Schizophrenia Research 150 (2013) 416–420

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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

Johan Reutfors [a,*], Shahram Bahmanyar [a,b], Erik G. Jönsson [c], Lena Brandt [a], Robert Bodén [a,d], Anders Ekbom [a], Urban Ösby [e,f]

[a] Centre for Pharmacoepidemiology (CPE), Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
[b] Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran
[c] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[d] Department of Neuroscience, Psychiatry, Uppsala University, Uppsala, Sweden
[e] Department of Neurobiology, Care Sciences, and Society, Centre of Family Medicine (CeFAM), Karolinska Institutet, Stockholm, Sweden
[f] Department of Psychiatry, Tiohundra AB, Norrtälje, Sweden

ARTICLE INFO

Article history:
Received 16 June 2013
Received in revised form 28 August 2013
Accepted 9 September 2013
Available online 2 October 2013

Keywords:
Schizophrenia
Suicide
Case–control study
Antipsychotic drugs
Antidepressant drugs
Lithium

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

* Corresponding author at: Centre for Pharmacoepidemiology (CPE), Department of Medicine Solna, Karolinska Institutet, Karolinska University Hospital Solna, T2, SE-171 76 Stockholm, Sweden.
E-mail addresses: johan.reutfors@ki.se, johan@reutfors.se (J. Reutfors).

0920-9964/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.schres.2013.09.001

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.