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REVIEW ARTICLE

Long-term effects of antipsychotics on mortality in patients with schizophrenia: a systematic review and meta-analysis

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Objective: To gather current evidence on the impact of antipsychotics on long-term mortality in patients with schizophrenia.
Methods: We systematically searched for articles in Embase, PubMed, and PsycINFO reporting the long-term mortality (follow-up > 1 year) of patients with schizophrenia who were using any antipsychotics. We then conducted multiple meta-analyses to determine differences in long-term mortality between different types of antipsychotics.
Results: We identified 45 articles that provided unadjusted long-term mortality rates, including 46,171 deaths during 2,394,911 person-years. The pooled mortality rate was 9.9 (95%CI = 7.4-12.7) per 1,000 person-years. The unadjusted crude mortality rate of antipsychotic drug users was lower than that of non-users (risk ratio [RR] = 0.546, 95%CI = 0.480-0.621), first-generation antipsychotics caused higher all-cause mortality than second-generation antipsychotics (RR = 1.485, 95%CI = 1.361-1.620), and polypharmacy had better effects than monotherapy on long-term mortality (RR = 0.796, 95%CI = 0.689-0.921). As for the causes of death, heart disease and cardiovascular disease ranked highest among cause-specific mortality (5.6 per 1,000 person-years).
Conclusion: Since antipsychotics had a beneficial effect on long-term mortality in schizophrenia, greater precaution should be taken with patients who do not take them. However, since disease severity, comorbidities, and other confounding factors cannot be fully controlled, further research and verification are needed.

Keywords: Schizophrenia; antipsychotics; long-term; mortality

Introduction

Although antipsychotics are the main treatment for schizophrenia (SCZ), they might be related to subsequent adverse reactions.[1] In the short term, the use of these drugs is associated with weight gain, dyslipidemia, glucose metabolism disorders, corrected QT prolongation, and sudden cardiac death.[2-4] Long-term use may negatively impact life expectancy due to metabolic impact.[5] The life gap between people with SCZ and the general population has been widening and is currently shorter by 15-20 years[6,7]; the highest risk of death in this population is due to cardiovascular disease.[8,9] Moreover, a U.S. cohort study reported that the risk of suicide in patients with SCZ was 4.5 times that of the general population,[10] which was similar to the results of a Canadian study.[11]

Nevertheless, SCZ patients who take antipsychotics have a lower risk of death than those who do not.[12] In a large-scale Korean cohort followed for 15 years, patients on antipsychotics had a lower risk of death from ischemic heart disease and stroke.[13] Another cohort study from Finland failed to find a link between antipsychotics and early death.[14] In addition, the type and quantity of antipsychotic drugs used during treatment could also affect mortality, since the combined use of multiple drugs may be related to reduced mortality and hospitalization.[15] This could contradict the idea of a relationship between long-term multi-drug therapy and death, which remains unclear.[16] Because patients receiving continuous clozapine treatment appeared to have lower mortality rates than those who took other drugs,[2] clozapine was considered effective for reducing suicidal behavior.[17] Therefore, since antipsychotics are the main treatment for SCZ, their impact on long-term mortality is crucial. Our study focused on the long-term mortality of patients with SCZ, summarizing the long-term deaths of patients who on antipsychotic therapy, aiming to obtain an all-cause mortality rate. Furthermore, we compared mortality in different subgroups, such as antipsychotic users vs. non-

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users, monotherapy vs. polypharmacy, and first-generation antipsychotics (FGA) vs. second-generation antipsychotics (SGA), to assess whether there are significant differences between each group. Finally, we estimated common cause-specific mortality for SCZ patients.

Methods

We searched for English-language articles published in Embase, PubMed, and PsycINFO before March 25, 2021 that reported the risk of death in SCZ patients using antipsychotic drugs. Our search strategy is described in detail in Supplement S1; in short, we used the following search terms: (SCZ) and (antipsychotics or a specific antipsychotic) and (mortality or common causes of death).

Study selection

Two researchers (NJ and YL) independently screened the literature according to the inclusion and exclusion criteria. A third researcher (ZL) intervened to resolve conflicts. We included: 1) studies of patients diagnosed with SCZ or related disorders (schizoaffective or psychosis not otherwise specified); if the study included psychiatric disorders other than SCZ (bipolar disorder or depression), these patients could account for no more than 30% of the total sample; 2) patients who had ever taken any kind of antipsychotic drug; 3) studies with more than 1 year of follow-up and an all-cause death outcome; and 4) randomized controlled trials, cohort studies, or case-control studies written in English. We excluded the following studies: 1) those in which SCZ patients accounted for less than 70% of the sample or in which specific data on SCZ were unavailable after contacting the author; 2) follow-up time $\leqslant$ 1 year; 3) studies without mortality as an outcome; and 4) unpublished manuscripts.

