



Do antipsychotic medications reduce or increase mortality in schizophrenia? A critical appraisal of the FIN-11 study

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ABSTRACT

Compared to the general population, people with schizophrenia are at risk of dying prematurely due to suicide and due to different somatic illnesses. The potential role of antipsychotic treatment in affecting suicide rates and in explaining the increased mortality due to somatic disorders is highly debated.

A recent study of death registers in Finland compared the cause-specific mortality in 66,881 patients versus the total population (5.2 million) between 1996 and 2006, suggesting that antipsychotic use decreased all-cause mortality compared to no antipsychotic use in patients with schizophrenia, and that clozapine had the most beneficial profile in this regard (Tiihonen et al., 2009). The benefits of clozapine were conferred by significant protective effects for suicide compared to perphenazine, whereas, a mixed group of 'other' antipsychotics, haloperidol, quetiapine and risperidone were reported to be associated with significantly higher all-cause mortality than perphenazine. By contrast, despite known differences in effects on cardiovascular risk factors, there were no significant differences between any of the examined antipsychotics regarding death due to ischemic heart disease. A number of methodological and conceptual issues make the interpretation of these findings problematic, including incomplete reporting of data, questionable selection of drug groups and comparisons, important unmeasured risk factors, inadequate control for potentially confounding variables, exclusion of deaths occurring during hospitalization leading to exclusion of 64% of deaths on current antipsychotics from the analysis, and survivorship bias due to strong and systematic differences in illness duration across the treatment groups.

Well designed, prospective mortality studies, with direct measurement of and adjustment for all known relevant risk factors for premature mortality, are needed to identify risk and protective medication and patient factors and to, ultimately, inform clinical practice.

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1. Introduction

Physical health and increased rates of premature mortality in people with schizophrenia have become a major concern in recent years (De Hert et al., 2009a; Fleischhacker et al., 2008;

Laursen et al., 2009; Leucht et al., 2007; Saha et al., 2007; Weinmann et al., 2009).

The publication by Tiihonen et al. (2009) on the association between antipsychotic medications and mortality, based on data from a large register of Finnish patients with schizophrenia, is the most recent contribution in this area. The authors applied a similar methodology in three previous register studies (Haukka et al., 2008; Tiihonen et al., 2006a, Tiihonen et al., 2006b) (Table 1).

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Table 1

Comparison of methods and results of Finnish registry studies by the same research group.

	Tiihonen et al. (2006b)	Haukka et al. (2008)	Tiihonen et al. (2009)
Study inclusion period	1/1/1995 to 31/12/2001	1/1/1997 to 1/12/2003	1/1/1973 to 31/12/2004
Duration inclusion	7 years	7 years	32 years
Study start	At discharge	At discharge	1/1/1996
Duration of follow-up	3.6 years	4.3 years	11 years (7.8 years and 8.9 years)
N patients	2230	1611	66,881 ^a N at start follow-up unclear
Mean age patients	30.7 years	37.8 years	51 years
Inclusion criteria clinical	First admission for schizophrenia	First admission for schizophrenia	Diagnosis of schizophrenia and admission for suicide attempt
Reference agent	Oral haloperidol	Not taking antipsychotics	Oral perphenazine
Antipsychotics assessed	Not taking antipsychotics 10 most commonly used Group mixed or rare (with data on perphenazine depot)	5 most commonly used Group mixed or rare (no data on depot drugs)	Not taking antipsychotics 6 most commonly used plus perphenazine Polypharmacy group Group other (=rare) (no data on depot drugs)
N deaths	84 (3.8%) (75 (3.4%) no AP, 9 (0.4%) on AP)	195 (12.1%) (98 (6.1%) current AP, 81 (5.0%) past AP, 16 (1.0%) no AP)	19,735 (29.5%) (11,458 (17.1%) current AP, 8277 (13.4%) no AP) N death before start follow-up unknown
N suicides	27 (1.2%) (26 (1.1%) no AP, 1 (0.1%) on drug)	99 (6.2%) (56 (3.5%) current AP, 37 (2.3%) past AP, 6 (0.4%) no AP)	Data only on current AP use sample, 4100 death of which 637 suicides (15.5% of deaths) 64% of the sample on drugs excluded from the current use analysis
Main outcomes	Mortality highest in no AP group Lowest discontinuation for clozapine, perphenazine depot and olanzapine	Current use AP lowest mortality Compared to no AP use, olanzapine and mixed group reduced all-cause mortality Mixed group reduced suicide risk	Compared to current perphenazine, clozapine had a significant lower all-cause mortality Other APs, quetiapine, haloperidol and risperidone had significantly higher all-cause mortality Clozapine had significantly lower mortality due to suicide There were no differences across all AP groups due to ischemic heart disease Long-term exposure to AP had lower mortality than no AP
N readmitted	469 (21.0%) (4620 readmissions, 89% psychiatric hospital and 11% in general hospital)	Not mentioned	Not mentioned
Exclusion of data of death in hospital (>2 days admission)	Not mentioned	Exclusion of 31 deaths	Exclusion of 7358 deaths from current AP analysis (37.3% all deaths, 11.0% of patients)
Patients who stopped AP who restarted AP during follow-up	394 or 49.4% of 797 initially no AP	96% at least once during follow-up	None
Additional comments	N 10 most common AP only account for 46.9% of sample		In current use analysis N death not on AP not mentioned Largest groups are Polypharmacy (40.3% of total patient years) and other APs (21.5% of total patient years)

