Suicide in schizophrenia and adverse events during antipsychotic medication

ERIC CLAPHAM
Dissertation presented at Uppsala University to be publicly examined in H:son-Holmdahlsalen, Ingång 100, Akademiska sjukhuset, Uppsala, Wednesday, 23 November 2022 at 13:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Docent Ursula Werneke (Institutionen för klinisk vetenskap, Umeå universitet).

Abstract

This thesis considers side effects and other adverse events during treatment with antipsychotic medication. All included studies use an epidemiological methodology with data from Swedish population-based health registers. The first two studies utilise a nested case-control design, whereas the third and fourth studies rely on cohort designs.

The first study considers the impact of extrapyramidal symptoms on suicidality in a schizophrenia spectrum patient group in Stockholm County in Sweden. In this sample, extrapyramidal symptoms are found to be associated with a decreased risk of suicide.

The second study involves suicidal communication, blindly extracted from patient records, as risk factors for suicide among patients with schizophrenia spectrum disorders. More severe forms of suicidal ideation and behaviour, such as suicide attempt, are associated with a higher risk of death by suicide, which is consistent with current clinical practice regarding suicide risk assessments.

The third study considers the risk of bone fracture during treatment with antipsychotic medications. The study finds that risperidone is not associated with an increased risk of fracture compared with first-generation antipsychotics.

The fourth study considers the risk of perimyocarditis and heart failure during treatment with clozapine and the chemically similar medications olanzapine and quetiapine. It finds that clozapine is associated with a substantially elevated risk of perimyocarditis in the short term and a more modest risk of heart failure in the long term, compared with no antipsychotic treatment. Treatment with at least one of olanzapine or quetiapine is not found to be associated with an increased risk of these adverse cardiac events, compared with no antipsychotic medication.

Keywords: schizophrenia, antipsychotics, clozapine, suicide, osteoporosis, myocarditis

Eric Clapham, Psychiatry, Akademiska sjukhuset, Uppsala University, SE-751 85 Uppsala, Sweden.

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ISSN 1651-6206
URN urn:nbn:se:uu:diva-485764 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-485764)
For my parents
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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### Abbreviations

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<th>Description</th>
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<tr>
<td>aHR</td>
<td>Adjusted hazard ratio</td>
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<tr>
<td>aOR</td>
<td>Adjusted odds ratio</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DSM-III</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 3rd edition</td>
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<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 5th edition</td>
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<tr>
<td>EPS</td>
<td>Extrapyramidal symptoms</td>
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<td>FGA</td>
<td>First-generation antipsychotics</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>ICD-10</td>
<td>International Classification of Diseases, 10th revision</td>
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<td>NPR</td>
<td>National Patient Register</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PDR</td>
<td>Prescribed Drug Register</td>
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<td>SGA</td>
<td>Second-generation antipsychotics</td>
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<td>SD</td>
<td>Standard deviation</td>
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Introduction

Schizophrenia is a serious mental disorder with an estimated global point prevalence of just below 0.5% and a lifetime morbid risk of approximately 0.7% (1). The disorder is chronic and associated with significant individual suffering and societal cost (2). For a minority, the disorder has a favourable course, but the majority experiences significant difficulties in relation to activities of daily living, social relationships and work life (3). Cardiac disease is considered the single most important reason why average lifespan in schizophrenia is reduced by ten to twenty-five years (4).

Antipsychotic medication is a mainstay of treatment in schizophrenia and related disorders (5). The effect on overall symptoms in the acute phase of schizophrenia approaches moderate, based on evidence from a meta-analysis of randomised controlled trials (6). Evidence from observational studies indicates that antipsychotic treatment in schizophrenia is associated with a reduced risk of mental and physical health events, in particular reduced mortality, including death by suicide (7, 8), as well as psychotic relapse (9). However, there are substantial differences in individual responses (6). Treatment with antipsychotic medication is also associated with several adverse effects (10, 11).

Clozapine is the only antipsychotic medication indicated for treatment of refractory schizophrenia (12), which may be defined as unsatisfactory effect of at least two other antipsychotic medications at therapeutic doses for a sufficient time (5). It has been estimated that between one third and half of all individuals with schizophrenia may meet criteria for therapy resistance (13). Among those who initiate clozapine, some 40% tend to respond, in the sense of having a clinically relevant overall symptom reduction as measured on the Positive and Negative Syndrome Scale (14). Use of clozapine appears to be less widespread than expected given its indication and this may partly be related to the side effect profile, which includes a risk of agranulocytosis (5).

Schizophrenia spectrum disorders

While conditions such as mania and depression can be recognised in ancient texts, schizophrenia has a far shorter recorded history (15). Case studies by the physicians John Haslam and Philippe Pinel, both published in 1809, may
be considered the first descriptions of what today would be referred to as schizophrenia (15). There are many possible explanations for this, one being that with the expansion of mental hospitals from the late 18th century onwards, new opportunities arose to closely observe individuals over time.

Emil Kraepelin began using the term dementia praecox in 1893 and in 1899 presented a definite conceptualisation including the three subtypes catatonic, hebephrenic and paranoid dementia praecox (16). Previously, these subtypes had been introduced as separate syndromes by Karl Ludwig Kahlbaum, his disciple Ewald Hecker and Emil Kraepelin himself, respectively (16).

In 1899, Kraepelin also presented the so-called Kraepelinian dichotomy (17), which contrasted dementia praecox to manodepressive illness (now referred to as bipolar disorder), where the former was held to have an unfavourable long-term course and the latter a more favourable one.

Eugen Bleuler deemphasised poor outcome in favour of disassociation and negative symptoms (18) and suggested the term schizophrenia for the disorder in 1908. This gradually replaced dementia praecox (19). Kurt Schneider later focused on reality distortion and a subset of psychotic symptoms deemed central to schizophrenia, referred to as first rank symptoms. Kraepelin, Bleuler and Schneider represent the three major roots of the schizophrenia concept (18).

