11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study)

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Summary

Background **The introduction of second-generation antipsychotic drugs during the 1990s is widely believed to have adversely affected mortality of patients with schizophrenia. Our aim was to establish the long-term contribution of antipsychotic drugs to mortality in such patients.**

Methods **Nationwide registers in Finland were used to compare the cause-specific mortality in 66 881 patients versus the total population (5·2 million) between 1996, and 2006, and to link these data with the use of antipsychotic drugs. We measured the all-cause mortality of patients with schizophrenia in outpatient care during current and cumulative exposure to any antipsychotic drug versus no use of these drugs, and exposure to the six most frequently used antipsychotic drugs compared with perphenazine use.**

Findings **Although the proportional use of second-generation antipsychotic drugs rose from 13% to 64% during follow-up, the gap in life expectancy between patients with schizophrenia and the general population did not widen between 1996 (25 years), and 2006 (22·5 years). Compared with current use of perphenazine, the highest risk for overall mortality was recorded for quetiapine (adjusted hazard ratio [HR] 1·41, 95% CI 1·09–1·82), and the lowest risk for clozapine (0·74, 0·60–0·91; p=0·0045 for the difference between clozapine *vs* perphenazine, and p<0·0001 for all other antipsychotic drugs). Long-term cumulative exposure (7–11 years) to any antipsychotic treatment was associated with lower mortality than was no drug use (0·81, 0·77–0·84). In patients with one or more filled prescription for an antipsychotic drug, an inverse relation between mortality and duration of cumulative use was noted (HR for trend per exposure year 0·991; 0·985–0·997).**

Interpretation **Long-term treatment with antipsychotic drugs is associated with lower mortality compared with no antipsychotic use. Second-generation drugs are a highly heterogeneous group, and clozapine seems to be associated with a substantially lower mortality than any other antipsychotics. Restrictions on the use of clozapine should be reassessed.**

Funding **Annual EVO Financing (Special government subsidies from the Ministry of Health and Welfare, Finland).**

Published **Online** July 13, 2009 DOI:10.1016/S0140-6736(09)60742-X

See **Online/Comment** DOI:10.1016/S0140-6736(09)61072-2

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Introduction

Worldwide, several million patients with schizophrenia are treated with antipsychotic drugs, but whether long-term use is associated with either increased or decreased mortality remains unknown. Excess mortality in people with schizophrenia has been widely discussed[1] since publication of a report[2] by the National Association of State Mental Health Program Directors. This report showed that people with serious mental illness die on average 25 years earlier than do those in the general population, and although suicide and other unnatural causes account for about 40% of excess mortality, roughly 60% of premature deaths are from natural causes, such as cardiovascular and pulmonary disease. In people with schizophrenia, cardiovascular mortality rose from 1976 to 1995, with the greatest increase from 1991 to 1995.[2] Furthermore, results of a meta-analysis[3] revealed that the differential mortality gap between people with schizophrenia and the general population widened from the 1970s to the 1990s. The introduction of second-generation antipsychotic drugs during the 1990s was suggested to have had a major adverse effect on mortality in patients with schizophrenia, especially because of a raised risk of death from cardiovascular disease.[2,3]

Results of randomised effectiveness trials[4–6] show that olanzapine or clozapine might be better than are risperidone, quetiapine, ziprasidone, or oral perphenazine, but whether the cardiometabolic side-effects of olanzapine and clozapine outweigh their effectiveness during long-term treatment is unknown.[7] A delay of several years might occur between drug-induced weight gain, development of metabolic syndrome, and premature death. No large published datasets exist that include mortality data after 2000, and hence we do not know the answer to some questions. Has the differential mortality gap further worsened since the mid-1990s? What is the role of major natural and unnatural causes of death in people with schizophrenia? How are these issues associated with antipsychotic treatment? We aimed to answer these questions by assessing the contribution of antipsychotic drugs to mortality in patients with schizophrenia.

Methods

Study population

The patient population consisted of all patients in Finland who were admitted with a diagnosis of schizophrenia (International Classification of Diseases [ICD]-8: codes

295.00, 295.10, 295.20, 295.30, 295.40, 295.50, 295.60, 295.80, 295.99; ICD-9: 2951, 2952, 2953, 2954A, 2956, 2957A, 2959; ICD-10: F20, F21, F25) from Jan 1, 1973, to Dec 31, 2004 (the first hospital treatment was regarded as the index period). For patients discharged after Jan 1, 1996, follow-up began at discharge after their first stay in hospital for schizophrenia. Follow-up started Jan 1, 1996, for patients whose discharge after their first hospital admission took place before Jan 1, 1996, because prescription data are available only after 1995.

