Use and non-use of antipsychotics and other psychotropic drugs in schizophrenia

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Scientific environment

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Abstract

Background: Little is known about health-related outcomes for patients with schizophrenia when comparing periods with use and non-use of antipsychotic drugs in a real-life setting. Current evidence is also limited for the use of other psychotropic drugs, including antidepressants, mood stabilizers and benzodiazepines.

Aims: To investigate the association between use of different classes of psychotropic drugs and mortality (paper I), risk of acute psychiatric readmission (paper II) and risk of acute psychiatric readmission with overactive, aggressive, disruptive or agitated behaviour (OADA) (paper III).

Material and methods: A cohort study included all patients diagnosed with schizophrenia admitted to a psychiatric acute unit at Haukeland University Hospital in Bergen, Norway, during a 10-year period. Patients were followed until death (paper I), readmission (paper II) or readmission with OADA (paper III). Cox multiple regression analyses were conducted using antipsychotic drugs and other psychotropic drugs as time-dependent variables, and periods of use and non-use were compared within individual patients. Adjustments were made for gender, age at index admission, and excessive use of alcohol and illicit substances.

Results: Non-use of antipsychotics was associated with two-fold increased mortality risk compared to periods with use of antipsychotics (paper I). Compared to non-use, periods with use of antipsychotic drugs and benzodiazepines were associated with decreased and increased readmission risk, respectively (paper II). The risk of readmission with OADA was negatively associated with the use of antipsychotic drugs and antidepressants, and positively associated with the use of benzodiazepines (paper III).

Conclusion: For patients with schizophrenia, periods with non-use of antipsychotic drugs was associated with increased risk of death, readmission and readmission with

OADA. Periods with use of benzodiazepines were associated with increased risk of readmission and readmission with OADA.

Implications: We identified important modifiable risk factors associated with non-use of antipsychotic drugs and use of benzodiazepines that are directly or indirectly associated with mortality. This is important knowledge for patients facing decisions concerning use versus non-use of antipsychotic drugs, but also for the patients' families and carers.

List of Publications

I. Strømme MF, Mellesdal LS, Bartz-Johannesen C, Kroken RA, Krogenes M, Mehlum L, Johnsen E. Mortality and non-use of antipsychotic drugs after acute admission in schizophrenia: A prospective total-cohort study. Schizophr Res. 2021 Sep;235:29-35. doi: 10.1016/j.schres.2021.07.009. Epub 2021 Jul 21. PMID: 34303258

II. Strømme MF, Mellesdal LS, Bartz-Johannesen CA, Kroken RA, Krogenes ML, Mehlum L, Johnsen E. Use of Benzodiazepines and Antipsychotic Drugs Are Inversely Associated With Acute Readmission Risk in Schizophrenia. J Clin Psychopharmacol. 2022 Jan-Feb 01;42(1):37-42. doi: 10.1097/JCP.0000000000001497. PMID: 34928559.

III. Strømme MF, Bartz-Johannesen CA, Kroken RA, Mehlum L, Johnsen E. Overactive, aggressive, disruptive and agitated behaviour and use of psychotropic drugs in schizophrenia. *Under review*

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Abbreviations

AHR: Adjusted hazard ratio

ATC: The Anatomical Therapeutic Chemical system

AUS: Alcohol Use Scale

CMCH: Community Mental Health Centre

DUS: Drug Use Scale

FGA: First generation antipsychotic drugs

GABA: Gamma-aminobutyric acid

GAF: The Global assessment of Functioning scale

HoNOS: Health of the Nation Outcome Scale

HR: Hazard ratio

ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision

NMDA: N-methyl-D-aspartate

OADA: Overactive, aggressive, disruptive or agitated behavior

PANSS: Positive and Negative Syndrome Scale for Schizophrenia

SGA: Second generation antipsychotic drugs

SIPEA: Suicidality in Psychiatric Emergency Admissions

SMR: Standardized mortality rate

SPSS: Statistical Package for the Social Sciences

SSRI: Selective serotonin reuptake inhibitors

TGA: Third generation antipsychotic drugs

WHO: World Health Organization

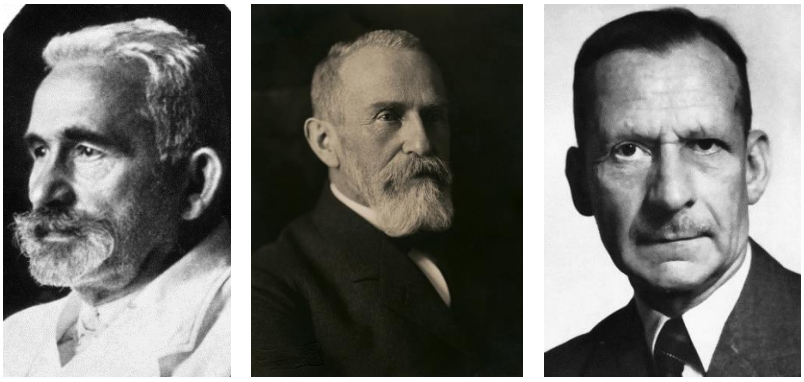
Contents

1. Introduction

1.1 Schizophrenia

1.1.1 The history of schizophrenia

Although schizophrenia most likely has affected humans since the dawn of time, the first certain description came in 1809, when John Haslam, an English pharmacist and physician described "a form of insanity that occurs in young persons."[1] Later on, in the 1890s, the German psychiatrist Emil Kraepelin described a disease characterized by mental dullness or dementia with early onset, sub-acute development, and tendency of poor long-term outcome.[1-3] He called the disease "dementia praecox." Although Kraepelin might be considered the individual with the greatest influence on our perception of the disease today, also Eugen Bleuler, a Swiss professor in medicine, made significant contributions. In April 1908, he gave a lecture to the German Psychiatric Association in Berlin, where he argued that dementia praecox was associated with neither dementia nor precociousness, and emphasized that splitting of psychic functioning is an essential feature of the disease.[4] He coined the term "schizophrenia," which is Greek for "split mind." Unlike Kraepelin, Bleuler believed that the time of onsets, clinical course and outcome may vary in patients with



Emil Kraepelin (1856-1926), Eugen Bleuler (1857-1939), Kurt Schneider (1887-1967)

schizophrenia.[5] He also defined a set of basic symptoms that he considered unique for patients with schizophrenia; abnormal associations, autistic behaviour, abnormal affect, and ambivalence.[4] These are termed Bleuler's 4 As, and correspond to what we today categorise as negative symptoms. In contrast to Bleuler, who considered hallucinations and delusions as accessory symptoms, Kurt Schneider introduced the term first rank symptoms some decades later, in 1957.[5] The 11 first rank symptoms included auditory hallucinations and delusions, as well as thought insertion, thought withdrawal and thought broadcasting, which we today categorise as positive symptoms.[6,7]

While Bleuler and Schneider provided sets of specific, yet very different symptoms, Kraepelin emphasized the long term course and clinical outcome, without demanding specific symptoms. Today's definition of schizophrenia includes aspects of all these three perspectives, as both the long term course described by Kraepelin and positive and negative symptoms described respectively by Schneider and Bleuler, are considered of importance.

1.1.2 Symptoms

Today, schizophrenia is characterized by altered perception of reality, and accordingly, all psychotic disorders can be potential differential diagnoses, including schizoaffective disorder, affective psychosis, substance induced psychosis, organic psychosis, acute transient psychosis and delusional disorder.[8] Although not unique for schizophrenia, positive and negative symptoms are important and characteristic for the disorder.[1] While negative symptoms represent *absence* of, or lack of normal mental functioning, positive symptoms represent a *presence* of psychiatric symptoms.

Positive symptoms include delusions and hallucinations, and typically contain elements of reality distortion.[1] Delusions of persecution are most common, but delusions may also include thought broadcasting, thought insertion and thought

withdrawal among others, in accordance with Kurt Schneider's first rank symptoms.[5] In some cases, the delusions are connected to the patient's everyday life, for example to a somatic disease, but they may also be far from reality and have a bizarre character, for example ideas about being an alien from a foreign universe. The degree of persistence, systematization and influence on daily functioning may vary. Hallucinations are most often auditory, and as described by Schneider,[6] the voices are typically commenting on the patient. It is also common that the voices are threatening and demanding.[5] As such, the patients often perceive the voices as stressful and burdensome. Although less common, hallucinations may occur in any sensory modality, including visual and tactile hallucinations and hallucinations of taste and smell.[1]

Negative symptoms represent lack of normal mental functioning, and include amongst others anhedonia (inability to experience pleasure), apathy (lack of interest), avolition (lack of initiative) abulia (lack of motivation) and alogia (poverty of speech).[5] Negative symptoms are of great clinical importance, as they may reduce the patient's level of function to a much greater extent than positive symptoms.[1,9]

In addition to positive and negative symptoms, other symptoms related to mood, cognition, disorganized thinking and motor function are commonly reported.[5] Schizophrenia is also associated with several comorbid psychiatric disorders, such as depression, suicidality and anxiety.[1,10]

1.1.3 Aetiology

The dopamine and glutamate hypotheses are currently leading theories of the aetiology underlying schizophrenia.[11] It is well established that positive symptoms of schizophrenia are associated with hyperdopaminergic activity in the brain, and in particular in the mesolimbic dopamine pathway.[12] Negative symptoms and impaired cognition are, on the other hand, associated with hypodopaminergic neurotransmission

in the mesocortical pathway.[12] Evidence suggests interactions between the glutamatergic and dopaminergic systems, and it has been hypothesized that glutamatergic NMDA (N-methyl-D-aspartate) receptor hypofunction, deficit in the glutamatergic neurotransmission and reduced gamma-aminobutyric acid (GABA) signalling can explain the symptoms of schizophrenia, but so far, no firm evidence have supported these theories.[11] Moreover, it has been hypothesized that cognitive impairment may be caused by neuroinflammation and abnormal myelination of the neurons.[13]

The underlying causes of schizophrenia are not fully known, but it is generally agreed that genetic factors and environmental factors are important and interact. Schizophrenia is highly heritable, and genetic factors contribute to around 80% of the liability for the disorder.[14] However, no single gene can explain the illness, and multiple chromosomal regions across the genome have proved to contribute to increased risk of illness.[15] Environmental risk factors are also reported to be associated with increased risk of developing schizophrenia, including amongst others cannabis use, migration, urbanicity during childhood, social stress and perinatal complications.[14,15] Nevertheless, it is important to underline that neither of the genetic or environmental risk factors are neither sufficient nor necessary to develop schizophrenia.[14]

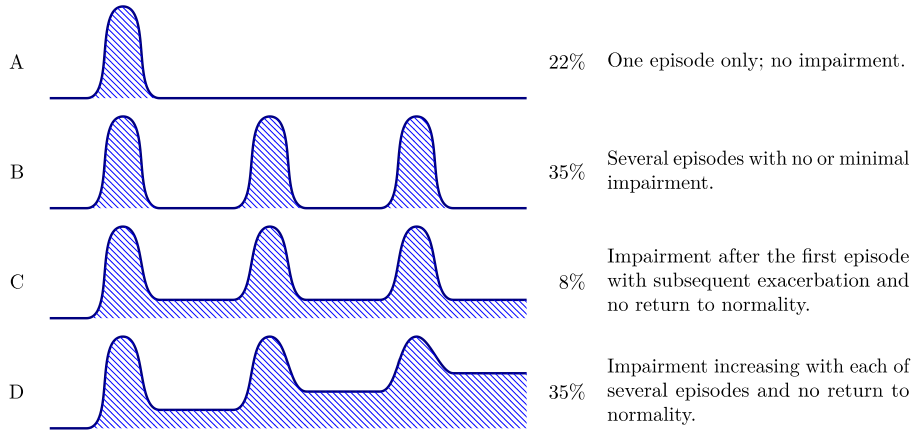
1.1.4 Epidemiology

The mean life time prevalence for schizophrenia is just below 1%,[16] and the median annual incident rate is reported to be around 5.5 per 100.000 persons.[17] The incident rates are higher in men than in women, and women often have a more benign course of illness.[17] The incident rates are also higher in immigrants and in persons living in large cities.[17]

1.1.5 Courses of illness

The first signs and symptoms of schizophrenia typically occur during late adolescence or early adult life.[1] However, patients with schizophrenia may experience very different courses of illness. As illustrated in a study by Shepherd et al.,[18] see Figure 1, 22% of the patients experience only one psychotic episode with no impairment of daily functioning, and 35% have several psychotic episodes with no or minimal impairment of daily functioning. While these two groups can return to normal after or in-between psychotic episodes, others will never achieve normal functioning again. Around 35% of all patients with schizophrenia experience several psychotic episodes and increasing impairment in-between relapses, while a small group, only 8%, experience several psychotic episodes and impaired, but stable functioning in-between

*Figure 1: Courses of illness**



*Shepherd M, Watt D, Falloon I, Smeeton N. The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. Psychol Med Monogr Suppl. 1989;15:1-46. doi: 10.1017/s026418010000059x. PMID: 2798648.

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relapses. Similar findings have also been reported in a 10 year follow-up study of patients with first episode psychosis.[19]

Taken together, schizophrenia is a diverse disorder, both in terms of symptoms and courses of illness. The human suffering associated with schizophrenia is significant, both for the patient, the family and the society.[20] Patients may experience disability to work, homelessness and social isolation,[10,20] which underlines the need and importance of effective treatment.

1.2 Treatment of schizophrenia

Patients with schizophrenia should be offered evidence-based and individually tailored treatment. In treatment of psychosis, there is evidence that both pharmacological treatment, psychoeducational family work and cognitive behavioral therapy are efficient.[17] Accordingly, patients should be offered a combination of these treatment options, adjusted to the patient's preferences, the severity of symptoms, the patient's social situation and other individual factors.[17] Furthermore, it is well documented that a good relation between patient and clinician, as well as continuous follow-up are of great importance for the recovery.[17] A brief review of evidence-based, non-pharmacological treatment options will be given in the following, after which pharmacological treatments will be presented in greater detail, being the main topic of the thesis.

1.2.1 Non-pharmacological treatment

Non-pharmacological treatment options are important in the treatment of schizophrenia, and scientific evidence suggests that both cognitive behavioural therapy and psychoeducational family work is efficient in the treatment. In a recent large meta-analysis by Bighelli et al.,[21] the authors conclude that compared to treatment as usual,

family interventions, family psychoeducation and cognitive behavioural therapy may reduce the risk of relapse. In accordance with these findings, Norwegian treatment guidelines for psychosis recommends that cognitive behavioural therapy and psychoeducational family work are offered in combination with pharmacological treatment.[17]

Cognitive behavioural therapy focuses on making the patient aware of negative or inaccurate thinking by offering alternative interpretations of situations and perceptions underlying delusions and hallucinations, in order to enable the patient to view challenging situations more clearly and handle them in a better way. Compared to standard treatment, there is scientific evidence that cognitive behavioural therapy may reduce symptoms and discomfort associated with auditory hallucinations, as well as depression and social anxiety[17,22] There is also some evidence that cognitive behavioural therapy may improve social functioning.[22]

Psychoeducational family work is education of patients and their families that aims to increase their knowledge about, and insight into the symptoms and treatment of schizophrenia. Specifically, high levels of expressed emotions, such as criticism and hostility within the families, are addressed. There is scientific evidence that psychoeducational family work may reduce the risk of relapse and rehospitalisation.[17] There is also evidence that psychoeducational family work may improve the social functioning and the adherence to prescribed medications, as well as the life quality both for the patients and their family members.[17]

Although there is evidence that non-pharmacological interventions may be efficient in the treatment of psychosis, it is important to underline that non-pharmacological interventions primarily should be offered in combination with antipsychotic drug treatment. A few studies have investigated the effect of cognitive behavioural therapy alone, but most research on non-pharmacological treatment in schizophrenia have been conducted in patients that also receive antipsychotic drug treatment. Whether

psychosocial treatment options alone may be safe and effective in some patients with schizophrenia, still needs to be determined.[23]

1.2.2 Pharmacological treatment

Antipsychotic drugs

The introduction of antipsychotic drugs in the 1950s has been described as a revolution in the treatment of psychosis.[1] Psychosocial treatment interventions that previously were not possible due to anxiety and psychiatric symptoms became possible, and previously hospitalized patients got a chance to live outside the closed hospitals.[1] Today, antipsychotic drugs still remain the cornerstone in treatment of schizophrenia. More than 400 double-blind studies have compared antipsychotic drugs to placebo in the acute treatment of schizophrenia, finding antipsychotic drugs to be more effective than placebo with respect to reducing symptoms of psychosis.[1,24] A review by Dixon et al.[24] reports that 75% of the users of antipsychotic drugs experienced improvement after 6 weeks, compared to 25% in the placebo-group. In patients with first episode of schizophrenia, a systematic review and meta-analysis by Zhu et al.[25] found that more than 80% of the patients achieved at least a 20% reduction of the PANSS- score (Positive and negative syndrome scale for schizophrenia[26]) from baseline and around 50% of the patients achieved at least a 50% PANSS reduction. However, it is important to underline that antipsychotic medications mainly are effective in reducing symptoms of psychosis, not necessary in improvement of functioning. Although a recent systematic review by Ceraso et al.[27] found that compared to placebo, social functioning and quality of life was better in patients treated with antipsychotic drugs, the quality of the evidence was considered low to moderate. Antipsychotic drugs are important also in the maintenance treatment of schizophrenia. In the review by Ceraso et al.,[27] antipsychotic drugs are found to prevent relapse to a much greater extent than placebo in the first two years of the maintenance treatment of schizophrenia. In line with these findings, current national

treatment guidelines[17] recommends use of antipsychotic drugs for two years after the first psychotic episode, followed by a gradual withdrawal of the medications under close surveillance by a clinician, to identify the subgroup that may successfully stop antipsychotic drug use without relapsing. For patients with relapse, long term maintenance treatment is recommended, with regular evaluations of symptoms, adverse effects and need of further treatment.[17]