In the early 1970s, it was observed that the United States used a substantially wider schizophrenia concept than the United Kingdom (18). This influenced the more narrow definition of schizophrenia in the third edition of the Diagnostic and Statistical Manual (DSM-III) published by the American Psychiatric Association in 1980 (18).

The fifth edition of the Diagnostic and Statistical Manual (DSM-5) from 2013 requires at least two psychotic symptoms (hallucinations, delusions, disorganised speech, disorganised or catatonic behaviour, negative symptoms), among which at least one must be a psychotic core symptom (hallucinations, delusions, disorganised speech). They must be present for six months, out of which at least one month in full form, unless treatment was initiated earlier. In the DSM-5, subtypes of schizophrenia are abolished and catatonia is no longer viewed as a specific symptom of schizophrenia. Further, first rank symptoms are no longer given special status (18).

Schizophrenia is typically conceptualised as one of several schizophrenia spectrum disorders. This spectrum also includes, for instance, schizoaffective disorder, which involves a mandatory mood component. It was originally conceptualised by the American psychiatrist Jacob Kasanin in the 1930s and is included in the DSM system (20). Unlike in bipolar disorder, psychotic symptoms may occur outside mood episodes. The DSM system also includes the diagnosis schizophreniform disorder (21). This disorder has the same symptomatology as schizophrenia, but does not necessarily involve functional impairment, and has a duration of at least one month and at most six months.
Suicide in schizophrenia

Bleuler, who gave the disorder schizophrenia its modern name, characterised the suicidal drive as ‘the most serious of all schizophrenic symptoms’ (22). The lifetime suicide risk in schizophrenia is estimated to be approximately 5% (23).

It has been argued that identification of risk factors for suicide in individuals diagnosed with schizophrenia is imperative to improve clinical management and develop strategies to reduce the incidence of suicide (24). Although the proper use of established risk factors in routine clinical practice is the subject of some debate (25), evaluation of suicide risk is typically viewed as important (26).

Given the increased risk of suicide in schizophrenia, it is of practical value to find risk factors that are associated with suicide (27). The most important risk factors, according to a systematic review published in 2014, are affective symptoms, a higher number of psychiatric admissions and a history of suicide attempt (24).

Suicidal ideation and suicide attempt remain incompletely understood as risk factors for completed suicide in schizophrenia. However, the status of suicide attempt as a major risk factor for suicide in schizophrenia was underlined by a prospective study including over 18,000 schizophrenia patients (28).

Regarding suicidal ideation as a risk factor in schizophrenia, the picture is less consistent. A meta-study of inpatient suicides across diagnostic categories reported a modest association between expressed suicidal ideation and subsequent suicide, but argued that the result could be due to publication bias (29). Another meta-analysis of suicidal ideation as a risk factor for suicide considered mood disorders and schizophrenia separately (30). It was found that suicidal ideation as a risk factor for suicide was insignificant in mood disorders, but significant in schizophrenia. However, the authors suggested that the result should be interpreted cautiously, due to between-study heterogeneity and because studies that used stronger methods of reporting had a weaker association between suicidal ideation and suicide. Further, a history of suicidal ideation was identified as a risk factor in a meta-analysis of suicide in schizophrenia, but was not included among the most robust findings due to a small number of studies (27). Suicide ideation may thus have a weaker association with suicide in schizophrenia compared with a history of suicide attempt.

Few published works have included suicidal ideation and suicide attempt as risk factors for suicide in schizophrenia over time, but several studies have explored the impact of having a history (27, 30). However, recent suicidal ideation appeared to be more strongly associated with suicide than past suicidal ideation (odds ratio (OR) 29.8 vs. 3.3) in patients with schizophrenia, as reported by a meta-analysis involving small and mostly mixed study samples (27). Suicidal ideation and suicide attempt within one month before hospital
admission, but not during hospitalisation, were found to be significant risk factors for completed suicide in a case-control study of suicide among Chinese inpatients with schizophrenia (31). However, suicide attempt ever and during the preceding year were not identified as potential risk factors for completed suicide in a Danish cohort study of first-episode psychosis including seven suicides (32); this is likely related to the limited number of suicide cases.

Risk of suicide may in clinical practice be assessed using among other things a suicide inquiry, which typically involves stepwise questioning, beginning with, e.g., feelings of hopelessness or thoughts of death and gradually progressing to suicide attempt (33). Such a sequence of gradually more serious communication of suicidality has been called the suicidal ladder (34, 35); that term has frequently been used in Sweden. Instruments used to determine the prevalence of suicidality or to assess suicide risk may involve a hierarchy similar to the suicidal ladder, examples being the Beck Scale of Suicide Ideation (36) and the Paykel questionnaire (37).

**Antipsychotic medication**

The first antipsychotic medication was chlorpromazine, which was synthesised by the chemist Paul Charpentier in December 1950, while working for the French pharmaceutical company Rhone-Poulenc (38). The French surgeon Henri Laborit was the first to recognise the psychiatric potential of the new compound, which was originally intended for potentiation of anaesthesia (39). The psychiatrists Jean Delay and Pierre Deniker made crucial contributions towards introducing chlorpromazine into psychiatry (38). Chlorpromazine came into clinical use globally in the 1950s. Psychiatrists at the time were impressed by the effect of chlorpromazine and no clinical trials were conducted initially; it was only in the early 1960s that major placebo-controlled, double-blind randomised trials were implemented (6). It has been argued that chlorpromazine was central in making psychopharmacology an established discipline (39).

During the decades following the synthesis of chlorpromazine, a substantial number of additional antipsychotic medications were introduced. From 1975, there was a longer hiatus that was broken following the reintroduction of clozapine in 1990 (40). The newer medications that followed are often referred to as second-generation antipsychotics (SGA), while the earlier medications are referred to as first-generation antipsychotics (FGA). An alternative terminology is typical and atypical antipsychotics for FGA and SGA, respectively.

