European Neuropsychopharmacology 2023; 68: 33-46. Publisher DOI: 10.1016/j.euroneuro.2022.12.010

Second-generation antipsychotics and seizures – a systematic review and meta-analysis of serious adverse events in randomized controlled trials

Word count: Abstract 298 main text 4439, 1 figure, 3 tables

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ABSTRACT

Seizures are suspected to be side effects of antipsychotics. To examine a possible causal relationship, we compared the risk of seizures on second-generation antipsychotics to the risk on placebo in randomized controlled clinical trials (RCTs) across diagnostic groups. The primary outcome was any seizure reported as International Conference on Harmonisation-Good Clinical Practice (ICH-GCP)-defined serious adverse event (SAEs). The risk ratio (RR) with antipsychotics versus placebo was synthesized in a pairwise common effects Mantel-Haenszel meta-analysis. For 314 of 597 idenitified placebo-controlled RCTs information about all SAEs could be retrieved from publications, original investigators, pharmaceutical companies and the European Medical Agency. In those, 37 seizures occurred in 42,600 participants on antipsychotics (0.09%) and 28 in 25,042 participants on placebo (0.11%). The meta-analytic results (RR 0,68; 95% Confidence Interval 0.41-1.12) indicated a reduced risk on antipsychotics with a confidence interval including no difference (i.e. RR=1). Neither in sensitivity analyses (excluding events in the safety-follow-up of trials or first-generation antipsychotics; using odds ratios) nor in subgroup analyses (on specific antipsychotics, drug combinations, diagnostic categories, age groups, and study duration) there was evidence for an increased risk on antipsychotics, except for some weak indications of an increased risk on antipsychotics in olderand/or demented participants (RRs 1.11 and 1.48, respectively, but with 95% CIs of 0.35-3.49 and 0.41-5.26 including no difference and subgroup test with p=0.54 and p=0.66 not indicating differences between age groups or diagnostic categories). Consequently, there are no indications that second-generation antipsychotics cause seizures in middle-aged adults and children in most diagnostic groups; rather our results provide some weak evidence for a protective effect. However, there was no data on SAEs available for clozapine, for which observational studies provide the strongest associations with increased seizure rates, and for older and/or demented patients a small additional risk on antipsychotics cannot be excluded.

Funding

German Ministry of Education and research (grant number 01KG1505)

Key words

Antipsychotic, Seizure, Serious adverse events, Randomized controlled trial

INTRODUCTION

Antipsychotic drugs are widely used in psychiatry to treat schizophrenia and other disorders such as bipolar disorder, depression, dementia, ADHD, or autism. Seizures are discussed as potential side effect of antipsychotics (Correll et al., 2015). They are characterized by focal or generalized paroxysmal synchronized neuronal activity that leads to temporary abnormalities in muscle tone, behaviors, sensations or state of awareness (Shorvon et al., 2012). For afflicated individuals, seizures mean a risk of injuries and accidents due to loss of consciousness and falls, stigmatization, and impairment in life (e.g. because driving cars and access to certain jobs is restricted). Moreover, they can result in a status epilepticus, which is fatal in about 10% of cases (Neligan and Shorvon, 2010). Factors that increase the risk of seizures are e.g. genetic determinants, brain injuries or tumors, fever, or use as well as withdrawal of medical or illicit drugs (Shorvon et al., 2012). Conversely, some medical drugs can increase the seizure threshold and be protective. In terms of neurotransmitter-systems, GABA and Glutamate are keyplayers (Shorvon et al., 2012) but also histamine (Yokoyama and Iinuma, 1996), serotonine (Bagdy et al., 2007), norepinephrine (Fitzgerald, 2010), and acetylcholine systems are involved (Cruickshank et al., 1994; Zimmerman et al., 2008).

Antipsychotics, which interact with multiple transmitter systems (Zohar et al., 2015), may thereby influence the risk of seizures. An increased rate of seizures has been mainly associated with the antipsychotic clozapine so far, but also associations with other antipsychotics, particularly with olanzapine and quetiapine have been reported (Bloechliger et al., 2015; Jeon et al., 2021; Kumlien and Lundberg, 2010; Lertxundi et al., 2013; Wu et al., 2016). Due to these concerns, regular electro-encephalograms are routinely applied in many clinics. However, these associations stem from observational data, where it is difficult to disentangle causal relationship from confounding (Davis, 2016). Consequently, there is still uncertainty whether antipsychotics really cause seizures and whether there are differences between the different compounds in this regard.

To fill this gap, we used the data of randomized controlled trials, in which potential confounders are distributed randomly, to investigate the risk of seizures with antipsychotics and with placebo in a meta-analysis of serious adverse events.

EXPERIMENTAL PROCEDURES

This analysis is part of a systematic review on mortality and serious adverse events with antipsychotics which is registered at Prospero #CRD42016033930 (Appendix1). Two meta-analyses from this review on i) mortality and ii) risk of any somatic serious adverse event have already been published (Schneider-Thoma et al., 2019; Schneider-Thoma et al., 2018). In reporting of methods and results we followed the PRISMA-guideline (Page et al., 2021) (checklist in Appendix2).

In this review, we included any randomized controlled trial (RCT) comparing second generation antipsychotics with placebo irrespective of the treated medical disorder, age, sex, or ethics of the study populations. Included second generation antipsychotics were all those available in Europe or the United States at the time of the search, namely amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone and zotepine. They were included in any form (oral, intravenous, intramuscular), scheme (fixed or flexible dose, as monotherapy or as additional medication) and dose of application. The comparator was always placebo. First-generation antipsychotics were only included when they were additional interventions in trials comparing second-generation antipsychotics to placebo. We did not include studies conducted only with first generation antipsychotics because our outcome "serious adverse events" (see below), was not yet defined when those studies were conducted. In terms of study design, we included RCTs irrespective of blinding, duration, and setting, and used only the controlled studies phases (i.e. we did not use data of the uncontrolled extention-phases of RCTs in which all participants were switched to active medication) and the first study phases from cross-over trials. We only excluded psychological studies in which solely a single drug dose was administered or whose duration was 24 hours or less, as well as trials conducted in China due to concerns about the methodological quality(Leucht et al., 2022; Tong et al., 2018).

To identify eligible trials, we searched multiple electronic databases (Medline, Embase, Cochrane Central Register of Randomized Trials (CENTRAL), Biosis, PsychINFO, Pubmed, Clinicaltrials.gov, WHO ICTRP; detailed search strategy in Appendix3) and two reviewers screened the found references independently. Moreover, we searched the webpages of pharmaceutical companies and the European trial registry (EUCTR), the US trial registry (clinical trials.gov), and the database of the US Federal-Drug-Administration (FDA). The search was the same as used for the two main analyses of this project on mortality and any serious adverse event (published in 2018 and 2019 (Schneider-Thoma et al., 2019; Schneider-Thoma et al., 2018); last search January 27, 2017).

