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Medication and suicide risk in schizophrenia: A nested case–control study

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ABSTRACT

Introduction: Patients with schizophrenia are at increased risk of suicide, but data from controlled studies of pharmacotherapy in relation to suicide risk is limited.
Aim: To explore suicide risk in schizophrenia in relation to medication with antipsychotics, antidepressants, and lithium.
Methods: Of all patients with a first clinical discharge diagnosis of schizophrenia or schizoaffective disorder in Stockholm County between 1984 and 2000 (n = 4000), patients who died by suicide within five years from diagnosis were defined as cases (n = 84; 54% male). Individually matched controls were identified from the same population. Information on prescribed medication was retrieved from psychiatric records in a blinded way. Adjusted odds ratios [OR] of the association between medication and suicide were calculated by conditional logistic regression.
Results: Lower suicide risk was found in patients who had been prescribed a second generation antipsychotic (clozapine, olanzapine, risperidone, or ziprasidone; 12 cases and 20 controls): OR 0.29 (95% confidence interval [CI], 0.09–0.97). When the 6 cases and 8 controls who had been prescribed clozapine were excluded, the OR was 0.23 (95% CI 0.06–0.89). No significant association was observed between suicide and prescription of any antipsychotic, depot injection antipsychotics, antidepressants, SSRI, or lithium.
Conclusions: Lower suicide risk for patients who had been prescribed second generation antipsychotics may be related to a pharmacological effect of these drugs, to differences in adherence, or to differences in other patient characteristics associated with lower suicide risk.

1. Introduction

About 5 to 6% of patients with schizophrenia die from suicide (Palmer et al., 2005; Nordentoft et al., 2011), and 4 to 8% of all suicides are attributable to inpatient treated schizophrenia spectrum disorder (Qin and Nordentoft, 2005; Reutfors et al., 2010b). Numerous studies have investigated predictors of suicide in schizophrenia; some of the established risk factors include previous suicide attempts, higher premorbid function, depression, and poor adherence to treatment (Hawton et al., 2005; Reutfors et al., 2010a).

Antipsychotic drugs are essential in reducing positive psychotic symptoms and the need for hospitalization in schizophrenia (NICE, 2009). However, their effect on the risk for completed suicide still remains a matter of debate (Ernst and Goldberg, 2004; Aguilar and Siris, 2007). Findings of reduced suicidal or self-injurious behavior in patients using antipsychotics, mainly clozapine, have led to suggestions that antipsychotics may also lower the risk of completed suicide (Meltzer et al., 2003; Aguilar and Siris, 2007). Among the few controlled studies of antipsychotic use and completed suicide in schizophrenia are two register-based cohort studies from Finland. These have demonstrated a reduction in suicide risk related to antipsychotic medication in general (Tiihonen et al., 2006), and a significantly lower risk of suicide associated with clozapine use than with any other antipsychotic (Tiihonen et al., 2009). However, a limitation in these studies was that some potential confounding factors, including socioeconomic status, were not adjusted for.

In addition to antipsychotics, other psychotropic drugs such as antidepressants and mood stabilizers are commonly used in schizophrenia (Vares et al., 2011). However, although the beneficial effect of lithium on suicide risk in bipolar disorder is relatively well documented (Cipriani et al., 2005), data on whether this extends to patients with schizophrenia or schizoaffective disorder are lacking (Leucht et al., 2007). There is also a paucity of studies about the effect on suicide risk

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of antidepressant treatment in schizophrenia (Ernst and Goldberg, 2004). Recently, a register based cohort study found that current antidepressant use in schizophrenia compared with no use was associated with a significant reduction in risk of completed suicide (Tiihonen et al., 2012).

When studying suicide risk in relation to drug use, clinical trials are commonly impossible to perform for ethical reasons and because suicides are rare, even in populations at increased suicide risk. Observational studies are therefore warranted to increase the knowledge of pharmacotherapy in schizophrenia and its relation to suicide risk. We performed a nested population based case–control study to assess suicide risk in relation to prescription of antipsychotics, antidepressants, and lithium in schizophrenia and schizoaffective disorder.