Information was obtained from the study population by register linkage with unique personal identification codes, which are routinely used in Finnish registers. In Finland, identification of all patients treated in hospital since 1969 is possible with the National Hospital Discharge Register (NHDR). Furthermore, the diagnostic validity of schizophrenia in the NHDR is very good.[8–11] Information about mortality and cause of death is recorded by Statistics Finland, and all reimbursed drug prescriptions purchased from pharmacies are registered by the Social Insurance Institution of Finland, which covers all residents. In this study, drug use refers to repeated purchase of medication from a pharmacy in outpatient care (although not all patients who purchased medication would have taken them as instructed). Prescriptions for antipsychotic and antidepressant drugs are filed by the Social Insurance Institution, which is responsible for administration of the national sickness insurance scheme. The data contained information for day of purchase, and dose, which was stated as the international standard defined daily dose.[12] Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[13]

Duration of antipsychotic treatment was calculated by use of the purchased defined daily dose (DDD).[14] The three most frequently used first-generation drugs (oral perphenazine, thioridazine, and oral haloperidol) and four most frequently used second-generation drugs (clozapine, olanzapine, oral risperidone, and quetiapine) were identified, and patients who used only one drug (monotherapy) were assigned to the respective group. Mixed use (ie, several antipsychotic medications) was classified as polypharmacy in the context of current use only, patients given rarely used drugs were assigned to a separate group (defined as other), and those who had not used any antipsychotic drugs during the 11-year follow-up (18 914) formed a separate group.

For the **Statistics Finland website** see http://www.tilastokeskus.fi/til/index_en.html

Acute and chronic effects need to be studied when the role of antipsychotic drugs in mortality is assessed. For example, an acute effect is sudden cardiac death, which is the reason for restriction of use of thioridazine, and a chronic effect is diabetes, which can lead to death from ischaemic heart disease. Therefore, we examined the acute effects in the analysis of current use, which identified the drug that patients were using when they died. In many cases, because the currently used medication had also been used during the past years, the analysis of current use suggests to some extent the risk associated with long-term cumulative use. For chronic effects, an analysis of cumulative use was done, which showed an association between the amount of exposure and risk of death. This method is similar to the idea of smoking years that is used in lung cancer research.

For each individual, the follow-up was divided into periods in which the value of time-dependent variables (ie, antipsychotic drug and number of admissions during follow-up) was constant. Thus, follow-up of each person consisted of several contiguous periods, each defined with specific entry and exit times. Each patient could contribute to several monotherapy categories, according to their medication history. For example, if a patient had received drug A for 3 years and drug B for 5 years, and died after 5 years of drug B, the death was attributed to drug B in the analysis of current use, and to both drug A (3 patient years) and drug B (5 patients years) in the analysis of cumulative use. This method is described in detail elsewhere.[15,16]

In the analysis of cumulative use, all deaths were included, but in the analysis of current use, hospital treatment periods were censored after the first 2 days (ie, deaths during hospital treatments after the first 2 days were not included in the analysis), because no information was available for the drugs given during hospital treatment. With this method, the currently used drug was always presumed to continue during outpatient care without discontinuation when the gaps in the calculated use were shorter than 3 days. For comparisons of specific antipsychotic drugs, perphenazine was used as the reference drug to enable a comparison with results of the CATIE study.[4]

The analysis of cumulative use was not restricted to monotherapies—ie, exposure to specific antipsychotic drugs during polypharmacy was also included in the analysis. Hazard ratios (HRs) were calculated for eight time intervals (0–0·5, >0·5–1, >1–2, >2–3, >3–4, >4–5, >5–7, and >7–11 years). For quetiapine, analysis was done for up to 4 years because this drug became available in Finland only in 2000. The reference group for the use of any drug versus no drug was composed of patients who had not used any antipsychotic during the 11-year follow-up. In the analysis of cumulative use, all hospital deaths were taken into account. General population mortality data were obtained from Statistics Finland.