As outcomes, we extracted information on serious adverse events (SAEs) as defined by the International-Council-for-Harmonization-Good-Clinical-Practice (ICH-GCP) guidelines (ICH Expert Working Group, 1994), which are mandatory to record in modern RCTs since the 1990ties (European Medicine Agency, 1995; Food and Drug Administration, 1995). SAEs are any untoward medical occurrences at any dose that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, lead to persistent or significant disability or are a congenital anomaly or birth defect. We did not categorize adverse events as SAEs ourselves but only used those reported by the original investigators.

Two reviewers independently entered the number of participants experiencing specific SAEs into a Microsoft-Access-database using Medical-Dictionary-for-Regulatory-Activities-(MedDRA)-preferred terms (Medical Dictionary for Regulatory Activities, Version 20.0). Moreover, we extracted basic and demographic information about the study (duration, blinding status of the trial, number, age, sex and diagnoses of patients; type, application, and dose (mean,

lower limit, upper limit) of the antipsychotic) and assessed the risk of bias using the Cochrane Risk of Bias 1 tool (Higgins et al., 2011). To request missing information, we contacted the original study authors, pharmaceutical companies, the European Medical Agency ((EMA) and the US Federal Drug Administration (FDA) (see acknowledgement).

From the resulting dataset, we identified SAEs related to seizures using the Standardized MedDRA-Query (SMQ) "Convulsion", which is a collection of terms of adverse events potentially related to seizures compiled by an expert group (Appendix4). Moreover, we manually searched all events, but found no further related terms. For analysis we used only studies which reported all SAEs for all participants (i.e we did not use studies when only selected SAEs were reported or when only the SAEs from those particpants that completed the trial were reported) because potentially there might have been seizures among the missing SAEs.

The primary outcome was the number of participants with "any seizure". Secondary outcomes were the specific types of seizures according to the MedDRA-preferred terms.

By dividing the number of participants with events by all participants randomized in the antipsychotic and placebo groups, respectively, we calculated the risk ratio (RR) for seizure-SAEs for each study. Then we meta-analysed those RRs with a common (i.e. fixed)-effects Mantel-Haenszel model without continuity correction, which is recommended for rare-event data (Efthimiou, 2018; Higgins, 2008), to obtain a pooled estimate for the risk ratio across studies.

Moreover, to provide information how often seizures occur, which is important to judge the clinical relevance together with the risk ratio, we calculated pooled absolute frequencies by dividing the number of all participants with events by all participants randomized across studies (grand mean). Furthermore, we calculated the number of events per patient-year on treatment by dividing the number of all participants with events by the total time participants were in the studies. The latter we calculated using the average time in the study per study arm provided by the original authors; if this information was unavailable, we estimated it using the study duration and the number of participants that discontinued the study early (drop-outs) assuming that those were in the study for half of the duration on average; if no information on drop-outs was available, the average drop-out rate of the other studies was used (4% of studies); if no information on study duration was available the average duration of the other studies was used (1% of studies).

In sensitivity analyses, we, first, excluded those seizure-SAEs that occurred in the safety-follow-up phase (usually approx. 30 days after the study participants are contacted again concerning additionally emerging adverse events) and those for which it was unclear in which study phase they occurred. The reason was that particularly in the safety-follow-up-phase, the risk of seizures could have been influenced by the withdrawal of study medications, the use of other medications (e.g. active antipsychotics in the placebo-groups) or by other factors, such as substance abuse, which are restricted during the main study phases. Second, we used odds ratios (ORs) instead of RRs as effect size measure because there is an ongoing discussion which of them should be preferred in meta-analysis (Xiao et al., 2022). Since RRs are very similar to ORs in the case of rare events, we used RRs for the primary analysis (and all other analyses except this sensitivity analysis) to increase interpretability. Third, we excluded first-generation antipsychotics to display results for second-generation antipsychotics only.

In subgroup analyses, to explore differences between different interventions, populations and study types, we meta-analysed separately i) specific antipsychotics used, ii) combinations of drugs (add-on to antidepressants, other antipsychotics, mood-stabilizers, other drugs, no other

drugs), iii) diagnostic categories, iv) age groups (children and adolescents <18 years, middle-aged adults 18-65 years, older adults> 65 years), and v) studies with different durations (<5 days, 6 days to 3 months,> 3 months).

Post-hoc, to further explore subgroups indicated in the literature (see discussion) and yielding the highest absolute event rates, we conducted a subgroup analysis by specific antipsychotics in studies in dementia and a subgroup analysis by diagnositic categories in studies comparing olanzapine to placebo.

Publication bias related to small-trial bias was assessed with a funnel plot and a Harbord test (Harbord et al., 2006). The strength of the evidence was assessed with GRADE (Schünemann et al., 2013).

RESULTS

Screening 23,139 electronic references and other sources, we identified 597 randomized placebo-controlled studies with second-generation antipsychotics (flow chart in Appendix5). For 314 studies with 67,642 participants information about all observed SAEs including descriptions of the specific events could be retrieved. The majority of studies (78%) were conducted in middle-aged adults (7% in older adults; 13% in children and adolescents) and lasted several weeks (median 6 weeks, IQR 4-10 weeks, range 1 day to 104 weeks). They were conducted in 21 different diagnostic groups - the most common were schizophrenia (100 studies, 28,252 participants), bipolar disease (81, 20,214), depression (28, 7184), and dementia (15, 3916) - and investigated 15 different antipsychotics – the most common were olanzapine (68 studies; 7106 participants), aripiprazole (59; 6925), risperidone (55; 4581), quetiapine (53; 4886), and paliperidone (27; 4864) (more information in the table with results of subgroup analyses below; characteristics per study in Appendix6).

Risk of bias was high in 0%, 0%, 2%, 2%, 43% and 3% of the 597 included studies in the domaines randomization, allocation concealment, blinding of participants and personal, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias, respectively (Appendix7). Of note, in the domaine selective reporting, we expected at least brief descriptions of each specific SAE, e.g. myocard infarct 1 person, from fully published studies. Otherwise we judged the study at high risk of bias due to possible underreporting (see discussion). Visual inspection of the funnel plot (Appendix8) and the Harbord test (p=0.15) yielded no indications for a publication bias. The strength of the evidence was judged as moderate (Appendix9).