2. Methods

2.1. Study subjects

The source population for the study was identified in the Swedish National Patient Register. This register contains individual-based information on psychiatric hospitalizations with complete coverage of Stockholm County since 1973. For each hospitalization, the register includes the patient's unique civic registration number, dates of admission and discharge, diagnoses at discharge, psychiatric department, and hospital. It is compulsory for all in-patient facilities to submit data on discharge and the register is therefore population-based. We identified the patients of age 18 to 64 years who were discharged for the first time with a primary (main) diagnosis of schizophrenia or schizoaffective disorder (index diagnosis; code 295 in the International Classification of Disease 8th revision (ICD-8), code 295 in ICD-9, and codes F20, F25 in ICD-10) from psychiatric departments in Stockholm County between June 1984 and December 2000 (N = 4000). All patients were then linked to the Swedish Cause of Death Register, which is nation-wide and covers more than 99% of all deaths in Sweden. We identified 84 individuals who had died by suicide (codes E950–E959 in ICD-8 and ICD-9 and codes X60–X84 in ICD-10) within five years from their index diagnosis. For each suicide case, one control was individually matched from the source population. Matching criteria were date (±1 year) and age (±5 years) at index diagnosis. Each control had to be alive at the time of death of the corresponding suicide case. After permission from the heads of the relevant psychiatric and non-psychiatric medical departments, we traced the clinical records for the 84 matched case–control pairs.

2.2. Data collection and definitions of exposures

The information about the prescribed pharmacological treatments as well as of psychosocial and demographic factors was retrieved from the clinical records of the cases and controls. To ensure that the time for documented follow-up data was similar for each matched pair, a research assistant truncated the control record at the date corresponding to the date of death of the case. Data about the prescribed drugs were collected until the day of death of the case and until the corresponding day for the control. To make the data reviewer blind as to whether a record belonged to a case or to a control, the assistant also removed that part of the clinical record that contained data regarding the death of the case.

All antipsychotic drugs prescribed to the cases and controls were included in the group 'any antipsychotic' and are listed in Table 2. Four of these drugs were defined as second generation antipsychotics (SGAs), namely clozapine, olanzapine, risperidone, and ziprasidone. The group 'any antidepressant' included SSRIs, SNRIs, tricyclic antidepressants, tetracyclic antidepressants, and MAO-inhibitors with the drugs specified in Table 2. Lithium was studied separately. The following formulations of lithium had been used: lithium, lithium citrate, and lithium sulfate.

2.3. Statistical analysis

Conditional logistic regression was used to estimate odds ratios (OR) with 95% confidence intervals (CI) for the associations between treatment with antipsychotic medications and death by suicide. The analysis was conditioned on the risk-set structure defined by the matching process, with additional adjustment for sex, education, and age at onset of symptoms. We also investigated the association between treatment with SGAs, clozapine separately, depot injection antipsychotics, antidepressants, SSRIs separately and lithium on the one hand and death by suicide on the other. The analyses were repeated after restricting the timing of prescription (exposure) to one month and one year before suicide in the cases and the corresponding dates in the matched controls. We also investigated if there was any association between the number of prescriptions for each drug category and the suicide risk (1 prescription, 2 prescriptions, ≥3 prescriptions). SAS statistical software (version 9.1) was used for all analyses.

2.4. Ethical permission

The study was approved by the ethics committee of Karolinska Institutet, Stockholm, Sweden (No. 01-375).

3. Results

Table 1 summarizes the characteristics of the cases and controls. The majority of patients received their diagnosis at an age younger than 35 years. The suicide risk estimates associated with these background factors have been reported previously (Reutfors et al., 2009).

Table 2 displays the information on the medications prescribed prior to the suicide for the suicide cases and controls. It also shows the relative suicide risk estimates for exposed vs. unexposed patients expressed as odds ratios (corresponding to suicide incidence rate ratios) (Pearce, 1993). Antipsychotic drugs had been prescribed to 99% of all the patients. The suicide risk was reduced by approximately 70% in patients who had ever been prescribed a second generation antipsychotic (clozapine, olanzapine, risperidone, or ziprasidone) compared to those who had not (adjusted odds ratio [OR] = 0.29, 95% CI 0.09–0.97).

Table 1
Characteristics of cases (patients with a diagnosis of schizophrenia or schizoaffective disorder who died by suicide, n = 84) and individually matched controls (patients with a diagnosis of schizophrenia or schizoaffective disorder who did not die by suicide, n = 84).