Ethics approval was obtained from all institutions participating in the study, and from the Finnish Ministry of Social Affairs and Health. The primary outcome measure was all-cause mortality during current and cumulative exposure to any antipsychotic drug versus no antipsychotic drug use, and current and cumulative exposure to the six most frequently used antipsychotic drugs (thioridazine, oral haloperidol, clozapine,

olanzapine, oral risperidone, and quetiapine) compared with perphenazine use in outpatient care. These measures were made by adjusting the effect of the most important confounding variables. Death from suicide and death due to ischaemic heart disease were secondary outcome measures.

Statistical analysis

We included all patients with schizophrenia in Finland to achieve high statistical power. (No power calculations were done because the number of subjects was expected to be substantially higher than in any previous study of mortality in schizophrenia,) Cox's proportional-hazard analysis with a counting process approach was used with the outcome variables, and the end of follow-up as a censoring time. To allow for the multiple periods for one individual, we calculated the robust variance estimators with a grouped jackknife method. In both models, (ordinal Cox's model, and marginal structural models [MSM]) sex, age, duration of illness, previous hospital treatment for attempted suicide, schizophrenia, cancer, ischaemic heart disease, and time since start of follow-up were used as background variables. We estimated hazard ratios (HRs) for the treatment groups using two different sets of models—ordinal Cox's proportional-hazards model with a counting process approach,[17] and MSM to estimate the causal effect of the drugs.

MSMs aim to appropriately control for the effects of time-dependent confounders affected by previous treatment. This model can be used to adjust for confounding and selection bias due to measured time-varying covariates affected by exposure. We used inverse probability weights in Cox's model to estimate marginal structure models. Weighting creates a pseudopopulation in which the exposure is independent of the measured confounders. The pseudopopulation is the result of assignment of a weight to each participant that is, informally, proportional to the patient's probability of receiving their own exposure history. The parameters of weighted regression models, which equal the parameters of MSMs, can be used to estimate the average causal effect of exposure in the original study population. MSM assume no unmeasured confounding, which is not empirically verifiable. We used stabilised weights in MSMs.[18] These models were calculated only for all-cause mortality with any use of medication regarded as an explanatory treatment variable.

The denominator of weights in MSMs consisted of: time-dependent drugs, time-dependent previous antipsychotic drugs, and previous hospital admissions since the start of follow-up; fixed age, sex, and hospital admissions before follow-up; and duration of illness before follow-up. Nominators were: time-dependent medications, with fixed age, sex, and hospital admissions before follow-up; and duration of illness before follow-up. Data for marital status of patients, diagnoses of substance abuse, socioeconomic status, and other social variables were not available.

Life expectancy was calculated for the schizophrenia population according to Toson and Baker.[19] A comparison of mortality between the general population and patients with schizophrenia was also made with Poisson regression, with schizophrenia status, age, and sex as explanatory variables, log-population at risk as an offset term, and number of deaths as a response variable. All data analyses were done with R software version 2.6.1.[20]

For the **schizophrenia population life expectancy calculation** see http://www.statistics.gov.uk/downloads/theme_other/GSSMethodology_No_33.pdf

Role of the funding source

The sponsor (The Ministry of Health and Welfare, Finland) 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 data in this study and had the final responsibility for the decision to submit for publication.

Results

The study population consisted of 30 803 men and 36 078 women with schizophrenia. The mean age at the start of follow-up was 51 years. Mean duration of psychiatric

	Number of deaths	Person-years	Mortality (per 1000)
Sex			
Male	8323	266 240	31·3
Female	11 412	307 620	37·1
Time since the onset of illness (years)			
0–5	8566	234 300	36·6
>5–10	3551	100 110	35·5
>10	7618	239 450	31·8
Age (years)			
<20	56	12 230	4·6
>20–30	433	63 620	6·8
>30–40	1078	110 210	9·8
>40–50	2561	153 540	16·7
>50–60	2794	102 700	27·2
>60–70	3793	69 020	55·0
>70	9020	62 540	144·2
Previous hospital admission for:			
Ischaemic heart disease			
Yes	6584	63 790	103·2
No	13 151	510 070	25·8
Attempted suicide			
Yes	209	4580	45·7
No	19 526	569 280	34·3
Cancer			
Yes	979	8040	121·8
No	18 756	565 830	33·1

The odds ratios describing the probability of being given certain antipsychotic drugs with respect to all clinical and sociodemographic background variables are in webappendix pp 1–11.