AP = antipsychotic.

^a Would be according to Heilä et al., 2005 an estimate of nearly all patients with schizophrenia in Finland.

In the latest study, patients with a first admission dating back up to 1973 were included. The 5 major outcomes of the study of 66,881 patients comprising 573,860 person-years are a) increased prescription of second generation-antipsychotics (from 13% (1996) to 64% (2006), b) modest reduction of the shortened life expectancy, from 25 years (1996) to 22.5 years (2006), compared to the general population, c) decreased mortality in users of antipsychotics compared to non-users, d) stratified increased all-cause mortality (other antipsychotics, haloperidol, quetiapine and risperidone) or decreased all-cause mortality (clozapine) compared to the first-generation antipsychotic perphenazine, and e) robust lowered mortality, from any cause and from suicide, without any difference in mortality from ischemic heart disease in users of the second-generation

drug clozapine. For reasons of design, power and outcome, this study deserves both attention and scrutiny (Basu and Aggarwal, 2009; De Hert et al., 2009b; Dervaux and Laqueille, 2009; Sperling and Biermann, 2009).

2. Conceptual and methodological aspects

The title of the paper, '11-year follow-up of mortality in patients with schizophrenia', seems misleading because the mean follow-up for patients who never used antipsychotics is given as 7.8 years and for all other patients as 8.9 years. The paper focuses on the potential association of antipsychotics, and individual drugs, with mortality. Overall, the study confirms the risk for both increased and premature death in

people with schizophrenia ($n = 19,735$ or 29.5% of the sample died, of which 20.9% ($n = 4128$) died before age 50).

However the paper fails to report essential data that are necessary to interpret the study results. This includes a table with demographic information per analyzed group, such as number of patients, mean age, sex, duration of illness, duration of treatment, distribution of antipsychotics used as part of polypharmacy (particularly including clozapine), and psychiatric and somatic co-medication. Although the authors describe state-of-the-art, but also fairly complicated statistical procedures to adjust their results for potentially confounding variables that can differ between the treatment groups, such a table would provide a clearer picture of these potentially crucial differences and shed more light on how successful the statistical adjustment procedures are expected to have been.

In their statistical analyses, the authors had to deal with differences between the examined, non-randomly assigned treatment groups, including fixed and time-dependent variables, as well as with missing data of measured variables. Variance estimators were calculated for both ordinal Cox regression models and for marginal structural models (MSM), using the following list of background variables: sex, age, illness duration, previous hospital treatment for attempted suicide, schizophrenia, cancer, ischemic heart disease, and time since start of follow-up. MSMs aim to adjust for confounding and selection biases due to measured, time-varying covariates affected by exposure. However, these models assume no unmeasured confounding. This is never true. In the data set that [Tiihonen et al. \(2009\)](#) analyzed, the following variables were not available: marital status, substance abuse diagnosis, socio-economic status, (un)healthy lifestyle variables, detailed cardiovascular history and risk assessment data ([Basu and Aggarwal, 2009](#); [Dervaux and Laqueille, 2009](#); [Sperling and Biermann, 2009](#)). To conduct weighted regression models that incorporate estimates of the 'average causal effect' of exposure, inverse probability weights in Cox's model were used and the results served to estimate the marginal structure models. To assign to each patient a statistical weight, the following list of individual variables was used for the denominator: 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. For the nominator of the inverse probability weight, these variables were used: time-dependent medications, with fixed age, sex, and hospital admissions before follow-up; and duration of illness before follow-up. Importantly, these models were calculated only for all-cause mortality with any use of medication.

