation antipsychotics (FGA) | 1.225 | 36.057 |
| ROR for SGA vs. FGA: 2.03 (1.90–2.16) | | |

Reporting odds ratio for antipsychotics and seizures in the WHO Pharmacovigilance database[10] (1968-February 2006) are shown in Table 4.

## 4. Discussion

We found that spontaneous seizure reports for second-generation antipsychotics are more frequent than for first-generation

antipsychotics. This is especially, but not only, due to clozapine. Olanzapine and quetiapine, both chemically related to clozapine, may carry a higher risk than expected.

Interestingly, our results are in line with one study carried out in 323 hospitalized patients which found that some atypical antipsychotics present a higher average risk of electroencephalographic (EEG) abnormalities than many typical neuroleptics.[11] The risk was greatest with clozapine and unexpectedly high with olanzapine, while risperidone was similar to standard high-potency neuroleptics. Quetiapine had a very low rate of EEG abnormality risk among the very few subjects who received this agent. Another study found that EEG changes were common with olanzapine doses of >20 mg.[12]

Although other variables such as dose, age, indication for which the antipsychotic was being used were not taken into account, the fact that the analysis of all three databases yielded similar results strengthens our conclusions.

On the other hand, several epidemiologic studies have found that psychiatric disease (including depression, anxiety disorders, bipolar disorder, and psychoses) is more frequent among people with epilepsy than in the general population.[2,3] Thus, a deeper understating of the epileptogenic risk of individual antipsychotics is urgently needed.

### 4.1. Limitations

The case/non-case method can be a very useful method for assessing and detecting associations between a specific adverse drug effect and drug exposure in real conditions of use, because it is simple, quick and used data are already available. Nevertheless, it is important to recall that these disproportionality studies should only be considered as exploratory in the context of signal detection, as they do not allow quantification of the true risk. Indeed, differences in reporting fractions by time, drug or type of event are difficult or impossible to distinguish from differences in the occurrence rates of adverse events making make inferences from such data problematic.[13]

## 5. Conclusions

Our findings suggest that second-generation antipsychotics may carry a greater epileptogenic risk than first-generation antipsychotics, especially but not only due to clozapine. Olanzapine and quetiapine, both chemically related to clozapine, may carry a higher risk than expected. Thus, a cautious approach seems advisable when prescribing these drugs to patients with known risk factors for a lowered seizure threshold, including the combination with other drugs causing potential pharmacokinetic and/or pharmacodynamic interactions.

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