The first antipsychotic drugs, today called first-generation or typical antipsychotic drugs (FGA), are strong dopamine (D_2) receptor antagonists.[1] Accordingly, FGAs are effective for dampening of positive symptoms, and may reduce the level of hallucinations and delusions in a large proportion of patients,[28] but have little or no beneficial effects on negative symptoms or cognitive dysfunctions.[1] However, due to the strong blockage of the dopamine (D_2)-receptor, FGAs are associated with several adverse effects.[1,28] Extrapyramidal side effects such as dystonia (involuntary muscle contractions), akathisia (motor restlessness), parkinsonism (rigidity, tremor and slow movement), and tardive dyskinesia (involuntary, repetitive body movements) are commonly reported in patients using FGAs.[29]

In 1958, clozapine was developed in Belgium.[30] Clozapine is a highly effective antipsychotic drug, but unfortunately, it is associated with the rather severe side effect agranulocytosis in a small, but unpredictable subgroup, necessitating regular blood cell counts throughout the duration of treatment for all patients using the drug.[28] In the pursuit of "a safer clozapine," several new antipsychotic drugs were developed in the 1990s. Clozapine and the subsequent new medications were called second-generation antipsychotic drugs (SGA) or atypical antipsychotic drugs. Compared to FGAs, SGAs have lower D_2-receptor affinity and block serotonin ($5HT_2$) receptors.[31] Because of these features, SGAs are less associated with extrapyramidal side effects than FGAs,[32] and some studies have even found an association between SGAs and improvement of negative and cognitive symptoms.[33,34] All antipsychotic drugs have until recently been full antagonists at the D2 receptors, whereas several partial D2 agonists have been introduced in the last decade. These have by some been labelled third generation

antipsychotics (TGAs), but is more commonly included among the SGA antipsychotics.

After the introduction of SGAs, several large-scale studies have aimed to compare the efficacy and effectiveness of FGAs versus SGAs. A recent review by Smith et al.[35] found small, but statistically significant differences in overall efficacy for some SGAs, clozapine, amisulpride, olanzapine and risperidone, compared to other antipsychotics. SGAs are often preferred over FGAs in the clinic because of the extrapyramidal side effects associated with FGAs, as well as the potential for improvement of negative and cognitive symptoms associated with SGAs.[31] Side effects and receptor binding affinities are strongly associated in antipsychotic drugs. An overview of the receptor binding affinities for selected antipsychotic agents is provided in Table 1. As mentioned earlier, extrapyramidal side effects are associated with FGAs and strong blockage of the D_2-receptor in the striatum. D_2-receptor antagonism in the hypothalamo-pituitary tract leading to hyperprolactinaemia is another frequent side effect of antipsychotic drugs.[36] Autonomic and cardiovascular side effects are, on the other hand, associated with blockage of the adrenergic (alpha) receptors and the muscarinic (M) receptors in the autonomic nervous system, regulating involuntary

*Table 1: Receptor binding affinities for selected antipsychotic agents**

	FGA		SGA			
	Chlorpromazine	Haloperidol	Amisulpride	Clozapine	Risperidone	Olanzapine
D_1	+	++	-	++	+	++
D_2	+++	++++	+++	+	+++	++
D_3	+++	+++	+++	+	+++	++
D_4	++	+++	-	++	+++	++
$5HT_{1A}$	-	-	-	+	+	-
$5HT_{2A}$	+++	++	-	++	++++	+++
$5HT_{2C}$	++	-	-	++	++	++
α1	++++	+++	-	+++	++++	++
α2	++	-	-	+	++	+
H_1	++++	++	-	+++	++	+++
M_1	++	-	-	+++	-	+++

**Partly based on Table 30.7 in «Lærebok i psykiatri» (Malt et al., 2018, page 912)*

physiologic processes including respiration, blood pressure, heart rate and digestion. Whereas blockage of adrenergic alpha receptors may lead to orthostatic hypotension, muscarinic receptor blockade may lead to tachycardia, constipation, dry mouth, confusion and accommodation problems (blurry vision). The antagonistic effect on alpha-receptors, muscarinic receptors and histamine receptors may also contribute to weight gain and other metabolic and endocrine side effects, for example diabetes

*Table 2: Potential side effects associated with antipsychotic drugs**

Extrapyramidal side effects
Dystonia (involuntary muscle contractions)
Akathisia (motor restlessness)
Parkinsonism (rigidity, tremor and slow movement)
Tardive dyskinesia (involuntary, repetitive body movements)
Akinesia (loss of ability to move the muscles voluntarily)
Autonomic and cardiovascular side effects
Dry mouth
Orthostatic hypotension
Anticholinergic syndrome
Prolonged QTc interval
Endocrine and metabolic side effects
Diabetes Mellitus type II
Weight gain
Abnormal levels of lipids
Menstrual disorders
Sexual dysfunction
Hyperprolactinemia
Psychiatric side effects
Sedation
Anhedonia (decreased ability to feel pleasure)
Haematological side effects
Agranulocytosis
Other side effects
Malign neuroleptic syndrome
Dermatological changes
Hepatic reaction

**Based on Table 30.9 in «Lærebok i psykiatri» (Malt et al., 2018, page 921)*

mellitus type II and sexual dysfunction.[1,37] The metabolic side effects are most often seen in users of SGAs. Severe cardiovascular side effects are rare. Most commonly seen is prolonged QTc-interval, which is caused by a blockage of potassium channels in the heart and following delayed repolarization of the heart muscle cells. Prolonged QTc interval is a well-known risk factor for malign arrhythmias and sudden cardiac death.[1,31] Furthermore, sedation is a common adverse effect, especially in users of antipsychotic drugs with a strong antagonistic effect on the H_1-receptors.[33] Other psychiatric side effects, such as anhedonia or intellectual impairment, may also occur.[1] An overview of potential side effects associated with antipsychotic drugs are provided in Table 2.[1]

Non-adherence to prescribed antipsychotic medications is a persisting problem in the treatment of schizophrenia,[38] and in a recent systematic review by Semahegn et al.,[39] the non-adherence rate was 56%. Medication non-adherence may have several different causes, and can be related to adverse effects of the medications, patient factors, the illness itself or environmental factors.[38] Some patients may be afraid of using medications as a consequence of paranoid delusions, while others suffer from cognitive impairment that makes them forgetful and unable to take the medications as prescribed.[38] Fear of adverse effects, impaired insight and lack of understanding of the severity of the illness are also factors that may contribute to increased non-adherence.[1,38] Furthermore, environmental factors, such as low support from family and friends or a poor relation to the treating clinician can also lead to non-adherence.[38] A study by Achtyes et al.[40] identified both the efficacy of the medications and side effects as key factors for the patients' willingness to use medications. In this regard, the patients identified the ability to think clearly as an important property of the medication, and weight gain, somnolence and physical restlessness as the most important side effects.[40]

Potential consequences of non-adherence includes exacerbation of the illness, reduced treatment effectiveness and decreased quality of life.[39] Furthermore, non-adherence and non-use of antipsychotic drugs have been identified as important risk factors for

both increased mortality,[41] risk of relapse and rehospitalisation[27] and aggression in patients with schizophrenia.[42]

Antidepressants

Most currently available antidepressants are based on the monoamine hypothesis, claiming that depression is associated with monoamine deficiency or imbalance in the brain.[31] Accordingly, most antidepressants increase the levels of the monoamines serotonin and norepinephrine in the synaptic cleft.[1] The most commonly prescribed type of antidepressants, selective serotonin reuptake inhibitors (SSRIs) increases the level of serotonin in the synaptic cleft by limiting its reabsorption into the presynaptic cell. Hence, a higher level of serotonin in the synaptic cleft are available to bind to the postsynaptic serotonin (5-HT) receptor.[1]

In schizophrenia, antidepressants are primarily used to treat depressive symptoms or persistent negative symptoms.[43,44] The scientific evidence for the use of antidepressants in schizophrenia is limited, but available evidence suggests that antidepressants may improve the control of negative symptoms,[43] and a review by Ballon et al.,[44] reports of a possible association between antidepressants and lower risk of suicide. However, use of antidepressants in patients with schizophrenia is rarely recommended in clinical guidelines.[45] Despite this, antidepressants are frequently used concomitantly with antipsychotic drugs in the treatment of schizophrenia. A study by Puranen et al.,[45] found that among persons with first-episode schizophrenia, as many as 35.4% initiated use of antidepressants within three years after receiving the diagnosis. They also reported that young age, female gender and use of benzodiazepines were associated with increased risk of antidepressant initiation, while a high number of previous psychoses was associated with decreased risk.[45]

Mood stabilizers

Mood stabilizers include lithium and some anticonvulsant medications, for example valproate and lamotrigine. Lithium interacts with a number of neurotransmitters and receptors in the central nervous system, and is hence associated with several biological effects, including amongst others hematological and neuroprotective effects.[1] Lithium is used to prevent manic, but also depressive symptoms in patients with bipolar disorders.[1] In schizophrenia, lithium is sometimes used as an add-on medication if a satisfactory response to ordinary antipsychotic drug treatments is missing.[46] However, the scientific evidence behind such treatment is sparse. In a review by Leucht et al.,[46] the authors report that there is some evidence that augmentation of antipsychotics with lithium is effective, but the evidence is of low quality.

Anticonvulsant medications have the ability to suppress excessive firing of neurons, and is used to prevent epileptic seizures.[31] Similar to lithium, some anticonvulsant also have a mood stabilizing effect[1] and is sometimes used in combination with antipsychotics in patients with schizophrenia. Combining antipsychotic drugs with anticonvulsants is not supported by any firm evidence,[43] but a systematic review by Wang et al.[47] found that augmentation of antipsychotics with valproate may improve both overall clinical response and also specific symptoms, in particular aggression and excitement.[47]

The use of mood stabilizers are not very common in patients with schizophrenia, but a study by Puranen et al.,[45] found that 14.1% of patients with first-episode schizophrenia initiated use of mood stabilizers within three years after receiving the diagnose. Increased risk of initiation of mood stabilizers was associated with female gender, young age, use of benzodiazepines and a high number of previous psychoses.[45]

Benzodiazepines

Benzodiazepines are a group of medications that amplifies the effect of gamma-aminobutyric acid (GABA), the most important inhibiting neurotransmitter in the central nervous system.[1] Accordingly, benzodiazepines have a strong sedative, sleep-inducing, anxiolytic and muscle relaxant effect.[1] In schizophrenia, benzodiazepines are often used as adjuvant medications for sleep disorders or anxiety. Lack of sleep and stress are well-known risk factor for relapse, and it has therefore been suggested that benzodiazepines may prevent relapse.[48] It has even been speculated that the GABA-enhancing effect of benzodiazepines may lead to inhibition of the dopamine neurotransmission and thus provide a direct antipsychotic effect, but no firm evidence have confirmed these speculations.[48,49] However, benzodiazepines have a large number of severe adverse effects, such as cognitive impairment and a potential for abuse, dependence and development of tolerance.[31] Accordingly, benzodiazepines are normally only recommended for short-term use.[1] A review by Dold et al. from 2012 concluded that there currently is no convincing evidence to confirm or refute the practise of administering benzodiazepines in combination with antipsychotics in the treatment of schizophrenia.[50]

1.2.3 Key controversies and clinical challenges in the pharmacological treatment

Excess mortality

The age adjusted mortality risk in patients with schizophrenia is significantly higher than in the general population, with studies reporting up to 20 years reduced life expectancy.[51,52] The underlying reasons behind the increased mortality are not fully known, but genetic vulnerability, lifestyle factors, increased risk of suicide and adverse effects of antipsychotic drugs are believed to contribute.[53,54] Diabetes type II, dyslipidemia and the metabolic syndrome are examples of rather common adverse effects of antipsychotic drugs that are likely to contribute to increased mortality.[54] Studies have also reported that antipsychotic drugs are associated with increased risk

of myocardial infarctions and cerebrovascular incidences,[55,56] and rarely also thromboembolism, myocarditis, malignant arrhythmia and sudden cardiac death.[57-61] Indeed, it has been claimed that use of antipsychotics increases the mortality in patients with schizophrenia.[62,63] In the light of these findings and claims, it may seem paradoxical that a large number of studies report that antipsychotic use is associated with decreased mortality risk.[41,64-70] In a nationwide cohort from Sweden, Torniainen et al.[69] find that high exposure to antipsychotic drugs is associated with higher mortality than low antipsychotic exposure. However, the highest mortality is found in patients that do not use antipsychotic drugs, and the authors conclude that the excess mortality in schizophrenia is attributable to other factors than long-term antipsychotic treatment when antipsychotic drugs are used in adequate dosages.[69] Furthermore, studies have suggested that dampening of psychosis may decrease the risk of suicide[71,72] and facilitate a healthier lifestyle and a more active health care-seeking behaviour.[73-75] Long-term adverse effects of antipsychotics may hence be outweighed by the increased risk of suicide, unhealthy lifestyle and reduced capacity for health-promoting behavior associated with untreated psychosis.

The use of add-on medications may also influence the mortality risk in patients with schizophrenia. A review by Ballon et al.,[44] reports of a possible association between antidepressants and lower risk of suicide, as well as lower all-cause mortality. A large, nationwide cohort study from Finland partly confirms these findings when they report that antidepressant use is associated with lower risk of suicide, but not lower over-all mortality.[76] However, the authors also found an association between use of benzodiazepines and increased risk of both suicidal and non-suicidal death, suggesting that use of benzodiazepines as an add-on medication contributes to the excess mortality in patients with schizophrenia.[76]

Relapse

With long-term readmission rates close to 70%, [77] relapses are a major challenge in the treatment of schizophrenia. Repeated relapses are associated with increased risk of persistent psychotic symptoms,[78,79] and as many as 35% of all patients with schizophrenia suffer from gradually impaired daily functioning after each relapse, as illustrated in Figure 1.[18,80] Active psychosis is also associated with increased risk of violence, accidents and death, [81] which underlines the importance of preventive measures. Several randomized controlled trials have found that maintenance treatment with antipsychotic drugs reduces the risk of relapse significantly.[27] In a recent systematic review, Ceraso et al.[27] reports relapse rates after 7-12 months to be 24% in the antipsychotics group, compared to 61% in the placebo group. For rehospitalisation, corresponding rates are 7% and and 18% for antipsychotics and placebo, respectively. Similar findings are also reported in large, nationwide cohort studies. For example, a study by Tiihonen et al.[82] found that compared to non-use, hazard ratios for psychiatric rehospitalisation were between 0.5–0.6 for users of antipsychotic drugs.

The risk of relapse and rehospitalisation may also be affected by the use of adjunctive psychotropic medications. A large study by Stroup et al.[83] found that compared to the initiating of a second antipsychotic drug, initiation of an antidepressant was associated with lower risk of rehospitalisation (HR 0.84). Initiation of a mood stabilizer was not different from initiating another antipsychotic drug, but initiating a benzodiazepine was significantly associated with increased risk of psychiatric rehospitalisation (HR 1.08).[83] A study by Takita et al.[84] also reported an association between use of benzodiazepines in high doses at discharge and risk of shorter timer to rehospitalisation, suggesting that the increased risk might be due to the well-known adverse effects of benzodiazepines, such as impaired cognitive function and risk of dependence and abuse.[84]

Aggression

In a systematic review and metaanalysis, Fazel et al.[85] report that the risk of homicide was up to 20% higher in patient with schizophrenia, compared to the general population. Indeed, violence and aggression is a serious problem in patients with schizophrenia, with aggression prevalence rates reported as high as 33%.[86] Aggression complicates the treatment, and represents obvious risks of death and injuries both for the victim and the attacker. A number of studies have found that agitation increases the risk of suicide, [87-89] and physical aggression have also been reported as a risk factor for sudden cardiac death in patients with schizophrenia.[90] The aetiology behind aggression and agitation in people with schizophrenia is heterogeneous, and aggressive behaviour might be directly linked to positive psychotic symptoms, increased impulsivity or substance abuse [85,91] Antipsychotic drugs are important in the treatment of aggression and agitation in patients with schizophrenia,[92-94] and clozapine has proven to be the most efficient drug in this regard.[95] The anti-aggressive effect of antipsychotic drugs in schizophrenia is not fully understood, but can at least partly be explained by studies reporting an association between aggression and high levels of positive symptoms.[42]

Whereas antipsychotic drugs are a well-established part of the treatment of aggression in patients with schizophrenia, the role of adjunctive psychotropic drugs is disputed and rather unclear. Antidepressants often contain warnings to the patient and clinician that aggression and violence are potential adverse effects, and indeed, antidepressants have been found to be disproportionally associated with violent incidents.[96] However, these findings have not been replicated in neither systematic reviews nor in nationwide cohort studies aiming to investigate the association between aggression and the use of antidepressants.[97,98] A review by Walsh et al.[99] even reported that use of antidepressants are associated with decreased risk of aggression, and the authors speculate that the anti-aggressive effect may be due to antidepressants positive effect on the serotonergic dysfunction associated with aggressive behaviour.