Data extraction

Data were independently extracted by two researchers (NJ and YL) and disagreements were resolved by consensus with a third researcher (ZL). We extracted the following data: first author's name, year of publication, research method, diseases and criteria diagnosed, country and data source, total sample size, follow-up time, patient characteristics (inpatient or outpatients treatment-resistant), specific antipsychotics, mean age, male ratio, number of deaths, causes of death, outcome criteria, and drug dosage (if reported). Since many cohort studies used data from national databases and might have contained overlapping samples, we only included the study with the largest sample size and excluded the rest. To assess the quality of randomized controlled trials, we used the Cochrane Collaboration Risk of Bias Tool,[18] while for cohort and case-control studies, Newcastle Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.) was applied. Studies scoring $>$ 6 were considered to have a low risk of bias.

Statistical analyses

For all-cause mortality, we collected data and conducted meta-analyses to calculate crude death rates for patients taking antipsychotics per 1,000 person-years (PEY). When a study did not provide the PEY data, we performed the calculation according to the following formula: ([number of patients at the beginning + number of patients at the end]/2) * (years of follow-up).[19,20] If the number of participants followed to the end of the study was not provided, we considered the sample size to have been the number at the beginning of the study minus the number of lost to follow-up and deaths. All studies reporting data on the number of deaths in patients treated with antipsychotics were used for single-group meta-analysis to summarize the mortality rate per 1,000 PEY. We investigated heterogeneity with χ^2-based Cochran's Q and Higgins's I^2 indices, and the heterogeneity between studies was considered significant when $p < 0.1$ and $I^2 \geqslant 50\%$. When high heterogeneity was observed between studies, we used the arcsine-Thompson test to determine publication bias.[21] To explore underlying causes of heterogeneity, we conducted sensitivity analysis and subgroup analysis of suspected factors. Additionally, we conducted a meta-regression to explore the potential effect between mortality and continuous variables.

Furthermore, we extracted data from original studies that distinguished between SGA and FGA to compare long-term mortality. We also determined whether all-cause mortality differed between patients who underwent monotherapy or polypharmacy, and between patients who did and did not use antipsychotic drugs. The statistical method was the same as that described above. Common specific causes of death in SCZ were suicide, heart disease, cardiovascular disease, cancer, etc. Thus, we extracted data to obtain the pooled cause-specific mortality rates. In some studies, the distinction between mortality due to cardiac or cardiovascular disease was insufficiently clear, so we joined these two causes into one category. All statistical analyses were performed in R (version 3.6.3) and Revman 5.4.

Results

Included studies and their characteristics

The initial search yielded 6,439 articles, of which 289 were selected after screening the titles and abstracts. After full text inspection, 52 studies were included: 10 randomized controlled trials, 38 cohort studies, and four case-control studies. Their basic characteristics are described in Table S1, available as online-only supplementary material, while the literature screening process is detailed in Figure 1. The study population was mostly from Europe, Asia, and North America, and the follow-up time for all studies ranged from 1.1 to 20 years. The mean overall age was 40.16 years old, including both adolescents and older adults. The studies included FGA and SGA drugs, of which clozapine, risperidone, and olanzapine were the most common. Since the sources of many studies were national databases, there were partial

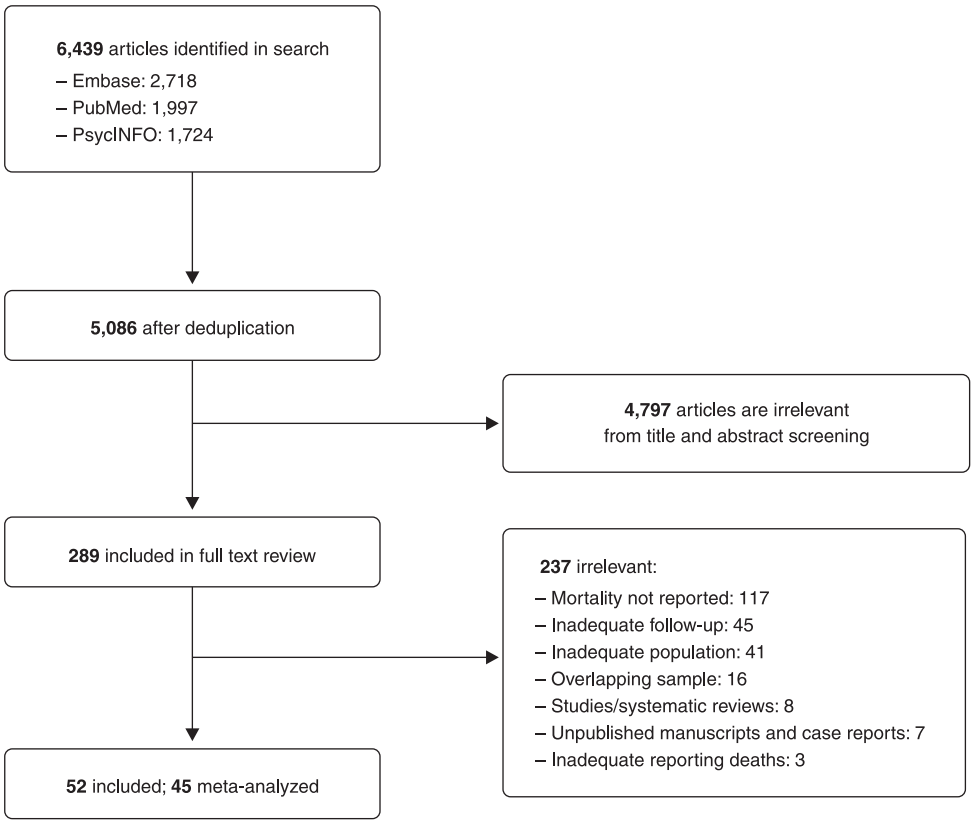

Figure 1 Flowchart of study identification and selection.

