Second-generation-antipsychotic drugs and short-term-mortality: A meta-analysis of placebo-controlled randomized controlled trials

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SUMMARY

Background

Acutely occurring, life-threatening side effects of antipsychotics may contribute to the reduced life expectancy observed in patients with severe mental disorders. We examined this question by a meta-analysis of deaths occurring in placebo-controlled antipsychotic drug trials.

Methods

We included randomized controlled trials (RCTs) comparing second-generation-antipsychotics with placebo across diagnostic categories. We searched MEDLINE, EMBASE, Cochrane CENTRAL, BIOSIS, PsycINFO, Pubmed, Clinicaltrials.gov and WHO ICTRP (last search 01/27/2017), and we contacted pharmaceutical companies and regulatory authorities for eligible trials. We examined mortality due to any reason (primary outcome), due to natural causes, suicide, and other unnatural causes. We synthesized the results with odds ratios (OR) in a common-effect meta-analysis. We investigated the effects of age, diagnostic category, gender, study duration, antipsychotic drug used, drug dose and polypharmacy with subgroup- and meta-regression-analyses (PROSPERO #CRD42016033930).

Findings

We included 596 RCTs that reported 207 deaths in 53804 patients on drug (0.38%) and 99 deaths in 31184 patients on placebo (0.32%). Most trials (85%) were 13 weeks (3 month) or less in duration (median 6, interquartile range 4 - 10 weeks). There was no evidence of difference between antipsychotics and placebo regarding mortality due to any reason (OR 1.19; 95% CI 0.93, 1.53), natural causes (OR 1.29; 95% CI 0.85, 1.94), suicide (OR 1.15; 95% CI 0.47, 2.81) and other unnatural causes (OR 1.55; 95% CI 0.66, 3.63). Most subgroup and meta-regression analyses did not indicate any important effect moderators. The

exceptions were increased mortality in patients with dementia (OR 1.56; 95% CI 1.10, 2.21), elderly patients (OR 1.38; 95% CI 1.01, 1.89), aripiprazole-treated patients (OR 2.20; 95% CI 1.00, 4.86), and in studies with a higher percentage of women (regression coefficient 0.0251; 95% Cr.I. 0.0104, 0.0399). However, the effects in the three latter subgroups were mainly based on the included dementia-trials. The result for schizophreniawas OR 0.69 (95% CI 0.35, 1.35).

Interpretation

Overall, and for the main indication schizophrenia, there is no evidence from RCTs that antipsychotics increase mortality. However, there may be an increased risk for vulnerable populations (particularly patients with dementia). Of note, this meta-analysis could only address acute treatment effects leading to death in the short-term, but not long-term effects of antipsychotics on mortality.

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INTRODUCTION

People with schizophrenia and other severe mental disorders have a reduced life expectancy compared to the general population.[1,2] Antipsychotic drugs are the mainstay of the treatment of schizophrenia[3], but they are also used for numerous other psychiatric and even non-psychiatric diseases.[4,5] If and how treatment with antipsychotics contributes to this increased mortality is strongly debated, with no consensus yet.[6] Acutely occurring, life-threatening side effects and the consequences of chronically persisting side effects such as weight gain may both cause premature death. Decreased suicidality, aggression and accidents as well as better lifestyle and healthcare following reduced symptomatology, may however exert protective effects. Several observational studies found that antipsychotic drugs have no effect on mortality, or even reduce it as compared to no-treatment.[7–15] Conversely, other observational studies reported increased mortality associated with antipsychotic treatment.[16–19] Synthesis and interpretation of these results is difficult and have led to spirited discussion[6,20–22] because of specific methodological issues in these studies, but also because of the general limitation that confounding can never be ruled out completely in observational data. Randomized controlled trials (RCTs) offer the best source of evidence for estimating treatment effects, but single RCTs in this area are clearly underpowered due to the rarity of the outcome. Nevertheless, there are many antipsychotic drugs, and they have been tried for many indications. Thus, hundreds of trials for antipsychotics are now available, making meta-analysis a more appropriate tool to examine these questions.

We, therefore, conducted a meta-analysis of randomized trials comparing second-generation antipsychotics with placebo, including all diagnoses. Of course, most RCTs are short-term so that this analysis is restricted to estimating the acute effects of antipsychotics. However, there are many such side-effects such as arrhythmias, thromboembolisms, seizures, hyperglycemias, accidents due to over sedation and others which could lead to sudden deaths. We examined mortality due to any reason, due to natural causes, due to suicides and due to

other unnatural causes. We also examined the effects in specific patient populations with various subgroup and meta-regression analyses.

METHODS

We published the study protocol in PROSPERO (see CRD42016033930 and webappendix) and followed the PRISMA statement[23] in the reporting of our results (checklist in webappendix). This meta-analysis was conducted in the context of a broader project sponsored by the German Ministry of Education and Research which also comprises an assessment of serious adverse events. This outcome will be published in another paper.

Search strategy and selection criteria

We searched for published and unpublished RCTs comparing the following second-generation antipsychotics (SGAs) available in Europe or the US with placebo: amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine. First-generation antipsychotic drugs, which were used as additional active treatments in these RCTs, were also included. There were no restrictions in terms of type of application (oral, intravenous, inhalers, short- and long-acting (depot) intramuscular applications, all either in monotherapy or as add-on-medication), and doses (any dose, in flexible and fixed dosing regimens).

Studies were included irrespectively of the diagnosis of the participants, because we deemed that side-effects (in contrast to efficacy) are relatively independent of the specific mental illness. Also we applied no restrictions in terms of age, sex, or ethnic groups. However we examined treatment effects in vulnerable subgroups, such as children and elderly patients, in predefined subgroup analyses (see below).

Double-blind, single-blind, or open-label RCTs were eligible, but studies with a high risk of bias in sequence generation for randomization or allocation concealment[24] were a priori

excluded. There were no restrictions in study length except for very short (≤24h) studies that addressed neuropsychological rather than treatment questions (e.g. measuring task-induced brain activation in fMRT). Also, there were no restrictions in publication year and language. Only studies from mainland China for which major quality concerns have been raised[25–27] were excluded.

The primary outcome was mortality for any reason. As secondary outcomes we examined mortality due to natural causes, suicide, and other non-natural causes (e.g. accidents).

We searched the following electronic databases, all from their inception, with broad terms for randomization, the generic names of the included SGAs, and terms for placebo: MEDLINE, EMBASE, Cochrane Central Register of Randomized Trials (CENTRAL), BIOSIS, PsycINFO, Pubmed, Clinicaltrial.gov and WHO ICTRP (last search 27th January 2017; detailed search terms in webappendix). The European Union Clinical Trials Register (EUCTR) was searched manually. We also contacted the manufacturers of the antipsychotics, the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the German "Bundesinstitut für Arzneimittel und Medizinprodukte" (BfArM), and searched their clinical trial websites.