Lithium is known for the ability to reduce impulsive-aggressive behaviour in patients with bipolar disorders,[100] but little is known about the effect on aggression in patients

with schizophrenia. Also for anticonvulsants, the evidence is sparse, but a review by Wang et al.[47] found that patients who received augmentation of antipsychotics with valproate were less aggressive than the control group. However, the evidence was of very low quality, and no conclusions could be drawn.[47] Benzodiazepines have, on the other hand, not been found to confer clear advantage in the treatment of psychosis-induced aggression.[101,102] In fact, a study by Fond et al.[103] even found that use of benzodiazepines as an add-on medication was associated with increased risk of aggression.

1.2.4 The medication-free treatment service

Some patients with schizophrenia do not want to use antipsychotic drugs, but want other treatment approaches, for example cognitive therapy, physical activity and music therapy.[104] Several issues have proven to complicate treatment with antipsychotic drugs, including 1) Adverse effects, 2) A significant subgroup of patients with schizophrenia have limited or no therapeutic benefit from use of antipsychotic drugs, as reflected in lack of achieving remission in 20-25% of those with first episode schizophrenia,[105,106] and 3) It is hard to predict which antipsychotic drug might be optimal for the individual patient.[107] In Norway, several patient organizations have described a situation with few treatment options for patients who prefer not to use antipsychotics, and where some patients feel under pressure to use antipsychotic drugs.[104] Hence, these organizations have advocated for the right to receive treatment that do not include antipsychotic drugs. Consequently, the Ministry of Health and Care Services in Norway instructed the Regional Health Trusts to establish "medication-free" treatment services in 2016.

However, the politicians have received substantial critique for introducing a treatment service without any scientific evidence for its safety and effectiveness. Whereas antipsychotic drugs are well investigated in more than 400 randomized controlled trials,[108] the scientific evidence for medication-free treatment is very limited. In a

recent systematic review by the Norwegian Institute of Public Health,[109] three small randomized, controlled trials were identified that compared antipsychotics to cognitive behavioural therapy, other psychosocial interventions, or placebo in first episode psychosis. All the included trials had serious methodological limitations, prohibiting any conclusions regarding effectiveness differences to be drawn. Another small randomized controlled study by Morrison et al.,[110] that investigated whether cognitive therapy reduced psychiatric symptoms in people with schizophrenia spectrum disorders who had chosen not to take antipsychotic drugs. The authors concluded that cognitive therapy seems to be a safe and acceptable treatment option for patients who have chosen not to take antipsychotic drugs.[110] However, large clinical trials aiming to compare treatment with antipsychotics to medication-free treatment head-to-head are missing. Non-use of antipsychotic drugs have been indicated as an important risk factor for both increased mortality,[41] relapse[27] and aggression in patients with schizophrenia.[42] Although methodological shortcomings of these studies prohibits any certain conclusions to be drawn, there are good reasons to suspect that medication-free treatment is associated with increased risk of adverse events. In order to ensure safe treatment options for patients with schizophrenia, there is now an urgent need to investigate health-related outcomes in patients with schizophrenia who choose not to use antipsychotic drugs.

The literature search for the introduction ended December 31st 2021.

2. Aims

The overarching objective of this thesis was to investigate health-related outcomes, directly or indirectly related to mortality, in patients with schizophrenia in periods of use and non- use of antipsychotic and other psychotropic drugs, and to acquire knowledge that may contribute to a safe establishment of the medication-free (non-pharmacological) treatment service.

Specific aims: To investigate the association between use of antipsychotic and other psychotropic drugs and

I. Mortality risk (Paper I)
II. Risk of acute psychiatric readmission (Paper II)
III. Risk of acute psychiatric readmission with overactive, aggressive, disruptive or agitated behaviour. (Paper III)

3. Methods

3.1 Sample

All three papers in the thesis are based on data from the Suicidality in Psychiatric Emergency Admissions (SIPEA)-study, conducted between 2005-2015 at the Division of Psychiatry, Haukeland University Hospital, Bergen, Norway. From a catchment population of about 400,000 inhabitants, Haukeland University Hospital receives approximately 95% of all patients in need of acute psychiatric hospital admission. Patients were considered eligible for the study if they were admitted to the Psychiatric Acute Unit between May 1st 2005 and June 15th 2014, and met the criteria of the ICD-10 (https://icd.who.int/browse10/2019/en) diagnosis of schizophrenia (F 20.0–F 20.9).[111]

In paper I a total of 772 eligible patients were admitted during the 10-year period. Of these, 76 patients were excluded; 66 patients due to lack of information about the use of antipsychotic drugs after discharge and 10 patients due to formal errors, for example incorrect coding of the ICD-10-diagnosis at discharge. Accordingly, 696 patients were included in the final sample.

In paper II and III the 10 patients with formal errors were removed from the dataset. Therefore, 762 patients were reported as eligible for inclusion in paper II and III. Of these, a total of 99 patients were excluded; 66 patients due to lack of information about the psychotropic drugs used after the patients were discharged, and 33 patients due to discharge date after the end of the study period. Thus, the final sample included 663 patients.

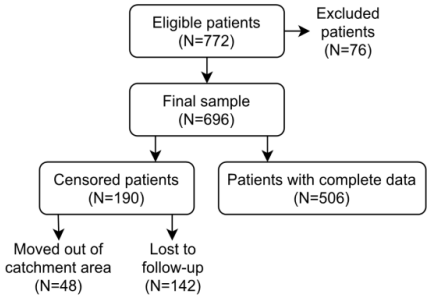
3.2 Procedure

Patients with a discharge diagnosis of schizophrenia were included at the first acute admission during the study period, hereafter named the index admission. In paper I, the follow-up started at the first day of the index admission, whereas in paper II and III, follow-up started at the discharge day of the index admission. The patients were followed until death (paper I), readmission (paper II), readmission with presence of overactive, aggressive, disruptive or agitated behaviour (OADA) (paper III) or until May 1st 2015 or the date of censoring. Patients were censored if they moved out of the hospital catchment area, or if they were lost to follow-up for other reasons. If information about the use of medications was missing, the patients were censored after the last day of registered medication use. Further details on the flow of patients through the study in the three papers are described in Figure 2.

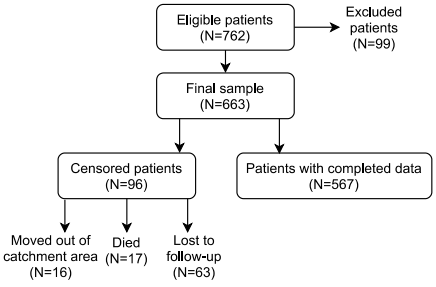
We obtained mortality data by linking the patients' 11-digit identity number to information from the Norwegian Cause of Death Registry (conducted November 14th 2016). Dates for moving out of the hospital's catchment area were retrieved from the medical records. Data on prescriptions of psychotropic drugs and adherence during the periods in-between admissions were collected retrospectively from the medical records, and the adherence was evaluated based on all available information from the mental health care records and serum level measurements of antipsychotic medications when available. To avoid overestimation of drug discontinuation, we allowed for periods of discontinuation lasting up to two weeks without classifying them as terminations, as long as the drug was restarted. In order to avoid discrepancy in how the information was obtained and coded, all the data extraction was done by Maria Fagerbakke Strømme and Marianne Leiknes Krogenes (research nurse in Bergen Psychosis Research group and co-author on paper I and II). All questions regarding the data extraction were logged and discussed in the researcher team. Clinicians involved

Figure 2: Flow of patients through the studies

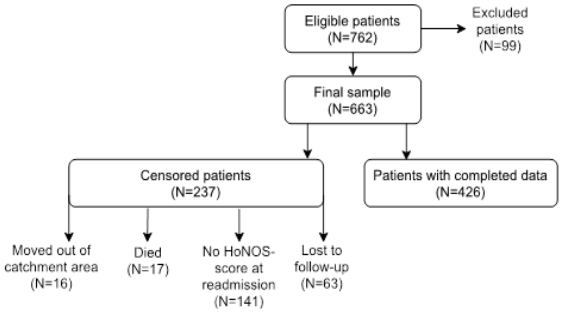
Paper I



Paper II



Paper III



in the assessment of patients at admission, for example assessment of overactive, aggressive, disruptive or agitated behaviour (OADA), underwent training in the rating scales used.

3.3 Variables

The use of antipsychotic drugs, antidepressants, mood stabilizers and benzodiazepines were recorded as time dependent variables. As such, the variables may change several times for the individual patient during the study period. For the time-period a patient used a psychotropic medication, the associated variable was coded as 1, otherwise it was coded as 0. The term “non-use” of psychotropic drugs included both patient non-adherence and drug discontinuation guided by a clinician.

Psychotropic drugs were classified in accordance with the Anatomical Therapeutic Chemical (ATC) system. For antipsychotic drugs, only antipsychotics given on the indication of psychosis were counted: amisulpride, aripiprazole, clozapine, flupentixol, haloperidol, olanzapine, paliperidone, perphenazine, pimozide, quetiapine, risperidone, sertindole, ziprasidone, and zuclopenthixol. The group of antidepressants included amitriptyline, bupropion, citalopram, clomipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, mianserin, mirtazapine, moclobemide, nortriptyline, paroxetine, phenelzine, reboxetine, sertraline, trimipramine, and venlafaxine. The included mood stabilizers were carbamazepine, gabapentin, lamotrigine, lithium (listed as an antipsychotic drug in the ATC-system), and valproic acid. The group of benzodiazepines included alprazolam, diazepam, flunitrazepam, nitrazepam, oxazepam, zolpidem, and zopiclone.

The use of alcohol and substances were measured by the Alcohol Use Scale (AUS) and the Drug Use Scale (DUS) at every admission. AUS and DUS are single-item clinician-rated indexes of alcohol and drug use that measure use on a five-point scale

from “no problems” to “extremely severe problems”.[49] In accordance with previous literature, we identified excessive use as a score of 3 or higher.[48] In paper I and III, the highest given score on AUS and DUS during the study period was used in the analyses. In paper II we used the AUS and DUS score given at the index admission in the analyses. Some values were missing for AUS (n=77) and DUS (n=69) in paper II and III. If values were missing, the AUS and DUS scores were set to 0.

In paper I acute psychiatric hospital admissions were included as a variable in the statistical analyses. The variable was recorded as a time-dependent variable, and was coded 1 if admitted to hospital, and 0 otherwise. The variable included inpatient treatment periods at Community Mental Health Centres (CMCH) directly following an acute admission. In paper II we used the Global assessment of Functioning scale (GAF)[112] to measure the overall functioning and symptoms. The GAF score at discharge from the index admission was used in the analysis. The split version of GAF is used in Norway, with function and symptoms measured in separate subscales.[112] The GAF-score is measured on a 100 point scale, with lower scores indication poorer functioning and more severe symptoms.

In paper III the level of overactive, aggressive, disruptive or agitated behavior (OADA) was measured by the first item of Health of The Nation Outcome Scale (HoNOS).[113] The item is measured on a five-point scale from “no problems” to “severe to very severe problems”, as presented in Table 3, and the assessment was based on the last 14 days prior to readmission. We defined presence of OADA as a score of 2 or higher.

*Table 3: Health of The Nation Outcome Scale (HoNOS); First item: Overactive, aggressive, disruptive or agitated behavior**

	Level of severity	Description
0	No Problem	No problems of this kind during the period rated
1	Minor problem requiring no formal action	Irritability, quarrels, restlessness etc. Not requiring action
2	Mild problem	Includes aggressive gestures, pushing or pestering others, threats or verbal aggression, lesser damage to property (e.g. broken cup or window), marked over-activity or agitation
3	Problem of moderate severity	Physically aggressive to others or animals (short of rating 4), threatening manner, more serious over-activity or destruction of property
4	Severe to very severe problem	At least one serious physical attack on others or on animals, destruction of property (e.g. fire-setting), serious intimidation or obscene behavior

**Based on the Australian Mental Health Outcomes and Classification Network (AMHOCN) HoNOS glossary available at:*
https://www.amhocn.org/sites/default/files/publication_files/honos_glossary_0.pdf

3.4 Statistics

Cox regression models were used to analyze the association between the use of psychotropic drugs and mortality (paper I), risk of rehospitalisation (paper II) and risk of rehospitalisation with overactive, aggressive, disruptive or agitated behavior (paper III), respectively. Both univariate and multivariate analyses were conducted in order to test the robustness of the results. However, we expected that the use of different psychotropic drug classes would interfere with each other and affect the primary outcome. Hence, we chose multivariate analyses as the primary analysis. R. 4.0.2 (https://www.r-project.org/) was used for the statistical analyses, and we checked the Cox-proportional hazard assumption by using the cox.zph() function.

In paper I we investigated the association between mortality risk and non-use of antipsychotic drugs. In the multivariate analysis, we adjusted for age at index admission, gender, acute psychiatric hospital admissions, excessive use of alcohol and illicit substances and the use of benzodiazepines and antidepressants. We conducted sensitivity analyses that included an interaction term between use of antipsychotic drugs and age, and also analyses in separate age groups.

In paper II the associations between risk of acute rehospitalisation and the use of antipsychotics, antidepressants, mood stabilizers and benzodiazepines were investigated. The model also adjusted for gender, age at index admission, and excessive use of alcohol and illicit substances. We conducted a sensitivity analysis adjusting for both previous history of hospitalization and GAF score at discharge of the index admission. The GAF score used in the sensitivity analyses was based on a joint mean of the symptom and function subscales in the split version of GAF divided by two.

In paper III we investigated the association between risk of acute readmission with overactive, aggressive, disruptive or agitated behavior and use of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines. We adjusted for gender, age at index admission, and excessive use of alcohol and illicit substances in the multivariate analyses. Chi-square tests and t-tests, comparing clinical and sociodemographic characteristics between the total group (n=663) and the group that was censored because the level of OADA was not reported at readmission (n=141) were conducted, as well as corresponding analyses between the total group and the group with presence of OADA (n=161). Furthermore we did a multivariate sensitivity analysis where patients with missing AUS/DUS scores were censored instead of set to 0, and also a sensitivity analysis where multiple imputation was used to estimate the missing AUS/DUS scores.

3.5 Ethics

All the papers in the present thesis are based on data from the Suicidality in Psychiatric Emergency Admissions (SIPEA)-study. In November 2019, the original SIPEA-study was terminated, but immediately continued as the SIPEA II-study. Both SIPEA I and SIPEA II have received approval from the Regional Committee for Medical Research Ethics (Approval No. 2009/1057 for SIPEA I and REK 46004 for SIPEA II), as well as from the Norwegian Centre for Research Data and the Norwegian Directorate of Health. In the SIPEA-study, patient information is used without informed consent from the patients. Such use of patient information was authorized by the mentioned authorities. Further elaboration on use of patient information without consent is provided in section 3.6.4 Ethical considerations.

3.6 Methodological considerations

3.6.1 Collection of data

The information on how the patients used antipsychotic and other psychotropic drugs was collected retrospectively from the medical records. Not all periods of non-adherence are discovered and described in the medical journals, and retrospective data collection increases the risk that some periods of non-adherence are overlooked. Furthermore, such data collection always involves elements of subjectivity. Predefined algorithms for the registration were used in cases of doubt, and if there were any uncertainty regarding the patients' use of psychotropic drugs, the patients were censored. In this way, we ensured a transparent and rigorous data collection.

3.6.2 Variables

In papers II and III, there were some missing scores for AUS (N=77) and DUS (N=69). For 61 patients, there were missing scores for both AUS and DUS. In these cases, the scores were set to 0. Ideally all patients with missing scores on AUS/DUS should be censored. However, such a solution would lead to fewer outcome events and weaker statistical power. An alternative strategy is to use imputation to estimate the scores. Excessive use of alcohol and illicit substances were not the main objective of these studies, and hence we decided to set missing scores to 0. In order to control the results, we conducted two sensitivity analyses, one where multiple imputation was used to estimate the missing scores and one multivariate sensitivity analysis where patients with missing values were censored. For paper II, these analyses were conducted after the paper was accepted and published, but the results were no different than in the main analysis. In paper III, the estimates of these sensitivity analyses were mainly not different from those in the main analysis, but the use of antidepressants was no longer significantly associated with readmission with OADA (p=0.06 in both analyses).