	Suicide cases	Controls
	n (%)	n (%)
Diagnosis		
Schizophrenia[a]	73 (87)	69 (82)
Schizoaffective disorder[b]	11 (13)	15 (18)
Age at diagnosis (years)		
18–34	52 (62)	54 (64)
35–44	19 (23)	18 (21)
45–64	13 (15)	12 (14)
Sex		
Men	45 (54)	50 (60)
Women	39 (46)	34 (40)
Age at onset of psychiatric symptoms		
<18 years	5 (6)	10 (12)
18–24 years	37 (44)	38 (45)
25–29 years	19 (23)	26 (31)
≥30 years	23 (27)	10 (12)
Education		
Primary school	23 (27)	29 (35)
Secondary school or higher	54 (64)	42 (50)
Unknown	7 (8)	13 (15)

[a] Diagnoses according to ICD-8: 295 (excluding 295.70); ICD-9: 295 (excluding 295H); ICD-10: F20.
[b] Diagnoses according to ICD-8: 295.70; ICD-9: 295H; ICD-10: F25.

Table 2
Odds ratios (OR) with 95% confidence intervals (CI) for the association between suicide and prescriptions of antipsychotics, antidepressants, and lithium.

	Suicide cases		Controls			
	n	(%)	n	(%)	OR (95% CI)	Adjusted OR (95% CI)[a]
Any antipsychotic[b]						
No	1	(1)	1	(1)	N/A	N/A
Yes	83	(99)	83	(99)		
Clozapine, olanzapine, risperidone, or ziprasidone						
No	72	(86)	64	(76)	Reference	Reference
Yes	12	(14)	20	(24)	0.33 (0.11–1.00)	0.29 (0.09–0.97)
Risperidone, olanzapine, or ziprasidone						
No	76	(90)	68	(81)	Reference	Reference
Yes	8	(10)	16	(19)	0.27 (0.08–0.98)	0.23 (0.06–0.89)
Clozapine						
No	78	(93)	76	(90)	Reference	Reference
Yes	6	(7)	8	(10)	0.67 (0.19–2.36)	0.75 (0.19–2.94)
Depot injection antipsychotic						
No	47	(56)	52	(62)	Reference	Reference
Yes	37	(44)	32	(38)	1.26 (0.69–2.31)	1.28 (0.68–2.40)
Any antidepressant[c]						
No	51	(61)	54	(64)	Reference	Reference
Yes	33	(39)	30	(36)	1.19 (0.61–2.31)	1.15 (0.58–2.28)
SSRI						
No	77	(92)	74	(88)	Reference	Reference
Yes	7	(8)	10	(12)	0.67 (0.24–1.87)	0.68 (0.23–2.00)
Lithium						
No	74	(88)	73	(87)	Reference	Reference
Yes	10	(12)	11	(13)	0.91 (0.39–2.14)	0.93 (0.38–2.24)

[a] Adjusted for sex, age at onset, and education.
[b] Alimemazine, dixyrazine, fluphenazine, flupentixol, haloperidol, clopenthixole, chlorpromazine, chlorprothixene, clozapine, levomepromazine, melperone, moperone, olanzapine, perphenazine, pericyazine, pimozide, pipotiazine, prochlorperazine, raclopride, remoxipride, reserpine, risperidone, sulpiride, thioridazine, trifluoperazine, ziprasidone, and zuclopenthixol.
[c] Amitriptyline, citalopram, fluoxetine, fluvoxamine, imipramine, clomipramine, lofepramin, maprotiline, mianserine, moclobemide, nortriptyline, paroxetine, sertraline, trimipramine, and venlafaxine.

Excluding the patients who had been prescribed clozapine did not change the association substantially (OR = 0.23, 95% CI 0.06–0.89). Although the point estimate was below unity for clozapine, the association was not statistically significant. There was no statistically significant association between depot-injection antipsychotics and suicide risk.

About one third of the cases and controls had a lifetime prescription of an antidepressant. A history of having been prescribed any type of antidepressant, SSRI or lithium did not affect the suicide risk significantly.

There was no statistically significant association when the number of recorded prescriptions of the drugs under study was examined. Restricting the exposure time to one month or one year before the completed suicide, and the corresponding time for the controls, did not show any statistically significant association (data not shown). An identical number of cases and controls were recorded as using any of the SGAs risperidone, ziprasidone or olanzapine in the last year (five cases and five controls) and last month (one case and one control) before the suicide. However, there was a slightly higher number of controls than suicide cases with a recorded use of clozapine in the last year (three cases and seven controls) and last month (one case and three controls). This corresponds to a non-significant lower suicide risk among clozapine users in the respective time periods (adjusted OR 0.38, 95% CI 0.07–1.93 and OR of 0.34, 95% CI 0.04–3.6).

4. Discussion

The main finding of this case–control study of suicide in schizophrenia was a lower suicide risk within five years from diagnosis among patients who had been prescribed a second generation antipsychotic. Neither a medication history of antidepressants nor lithium did affect the suicide risk. After adjusting the risk estimates for the potential confounders sex, education, and age at onset (Reutfors et al., 2009, 2010a), the main finding became more pronounced.