Screening of title and abstracts and selection of included studies (after full text retrieval and cross-referencing), was done in duplicate by JS and another reviewer (HR or LR) and disagreement was solved by discussion with SL.

Data extraction was done independently by at least two reviewers (JS, HR, LR, MH and MK), using an electronic database which allowed to automatically check whether extractions agreed. Disagreement was solved by discussion among reviewers; if it could not be resolved a third reviewer (JS or SL) was involved. Moreover, we sent personalized emails to all

corresponding authors and asked them for missing data (for 689 authors e-mail addresses were found). Risk of bias was also assessed in duplicate by the reviewers mentioned above using the Cochrane risk of bias tool.[24]

Data analysis

We used a common-effect ("fixed-effect") Mantel-Haenszel meta-analysis model to synthesize odds-ratios (OR).[28] We chose OR because time to event data, which are necessary for the calculation of hazard ratios were usually not reported. The Mantel-Haenszel-method synthesizes information from studies with at least one fatal event, i.e. it excludes studies with no events. We included all deaths that occurred in the randomized phase or within the studies' predefined safety follow-up phases after study discontinuation or completion (these usually last 30 days) in the primary analysis (see also sensitivity analysis 1 below). From cross-over studies we used only the first phases to avoid carry-over effects.[29] Heterogeneity was statistically assessed by estimating τ^2, I^2 and by performing a Q-test.[24] Small study effects (linked with the possibility of publication bias) were evaluated by visual inspection of a funnel plot and a Harbord test.[30]

We performed pre-planned sensitivity analyses to examine the robustness of the primary outcome:

1. Following an analysis by the FDA on suicidality associated with antidepressants,[31] we included only those deaths that occurred during the randomized phase or 24 hours after the last drug administration. In the safety-follow-up periods effects may be diluted, because patients, for example, take other pharmaceutical substances.
2. We synthesized mortality rates (number of deaths over total patient-years per study) to account for potential differences in premature study discontinuation between drug- and placebo-arms. If information on the total patient-years spent in the study was not

available, it was estimated from study duration and number of dropouts, after assuming a linear rate of discontinuation over time.

3. We performed additional sensitivity analyses using a hypergeometric normal model,[32] as well as a correlated beta-binomial (Sarmanov) model.[33] We also performed a Bayesian common-effects and Bayesian random-effects meta-analysis. For the latter we used an informative prior distribution for heterogeneity.[34] Of note, the beta-binomial model and the Bayesian models use information from studies without events.
4. The primary analysis included only studies in which the outcome (number of deaths) was actively reported. In a sensitivity analysis (Bayesian random effects model) we included studies that did not explicitly mention this outcome and assumed that no death had occurred (see discussion for further details concerning this assumption).

A priori planned subgroup analyses of the primary outcome addressed (i) study duration (less than 6 days; 6 days to 13 weeks; more than 13 weeks), (ii) age groups (children and adolescents; adults; elderly), (iii) diagnosis (e.g. schizophrenia or bipolar disorder), (iv) specific antipsychotic drug used and (v) monotherapy versus combinations of antipsychotics (any systematic combination; add-on to antidepressants, mood stabilizers or antipsychotics).

Meta-regression analyses were performed for the primary outcome to assess the effect of (i) the percentage of women, and (ii) antipsychotic dose in olanzapine equivalents based on the International Consensus Study of Antipsychotic Dosing.[3,35] In (ii) only studies of oral application in adult patients were included because other dose equivalencies may apply for other age groups and applications.

In *post-hoc* sensitivity analyses we excluded dementia trials, because dementia turned out to be a possible treatment effect modifier (see discussion for further reasoning).

Mantel-Haenszel-meta-analysis were performed in R using the `metabin` command from the package `meta`.[36] Mortality rates (sensitivity analysis 2) were synthesized in R using the `metafor` package,[37] fitting a common-effect effects Poisson regression model.

The hypergeometric-normal model and the correlated beta-binomial model (sensitivity analysis 3) were fitted in R using the `metafor` package,[37] and the code provided by Chen et al.,[33] respectively. Bayesian meta-analyses (sensitivity analyses 3 and 4) and meta-regressions were performed in OpenBUGS.[38,39] Details of the statistical models are presented in the webappendix. The strength of the evidence was assessed within the GRADE framework[40] using the online tool GRADE PRO (https://gradepro.org/).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We present the PRISMA[23] flow diagram in figure 1 and the characteristics of included studies in the webappendix. We included 596 trials published between 1978 and 2017 with a total of 108747 participants. 352 studies (84988 participants), of which 346 were double-blind, with actively reported information about deaths constitute the main dataset for our meta-analysis. 244 additional studies with no information on fatal events were included in a sensitivity analysis. In the main dataset, the most frequently used drugs were quetiapine (75 studies), olanzapine (73), aripiprazole (66), risperidone (65), paliperidone (30), haloperidol (19; the only first-generation antipsychotic for which studies were found), ziprasidone (14), asenapine (12), cariprazine (10), and lurasidone (10). For all other drugs less than 10 studies were available. Most trials included patients diagnosed with schizophrenia (111 of 352 RCTs), but there were also 22 other diagnostic categories. The latter comprise other approved indications for some antipsychotics, such as bipolar disorder (90 RCTs) or major depressive disorder (32 RCTs), but also diagnostic categories without official approval. Most studies were conducted in adults (usually 18-65 years), but 11% and 12% of the studies were on "elderly patients" and on "children and adolescents", respectively. The median percentage of females was 43% (interquartile range (IQR) 29% - 58%). As there were studies on acute agitation as well as studies for relapse-prevention, trial durations varied between 1.5 hours to 104 weeks (median 6 weeks, IQR 4-10). 300 (85%) of 352 studies were 13 weeks (3 month) or less in duration. Of note, only 20 studies (5.7%) fell in the very short-term category (<5 days), and duration was examined in a subgroup analysis.

The risk of bias assessment is shown in the webappendix. We conservatively judged all studies that did not *explicitly* report on death as possible selective reporting. Therefore high risk of bias was frequent in this category (210 reports, 35% of all studies). Studies rated at high risk of bias were rare in the other categories: Randomization 0 (0%), allocation

concealment 0 (0%), blinding of participants and personal 19 (3.2%), blinding of outcome assessment 14 (2.3%), incomplete outcome data 11 (1.8%) and other bias 17 (2.9%).

Outcome results

Overall there were 306 deaths; 207 in 53804 patients on drug (0.38%), 99 in 31184 patients on placebo (32%). In all results, an odds ratio >1 corresponds to higher odds of mortality with antipsychotics (favors placebo). In the following text the number of studies (k) and participants (n) vary depending on the statistical model. The Mantel-Haenszel model uses only studies with at least one event whereas in sensitivity analyses studies with zero events were also included.