3.6.3 Statistical methods

Cox models are based on a fundamental assumption that the hazards are proportional. We tested that the assumption was met by using the cox.zph() function in R. When the assumption of proportional hazards is met, it means that the hazard ratio between two patients with a different set of predictor variables remains constant. Another important advantage is that Cox regression models can handle time dependent variables. As the use of psychotropic drugs were recorded as time dependent variables, reflecting periods on and off psychotropic drugs, this was essential for our decision to use Cox models in our main statistical analysis.

3.6.4 Ethical considerations

The use of patient information without informed consent was authorized by the Regional Committee for Medical Research Ethics, the Norwegian Centre for Research Data and the Norwegian Directorate of Health. From an ethical perspective, such use of patient data without consent can be questioned, given the Helsinki declaration (WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects – WMA – The World Medical Association) that underlines the importance of informed consent. According to the Health Research Act (Lov om medisinsk og helsefaglig forskning (helseforskningsloven) - Lovdata), exceptions from the rule of informed consent can only be done if "a) the potential risks or disadvantages for the person are insignificant, b) the individual involved is not averse to it, and c) there is reason to assume that the results of the research may be of use to the person concerned or other people with the same age-specific disorder, disease, injury or condition." For the SIPEA-study, the potential gain of a study with a high number of participants and without any patient selection was considered to be of high importance. Furthermore, the SIPEA-study did not interfere with the treatment in any way, and the inconvenience associated with being included in the study was

considered to be very small. The data collection was based on standard assessment at admission, as well as information from the medical records and register data. Accordingly, participation in the study was not associated with any excess risk, harm or burden for the included patients.

4. Results

4.1 Summary of the results of Paper I

The patients were followed for 4.6 years on average (SD=3.1), and the median number of admissions were 0.65 per year. A total of 142 (20.4%) patients were censored during the study period due to lack of information about their use of antipsychotic medications. Throughout the follow-up, 48 patients (6.9%) were censored because they moved out of the hospital's catchment area, and 68 patients (9.8%) died. Of these, 40 patients (58.8%) died from natural causes and 26 (38.2%) died from unnatural causes. Cardiovascular disease and accidental poisoning were the most frequent causes of natural and unnatural death, respectively.

In the multivariate analysis, we found a significant positive association between mortality and non-use of antipsychotic drugs (Adjusted hazard ratio (AHR) =2.15, p=.006 CI: 1.24-3.72), meaning that the risk of death at any time point is 2.15 times higher in periods without use of antipsychotic drugs compared to periods with antipsychotic drug use. A positive association was also found between mortality and age (AHR=1.05, p<.001, CI: 1.04-1.07), meaning that the mortality risk increases by 5% per year. A significant negative association was found between mortality and female gender (AHR=0.50, p=.01, CI: 0.30-0.87), meaning that compared to men, the mortality risk at any time point is 50% lower for women. We did not find any significant associations between mortality and hospitalization, excessive use of alcohol, excessive use of illicit substances, use of benzodiazepines and use of antidepressants. In the univariate analyses the results were not different from those in the multivariate analyses, except for gender, where no significant association was found between mortality and gender.

In the sensitivity analysis including the interaction term between age and use of antipsychotic drugs, we found a significant negative association for the interaction effect between age and use of antipsychotic drugs (AHR=0.95, p=.01, CI: 0.92-0.99).

The interaction term reflects a linear slope, meaning that the difference in mortality risk between use and non-use of antipsychotic drugs decreases by 5% per year. The results of the sensitivity analysis were not different from those in the main analysis, and the significant positive association found between mortality and non-use of antipsychotic medications in the main analysis remained (AHR=2.88, p <.001, CI: 1.60-5.20), the AHR estimate now referring to a patient with mean age of 41.1 years. In the analyses where the association between mortality and non-use of antipsychotics were investigated separately in different age categories, the direction for the interaction effect was supported, as the largest risk differences between use and non-use were found in the youngest patients. The strongest association between mortality and non-use of antipsychotic medications was found for patients under 30 years (AHR =3.54, p=.02, CI: 1.18-10.56). We found no significant association between mortality and non-use of antipsychotic drugs in patients more than 70 years old. Calculated AHRs based on the interaction term were 6.06 and 0.60 for a 25 year old and a 75 year old, respectively. Hence, the estimated AHR in the youngest patients were smaller than the calculated AHR based on the interaction term, indicating that the magnitude of the risk difference may be overestimated by the interaction term in the youngest patients.

4.2 Summary of the results of paper Ⅱ

Throughout the follow-up period, 410 (61.8%) patients were readmitted, and the mean and median times in days to readmission were 709 and 575, respectively. During the follow-up, 17 (2.6%) patients died, 16 patients (2.4%) were censored because they moved out of the hospital's catchment area and 63 patients (9.5%) were censored due to the lack of information about their use of medications.

In the multivariate analysis, we found a significant negative association between the risk of readmission and the use of antipsychotic drugs (adjusted hazard ratio [AHR]=0.20, $p<0.01$, CI: 0.16–0.24), meaning that the risk of readmission at any time point was reduced by 80% in periods with antipsychotic drug use compared to periods without use of antipsychotic drugs. Furthermore, we found a significant positive association between the use of benzodiazepines and the risk of readmission (AHR=1.51, $p<0.01$, CI: 1.13–2.02), meaning that the risk of readmission at any time point was 51% higher when benzodiazepines were used compared to periods without use of these drugs. We found no significant associations between the risk of readmission and the use of antidepressants or mood stabilizers, or age, gender, or excessive use of alcohol or illicit substances. In the univariate analysis we found a positive association between the risk of readmission and the excessive use of illicit substances (HR=1.63, $p<0.01$, CI: 1.25–2.12), a negative association between the risk of readmission and the use of antidepressants (HR=0.60, $p<0.01$, CI: 0.45–0.80) and mood stabilizers (HR=0.70, $p<0.04$, CI: 0.50–0.99), and no significant association between the risk of readmission and the use of benzodiazepines. Otherwise, the results of the univariate analyses were similar to those of the primary analysis. In the sensitivity analysis adjusted for previous history of hospitalizations and GAF score at discharge, the results were the same as those in the primary analysis.

4.3 Summary of the results of Paper Ⅲ

During the follow-up period, 410 (61.8%) patients were readmitted at least once and of these, 161 patients were readmitted with OADA. The mean (SD) and median times in years to readmission with OADA were 2.8 (2.6) and 2.1, respectively. Throughout the study period, 237 (35.7%) were censored. Of these, 17 patients died, 16 patients moved out of the hospital's catchment area, 63 patients were censored due to the lack of information about their use of medications and 141 (21.3%) were censored because the level of OADA was not reported at readmission.

In the multivariate analyses, we found a significant negative association between readmission with OADA and the use of antipsychotic medications (Adjusted hazard ratio (AHR) =0.33, p<0.01, CI: 0.24-0.46) and antidepressants (AHR=0.57, p=0.03, CI: 0.34-0.95), meaning that compared to periods of non-use, the risk of readmission with OADA at any time point is reduced by 67% and 43% for use of antipsychotics and antidepressants, respectively. We also found a significant negative association between readmission with OADA and female gender (AHR=0.59, p<0.01, CI: 0.41-0.84),), meaning that compared to men, the risk of readmission with OADA at any time point is 41% lower for women. Furthermore, we found a significant positive association between readmission with OADA and the use of benzodiazepines (AHR=1.95, p<0.01, CI: 1.31-2.90) and excessive use of illicit substances (AHR=1.59, p=0.04, CI: 1.02-2.45), meaning that compared to in periods of non-use, the risk of readmission with OADA is increased by 95% and 59% for use of benzodiazepines and excessive use of alcohol and illicit substances, respectively. We did not find any significant associations between readmission with OADA and age, use of mood stabilizers and excessive use of alcohol. The results of the univariate analyses were not different from those in the main analysis. Furthermore, the results from the two sensitivity analysis, one where missing AUS/DUS scores were censored and one where multiple imputation was used to estimate the missing AUS/DUS scores, were also similar to those in the main analysis. However, despite unchanged effect sizes, the

use of antidepressants was no longer significantly associated with readmission with OADA in any of the sensitivity analyses (p=0.06 in both analyses).

A total of 141 patients were censored because the level of OADA was not reported at readmission, but no differences were found between the total group (n=663) and the censored group (n=141) when we investigated clinical and sociodemographic characteristics at first discharge. In corresponding analyses between the total group and the group with presence of OADA (n=161), we found a significantly higher (p=0.01) proportion of men in the group with presence of OADA compared to in the total group. Otherwise, no differences were found between these groups.

5. Discussion

5.1 Summary

The unifying theme of all the studies addresses the dramatically elevated risk of death in schizophrenia by investigating health-related outcomes, directly or indirectly related to mortality. Our main findings were that use of antipsychotic drugs are associated with reduced risks of death, readmission and readmission with OADA in patients with schizophrenia. We also found that the use of antidepressants is associated with reduced risk of acute readmission with OADA and that the use of benzodiazepines is associated with increased risk of acute readmission and acute readmission with OADA. To the best of our knowledge, these are the first studies that investigate the association between use of psychotropic drugs and the risk of death, readmission and readmission with OADA in a time dependent manner, reflecting periods on and off psychotropic drugs. The studies are based on a total-cohort consisting of all patients consecutively admitted to a psychiatric acute unit during a 10 year period, and accordingly, our sample is highly representative for patients with schizophrenia admitted to a psychiatric acute unit.

5.2 Findings in relation to previous reseach

5.2.1 Mortality and antipsychotic drugs

We found that non-use of antipsychotic drugs are associated with more than a two-fold increased risk of death. This finding is in accordance with a large number of studies concluding that non-use of antipsychotic drugs increases the mortality risk.[41,64-70,114] In line with our findings, most of these studies report that non-use of antipsychotic drugs increases the mortality with a factor close to 2. The reason for the increased mortality is most likely multifactorial, but may include that non-use of antipsychotic drugs is associated with higher risk of suicide, accidents, violent incidents and a less active health care-seeking behavior, which are factors that are

associated with active psychosis.[71-74,81] A recent study also found that use of antipsychotic drugs is associated with greater adherence to cardiometabolic medications, including statins, antidiabetic drugs, antihypertensive drugs and beta-blockers.[75] Drug class differences may exist, however, as first generation antipsychotic drugs (FGAs) have been associated with increased risk of death,[63] and a few studies conducted in the era of FGAs found an association between high exposure to antipsychotic drugs and increased mortality.[115,116] Differences in the mortality risk between FGAs and SGAs, combined with different patterns of dosing across the decades probably contribute to the inconsistency in the findings in older versus more recent studies.

In our study, female gender was associated with reduced risk of mortality. Previous studies have found similar results, and report that in patients with schizophrenia, the risk of both cardiovascular mortality, lung cancer mortality and suicide are higher in men than in women.[117] Furthermore, we found that the mortality risk associated with non-use of antipsychotic drugs was age dependent, and highest in the youngest patients. In elderly patients, we found no difference in mortality risk between use and non-use of antipsychotic drugs. Previous studies have also reported that the standardized mortality rate (SMR) is higher in young patients with schizophrenia, and lower in elderly patients.[118] Moreover, a recent systematic review on short-term mortality of second-generation antipsychotics by Schneider-Thoma et al.,[119] found no evidence of increased mortality, except in elderly patients. Accordingly, our findings are in agreement with previous studies, indicating that the side effects of antipsychotic drugs may have a relatively larger impact on the mortality risk in elderly patients, and that the beneficial effect of antipsychotic drugs may be most important in the younger patients.

5.2.2 Readmission and psychotropic drugs

Our finding that use of antipsychotic drugs are associated with 80% lower risk of rehospitalisation is in line with previous literature in the field. A large number of studies, including RCTs, nationwide register studies and cohort studies have found that use of antipsychotic drugs has a strong risk-reducing effect, with hazard ratios between 0.25-0.5.[27,82,120,121] Furthermore, a systematic review and meta-analysis by Alvarez-Jimenez et al.[122] identified non-adherence to antipsychotic drugs as the most important risk factor for relapse, and reported that non-adherence was associated with a fourfold increase in the risk of relapse. It has been hypothesized that long term use of antipsychotic drugs may lead to increased sensitivity to dopamine, possibly mediated by an up-regulation of dopamine receptors and other unknown mechanisms. This may result in rebound psychosis (super-sensitivity psychosis), especially if the use of antipsychotic drugs is terminated abruptly.[27,123] However, in a recent systematic review based on 75 RCTs,[27] no statistical significant differences in relapse rates were found between studies where antipsychotics were abruptly withdrawn and studies with a more gradual withdrawal. Nevertheless, the authors underline that due to methodological limitations, the theory of "super-sensitivity psychosis" cannot be ruled out, and accordingly, gradual withdrawal of antipsychotic drugs is strongly recommended.[27]

With regard to other psychotropic drugs, we found that use of benzodiazepines was significantly associated with increased risk of readmission, but no significant associations were found between the risk of readmission and the use of antidepressants and mood stabilizers. In general, very few previous studies have investigated the association between risk of readmission and the use of these add-on medications in patients with schizophrenia. However, our findings are in accordance with a study by Takita et al.[84] reporting that high doses of benzodiazepines at discharge are associated with shorter time to rehospitalisation in patients with schizophrenia. Moreover, our results are in line with a large, recent study by Stroup et al.[83] that found no significant association between risk of readmission and the

initiation of a mood stabilizer as an adjunction to antipsychotic drugs. The study did, however, find a significant association between reduced risk of psychiatric rehospitalisation and the initiation of an antidepressant as add-on medication (HR=0.84).[83] Similar effect sizes were found in our study, but they did not reach statistical significance, perhaps due to a substantially smaller sample in our study.

5.2.3 Aggression and psychotropic drugs

Previous literature underlines that antipsychotic drugs, and clozapine in particular, are the most effective treatment for aggression in schizophrenia.[92-95] Furthermore, non-adherence to antipsychotic drugs have been identified as the most important risk factor for aggression in patients with schizophrenia.[42] As such, our finding of an association between use of antipsychotic drugs and reduced risk of OADA is completely in accordance with previous literature.

In our study, we found that use of benzodiazepines was associated with increased risk of acute readmission with OADA. In line with this, other studies have found that patients receiving benzodiazepines had higher aggressiveness scores than patients who did not,[103] and a systematic review by Zaman et al.[101] concluded that use of benzodiazepines as an add-on medication in the treatment for psychosis-induced aggression don't seem to confer clear advantages.

In previous literature, the association between aggression and use of antidepressants is rather disputed. Whereas antidepressants have been reported to be disproportionally involved in violent incidents,[96] no such positive associations have been identified in neither systematic reviews[97] or nationwide registry data.[98] In fact, a review by Walsh et al.[99] found a negative association between use of antidepressants and aggression. In agreement with this, we found that use of antidepressants was associated with lower risk of readmission with OADA.

The role of mood stabilizers in the treatment of aggression in schizophrenia is also disputed. Recently, mood stabilizers were recommended as add-on medication in cases of clozapine-resistant aggression by an international expert survey,[124] and despite limited evidence, systematic reviews have indeed suggested that anticonvulsants may reduce aggression.[47,125] However, a cross-sectional study by Fond et al.[103] found no significant association between aggression and the use of mood stabilizers in patients with schizophrenia, which is completely in line with our findings.

5.3 Strengths and limitations

The large and comprehensive sample and the long follow-up period are two major strengths of the studies presented in this thesis. The maximum follow-up time was 10 years, with average follow-up of 4.6 years, 1.9 years and 2.8 years in paper I, II and III, respectively. The studies benefit from the transparency and completeness of the public health care system in Norway, making it possible to follow the patients through different levels of health care. In the SIPEA study, use of patient information without informed consent was authorized. Accordingly, our sample constitutes a total-cohort where all patients with a discharge-diagnosis of schizophrenia consecutively admitted to the psychiatry acute unit at Haukeland University Hospital were included. Many antipsychotic drug trials, and in particular RCTs, are typically limited by small sample sizes and highly selected samples.[126] The psychiatric acute unit at Haukeland University Hospital covers 95% of the population in the catchment area, and hence the results of our studies may be compared to results from nationwide population-based register studies with larger sample sizes. Even severely ill patients who otherwise would be unable to consent and cooperate were included, resulting in a sample that is highly representative of the population under investigation. In our sample, the median number of admissions were 0.65 per year, meaning that the

majority of patients had several relapses and readmissions during the follow-up. Although our sample is representative for the subgroup of patients suffering from several relapses (see Figure 1 in the introduction), it is not necessary representative for the subgroup with only one psychotic episode, and especially not for patients without need for inpatient treatment. Thus, the clinical and demographical characteristics of our sample may differ from corresponding characteristics in studies with less severely ill patients.

Another important strength is that the studies are based on a real-life setting. The clinical reality where patients have periods on and off psychotropic drugs, and in particular antipsychotic drugs, was accounted for. We also adjusted for other important confounders, for example excessive use of alcohol and illicit substances. Accordingly, our studies can provide valid analyses of the associations between use of different classes of psychotropic drugs and the risk of death, readmission and readmission with OADA.