4.1. Strengths and limitations

A strength of this study is the use of a comprehensive national database to identify a total schizophrenia patient cohort from which the cases and controls were identified. This promotes the generalizability of the findings. The prospective registration of all data in the case records means that no recall bias occurred, and a differential validity of data between cases and controls is therefore unlikely. A potential bias in the collection of data was minimized by blinded data retrieval. The clinical diagnoses of schizophrenia reported to the patient register have been shown to have a high concordance with the corresponding diagnoses in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R or DSM-IV) (Ludvigsson et al., 2011).

A limitation of this study is that information about the patients' adherence to prescribed drugs was not systematically recorded. In our analyses we were also unable to assess the drug intake in the period near in time to the suicide, as we believe the data were not reliable. Many of the patients who committed suicide had not seen their psychiatrist in the time period near to the suicide and their current drug use was therefore not recorded. The same situation was found for the corresponding time period in the controls. This means that we could not know to what degree the patients were actually taking their prescribed drug at the time of suicide. If we assume a similar degree of medication non-adherence among subsequent suicide victims as among controls, our risk estimates associated with drug classes would likely be decreased, and may therefore be conservative. If, on the other hand, there was a differential non-adherence between cases and controls, the true associations with drug classes could be either higher or lower than those presented here. A further constraint was that the sample size did not allow the evaluation of suicide risk for each individual antipsychotic and antidepressant drug or co-medication with other psychotropic drugs. For the same reason, we were unable to assess the suicide risk associated with the various drugs separately for schizophrenia and schizoaffective disorder. Because of the complexity and frequent

changes in dosing regimens, we could not evaluate the relationship between drug dose and suicide risk.

When interpreting our results, one should also recognize the potential role of 'confounding by indication' inherent to observational studies of drug use and the effects thereof. This means that patients who are prescribed certain drugs can be assumed to be different than patients who have not received such treatment. In other words, prescription of SGAs may have been driven by unmeasured determinants of outcome so that other characteristics than the drug itself have made the suicide risk lower in users of SGAs.

4.2. Antipsychotics and suicide risk

Most of the previous studies suggesting a suicide lowering effect of SGAs concern clozapine. Meltzer and Okayli (1995) noted a decrease of suicidal behavior in an uncontrolled study of 88 treatment resistant patients with schizophrenia who were started on clozapine. In a subsequent randomized clinical trial, clozapine was compared with olanzapine in 980 patients with schizophrenia or schizoaffective disorder classified as having a high risk of suicide because of current suicidal thoughts or a previous suicide attempt (Meltzer et al., 2003). During an 18 month follow-up, there was less suicidal behavior in patients treated with clozapine compared with patients treated with olanzapine (HR 0.76, 95% CI 0.58–0.97), although five clozapine treated patients vs. three olanzapine-treated patients committed suicide. Among the few studies of completed suicide, a cohort study in Finland between 1996 and 2006 of 66,881 patients with schizophrenia, found that clozapine use was associated with a reduced suicide risk (HR 0.34, 95% CI 0.20–0.57) when compared with perphenazine use (Tiihonen et al., 2009). Comparable results of a significantly lower suicide rate among clozapine treated patients with schizophrenia (Reid et al., 1998) and during current clozapine use compared with periods of non-use have been reported (Walker et al., 1997). In contrast, however, Sernyak et al. (2001) reported no significantly lower suicide risk in 1415 patients with schizophrenia who were clozapine users when compared with a control group of 2830 patients with schizophrenia. Nevertheless, they did identify a lower overall mortality among clozapine users, and a limitation of the study was that they did not take into account when in the history of illness the patient had received clozapine (Meltzer, 2002).

Studies of the risk of completed suicide in relation to use of other SGAs than clozapine are few and comparisons of different SGAs have not yet revealed any significant differences in suicide risk, except for clozapine (Tiihonen et al., 2009; Strom et al., 2011). As for results from studies of suicidal behavior in general, an analysis of pooled data from seven randomized clinical trials of antipsychotics found no differences in suicidal behavior when comparing olanzapine, risperidone, and quetiapine (Khan et al., 2001), and there was no significant difference in the number of suicides in the treatment arms receiving an antipsychotic compared to those who had received placebo (Khan et al., 2001; Storosum et al., 2003). In the CATIE clinical trial there was no difference in the rates of suicide attempts or suicidal ideation between users of the first generation antipsychotic perphenazine and SGAs (Lieberman et al., 2005). One case–control study identified a lower risk of suicide attempts among users of risperidone and olanzapine (Barak et al., 2004); among 378 patients who attempted suicide, 16% were prescribed SGAs compared to 37% of the control group. Likewise, another study comparing 22 suicide attempters with 81 non-attempters found a significantly higher proportion of non-attempters to have used SGAs than the suicide attempters (Altamura et al., 2003).