overlaps between the participants and follow-up times. Some of these overlapping samples[5,13,22-24] were used to calculate pooled all-cause mortality, and the rest were used separately to compare FGA and SGA,[25,26] monotherapy and polypharmacy,[16,27] or mortality for treatment-resistant SCZ[28,29] or cause-specific mortality.[30] The main participant diagnosis was SCZ (n=32) or related disorders (n=20), which matched the inclusion and exclusion criteria. In one study,[23] whose sample included more than 30% bipolar disorder patients, we referenced a previously published meta-analysis that contacted the author for data on SCZ and schizoaffective disorder.[20,31] A national cohort from Denmark provided detailed data only for patients newly diagnosed with SCZ during the follow-up period and not for chronic patients, so we contacted the author to obtain additional data. Most of the included randomized controlled trials had a high risk of bias (n=8) (Figure S1, available as online-only supplementary material), while the Newcastle Ottawa Scale scores of observational studies ranged from 4 to 9, with 54.7% determined to have a low risk of bias (Table S2).

Mortality rate for patients using antipsychotic medications

A total of 46,171 deaths during 2,394,911 PEY among patients with SCZ taking antipsychotic drugs were reported in 45 articles; crude death rates ranged from 0-40.5 per 1,000 PEY. Our meta-analysis determined a pooled mortality rate of 9.9 (95%CI = 7.4-12.7) per 1,000 PEY (Figure 2). Publication bias was not indicated by the arcsine-Thompson test ($p = 0.82$). However, heterogeneity was rather significant ($Q = 5,505.06$, $p < 0.01$, $I^2 = 99.2\%$). The results of our detailed subgroup analyses are shown in Table 1. Patients with first-episode SCZ who took antipsychotic drugs, excluding those who were recently diagnosed or were overlapped between studies, had a mortality rate of 7.5 per 1,000 PEY. A pooled mortality rate of 6.9 per 1,000 PEY was calculated for treatment-resistant patients. We conducted a mortality analysis for various individual drugs (Figure S2). In antipsychotic monotherapy, olanzapine had the highest (13.7 per 1,000 PEY) and aripiprazole and paliperidone the lowest mortality rate (2.4 per 1,000 PEY). These two subgroup analyses included studies unavailable in the all-cause mortality analysis. When two samples overlapped, the study with the larger sample was used for the all-cause mortality analysis, while those including first-episode patients or treatment-resistant patients were used for the subgroup analysis.

Subsequently, we conducted a series of sensitivity analyses. The results indicated that observational studies had higher mortality rates than randomized trials ($p < 0.05$), and the mortality rates differed significantly between age groups ($p < 0.0001$). We also found significant differences between inpatients and outpatients ($p < 0.05$) and between different groups of PEY ($p < 0.01$). Groups with a higher mean age, outpatients, and groups of larger PEY had higher all-cause mortality than other groups. There were no significant differences in all-cause mortality