Table: **All-cause mortality by background variables at start of follow-up**

See **Online** for webappendix

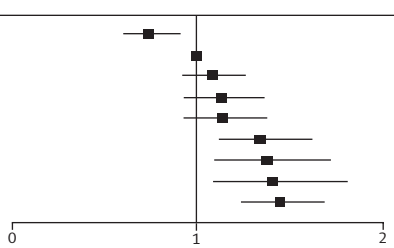
hospital treatment was less than 0·4 years (5% of the mean total follow-up of 7·8 years) for patients who had never used an antipsychotic drug in outpatient care (18 914), and was less than 0·3 years (3% of the mean total follow-up of 8·9 years) for all other patients (47 967). Patients used 156 456 368 DDDs of antipsychotic drug during the 11-year follow-up (average follow-up 8·6 years). Of all antipsychotic treatments, the proportion of second-generation antipsychotic drugs (risperidone, olanzapine, clozapine, and quetiapine) rose from 12·6% (1·49 million of 11·84 million DDDs) in 1996, to 64·0% (10·22 million of 15·98 million) in 2006. Altogether, aripiprazole, sertindole, and ziprasidone accounted for 0·3% of all DDDs (0·45 million of 156·46 million). Mean DDDs of perphenazine, haloperidol, and thioridazine were 0·34, 0·66, and 0·54 in 1996, and 0·35, 0·65, and 0·57 in 2006, (and in 2005, for thioridazine), respectively.

At age 20 years, patients with schizophrenia had a life expectancy of 32·5 years in 1996, compared with 57·5 years in the general population, with a difference of 25 years. In 2006, the difference was 22·5 years (37·4 years for patients with schizophrenia *vs* 59·9 years in the general population). For patients aged 40 years, life expectancy differed by 18·5 years (1996) and 17·0 years (2006). These data show that life expectancy of patients with schizophrenia had not declined during the study period compared with the general population. The table shows the sociodemographic and clinical data for patients and the effect of background variables on risk of death from all causes. These data for each treatment population are shown in webappendix p 1.

Overall risk of death was lower (adjusted HR 0·68, 95% CI 0·65–0·71, p<0·0001) during the current use of any antipsychotic drug than it was with no antipsychotic use. In analysis of all-cause mortality during current specific antipsychotic monotherapy versus perphenazine use, quetiapine was associated with the highest risk, and clozapine with the lowest risk of death (figure 1A). Clozapine use was associated with the lowest risk of death, which was substantially lower than for any other

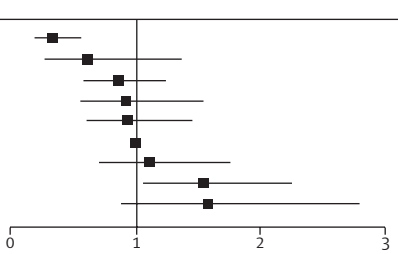
A

	Number of deaths	Person-years	Mortality*	Crude rate ratio (95% CI)	Adjusted HR (95% CI)
Clozapine	182	32 000	5·69	0·53 (0·43–0·65)	0·74 (0·60–0·91)
Perphenazine	193	17 930	10·77	1·00	1·00
Polypharmacy	1481	132 320	11·19	1·04 (0·89–1·21)	1·08 (0·92–1·26)
Olanzapine	264	25 130	10·50	0·98 (0·81–1·17)	1·13 (0·93–1·36)
Thioridazine	227	18 420	12·32	1·14 (0·94–1·39)	1·14 (0·93–1·38)
Risperidone	295	19 410	15·20	1·41 (1·18–1·69)	1·34 (1·12–1·62)
Haloperidol	135	7040	19·19	1·78 (1·43–2·22)	1·37 (1·10–1·72)
Quetiapine	89	5360	16·60	1·54 (1·20–1·98)	1·41 (1·09–1·82)
Other	1234	70 520	17·50	1·63 (1·40–1·89)	1·45 (1·24–1·69)



B

Clozapine	27	32 000	0·84	0·46 (0·28–0·76)	0·34 (0·20–0·57)
Haloperidol	7	7040	1·00	0·54 (0·24–1·22)	0·61 (0·27–1·37)
Polypharmacy	226	132 320	1·71	0·93 (0·64–1·34)	0·86 (0·59–1·24)
Thioridazine	27	18 420	1·47	0·80 (0·48–1·32)	0·93 (0·56–1·55)
Olanzapine	57	25 130	2·27	1·23 (0·80–1·89)	0·94 (0·61–1·45)
Perphenazine	33	17 930	1·84	1·00	1·00
Risperidone	47	19 410	2·42	1·32 (0·84–2·05)	1·12 (0·72–1·76)
Other	194	70 520	2·75	1·49 (1·03–2·16)	1·55 (1·07–2·25)
Quetiapine	19	5360	3·54	1·93 (1·09–3·39)	1·58 (0·89–2·79)