Both FGA and SGA have considerable chemical diversity. The main, largely undisputed difference between the two groups is that they were introduced on the market at different times. Evidence from a meta-analysis suggests that differences in the side effect profile of antipsychotic medications
are more pronounced than efficacy differences (41). All established antipsychotic medications have antidopaminergic effects and block postsynaptic D2 receptors (6).

The introduction of SGA led to substantial research and debate, where the conclusion in the 2000s was that SGA, on the whole, produced fewer movement-related side effects but more metabolic side effects and that some SGA are modestly more efficacious than FGA (42). However, this conclusion has been called into question, not least due to several exceptions in both groups. An alternative interpretation of the available evidence is that SGA are typically preferable, but that the substantial group of FGA, which are often less well-researched, may contain interesting candidates for further investigation (42, 43).

**Clozapine**

The substance imipramine was originally intended as an antipsychotic medication, but proved ineffective in this regard. Following observations made during clinical trials, it was instead launched as the first so-called tricyclic antidepressant. Research continued at the Swiss pharmaceutical company Wander AG and, in 1958, clozapine was synthesised based on the chemical structure of imipramine (44). Introduction to the market was delayed – among other things due to the absence of movement disorders, which at the time were widely believed to be necessary for antipsychotic effectiveness (44). Clozapine was finally launched in several European countries, starting in 1972 (44). However, following a case series of agranulocytosis from Finland, published in *The Lancet* in 1975 (45), clozapine was withdrawn from the market. An exception was made for so-called compassionate use, which meant that the medication continued to be used on a small scale in Europe for instance. The seminal contribution by Kane and collaborators (46), published in 1988, showed that clozapine was significantly superior to chlorpromazine in therapy-refractory schizophrenia. This lead to the reintroduction of clozapine with an indication of therapy-refractory schizophrenia.

The risk of agranulocytosis is now largely controlled through mandatory blood monitoring. As a result, other side effects have been given more attention. Myocarditis is perhaps foremost among them. This side effect was first described in a case report from 1980 and from the late 1990s began to be viewed by some as potentially more common than previously thought (47).

Clozapine has been referred to as the prototypical atypical antipsychotic (43) and has served as a model for some SGA. For instance, the widely used antipsychotic olanzapine was found among substances synthesised as chemical analogues of clozapine that would not require blood testing and was approved for market release in 1996 (48). Quetiapine is another antipsychotic
that is chemically similar to clozapine. It was synthesised in 1985 and approved in the late 1990s (49). Olanzapine and quetiapine have wider application than clozapine and have official indications related to bipolar disorder and depression as well as schizophrenia and various off-label uses (50, 51).

**Extrapyramidal side effects**

Continuous antipsychotic medication is a mainstay of treatment in schizophrenia but may give rise to occasionally troublesome side effects. In particular, treatment with antipsychotic drugs may lead to the development of movement disorders. These conditions are typically divided into acute side effects, such as extrapyramidal symptoms (EPS), and later onset side effects, such as tardive dyskinesia and tardive dystonia (52).

Acute dystonia and parkinsonism are among the motor syndromes that may occur as acute EPS. Parkinsonism is characterised by bradykinesia, rigidity and tremor (53). Akathisia is a syndrome of inner restlessness, which also may have physical manifestations such as pacing and lifting the feet as if marching in place (54). EPS are often defined as including akathisia, but this may also be considered a separate movement disorder, since it may have a separate underlying neural mechanism (55, 56).

Although a possible link between antipsychotic side effects and suicide in schizophrenia has been discussed in the literature, the relationship is not well understood. A few case reports and case series have suggested associations between akathisia and higher suicide risk (57). An association has also been found between a higher score on the Extrapyramidal Symptom Rating Scale and suicide attempt among patients treated with olanzapine or clozapine (58). In a recent follow-up of patients with first-episode schizophrenia, suicidal ideation was significantly associated with clinician-observed akathisia (59). However, a study comprising 90 patients with treatment-resistant schizophrenia found no association between akathisia or parkinsonism and suicidality (53). This is in line with a systematic review from 2021 that found very few studies of this, but concluded that there was no clear link between akathisia and suicidal behaviour during treatment with antipsychotic mediation and also emphasised the need for further research (60). Akathisia and parkinsonian symptoms were not included in a meta-analysis from 2013 of risk factors for completed suicide in schizophrenia due to lack of available studies (27). Thus, improved understanding of antipsychotic side effects as risk factors for suicide in schizophrenia is desirable.
Hyperprolactinemia

Hyperprolactinemia is another side effect of antipsychotic medication that, like EPS, is due to dopaminergic receptor blockade. The antidopaminergic mechanism affects the tubero-infundibular pathway such that the inhibition of the secretion of the hormone prolactin from the anterior pituitary is reduced; causing elevated levels of circulating prolactin (61).

An association exists between reduced bone mineral density and increased prolactin levels (62). Further, there may be a link between prolactin levels and an elevated risk of osteoporosis-related fractures, as indicated by some epidemiological studies (61, 63). Risperidone, a second-generation or atypical antipsychotic medication, is associated with a larger and more frequent increase of blood prolactin level compared with other SGA (64, 65). As a result, it has been discussed whether risperidone may confer an elevated risk of osteoporosis-related fractures.

The risk for fractures might also be elevated among users of antipsychotics for reasons other than osteoporosis induced by hyperprolactinemia. Other side effects of antipsychotics, such as somnolence, postural hypotension, motor and sensory instability, may lead to falls and, consequently, fractures or other injuries (66), as well as comorbid somatic illnesses. Such comorbid illnesses may include diabetes mellitus type 2 and cerebrovascular disease as long-term consequences of metabolic side effects; an association between cerebrovascular disease and osteoporosis is suggested by epidemiological studies (67) and the risk of fracture is increased in patients with diabetes mellitus type 2 (68).