The summary OR for the primary outcome all-cause mortality was 1.19 (95% confidence interval (CI) 0.93 to 1.53; k=91, n=29049). For mortality due to natural causes it was 1.29 (95% CI 0.85, 1.94; k=43, n=13994), for suicides 1.15 (95% CI 0.47, 2.81; k=18, n=6749) and for mortality due to other unnatural causes 1.55 (95% CI 0.66, 3.63; k=23, n=7493) (table 1; forest plots and table of specific causes of death in webappendix).

Sensitivity analyses

The sensitivity analyses of the primary outcome did not materially change the results (table 2). When studies that did not explicitly report on death were included, the summary OR for mortality from was 1.13 (95% Cr.I. 0.87, 1.47; crude mortality of drug 0.31% and placebo 0.25%; k=581, n=107655). When we excluded fatal events that occurred more than 24 hours after the last drug administration, the odds ratio was 0.90 (95% CI 0.55, 1.47; k=31, n=10618). Moreover, when we used mortality rates instead of frequencies, we found an incidence rate ratio of 0.89 (95% CI 0.54, 1.47; k=30, 2363 patient-years) referring to 6.4 and 6.7 events per 1000 patient-years for drug and placebo, respectively. Analyses with hypergeometric-normal, beta-binomial and Bayesian models did not change our conclusions. .

Excluding dementia studies in the post-hoc sensitivity analysis resulted in an OR of 0.85 (95% CI 0.59, 1.23; k=69, n=22704) in the primary outcome.

Subgroup and meta-regression analyses

Most subgroup and meta-regression analyses did not indicate any important effect moderators (table 3). The exceptions were increased mortality in elderly patients, patients with dementia, aripiprazole-treated patients, and in studies with a higher percentage of women. However, tests for subgroup differences were not significant. Furthermore, when dementia studies were excluded in the post-hoc sensitivity analyses none of these subgroups revealed significantly increased mortality (table 3 and discussion).

For patients with schizophrenia – the main indication of all antipsychotics – there was no evidence of an effect (OR 0.69; 95% CI 0.35, 1.35; k=31, n=11680). Of note, although schizophrenia (and related disorders) was the most frequent diagnostic category in the primary analysis (111/352 studies (32%), 32807/84988 patients (39%)), only few deaths were reported for this subgroup (20 deaths in 22355 patients on drug (0.09%) and 16 deaths in 10452 patients on placebo (0.15%)).

There was no indication of small study effects (Harbord test p=0.50, funnel plot in webappendix). Regarding heterogeneity, for all analyses the standard deviation of random effects (τ^2) was estimated to be 0, $I^2 = 0$ and also all Q-tests did not provide evidence for heterogeneity for any of the analyses (p-values > 0.89 in all analyses). One should keep in mind, however, that for the case of rare events the estimation of statistical heterogeneity can be very difficult. Thus, in order to assess the robustness of our results, we also performed a Bayesian sensitivity analysis including external information (in the form of informative prior distributions) for heterogeneity. This analysis did not give markedly different results from the

primary analysis. The strength of the evidence was rated to be moderate for all outcomes according to GRADE (summary of findings tables in webappendix).[40]

DISCUSSION

In this meta-analysis of 596 RCTs, we did not find evidence that mortality related to acute antipsychotic drug effects differs between patients treated with antipsychotic drugs or placebo, neither for all-cause mortality nor for death due to natural causes, suicides or other unnatural causes, except for people with dementia.

Strengths of the analysis are the comprehensive search and the resulting large sample size (84988 patients with information about mortality). This large sample size was in part achieved by including studies across diagnostic categories, assuming that severe side-effects leading to death are relatively independent of the treated mental disorders. Moreover, we also examined the impact of clinically important effect modifiers such as diagnosis, age, gender, specific antipsychotic drug, antipsychotic doses and polypharmacy.

In contrast to Khan et al. 2007 and 2013[41,42] who found a significantly reduced mortality for people with schizophrenia treated with antipsychotics compared to placebo, we did not find a significant difference. Khan et al. evaluated deaths per cumulative patient-years in FDA-approval-trials for schizophrenia. However, this analysis also included trials that compared two antipsychotics with each other rather than with placebo. The death rates in the pooled drug groups were compared with the pooled placebo groups, instead of first calculating an effect size for each study separately. This method breaks the randomization of the studies, and thus it is a suboptimal approach. Moreover, the authors included non-randomized open-label long-term-extensions, in which all patients were on drug, which can lead to a selection bias of patients who tolerate antipsychotics. Therefore, as Khan et al.[41,42] and others[43] discuss, these findings might be biased in favor of drug-treatment. Nevertheless, our point estimate in the schizophrenia subgroup was similar to that of Khan et al. 2013 (0.69 vs. ca. 0.40 there). Although our confidence interval was very large (95% CI 0.35, 1.35), it is possible that

antipsychotic drugs have protective effects for indications in which they are efficacious (in particular schizophrenia). A much smaller meta-analysis (5919 participants) restricted to long-acting injectable antipsychotics in schizophrenia[44] came to conclusions similar to ours.

Our findings concur with those of a meta-analysis which also found an increased risk of death associated with second-generation-antipsychotics in the treatment of dementia;[45] however, our dataset included nine (=60%) more studies, 1264 (25%) more participants and 27 (17%) more fatal events. Therefore, our study is more than just a replication. Of note, Hulshoff et al.[46] found no significant differences between *first-generation* antipsychotics and placebo in elderly patients with dementia or delirium, but the sample size was small (17 RCTs with 2387 participants). Interestingly, when we excluded dementia studies from the overall sample in a sensitivity analysis, the all-cause-mortality (OR 0.85; 95% CI 0.59, 1.23) suggested decreased mortality with antipsychotics.

Our subgroup analyses also indicated increased mortality in elderly patients, women and aripiprazole-treated patients. However, the dementia studies had a relatively high impact on the results in these subgroups. 87% (186/214) of all fatal events in elderly people occurred in patients with dementia. Women are overrepresented in dementia trials; in these studies they contributed 68% (4023/5886) of the sample, compared to 47% (37907/81122) overall. Most deaths (69%, 29/42) in the aripiprazole-trials occurred in dementia-patients and there is no external evidence for an elevated risk related to this drug. On the contrary, aripiprazole is known for producing comparably few side effects,[3] and in recent analyses of Swedish registers it was associated with less mortality than many other antipsychotics.[12,47] Therefore, it was not surprising that in sensitivity analyses without dementia studies there was no evidence of an effect in any of these subgroups. Moreover, there is a chance that subgroup-findings are false positive, due to multiple testing issues.