Based on the above, it is doubtful that the statistical methods available to adjust for potentially very powerful biases are sufficient. A crucial example of this concern is the effect of illness duration. Although this potentially critical variable was used in the calculations, it was only one of many variables that assigns a certain percent of the weight used in the adjusted analyses. This is particularly relevant, as all second-generation antipsychotics, except for clozapine, were preferentially prescribed to patients with 1–4 years of illness duration. By contrast, all first-generation antipsychotics and clozapine

were preferentially prescribed to patients with >10 years of illness duration ([Tiihonen et al., 2009](#), supplemental tables). Since, as discussed below (see [Section 2.4](#)), suicide occurs earlier in the illness course, this represents a very strong and systematic cohort effect, which might not be amenable to efforts of statistical control via complicated statistical methodology ([De Hert et al., 2009b](#)). Rather, a confirmatory sensitivity analysis should have been performed as well, matching all antipsychotic groups on illness duration. Although this would decrease the sample size of antipsychotics with predominantly longer illness sample characteristics, such a post-hoc analysis could have tested whether or not the cohort effect is responsible for the finding of a lower suicide risk for clozapine.

2.1. The choice for analysis of cumulative use: advantage and disadvantage

When death occurred, this event was attributed to the current antipsychotic and to the previously prescribed antipsychotic drug(s), proportionally to treatment duration. This fair method has a serious disadvantage, namely when a certain drug is never used as first or second choice, but always as drug of last resort. In this case, death of patients on such a drug always contributes to the risk of the previously used drugs, while the reverse is impossible. In other words, the result of this methodological decision is a one-sided effect, namely an inflated death risk for all antipsychotic drugs except for clozapine. Clozapine fulfills the criteria of drug of last resort and indeed, in all analyses of mortality rates, clozapine comes out most favorably. A comparison with the mortality rates in other studies underscores this point: with 5.69/1000 person years, the mortality for clozapine was, the lowest in the study by [Tiihonen et al. \(2009\)](#). By contrast, in other studies the mortality rates for clozapine were 8.5 ([Taylor et al., 2009](#)), 11.3 ([Munro et al., 1999](#)) and 12.5 ([Meltzer et al., 2003](#)), as well as 4.6 for persons under 55 years and 45.6 for persons over 55 years ([Walker et al., 1997](#)). It is unclear whether the considerably lower mortality risk with clozapine in the study by [Tiihonen and colleagues \(2009\)](#) is a true effect or whether it is the result of the chosen methodology. For a fair judgment of the resulting death risks, a calculation of the effect of the one-sidedness of the chosen methodology is needed.

2.2. Categorization of antipsychotic treatment in current and cumulative treatment groups

Patients were assigned to one of the seven groups of most frequently prescribed antipsychotics. The remaining patients on medication were assigned to one of two additional, compounded categories: patients with more than one current antipsychotic drug were assigned to 'polypharmacy', patients who were given rarely used drugs were assigned to a separate group 'other' (all groups 328,130 person-years antipsychotic exposure). A final group was not taking antipsychotic medication at the time of death.

The 'polypharmacy' and 'other' groups receive too little attention in comparison to the seven antipsychotic most frequently prescribed drugs. With 132,320 person-years (comprising 40.3% of total person-years), the size of the polypharmacy group by itself exceeds the size of all seven

most frequently prescribed antipsychotics combined (125,290 person years or 38.2%): it is by and large the biggest individual group. The size of the group 'other', 70,520 person years (21.5% of total person-years), defies its definition as 'rarely used drugs', as its size is bigger than any one of the individual 'most frequently prescribed drugs'. Second, the sheer size of the polypharmacy group more than justifies a detailed analysis of the contribution of the drugs prescribed in the context of polypharmacy to the death risk of the seven identified antipsychotic drugs analysis, especially since polypharmacy has been reported to increase mortality in schizophrenia (Joukamaa et al., 2006; Waddington et al., 1998). This is particularly relevant, as the currently best evidence for antipsychotic polypharmacy exists for combinations involving clozapine (Correll et al., 2009a). Therefore, the contribution of clozapine use in combination with other antipsychotics needs to be examined regarding cause-specific mortality. Third, no explanation is given for the missing detailed analysis of the contribution by the so called 'rarely prescribed drugs' to the deaths risk. We feel that, given its size, such an analysis is certainly warranted, if not required.