The term "non-use" of antipsychotic drugs is used in all three papers, and includes both non-adherence and drug discontinuation in cooperation with a clinician. It is possible that the risk of death, readmission and readmission with OADA would have been lower if we only investigated gradual discontinuation guided by a clinician, but we don't know if or to what extent the compilation of abrupt and gradual discontinuation have affected our results. It is generally assumed that abrupt discontinuation of antipsychotics increases the risk of relapse compared to gradual discontinuation, but as already mentioned, a comprehensive meta-analyses of RCTs did not find statistically significant differences between the two strategies.[27] In line with other studies in the field, only discontinuation periods lasting two weeks or longer were recorded.[127,128] Accordingly, the differences we found between use and non-use of psychotropic drugs on risk of death, readmission and readmission with OADA are likely to be conservative estimates. Poor drug adherence is not always discovered by the health care professionals, and it is therefore possible that the adherence was poorer than registered. If so, what we registered as "use of

antipsychotic drugs" actually represent a mix of use and non-use. Thus, the differences we found in the risk of death, readmission and readmission with OADA may have been underestimated.

We recorded periods on and off psychotropic drugs, but we did not register the doses of the prescribed medications. For antipsychotic drugs, other studies in the field have suggested that the dose can be of importance. For instance, a study by Torniainen et al.,[69] found that high dose exposure to antipsychotic drugs was associated with higher overall mortality than low to moderate exposure. Thus, it is possible that the results would be different if we adjusted for doses when we investigated the associations between use of psychotropic drugs and the risk of death, readmission and readmission with OADA. However, it is impossible to know how or to what extent such an adjustment would have affected our results.

Our selection of variables for the statistical analyses reflects the main objective of our study, which was to investigate the association between use of psychotropic drugs and the risk of death, readmission and readmission with OADA. Accordingly, we chose to adjust for the most relevant factors based on previous literature, being use of different classes of psychotropic drugs, as well as for important confounding clinical variables, such as age, gender and excessive use of alcohol and illicit substances. Ideally, all potential confounding variables should be adjusted for, but it is also necessary to restrict the number of variables in the analyses for statistical reasons. In a paper by Vittinghoff et al.,[129] it is reported that the number of outcome events per predictor variable ideally should be 10 or more in Cox regression models, but that 5-9 outcome events per variable is usually sufficient. In paper I, the number of outcome events (deaths) was 68. We used 8 predictor variables in the analysis, resulting in 8.5 deaths per variable, which is considered suboptimal. However, the results of the univariate analyses were not different from those in the main analysis, except for gender. In the univariate analyses, gender was not significantly associated with mortality, most likely because women had a higher mean age (44.1 years) at index than men (39.3 years). Hence, there is no indications that the results in the main

analysis would be different with a lower number of predictor variables. The number of outcome events were considerably higher in paper II (410 patients were readmitted), and in paper III (161 patient were readmitted with OADA). We used 8 predictor variables in both papers, and accordingly, the number of outcome events per predictor variable was higher than 10 in both paper II and paper III.

Lack of variables for some possible confounding factors in the dataset also restricts which variables can be used in the analyses. Residual confounding is the distortion that remains after the analyses are adjusted for all the included confounding variables, and will always be a limitation in studies like ours. We did not have information about certain environmental factors, for example living conditions and psychosocial strains, which most likely are associated with both non-use of antipsychotic drugs and the risk of death, readmission and readmission with OADA. Furthermore, we lacked information about the non-pharmacological treatment after discharge from the hospital. Such treatments may include psychoeducation, psychotherapy, family intervention, art therapy and physical exercise. Although these variables do not represent the main objective of the study, an adjustment for such confounding variables would indeed have added value to the studies. In paper I, we lacked information about important risk factors of premature death, such as smoking habits, somatic diseases, blood pressure, cholesterol, and body mass index. It is well known that the use of antipsychotic drugs is associated with increased risk of obesity, diabetes and dyslipidemia,[54,130,131] and the burden of cardiovascular disease may as such be higher in users of antipsychotic drugs. Adding to this, smoking has been suggested to be associated with use of antipsychotic drugs, as it is speculated that smoking may reduce extrapyramidal side-effects induced by antipsychotic medications.[132] In our study, the increased mortality associated with non-use of antipsychotic drugs may therefore represent an underestimation.

An important limitation in the interpretation of our result is that it is not possible to conclude on the causal direction between use of different classes of psychotropic drugs and the risk of risk of death, readmission and readmission with OADA. For

example, we found an association between non-use of psychotropic drugs and increased mortality risk, but in principle we cannot finally conclude on whether it is non-use of antipsychotics that leads to increased mortality, or if patients with increased mortality risk tend to stop their use of antipsychotics. In order to investigate this, we conducted a univariate sensitivity analysis where only cardiovascular death was counted as an outcome event and patients who died from other causes were censored. Cardiovascular deaths are most often sudden, and even if a patient have increased risk of cardiovascular death, it is not possible to predict the time of death. Hence, it is unlikely that patients who died from cardiovascular disease stopped their use of antipsychotic drugs because they knew they were going to die. The results from this sensitivity analysis were similar to those in the main analysis, and accordingly there is support in the data that non-use of antipsychotics leads to increased mortality risk. Another example is the association between use of benzodiazepines and increased risk of readmission with OADA. Whereas use of benzodiazepines may be a direct reflection of high levels of OADA, it is also a chance that high levels of OADA is caused by the use of benzodiazepines and associated addiction and withdrawal symptoms.

A limitation of paper III is that the levels of OADA only were measured at the first day of every readmission. Although it is a common clinical experience that severe aggression or violent episodes very often lead to readmission, it is likely that some episodes of OADA didn't result in readmission and therefore escaped our registration. Furthermore, a total of 141 patients (21.3%) were censored because the level of OADA was not reported at readmission. Nevertheless, analyses comparing clinical and sociodemographic characteristics at first discharge found no differences between the total group (n=663) and the censored group (n=141). Accordingly, there is little reason to believe that the censored group deviates from the total group with respect to clinical and sociodemographic characteristics.

Further elaborations on methodological limitations are provided in section 3.6 Methodological considerations.

6. Conclusion

In this thesis we have provided evidence that use of antipsychotic drugs is associated with reduced risk of death, as well as with reduced risk of readmission and readmission with OADA, which may be indirectly related to the mortality risk in patients with schizophrenia. For the use of other psychotropic drugs, we found that antidepressants are associated with reduced risk of acute readmission with OADA and that benzodiazepines are associated with increased risk of acute readmission and acute readmission with OADA.

Accordingly, we have identified important modifiable risk factors associated with non-use of antipsychotic drugs and use of benzodiazepines. This is important knowledge for patients facing decisions concerning use versus non-use of antipsychotic drugs, but also for the patients' families and carers. In particular, health authorities and health professionals involved in the establishment of the medication-free treatment service should be aware of these findings, so that a safe treatment service for patients who do not want to use antipsychotic drugs can be ensured.

7. Future perspectives

We identified important risk factors associated with non-use of antipsychotic drugs, and our findings emphasize the importance of reducing the high rates of non-adherence in users of antipsychotic drugs. Better psychoeducation, motivational work and targeted treatment to reduce adverse effects are important measures in this regard. In general, measures to optimise the use of antipsychotic drugs and adjuvant medications should be strengthened and systematized.

Future research should aim to identify efficient strategies to reduce the antipsychotic non-adherence. An important question to address is whether a more proactive approach to treatment of side effects may reduce the non-adherence rate in patients with schizophrenia. Moreover, there is a need for further research on the association between use of benzodiazepines and risk of relapse and aggression. In this thesis, we found a significant association between use of benzodiazepines and increased risk of readmission and readmission with OADA, but we could not conclude on the direction of the causality. Future studies should use other study designs, ideally randomized controlled trials (RCTs), as this study design is well suited for research on this matter.

However, the most urgent question to address in future research is whether the newly established medication-free treatment service is safe. From a scientific point of view, a randomized controlled trial where some patients are randomized to treatment with antipsychotic drugs and others to treatment without antipsychotic drugs would be ideal. However, a study like this requires large financial resources and is affiliated with ethical considerations regarding randomizing patients to treatment without antipsychotic drugs. For obvious safety reasons, the study sample needs to be highly selected and only include patients with low risk of mortality, relapse and violent behavior. Accordingly, the sample will most likely not be representative for the average patient with schizophrenia. The study design also has to be flexible with regard to the different study groups, so that patients randomized to medication-free treatment can use antipsychotic drugs if needed, and vice versa. A small pilot study

by Morrison et al.[110] has proven that it is feasible to conduct such a study, but even with unlimited resources to conduct a large international multicenter-study, these methodological issues still can't be avoided. An alternative approach is to use other study designs to investigate this question. An example of this is the NonPharm-study, an ongoing cohort study following patients with a schizophrenia spectrum disorder who have chosen a medication-free treatment course. The patients are followed for a year with close monitoring of amongst others symptoms, function and adverse events, and the results are to be compared to the results of a control group of users of antipsychotic drugs, adjusted for age, gender and diagnosis. If the study sample is sufficiently large, the NonPharm study and similar studies can provide important information about the best clinical practice for patients with schizophrenia who chose not to use antipsychotic drugs.

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Mortality and non-use of antipsychotic drugs after acute admission in schizophrenia: A prospective total-cohort study

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ABSTRACT

Background: In society at large, it is debated whether use of antipsychotic drugs is associated with increased or decreased mortality among patients with schizophrenia. Large register studies have demonstrated an increased mortality risk associated with non-use of antipsychotic drugs, but prospective studies are missing.
Aims: To investigate the association between mortality and non-use of antipsychotics in patients with schizophrenia.
Method: An open cohort study included and followed all patients with a discharge-diagnosis of schizophrenia consecutively admitted to a psychiatric acute unit at Haukeland University Hospital, Bergen, Norway during a 10 year period ($n = 696$). Cox multiple regression analyses were conducted with use of antipsychotic drugs as a time dependent variable, and periods of use and non-use were compared within individual patients. Adjustments were made for gender, age at index admission, number of acute psychiatric hospital admissions, excessive use of alcohol and illicit substances and use of benzodiazepines and antidepressants.
Results: A total of 68 (9.8%) deaths were registered during follow-up. Of these, 40 (59%) had natural causes, whereas 26 (38%) had unnatural causes. Non-use of antipsychotics was associated with 2.15 ($p = .01$, CI: 1.24–3.72) times higher mortality risk compared to use of antipsychotics. The difference in mortality risk between use and non-use of antipsychotic drugs was age dependent, with the largest risk difference in young patients.
Conclusions: Non-use of antipsychotic drugs was associated with twofold increased mortality risk in patients with schizophrenia.

1. Introduction

Schizophrenia is a serious mental disorder with a prevalence just below 1% (Janoutova et al., 2016; Kahn et al., 2015), and is associated with severe problems in many areas of life, including inability to work, social disability and drug abuse (Tandon et al., 2009). Antipsychotic drugs remain a cornerstone in treatment guidelines worldwide (Hasan et al., 2013; Lally and MacCabe, 2015), but treatment can be challenging, reflected by non-adherence rates as high as 40–75% (Lacro et al., 2002; Leucht and Heres, 2006). Recently, patient organizations have advocated for the need of psychosis treatment without antipsychotic drugs. As a result, «medication-free» treatment services have been established within the Norwegian public health care system. Although some studies on psychosocial interventions for schizophrenia without the use of antipsychotic drugs have been conducted, the evidence is generally of low quality (Cooper et al., 2020). Hence, there is an urgent need to evaluate the consequences of choosing not to use antipsychotic drugs.

The mortality risk among patients with schizophrenia is considerably higher than in the general population (Heiberg et al., 2018; Nome and

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Holsten, 2012), with reduced life expectancy reported in the range of 11 to 20 years (Hjorthoj et al., 2017; Laursen et al., 2013). Increased risk of premature death from both natural and unnatural causes have been found, with cardiovascular disease (CVD), respiratory disease and suicide being major causes (Olfson et al., 2015). Although reasons are likely to be multifactorial, spanning from genetic vulnerability to lifestyle factors (Andreassen et al., 2013), it is evident that common adverse effects of antipsychotic drugs such as obesity, dyslipidaemia, and diabetes contribute to the increased mortality risk (Mackin et al., 2007). Paradoxically, however, a great number of studies find a decreased risk of death associated with the use of antipsychotics compared to non-use, as demonstrated in a recent meta-analysis (Vermeulen et al., 2017). Methodological shortcomings of the studies, particularly related to their retrospective designs (Chen et al., 2019; Vermeulen et al., 2017), make them vulnerable to incomplete reporting of data and inadequate control for potentially confounding variables (De Hert et al., 2010; Thygesen and Ersboll, 2014). There is thus a need of prospective studies with predefined research questions and targeted data acquisition that account for crucial factors such as non-adherence and the high drug discontinuation rates. Accordingly, we aimed to investigate how use versus non-use of antipsychotic drugs is associated with mortality in a total-cohort of patients with schizophrenia consecutively admitted to a large psychiatry acute unit.

2. Material and methods

2.1. Sample

The study was conducted at the Division of Psychiatry, Haukeland University Hospital, Bergen, Norway. Haukeland University Hospital receives approximately 95% of all patients in need of acute psychiatric hospital admission from a catchment area of about 400,000 inhabitants. All patients consecutively admitted to the Psychiatry Acute Unit between May 1st 2005 and June 15th 2014, who met the criteria of a discharge ICD-10 (https://icd.who.int/browse10/2019/en) diagnosis of schizophrenia (F 20.0-F 20.9) were eligible for inclusion. As presented in Fig. 1, a total of 772 eligible patients were admitted during the 10-year period. Of these, 76 patients were excluded due to lack of information about the use of antipsychotic drugs after discharge. Accordingly, 696 patients were included in the final sample.

2.2. Procedure

Patients with a diagnosis of schizophrenia were included at the first acute admission during the study period, hereby named the index admission. Clinicians who were involved in the assessment of patients at admission underwent training in the rating scales used. The patients were followed from the first day of the index-admission and until May 1st 2015 or the date of death or censoring. Patients were censored when they moved out of the hospital catchment area ($n = 48$), or if they were lost to follow-up for other reasons ($n = 142$). If no information about the patients use or no-use of antipsychotic medication was available, the patient was censored after the last day of information. Data, including periods of use and periods of non-use of antipsychotic drugs, were collected from the medical records for each patient both during and in-between any hospital admissions. The study benefits from the complete and transparent public mental health system in Norway, which makes it possible to follow individual patients through the follow-up at different levels of care. Data on drug prescriptions and adherence during the periods in-between admissions were obtained retrospectively from the patients' medical records. Drug adherence in-between admissions was evaluated based on all available information from the patients, families, mental health care records and serum level measurements of antipsychotic medications when available. To avoid discrepancy in how information was obtained and registered, M.F.S. and M.K. did all the data extraction. Any questions regarding registrations were logged and discussed in the researcher team. In order to avoid overestimation of drug discontinuation, we allowed for periods of discontinuation lasting up to two weeks without registering a termination, as long as the drug was restarted. Data on death were obtained by linking the patients' 11-digit identity number to information from the Norwegian Cause of Death Registry (conducted November 14th 2016). Dates for moving out of the hospital's catchment area were recorded from the medical records.

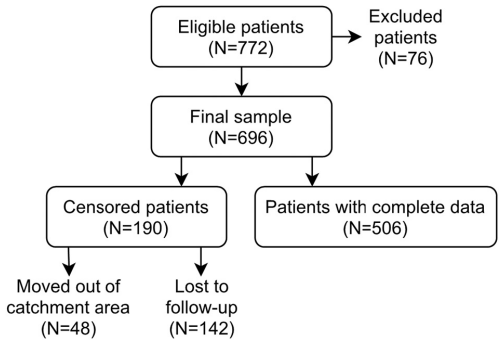

Fig. 1. Flow of patients through the study.

2.3. Measurements

To reflect treatment periods with and without antipsychotic drugs, we recorded the use of as a time dependent variable, meaning that the variable may change for an individual patient during the follow-up period. The antipsychotic drug-variable was coded 1 for the time period a patient used antipsychotic drugs, and 0 otherwise. The term "non-use" of antipsychotic drugs included both patient non-adherence and clinician-guided drug discontinuation. Medications were classified according to the Anatomical Therapeutic Chemical- (ATC) system, and only antipsychotics primarily given on the indication of psychosis were counted. Included antipsychotic drugs were amisulpride, aripiprazole, clozapine, flupentixol, haloperidol, olanzapine, paliperidone, perphenazine, pimozide, quetiapine, risperidone, sertindole, ziprasidone and zuclopenthixol. The use of alcohol and illicit substances were measured using the Alcohol Use Scale (AUS) and the Drug Use Scale (DUS), single-item clinician-rated indexes of alcohol and drug abuse (Drake et al., 1996). Use is measured on a 5-point scale from no problems to extremely severe problems. In accordance with previous literature, a score of 3 or higher was classified as excessive use (Van Wormer, 2010). For patients with two or more admissions during the study period, the highest given score on AUS and DUS was used in the analyses. When values were missing ($n = 30$), the AUS and DUS score were set to 0. Acute psychiatric hospital admissions and the use of benzodiazepines and antidepressants were recorded as time dependent variables. The variables were coded 1 if admitted to hospital or when benzodiazepines and antidepressants where used, and 0 otherwise. Acute psychiatric hospital admissions included inpatient treatment periods at Community Mental Health Centres (CMCH) directly following an acute admission.