C

Clozapine	42	32 000	1·31	0·25 (0·17–0·35)	0·78 (0·54–1·12)
Quetiapine	21	5360	3·92	0·73 (0·46–1·17)	0·83 (0·52–1·34)
Olanzapine	65	25 130	2·59	0·48 (0·35–0·66)	0·88 (0·63–1·21)
Thioridazine	104	18 420	5·65	1·05 (0·80–1·39)	0·97 (0·73–1·29)
Polypharmacy	522	132 320	3·94	0·74 (0·59–0·92)	0·97 (0·77–1·21)
Perphenazine	96	17 930	5·35	1·00	1·00
Risperidone	119	19 410	6·13	1·15 (0·88–1·50)	1·17 (0·89–1·54)
Other	520	70 520	7·37	1·38 (1·11–1·71)	1·21 (0·97–1·51)
Haloperidol	72	7040	10·23	1·91 (1·41–2·59)	1·24 (0·91–1·69)

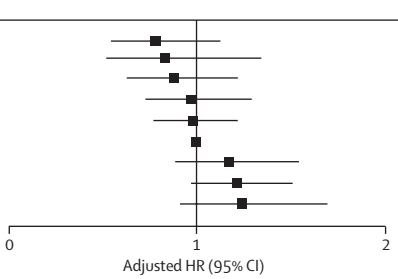


Figure 1: **Risk of death during current monotherapies**
(A) Risk of death from any cause. (B) Risk of death from suicide. CIs for haloperidol and quetiapine are wide because of the low number of incidents in patients using these drugs. (C) Risk of death from ischaemic heart disease. *Mortality=unadjusted absolute risk per 1000 person-years. HR=hazard ratio. Other=rarely used antipsychotic drugs.

www.thelancet.com **Published online July 13, 2009 DOI:10.1016/S0140-6736(09)60742-X**

	Person-years	Number of deaths	Mortality*	Crude rate ratio (95% CI)	Adjusted HR (95% CI)
No antipsychotic drugs†	146 930	8277	56·33	1·00	1·00
0–0·5 years	59 920	1183	19·74	0·35 (0·33–0·37)	0·49 (0·46–0·52)
≥0·5–1·0 years	14 400	591	41·03	0·73 (0·67–0·79)	1·05 (0·96–1·15)
≥1·0–2·0 years	33 700	1272	37·74	0·67 (0·63–0·71)	0·99 (0·93–1·05)
≥2·0–3·0 years	34 030	1111	32·65	0·58 (0·54–0·62)	0·89 (0·84–0·95)
≥3·0–4·0 years	31 990	891	27·85	0·49 (0·46–0·53)	0·81 (0·76–0·87)
≥4·0–5·0 years	29 920	797	26·63	0·47 (0·44–0·51)	0·79 (0·73–0·85)
≥5·0–7·0 years	57 620	1359	23·59	0·42 (0·40–0·44)	0·73 (0·69–0·77)
≥7·0–11·0 years	165 360	4254	25·73	0·46 (0·44–0·47)	0·81 (0·77–0·84)

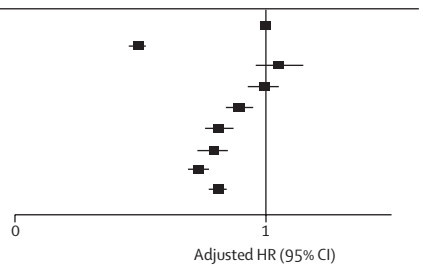


***Figure 2*: Risk of death from any cause versus cumulative use of any antipsychotic drug**
*Mortality=unadjusted absolute risk per 1000 person-years. †No antipsychotic drug=patients (18 914) who had not used any antipsychotic drugs during follow-up.

antipsychotic treatment (p=0·0045 for perphenazine, and p<0·0001 for all other comparisons). HR for overall mortality with the MSM method was 0·33 (0·25–0·42), when use of any antipsychotic drug was compared with no use of antipsychotic drugs.