The importance of antipsychotic-induced hyperprolactinemia in bone mineral loss remains uncertain (69). While use of antipsychotics has been associated with increased risk of fracture in some epidemiological studies (70-72), the precise role of prolactin-elevating drugs has not been disentangled from those of other factors contributing to osteoporosis and fracture (73).

A review and meta-analysis of the relationship between antipsychotics and fractures included 19 observational studies, the majority of which involved hip fractures among older people (70). The meta-analysis included studies covering six antipsychotics (chlorpromazine, haloperidol, olanzapine, quetiapine, risperidone and thioridazine). Risperidone was associated with the lowest fracture risk, with small differences between atypical antipsychotics. Further, a recently published Danish population-based cohort study of patients aged 65 years or more did not find any significant differences in risk between the included atypical antipsychotics (risperidone, olanzapine and quetiapine) (72). Moreover, another Danish population-based cohort study on the risk of hip fracture among patients with schizophrenia did not find an association with any specific antipsychotic drug (71). Thus, the literature remains inconsistent regarding the association between exposure to antidopaminergic drugs and osteoporosis-related fractures.
**Myocarditis**

Cardiovascular disease is considered the single most important reason why the average lifespan in schizophrenia is reduced by ten to twenty-five years compared with the general population (4). In addition to potentially increasing the risk of ischemic heart disease in the long term via weight gain and diabetes mellitus, treatment with the antipsychotic clozapine and possibly other antipsychotic agents is associated with the feared and sometimes fatal side effect myocarditis. However, knowledge of myocarditis as a side effect of antipsychotic treatment is incomplete. Clozapine may be associated with pericarditis (74, 75) and there may also be an association with the longer term outcome of heart failure (76). The term perimyocarditis can be used in reference to a condition with pericarditis and myocarditis.

As already mentioned, clozapine is generally considered to be the most effective antipsychotic and is primarily indicated in treatment-refractory schizophrenia (77). Moreover, clozapine is believed to have anti-suicidal properties (78-80). While indisputably having significant effectiveness, clozapine has also been associated with some significant side effects, such as myocarditis.

A systematic review found approximately 250 published case studies on clozapine-associated myocarditis, with the first published in 1980 (47). One example was an uncontrolled study of 503 patients who had initiated treatment with clozapine during the course of six years at a psychiatric clinic in Australia, with results suggesting that myocarditis was a clinically important side effect during treatment with clozapine (81). In particular, there were 10 cases of sudden death and 14 cases of myocarditis, corresponding to incidence rates of 2% and 3%, respectively. Another Australian study comprising 129 patients who had initiated treatment with clozapine, noted an association between current treatment with a selective serotonin reuptake inhibitor antidepressant and myocarditis during clozapine treatment (82). This study reported a myocarditis incidence rate of 3.88% (82). Results – mainly from Australia – have suggested that myocarditis is a commonly overlooked side effect (47). A recent systematic review and meta-analysis found that myocarditis occurred in 7 out of 1,000 people treated with clozapine, but with higher figures from Australia, indicating a possible surveillance bias (83). A Danish population-based study did not find an increased incidence of myocarditis during clozapine treatment compared with other antipsychotic medications (84).

Clozapine-associated myocarditis is a non-infectious heart muscle inflammation. It often appears during the first month of treatment with clozapine, but may occur at any time. The etiology is not fully understood, but this may be an immunoglobulin E-mediated super-sensitivity syndrome, as up to two thirds of clozapine patients with myocarditis have hypereosinophilia (85).

The widely used antipsychotics olanzapine and quetiapine are chemically similar to clozapine and have also been associated with myocarditis in some
case studies (86-88). The incidence rates of myocarditis in olanzapine- and quetiapine-treated patients are not well-documented.

In Sweden, a total of 6,266 patients were prescribed clozapine in 2016, whereas 37,787 and 39,903 were prescribed olanzapine and quetiapine during the same year. A total of 148,957 individuals were prescribed at least one antipsychotic during that year (89). A study of treatment with clozapine in seventeen countries published in 2017 found a tendency towards increased rates of prescription and prevalence that varied from just below 120 per 100,000 in New Zealand to slightly less than 190 per 100,000 in Finland (90). Thus, as a considerable number of patients are treated with olanzapine and clozapine, meaning that a low incidence, yet severe, side effect like myocarditis may create an important issue.
The general aim is to study suicide in schizophrenia and adverse events in the presence of antipsychotic medication. The specific aims of each paper are listed below.

I Investigate suicidal ideation and behaviour as risk factors for subsequent suicide among schizophrenia spectrum patients. Analyse data retrieved from patient records using a population-based approach to study the relationship between suicidal ideation or behaviour and suicide.

II Improve understanding of antipsychotic side effects as a risk factor for suicide among schizophrenia spectrum patients. Analyse data retrieved from patient records using a population-based approach to study the relationship between extrapyramidal symptoms and suicide.

III Compare the risk of osteoporosis-related fractures among patients treated with different types of antipsychotics. Analyse data from Swedish health registers to study the relative risk of osteoporosis-related fractures during antipsychotic treatment.

IV Study the risk of perimyocarditis and heart failure during treatment with clozapine and chemically similar antipsychotics. Analyse data from Swedish health registers to study the risk of perimyocarditis and heart failure during treatment with clozapine, olanzapine, or quetiapine.
Methods

Setting
The thesis is based on an epidemiological research approach and all studies were conducted in Sweden.

Data sources
The thesis uses Swedish population-based health registers. Data can be linked between registers using the unique personal identification number assigned to a Swedish resident at birth or immigration (91).

The Prescribed Drug Register (PDR) provides information on exposure to antipsychotics and other types of medication. The register contains information on all dispensed drugs at Swedish pharmacies since July 2005 (92) and includes information on Anatomical Therapeutic Chemical classification, quantity and dates of dispensing. The medical indication of the drug is not included in the register. The PDR does not include drugs administered during hospitalisation.