Tiihonen and colleagues (2009) report that 18,914 patients with schizophrenia had not received any antipsychotic drug during the mean follow-up of 7.8 years (146,930 person-years). It seems somewhat unlikely that 28.2% of the total number of patients would never have used antipsychotics nor have been hospitalized for a relapse during the follow-up period. Previous studies from the same authors on smaller cohorts found indeed that a substantial number of these patients were taking antipsychotic medications at some time during follow-up (49% and 96%) (Tiihonen et al., 2006b; Haukka et al., 2008), and that 21% were admitted during a much shorter follow-up of only 3.6 years (Table 1). Another Finnish study on the effect of the decreasing number of psychiatric beds found that less than 4% of the patients were not in psychiatric care (Salokangas et al., 2002).

Finally, since the registry does not record medications dispensed during hospitalization, antipsychotic exposure during hospitalization was not counted in this study, a factor that will be discussed below.

As a more minor point, Tiihonen et al. (2009) used Defined Daily Dose (DDD) to estimate the proportional use of specific antipsychotics. However, this is problematic, as DDD use does not reflect actual use in individual patients (Sperling and Biermann, 2009).

2.3. Mortality data

The authors do not report the absolute number of deaths for each of the medications or treatment groups. The data could have been presented more clearly (e.g., mortality rate ratios, standardized mortality ratios) to enable comparisons with other recent register studies from Nordic countries. Moreover, comparisons with general population data are not presented. Presenting mortality events in person years of exposure obscures the actual importance of drug-related toxicity.

Interpretation of the overall mortality data is problematic because patients who died before 1996 were excluded, they had a potential exposure to antipsychotics of up to 23 years (some of which likely involved clozapine). Moreover, the

number of survivors of the older cohort is not mentioned. Therefore the actual *N* of patients in the analyses is unclear. This information would have allowed an analysis of trends over time, which is relevant because, at least, recent Swedish register studies have indicated an increase in cardiovascular mortality over time (Osby et al., 2000; Osby, 2008).

The patient selection led to a mean age of 51 years at start of the follow-up. Given the mortality gap between schizophrenia patients and the general population of 22.5 to 25 years (Tiihonen et al., 2009), this age might be appropriate to evaluate the risk of mortality due to somatic causes. However, this mean age is problematic for the assessment of risk for suicide as discussed below. Furthermore, the high mortality in the group of no antipsychotic drug users does not concur with other Finnish data. Out of 18,914 patients, 8277 (43.8%) had died during the mean follow-up of 7.8 years, equaling an annual mortality rate of 5.6%. Comparison of this figure with those by another Finnish study by Salokangas et al. (2002) is instructive. In four different cohorts covering 1982–1994, they found a mean mortality rate of 5.2% for three years, or an annual mortality rate 1.7%. The reasons for the much higher mortality rates found by Tiihonen et al. (2009) are not discussed by the authors and remain therefore unclear, but in our opinion this finding well deserves to be elaborated upon by a detailed analysis.

2.4. Risk of death from suicide

One of the main findings that antipsychotic use is associated with a lower suicide risk is consistent with clinical evidence that acute psychotic episodes are associated with significantly increased suicide risk (Palmer et al., 2005). The suicide preventive effect of antipsychotic treatment was confirmed by another recent study from this group, which selected patients with schizophrenia hospitalized for a suicide attempt (Haukka et al., 2008). In this study, the mean age at inclusion was lower (37.8 years), and 1611 patients were followed on average for 4.3 years. Further, in this study, which is not referenced in the current paper, the mixed antipsychotic group performed best regarding suicide reduction. Finally, another previous study by the Finnish group, focusing on differential efficacy of antipsychotics, showed a 37-fold increased risk for suicide in patients not taking antipsychotics (Tiihonen et al., 2006b).