Overall, seizures of any kind (primary outcome) occurred in 37 of 42,600 participants on antipsychotics (i.e. in 0.09% of the participants randomized to this group) and in 28 of 25,042 participants on placebo (0.11%). Accordingly, 6.3 partipants on antipsychotics and 7.8 participants on placebo had an event for 1000 observed patient-years (py). The meta-analytic risk ratio (RR) of any seizure between antipsychotics as a group and placebo was 0.68 with a 95% confidence interval (95%CI) spanning from 0.41 to 1.12. Thus, there was no evidence of an increased risk of seizures with antipsychotics as compared to placebo but some weak evidence (i.e. point estimate in this direction but 95% CI including the possibility of no difference) for a decreased risk with antipsychotics (Table1). The figure shows the forest plot with all studies with at least one event (Appendix10 shows the forest plot including studies in which explicitly no events occured).

In terms of specific seizures (secondary outcomes) study investigators reported 36 “seizures” without further specification, 19 “generalized tonic-clonic seizures”, 5 “epilepsy” without further specification, 2 “complex partial seizures”, 1 “status epilepticus, 1 “partial seizure”, and 1 “temporal lobe epilepsy”. The RRs yielded no evidence of a differences between antipsychotics and placebo for any of the specific events (Table1; Appendix11 lists numbers and types of seizure per study).

In a sensitivity analysis, we exluded 2 seizures that occurred in the safety-follow-up (2 in 430 participants (0.47%) on antipsychotics, 0 on placebo) and 37 seizures for which it was unclear in which study phase they occured (18 in 7533 participants (0.24%) on antipsychotics, 20 in 3708 participants (0.54%) on placebo). For 18 events in 35067 participants on antipsychotics (0.05%; 3.7/1000 py) and 8 events in 21334 participants on placebo (0.04%; 2.6/1000 py) it was specified that they occurred during the main study phase (i.e. while participants received the randomized study treatment) and meta-analytically, there was no evidence of a difference between antipsychotics and placebo (RR 1.05; 95% CI: 0.45-2.43). The result of the sensitivity

analysis using ORs was identical to the primary analysis. The result after excluding first-generation antipsychotics was RR 0.69 (95% CI 0.42, 1.13).

In the subgroup analysis (Table3) by specific antipsychotics the absolute frequencies of seizures on drug ranged between 0% and 0.15% with olanzapine (11.8/1000 py) with no strong evidence for an increased or decreased risk with any of the specific antipsychotics (as the 95% CIs of all RRs were wide and included the possibility of no difference) and no indication for differences between antipsychotics (test for subgroup differences: p=1.00). The very uncertain point estimates for quetiapine (4 vs. 1 event) and brexpiprazole (2 vs.1) were the only ones in the direction of an increased risk with drug.

In the subgroup analysis by combinations of drugs the absolute frequencies ranged between 0% and 0.11% when no other drug was added (8.4/1000py) with no strong evidence for an increased or decreased risk with any of the combinations and no indication of a difference in the effect of antipsychotics between the different combination therapies (test for subgroup differences: p=1.00). No point estimate was in the direction of an increased risk with drug.

In the subgroup analysis by diagnostic categories the absolute frequencies ranged between 0% and 0.31% in participants with dementia (19/1000py) with no strong evidence for an increased or decreased risk with antipsychotics in any of the diagnostic categories and no indication of a difference in the effect of antipsychotics between diagnostic categories (test for subgroup differences: p=0.73). Only the point estimate in dementia was in the direction of an increased risk with drug.

In the subgroup analysis by age groups, seizures were reported in 0.25% of older adults (15.9/1000py), 0.12% of middle-aged adults (6.5%/1000py) and 0.02% of children or adolescents (1.2/1000py) with no strong evidence for an increased or decreased risk with antipsychotics in any of the age groups and no indication of a difference in the effect of antipsychotics between age groups (test for subgroup differences: p=0.62). Only the point estimate for older adults was in the direction of an increased risk with drug.

In the subgroup analysis by study duration, seizures occurred in 0.01% of participants in studies lasting 6 days to 3 months (9.7/1000py) and 0.09% of participants in studies lasting more than 3 months (2/1000py) with no strong evidence of an increased or decreased risk with antipsychotics in any of the different duration categories and no indication for a difference in the effect of antipsychotics between the different study lengths (test for subgroup differences: p=0.70). No point estimate was in the direction of an increased risk with drug.

In the post-hoc subgroup analysis by specific antipsychotics in studies in dementia (Appendix12.1) olanzapine and risperidone showed point estimates in the direction of an increase in risk with drug, based on 14 studies with 11 events in 3215 participants, but with 95% CIs including the possibility of no difference; for other antipsychotics only 4 studies with 1 event in 733 participants were available. The test for subgroup differences (p=0.74) yielded no indication for differences between antipsychotics.

In the post-hoc subgroup-analysis by diagnostic categories in studies with olanzapine (Appendix12.2), there was no indication for an increased risk with olanzapine in schizophrenia and bipolar disorder, whereas, the point estimate in dementia was in the direction of an increased risk with antipsychotics, albeit with a 95% CI including no difference and a test of subgroup difference (p=0.67) yielding no indication of a difference between diagnostic categories.

DISCUSSION

This study quantified the risk of seizures on antipsychotic drugs in comparison to placebo based on serious-adverse events (SAEs) reported from 314 randomized controlled trials with 67,642 participants.

Using the meta-analytical approach, which preserves the randomization of the original trials, we found no indication for an increased risk with antipsychotics as a group.

To further investigate potential differences in the risk of seizures with specific treatments, and in specific groups of patients, we conducted several subgroup analyses. This is particularly relevant because in observational data (Bloechliger et al., 2015; Jeon et al., 2021; Kumlien and Lundberg, 2010; Lertxundi et al., 2013; Wu et al., 2016) and clinical trial data analysed in an observational way (Alper et al., 2007), olanzapine, quetiapine, first-generation antipsychotics and particularly clozapine were associated with increased rates of seizures, whereas other second-generation antipsychotics were not or less. Moreover, the increased risk with these drugs appeared to be most pronounced in individuals with dementia (Bloechliger et al., 2015).

In our subgroup analyses by specific antipsychotics, we found no strong evidence for an increased risk with any of the antipsychotics including those mentioned just above: For olanzapine there was very weak evidence (i.e. confidence intervals were wide and included 1) of decreased risk on drug across indications and in participants with schizophrenia and bipolar disorder, but a very weak increased risk in participants with dementia. For quetiapine, there was very weak increased risk across indications but based on only 5 events in 8597 participants, 1 of those in participants with dementia. For the two first-generation antipsychotics in our analysis, there was a very weak decreased risk on haloperidol across indications and no events occurred in chlorpromazine-studies. Of note, information on first-generation antipsychotics is very limited because we did not include studies solely investigating first generation antipsychotics as no information about SAEs could have been expected in these trials conducted decades ago (see methods). For clozapine, unfortunately, there was no information as there were only 6 small placebo-controlled studies (107 particpants on clozapine in total) that did not report specific SAEs.