The National Patient Register (NPR) provides information on inpatient discharge diagnoses, which have been recorded since 1964 with complete national coverage from 1987 (93). Information on outpatient visits to hospital (specialist care) is registered as of 2001 and coverage improved during the following years. Since 1997, diagnoses have been coded in accordance with the International Classification of Disease, 10th revision (ICD-10). The quality of the register has been claimed to be high (93). The register has been used in the studies included in the thesis to find, e.g., individuals discharged with a schizophrenia spectrum diagnosis or who suffered an osteoporosis-related fracture.

The Cause of Death Register (94) and the Register of Population and Population Changes provide information on important covariates and censoring variables. The Swedish Cancer Register (95) was used to exclude individuals with cancer in Study III.

Studies I and II also used information blindly extracted from patient records.
Study design

Studies I and II used a case-control design with matched controls. Studies III and IV relied on a cohort design. Study IV also incorporated time-dependent exposure to medication.

Studies I and II

(I. Suicide risk and antipsychotic side effects in schizophrenia. II. Suicidal ideation and behaviour as risk factors for subsequent suicide in schizophrenia.)

The first two studies used the same population-based dataset and considered risk factors for suicide in schizophrenia using a nested case-control study design. The dataset comprised 84 suicide victims with schizophrenia spectrum disorders and matched controls. The cases died by suicide within five years of diagnosis. They were taken from a cohort of all patients discharged for the first time from psychiatric hospitals in Stockholm County, Sweden, with a diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder. In addition to information from the NPR, the study also comprised data from clinical records. In the analysis of risk factors, multivariate conditional logistic regression was used.

The first study considered antipsychotic side effects as risk factors for suicide in schizophrenia. In particular, akathisia, extrapyramidal side effects and anti-cholinergic medication were considered.

The second study considered suicidal ideation and behaviour as risk factors for suicide in schizophrenia. Suicidal ideation and behaviour were classified as thoughts of death, thoughts of suicide, suicide plan or suicide attempt.

Study III

(Exposure to risperidone versus other antipsychotics and risk of osteoporosis-related fractures: A population-based study.)

The third and fourth study used the same population-based dataset and cohort study designs to explore the association between use of antipsychotic medication and side effects. Osteoporosis-related fractures and primarily selected cardiac adverse events were considered in particular.

The studies used data from national longitudinal population-based registers in Sweden. Data from 2006 are available at the Centre for Clinical Epidemi-
ology at the Karolinska Institutet and necessary ethical approvals were obtained. Both studies used data extracted from the NPR, the PDR and the Cause of Death Register.

The third study included three sub-cohorts with different antipsychotic exposures, namely risperidone, any other atypical antipsychotics (except paliperidone, the active metabolite of risperidone) or typical antipsychotics.

Cases of newly diagnosed fractures, which met an empirical definition of being osteoporosis-related, were identified based on the presence of a diagnosis in the NPR, coded in accordance with ICD. The incidence rates of fractures were estimated for the three exposure groups based on the person-time of the total cohort follow-up, as well as the person-time of active treatment exposure follow-up.

The primary outcome was non-open hip/femur fractures. An inpatient diagnosis was required for defining hip/femur fractures. Osteoporosis-related fractures were empirically defined as non-open fractures that occurred in the absence of major traumas or bone metastases. Non-hip/femur fractures were the secondary outcome and defined as fractures in the spine, rib, clavicle, humerus, radius/ulna, wrist, pelvis or tibia/fibula. Non-hip/femur fractures were identified from both inpatient (including emergency room) and outpatient diagnoses recorded in the NPR.

Study IV

(Exploring the risk of perimyocarditis and heart failure during treatment with clozapine, olanzapine, and quetiapine.)

The fourth study considered cardiac adverse events, in particular perimyocarditis, comprising myocarditis and pericarditis, and heart failure, during treatment primarily with the antipsychotic medication clozapine. However, the chemically similar antipsychotics olanzapine and quetiapine were also included. The fourth study was based on an updated version of the cohort in the third study, adding another five years of data.

The focus in Study IV was on a shorter time span, as perimyocarditis often occurs early in treatment, but a longer-term analyses was also included. The aim of the study was to map the relative risk of perimyocarditis and heart failure as side effects of treatment with clozapine, olanzapine and quetiapine.

The main cohort included all individuals aged 16–75 years who were prescribed a new antipsychotic. A limited cohort comprised individuals who were aged 15–55 years and had a schizophrenia spectrum disorder, defined as a diagnosis of schizophrenia, schizoaffective disorder, or unspecified non-organic psychosis (ICD-10: F20, F25 or F29), prior to filling the first prescription of the new antipsychotic.
Clozapine is primarily used by patients with schizophrenia spectrum disorders. However, it also has an indication for psychosis in Parkinson’s disease and is sometimes used off-label for other patient groups, such as individuals with psychiatric disorders and high risk of suicide or refractory bipolar disorder. Hence, analyses were also performed for a larger cohort.

Both olanzapine and quetiapine are widely used outside the schizophrenia spectrum patient group. In addition, the incidence of perimyocarditis is expected to be substantially lower for these substances than for clozapine, making it desirable to cast the net more widely in order to obtain as large a cohort as possible to increase statistical power.

Short-term and long-term cardiac adverse events were included in the study. The short-term outcome was perimyocarditis within two months. The long-term outcome was heart failure within three years.

Somatic covariates that were controlled for included sex and age, as well as identified risk factors for myocarditis, cardiomyopathy and heart failure. Psychiatric covariates that were controlled for included presence of anti-psychotic polypharmacy and depot injections.

Statistical analyses

Studies I and II were case-control studies which used logistic regression to compute unadjusted and adjusted odds ratios (OR and aOR) as well as 95% confidence intervals (CIs). As the study involved matched controls, a conditional logistic regression approach was used.