Despite these consistent results, the difference between drugs regarding all-cause mortality in the current use of antipsychotics analysis is mainly driven by a clozapine effect on the reduction of suicide. This potential anti-suicidal effect of clozapine is a confirmation of the InterSePT study (mean age at baseline: 37.1 years), a head to head study between clozapine and olanzapine (Meltzer et al., 2003). Apart from closer monitoring of patients on clozapine, the later time during the illness and higher age of clozapine initiation in part limits the interpretation of a potential anti-suicidal effect of clozapine in the study by Tiihonen et al. (2009). Previous studies have shown that the most critical period for suicide is early after the onset of the disorder (De Hert et al., 2001; Heilä et al., 2005; Laursen et al., 2007; Palmer et al., 2005; Tidemalm et al., 2008). Thus, a large proportion of the clozapine cohort 'suffers from' a survivor bias, being a selection of survivors of early suicide risk after the onset of

their illness. Moreover, this bias was distributed unevenly among the individual antipsychotic drugs (see Section 2.1), a fact that cannot be ‘controlled away’ by statistical methods. There is indeed evidence to support a greater efficacy of clozapine and even better compliance compared to other antipsychotics, but the authors’ suggestion that clozapine might lead to better health-related lifestyle is not supported by any study to date and is highly speculative.

The mortality gap between patients with schizophrenia compared to the general population over time was slightly reduced. This could be attributed to reduction of mortality at younger ages. Although suicide rates remain high in Finland, reduced rates of suicide have been confirmed in the general population and specifically in patients with different, severe mental illnesses, including schizophrenia (Heilä et al., 2005; Korkeila, 2009; Pirkola et al., 2007, 2009; Rantanen et al., 2009). If this is the case, mortality due to other causes (e.g., cardiovascular disease) could have increased over time, but this very important issue was not evaluated in the paper.

2.5. Exclusion of death in the hospital

Analysis of current use of antipsychotics is appropriate to study acute toxicity effects such as sudden death (Ray et al., 2009), agranulocytosis or cardiomyopathy in clozapine users.

In the analysis of current use, patients’ deaths during hospitalization for longer than 2 days were excluded because medication prescription data as part of the inpatient treatment are not recorded in the Finnish register. The result is a reduction of the risk of death attributable to current antipsychotic use, but an increased risk associated with previously prescribed antipsychotics. For a calculation of the size of this effect, additional data are needed, each per individual treatment, that include the number and length of hospitalizations and the number of deaths during included (occurring during the first 2 days of hospitalization) and excluded (occurring >2 days of hospitalization).

Mortality analysis of patients on current antipsychotic therapy was performed on 4100 deaths (figure 1a, Tiihonen et al., 2009). Since 8277 deaths occurred in patients without antipsychotic drugs (figure 2, Tiihonen et al., 2009), this amounts to 12,377 deaths analyzed. However, altogether, 19,735 deaths occurred in this study (table all-cause mortality, Tiihonen et al., 2009). This leaves a difference of 7358 deaths that are unaccounted for, with death after hospitalization of two days or longer being the only exclusion for their analyses mentioned by the authors. In another approach, all death (19,735) minus death in untreated patients (8277) amounts to a total of 11,458 deaths during current antipsychotic therapy. If correct, this reasoning leads us to the conclusion that 64.2% of fatalities in patients treated with antipsychotic medications (7358 of the total of 11,458) were not included in the ‘current use’ analyses.

It is likely that many of these patients died from the effects of suicide or cardiovascular disease while admitted to a hospital. As this approach likely underestimates mortality in patients treated with antipsychotic medications, this critical methodological factor might help to explain why the previous literature arrived at different findings with regard to antipsychotic-related mortality risk (Osborn et al., 2007; Weinmann et al., 2009).

2.6. Exclusion of data from psychiatric hospitalizations

Although deinstitutionalization in Finland has been extensive, psychiatric beds are still available and accessible (1996: 6255 beds, 2004: 4898 beds, and 2 medium sized, forensic psychiatric hospitals), significant proportions of patients reside in long-stay care (1996: 1918 patients; 2004: 1544 patients), and there are also possibly patients residing in other residential facilities in the community (Eronen et al., 2000; STAKES, 2009). These significant numbers of patients would once again have been excluded from the analyses in both this study and previous studies conducted by this group (exact number not reported in the present study; 31 additional deaths in the suicide study (Haukka et al., 2008)).

Of note, the introduction of second-generation antipsychotics occurred concurrently with the progressive reduction in beds and the development of comprehensive community care, which also likely affect suicide and death rates.