Furthermore, in our subgroup analysis by specific diagnostic categories, we found no strong evidence for an increased risk within specific groups of patients, but, in accordance with Bloechlinger et al. (Bloechliger et al., 2015), there was very weak evidence for an increased risk on antipsychotics in participants with dementia. This was due to an increased risk with both, olanzapine and risperidone; for other antipsychotics much fewer trials with much fewer participants were conduced so that there is lack of information and not evidence of no risk.

The weak evidence for an increased risk in dementia was also reflected by a similar increase in older adults, whereas in middle-aged adults and children and adolescents, there was no indication of an increased risk.

Concerning major limitations of our analysis, we already mentioned the lack of data on first-generation antipsychotics and clozapine (and therefore further studies, e.g. using data of head-to-head RCTs, are warranted to pin-point the risk of seizures and causality). Moreover, for interpretation of our findings we would like to discuss the following additionally limiting aspects: First, participants in RCTs are selected and those with an increased risk for seizures, such as those with brain damages or drug abuse are typically not included. However, also in the subgroup “drug abuse” there was no increased risk with antipsychotics. Second, potentially not all seizures are necessarily reported as serious adverse events (e.g. a seizure in a patient with well-known epilepsia may not meet SAE-criteria), but we deem it likely that newly occurring

seizures, i.e. those particularly suspicious to be related to the study treatment, are reported as SAEs. Thus, the absolute frequencies might be an underestimation but the estimated risk ratios in comparison to placebo should be not affected much. Nevertheless, the absolute frequencies and event rates per patient-year are in the same range as in other studies in patients with mental disorders using common adverse event data (Alper et al., 2007; Bloechliger et al., 2015), and similarily increased towards the general population where absolute frequencies are ca. 0.08% per year (i.e. 0.015% per 10 weeks, which is our mean study duration) (Pisani et al., 2002) and event rates 0.6/1000py (Alper et al., 2007). Third and related, reporting of adverse events is not always complete because participants may not report or recall all adverse events, particularily when they are not asked actively for specific events. However, for seizures and SAEs in general this may be less of a problem because those are dramatic events which are likely to be noted. Fourth, for 47% of all trials (ca. 38% of all participants) information on SAEs was not available or incomplete, despite our extensive efforts to request information (see acknowledgement). Thus, we do not know about SAEs and seizures in these trials. To highlight this issue of underreporting for this important type of outcome, we rated these studies at high risk of bias for selective reporting. However, it seems unlikely that there was substantial non-reporting of SAE-information hiding an increased risk of seizures with antipsychotics. Other reasons for non-reporting detailed trial results, such as infavorable efficacy results or limited word-count in journal publications seem more likely. Fifth, partly resulting from the limitations one to four, the available overall number of events was low (65) which limits the statistical power of the meta-analysis. Conversely, given that we included data from 314 trials with 67,642 participants, this indicates that seizures, related to antipsychotics or not, are of limited relevance during the course of clinical trials.

Interestingly, overall and in many subgroups, the point estimate for the RR was below 1, which allows to speculate about a protective effect of antipsychotics, as already suggested by others (Okazaki et al., 2014). Potentially, this could be due to direct effects on neurotransmitter-receptors. Alternatively, antipsychotic use could stabilize the mental illness and thereby reduce related stress and inadequate copying strategies such as use of illicit and other medical drugs and improve self-care including correct use of other medications in terms of dosing and tapered discontinuation). However, as anotherhypothetical explanation in our data, withdrawal of antipsychotics used directly before the trial may have led to increased seizures in the placebo group. Unfortunately, this hypothesis is difficult to investigate because it was not reported whether individual participants used antipsychotics before, because only for 4 out of 28 events on placebo the time point was reported (1, 11, 12 and 50 days after randomization) and because events in trials in which all particpants used antipsychotics before (enriched design studies; studies for relapse prevention of schizophrenia) were too scarce for meaningful analysis (antipsychotic vs placebo: 1/3867 vs 3/3046; 1/1925 vs. 2/1612). In any case, the event rates on placebo in the latter studies are low (ca. 1/1000), which means that seizures potentially induced by antipsychotic-withdrawal would be of limited clinical relevance. Moreover, after subtracting this hypothetical rate of withdrawal-related seizures of 1/1000=0.1% from the rate on placebo in the schizophrenia-subgroup (the population in which pretreatment with antipsychotics is the most possible; assuming the extreme case scenario that all participants used antipsychotics before), the rates on drug and placebo are virtually identical (0.08% vs 0.07%, table 3). Thus, it is unlikely that an increased risk on antipsychotics could be hidden by withdrawal-related seizures. Furthermore, in a recent individual-patient-data meta-analysis (Brandt et al., 2022), seizures did not emerge as associated with withdrawal of antipsychotics which makes this explanation for the observed RR below 1 improbable.

Concerning other potential causes of the observed seizures, doses and titration modality of antipsychotics, co-morbidities and co-medication can be relevant. However, those factors could not be systematically controlled because additional information on the patient-level was only

available for 14 events on antipsychotic and 7 on placebo. In the latter exemplary information, all events on antipsychotics occurred with doses within the therapeutic range, and many of them happened in the first days and weeks after start of trial medication (days 2, 3, 3, 5, 5, 5, 7, 9, 9, 10, 13, 13, 15, 27 on drug; days 1, 11, 12, 50 on placebo). This speaks against a major causal role of excess doses of antipsychotics, but too rapid titration cannot be ruled out. Moreover, it suggests that some seizures could be related to changes in medication which take place early in trial. Indeed, in 4 out of 8 case reports (3 on antipsychotic, 1 on placebo) too rapid withdrawal of benzodiazepines or topiramate was reported; in the 4 other case reports potential reasons for seizures were use of pantoprazole (1) and know history of seizures (1) on drug and subdural hygroma (1) and intracranial haemorrhage (1) on placebo.

In conclusion, considering these findings and limitations, in our analysis of randomized data, we did not find indications for an increased risk of seizures due to antipsychotics in middle-aged adult patients in most diagnostic categories, including the major indications schizophrenia and bipolar disorder. Moreover, we did not find clear differences between the specific second-generation antipsychotics, except clozapine for which no data was available. In clinical practice, this means that for most patients and antipsychotics, concerns about inducing seizures by antipsychotic treatment and routine monitoring with electro-encephalograms are of little importance. However, in demented and/or older patients there is a hint of an evidence of increased risk of seizures with antipsychotics. Nevertheless, also in those patients, which had the highest absolute frequencies of all diagnostic and age groups (0.31%; 0.25%), the frequencies of seizures considered as serious adverse events were in the range of uncommon adverse events according to the definition of the world health organisation (≥1/1000, <1/100) (Council for International Organizations of Medical Sciences, 1999) and the frequency of seizures attributable to antipsychotics ((RR 1.48 x risk on placebo 0.22%) - risk on placebo 0.22% = 0.11%) is nearby 1/1000, which probably limits the clinical relevance.