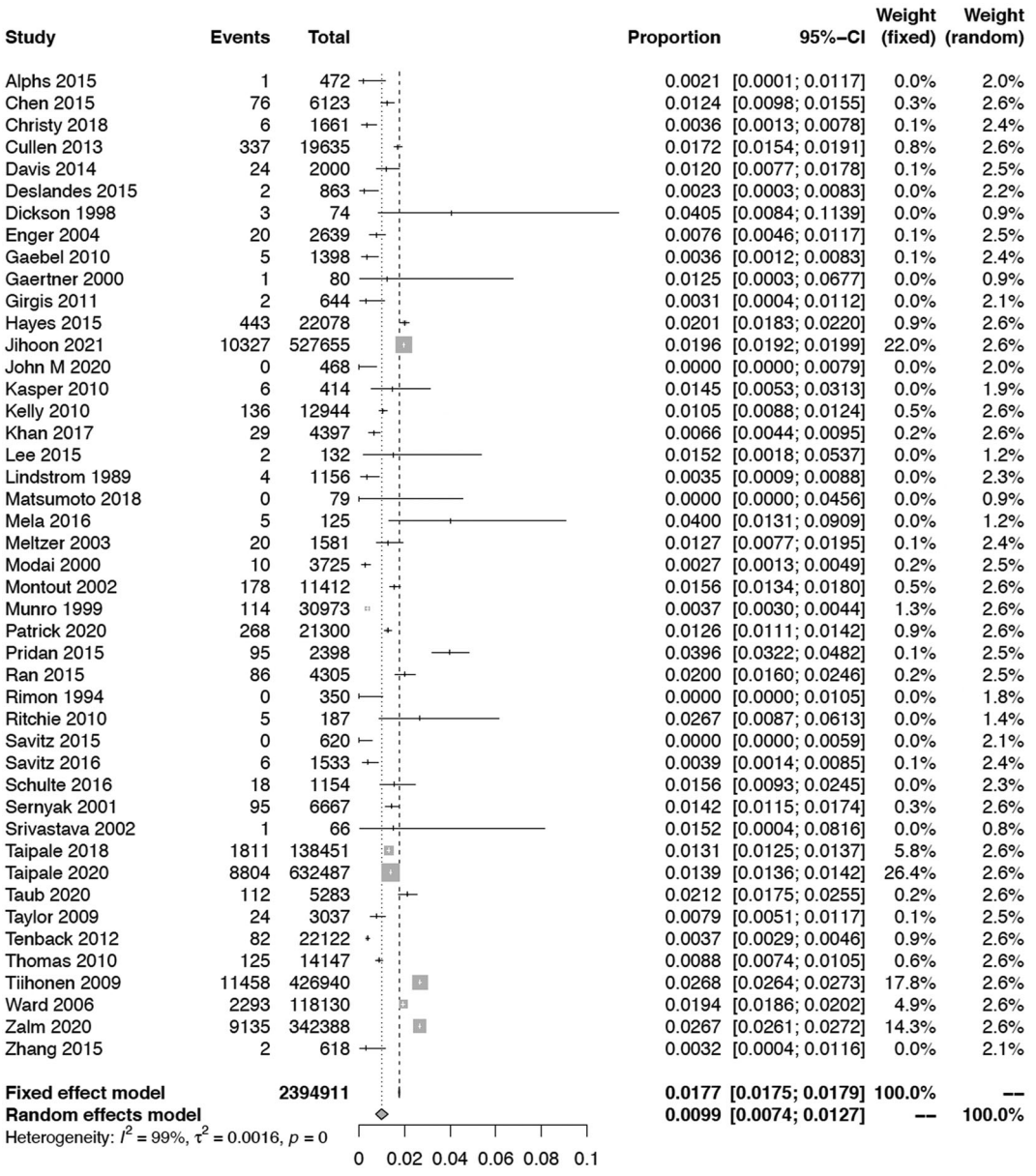

Figure 2 Meta-analysis of mortality among schizophrenia patients on antipsychotics.

regarding location (i.e., continent) (p = 0.23), follow-up time (p = 0.09), diagnosis (p = 0.34), or study quality (p = 0.15). The robustness of the results was good, since the results were unaffected by deleting single studies. The meta-regression analyses of continuous variables included follow-up time, mean age, proportion of males, and sample size. Mean age was significantly associated with all-cause mortality of patients on drug therapy, and the mortality rate of older patients was higher (β = 0.0018, $p < 0.01$) (Table S3).

Meta-analysis of different groups

First, we compared patients using SGA or FGA to assess the therapeutic efficacy of both generations of antipsychotics. Five observational studies with patients who used only FGA or SGA were included, with a total of 2,362 deaths in 475,892 PEY, including a mean follow-up time of 4.13 years. The pooled relative risk (RR) for FGA and SGA was 1.485 (95%CI = 1.361-1.620) (Figure 3A), indicating SGA may lead to lower all-cause mortality than FGA. The statistical heterogeneity between the studies was extremely low (I^2 = 0%), and publication bias was not significant (p = 0.607).

Four studies compared mortality in polypharmacy vs. monotherapy, with a total of 5,172 deaths in 401,322 PEY. The pooled RR was 0.796 (95%CI = 0.689-0.921, p = 0.0021) (Figure 3B), indicating that polypharmacy was superior to monotherapy for all-cause mortality in SCZ patients. The results showed moderate heterogeneity (I^2 = 54%, Q = 6.52), and there was no publication bias (p = 0.529).