2.7. Cardiovascular mortality.

Another puzzling finding of the study is that drugs with the highest potential to induce cardiometabolic abnormalities, such as clozapine and olanzapine (De Hert et al., 2008, 2009a; Cohen and Correll, 2009), were not associated with higher cardiovascular mortality than perphenazine or any of the other antipsychotic groups. As argued above (see Section 2.5), this finding seems to be based on analyses of 36% of the total number of deaths of the patients actually treated with antipsychotics. Furthermore, the analyses suggesting an overall advantage of being on antipsychotic drugs versus no treatment is based on a comparison with 18,914 patients with schizophrenia who supposedly never used antipsychotics during an average follow-up of 7.8 years (see Section 2.2).

Recent studies (Laursen et al., 2007, 2009; Osby et al., 2000; Osby, 2008; Saha et al., 2007), including Finnish datasets (Heilä et al., 2005; Joukamaa et al., 2006) have found high mortality rates due to cardiovascular disease in patients with severe mental illness. A recent review of 12 studies found that most data sets showed a consistently increased risk of cardiovascular mortality associated with antipsychotics (Weinmann et al., 2009).

3. Discussion and conclusion

The recent study by Tiihonen et al. (2009) has yielded an important and clinically relevant finding: patients with schizophrenia not taking antipsychotics have a higher mortality risk than those treated with antipsychotics. Thus, these patients require increased attention and observation, and attempts need to be intensified to use pharmacologic and/or psychosocial treatments that can decrease that increased mortality. Nevertheless, as indicated above, we feel that there might be potential problems in the approach and analyses that the investigators used that might well have influenced a number of the results. The authors have argued the validity of their methodology, referring to the Million Women study, the largest study ever performed on the effects of hormonal replacement therapy and cancer risk (Beral et al.,

2003, 2005; Tiihonen et al., 2006a). Initially, this study got large exposure to and acclaim from clinicians, the general public and government bodies. But in the years following the publication, this study became the subject of debate and criticism. Although the study was large, it had a number of the same methodological and sampling problems discussed above in relationship to the study by Tiihonen et al. (2009). Most importantly, the results of this observational study were contradicted by the findings of several well-designed, randomized controlled trials, as well as several other large observational studies (van der Mooren and Kenemans, 2004; Whitehead and Farmer, 2004). Apart from methodological concerns, the authors acknowledged themselves that the observation of a potential statistical association between an exposure and a particular outcome is no proof for a causal relationship (Hill, 1965).

We put forward the hypothesis that the methodological issues reviewed above go a long way to explain the discrepant result of the FIN-11 study with other studies. Consequently, the validity of the results needs to be confirmed. A discussion of consequences for clinical practice seems to be at this stage premature. Most of the evidence supports a beneficial effect of antipsychotics (especially clozapine) on suicide risk, but the data also support the view that the use of many though not all atypical antipsychotic drugs can increase cardiovascular morbidity and mortality (De Hert et al., 2009a; Cohen and Correll, 2009; Correll et al., 2009b).

Therefore, it is crucial that the effects of antipsychotics on overall mortality are adjusted for the most important, known risk factors for premature mortality, mainly cardiovascular risk factors. In order to provide clinically relevant risk data for each individual antipsychotic drug that takes into account the patient characteristics related to premature death from suicide, cardiac disease or all-cause death, well designed, prospective studies, which directly measure these risk factors and validate causes of death, are needed.

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Contributors

M De Hert wrote the first draft, C U Correll and D Cohen commented on this draft and contributed to the subsequent revisions.

Conflict of Interest

M De Hert has been a consultant for and received grant/research support and been on the speakers/advisory boards of Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Pfizer and Sanofi-Aventis.

C U Correll has been a consultant to or has received honoraria from AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Medicure, OrthoMcNeil-Janssen, Otsuka, Pfizer, Schering-Plough, Supernus, and Vanda, and has served on the speaker's bureau of AstraZeneca, Bristol-Myers Squibb/Otsuka and Pfizer.

D Cohen received honoraria from, and has been on the speakers/advisory boards of AstraZeneca, Bristol-Myers Squibb and Eli Lilly.

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References

Basu, D., Aggarwal, M., 2009. Mortality in patients with schizophrenia. *Lancet* 374 (9701), 1591.