Our review has some limitations. We judged the strength of the evidence for the primary outcome to be only moderate according to the GRADE framework. The reason was that, despite the large sample size, effect sizes were imprecise. The number-needed-to-harm (NNH) for all-cause mortality was 6 more deaths in 10 000 patients treated with antipsychotics compared to placebo, with a 95% CI ranging from 2 less to 14 more. Although the numbers are more favorable for the drug when dementia patients are excluded (3 deaths less under antipsychotics in 10 000 patients, 95% CI 9 less to 4 more), there is still uncertainty. We decided to downgrade for imprecision if the confidence interval included both, the possibility of no difference *and* the possibility of one death more in the drug group compared to placebo for one thousand patients treated (i.e. 10 more in 10 000 patients treated). This decision is corroborated by a post-hoc power analysis that yielded a power of 27% of finding a statistical significant result for our primary outcome. We feel that despite this limitation our data are clinically useful because the just mentioned confidence intervals provide boundaries within which the real effect is reasonably expected to lie (details and NNH for secondary outcomes see GRADE in webappendix). Second, in many studies it was not explicitly reported whether deaths had occurred. Because death is a rare event, we assumed it to be likely that in most of these cases no deaths had occurred, and that usually the original authors did not find it important to report “no deaths”, rather than intentionally suppressing information. Also, we did not judge the studies, for which we only found protocols (see PRISMA diagram in webappendix), to represent an important publication bias for our analysis of mortality. Other reasons than occurrence of fatal events, such as recruiting failure or unfavorable efficacy data, seem more probable for not further conducting or reporting these trials, and the statistical tests did not provide any evidence of small study effects. Third, participants in randomized-controlled trials are selected populations. Particularly vulnerable patients, such as those with serious medical illness, are often excluded.

Finally, the duration of RCTs is limited and 85% of the trials in the analysis were conducted over a time-span of 13 weeks (3 month) or less (median 6, IQR 4 - 10 weeks). Consequently, our analysis focused on acute treatment effects leading to death on the short term. Therefore, we could not assess how much chronic antipsychotic side effects, such as weight gain, contribute to the documented excess mortality over the patients' life-span.[1] The impact of such long-lasting adverse events can only be explored in observational studies. These designs, however, as already explained in the introduction section, have their own limitations and yielded conflicting results.[7–19] We therefore hope that this work, which represents the largest meta-analysis of mortality in randomized antipsychotic drugs trials to date, will inform the polarized discussion about the safety of these drugs.

Contributors

SL was the principal investigator of the review and obtained the funding. JS, JD, GS, and SL designed the meta-analysis. JS, MH and SL set up the database. JS, HR, MH, MK, LR, and SL screened the literature search, acquired reports of relevant trials, selected included studies and extracted data. JS and SL contacted pharmaceutical companies, drug regulatory organizations and trial investigators for additional information. OE and GS performed all statistical analysis. JS, OE, GS, JD, and SL analyzed and interpreted the data. JS, OE, GS, and SL wrote the draft and the final version of the report. All authors critically reviewed the report for important intellectual content and approved the final submitted version.

Declaration of interests

In the last three years Dr. Leucht has received personal fees from LB Pharma, Lundbeck, Otsuka, TEVA pharmaceuticals, LTS Lohmann, Geodon Richter, Recordati, Boehringer Ingelheim, SanofiAventis, Janssen/Johnson and Johnson, EliLilly and Servier. MH received

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RESEARCH IN CONTEXT

Evidence before this study:

It is heatedly debated whether and how much antipsychotic drugs may contribute to the documented excess mortality of people with severe mental illnesses. Acutely occurring, life-threatening side effects and the consequences of persisting chronic side-effects may both cause premature death. Observational studies on the topic were contradictory, and, in those studies, confounding can never be ruled out completely. Randomized controlled trials (RCTs) are the best evidence to estimate causal effects, but given the rarity of death as an event, single RCTs are clearly underpowered. We, therefore, searched PubMed for meta-analyses of randomized-controlled trials with the question whether antipsychotic drugs increase or decrease mortality compared to placebo (search terms: "antipsychotic* AND (death OR mortality), publication type: review OR meta-analysis", last search: September 2017). We found two such systematic reviews restricted to people with dementia, in one of which a significantly increased mortality was documented for second generation antipsychotics, and a small meta-analysis restricted to depot antipsychotics for schizophrenia which showed no difference. A comprehensive systematic review and meta-analysis across all diagnostic categories did not exist.

Added value of this study:

We present the first meta-analysis of randomized controlled trials comparing antipsychotic drugs with placebo over all diagnostic categories and age-groups, thus reaching a sample size of 596 trials with 108747 participants. The primary outcome was all-cause mortality, but we also examined mortality due to natural causes, suicides and other unnatural causes. Moreover, we addressed important subgroups such as diagnostic categories, age groups, gender, specific antipsychotic drugs used, antipsychotic doses and polypharmacy. We found no evidence for

increased mortality in people treated with antipsychotics in the overall population and in most subgroups. The exception is patients with dementia for whom a subgroup analysis suggested an increased risk. Of note, our analysis could only address mortality related to acute effects of antipsychotics because most RCTs are short-term studies.

Implications of all the available evidence:

Overall, there is no randomized evidence for increased short-term-mortality to be associated with antipsychotic drugs. However, for vulnerable subgroups, such as patients with dementia, antipsychotic treatment may add an additional risk of death which should be considered when prescribing such drugs.

REFERENCES

1 Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia. A systematic review and meta-analysis. *The Lancet Psychiatry* 2017; **4:** 295–301. doi:10.1016/S2215-0366(17)30078-0.

2 Chang C-K, Hayes RD, Perera G, et al. Life expectancy at birth for people with serious mental illness and other major disorders from a secondary mental health care case register in London. *PloS one* 2011; **6:** e19590. doi:10.1371/journal.pone.0019590.

3 Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet (London, England)* 2013; **382:** 951–62. doi:10.1016/S0140-6736(13)60733-3.

4 Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA* 2011; **306:** 1359–69. doi:10.1001/jama.2011.1360.

5 Carton L, Cottencin O, Lapeyre-Mestre M, et al. Off-Label Prescribing of Antipsychotics in Adults, Children and Elderly Individuals: A Systematic Review of Recent Prescription Trends. *Current pharmaceutical design* 2015; **21:** 3280–97.

6 Vermeulen J, van Rooijen G, Doedens P, Numminen E, van Tricht M, Haan L de. Antipsychotic medication and long-term mortality risk in patients with schizophrenia; a systematic review and meta-analysis. *Psychological medicine* 2017: 1–12. doi:10.1017/S0033291717000873.

7 Tiihonen J, Mittendorfer-Rutz E, Torniainen M, Alexanderson K, Tanskanen A. Mortality and Cumulative Exposure to Antipsychotics, Antidepressants, and Benzodiazepines in Patients With Schizophrenia: An Observational Follow-Up Study. *The American journal of psychiatry* 2016; **173:** 600–06. doi:10.1176/appi.ajp.2015.15050618.

8 Tiihonen J, Wahlbeck K, Lönnqvist J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ (Clinical research ed.)* 2006; **333:** 224. doi:10.1136/bmj.38881.382755.2F.