4.3. Antidepressants and lithium

We found no association between antidepressant use and suicide risk. More than a third of both suicide cases and controls had been prescribed antidepressants which can be compared with a French study of 3474 patients with schizophrenia, of whom about 20% were using antidepressants (Montout et al., 2002). However, Roy (1982) reported that 14 out of 30 schizophrenia suicide cases had a history of drug treatment for depression compared to seven out of 30 controls, yielding a suicide preventive association for antidepressants ($p < 0.05$). Similarly, Tiihonen et al. (2012) found a significantly lower suicide risk among patients with schizophrenia with current vs. no antidepressant use. One reason for our contrasting result could be that we studied history of antidepressant use and that depressed patients at higher risk of suicide might have received antidepressants to a higher degree than patients without depression. If the depression was thereby alleviated, some suicides may have been prevented and such patients would then be found among the controls and not among the cases in our study.

Lithium was used relatively frequently in our study sample, and may have been prescribed mainly for patients with prominent mood swings. We did not find any effect on suicide risk by lithium use, although the absence of association should be interpreted with caution, as the same mechanisms as suggested for antidepressants may have been in effect also for lithium treatment.

4.4. Potential mechanisms

A possible suicide risk lowering effect of clozapine and other SGAs may have a number of pharmacological explanations. Although the pharmacological differences between first and second generation antipsychotics may not be clear cut, some of the SGAs (e.g. olanzapine, quetiapine, and clozapine) have appeared to show a better antidepressant effect in schizophrenia than first generation antipsychotics (Leucht et al., 2009). This may be important for suicide prevention, because hopelessness and depression are prominent risk factors for suicide in schizophrenia (Hawton et al., 2005; Pompili et al., 2009). It has also been suggested that a higher serotonergic effect in clozapine and certain other SGAs compared to first generation antipsychotics may reduce impulsivity, aggression, and suicidality (Ernst and Goldberg, 2004).

Another reason may be that SGAs may have fewer side effects than first generation antipsychotics according to a number of reports (Leucht et al., 2009). For example, clozapine has a low propensity to cause akathisia or tardive dyskinesia, which are side effects that according to case reports may increase suicidal behavior (Hawton et al., 2005; Aguilar and Siris, 2007). Psychomotor agitation, restlessness and insomnia are other factors which may entail increased suicide risk in schizophrenia (Hawton et al., 2005; Pompili et al., 2009). These factors may in certain situations be better treated by SGAs than by first generation antipsychotics to lower the risk for extrapyramidal symptoms (Mantovani et al., 2013) and to improve the quality of sleep (Miller, 2004). It is also possible that adherence to medication was higher among those prescribed clozapine and other SGAs. The frequent monitoring of clozapine patients may in itself be beneficial for lowering the suicide risk (Meltzer and Okayli, 1995; Walker et al., 1997). Nevertheless, as clozapine use carries a risk of other serious side effects limiting its use (Sernyak et al., 2001), a suicide risk lowering potential for other SGAs would be a great advantage. Because the suicide risk elevation in schizophrenia and other psychoses is most pronounced in the early phase of illness (Pompili et al., 2011), the choice of pharmacological treatment may exert its biggest influence on suicide risk in this period.

4.5. Conclusion

The results of our study indicate that in schizophrenia suicide risk is lower in patients who have used SGAs than in patients who have not. Since our study is observational, this finding may be due to a pharmacological effect, but also to other unmeasured characteristics of patients who are prescribed SGAs.

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Contributors

AE, JR, LB, and UÖ designed the study. The clinical records were scrutinized by JR in collaboration with EGJ. JR, SB and LB managed the data analyses. All authors took part in the interpretation of the results. JR managed the literature searches and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

JR has been a speaker for Eli Lilly, received unrestricted grant support from Schering-Plough, and has been in research collaboration with AstraZeneca and Janssen-Cilag for which grant support has been received by Karolinska Institutet. UÖ has received honoraria as a speaker or adviser or for attending congresses from AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Eli Lilly, and Pfizer, and grant supports from Bristol-Myers Squibb and Janssen-Cilag. The other authors report no financial or other relationship relevant to the subject of this article.

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