Table 1 Calculated mortality rates in subgroup and sensitivity analyses

	Study ID number	Total deaths	Total patient years	Mortality rate (death/patient years)	Lower 95%CI	Upper 95%CI	I^2 (%)
Patients (p = 0.8692)							
First-episode	4	2,631	135,020	0.0075	0.0034	0.0164	96.3
Treatment-resistant	7	425	66,808	0.0069	0.0042	0.0114	93.8
Antipsychotics (p < 0.001)							
Olanzapine	7	1,782	105,251	0.0132	0.0070	0.0212	98.7
Quetiapine	5	2,518	61,686	0.0128	0.0014	0.0346	99.3
Risperidone	10	3,137	175,983	0.0116	0.0070	0.0172	97.9
Clozapine	25	1,618	226,677	0.0090	0.0064	0.0121	95.3
Paliperidone	5	11	3,500	0.0024	0.0007	0.0049	14.4
Aripiprazole	5	150	22,686	0.0023	0.0001	0.0062	89.5
Study design (p < 0.05)							
Randomized trial	10	164	21,103	0.0039	0.0014	0.0073	78.4
Cohort study	31	45,807	2,357,856	0.0117	0.0095	0.0141	99.4
Case-control	4	200	15,952	0.0115	0.0077	0.0160	75.9
Continent (p = 0.23)							
Asia	11	10,717	552,557	0.0109	0.0063	0.0164	95.8
Europe	14	32,074	1,633,491	0.0104	0.0070	0.0144	99.7
North America	12	3,184	184,586	0.0110	0.0081	0.0143	93.5
Australia	2	34	4,584	0.0129	0.0001	0.0408	82.7
Multinational	6	162	19,693	0.0060	0.0028	0.0102	81.4
Follow-up time (p = 0.0906)							
⩽ 3	18	2,683	169,901	0.0070	0.0033	0.0119	97.4
⩽ 5	9	824	46,528	0.0126	0.0078	0.0185	93.6
⩽ 10	10	13,998	646,037	0.0091	0.0047	0.0150	99.6
> 10	7	28,642	1,530,445	0.0157	0.0117	0.0204	99.7
Mean age (p < 0.0001)							
⩽ 18	2	0	699	0.0000	0.0000	0.0010	0.0
⩽ 30	4	10	3,391	0.0026	0.0010	0.0048	0.0
⩽ 40	18	9,869	430,609	0.0091	0.0044	0.0152	99.1
⩽ 50	14	22,425	1,408,641	0.0126	0.0104	0.0149	98.9
> 50	4	11,568	433,250	0.0204	0.0061	0.0425	98.5
Treatment setting (p < 0.05)							
Inpatient	5	473	34,215	0.0161	0.0076	0.0276	97.0
Outpatient	6	20,961	793,912	0.0171	0.0142	0.0203	97.7
In- and outpatient	17	21,969	1,381,926	0.0103	0.0082	0.0126	98.6
Diagnosis (p = 0.3396)							
Schizophrenia	28	34,280	1,842,961	0.0107	0.0083	0.0132	99.3
Other	17	11,891	551,950	0.0090	0.0057	0.0129	98.9
Patient years (p < 0.01)							
⩽ 1,000	15	30	5,192	0.0048	0.0011	0.0102	71.5
⩽ 10,000	16	630	49,507	0.0103	0.0069	0.0144	94.0
⩽ 100,000	8	1,683	154,611	0.0107	0.0064	0.0160	98.8
> 100,000	6	43,828	2,186,051	0.0196	0.015	0.0248	99.9
Risk (p = 0.1463)							
High	26	3,301	223,969	0.0083	0.0053	0.0119	97.4
Low	19	42,870	2,170,942	0.0123	0.0098	0.0152	99.6

A total of seven studies included data on SCZ patients with or without antipsychotic therapy, and the respective mortality rates were 33,024 deaths in 1,764,403 PEY and 17,087 deaths in 443,814 PEY, respectively. The combined RR was 0.546 (95%CI = 0.480-0.621) (Figure 3C), indicating that the mortality rate was lower in patients who used antipsychotics than in those who did not. The result showed a high level of statistical heterogeneity (I^2 = 88%, Q = 49.68), and Egger's test revealed publication bias (p = 0.034).

Cause-specific mortality

A total of 26 articles described the causes of death, including suicide, cardiovascular disease, cancer, and sudden death. The combined death rate by suicide (Figure 4A) was 1.8 per 1,000 PEY, with a total of 1,710 deaths in 857,977 PEY reported in 16 articles. Statistical heterogeneity was high (Q = 415.11, I^2 = 96%), but no publication bias was found (p = 0.671). The combined death rate due to cardiac and cardiovascular diseases