9 Tiihonen J, Lönnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia. A population-based cohort study (FIN11 study). *The Lancet* 2009; **374:** 620–27. doi:10.1016/S0140-6736(09)60742-X.

10 Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *The American journal of psychiatry* 2011; **168:** 603–09. doi:10.1176/appi.ajp.2011.10081224.

11 Baandrup L, Gasse C, Jensen VD, et al. Antipsychotic polypharmacy and risk of death from natural causes in patients with schizophrenia: a population-based nested case-control study. *The Journal of clinical psychiatry* 2010; **71:** 103–08. doi:10.4088/JCP.08m04818yel.

12 Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. *The American journal of psychiatry* 2013; **170:** 324–33. doi:10.1176/appi.ajp.2012.12050599.

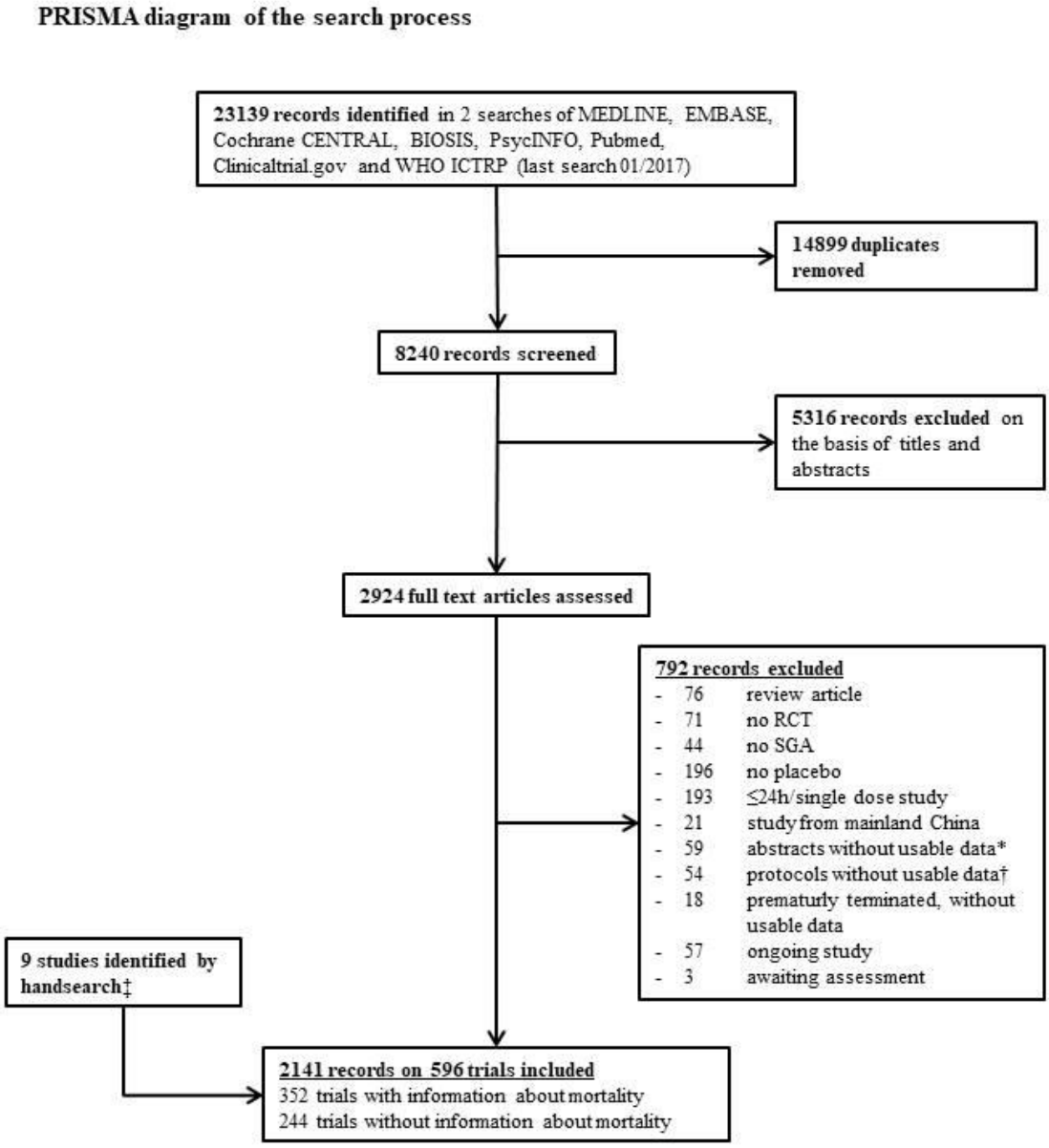
13 Rubio JM, Correll CU. Reduced all-cause mortality with antipsychotics and antidepressants compared to increased all-cause mortality with benzodiazepines in patients with schizophrenia observed in naturalistic treatment settings. *Evidence-based mental health* 2017; **20:** e6. doi:10.1136/eb-2016-102525.

14 Thu Trang D, Cool C, Laffon de Mazieres C, et al. Mortality and Antipsychotic Drug Use in Elderly Patients With Parkinson Disease in Nursing Homes. *Journal of the American Medical Directors Association* 2017. doi:10.1016/j.jamda.2017.04.014.
15 Torniainen M, Mittendorfer-Rutz E, Tanskanen A, et al. Antipsychotic treatment and mortality in schizophrenia. *Schizophrenia bulletin* 2015; **41:** 656–63. doi:10.1093/schbul/sbu164.
16 Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *The New England journal of medicine* 2009; **360:** 225–35. doi:10.1056/NEJMoa0806994.
17 Murray-Thomas T, Jones ME, Patel D, et al. Risk of mortality (including sudden cardiac death) and major cardiovascular events in atypical and typical antipsychotic users: a study with the general practice research database. *Cardiovascular psychiatry and neurology* 2013; **2013:** 247486. doi:10.1155/2013/247486.
18 Joukamaa M, Heliövaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V. Schizophrenia, neuroleptic medication and mortality. *The British journal of psychiatry : the journal of mental science* 2006; **188:** 122–27. doi:10.1192/bjp.188.2.122.
19 Koponen M, Taipale H, Lavikainen P, et al. Risk of Mortality Associated with Antipsychotic Monotherapy and Polypharmacy Among Community-Dwelling Persons with Alzheimer's Disease. *Journal of Alzheimer's disease : JAD* 2017; **56:** 107–18. doi:10.3233/JAD-160671.
20 Weinmann S, Read J, Aderhold V. Influence of antipsychotics on mortality in schizophrenia: systematic review. *Schizophrenia research* 2009; **113:** 1–11. doi:10.1016/j.schres.2009.05.018.
21 Tandon R, Nasrallah HA, Keshavan M. Antipsychotics, mortality and schizophrenia. What are the facts? *Schizophrenia research* 2011; **133:** 262–63. doi:10.1016/j.schres.2011.08.020.
22 Hert M de, Correll CU, Cohen D. Do antipsychotic medications reduce or increase mortality in schizophrenia? A critical appraisal of the FIN-11 study. *Schizophrenia research* 2010; **117:** 68–74. doi:10.1016/j.schres.2009.12.029.
23 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS medicine* 2009; **6:** e1000100. doi:10.1371/journal.pmed.1000100.
24 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011): The Cochrane Collaboration, 2011.
25 Wu T, Li Y, Liu G, Bian Z, Li J, Zhang J, Xie L, Ni J. Investigation of authenticity of 'claimed' randomized controlled trials (RCTs) and quality assessment of RCT reports published in China. Dublin, UK, 2006 23-26 Oct.
26 Woodhead M. 80% of China's clinical trial data are fraudulent, investigation finds. *BMJ (Clinical research ed.)* 2016; **355:** i5396. doi:10.1136/bmj.i5396.
27 Parry J. China vows to clamp down on academic fraud amid medical journal scandal. *BMJ (Clinical research ed.)* 2017; **357:** j2970. doi:10.1136/bmj.j2970.
28 Efthimiou O. Practical guide to the meta-analysis of rare events. *Evidence-based mental health* 2018. doi:10.1136/eb-2018-102911.
29 Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials. Methodological issues. *International Journal of Epidemiology* 2002; **31:** 140–49. doi:10.1093/ije/31.1.140.
30 Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in medicine* 2006; **25:** 3443–57. doi:10.1002/sim.2380.