2.4. Statistics

Cox regression models were used to analyse the effect of antipsychotic drugs use on mortality, which was the primary endpoint of the study. In order to test the robustness of the results, both univariate and multivariate analyses were conducted. The models compare the continuous mortality risk of use versus non-use of antipsychotic drugs. The multivariate model adjusted for gender, age at index admission, acute psychiatric hospital admission, excessive use of alcohol and illicit substances and use of benzodiazepines and antidepressants. Sensitivity

analyses including an interaction term between use of antipsychotic drugs and age were undertaken, as well as analyses in separate age categories. The statistical software *R version 4.0.2* (https://www.r-project.org/) and the package *survival* were used for the statistical analyses. The cox-proportional hazard assumption was checked using the cox.zph() function.

2.5. Ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Norwegian Social Science Data Service, the Norwegian Directorate of Health Care and the Regional Committee for Medical Research Ethics (Approval number REK 46004). Use of patient information without informed consent was authorized by these instances.

3. Results

Clinical and sociodemographic characteristics are presented in Table 1. On average, patients were followed for 4.6 years (SD = 3.1). The median number of admissions were 0.65 per year. Throughout the study period, 142 (20.4%) patients were censored due to lack of information about their use of antipsychotic medications. During follow-up, 48 patients (6.9%) were censored because they moved out of the hospital's catchment area, and 68 patients (9.8%) died. A total of 40 patients (58.8%) died from natural causes and 26 (38.2%) died due to unnatural causes. The most frequent causes of death were cardiovascular disease and accidental poisoning for natural and unnatural death, respectively. Causes and age at time of death are presented in Table 2.

Results of the Cox multivariate and univariate analyses are presented in Table 3. In the univariate analysis, there was a significant positive association between mortality and non-use of antipsychotic medications (*Adjusted hazard ratio (AHR) = 2.31, p = .002 CI: 1.36–3.94*), meaning that the risk of death at any timepoint is 2.31 times higher when antipsychotic drugs are not used compared to periods with antipsychotic drug use. There was also a positive association between mortality and age (*AHR = 1.05, p < .001, CI: 1.03–1.06)*, meaning that mortality risk increases by 5% per year. No significant associations were found between mortality and gender, hospitalization, excessive use of alcohol, excessive use of illicit substances, use of benzodiazepines and use of antidepressants. Results of the multivariate analysis were not different from those in the univariate analyses, except gender, where a significant negative association was found between mortality and female gender in the multivariate analysis (*AHR = 0.50, p = .01, CI: 0.30–0.87*).

Results of the sensitivity analysis including the interaction term between age and use of antipsychotic drugs are presented in Table 4. A significant negative association was found for the interaction effect between use of antipsychotic drugs and age (*AHR = 0.95, p = .01, CI: 0.92–0.99*). As the interaction term reflects a linear slope, this means that the difference in mortality risk between use and non-use of antipsychotic drugs decreases by 5% per year. Results of the sensitivity analysis were not different from those in the main analysis. The significant positive association between mortality and non-use of antipsychotic medications remained in the sensitivity analyses (*AHR = 2.88, p < .001, CI: 1.60–5.20*), the AHR estimate now referring to a patient at mean age (41.1 years). When the association between mortality and non-use of antipsychotics were investigated separately in different age categories, the direction for the interaction effect was supported, as the largest risk differences between use and non-use were found in the youngest patients. In the analyses for separate age categories, the strongest association between mortality and non-use of antipsychotic medications was found for patients under 30 years (*AHR = 3.54, p = .02, CI: 1.18–10.56*). For patients over 70 years, no significant association between mortality and non-use of antipsychotic drugs was found. Based on the interaction term, calculated AHR was 6.06 and 0.60 for a 25 year old and a 75 year old, respectively. Thus, the AHR estimate in the youngest age categories was smaller than that found by extrapolating the linear interaction term. Accordingly, the magnitude of the risk difference seemed to be overestimated by the interaction term in the

Table 1
Baseline characteristics of the sample ($n = 696$)[a].

	N	Percent
Gender		
Male	431	61.9%
Female	265	38.1%
Receiving social benefits at index admission (*n = 676*)	612	90.5%
Non-Norwegian ethnicity	85	12.2%
Highest completed education (*n = 617*)		
Primary school, 7–9 years	335	54.3%
Secondary school, 12 years	207	33.5%
University or college	75	12.2%
Previous treatment contact		
Outpatient care	41	5.9%
Inpatient care	620	89.1%
No previous treatment contact	35	5.0%
Schizophrenia diagnosis at discharge from index admission		
F20.0	533	76.6%
F20.1	50	7.2%
F20.2	6	1.0%
F20.3	40	5.7%
F20.4–9	67	9.6%
Comorbid alcohol or drug problem at index admission		
AUS score ≥ 3 (*n = 618*)	68	11.0%
DUS score ≥ 3 (*n = 625*)	93	14.9%
Comorbid ICD-10 diagnosis, F10.0-F19.9	97	13.9%

	Mean (range)	SD
Age at index admission	41.1 (16–92)	14.7

N = number.
SD = standard deviation.
AUS = Alcohol Use Scale.
DUS = Drug Use Scale.
ICD10 diagnoses:
F20.0 = paranoid schizophrenia.
F20.1 = hebephrenic schizophrenia.
F20.2 = catatonic schizophrenia.
F20.3 = undifferentiated schizophrenia.
F20.4–9 = post-schizophrenic depression, residual schizophrenia, simple schizophrenia, other schizophrenia and unspecified schizophrenia.
F10.0-F19.9 = mental and behavioral disorders due to psychoactive substance abuse.
[a] If values are missing, the total *n* is presented.

Table 2
Causes of mortality.

	N	Percent
Died during follow-up	68	9.8%[a]
Natural death	40	58.8%[b]
Neoplasms	7	10.3%[b]
Cardiovascular disease	18	27.9%[b]
Chronic lower respiratory disease	9	13.2%[b]
Others	6	7.4%[b]
Unnatural death	26	38.2%[b]
Suicide	9	13.2%[b]
Accidental poisoning	13	19.1%[b]
Other accidents	4	5.9%[b]
Unknown cause of death	2	2.9%[b]

	Mean (range)	SD
Age at time of death	51.3 (19–93)	17.8

[a] Percent of total ($n = 696$).
[b] Percent of deceased ($n = 68$).

Table 3
Predictors of death.

T	Multivariate analysis			Univariate analyses		
	AHR	95% CI	*P*-value	HR	95%CI	P-value
Age at index admission, per year	1.05	1.04–1.07	<.001	1.05	1.03–1.06	<.001
Gender (male gender = 1)	0.50	0.30–0.87	.01	0.68	0.40–1.15	.15
Non-use of antipsychotic drugs (use = 1)	2.15	1.24–3.72	.006	2.31	1.36–3.94	.002
Acute psychiatric hospital admission (no = 1)	1.37	0.71–2.65	.34	1.25	0.66–2.38	.49
Excessive use of alcohol[a] (no = 1)	0.87	0.44–1.74	.69	1.02	0.58–1.79	.94
Excessive use of illicit substances[b] (no = 1)	1.99	0.98–4.05	.06	1.19	0.69–2.07	.53
Use of benzodiazepines (no = 1)	1.27	0.68–2.35	.45	1.35	0.74–2.47	.33
Use of antidepressants (no = 1)	0.59	0.27–1.31	.20	0.48	0.22–1.05	.07

AHR = adjusted hazard ratio.
[a] AUS ≥ 3.
[b] DUS ≥ 3.

Table 4
Predictors of death: sensitivity analysis including interaction term between age and use of antipsychotic drugs.

T	Multivariate analysis		
	AHR	95% CI	P-value
Age at index admission, per year	1.07	1.05–1.09	<.001
Gender (male gender = 1)	0.49	0.28–0.85	.01
Non-use of antipsychotic drugs (use = 1)	2.88	1.60–5.20	<.001
Interaction between age and use of antipsychotic drugs	0.95	0.92.0.99	.01
Acute psychiatric hospital admission (no = 1)	1.50	0.77–2.89	.23
Excessive use of alcohol[a] (no = 1)	0.90	0.45–1.81	.77
Excessive use of illicit substances[b] (no = 1)	1.84	0.90–3.77	.09
Use of benzodiazepines (no = 1)	1.26	0.68–2.35	.46
Use of antidepressants (no = 1)	0.63	0.28–1.39	.25

AHR = adjusted hazard ratio.
[a] AUS ≥ 3.
[b] DUS ≥ 3.

youngest patients.

4. Discussion

In this cohort of acutely admitted patients with schizophrenia, non-use of antipsychotic drugs after discharge was associated with increased mortality risk. The risk difference between use and non-use of antipsychotic drugs was age dependent, with the largest risk difference in young patients. The association between mortality and use versus non-use of antipsychotic drugs was analysed in a time dependent manner, and we are not aware of similar studies conducted in a consecutively included total-cohort. As even the most severely ill patients were included, our sample is representative for patients with schizophrenia discharged from hospital after an acute admission.

It is generally assumed that common adverse effects of antipsychotic drugs such as obesity, dyslipidaemia, and diabetes mellitus contribute to premature mortality in schizophrenia (Mackin et al., 2007). Indeed, antipsychotics seem to increase the risk of myocardial infarction and cerebrovascular incidences (Correll et al., 2017; Yu et al., 2016). Rarely, antipsychotic drugs may cause malignant arrhythmias, myocarditis, thromboembolism and sudden cardiac death (Bellissima et al., 2018; Jonsson et al., 2018; Ray et al., 2009; Wu et al., 2015; Zhu et al., 2019). Some studies conducted in the era of first generation antipsychotic drugs have found an association between high exposure to antipsychotic drugs and increased mortality (Joukamaa et al., 2006; Waddington et al., 1998). Further, first generation antipsychotics, but not second generation drugs, were found to be associated with increased mortality risk in a health insurer database (Tenback et al., 2012). Different mortality risk between antipsychotic drug classes may contribute to some inconsistent findings in old versus more recent studies, reflecting temporal different patterns of antipsychotic drug use and dosing across decades. A study by Torniainen et al. (Torniainen et al., 2015) also reported higher risk of death in patients with higher exposure to antipsychotic drugs compared to patients with low or moderate exposure. Paradoxically, the highest risk of death was found in patients that do not use antipsychotic drugs, suggesting that poor life-style and reduced capacity for health promoting behaviour associated with untreated psychosis may outweigh the long-term adverse effects of antipsychotic drugs (Tiihonen et al., 2009).

Our results are in line with the study by Torniainen et al. (Torniainen et al., 2015) as well as a large number of studies concluding that use of antipsychotic drugs decreases the mortality risk (Baxter et al., 2016; Crump et al., 2013; Cullen et al., 2013; Taipale et al., 2018; Tiihonen et al., 2011; Tiihonen et al., 2009; Tiihonen et al., 2016; Tiihonen et al., 2006; Torniainen et al., 2015; Vermeulen et al., 2017). Completely in accordance with our findings, most of these studies report that non-use of antipsychotic drugs increases the mortality risk with a factor close to 2. Reasons are most likely multifactorial, but may include that patients with untreated psychosis have a higher risk of suicide (Aydin et al., 2019; Nielssen et al., 2012). Symptoms associated with psychosis, such as distorted perception of reality, disorganized thoughts, impulsivity and poor problem solving skills can compromise the patients' ability to perceive risks and protect themselves, and these patients are more likely to be involved in accidents and violent incidents (Teplin et al., 2005). Adding to this, studies have shown that CVD risk factors are not only associated with antipsychotic medications, but also with schizophrenia itself (Andreassen et al., 2013; Rajkumar et al., 2017). This association is extra unfortunate bearing in mind that patients with psychosis tend to seek medical care for somatic problems less often than the general population, and are likely to demonstrate poor understanding of physical illnesses and preventive behaviour (Kim et al., 2019; Swildens et al., 2016). Thus, dampening of psychosis may facilitate a healthier lifestyle and more active health care-seeking behaviour in case of emerging somatic symptoms. Antipsychotic drugs may as such contribute to decreased risk of premature natural death.

Moreover, the risk difference between use and non-use of antipsychotic drugs was age dependent. The largest difference in mortality risk between use and non-use of antipsychotic drugs was found in the youngest age group. In previous studies, the highest standardized mortality rates (SMR) have been found among the youngest patients with schizophrenia, with elderly patients having the lowest SMR (Piotrowski et al., 2017). Based on this, it may be plausible that any mortality risk-reducing effect of antipsychotic drugs is most pronounced in the youngest age group, and with limited effect among the elderly. Indeed, no difference in mortality risk between use and non-use of antipsychotic drugs in elderly patients was found in our study. Interestingly, a recent systematic review on short-term mortality of second-generation antipsychotics found no evidence of increased mortality, except in elderly patients (Schneider-Thoma et al., 2018). Theoretically, the substantially reduced life expectancy found in schizophrenia may lead to survival bias, meaning that those who live to reach a high age represents a healthier subgroup. Any secondary beneficial effect of psychosis-reduction on life style and health seeking behaviour may therefore be

less important in this sub-group, whereas long-term adverse antipsychotic drug effects have relatively larger impact on mortality risk.

Our results also indicate that gender is an important factor in regard to mortality. For women, the all-cause mortality risk was significantly lower compared to men (AHR = 0.5). Similar results are found in other studies in the field, where male gender has been associated with increased risk of both natural and unnatural death. Reasons for this gender differences are multifactorial, and studies have reported that cardiovascular mortality, lung cancer mortality and suicide are higher in men than in women (Olfson et al., 2015).

4.1. Limitations and strengths

Data collection such as ours will always involve some elements of subjectivity, but we have ensured transparent and rigorous methods of data collection by using defined algorithms in cases of doubt. In cases of uncertainty regarding the use of medications, the patients were censored. In the present study, the term "non-use" of antipsychotic drugs included both non- adherence and drug discontinuation guided by a clinician. We do not know how and to what extent non-adherence and sudden discontinuation of antipsychotic drugs may have affected our results. The mortality risk may be lower if the discontinuation of antipsychotic drugs is gradual under the supervision of a clinician. Poor drug adherence is not always discovered and described in the patients' medical records, and it is possible that some of the patients on oral medications had a poorer adherence than registered. If so, that would indicate that "use of antipsychotic drugs" actually is a mix of use and non-use. As such, the differences found for mortality may represent underestimations. In accordance with other studies in the field, we allowed for periods of discontinuation lasting up to two weeks without recording a termination, as long as the drug was restarted (Mullins et al., 2008; Sikka et al., 2005). This may also have caused an underestimation of the differences we found in mortality between use and non-use of antipsychotic drugs. Another limitation is the lack of information about the doses of the antipsychotic medications.

We did not have information about the patients' somatic diseases, body mass index, blood pressure, cholesterol or smoking habits, which all are potential risk factors of premature death. It has been suggested that smoking may reduce extrapyramidal side-effects induced by antipsychotic medication (Sagud et al., 2009). Therefore, it is possible that use of antipsychotic drugs is associated with more smoking than non-use. Antipsychotic drugs are also associated with increased risks of diabetes, obesity and dyslipidaemia (Liebzeit et al., 2001; Mackin et al., 2007; Stahl et al., 2009). Hence, as the burden of cardiovascular risk factors may be higher during use of antipsychotic drugs, the mortality difference attributed to use versus non-use of antipsychotic drugs may be underestimated.

As a rule of thumb, the number of outcome events per predictor variable should be 10 or more in Cox regression models (Vittinghoff and McCulloch, 2007). We used 8 predictor variables in the main analysis, and the number of outcome events (deaths) was 68. This results in 8.5 deaths per variable, which is not ideal from a statistical point of view. However, Vittinghoff et al. (Vittinghoff and McCulloch, 2007) concluded that 5–9 outcome events per variable are usually sufficient. Furthermore, results of univariate analyses were not different from those in the main analysis, except for gender. Gender was not significantly associated with mortality in the univariate analysis, probably due to higher mean age at time of index in women (44.1 years) than in men (39.3 years). Accordingly, there is little reason to assume that the results would be different with a lower number of predictor variables in the main analysis.

The large and comprehensive sample and the long follow-up time are major strengths of the present study. In average, patients were followed for 4.6 years, and the maximum follow-up time was 10 years. As use of patient information without informed consent was authorized, all patients with a discharge-diagnosis of schizophrenia consecutively admitted to a large psychiatry acute unit was included in this total-cohort. Hence, even the most severely ill patients, who would otherwise not be able to cooperate and consent, were included. Consequently, our sample is highly representative for patients with schizophrenia admitted to a psychiatric acute unit. As our sample includes *all* acutely admitted patients with schizophrenia, not only a selection, our study can be compared to nationwide register studies with larger sample sizes. However, it is important to emphasize that the majority of our participants had several relapses and readmissions. The median number of admissions were 0.65 per year, and our sample is therefore representative for the subgroup suffering from several relapses, but not necessarily for all patients with schizophrenia, and particularly not those without the need for inpatient treatment. Hence, clinical and demographical characteristics of our sample may differ from those of studies with less severely ill patients.