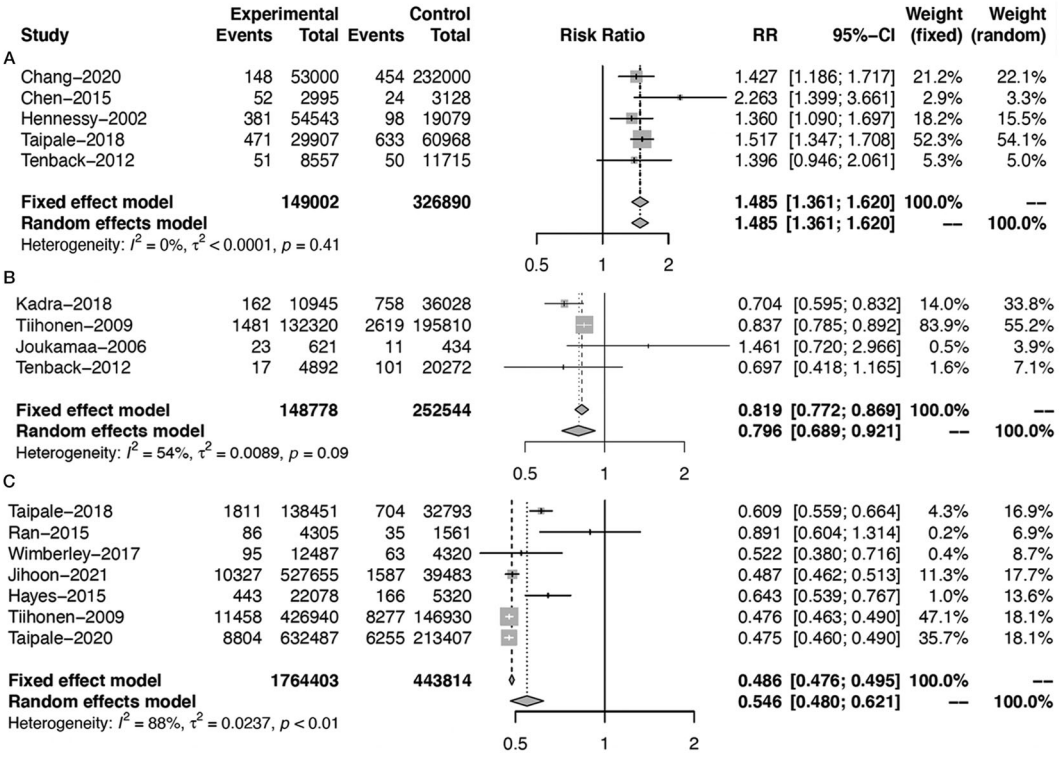

Figure 3 Meta-analysis of long-term mortality in different groups. A) first- vs. second-generation antipsychotics (control). B) polypharmacy vs.monotherapy (control). C) antipsychotic users vs.non-users (control).

(Figure 4B) was 5.6 per 1,000 PEY, with a total of 564 deaths in 121,123 PEY reported in 10 articles. Statistical heterogeneity was still high (Q = 181.84, I^2 = 95%), with no publication bias (p = 0.557). The combined death rate due to cancer (Figure 4C) was 1.9 per 1,000 PEY, with 47 deaths in 24,534 PEY reported in four articles. Statistical heterogeneity was high (Q = 5.57, I^2 = 60.6%), but no publication bias was found (p = 0.120).

Discussion

As far as we know, this is the largest meta-analysis to date on the long-term risk of death associated with antipsychotic use in SCZ, including 52 articles and 317,616 individuals. The main finding of our research was that the unadjusted crude mortality rate of antipsychotic users was lower than that of non-users, despite the potential side effects of antipsychotics. SGA caused lower all-cause mortality than FGA and polypharmacy was superior to monotherapy regarding long-term mortality. We also obtained crude death rates in multiple comparison groups based on a large number of studies, as well as the rates attributable to specific causes, such as suicide, heart disease, and cancer.

The unadjusted mortality rates of all participants in the study ranged from 0-40.5 per 1,000 PEY, and the overall mortality rate was 9.9 per 1,000 PEY. Several factors that may have influenced mortality, resulting in the magnitude of the change in overall mortality in this review vs. the mortality rates of all included studies. Three of the four studies with mortality rates of 0 were randomized controlled trials conducted in the presence of a physician, with the follow-up periods $\leqslant$ 2 years.[32-34] In two studies[33,34] the sample consisted of adolescents or recently hospitalized individuals. Thus, age of onset, disease severity, better compliance, and an insufficient period of time to observe deaths might explain this situation. The highest mortality rate (40.5 per 1,000 PEY) was found in a Canadian study[35] However, all of the deaths occurred in the group that stopped using clozapine and none occurred in the continuous and discontinued drug-use groups. Nevertheless, the sample size was relatively small (n = 74). The results of a previous meta-analysis[20] showed that patients who continuously used clozapine had a lower mortality rate than those who stopped taking it, and some findings[28] suggested that patients who stopped taking clozapine had a higher death risk than those who never used it. Another possible explanation was the limited sample size.

The two previous meta-analyses[31,36] on the relationship between antipsychotics and death in SCZ patients did not combine mortality rates due to the large differences in study design, follow-up time, and population characteristics. Due to the publication of more prospective cohorts with detailed subgroup divisions, we combined the results of 45 studies to obtain an overall mortality rate. The crude death rate we calculated (10/1,000 PEY) was close to that reported in previous findings