31 Stone M, Laughren T, Jones ML, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ (Clinical research ed.)* 2009; **339:** b2880.
32 Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Statistics in medicine* 2010; **29:** 3046–67. doi:10.1002/sim.4040.
33 Chen Y, Chu H, Luo S, Nie L, Chen S. Bayesian analysis on meta-analysis of case-control studies accounting for within-study correlation. *Statistical methods in medical research* 2015; **24:** 836–55. doi:10.1177/0962280211430889.
34 Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JPT. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Statistics in medicine* 2015; **34:** 984–98. doi:10.1002/sim.6381.
35 Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. *The American journal of psychiatry* 2010; **167:** 686–93. doi:10.1176/appi.ajp.2009.09060802.
36 Schwarzer G. meta: General Package for Meta-Analysis. https://cran.r-project.org/web/packages/meta/meta.pdf (accessed Jun 29, 2017).
37 Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software* 2010; **36:** 1–48.
38 Lunn D, Spiegelhalter D, Thomas A, Best N. The BUGS project: Evolution, critique and future directions. *Statistics in medicine* 2009; **28:** 3049–67. doi:10.1002/sim.3680.
39 Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS - A Bayesian Modelling Framework: Concepts, Structure, and Extensibility. *Statistics and Computing* 2000; **10:** 325–37. doi:10.1023/A:1008929526011.
40 Schünemann H, Brożek J, Guyatt G, Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. *Updated October* 2013.
41 Khan A, Faucett J, Morrison S, Brown WA. Comparative mortality risk in adult patients with schizophrenia, depression, bipolar disorder, anxiety disorders, and attention-deficit/hyperactivity disorder participating in psychopharmacology clinical trials. *JAMA psychiatry* 2013; **70:** 1091–99. doi:10.1001/jamapsychiatry.2013.149.
42 Khan A, Schwartz K, Stern C, et al. Mortality risk in patients with schizophrenia participating in premarketing atypical antipsychotic clinical trials. *The Journal of clinical psychiatry* 2007; **68:** 1828–33.
43 Gøtzsche PC. Tödliche Psychopharmaka und organisiertes Leugnen. Wie Ärzte und Pharmaindustrie die Gesundheit der Patienten vorsätzlich aufs Spiel setzen. München: riva, 2016.
44 Kishi T, Matsunaga S, Iwata N. Mortality Risk Associated With Long-acting Injectable Antipsychotics: A Systematic Review and Meta-analyses of Randomized Controlled Trials. *Schizophrenia bulletin* 2016; **42:** 1438–45. doi:10.1093/schbul/sbw043.
45 Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005; **294:** 1934–43. doi:10.1001/jama.294.15.1934.
46 Hulshof TA, Zuidema SU, Ostelo RWJG, Luijendijk HJ. The Mortality Risk of Conventional Antipsychotics in Elderly Patients: A Systematic Review and Meta-analysis of Randomized Placebo-Controlled Trials. *Journal of the American Medical Directors Association* 2015; **16:** 817–24. doi:10.1016/j.jamda.2015.03.015.
47 Taipale H, Mittendorfer-Rutz E, Alexanderson K, et al. Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. *Schizophrenia research* 2017. doi:10.1016/j.schres.2017.12.010.

FIGURES:

Figure 1: Study selection



* abstracts without usable data, reporting on pooled data analyses and other posthoc analyses. It is most likely, that these abstracts refer to studies already included in the analysis, but it could not be decided with full certainty

† protocols of clinical trials (all without data), for which the status of the trial is unclear. i.e. it is unclear if they have ever been conducted, if they have been terminated or if their results were not published yet

‡ handsearch has been conducted in own database of schizophrenia trials and on the webpages of pharmaceutical companies, the Federal Drug Administration, and the European Medicine Agency

TABLES

Table 1: Results of primary and secondary outcomes

		Total			Drug			Placebo			Results	
Category of death	**Studies**	**Deaths**	**Patients**	**Death/patients**	**Deaths**	**Patients**	**Death/patients**	**Deaths**	**Patients**	**Death/patients**	**OR**	**95% CI**
Any	352 (91)	306	84988 (29049)	0.36%	207	53804 (18546)	0.38%	99	31184 (10503)	0.32%	1.19	0.93, 1.53
Natural cause	337 (43)	111	80774 (13994)	0.14%	74	50961 (8779)	0.15%	37	29813 (5215)	0.12%	1.29	0.85, 1.94
Suicide	337 (18)	21	80774 (6749)	0.026%	13	50961 (4127)	0.026%	8	29813 (2622)	0.027%	1.15	0.47, 2.81
Other unnatural cause	337 (23)	26	80774 (7493)	0.032%	18	50961 (4635)	0.035%	8	29813 (2858)	0.027%	1.55	0.66, 3.63

OR=Odds ratio; 95% CI = 95% Confidence Interval; Numbers in parentheses are based on studies with at least one fatal event; Crude frequencies (Death/patients in %) are based on all studies with information about mortality, i.e. including studies that reported that no deaths occurred