The reflection of the clinical reality where patients have periods on and off psychotropic drugs is another strength. Unlike most studies on mortality and use of antipsychotic drugs, we accounted for non-adherence and drug discontinuation, as well as important confounders such as use of alcohol, illicit substances, benzodiazepines and antidepressants. Accordingly, the present study is able to provide a good analysis of the association between antipsychotic drugs and death in patients with schizophrenia, and thus provide important information with regard to decision-making concerning use versus non-use of antipsychotic drugs for patients and their caretakers.

5. Conclusion

This study provides evidence that non-use of antipsychotic drugs is associated with more than twofold increased mortality risk in patients with schizophrenia. In the light of our findings, measures to optimise use of antipsychotic drugs should be strengthened and systematized. The increased mortality associated with non-use of antipsychotic drugs emphasizes the need for better psychoeducation, motivational work and tailored treatment that focuses on reduction of adverse effects.

CRediT authorship contribution statement

M.F.S drafted the manuscript and contributed to extraction of the data, study design, statistical analysis and interpretation of the results. C.B.J performed statistical analysis and contributed to study design and interpretation of the results. L.S.M. contributed to the study design, supervised the data collection of baseline-data and revised the manuscript. R.A.K. contributed to the study design and revised the manuscript. M.K. contributed to extraction of the data. L.M. contributed to the study design and revised the manuscript. E.J. revised the manuscript and contributed to study design and interpretation of the results. All authors have approved the final version of this work.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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OPEN

Use of Benzodiazepines and Antipsychotic Drugs Are Inversely Associated With Acute Readmission Risk in Schizophrenia

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Abstract:

Purpose: Little is known about the impact of different psychotropic drugs on acute readmission risk, when used concomitantly in a real-life setting. We aimed to investigate the association between acute readmission risk and use of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines in patients with schizophrenia.

Methods: A cohort study included all patients diagnosed with schizophrenia admitted to a psychiatric acute unit at Haukeland University Hospital in Bergen, Norway, during a 10-year period (N = 663). Patients were followed from discharge until first readmission or censoring. Cox multiple regression analyses were conducted using antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines as time-dependent variables, and periods of use and nonuse were compared within individual patients. Adjustments were made for sex, age at index admission, and excessive use of alcohol and illicit substances.

Results: A total of 410 patients (61.8%) were readmitted during follow-up, and the mean and median times in days to readmission were 709 and 575, respectively. Compared with nonuse, the use of antipsychotic drugs was associated with reduced risk of readmission (adjusted hazards ratio, 0.20; $P < 0.01$; confidence interval, 0.16–0.24), and the use of benzodiazepines was associated with increased risk of readmission (adjusted hazards ratio, 1.51; $P < 0.01$; confidence interval, 1.13–2.02). However, no relation to readmission risk was found for the use of antidepressants and mood stabilizers.

Conclusions: We found that use of benzodiazepines and antipsychotic drugs are inversely associated with acute readmission risk in schizophrenia.

Key Words: antipsychotic drugs, antidepressants, mood stabilizers, benzodiazepines, schizophrenia

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Schizophrenia has a lifetime prevalence rate just below 1%[1] and is a serious mental disorder characterized by delusions, hallucinations, and impaired daily functioning.[2] Relapses and rehospitalizations are common in schizophrenia with long-term readmission rates close to 70%.[3] Relapses are associated with severe challenges both at socioeconomic and individual levels. For society, the treatment cost is 4 times greater in relapsing psychosis compared with psychosis disorders without relapses.[4] At the individual level, studies have shown that relapses are associated with progressive loss of gray matter of the brain.[5] Approximately 35% experience gradually impaired daily functioning after each relapse,[6] and repeated relapses increase the risk of persistent psychotic symptoms.[7,8] Finally, active psychosis is associated with increased risks of accidents, violence, and death.[9]

Antipsychotic drugs have been found to reduce relapse and rehospitalization risks substantially. In their systematic review of randomized controlled trials (RCTs), Ceraso et al[10] observed relapse rates of 24% in the drug group compared with 61% in the placebo group at 7 to 12 months, and the number needed to benefit was 3. The corresponding risks for hospitalization were 7% and 18% for drug and placebo, respectively, with 8 as the number needed to benefit.[10] In a nationwide cohort study, the hazards ratios (HRs) for psychiatric rehospitalization were 0.5 to 0.6 compared with nonuse of antipsychotic medication.[11] With nonadherence rates as high as 50% to 75%,[12] drug discontinuation is a major challenge in the treatment of schizophrenia. Thus, optimized medication use and patient adherence are important factors in preventing relapses.

Antidepressants, mood stabilizers, and benzodiazepines are frequently used concomitantly with antipsychotic drugs in patients with schizophrenia, with reports that 70% receive a combination of antipsychotic drugs and other psychotropics.[13] Whereas antidepressants are indicated for the treatment of depression or persisting negative symptoms, benzodiazepines are primarily used for the short-term management of anxiety and sleep disorders and the tranquilization of acutely psychotic patients.[14] Mood stabilizers, such as lithium and anticonvulsants, are sometimes used as add-on medications if the patient is agitated or in the absence of a satisfactory response to ordinary antipsychotic drug treatments.[15,16] A combination of antipsychotic drugs and adjuvant psychotropics is thus a common clinical practice in the treatment of schizophrenia, but the underlying scientific evidence for the consequences of such treatment is rather shallow and inconsistent.[17]

Taken together, there is a need for prospective, naturalistic studies to investigate not only the association between unplanned admissions and the nonuse of antipsychotic drugs, but also the potential benefits and disadvantages of adjuvant medical treatment with commonly used psychotropic drugs. Accordingly, we followed a total cohort of patients with schizophrenia who were consecutively admitted to a large acute psychiatry unit. We investigated how the use and nonuse of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines are associated with the risk of unplanned readmission.

MATERIALS AND METHODS

The material and methods have been described in greater detail in an article by Stromme et al,[18] and partly also in a publication by Kroken et al,[19] which was based on the same cohort, but with substantially fewer patients, shorter follow-ups, and a focus on antipsychotic drug use only.

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Sample

This naturalistic cohort study was conducted at the Division of Psychiatry, Haukeland University Hospital, Bergen, Norway. From a catchment area of approximately 400,000 inhabitants, Haukeland University Hospital receives approximately 95% of all patients in need of acute psychiatric hospital admission. Patients were eligible for the study if they were admitted to the Psychiatry Acute Unit between May 1, 2005, and June 15, 2014, and met the criteria of the *ICD-10* (*International Classification of Diseases, Tenth Revision*) (https://icd.who.int/browse10/2019/en) diagnosis of schizophrenia (F20.0–F20.9).[20] As presented in Figure 1, 762 eligible patients were admitted during the 10-year period. Because of the discharge date after the end of the study period or the lack of information about the psychotropic drugs used after the patients were discharged, 99 patients were excluded. The final sample included 663 patients.

Procedure

Patients diagnosed with schizophrenia were included at their first acute admission during the study period, hereafter named the index admission. The follow-up started at the discharge day of the index admission and ended on May 1, 2015, or at the date of the patients' acute psychiatric readmission or censoring. If patients moved out of the hospital catchment area (n = 16), died (n = 17), or were lost to follow-up for other reasons (n = 63), they were censored. In cases where no information about the use of medications was available, the patients were censored after the last day of receiving information. Clinicians involved in the assessment of patients at admission were trained in the rating scales used. The data on drug prescriptions and adherence during follow-up were obtained retrospectively from the medical records. We evaluated drug adherence based on all available information from patients, families, medical records, and serum-level measurements of antipsychotic medications when available. To avoid discrepancy in how information was obtained and coded, 2 of the authors, M.F.S. and M.L.K., did all the data extraction. Questions regarding coding were logged and discussed by the research team. To avoid overestimation of drug discontinuation, we allowed for periods of discontinuation lasting up to 2 weeks without registering a termination as long as the drug was restarted. Dates for moving out of the hospital's catchment area were retrieved from the medical records.

Variables

Uses of antipsychotics, antidepressants, mood stabilizers, and benzodiazepines were recorded as time-dependent variables, meaning that the variables may change for an individual patient during the follow-up period. The variables were coded as 1 for the period a patient used medications, and 0 otherwise. Both patient nonadherence and clinician-guided drug discontinuation were included in the term "nonuse" of psychotropic drugs. Medications were classified according to the Anatomical Therapeutic Chemical system. Only antipsychotics primarily given and indicated for psychosis were counted: amisulpride, aripiprazole, clozapine, flupentixol, haloperidol, olanzapine, paliperidone, perphenazine, pimozide, quetiapine, risperidone, sertindole, ziprasidone, and zuclopenthixol. The included antidepressants were amitriptyline, bupropion, citalopram, clomipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, mianserin, mirtazapine, moclobemide, nortriptyline, paroxetine, phenelzine, reboxetine, sertraline, trimipramine, and venlafaxine. The group of mood stabilizers included carbamazepine, gabapentin, lamotrigine, lithium, and valproic acid. The included benzodiazepines were alprazolam, diazepam, flunitrazepam, nitrazepam, oxazepam, zolpidem, and zopiclone.

The Alcohol Use Scale (AUS) and Drug Use Scale (DUS) are single-item clinician-rated indexes of alcohol and drug use.[21] Use is measured on a 5-point scale from "no problems" to "extremely severe problems." A score of 3 or higher was classified as excessive use, which is in accordance with the previous literature.[22] When values were missing, the AUS (n = 77) and DUS (n = 69) scores were set to 0. Overall symptoms and functioning were measured by the Global Assessment of Functioning (GAF) scale score at discharge from the index admission.[23] The GAF score is measured on a 100-point scale, with lower scores indicating more severe symptoms and poorer functioning. In Norway, the split version of GAF is used, with symptoms and functioning measured in separate subscales.[23]

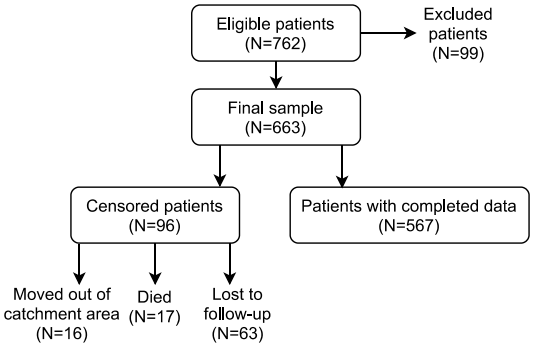

FIGURE 1. Flow of patients through the study.

Statistics

We used a Cox regression model to analyze the association between the use and nonuse of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines and the risk of unplanned psychiatric readmission, which was the primary outcome of the study. As we expected that the different psychotropic drug classes would interact with each other and affect the primary outcome, we chose to use multivariate analyses as the primary analysis. The model was adjusted for sex, age at index admission, and excessive use of alcohol and illicit substances. Univariate sensitivity analyses, as well as a sensitivity analysis adjusting for both previous history of hospitalization and GAF score at discharge, were undertaken. As the split version of the GAF was used,[23] we calculated a joint mean GAF score for the sensitivity analysis by combining the symptoms and functioning subscale scores and dividing by 2.

For the statistical analyses, we used R. 4.0.2 (https://www.r-project.org/). The Cox proportional hazards assumption was checked using the cox.zph() function.

Ethics

The study was approved by the Norwegian Directorate of Health, the Norwegian Centre for Research Data, and the Regional Committee for Medical Research Ethics (approval no. REK 46004). The use of patient information without informed consent was authorized by these authorities.

RESULTS

Clinical and sociodemographic characteristics at the baseline are shown in Table 1. A total of 410 patients (61.8%) were readmitted during the follow-up period, and the mean and median times in days to readmission were 709 and 575, respectively. Throughout the follow-up period, 17 patients (2.6%) died, 63 (9.5%) were censored due to the lack of information about their

TABLE 1. Characteristics of the Sample at Discharge (N = 663)*

	n	%
Sex		
Male	411	62.0%
Female	252	38.0%
Receiving social benefits at index admission (n = 644)	564	87.6%
Non-Norwegian ethnicity	80	12.1%
Highest completed education (n = 587)		
Primary school, 7–9 y	317	54.0%
Secondary school, 12 y	199	33.9%
University or college	71	12.1%
Previous treatment contact		
Outpatient care	40	6.0%
Inpatient care	591	89.1%
No previous treatment contact	32	4.8%
Schizophrenia diagnosis at discharge from index admission		
F20.0	503	75.9%
F20.1	49	7.4%
F20.2	7	1.1%
F20.3	38	5.7%
F20.4–9	66	10.0%
Comorbid alcohol or drug problem at index admission		
AUS score ≥3 (n = 586)	64	10.9%
DUS score ≥3 (n = 594)	90	15.2%
Comorbid *ICD-10* diagnosis, F10.0–F19.9	94	14.2%
Use of medications		
Antipsychotics	618	93.2%
Antidepressants	128	19.3%
Mood stabilizers	90	13.6%
Benzodiazepines	112	16.9%

	Mean (Range)	SD
Age at index admission	40.8 (16–92)	14.4

ICD-10 diagnoses: F20.0, paranoid schizophrenia; F20.1, hebephrenic schizophrenia; F20.2, catatonic schizophrenia; F20.3, undifferentiated schizophrenia; F20.4–9, postschizophrenic depression, residual schizophrenia, simple schizophrenia, other schizophrenia, and unspecified schizophrenia; F10.0–F19.9, mental and behavioral disorders due to psychoactive substance abuse.

*If values are missing, the total n is presented.

use of medications, and 16 (2.4%) were censored because they moved out of the hospital's catchment area.

See Figure 2 for a visual presentation of the main results and Table 2 for the complete results of the Cox multivariate and univariate analyses. In the multivariate analysis, there was a significant negative association between the risk of readmission and the use of antipsychotic drugs (adjusted hazards ratio [AHR], 0.20; $P < 0.01$; confidence interval [CI], 0.16–0.24), meaning that the risk of readmission at any time point was reduced by 80% when antipsychotic drugs were used compared with periods with no antipsychotic drug use. A positive association was found between the risk of readmission and the use of benzodiazepines (AHR, 1.51; $P < 0.01$; CI, 1.13–2.02), meaning that the risk of readmission at any time point was 1.51 times higher when benzodiazepines were used than during periods without the use of these drugs. No significant associations were found between the risk of readmission, the use of antidepressants or mood stabilizers, and age, sex, or excessive use of alcohol or illicit substances. The results of the univariate sensitivity analyses were the same as those of the main analysis for age, sex, use of antipsychotic drugs, and excessive use of alcohol. However, in the univariate analysis, there was a positive association between the risk of readmission and the excessive use of illicit substances (HR, 1.63; $P < 0.01$; CI, 1.25–2.12), a negative association between the risk of readmission and the use of antidepressants (HR, 0.60; $P < 0.01$; CI, 0.45–0.80) and mood stabilizers (HR, 0.70; $P < 0.04$; CI, 0.50–0.99), and no significant association between the risk of readmission and the use of benzodiazepines. The results of the sensitivity analysis adjusting also for previous history of hospitalizations and GAF score at discharge were not different from those in the main analysis.

DISCUSSION

The main finding was that the use of antipsychotic drugs was associated with an 80% risk reduction for unplanned rehospitalization compared with nonuse. Benzodiazepines were, on the other hand, associated with a 51% increased risk of readmissions, whereas no associations were found between the readmission risk and the use of antidepressants or mood stabilizers. The results were also confirmed in sensitivity analyses. To the best of our knowledge, this is the first study where associations between the risk of readmission and the use versus nonuse of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines have been analyzed collectively in a time-dependent manner and in a prospectively and consecutively included hospital total cohort. As even the most severely ill patients were included, our sample is highly representative of patients with schizophrenia who were discharged from the hospital after an acute admission, in general.

Antipsychotic drugs represent a cornerstone in the maintenance phase of schizophrenia remission. Most treatment guidelines worldwide recommend at least 1 to 2 years of pharmacological treatment in the first episode of schizophrenia and at least 5 years to treat multiple-episode schizophrenia.[24] For those who discontinue their treatment, the relapse rate after 12 to 18 months is 75%.[25] Nonadherence is very common among patients with schizophrenia.[12] A systematic review and meta-analysis of longitudinal studies by Alvarez-Jimenez et al[26] found that medication nonadherence was associated with a 4-fold increase in the risk of relapse and that nonadherence was the most important risk factor. Nonuse of antipsychotic drugs has also been associated with the increased risk of rehospitalization in RCTs,[10] large register

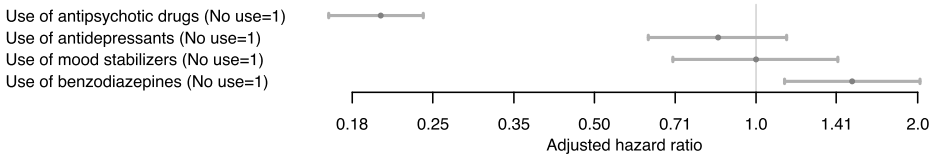

FIGURE 2. Pharmacological predictors of acute psychiatric readmission. The forest plot from the multivariate Cox regression analysis displays the AHR and the corresponding 95% CI bounds.