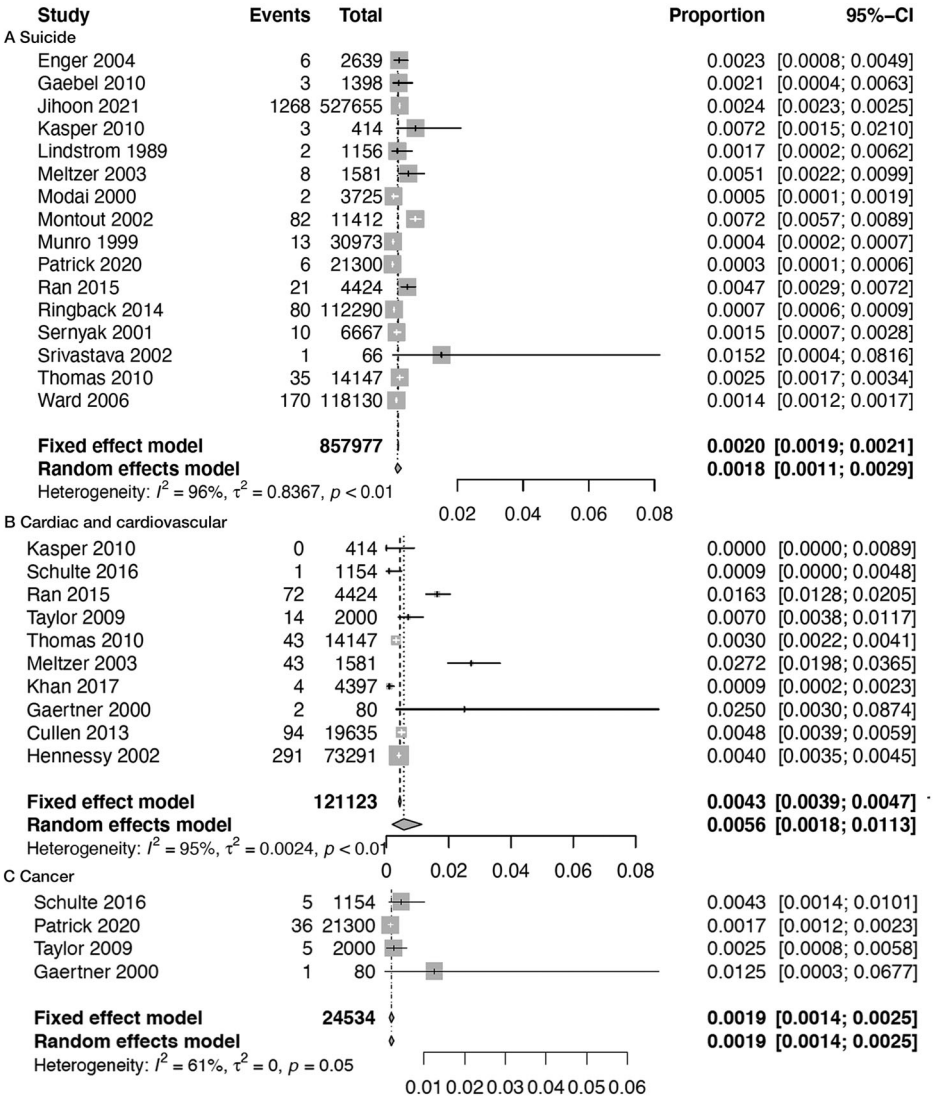

Figure 4 Meta-analysis results for cause-specific mortality rates among schizophrenia patients on antipsychotics who died from suicide, cardiac and cardiovascular disease, or cancer.

by the U.S. Food and Drug Administration (1,249/100,000 PEY).[37] The mortality rates reported in three studies in the present review[2,13,24] were based on national samples from international databases (13.9, 19.6, and 13.1 per 1,000 PEY). In our study, patients on aripiprazole had the lowest mortality rate, which was consistent with previous conclusions,[30,38] regardless of whether administration was oral or long-acting injection. Previous studies have suggested that aripiprazole was more beneficial than other antipsychotics regarding metabolic parameters,[39,40] although whether this might be related to lower mortality still requires in-depth investigation. However, it should be pointed out that our results could not be generalized because confounding factors, such as smoking, lifestyle, comorbid chronic diseases, and drug dosage, might affect mortality and were not reported in most articles, nor were measurement criteria.

Compared with FGA, SGA were less prone to induce extrapyramidal symptoms, but were associated with weight gain, diabetes, hyperlipidemia, and myocarditis.[41] These adverse effects may lead to higher mortality. Our results showed that long-term mortality in SCZ patients who received SGA was lower than in those who received FGA. Similarly, a meta-analysis of adult and older populations showed that being overweight was associated with significantly lower all-cause mortality.[42] Another study suggested that these metabolic and cardiovascular abnormalities may appear years after SGA use and lead to premature death.[43] Thus, greater follow-up times may be required to observe longer-term deaths.

Regarding monotherapy vs. polypharmacy, British guidelines only recommend a combination of antipsychotics as a last resort. The results of one study confirmed

this conclusion, demonstrating that antipsychotic monotherapy was negatively correlated with hospitalization in patients with severe mental illness.[44] Nevertheless, our review suggested that polypharmacy was negatively associated with long-term death in SCZ. A meta-analysis[19] showed that regardless of adjusted or unadjusted mortality, monotherapy and polypharmacy did not differ significantly regarding long-term mortality among patients with severe mental illness. They concluded that this might be because the quality of the studies supporting monotherapy or polypharmacy was negatively correlated with mortality. As the number of included studies changes, so could the results; thus, it cannot be absolutely confirmed whether monotherapy is related to a higher risk of death. We re-examined significant results from two of the studies: one was the weak link between polypharmacy and long-term death rate after adjusting for age and sex,[16] while the other[14] was that polypharmacy was moderately associated with risk of death from ischemic heart disease, although the overall mortality rate was not higher than that of monotherapy. Consequently, despite our finding that polypharmacy had a lower mortality rate than monotherapy, the small sample sizes of the included studies and various uncontrolled factors indicate that further in-depth studies are required.