Table 2: Sensitivity analysis

		Total			Drug			Placebo			Results	
Sensitivity analysis	**Studies**	**Deaths**	**Patients**	**Death/patients**	**Deaths**	**Patients**	**Death/patients**	**Deaths**	**Patients**	**Death/patients**	**OR**	**95% CI**
Deaths during randomized phase only (+24h)	320 (31)	72	75012 (10618)	0.096%	43	47498 (6701)	0.091%	29	27514 (3917)	0.11%	0.90	0.55, 1.47
Excluding dementia-trials (post hoc)	328 (69)	120	78594 (22704)	0.15 %	67	49527 (14292)	0.14%	53	29067 (8412)	0.18%	0.85	0.59, 1.23
	Studies	**Deaths**	**Patients**	**Death/patients**	**Deaths**	**Patients**	**Death/patients**	**Deaths**	**Patients**	**Death/patients**	**OR**	**95% Cr.I.**
Bayesian common effects model	352 (91)	306	84988 (29049)	0.36%	207	53804 (18546)	0.38%	99	31184 (10503	0.32%	1.18	0.93, 1.53
Bayesian random effects model	352 (91)	306	84988 (29049)	0.36%	207	53804 (18546)	0.38%	99	31184 (10503	0.32%	1.16	0.89, 1.50
Hypergeometric normal,	352 (91)	306	84988 (29049)	0.36%	207	53804 (18546)	0.38%	99	31184 (10503	0.32%	1.19	0.93, 1.52
Correlated beta-binomial (Sarmanov)	352 (91)	306	84988 (29049)	0.36%	207	53804 (18546)	0.38%	99	31184 (10503	0.32%	1.05	0.63, 1.76
Including studies not reporting on mortality (assuming that no deaths occurred) *	581 (92)	306	107655 (29080)	0.28%	207	67337 (18567)	0.31%	99	40318 (10503)	0.25%	1.13	0.87, 1.47
	Studies	**Deaths**	**Patient-years**	**Events/1000 patient-years**	**Deaths**	**Patient-years**	**Events/1000 patient-years**	**Deaths**	**Patient-years**	**Events/1000 patient-years**	**IRR**	**95% CI**
Mortality rates	298 (30)	70	10727 (2363)	6.53	43	6702 (1442)	6.42	27	4025 (921)	6.71	0.89	0.54, 1.47

OR = Odds ratio; 95% CI = 95% Confidence Interval; 95% Cr.I. = 95% Credibility Interval; IRR = Incidence Rate Ratio; Numbers in parentheses are based on studies with at least one fatal event; Crude frequencies (Death/patients in %) are based on all studies with information about mortality, i.e. including studies that reported that no deaths occurred
* 15 studies were not included in the sensitivity analysis because the number of patients in total or per study arm was missing (13 studies) or because it was indicated that there were deaths, but it was unclear in which study phase or study arm (2 studies). One study (31 patients) reported deaths only for the control arm, but not for the active arm. Therefore, this study with events was only included in this sensitivity analysis.

Table 3: Subgroup and meta-regression analyses

		Total			Drug			Placebo			Results	
Subgroup analysis	**Studies**	**Deaths**	**Patients**	**Death/patients**	**Deaths**	**Patients**	**Death/patients**	**Deaths**	**Patients**	**Death/patients**	**OR**	**95% CI**
STUDY DURATION												
1 < 5 days	20 (4)	8	3171 (600)	0.25%	5	2181 (414)	0.23%	3	990 (186)	0.30%	1.27	0.25, 6.39
5 days – 13 weeks	280 (67)	260	68371 (22159)	0.38%	180	44441 (14808)	0.41%	80	23930 (7351)	0.33%	1.21	0.91, 1.59
> 13 weeks	52 (20)	38	13446 (62920)	0.28%	22	7182 (3324)	0.31%	16	6264 (2966)	0.26%	1.12	0.58, 2.14
AGE GROUP*												
Children and adolescents	41 (0)	0	5610 (0)	0	0	3472 (0)	0	0	2138 (0)	0	n. e.	n. e.
Adults	270 (60)	92	70470 (20783)	0.13%	52	44561 (13098)	0.12%	40	25909 (7685)	0.15%	0.89	0.58, 1.37
Elderly	38 (31)	214	8803 (8266)	2.43%	155	5719 (5448)	2.71%	59	3084 (2818)	1.91%	**1.38†**	**1.01, 1.89**
COMBINATIONS OF DRUGS												
Monotherapy	256 (74)	282	69681 (25051)	0.40%	191	45377 (16551)	0.42%	91	24304 (8500)	0.37%	1.13	0.87, 1.47
Any combination	86 (15)	21	14649 (3633)	0.086%	13	8069 (1815)	0.16%	8	6581 (1818)	0.12%	1.60	0.66, 3.88

Add-on to antidepressants	33 (3)	3	6508 (698)	0.046%	2	3807 (355)	0.053%	1	2701 (343)	0.043%	1.93	0.18, 20.98
Add-on to antipsychotics	13 (1)	1	992 (50)	0.10%	1	527 (25)	0.19%	0	466 (25)	0	n. e.	n. e.
Add-on to mood stabilizers	26 (7)	11	5662 (2543)	0.19%	6	2971 (1250)	0.20%	5	2691 (1293)	0.19%	1.25	0.38, 4.11
DIAGNOSTIC CATEGORY												
Acute agitation	3 (0)	0	376 (0)	0	0	191 (0)	0	0	185 (0)	0	n. e.	n. e.
ADHD/disruptive behaviour disorder	7 (0)	0	884 (0)	0	0	440 (0)	0	0	444 (0)	0	n. e.	n. e.
Anorexia nervosa	2 (0)	0	64 (0)	0	0	30 (0)	0	0	34 (0)	0	n. e.	n. e.
Anxiety disorder	10 (1)	1	3646 (450)	0.027%	0	2289 (223)	0	1	1357 (227)	0.074%	n. e.	n. e.
Autism/Pervasive developmental disorder	10 (0)	0	864 (0)	0	0	500 (0)	0	0	364 (0)	0	n. e.	n. e.
Bipolar disorder	90 (21)	32	25150 (6910)	0.13%	18	15064 (3869)	0.12%	14	10086 (3041)	0.14%	1.09	0.53, 2.25
Borderline	5 (0)	0	928 (0)	0	0	558 (0)	0	0	370 (0)	0	n. e.	n. e.
Chemotherapy-induced nausea and vomiting	2 (0)	0	424 (0)	0	0	214 (0)	0	0	210 (0)	0	n. e.	n. e.
Delirium	4 (4)	29	280 (280)	10.36%	16	155 (155)	10.32%	13	125 (125)	10.40%	0.92	0.42, 2.02