Studies III and IV were cohort studies using Cox regressions to compute unadjusted and adjusted hazard ratios (HRs and aHRs) as well as 95% CIs. Study III relied on a conventional Cox proportional hazard approach. However, Study IV used a time-dependent exposure approach, where exposure to medication type could change over time. Therefore, the conventional Cox proportional hazard model could not be used. It is, from a theoretical viewpoint, straightforward to extend the Cox model to include both time-varying coefficients and a time-varying exposure, but the computational burden is noticeably increased. In Study IV, exposure was time-varying, while the coefficient was constant. The robust sandwich estimator was used to compute coefficient variances.
Ethical considerations

All studies have been approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr 2011/1358-31/3, 2012/262-32 and 2017/1236-31/2).

As all studies were based on available register data, no individual was subjected to any type of further intervention. All study results were reported in aggregate form, meaning that no individual persons are identifiable.

The type of non-interventional, register-based epidemiological studies that are included in the thesis are typically thought not to give rise to major ethical challenges, at least not from a narrow medical perspective. Exceptions may exist, such as when the study question in itself is controversial, but the nature of the controversy is then likely to diverge from that seen in interventional experimental studies. Nonetheless, the present studies involved groups of individuals who may be vulnerable and subject to societal stigmatisation. This underscores the ever-present need to use correct and respectful terminology, for instance when referring to patient groups and outcomes.

The existence of population-based registers with highly sensitive data could obviously have significant ethical implications if the data are misused for purposes unrelated to scientific research, either at a central level or for a specific extracted dataset. A deeper discussion of this is deemed to be beyond the scope of the thesis.

In Studies I and II, a dataset was extracted from medical records, in addition to register data. Following approval by the ethics committee and the heads of department where the patients were treated, the medical records were made available for research. They were reviewed manually, in blocks of matched case-control pairs. Data were anonymized and then transferred to a spreadsheet (96).
Summary of results

Study I
The key finding of Study I was that a history of EPS was associated with a statistically significant lower risk of suicide (aOR 0.33, 95% CI 0.12–0.94). A history of akathisia was associated with a non-significantly higher risk of suicide (aOR 1.29; CI 0.44–3.33). Further, a history of treatment with an anticholinergic drug was associated with a non-significantly lower risk of suicide (aOR 0.77; CI 0.33–1.80).

There could be several different reasons for the key finding of an association between EPS and lower rate of completed suicidality. Potential explanations include more antipsychotic polypharmacy among controls, higher average antipsychotic dosage among controls and greater adherence among controls. More specifically, antipsychotic polypharmacy is believed to increase the risk of side effects, including EPS (97). A higher dosage is generally more likely to produce EPS and a lower dose of prescribed antipsychotic medication among suicide cases has been found in a limited number of case-control studies (98-100), although reviews of the association between antipsychotic dosage and suicidal behaviour in schizophrenia have not consistently found this result (101, 102). Adherence to a prescribed antipsychotic medication is more likely to produce EPS and there is also evidence that adherence is associated with lower suicide risk in schizophrenia (27).

Study II
The key result of Study II was that a suicide attempt was strongly associated with suicide in the following year (aOR 9.9, CI 2.5–39.0). Notes of suicidal thoughts in medical records were associated with suicide both overall (aOR 2.3, 95% CI 1.1–4.9) and in the following year (aOR 5.3, 95% CI 2.1–13.2). Further, indications in medical records of a suicide plan were also associated with suicide in the following year (aOR 6.2, 95% CI 1.3–29.1). For all types of suicidal ideation and behaviour, the numerical value of the OR was higher for shorter time periods.

An important finding in the study was the declining association between suicidality and future completed suicide over time. For comparison, among
individuals in a Swedish population-based cohort study who had made a suicide attempt requiring inpatient care (103), a high proportion of suicides in all diagnostic categories, including schizophrenia, took place within the first year of follow-up. It may be desirable to consider not just a history of suicidality, but also its timing, to better evaluate suicide risk.

Study III

The major finding of Study III was the absence of clinically important associations between different antipsychotic drug exposures and osteoporosis-related fractures.

More specifically, there was no statistically significant difference in the risk of fracture for risperidone compared with other atypical antipsychotics (aHR 1.04; 95% CI 0.91–1.19) for the primary outcome of non-open hip/femur fractures. For typical antipsychotics, there was a modest statistically significant higher risk (aHR 1.24; 95% CI 1.07–1.45), compared with other atypical antipsychotics. Further, regarding the secondary outcome of non-hip/femur fractures, there were no statistically significant differences for risperidone or other atypical antipsychotics compared with atypical antipsychotics.

In addition, age-stratified analyses were performed. For the primary outcome, the risk increase for typical antipsychotics compared with other atypical antipsychotics remained statistically significant for the age groups 45–64 years (aHR 1.56; 95% CI 1.05–2.32) and ≥65 years (aHR 1.21; 95% CI 1.03–1.43). For the secondary outcome, and comparing typical antipsychotics with other atypical antipsychotics, the age-stratified analysis showed a somewhat increased risk in the age group ≥65 years (aHR 1.19; 95% CI 1.01–1.40). No significant results were found for risperidone in the age-stratified analyses.

Osteoporosis-related fractures can arise as a result of several different causal mechanisms. Multiple risk factors are linked to osteoporosis-related fractures, such as age, female sex, lifestyle, certain diseases and medications. As a result, it may be difficult to find the specific risk contribution of risperidone or other prolactin-increasing agents. However, several potential confounding factors were considered and those that met a predetermined change-in-estimate criterion were included. There was a moderately increased fracture risk for typical antipsychotics in some cases, but not for risperidone compared with other atypical antipsychotics. The risk increase noted for typical antipsychotics may be related to residual confounding.
Study IV

Study IV involved analyses for both the full cohort and a schizophrenia cohort. Treatment with clozapine was found to be associated with a clearly increased risk of perimyocarditis within two months compared with no antipsychotic treatment in both the full cohort (aHR 3.40; 95% CI 1.59–7.25) and the schizophrenia cohort (aHR 5.38; 95% CI 1.20–24.08) compared with no antipsychotic treatment. However, results for treatment with at least one of olanzapine and quetiapine were not statistically significantly different compared with no antipsychotic treatment.