- Beral, V., the Million Women Study collaborators, 2003. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet* 362, 419–427.
- Beral, V., Bull, D., Reeves, G., Million Women Study Collaborators, 2005. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 365, 1543–1551.
- Cohen, D., Correll, C.U., 2009. Second-generation antipsychotic-associated diabetes mellitus and diabetic ketoacidosis: mechanisms, predictors and screening need. *J. Clin. Psychiatry* 70, 765–766.
- Correll, C.U., Rummel-Kluge, C., Corves, C., Kane, J.M., Leucht, S., 2009a. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophr. Bull.* 35 (2), 443–457.
- Correll, C.U., Manu, P., Olshansky, V., Napolitano, B., Kane, J.M., Malhotra, A.K., 2009b. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 302 (16), 1765–1773.
- De Hert, M., McKenzie, K., Peuskens, J., 2001. Risk factors for suicide in young people suffering from schizophrenia: a long-term follow-up study. *Schizophr. Res.* 47 (2–3), 127–134.
- De Hert, M., Schreurs, V., Sweers, K., Van Eyck, D., Hanssens, L., Sinko, S., Wampers, M., Scheen, A., Peuskens, J., van Winkel, R., 2008. Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: a retrospective chart review. *Schizophr. Res.* 101 (1–3), 295–303.
- De Hert, M., Dekker, J.M., Wood, D., Kahl, K.G., Holt, R.I., Möller, H.J., 2009a. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur. Psychiatry* 24 (6), 412–424.
- De Hert, M., Peuskens, J., van Winkel, R., 2009b. Mortality in patients with schizophrenia. *Lancet* 374 (9701), 1591.
- Dervaux, A., Laquaille, X., 2009. Mortality in patients with schizophrenia. *Lancet* 374 (9701), 1592.
- Eronen, M., Repo, E., Vartiainen, H., Tiihonen, J., 2000. Forensic psychiatric organization in Finland. *Int. J. Law Psychiatry* 23 (5–6), 541–546.
- Fleischhacker, W.W., Cetkovich-Bakmas, M., De Hert, M., Hennekens, C., Lambert, M., Leucht, S., Maj, M., McIntyre, R.S., Naber, D., Newcomer, J.W., Olfson, M., Osby, U., Sartorius, N., Lieberman, J.A., 2008. Cormorbid somatic illnesses in patients with severe mental disorders: clinical, policy and research challenges. *J. Clin. Psychiatry* 69, 514–519.
- Haukka, J., Tiihonen, J., Härkönen, T., Lönnqvist, J., 2008. Association between medication and risk of suicide, attempted suicide and death in nationwide cohort of suicidal patients with schizophrenia. *Pharmacoepidemiol. Drug Saf.* 17 (7), 686–696.
- Heilä, H., Haukka, J., Suvisaari, J., Lönnqvist, J., 2005. Mortality among patients with schizophrenia and reduced psychiatric hospital care. *Psychol. Med.* 35 (5), 725–732.
- Hill, A.B., 1965. The environment and disease; association or causation. *Proc. Royal Soc. Med.* 8, 295–330.
- Joukamaa, M., Heliövaara, M., Knekt, P., Aromaa, A., Raitasalo, R., Lehtinen, V., 2006. Schizophrenia, neuroleptic medication and mortality. *Br. J. Psychiatry* 188, 122–127.
- Korkeila, J., 2009. Current trends in psychiatry care in Finland with special focus on private practice psychiatry and psychotherapy. *Nord. J. Psychiatry* 63 (1), 87–90.
- Laursen, T.M., Munk-Olsen, T., Nordentoft, M., Mortensen, P.B., 2007. Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. *J. Clin. Psychiatry* 68 (6), 899–907.
- Laursen, T.M., Munk-Olsen, T., Agerbo, E., Gasse, C., Mortensen, P.B., 2009. Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. *Arch. Gen. Psychiatry* 66 (7), 713–720.
- Leucht, S., Burkard, T., Henderson, J., Maj, M., Sartorius, N., 2007. Physical illness and schizophrenia. *Acta Psychiatr. Scand.* 116 (5), 317–333.
- Meltzer, H.Y., Alphas, L., Green, A.I., Altamura, A.C., Anand, R., Bertoldi, A., Bourgeois, M., Chouinard, G., Islam, M.Z., Kane, J., Krishnan, R., Lindenmayer, J.P., Potkin, S., International Suicide Prevention Trial Study Group, 2003. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch. Gen. Psychiatry* 60 (1), 82–91.
- Munro, J., O'Sullivan, D., Anderws, C., Arana, A., Mortimer, A., Kerwin, R., 1999. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. *Brit. J. Psych.* 175, 576–580.
- Osborn, D.P., Levy, G., Nazareth, I., Petersen, I., Islam, A., King, M.B., 2007. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. *Arch. Gen. Psychiatry* 64 (2), 242–249.