The SCZ patients treated with antipsychotics in our review had an approximately 50% lower long-term mortality rate than those who did not, which indicates the beneficial effects of antipsychotic drugs. The results also indicated that antipsychotic drugs could effectively reduce the risk of death from ischemic heart disease, implying that antipsychotic drugs might be a protective factor due to vascular occlusion, thus leading to reduced mortality.[13] The mental state of untreated SCZ patients tends to be poorer, especially positive and negative symptoms,[45] physical health, and psychological stress, all of which could contribute to suicide. Therefore, medical and health care departments should pay careful attention to patients with SCZ who are not in any form of treatment, since the longer they remain untreated, the more serious the deterioration of their clinical condition and the greater the risk of harm to their bodies.[46]

Since most data from death certificates lacked a specific cause of death, we only summarized deaths from suicide, heart disease, and cancer, even though the criteria for defining them differed. Previous studies have shown that clozapine reduces the risk of death from SCZ.[47] Antipsychotic drugs relieve the symptoms and pain of SCZ patients, which may be the reason for the lower suicide rates. Moreover, relieving stress may also reduce mortality from cardiovascular diseases.[2] It is believed that the main mechanism by which antipsychotic drugs damage the heart is their blockage of sodium-potassium channels, which lowers action potentials and prolongs depolarization and negative polarization.[48] Curiously, studies have found that people with SCZ who use antipsychotic drugs have a lower risk of certain types of cancer.[49,50] In preclinical studies, valproic acid, olanzapine, and phenothiazine have been shown to prevent cancer cell proliferation and induce apoptosis.[51]

According to our results, the death rate due to heart and cardiovascular diseases was the highest, while deaths due to suicide and cancer were similar. However, there is evidence that cardiovascular death rates may be similar to those of cancer.[52] One possible reason for the divergence is that we combined deaths from heart and cardiovascular diseases into one category. Another important reason is that we believe the three causes of death are not comparable. Since the studies included in our analysis are diverse in many aspects, such as design, follow-up time, and mean patient age. Therefore, in future research we hope to determine the most common causes of death in SCZ to help reduce deaths and improve quality of life in a targeted manner.

Limitations

Our meta-analysis investigated the long-term death rate among SCZ patients on antipsychotics. Although we tried our best to include as many studies as possible, resulting in the largest sample yet on this topic, we still may have overlooked some pertinent studies. Further research is needed for a more comprehensive summary. Second, due to limitations in study design, the heterogeneity of the single-group meta-analysis was difficult to control, although we also subsequently conducted subgroup and sensitivity analyses. Our subgroup analyses involved a variety of factors, but most did not greatly reduce the heterogeneity of the studies. Thirdly, most of the studies we included were observational studies; case-control studies are usually considered to have a higher evidence level since they restrict the use of additional medications or exclude those who fail to adhere to treatment. Thus, it is preferable to analyze RCT separately. In addition, the follow-up periods of the experimental studies were generally short, which reduced the probability that deaths would occur and may have affected the combined mortality to a certain extent. Fourth, disease severity, medication duration, and medication dose also may have affected mortality, although we could not discuss this in details due to missing data. We only compared the effects of follow-up length, although in the original studies, follow-up time was not exactly equal to medication duration. Fifth, long-term mortality may also be affected by patient behavior and lifestyle, e.g. smoking, drug abuse, exercise, and especially co-morbidities, although much relevant data was unavailable in the original studies. Sixth, lithium is widely considered an anti-suicide drug,[53] but we could not compare it with other antipsychotic drugs due to the lack of appropriate research. Finally, previous studies have shown that long-term deaths have a U-shaped relationship with cumulative medication use, i.e., patients using no or high doses of antipsychotic drugs have the highest mortality rates, while users of moderate doses had the lowest.[54] However, there were not enough available articles to verify this conclusion.

In conclusion, we conducted the largest yet meta-analysis of long-term mortality in patients with SCZ on antipsychotic medication, summarizing unadjusted long-term mortality for the first time. However, due to the large

clinical and statistical heterogeneity, our results can only be considered as a reference. We found that the mortality rate of SCZ patients who took antipsychotics was lower than that of those who did not, that the mortality rate of those who took SGA was lower than that of those who took FGA, and that polypharmacy seemed to have a protective effect compared to monotherapy. However, further research is needed, since disease severity, comorbidities, and other confounding factors could not be controlled in this study. Future investigations should also investigate the dosage and order of administration of antipsychotics.

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Disclosure

The authors report no conflicts of interest.

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