The risk of heart failure within three years was also analysed. The risk was elevated for the full cohort (aHR 1.33; 95% CI 1.06–1.67), but results were not statistically significant for the schizophrenia cohort compared with no antipsychotic treatment. Results were also not statistically significant for treatment with at least one of olanzapine and quetiapine, compared with no antipsychotic treatment.
Discussion and conclusions

The studies in this thesis have explored suicide in schizophrenia and adverse events during antipsychotic treatment.

Study I found an inverse relationship between EPS and suicide. The relationship between EPS and suicidality began to be discussed decades ago, but a definitive conclusion remains elusive. Study I is consistent with the notion that EPS do not necessarily imply an acute risk of suicidality.

Study II found that suicidal ideation and behaviour that is more recent and conventionally viewed as more serious are associated with a higher risk of completed suicide. This is largely in line with current clinical practice.

Study III did not find that risperidone was associated with an increased risk of osteoporotic fractures compared with FGA. The consequences of prolactin-elevating antipsychotics for bone health have been the subject of considerable debate. The underlying theoretical argument that prolactin elevation should promote bone demineralisation over the long term appears solid. The question is arguably more about degree, time frame and importance relative to other circumstances that increase the risk of osteoporosis and bone fracture. An antipsychotic with sedative properties or leading to postural hypotension might increase falls and thus risk of fractures, especially among individuals who already have osteoporosis. There might be subgroups where prolactin elevation is a more relevant risk for osteoporosis-related fractures.

Study IV found a clear association between increased risk of perimyocarditis within two months and use of clozapine. This was true in both the full cohort and the schizophrenia cohort. This is in line with evidence accumulated since the first case study on myocarditis during clozapine treatment was published in 1980 (47). However, the cumulative incidence was lower than in some clinical surveillance programmes, especially in Australia, which have indicated a risk of around 3% (83).

Strengths and limitations

The included studies are observational, where the first two used a case-control design and the last two were based on a cohort design. Regarding their strengths and limitations, many aspects could be discussed. A few points will be reviewed in the following.
The strengths of the studies include their population-based design using Swedish health registers, which are typically considered to provide data of high quality (92, 93). Hence, the study subjects should be representative of the population they belonged to, thereby reducing the risk of biased results.

Observational studies by definition do not randomise subjects to different exposures, but instead record exposures that have occurred. Differences in outcome may therefore be the result of systematic differences in the characteristics of those who were exposed and unexposed, rather than the exposure in itself. The risk of such confounding may be managed using a variety of design approaches and statistical techniques but cannot be eliminated. The two cohort studies relied on a substantial dataset, which generated sufficient statistical power to control for several potential confounding variables. In the smaller case-control studies, the possibilities of such statistical adjustments were more limited, although the greater homogeneity of study subjects may have reduced the risk of significant confounding.

A particular type of confounding is confounding by indication (104). In the context of pharmacoepidemiology, this may for instance arise when an individual is prescribed a specific medication for reasons related to the outcome. Attempts have been made to limit the extent of confounding by indication through consistent multivariate adjustment in regression analyses. Studies I and II used matched controls. Study III included substantial age-stratified analyses. Study IV included variables likely to be related to disease severity, such as presence of long-acting injections. However, a certain extent of residual confounding probably remained.

The third and fourth study crucially relied on the PDR to track use of especially antipsychotic medication. However, this register only includes prescriptions filled and thus contains no information about whether or not the medication was actually taken. Hence, bias may be introduced if the probability to take a medication systematically varies between patients prescribed different types of antipsychotic medication. In particular, if filling prescriptions of medication A is more likely to be associated with an outcome in the form of an adverse event than filling prescriptions of medication B, the explanation for the differing filling rates could be that individuals prescribed medication A were simply more likely to actually take the medication. Controlling for this in a completely register-based observational study appears very difficult. If there was a variable known to be highly correlated with actually taking a medication after filling a prescription, it could conceivably be used for adjustment purposes. For the present studies, one must rely on the fact that there does not appear to be any strong reason to believe that there are substantial systematic differences in the tendency for individuals to actually take medications for which prescriptions are repeatedly filled.
Conclusions

The studies included in the thesis invite some conclusions. The first study indicated that EPS, while distressing for the patient and therefore a side effect clinicians should strive to avoid, need not be associated with an increased risk of suicide. The second study suggested that suicidal ideation and behaviour that is more recent and conventionally viewed as more serious is associated with a higher risk of suicide. This was shown in the context of a single study, comprising several types of suicidal communication and behaviour. The result is largely in line with the current clinical understanding of suicide risk.

The third study highlighted the complex relationship between antipsychotic medication and osteoporotic fractures. Prolactin-increasing antipsychotic medications might, from a theoretical viewpoint, be expected to increase the risk of osteoporotic fractures compared with medications that are prolactin-sparing. However, especially in the short term, many other factors appear to matter. Managing the risk of osteoporotic fractures during antipsychotic treatment therefore arguably requires a holistic approach.

The fourth study indicated that myocarditis is a clinically relevant side effect of clozapine treatment that should be kept in mind by clinicians. However, it does not appear to be as common as suggested by some previous research. The chemically similar antipsychotic medications olanzapine and quetiapine do not appear to be associated with an increased risk of this cardiac adverse event.

Future directions

Much research on suicidality, including among individuals with schizophrenia spectrum disorders, has been focused on finding risk factors. While such research is important and has improved the understanding of suicidality, it also has limitations. In particular, some risk factors may be static, such as sex or a history of suicidal behaviour, and therefore of limited use in directing interventions over time. Identifiable risk factors also do not necessarily decisively pinpoint a subset of patients with substantially elevated risk of suicide. Other approaches are therefore also valuable. Research on protective factors and effective preventive strategies, including indirect approaches such as programmes to increase opportunities for meaningful social contacts and daily activities, should continue to receive attention.