Clozapine was also associated with a substantially lower risk of suicide than was any other drug (figure 1B). No pronounced differences between antipsychotic drugs were noted for mortality from ischaemic heart disease (figure 1C). Figure 2 shows risk of death during any antipsychotic drug use versus no use, and figure 3 shows relative risk of death for specific antipsychotic treatments compared with perphenazine during the 11-year period of cumulative use.

The risk of death was significantly lower in patients with long-term (7–11 years) antipsychotic treatment than in those who had not used any antipsychotic drugs during follow-up (HR 0·81, 0·77–0·84; p<0·0001). In patients with at least one filled prescription, an inverse relation was noted between mortality and duration of cumulative use of antipsychotic drug (HR for trend per exposure year 0·991; 0·985–0·997). No signs of increased risk of death from ischaemic heart disease were noted after 7–11 years of cumulative exposure to antipsychotic treatments. HRs for mortality between 7 years and 11 years compared with perphenazine were 0·74 (0·45–1·22) for olanzapine, 0·83 (0·65–1·07) for clozapine, 1·10 (0·91–1·34) for thioridazine, 1·11 (0·88–1·41) for haloperidol, 1·12 (0·82–1·53) for risperidone, and 1·54 (1·04–2·29) for quetiapine (at 3–4 years). For overall risk of death, the most consistent differences compared with the perphenazine group were reported for clozapine (significantly lower risk during two time intervals; 0·68 [0·52–0·90] at 1–2 years and 0·70 [0·51–0·96] at 2–3 years) and for haloperidol (1·30 [1·11–1·52] at 0–0·5 years, 1·33 [1·05–1·70] at 0·5–1 years, and 1·41 [1·08–1·84] at 3–4 years) and quetiapine (1·26 [1·03–1·55], at 0–0·5 years and 1·54 [1·04–2·29] at 3–4 years; figure 3).

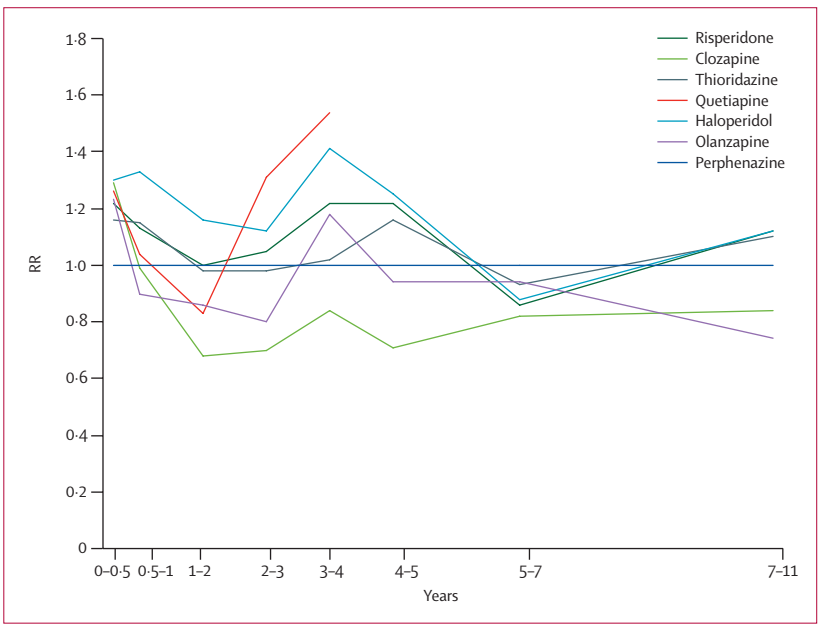


***Figure 3*: Relative risk of death according to cumulative use of specific antipsychotic drugs**
RR=relative risk.

Discussion

Our results show that life expectancy at age 20 years rose by 2·4 years in the general Finnish population and by 4·9 years in patients with schizophrenia, while the proportion of use of second-generation antipsychotic drugs increased from 13% to 64% during 1996–2006. This difference in life expectancy was greater at age 20 years than it was at age 40 years, implying that the mortality gap is largely attributable to deaths at an early age, even though the mean age of the cohort was 51 years. We showed that long-term use of any antipsychotic drug was associated with a lower mortality than was no use of antipsychotic drugs. An inverse relation between mortality and duration of cumulative use in patients with at least one filled prescription. Patients who used antipsychotics for less than 6 months had especially low mortality rates, possibly because of mild symptoms and recovery from an acute episode.