Dementia	24 (22)	186	6394 (6345)	2.91%	140	4227 (4254)	3.31%	46	2117 (2091)	2.17%	**1.56**	**1.10, 2.21**
Drug abuse	14 (2)	2	1219 (393)	0.16%	2	642 (192)	0.31%	0	577 (201)	0	n. e.	n. e.
Dysthymia	1 (0)	0	39 (0)	0	0	20 (0)	0	0	19 (0)	0	n. e.	n. e.
Fibromyalgia	1 (0)	0	51 (0)	0	0	25 (0)	0	0	26 (0)	0	n. e.	n. e.
Gambling addiction	2 (0)	0	63 (0)	0	0	30 (0)	0	0	33 (0)	0	n. e.	n. e.
Healthy subjects	11 (0)	0	286 (0)	0	0	173 (0)	0	0	113 (0)	0	n. e.	n. e.
Major depressive disorder	32 (5)	5	9252 (1935)	0.054%	3	5412 (1050)	0.055%	2	3840 (885)	0.052%	1.31	0.21, 8.16
Obsessive compulsive disorder	6 (0)	0	259 (0)	0	0	141 (0)	0	0	118 (0)	0	n. e.	n. e.
Organic brain syndrome	1 (1)	10	815 (815)	1.23%	5	612 (612)	0.82%	5	203 (203)	2.46%	0.33	0.09, 1.14
Parkinson disease	6 (4)	5	361 (241)	1.39%	3	196 (134)	1.53%	2	165 (107)	1.21%	n. e.	n. e.
Post-traumatic stress disorder	3 (0)	0	340 (0)	0	0	171 (0)	0	0	169 (0)	0	n. e.	n. e.
Schizophrenia	111 (31)	36	32807 (11680)	0.11%	20	22355 (8057)	0.09%	16	10452 (3623)	0.15%	0.69	0.35, 1.35
Stuttering	2	0	40	0	0	20	0	0	20	0	n. e.	n. e.

	(0)		(0)			(0)			(0)			
Tourette syndrome	5 (0)	0	446 (0)	0	0	289 (0)	0	0	157 (0)	0	n. e.	n. e.
ANTIPSYCHOTIC SUBSTANCE ‡												
Amisulpride	8 (0)	0	250 (0)	0	0	137 (0)	0	0	113 (0)	0	n. e.	n. e.
Aripiprazole	66 (13)	39	14503 (4061)	0.27%	31	8583 (2504)	0.36%	8	5920 (1557)	0.14%	**2.20§**	**1.00, 4.86**
Asenapine	12 (2)	2	3304 (626)	0.061%	1	2098 (405)	0.048%	1	1206 (221)	0.083%	n. e.	n. e.
Brexpiprazole	7 (1)	1	2351 (409)	0.043%	1	1533 (314)	0.065%	0	818 (95)	0	n. e.	n. e.
Cariprazine	10 (2)	3	4542 (962)	0.066%	3	3010 (648)	0.100%	0	1532 (314)	0	1.96	0.22, 17.55
Clozapine	2 (0)	0	120 (0)	0	0	62 (0)	0	0	58 (0)	0	n. e.	n. e.
Haloperidol ¶	19 (5)	35	3294 (929)	1.06%	18	1691 (462)	1.06%	17	1603 (467)	1.06%	1.07	0.54, 2.12
Iloperidone	6 (1)	1	2287 (303)	0.044%	1	1532 (153)	0.065%	0	755 (150)	0	n. e.	n. e.
Lurasidone	10 (0)	0	3485 (0)	0	0	2205 (0)	0	0	1280 (0)	0	n. e.	n. e.
Olanzapine	73 (20)	53	13537 (4891)	0.39%	39	7899 (2931)	0.49%	14	5638 (1960)	0.25%	1.60	0.83, 3.08

Paliperidone	30 (12)	17	8097 (4057)	0.21%	8	5159 (2610)	0.15%	9	2938 (1447)	0.31%	0.60	0.23, 1.53
Quetiapine	75 (20)	64	20366 (6464)	0.31%	36	12389 (3542)	0.29%	28	7977 (2922)	0.35%	1.00	0.59, 1.62
Risperidone	65 (21)	99	11560 (5636)	0.86%	61	6402 (3326)	0.95%	38	5158 (2310)	0.74%	1.06	0.70, 1.62
Sertindole	1 (1)	1	50 (50)	2.00%	1	25 (25)	4.00%	0	25 (25)	0	n. e.	n. e.
Ziprasidone	14 (2)	11	1591 (272)	0.69%	5	916 (170)	0.55%	6	675 (102)	0.89%	0.90	0.24, 3.35
Zotepine	1 (0)	0	121 (0)	0	0	63 (0)	0	0	58 (0)	0	n. e.	n. e.
Meta-regression	**Studies**	**Deaths**	**Patients**	**Death/patients**	**Deaths**	**Patients**	**Death/patients**	**Deaths**	**Patients**	**Death/patients**	**Regression coefficient**	**95% Cr. I**
ANTIPSYCHOTIC DOSE	207 (43)	55	56703 (15643)	0.097%	31	35487 (10103)	0.087%	24	21186 (5440)	0.11%	0.038‖	-0.018, 0.090
PERCENTAGE OF WOMEN	326 (86)	274	81926 (27449)	0.33%	189	51998 (9973)	0.36%	85	29928 (17476)	0.28%	**0.0251** **††	**0.0104, 0.0399**

OR = Odds ratio; 95% CI = 95% Confidence Interval; 95% Cr.I. = 95% Credibility Interval: n.e. = not estimable; Numbers in parentheses are based on studies with at least one fatal event. Crude frequencies (Death/patients in %) are based on all studies with information about mortality, i.e. including studies that reported that no deaths occurred

* 3 studies with 105 patients included several age groups.

† Excluding dementia trials from the analysis resulted in an OR of 0.74 (95% CI 0.35, 1.57), corresponding to 15 deaths in 1442 patients (1.04%) exposed to drug and 13 deaths in 967 patients (1.34%) exposed to placebo

‡ 3 studies allowed several SGAs (drug 100 patients, placebo 144 patients) in the intervention group. Additionally chlorpromazine was used as active comparator in 2 studies, but no information on mortality was available. The latter 2 studies were only included in the sensitivity analysis "Including studies not reporting on mortality (assuming that no deaths occurred)"

§ Excluding dementia trials from the analysis resulted in an OR of 2.92 (95% CI 0.62, 13.63), corresponding to 8 deaths in 7878 patients (0.10%) exposed to drug and 2 deaths in 5546 patients (0.04%) exposed to placebo

¶ The first-generation antipsychotic haloperidol was included, because it was used as an active control in studies comparing second-generation antipsychotics to placebo (see methods).
‖ Regression coefficient for increase in logOR (logarithmic Odds ratios) per mg olanzapine equivalent, corresponding to Odds ratios of 0.55, 0.66, 0.80, 0.97, and 1.18 for studies with mean doses of 5, 10, 15, 20, and 25 mg olanzapine equivalents, respectively.
** Regression coefficient for increase in logOR (logarithmic Odds ratios) per 1% increase in women, corresponding to Odds ratios of 0.56, 1.05 and 1.97 for study populations with 25%, 50%, and 75% female patients, respectively.
††Excluding dementia trials from the analysis resulted in a regression coefficient of -0.16 (95% Cr.I. -2.30, 1.95