Antipsychotic medication is sometimes prescribed to manage the psychological and behavioural symptoms of dementia. Given that such medication is associated with a risk of side effects, including risk of bone fractures, continued research into non-pharmacological strategies to manage behavioural symptoms of dementia is desirable.
Observational studies involving antipsychotic medication, which rely on the Swedish PDR, can assess whether individuals fill prescriptions, but not whether medications are taken. There are also several lifestyle factors that are difficult to obtain accurate information on from available registers, such as nicotine use, exercise and diet. Hence, randomised controlled trials of for instance osteoporotic fractures during antipsychotic treatment would be valuable.

The two case-control studies in this thesis were based on data from Stockholm County, while the two cohort studies were nationwide Swedish studies. The smaller data samples made subgroup analyses difficult. Hence, repeated studies on larger samples could be valuable to explore whether there are sex- and age-related differences, for instance.

It would be valuable to use population-based health care registers in other regions to further explore the risk of cardiac adverse events during treatment with clozapine. Further, clinical surveillance programmes following initiation of clozapine may choose to have low thresholds for interpreting electrocardiographic aberrations or heart-related biomarkers as indicative of myocarditis. Myocarditis is potentially lethal, and it is desirable to manage the condition at an early stage, which is one argument for having a low threshold. A potential clinical study could involve offering individuals initiating clozapine treatment and who have marginally elevated biomarkers possibly indicating mild myocarditis an option of continuing clozapine treatment with intensified monitoring. This could avoid unnecessary cessation of valuable clozapine treatment but would also explore to what extent elevated biomarkers emerging early during clozapine treatment reverse to normal levels spontaneously.
Sammanfattning på svenska

Bakgrund


Vid schizofreni är risken för självmord påtagligt förhöjd och omkring 5 % av personer med schizofreni avlider till följd av självmord. En ökad förståelse av självmord vid schizofreni är önskvärd. Risken för självmord kan bland annat påverkas av läkemedelsbehandling – genom eftersträvad effekt, men även potentiellt genom oönskade biverkningar.

Bland de antipsykotiska läkemedlen har substansen klozapin en särstäällning som det enda preparatet med indikationen terapirefraktär schizofreni, vanligen definierat som otillräckligt effekt av åtminstone två andra antipsykotiska läkemedel. Läkemedlet har god effekt, men kan också ha flera olika biverkningar. Ett exempel på detta är inflammation i hjärtmuskeln och hjärt-säcken (perimyokardit), vilket vanligen inträffar tidigt i behandlingsförloppet. På flera års sikt kan följden ibland bli hjärtsvikt, vilket innebär att hjärtmuskeln får en försämrad pumpfunktion. Under senare år har risken för hjärtmuskelinflammation uppmärksammats inte minst då observationella studier vid kliniker i främst Australien indikerat att tillståndet skulle kunna vara vanligare än vad man tidigare har trott.
Ingående studier

Avhandlingen omfattar fyra olika studier. Alla ingående studier använder en epidemiologisk metod och bygger på data från svenska nationella hälsoregister. Dessa register anses hålla en god kvalitet och ha hög täckningsgrad. Användning av sådana populationsbaserade register ökar förutsättningarna för representativa studier som inte är baserade på ett skevt urval av individer, vilket kan bli fallet i kliniska studier där de psykiskt mest sjuka patienterna ofta inkluderas.

Den första studien undersökte betydelsen av extrapyramidala symptom för självmordsrisk bland individer med schizofrenispektrumdiagnos i Stockholms län. I denna studie var extrapyramidala symtom associerade med en lägre risk för självmord.

Den andra studien analyserade självmordskommunikation, som extraherrats blint från patientjournaler, som en riskfaktor för suicid bland patienter med schizofrenispektrumsyndrom. Studien visade att allvarligare självmordskommunikation och beteenden, exempelvis självmordsförsök, var associerade med en större risk för självmord. Studiens resultat ligger i linje med den så kallade självmordsstegen, som ofta används i svensk klinisk praxis.

Den tredje studien analyserade risken för benbrott i samband med antipsykotisk läkemedelsbehandling. Studien fann att det antipsykotiska läkemedlet risperidon inte var associerat med en högre risk för benbrott jämfört med den första generationens antipsykotiska läkemedel.

Den fjärde studien analyserade risken för perimyokardit och hjärtsvikt under behandling med klozapin och de kemiskt närbesläktade läkemedlen olanzapin och quetiapin. Studien visade att klozapin var associerat med en påtaglig risk för perimyokardit på kort sikt jämfört med i en kontrollgrupp utan antipsykotisk läkemedelsbehandling, även om den absoluta risken fortfarande var blygsam. Risken för hjärtsvikt på lång sikt var något förhöjd jämfört med vid ingen antipsykotisk läkemedelsbehandling. Behandling med olanzapin och quetiapin var inte associerad med förhöjd risk för dessa hjärttillstånd, jämfört med vid ingen antipsykotisk läkemedelsbehandling.
Acknowledgements

Many people have been involved in making the studies included in this thesis possible. In particular, I am grateful for the support and guidance provided by my supervisor Robert Bodén and my co-supervisors Johan Reutfors and Helle Kieler. I would also like to express my appreciation for the contributions of the biostatisticians Lena Brandt, Marie Linder and Tobias Svensson.

The contributions of all my co-authors are gratefully acknowledged. Specifically, Shahram Bahmanyar was a valuable senior collaborator in three of the four studies and Johan Sundström’s cardiological expertise and encouragement helped shape the study on clozapine. Support from my clinical supervisor Björn Nilsson was decisive in initiating the thesis project.

I also extend my gratitude to my wife Sarah, for your love and patience during this time.
References


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)