TECHNICAL COMMENTARY

Mortality

Introduction

On average, the life expectancy of people with schizophrenia may be reduced by as much as 15-20 years, compared to the general population. The reasons for increased mortality in schizophrenia are largely unclear, but may in part be related to lifestyle factors such as weight gain, smoking, unhealthy diet and low physical activity levels. Adverse effects of antipsychotics may also contribute to high mortality rates in schizophrenia. This summary table assesses the current evidence describing the relationship between mortality rates and different antipsychotic medications.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found four systematic reviews that met our inclusion criteria[3-6].

- Moderate quality evidence suggests no differences in all-cause mortality or suicide rates between people with schizophrenia who are on long-acting injectable antipsychotics, oral antipsychotics or placebo. There were no significant differences in effect sizes according to antipsychotic type (first vs. second generation), study duration, industry vs. non-industry trials, illness status (acute vs. other), or antipsychotic dose.

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- Moderate to high quality evidence suggests a medium-sized effect of fewer deaths in people with schizophrenia taking any antipsychotic than people with schizophrenia not taking antipsychotics. Study follow-up was between 5 and 14 years.
- Moderate to high quality evidence suggests the mortality rate in people taking clozapine over the long-term (up to 12 years) is 6.7, which is lower than patients taking other antipsychotics.

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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(6): 1438-45

View review abstract online

Comparison 1	**Mortality rates in people with schizophrenia on long-acting injectable antipsychotic medications (aripiprazole, fluphenazine, olanzapine, paliperidone, or risperidone) vs. placebo.** **Mean study duration = 28.9 weeks**
Summary of evidence	**Moderate to high quality evidence (large samples, imprecise, consistent, direct) suggests no differences in all-cause mortality or suicide rates between people with schizophrenia on long-acting injectable antipsychotic medications or placebo.**
All-cause mortality or suicide	
No significant differences in all-cause mortality or suicide rates between people receiving long-acting injectable antipsychotic medications and placebo; All-cause mortality: 18 RCTs, N = 5,919, RR = 0.64, 95%CI 0.24 to 1.70, $p = 0.37$, $I^2 = 0\%$, $p = 0.67$ Suicide: 18 RCTs, N = 5,919, RR = 0.98, 95%CI 0.16 to 6.08, $p = 0.98$, $I^2 = 0\%$, $p = 0.62$ Subgroup analysis showed a trend towards lower incidence of all-cause mortality in shorter duration RCTs (≤13 weeks, RR = 0.29, $p = 0.08$), than in longer duration RCTs (>13 weeks, RR = 1.40, $p = 0.64$). There were no differences in effect sizes for all-cause mortality according to; individual antipsychotics, antipsychotic type (first vs. second generation), industry vs. non-industry trials, illness status (acute vs. other), or antipsychotic dose. Authors report no evidence of publication bias.	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	**Mortality rates in people with schizophrenia on long-acting injectable antipsychotic medications (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, risperidone, and**

	zuclopenthixol) vs. oral antipsychotics. **Mean study duration = 64.5 weeks**
Summary of evidence	**Moderate to high quality evidence (large samples, imprecise, consistent, direct) suggests no differences in all-cause mortality or suicide rates between people with schizophrenia on long-acting injectable or oral antipsychotic medications.**
All-cause mortality or suicide	
No significant differences in all-cause mortality or suicide rates between people receiving long-acting injectable antipsychotic medications or oral antipsychotics; All-cause mortality: 24 RCTs, N = 7,879, RR = 0.71, 95%CI 0.38 to 1.34, $p = 0.30$, $I^2 = 0\%$, $p = 0.97$ Suicide: 24 RCTs, N = 7,879, RR = 0.94, 95%CI 0.33 to 2.68, $p = 0.91$, $I^2 = 0\%$, $p = 0.77$ There were no differences in effect sizes for all-cause mortality according to; individual antipsychotics, antipsychotic type (first vs. second generation), study duration, industry vs. non-industry trials, illness status (acute vs. other), or antipsychotic dose. There were also no differences between effect sizes in all-cause mortality or suicide rates when individual long-acting injectable antipsychotics were compared with each other. Authors report no evidence of publication bias.	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Schneider-Thoma J, Efthimiou O, Huhn M, Krause M, Reichelt L, Roder H, Davis JM, Salanti G, Leucht S

Second-generation antipsychotic drugs and short-term mortality: a systematic review and meta-analysis of placebo-controlled randomised controlled trials

The Lancet Psychiatry 2018; 5: 653-63

View review abstract online

Comparison	**Short-term mortality rates in people with schizophrenia taking**

	second generation antipsychotics vs. placebo. **Studies had follow-up periods ≤13 weeks.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) finds not differences in mortality rates between patients on second generation antipsychotics or placebo.**
Mortality	
There were no significant differences in mortality rates in people with a schizophrenia diagnosis; 31 studies, N = 11,680, OR = 0.69, 95%CI 0.35 to 1.35, $p > 0.05$	
Consistency in results	Authors report results are consistent
Precision in results	Imprecise
Directness of results	Direct

Vermeulen J, van Rooijen G, Doedens P, Numminen E, van Tricht M, de Haan L

Antipsychotic medication and long-term mortality risk in patients with schizophrenia; a systematic review and meta-analysis

Psychological Medicine 2017; 47: 2217-28

View review abstract online

Comparison	**Long-term mortality rates in people with schizophrenia taking antipsychotics vs. people with schizophrenia not taking antipsychotics.** **Studies included in the meta-analysis had follow-up periods from 5 to 14 years.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a medium-sized effect of fewer deaths in people with schizophrenia taking any antipsychotic.**
Mortality	
A medium-sized effect of fewer deaths in people with schizophrenia taking any antipsychotic; 4 studies, N = 99,550, RR = 0.57, 95%CI 0.46 to 0.76, $p < 0.001$, $I^2 = 92.37\%$, $p < 0.001$	

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Vermeulen JM, Van Rooijen G, Van De Kerkhof MPJ, Sutterland AL, Correll CU, De Haan L

Clozapine and Long-Term Mortality Risk in Patients with Schizophrenia: A Systematic Review and Meta-analysis of Studies Lasting 1.1-12.5 Years

Schizophrenia Bulletin 2019; 45: 315-29

View review abstract online

Comparison	**Long-term mortality rates in people with schizophrenia taking clozapine.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests the mortality rate in people taking clozapine over the long-term is 6.7, which is lower than patients taking other antipsychotics.**
Mortality	
24 studies, 217,691 person-years The unadjusted mortality rate = 6.7, 95%CI 5.4 to 7.9 per 1000 patient years The rate was significantly lower in patients continuously treated with clozapine compared to patients on other antipsychotics.	
Consistency in results	Authors report data were inconsistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, RR = relative risk

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.

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† Different effect measures are reported by different reviews.

Median rate ratio refers to the ratio between prevalence or incidence rates of two groups, based on the median rather than the mean. The median is often used as a better measure of central tendency than the mean when data are skewed. Harmonic means are also used when data are skewed and are appropriate for rate data.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[7].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[8]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[9].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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