Comparisons of specific antipsychotics versus perphenazine showed that current use of quetiapine, haloperidol, and risperidone were associated with an

increased mortality (41, 37%, and 34%) and clozapine with a reduced mortality (–26%). These results suggest that heightened use of second-generation antipsychotics, rather than first-generation drugs, has not had a harmful effect on life-expectancy of patients with schizophrenia, with the possible exception of quetiapine and risperidone. The median DDDs of the first-generation antipsychotic drugs did not change much between 1996 and 2006, suggesting that this factor has not played a substantial part in reduction of mortality. It is noteworthy that, although current use of polypharmacy was associated with a moderate mortality from ischaemic heart disease, it was not associated with a higher total mortality than was recorded with most of the drugs given as monotherapy. Our results suggest that corrected Q-T interval prolongation is not a powerful predictor for risk of acute death during antipsychotic treatment, because thioridazine was not associated with high overall mortality in the analysis of current use. However, careful monitoring of patients using thioridazine might have contributed to low overall mortality in these patients.

The difference in mortality between clozapine and other antipsychotic drugs might be attributable to more intensive monitoring during clozapine treatment, increased effectiveness of clozapine, low safety of other drugs, or all these factors. In fact, all causes of death were recorded as adverse events. Our results for the antisuicidal effect of clozapine are in line with the InterSePTT study,[21] in which the intensity of monitoring was reported to be identical in patients who were treated with clozapine versus those given with olanzapine. This finding suggests that monitoring of patients might not be the main reason for good outcomes in those using clozapine.

Analyses of cumulative use differed slightly from the results for current use, because exposure to specific antipsychotics during polypharmacy and deaths during psychiatric hospital stays longer than 2 days were included in cumulative-use analyses. These periods were only 5% of the total follow-up in patients with no use of antipsychotic drugs in outpatient care, and 3% in the remaining patients. Clozapine and olanzapine did not seem to heighten risk of death from ischaemic heart disease when compared with other antipsychotic medication. Moreover, these drugs were associated with a slightly lower total mortality and deaths due to ischaemic heart disease than were other antipsychotic drugs at the 7–11 year interval of cumulative exposure.

We have shown[15] that clozapine use is associated with the best treatment compliance. In the long term, good adherence to treatment might lead to a healthy lifestyle, which might compensate for the adverse cardiometabolic effects of clozapine. More than 11 years might be needed to record the putative rise in cardiovascular mortality induced by antipsychotic drugs. Although many of our patients had been using this drug for up to 17 years, a longer time might be needed for some adverse events to present. Nevertheless, our results raise the issue of whether clozapine should be used as a first-line treatment, because it seems to be the safest antipsychotic in terms of mortality and it is also the most effective.[22,23]

However, clozapine is inexpensive, and hence it is unprofitable for the pharmaceutical industry to market compared with other second-generation antipsychotic drugs. Additionally, monitoring schedules are a drawback that would be encountered with heightened use of clozapine, and physicians and other hospital staff might therefore be reluctant to initiate clozapine treatment. However, clozapine is associated with a lower discontinuation rates than is any other antipsychotic,[15] and monitoring is not likely to be a major difficulty for patients after the initiation of treatment.

Selection bias should be controlled by adjustment for the most important confounding factors. We recorded some differences in the distribution of background variables. Patients who used clozapine were more likely to have had previous admissions because of relapses of schizophrenia than were patients using other specific antipsychotics, and those using first-generation drugs were somewhat older than were those using second-generation drugs.

We had no data available for health behaviour, general health status, quality of life, and economic and lifestyle factors. Although a residual bias can never be totally eliminated, the large differences—such as substantially lower suicide mortality during clozapine use than during treatment with other drugs—are probably not explained by a residual bias. Patients who died before January, 1996, were not included, and those who had a long history of illness and use of first-generation drugs and who were alive in 1996, represent a cohort of survivors. Therefore, mortality of patients using first-generation antipsychotic drugs (*vs* second-generation antipsychotic drugs) might be underestimated.

Fewer than 5% of all Finnish patients with schizophrenia are estimated to have not been admitted during the past few decades.[11] These patients might have included those who had only mild symptoms and those who committed suicide before obtaining treatment. The group of our patients who did not use any antipsychotic drugs is probably a heterogeneous group. Estimates show that about 20% of patients with schizophrenia will not be admitted because of relapse, despite not using any antipsychotic treatment since discharge. These patients probably had a milder symptom profile and better long-term prognosis than did others. However, some with poor compliance and insight into their illness are not willing to use any antipsychotic drugs in outpatient care, resulting in recurrent relapses and hospital admissions. A substantial proportion of our group not receiving antipsychotic drugs probably consisted of these two patient populations.