AUTOR DISCLOSURES

Role of Funding Source

This study was supported by a grant from the German Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF, grant number: 01KG1505). OE was supported by the Swiss National Science Foundation (Ambizione grant number 180083). The funding agencies had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

SL was the principal investigator, who supervised the study and obtained the funding. LR, in supervision by JS-T and SL, developed the plan for analysis. LR identified the seizure-related serious adverse events from the database of SAEs created for the larger systematic review on any SAEs with antipsychotics (Schneider-Thoma et al., 2019), controlled the information and calculated absolute frequencies. JS-T, together with OE, conducted the meta-analyses. JS-T and LR drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the final submitted version.

Conflict of Interest

In the past 3 years, Stefan Leucht has received honoraria as a consultant and/or advisor and/or for lectures from Alkermes, Angelini, Eisai, Gedeon Richter, Janssen, Lundbeck, Lundbeck Institute, Merck Sharpp and Dome, Otsuka, Recordati, Rovi, Sanofi Aventis, TEVA, Medichem, and Mitshubishi. All other authors declare that they have no conflicts of interest.

Acknowledgements

Part of the results of this analysis are part of the academic thesis (Dr. med.) of Leonie Reichelt at the Technical Univeristy of Munich (Reichelt, 2020).

We thank Samanta Roberts for help in the literature search, Georgia Salanti for conceptualizing the statistical analysis and all reviewers who originally selected studies and extracted data, namely Thomas Arndt, Lio Bäckers, Irene Bighelli, Carola Dörries, Maximilian Huhn, Marc Krause, Natalie Peter, Hannah Röder, and Philip Rothe.

For providing additional information about trials we thank the 112 original authors who answered to our requests (sharing data for 86 trials), the European Medicines Agency (EMA) (for 31 trials of aripiprazole and 3 of lurasidone) and the pharmaceutical companies Eli Lilly (25 trials of olanzapine), Janssen (50 trials of risperidone, via the YODA project, # 2016-0880, http://yoda.yale.edu/), Merck Sharp & Dohme (15 trials of asenapine), Otsuka (10 trials of aripiprazole) and Vandapharma (4 trials of iloperidone). We state that the analysis, interpretation and reporting of research using provided data are solely our responsibility and do not necessarily represent the official views of the data-sharing institutions. Moreover, we thank

MedDRA for providing a free academic license of the Medical Dictionary for Regulatory Activities terminology (MedDRA®, owned by IFPMA on behalf of ICH).

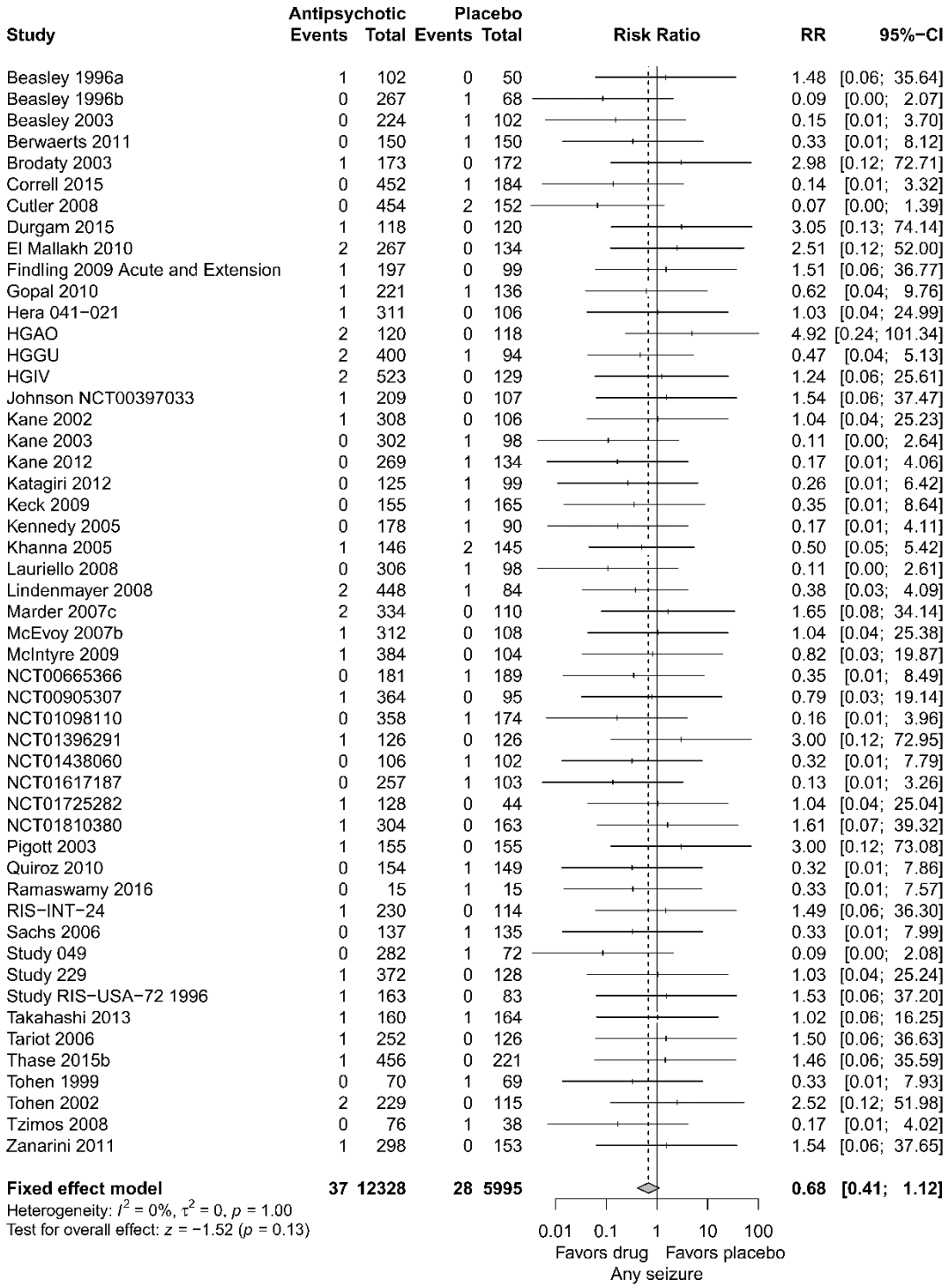

Figure: Forest plot of the primary outcome “any seizures”. RR: Risk ratio of seizures of antipsychotics versus placebo; 95% CI: 95% confidence interval.