- Osby, U., 2008. Cardiovascular outcome and schizophrenia in Sweden. *Schizophr. Res.* 103 (1–3), 18.
- Osby, U., Correia, N., Brandt, L., Ekblom, A., Sparén, P., 2000. Time trends in schizophrenia mortality in Stockholm county, Sweden: cohort study. *BMJ* 321 (7259), 483–484.
- Palmer, B.A., Pankratz, V.S., Bostwick, J.M., 2005. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch. Gen. Psychiatry* 62 (3), 247–253.
- Pirkola, S., Sohlman, B., Heilä, H., Wahlbeck, K., 2007. Reductions in postdischarge suicide after deinstitutionalization and decentralization: a nationwide register study in Finland. *Psychiatr. Serv.* 58 (2), 221–226.
- Pirkola, S., Sund, R., Sailas, E., Wahlbeck, K., 2009. Community mental-health services and suicide rate in Finland: a nationwide small-area analysis. *Lancet* 373 (9658), 147–153.
- Rantanen, H., Koivisto, A.M., Salokangas, R.K., Helminen, M., Oja, H., Pirkola, S., Wahlbeck, K., Joukamaa, M., 2009. Five-year mortality of Finnish schizophrenia patients in the era of deinstitutionalization. *Soc. Psychiatry Psychiatr. Epidemiol.* 44 (2), 135–142.
- Ray, W.A., Chung, C.P., Murray, K.T., Hall, K., Stein, C.M., 2009. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N. Engl. J. Med.* 360 (3), 225–235.
- Saha, S., Chant, D., McGrath, J., 2007. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch. Gen. Psychiatry* 64 (10), 1123–1131.
- Salokangas, R.K.R., Honkonen, T., Stengard, E., Koivisto, A.M., 2002. Mortality in chronic schizophrenia during decreasing number of psychiatric beds in Finland. *Schizophr. Res.* 54, 265–275.
- Sperling, W., Biermann, T., 2009. Mortality in patients with schizophrenia. *Lancet* 374 (9701), 1592.
- STAKES, 2009. www.info.stakes.fi/mindful/EN/database/indicators.htm (accessed 28 07 2009).
- Taylor, D.M., Douglas-Hall, P., Olofinjana, B., Whiskey, E., Thomas, A., 2009. Reasons for discontinuing clozapine: matched, case–control comparison with risperidone long-acting injection. *Br. J. Psychiatry* 194 (2), 165–167.
- Tidemalm, D., Margda Waern, M., Stefansson, C.G., Elofsson, S., Runeson, B., 2008. Excess mortality in persons with severe mental disorder in Sweden: a cohort study of 12,103 individuals with and without contact with psychiatric services. *Clin. Pract. Epidemiol. Ment. Health* 4, 23. doi:10.1186/1745-0179-4-23.
- Tiihonen, J., Lönnqvist, J., Wahlbeck, K., Klaukka, T., Tanskanen, A., Haukka, J., 2006a. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. *Arch. Gen. Psychiatry* 63 (12), 1358–1367.
- Tiihonen, J., Wahlbeck, K., Lönnqvist, J., Klaukka, T., Ioannidis, J.P., Volavka, J., Haukka, J., 2006b. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalization due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ* 333, 224–227.
- Tiihonen, J., Lönnqvist, J., Wahlbeck, K., Klaukka, T., Niskanen, L., Tanskanen, A., Haukka, J., 2009. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 374 (9690), 620–627.
- van der Mooren, M.J., Kenemans, P., 2004. The Million Women Study: a licence to kill other investigations? *Eur. J. Obstet. Gynecol. Reprod. Biol.* 113 (1), 3–5.
- Waddington, J.L., Youssef, H.A., Kinsella, A., 1998. Mortality in schizophrenia. Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. *Br. J. Psychiatry* 173, 325–329.
- Walker, A.M., Lanza, L.L., Arellano, F., Rothman, K.J., 1997. Mortality in current and former users of clozapine. *Epidemiology* 8 (6), 671–677.
- Weinmann, S., Read, J., Aderhold, V., 2009. Influence of antipsychotics on mortality in schizophrenia: systematic review. *Schizophr. Res.* 113 (1), 1–11.
- Whitehead, M., Farmer, R., 2004. The million women study. A critique. *Endocrine* 24 (3), 187–193.