This database for mortality in schizophrenia almost has as many patients with schizophrenia as do all previous studies combined.[3,24] Our findings of higher mortality in patients who had not used any antipsychotic drugs than in those with 7–11 years of cumulative use and in those with at least one filled prescription, indicate that long-term use is associated with lower mortality than is no use or short-term use. Thus, lifestyle issues and poor living circumstances associated with the illness might be more important factors than are long-term adverse events from medication. Because our database included the whole population of the country, results can be generalised to countries with similar health-care system and sociodemographic features.

For drugs with a broad range of potentially serious side-effects or that are used to treat patients at a high risk of disease, overall mortality might be a good integrated measure of overall benefit in comparison with risk.[25] A surprising finding was that clozapine—the antipsychotic drug restricted by authorities because of safety concerns—was associated with the lowest mortality. Clearly, safety restrictions have not caused a selection bias in this study, whereby patients in the best health and with the lowest risk of death would have been more likely to receive this drug. Conversely, clozapine has been used only in the most severely ill patients who are resistant to other drugs and have the highest risk of suicide.[21] In our database, patients who had previous hospital admissions because of schizophrenic relapses also had a higher likelihood of receiving clozapine than any other specific antipsychotic drug. Despite this selection bias, even the crude RR of suicide was much lower for clozapine than for any other antipsychotic drug.

Weight gain associated with olanzapine use became known to psychiatrists after a study[26] in November, 1999, reported weight gain associated with different antipsychotic drugs. Therefore, we can assume that this issue has not contributed to selection of patients who had used olanzapine for more than 7 years (treatment started before Dec 31, 1999). Our results show that patients who began olanzapine treatment before the end of 1999 did not have a higher risk of death due to ischaemic heart disease. According to national recommendations, clozapine can be used only after two unsuccessful trials with other antipsychotic drugs—ie, as a last-resort. Thus, patients rarely switch from clozapine to other monotherapies. In the analysis of current use, death is assigned to the current (last) drug. This factor suggests that the superiority of clozapine is not attributable to the order in which monotherapies are given.

In trials in populations of low risk, reporting of severe and rare adverse events, is difficult, because thousands of patients and several years follow-up is needed. Restrictions on use of clozapine and thioridazine have not been based on any evidence for their overall ratio of risk to benefit. Our results suggest that these instructions and recommendations (except for blood monitoring) might have caused thousands of premature deaths worldwide in patients who have been exposed to other antipsychotic drugs, which might be associated with increased mortality. In our opinion, such restrictions and recommendations should be based on solid scientific evidence for the safety of drugs. This example underscores the need for large nationwide databases to be used for surveillance of drug safety.[27]

Contributors

All authors contributed to the study design, and drafting of the report. JT led the study, and statistical analyses were done by JH and AT. All authors have seen and approved the final version of the report.

Conflicts of interest

JT has served as a consultant to Lundbeck, Organon, Janssen-Cilag, Eli Lilly, and Bristol-Myers Squibb, and has received fees for giving expert opinions to Bristol-Myers Squibb and GlaxoSmithKline, and lecture fees from Janssen-Cilag, Bristol Myers-Squibb, Eli Lilly, Pfizer, Lundbeck, GlaxoSmithKline, and Astra Zeneca. JT has not served as consult, received any fees or had interest with any pharmaceutical company manufacturing, marketing, or selling clozapine. JH has served as a consultant to Janssen-Cilag. LN has served as consultant to Eli Lilly and Bristol Myers-Squibb, and has received fees for giving expert opinions to Bristol Myers-Squibb, and lecture fees from Janssen-Cilag, Bristol Myers-Squibb, Eli Lilly, and Astra Zeneca. JL, AT, TK, and KW declare that they have no conflicts of interest.

Acknowledgments

This study was supported by funding from the Annual EVO Financing (special government subsidies from the Ministry of Health and Welfare, Finland). The researchers were independent from the funder. We thank Simo Pelanteri (STAKES Information) for his work with different registers in selection of and merging of data for this project, and Aija Räsänen for secretarial assistance.

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