Table 1: Primary and secondary outcomes

Type of event	Intervention	Studies	Duration	Events	Participants	Frequency	Patient-years	Events/ 1000 patient-years	RR (95% CI)
Any seizure (primary outcome)	**Total**	**314 (51)**	**10**	**65**	**67642 (18323)**	**0.1 %**	**9476.5**	**6.9**	**0.68 (0.41-1.12)**
	Antipsychotic	314	9	37	42600	0.09 %	5888.8	6.3	
	Placebo	314	11	28	25042	0.11 %	3587.6	7.8	
Specific seizures (secondary outcomes)									
Complex partial seizure	**Total**	**314 (2)**	**10**	**2**	**67642 (959)**	**0 %**	**9476.5**	**0.2**	-
	Antipsychotic	314	9	2	42600	0 %	5888.8	0.3	
	Placebo	314	11	0	25042	0 %	3587.6	0	
Epilepsy	**Total**	**314 (5)**	**10**	**5**	**67642 (2196)**	**0.01 %**	**9476.5**	**0.5**	**0.14 (0.01-1.47)**
	Antipsychotic	314	9	1	42600	0 %	5888.8	0.2	
	Placebo	314	11	4	25042	0.02 %	3587.6	1.1	
Generalized tonic clonic seizure	**Total**	**314 (8)**	**10**	**19**	**67642 (6505)**	**0.03 %**	**9476.5**	**2**	**0.55 (0.22-1.38)**
	Antipsychotic	314	9	10	42600	0.02 %	5888.8	1.7	
	Placebo	314	11	9	25042	0.04 %	3587.6	2.5	
Partial seizures	**Total**	**314 (1)**	**10**	**1**	**67642 (172)**	**0 %**	**9476.5**	**0.1**	-
	Antipsychotic	314	9	1	42600	0 %	5888.8	0.2	
	Placebo	314	11	0	25042	0 %	3587.6	0	
Seizure	**Total**	**314 (29)**	**10**	**36**	**67642 (10142)**	**0.05 %**	**9476.5**	**3.8**	**0.84 (0.44-1.62)**
	Antipsychotic	314	9	22	42600	0.05 %	5888.8	3.7	
	Placebo	314	11	14	25042	0.06 %	3587.6	3.9	
Status epilepticus	**Total**	**314 (1)**	**10**	**1**	**67642 (224)**	**0 %**	**9476.5**	**0.1**	-
	Antipsychotic	314	9	0	42600	0 %	5888.8	0	
	Placebo	314	11	1	25042	0 %	3587.6	0.3	
Temporal lobe epilepsy	**Total**	**314 (1)**	**10**	**1**	**67642 (417)**	**0 %**	**9476.5**	**0.1**	-
	Antipsychotic	314	9	1	42600	0 %	5888.8	0.2	
	Placebo	314	11	0	25042	0 %	3587.6	0	

Studies: number of all studies with complete information about SAEs (number of studies with at least one seizure); Duration: mean study duration in weeks; Events: number of seizures; Participants: number of participants randomized in all studies (number of participants in studies with at least one seizure); Frequency: number of seizures divided by the number of participants randomized in all studies; Patient-years: total number of years participants were observed in all studies; Events/ 1000 patient years: Number of seizures per 1000 patient-years; RR (95% CI): Risk ratio of seizures of antipsychotics versus placebo (95% confidence interval).

Table 1: Sensitivity analyses

Type of sensitivity analysis	Intervention	Studies	Duration	Events	Participants	Frequency	Patient-years	Events/ 1000 patient-years	RR (95% CI)
Main study phase	**Total**	**281 (19)**	**10**	**26**	**56401 (7084)**	**0.05 %**	**7946.1**	**3.3**	**1.05 (0.45-2.43)**
	Antipsychotic	281	9	18	35067	0.05 %	4870.3	3.7	
	Placebo	281	11	8	21334	0.04 %	3075.8	2.6	
Odds ratio	**Total**	**314 (51)**	**10**	**65**	**67642 (18323)**	**0.10 %**	**9476,5**	**6.9**	**0.68 (0.41-1.12)**
	Antipsychotic	314 (51)	9	37	42600	0.09 %	5888.8	6.3	
	Placebo	314 (51)	11	28	25042	0.11%	3587.6	7.8	
Second-generation antipsychotics only	**Total**	**314 (50)**	**10**	**64**	**65938 (17506)**	**0.10 %**	**9350.66**	**6.8**	**0,69 (0.42-1.13)**
	Antipsychotic	314 (50)	9	36	40895	0.09 %	5762.56	6.2	
	Placebo	314 (50)	11	28	25043	0.11%	3588.10	7.8	

Studies: number of all studies with complete information about SAEs (number of studies with at least one seizure); Duration: mean study duration in weeks; Events: number of seizures; Participants: number of participants randomized in all studies (number of participants in studies with at least one seizure); Frequency: number of seizures divided by the number of participants randomized in all studies; Patient-years: total number of years participants were observed in all studies; Events/ 1000 patient years: Number of seizures per 1000 patient-years; RR (95% CI): Risk ratio of seizures of antipsychotics versus placebo (95% confidence interval). For the second sensitivity analysis this is odds ratio instead of risk ratio.

