

Finn 11 Study Shows Long-term Antipsychotic Use Associated with Decreased Mortality, Clozapine Linked to Better Survival Rates than Other Antipsychotics

The following is an extract of:

Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009;374:620-7

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Bottom Line:

- The gap in life expectancy between those with schizophrenia and the general population remained essentially the same (25 years' difference in 1996 vs. 22.5 years in 2006).
- Consumers with schizophrenia who received long-term antipsychotic treatment had lower mortality rates than those who did not receive antipsychotics.
- Clozapine had substantially lower overall mortality than other antipsychotics.
- Those with a longer duration of cumulative exposure had lower mortality.
- Current use of quetiapine was associated with the highest risk of all-cause mortality, followed by haloperidol, and then risperidone (1.34, 95% CI 1.12-1.62).

Originally published in *The Lancet* in 2009, this study was featured in a Medscape video by NYSPI director Dr. Jeffrey Lieberman, a Medscape article, and a critique published in *Schizophrenia Research* in 2010.¹ The main criticisms raised by these authors had to do with methodological issues and statistical analysis of the raw data. Because of the important implications of this study to clinical practice, we provide the following summary of the somewhat controversial findings from this study.

Study Background

The National Association of State Mental Health Program Directors reported in 2007 that those with serious mental illness (SMI) die, on average, 25 years earlier than the general population. Suicide and other unnatural causes contribute to 40% of this excess mortality, while the remaining 60% are attributed to natural causes, especially cardiovascular disease. Since 1976, deaths from cardiovascular disease have increased, with the most marked increase occurring between 1991-1995. Observations like these, in conjunction with information about the widening mortality gap between those with SMI and the general population, have led many to hypothesize that SGAs have adversely affected mortality rates of those with SMI. However, this hypothesis remains to be proven. Also unknown is the impact on mortality rates of long-term use of SGAs in particular. This study was conducted in order to assess the long-term effect of antipsychotics on mortality in those with schizophrenia. Prior to this study no large datasets that included mortality had been published since 2000.

Study Details

Data from Finnish population registers was examined to identify patients with first hospitalizations from 1973-2004 and followed mortality information from 1996-2006. Maximum follow-up was 11 years. Mortality and cause of death were obtained from Statistics Finland, and drug prescription, information available beginning in 2006, was obtained from the Social Insurance Institution of Finland. Duration of treatment was calculated using the purchased defined daily dose (DDD) for the most frequently used

¹ De Hert M, Correll CU, Cohen D. Do antipsychotic medications reduce or increase mortality in schizophrenia? A critical appraisal of the FIN-11 study. *Schizophrenia Bulletin* 2010;117:68-74

oral antipsychotics: clozapine, haloperidol, olanzapine, perphenazine, quetiapine, risperidone and thioridazine. Study groups included participants on: monotherapy, polypharmacy, rarely used “other” drugs, and no antipsychotic use. The primary outcome looked at acute and chronic effects of antipsychotic medication on all-cause mortality during current and cumulative exposure to any antipsychotic drug, to the six antipsychotics under study and to no antipsychotic use. Perphenazine was used as the comparison antipsychotic for the other agents. Secondary outcomes included death from suicide or heart disease.

Results and Limitations

The study identified a population of 66,881 consumers with schizophrenia out of a total population of 5.2 million. At start of follow-up the average age of the study population was 51 years, with an average follow up of 8.6 years. The gap in life expectancy between those with schizophrenia and the general population was 25 years in 1996 vs. 22.5 years in 2006 (a nonsignificant finding). The change in the difference in life expectancy between the general population and those diagnosed with schizophrenia was not statistically significant (25 years in 1996, vs. 22.5 years in 2006). During this same time period, the use of SGAs increased from 13% to 64%. Risk of death was significantly lower in consumers with long-term (7-11 years) antipsychotic treatment than in those with no antipsychotic use (HR 0.81, 95% CI 0.77-0.84, $p < 0.0001$). There was an inverse relationship between mortality and duration of cumulative exposure (HR for trend per exposure year 0.991; 0.95-0.997). Current use of quetiapine, which was only available for the last four years of the study, was associated with the highest risk of all-cause mortality (1.41, 1.09-1.82), followed by haloperidol (1.37, 1.10-1.72), and then risperidone (1.34, 1.12-1.62). Clozapine had the lowest risk of death in relation to the comparator drug perphenazine (0.74, 0.60-0.91, $p = 0.0045$ and $p < 0.0001$ for all other comparisons). No significant differences were found for the drugs under study and ischemic heart disease. Contrary to results from past studies showing that clozapine and olanzapine increase cardiovascular risk, this study found that both drugs were associated with slightly lower mortality due to ischemic heart disease (clozapine adjusted HR 0.78; olanzapine adjusted HR 0.88).

Study limitations include: the inability to control for potential confounders (health behavior, economic and lifestyle factors); possible survivor bias (e.g. those on antipsychotics for a long time prior to 1996, and who were still surviving in 1996, might be a cohort of survivors); selection bias (those with mild illness and without inpatient admissions, those with poor insight who refused treatment and medications, or those who committed suicide before obtaining treatment were not in the study population), and generalizability to the US (which has a different healthcare system and more heterogeneous population than Finland). Finally, assessing cardiovascular mortality associated with antipsychotics may require longer follow up than 7-11 years.

Clinical Implications

One of the main findings emphasized by the authors is that long term use of any antipsychotic drug was associated with lower mortality than was no antipsychotic treatment. With the possible exception of quetiapine and risperidone, which were associated with increased mortality, the authors argue that increased use of SGAs has not had a harmful effect on life expectancy in schizophrenia. The finding that clozapine was associated with the lowest mortality is important given its curtailed use in clinical practice. The authors acknowledge that the difference in mortality found with clozapine may be related to more intensive monitoring during clozapine treatment, increased effectiveness of clozapine, low safety of other drugs or a combination of these factors. However, given the implications that clozapine is the safest antipsychotic in terms of mortality and given its proven effectiveness, the authors raise the issue of whether clozapine should be used as a first-line treatment.

Drs Tiihonen, Haukka, Niskanen, report serving as consultants and/or receiving expert opinion fees from various pharmaceutical companies.