Table 3: Subgroup analyses

Subgroup	Intervention	Studies	Duration	Events	Participants	Frequency	Patient-years	Events/ 1000 patient-years	RR (95% CI)
PER ANTI-PSYCHOTIC									
Amisulpride vs. Placebo	**Total**	**7**	**8**	**0**	**250**	**0%**	**30.9**	**0**	-
	Amisulpride	7	8	0	137	0 %	17.4	0	
	Placebo	7	8	0	113	0 %	13.6	0	
Aripiprazole vs. Placebo	**Total**	**59 (10)**	**13**	**11**	**11926 (3145)**	**0.09 %**	**1874.4**	**5.9**	**0.90 (0.26-3.14)**
	Aripiprazole	59	13	6	6925	0.09 %	1101.4	5.4	
	Placebo	59	13	5	5001	0.1 %	773.1	6.5	
Asenapine vs. Placebo	**Total**	**16 (3)**	**8**	**3**	**4596 (1098)**	**0.07 %**	**544.0**	**5.5**	**0.37 (0.05-2.71)**
	Asenapine	16	8	1	2836	0.04 %	330.5	3	
	Placebo	16	9	2	1760	0.11 %	213.5	9.4	
Brexpiprazole vs. Placebo	**Total**	**9 (3)**	**6**	**3**	**3534 (1626)**	**0.08 %**	**357.2**	**8.4**	**1.19 (0.15-9.50)**
	Brexpiprazole	9	6	2	2375	0.08 %	240.2	8.3	
	Placebo	9	6	1	1159	0.09 %	117.0	8.5	
Cariprazine vs. Placebo	**Total**	**4 (1)**	**7**	**1**	**1971 (238)**	**0.05 %**	**218.1**	**4.6**	-
	Cariprazine	4	7	1	1273	0.08 %	146.8	6.8	
	Placebo	4	6	0	698	0 %	71.3	0	
Chlorpromazine vs. Placebo	**Total**	**1**	**8**	**0**	**106**	**0 %**	**12.4**	**0**	-
	Chlorpromazine	1	8	0	53	0 %	6.2	0	
	Placebo	1	8	0	53	0 %	6.2	0	
Haloperidol vs. Placebo	**Total**	**17 (4)**	**5**	**4**	**3225 (611)**	**0.12 %**	**241.8**	**16.5**	**0.43 (0.04-4.74)**
	Haloperidol	17	5	1	1658	0.06 %	121.0	8.3	
	Placebo	17	5	3	1567	0.19 %	120.8	24.8	
Iloperidone vs. Placebo	**Total**	**5 (1)**	**6**	**2**	**1984 (455)**	**0.1 %**	**147.1**	**13.6**	-
	Iloperidone	5	6	0	1379	0 %	104.3	0	
	Placebo	5	5	2	605	0.33 %	42.8	46.8	
Lurasidone vs. Placebo	**Total**	**14 (2)**	**6**	**2**	**4423 (781)**	**0.05 %**	**469.8**	**4.3**	**0.34 (0.02-5.51)**
	Lurasidone	14	6	1	2818	0.04 %	295.4	3.4	
	Placebo	14	6	1	1605	0.06 %	174.4	5.7	
Olanzapine vs. Placebo	**Total**	**68 (15)**	**8**	**19**	**12004 (4394)**	**0.16 %**	**1487.7**	**12.8**	**0.80 (0.32-2.00)**
	Olanzapine	68	9	11	7106	0.15 %	930.5	11.8	
	Placebo	68	8	8	4898	0.16 %	557.2	14.4	
Paliperidone vs. Placebo	**Total**	**27 (6)**	**11**	**9**	**7590 (1745)**	**0.12 %**	**1545.9**	**5.8**	**0.83 (0.21-3.26)**
	Paliperidone	27	10	5	4864	0.1 %	966.6	5.2	
	Placebo	27	12	4	2726	0.15 %	579.3	6.9	
Quetiapine vs. Placebo	**Total**	**53 (3)**	**10**	**5**	**8597 (954)**	**0.06 %**	**1136.0**	**4.4**	**1.28 (0.19-8.39)**
	Quetiapine	53	9	4	4886	0.08 %	634.3	6.3	
	Placebo	53	10	1	3711	0.03 %	501.7	2	
Risperidone vs. Placebo	**Total**	**55 (7)**	**12**	**10**	**8513 (2104)**	**0.12 %**	**1386.4**	**7.2**	**0.73 (0.22-2.41)**
	Risperidone	55	12	5	4581	0.11 %	767.9	6.5	

	Placebo	55	13	5	3932	0.13 %	618.5	8.1	
Ziprasidone vs. Placebo	**Total**	**18 (2)**	**8**	**3**	**2645 (333)**	**0.11 %**	**310.0**	**9.7**	
	Ziprasidone	18	7	0	1484	0 %	171.6	0	-
	Placebo	18	8	3	1161	0.26 %	138.4	21.7	
Zotepine vs. Placebo	**Total**	**3**	**15**	**0**	**312**	**0 %**	**50.7**	**0**	
	Zotepine	3	15	0	155	0 %	27.0	0	-
	Placebo	3	15	0	157	0%	23.7	0	
PER ADD-ON TO									
Antidepressants	**Total**	**34 (1)**	**7**	**1**	**6088 (677)**	**0.02 %**	**740,08**	**1,4**	
	Antipsychotic	34	7	1	3609	0.03 %	430,73	2,3	-
	Placebo	34	7	0	2479	0 %	309,36	0	
Antipsychotics	**Total**	**10**	**9**	**0**	**403**	**0 %**	**65,55**	**0**	
	Antipsychotic	10	9	0	205	0 %	32,27	0	-
	Placebo	10	10	0	198	0 %	33,28	0	
Mood stabilizers	**Total**	**24 (3)**	**16**	**4**	**4323 (1014)**	**0.09 %**	**917,21**	**4,4**	
	Antipsychotic	24	16	2	2321	0.21 %	490,27	4,1	**0.68 (0.06-7.03)**
	Placebo	24	17	2	2002	0.24 %	426,95	4,7	
Other substances	**Total**	**23**	**19**	**0**	**2139**	**0 %**	**585,99**	**0**	
	Antipsychotic	23	19	0	1115	0 %	312,6	0	-
	Placebo	23	20	0	1024	0 %	273,39	0	
No other drug	**Total**	**223 (47)**	**9**	**60**	**54689 (16632)**	**0.11 %**	**7167,6**	**8,4**	
	Antipsychotic	223	9	34	35350	0.06 %	4623,0	7,4	**0.66 (0.40-1.10)**
	Placebo	223	10	26	19339	0.08 %	2544,7	10,2	
PER DIAGNOSTIC CATEGORY									
Acute agitation	**Total**	**1**	**0**	**0**	**120**	**0%**	**0.0**	**0**	
	Antipsychotic	1	0	0	60	0%	0.0	0	-
	Placebo	1	0	0	60	0%	0.0	0	
ADHD or disruptive behaviour disorder	**Total**	**6**	**15**	**0**	**800**	**0%**	**157.7**	**0**	
	Antipsychotic	6	15	0	398	0%	87.8	0	-
	Placebo	6	14	0	402	0%	69.9	0	
Anorexia nervosa	**Total**	**3**	**8**	**0**	**79**	**0%**	**6.0**	**0**	
	Antipsychotic	3	8	0	36	0%	2.7	0	-
	Placebo	3	8	0	43	0%	3.3	0	
Anxiety disorder	**Total**	**9**	**8**	**0**	**1874**	**0%**	**244.3**	**0**	
	Antipsychotic	9	8	0	948	0%	122.4	0	-
	Placebo	9	8	0	926	0%	121.9	0	
Autism or pervasive developmental disorder	**Total**	**10**	**8**	**0**	**991**	**0%**	**135.6**	**0**	
	Antipsychotic	10	8	0	589	0%	82.1	0	-
	Placebo	10	8	0	402	0%	53.5	0	
Bipolar disorder	**Total**	**81 (14)**	**11**	**18**	**20214 (4238)**	**0.09 %**	**3073.5**	**5.9**	
	Antipsychotic	81	10	9	12089	0.07 %	1844.6	4.9	**0.74 (0.27-2.09)**
	Placebo	81	12	9	8125	0.11 %	1228.9	7.3	
	Total	**4 (1)**	**12**	**1**	**900 (451)**	**0.11 %**	**161.4**	**6.2**	**-**

Borderline personality disorder	Antipsychotic	4	12	1	539	0.19 %	96.3	10.4	
	Placebo	4	12	0	361	0%	65.1	0	
Chemotherapy - induced nausea and vomiting	**Total**	**1**	**1**	**0**	**44**	**0%**	**0.6**	**0**	
	Antipsychotic	1	1	0	22	0%	0.3	0	-
	Placebo	1	1	0	22	0%	0.3	0	
Dementia	**Total**	**15 (8)**	**10**	**12**	**3916 (2927)**	**0.31 %**	**631.9**	**19**	
	Antipsychotic	15	10	9	2566	0.35 %	411.0	21.9	**1.48 (0.41-5.26)**
	Placebo	15	10	3	1350	0.22 %	220.9	13.6	
Drug abuse	**Total**	**18**	**11**	**0**	**1375**	**0%**	**246.0**	**0**	
	Antipsychotic	18	11	0	719	0%	125.8	0	-
	Placebo	18	12	0	656	0%	120.3	0	
Dysthymia	**Total**	**1**	**4**	**0**	**39**	**0%**	**3.0**	**0**	
	Antipsychotic	1	4	0	20	0%	1.5	0	-
	Placebo	1	4	0	19	0%	1.5	0	
Fibromyalgia	**Total**	**1**	**12**	**0**	**51**	**0%**	**10.8**	**0**	
	Antipsychotic	1	12	0	25	0%	5.2	0	-
	Placebo	1	12	0	26	0%	5.6	0	
Gambling addiction	**Total**	**2**	**10**	**0**	**63**	**0%**	**10.4**	**0**	
	Antipsychotic	2	10	0	30	0%	4.6	0	-
	Placebo	2	10	0	33	0%	5.8	0	
Healthy subjects	**Total**	**12**	**2**	**0**	**369**	**0%**	**12.5**	**0**	
	Antipsychotic	12	2	0	227	0%	7.7	0	-
	Placebo	12	2	0	142	0%	4.8	0	
Major depressive disorder	**Total**	**28 (2)**	**7**	**2**	**7184 (849)**	**0.03 %**	**835.4**	**2.4**	
	Antipsychotic	28	7	2	4356	0.05 %	500.2	4	-
	Placebo	28	7	0	2828	0%	335.2	0	
Obsessive-compulsive disorder	**Total**	**6**	**9**	**0**	**272**	**0%**	**44.9**	**0**	
	Antipsychotic	6	9	0	147	0%	23.5	0	-
	Placebo	6	10	0	125	0%	21.4	0	
Parkinson's disease	**Total**	**3**	**4**	**0**	**183**	**0%**	**12.1**	**0**	
	Antipsychotic	3	4	0	104	0%	6.5	0	-
	Placebo	3	4	0	79	0%	5.6	0	
Post-traumatic stress disorder	**Total**	**6 (1)**	**20**	**1**	**430 (30)**	**0.23 %**	**132.4**	**7.6**	
	Antipsychotic	6	20	0	214	0%	62.4	0	-
	Placebo	6	20	1	216	0.46 %	70.0	14.3	
Schizophrenia	**Total**	**100 (25)**	**9**	**31**	**28252 (9828)**	**0.11 %**	**3685.1**	**8.4**	
	Antipsychotic	100	9	16	19202	0.08 %	2458.7	6.5	**0.45 (0.23-0.88)**
	Placebo	100	11	15	9050	0.17 %	1226.4	12.2	
Stuttering	**Total**	**2**	**10**	**0**	**40**	**0%**	**7.4**	**0**	
	Antipsychotic	2	10	0	20	0%	3.7	0	-
	Placebo	2	10	0	20	0%	3.7	0	
Tourette syndrome	**Total**	**5**	**8**	**0**	**446**	**0%**	**65.4**	**0**	
	Antipsychotic	5	8	0	289	0%	41.9	0	-
	Placebo	5	8	0	157	0%	23.6	0	

PER AGE GROUP									
Middle-aged adults (18-65 years)	**Total**	**246 (41)**	**10**	**51**	**56301 (14986)**	**0.09 %**	**7844.1**	**6.5**	**0.58 (0.33-1.02)**
	Antipsychotic	246	9	27	35585	0.08 %	4862.4	5.6	
	Placebo	246	11	24	20716	0.12 %	2981.7	8	
Children or adolescents (<18 years)	**Total**	**42 (1)**	**10**	**1**	**6047 (296)**	**0.02 %**	**808.4**	**1.2**	**-**
	Antipsychotic	42	10	1	3731	0.03 %	516.5	1.9	
	Placebo	42	11	0	2316	0 %	291.9	0	
Older adults (>65 years)	**Total**	**23 (9)**	**10**	**13**	**5189 (3041)**	**0.25 %**	**815.7**	**15.9**	**1.11 (0.35-3.49)**
	Antipsychotic	23	10	9	3232	0.28 %	505.9	17.8	
	Placebo	23	10	4	1957	0.2 %	309.8	12.9	
PER STUDY DURATION									
1 to <6 days	**Total**	**12**	**0**	**0**	**1850**	**0 %**	**5.8**	**0**	**-**
	Antipsychotic	12	0	0	1336	0 %	4.1	0	
	Placebo	12	0	0	514	0 %	1.7	0	
6 days to 3 months	**Total**	**264 (44)**	**7**	**58**	**57635 (16165)**	**0.1 %**	**6004.7**	**9.7**	**0.70 (0.41-1.20)**
	Antipsychotic	264	7	34	36813	0.09 %	3820.5	8.9	
	Placebo	264	7	24	20822	0.12 %	2184.2	11	
> 3 months	**Total**	**38 (7)**	**41**	**7**	**8157 (2158)**	**0.09 %**	**3466.0**	**2**	**0.53 (0.14-2.07)**
	Antipsychotic	38	41	3	4451	0.07 %	2064.2	1.5	
	Placebo	38	41	4	3706	0.11 %	1401.7	2.9	

Studies: number of all studies with complete information about SAEs (number of studies with at least one seizure); Duration: mean study duration in weeks; Events: number of seizures; Participants: number of participants randomized in all studies (number of participants in studies with at least one seizure); Frequency: number of seizures divided by the number of participants randomized in all studies; Patient-years: total number of years participants were observed in all studies; Events/ 1000 patient years: Number of seizures per 1000 patient-years; RR (95% CI): Risk ratio of seizures of antipsychotics versus placebo (95% confidence interval).

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