TABLE 2. Predictors of Acute Psychiatric Readmission

	Multivariate Analysis			Univariate Analyses		
	AHR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age at index admission, per year	1.00	0.99–1.01	0.85	1.00	0.99–1.00	0.37
Sex (male sex =1)	1.01	0.81–1.22	0.93	0.99	0.81–1.21	0.93
Use of antipsychotic drugs (no use = 1)	0.20	0.16–0.24	<0.01	0.19	0.16–0.24	<0.01
Use of antidepressants (no use = 1)	0.85	0.63–1.14	0.27	0.60	0.45–0.80	<0.01
Use of mood stabilizers (no use = 1)	1.00	0.70–1.42	0.98	0.70	0.50–0.99	0.04
Use of benzodiazepines (no use =1)	1.51	1.13–2.02	<0.01	1.20	0.91–1.59	0.20
Excessive use of alcohol* (no = 1)	1.10	0.80–1.53	0.56	1.31	0.96–1.79	0.08
Excessive use of illicit substances† (no = 1)	1.25	0.94–1.67	0.13	1.63	1.25–2.12	<0.01

*AUS ≥ 3.

†DUS ≥ 3.

studies,[11,27] and cohort studies.[19] These studies found that antipsychotic drugs had a strong risk-reducing effect, with HRs between 0.25 and 0.5. Accordingly, our naturalistic longitudinal cohort findings are in line with and corroborate current evidence.

Antidepressants and mood stabilizers are rarely recommended as adjuvant treatment in patients with schizophrenia in clinical guidelines. Despite this, a study by Puranen et al[28] found that among persons with first-episode schizophrenia, 35.4% initiated the use of antidepressants and 14.1% initiated the use of mood stabilizers within 3 years from receiving the diagnosis. Antidepressants were primarily given to treat depression or persisting negative symptoms,[17,29] whereas mood stabilizers are used as add-on medication in cases without satisfactory treatment response from antipsychotic monotherapy or if the patient is aggressive and agitated.[15,16] Valproic acid has sometimes been used to accelerate the response to antipsychotic drugs in patients with acute exacerbation of schizophrenia,[30] but no long-term benefit has been demonstrated.[31] The scientific evidence in support of the use of antidepressants and mood stabilizers in schizophrenia is limited, but Stroup et al[32] found that the initiation of an antidepressant was associated with a lower risk (HR, 0.84) of psychiatric rehospitalization compared with the initiation of another antipsychotic drug. In the present study, we found a similar effect size when investigating the association between the use of antidepressants and the risk of readmission. However, the finding did not reach statistical significance, which may be related to the substantially smaller sample in our study. In line with our results, Stroup et al[32] did not find any association between the use of mood stabilizers and the risk of psychiatric readmission.

Benzodiazepines have traditionally been used as adjuvant medication for anxiety or sleep disorders in patients with schizophrenia. However, it has also been speculated that the use of antipsychotic drugs and benzodiazepines together may provide better general outcomes than antipsychotics administrated alone.[14] Stress is a mediator of relapse in schizophrenia, and benzodiazepines may, as such, have a preventive effect.[33] Furthermore, it has been suggested that benzodiazepines may provide a direct antipsychotic effect, as they inhibit dopamine neurotransmission through their γ-aminobutyric acid–enhancing activity,[14,33] but the scientific support for this theory is limited and inconclusive. On the other hand, benzodiazepines may increase the risk of rehospitalization due to their well-known adverse effects, such as sedation, cognitive impairment, exacerbation of psychotic symptoms, and the potential for dependence, abuse, and development of tolerance.[34] Taken together, the effect of benzodiazepines in schizophrenia is disputed and rather unclear. In the present study, we found that use of benzodiazepines was significantly associated with the increased risk of readmission in patients with schizophrenia. This is in line with a study by Takita et al,[35] reporting that high doses of benzodiazepines at discharge were associated with shorter rehospitalization periods in patients with schizophrenia. However, in an observational study like ours, it is not possible to infer the causal direction of the association between use of benzodiazepines and readmission. Theoretically, use of benzodiazepines may reflect more severe symptoms, which by themselves are associated with higher risks of readmission. Alternatively, benzodiazepines may, by means of tolerance development, elicit increased anxiety and readmission risk.

We conducted both multivariate and univariate analyses. The results of univariate analyses were not different from those of the main analysis, except for the excessive use of illicit substances and the use of antidepressants, mood stabilizers, and benzodiazepines. The latter are adjuvant medications and are rarely prescribed alone for patients with schizophrenia. Accordingly, it is hard, if not impossible, to isolate the effects of antidepressants, mood stabilizers, and benzodiazepines without adjusting for the use of antipsychotic drugs in real-life studies of people with schizophrenia. Furthermore, we were not able to adjust for comorbidities, such as depression, anxiety, and sleep disorders, which may lead to the use of adjuvant medications. It is possible that the increased risk of readmission associated with the use of benzodiazepines is caused by higher levels of anxiety, not by the use of benzodiazepines.

Limitations and Strengths

Data collection, such as ours, always involves elements of subjectivity. By using defined algorithms in cases of doubt, we have ensured transparent and rigorous methods of data collection. In cases of uncertainty regarding the use of medications, the patients were censored. Another limitation of the present study is the lack of information about the patients' nonpharmacological treatment after being discharged from the hospital. Another limitation of the present study is the lack of information about the patients' nonpharmacological treatment after being discharged from the hospital. Nonpharmacological treatment may include a diverse array of therapies including various psychotherapies, art therapy, physical exercise, family interventions, and psychoeducational work, and as this was not the main objective of the present study, this information was not collected, although we recognize it may have added value to the analyses. Furthermore, we recorded periods of use and nonuse of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines, but the lack of information about

the doses was a limitation. Periods of nonuse include both nonadherence and drug discontinuation guided by a clinician. The readmission risk may be lower if the discontinuation of antipsychotic drugs is gradual under the supervision of a clinician, but we do not know how and to what extent this may have affected our results. In accordance with other studies in the field, we allowed for periods of discontinuation lasting up to 2 weeks without recording a termination as long as the drug was restarted.[36] Thus, the differences we found in the readmission risk between the use and nonuse of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines are probably conservative estimates. It is possible that some patients on oral medications had poorer adherence than registered. Poor drug adherence is not always discovered and described in the patients' medical records, and in these cases, "use" is actually a mix of use and nonuse. As such, the differences found for readmission risk may represent underestimations.

Common limitations in antipsychotic drug trials and RCTs, in particular, include methodological challenges, such as limited generalizability of outcomes due to the patient selection and sample size.[37] A major strength of our study is its large and comprehensive sample. As the use of patient information without informed consent was authorized, even the most severely ill patients, who would otherwise not be able to cooperate and consent, were included. Our sample is, therefore, highly representative of patients with schizophrenia admitted to a psychiatric acute unit. As our sample includes all acutely admitted patients with schizophrenia, not only a selection, our study can be compared with nationwide register studies with larger sample sizes. The majority of our patients experienced several relapses and readmissions. Hence, the sample is representative of the subgroup in need of at least 1 inpatient treatment period, but not necessarily for all patients with schizophrenia and not those without the need for inpatient treatment. Thus, the clinical and demographic characteristics of our sample may differ from those of studies with less severely ill patients. Another strength of this study is the real-life setting, showing the clinical reality where patients have periods on and off psychotropic drugs. We accounted for nonadherence and drug discontinuation as well as important confounders, such as the use of alcohol and illicit substances. Accordingly, our study can give a valid analysis of the association between the readmission risk and the use of different psychotropic drugs. Thus, it can provide important information with regard to decision-making concerning the use versus nonuse of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines among patients with schizophrenia.

This study provides evidence that the use of antipsychotic drugs is associated with an 80% reduced risk of unplanned rehospitalization. On the other hand, benzodiazepines were associated with a 51% increased risk of readmissions, whereas no associations were found between the readmission risk and the use of antidepressants or mood stabilizers. Considering our findings, measures to optimize the use of antipsychotic drugs and adjuvant medications should be strengthened and systematized. The strong risk-reducing effect of using antipsychotic drugs emphasizes the need for better psychoeducation and motivational work to avoid nonadherence. Before benzodiazepines are used in patients with schizophrenia, other pharmacological and nonpharmacological treatment options for anxiety and sleep disorders should be considered.

AUTHOR DISCLOSURE INFORMATION

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Overactive, aggressive, disruptive and agitated behaviour and use of psychotropic drugs in schizophrenia

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Abstract

Background: Evidence is limited for the associations between use of psychotropic drugs and overactive, aggressive, disruptive or agitated behavior (OADA)[a] in clinical practice.

Aims: To investigate the associations between risk of acute readmission with OADA and use of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines in patients with schizophrenia.

Method: A consecutive total cohort diagnosed with schizophrenia (N=663) after admittance to the Haukeland University Hospital psychiatric acute unit in Bergen, Norway, were followed form discharge during a 10-year period. At every following readmission, the level of OADA was assessed using the first item of the Health of The Nation Outcome Scale (HoNOS). Periods of use versus no-use of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines were recorded as time-dependent variables in each patient, and compared in cox multiple regression analyses.

Results: A total of 161 (24.3%) patients were readmitted with OADA, and the mean (SD) and median times in years to readmission with OADA were 2.8 (2.6) and 2.1, respectively. We found that the risk of readmission with OADA was negatively associated with use of antipsychotics drugs (Adjusted hazard ratio (AHR) =0.33, p<0.01, CI: 0.24-0.46) and antidepressants (AHR=0.57, p=0.03, CI: 0.34-0.95), positively associated with use of benzodiazepines (AHR=1.95, p<0.01, CI: 1.31-2.90 and not significantly associated with use of mood stabilizers.

Conclusions: Use of antipsychotics and antidepressants is associated with reduced risk of readmission with OADA, whereas benzodiazepines are associated with an increased risk of readmission with OADA in patients with schizophrenia.

Keywords: Schizophrenia; Aggression; Antipsychotic drugs; Antidepressants; Mood stabilizers; Benzodiazepines

[a] OADA: Overactive, aggressive, disruptive or agitated behavior

1. Introduction

Overactive, aggressive, disruptive or agitated behavior (OADA) can pose major challenges to some patients with schizophrenia, their families and carers. These behaviours represent obvious risks of injury and even death, and odds ratio close to 20 for homicide has been found in persons with psychosis compared to the general population. (Fazel et al., 2009). A systematic review and meta-analysis by Whiting et al., also found that the risk of perpetrating intrapersonal violence, including homicide, was significantly higher in persons with schizophrenia compared to in the general population (Whiting et al., 2021). Adding to this, acts of violence in the psychiatric population also significantly increase the stigma of mental illness (Torrey, 2011). Perhaps less obvious, physical aggression has also been identified as a risk factor for sudden cardiac death in people with schizophrenia (Hou et al., 2015), and agitation is associated with risk for suicide in this population (McGirr and Turecki, 2008; Pompili et al., 2009; Stephens et al., 1999). OADA may, accordingly, be highly pertinent as a contributor to the premature mortality in people with severe mental illness. The aetiology behind OADA in people with schizophrenia is heterogeneous, and aggressive behaviour might be directly linked to positive psychotic symptoms, increased impulsivity or substance abuse (Fazel et al., 2009; Volavka and Citrome, 2008). OADA is a common cause of hospitalization, and often requires longer inpatient treatment and more staff resources (Volavka, 2013).

Antipsychotic drugs, and clozapine in particular, remain the treatment of choice for management of persistent aggression in schizophrenia (Correll et al., 2017; Frogley et al., 2012; Serper, 2011). Although some studies have indicated that the drug adherence is slightly better in users of clozapine compared to in users of other antipsychotic drugs (Kroken et al., 2014; Takeuchi et al., 2020), non-adherence to antipsychotic drugs remain a major challenge, with non-adherence rates reported between 50% and 75% (Leucht and Heres, 2006). A recent study by Wu et al. (Wu et al., 2018) found that non-adherence was one of the most important risk factors associated with aggression in schizophrenia. Hence, optimized medication use and patient adherence are important factors in preventing aggression and violence. On the other hand, akathisia which commonly accompany antipsychotic drug use, may contribute to agitation (Lohr et al., 2015).

Antipsychotic medicines is the only drug class specifically targeting symptoms of psychosis in schizophrenia, but depending on the clinical picture, antidepressants, mood stabilizers and benzodiazepines are frequently co-prescribed to mitigate comorbid symptoms of depressed mood and anxiety. Despite limited evidence, many of these drugs, including zolpidem and most antidepressants, contain warnings to clinicians and patients about the possibility of aggressive or violent acts (Summary of product characteristics | European Medicines Agency (europa.eu)). In particular, there is an ongoing debate on the relation between risk of violence and the use of antidepressants (Bouvy and Liem, 2012). An analysis of adverse events reported to the U.S. Food and Drug Administration (FDA), showed that persons using antidepressants were more often involved in cases of violence (Moore et al., 2010). However, a systematic review and meta-analysis by Sharma et al. (Sharma et al., 2016) reported no increased aggression in adults using antidepressants, and another review by Walsh et al. (Walsh and Dinan, 2001) actually reported a negative association between use of antidepressants and aggression and violence. Mood stabilizers were recommended as augmentation treatment in cases of clozapine-resistant aggression in schizophrenia in a recent international expert survey (Wagner et al., 2020). Despite limited evidence, systematic reviews have suggested that anticonvulsants may be associated with reduced aggression (Huband et al., 2010; Wang et al., 2016). However, a cross-sectional study by Fond et al. (Fond et al., 2016) reported no significant association. It is well-known that lithium reduces impulsive-aggressive behaviour in patients with bipolar disorder (Benard et al., 2016), but little is known about the use of lithium for aggression in patients with schizophrenia. Benzodiazepines are often used as an add-on medication in acute situations of violent behaviour and need for urgent pharmacological tranquillisation. The scientific evidence behind the use of benzodiazepines as an add-od medication is limited and of poor quality, but so far such treatment have not been associated with any major advantages, only risk of adverse events when the use extend beyond the acute situation (Zaman et al., 2018).

Taken together, OADA are major problems in the treatment of schizophrenia, and may contribute to premature mortality. However, evidence is limited for associations between use of psychotropic drugs and overactive, aggressive, disruptive or agitated behavior (OADA) in clinical practice. Accordingly, in a consecutive total cohort of patients with schizophrenia, the study aimed to explore how unplanned psychiatric readmission with OADA might be related to use and non-use of antipsychotic drugs, antidepressants, mood stabilizers and benzodiazepines.

2. Material and methods

Parts of the material and methods have previously been described in two papers by Stromme et al. (Stromme et al., 2021; Stromme et al., 2022), based on the same cohort.

2.1. Sample

Participants were eligible for the study if they were admitted to the Psychiatric Acute Unit at Haukeland University Hospital, Bergen, Norway between May 1st 2005 and June 15th 2014, and met ICD-10 criteria (https://icd.who.int/browse10/2019/en) for schizophrenia (F 20.0–F 20.9) (Uysal, 2019). The hospital serves a catchment area population of approximately 400,000, and receives 95% of acute psychiatric hospital admissions in the area. A total of 762 patients were admitted during the 10-year period (Figure 2), but 99 could not be included as they were discharged after the end of the study period or post-discharge data about psychotropic drugs use were missing. The net sample included 663 patients.

2.2. Procedure

The first acute admission for each patient during the study period was termed the index admission. Follow-up started at discharge of the index admission, and ended May 1st 2015 or at the date of first acute psychiatric readmission with presence of OADA, the primary endpoint, or at the date of censoring. Missing OADA assessment at acute psychiatric readmissions resulted in censoring of the patients (n=141), as did moving out of the hospital catchment area (n=16), death (n=17), or loss to follow-up for other reasons (n=63).

Drug prescriptions during follow-up were registered retrospectively based on medical records, whereas all available information from patients, families, medical records, and serum-level measurements when available, was used to evaluate drug adherence. M.F.S. and M.K., did all the data extraction and any questions were continuously logged and resolved within the research team. In cases of doubt, predefined algorithms were used, and uncertainty regarding the use of medications resulted in censoring of the patient. Periods of non-use of medication lasting up to two weeks, was not registered as a termination as long as the drug was restarted thereafter. If information was missing for medication use, the patients were censored after the last day of obtained information.

2.3. Variables

The first item of Health of The Nation Outcome Scale (HoNOS) (Wing et al., 1998) is a clinician-rated instrument that measures the level of overactive or aggressive or disruptive or agitated behavior (OADA) on a five-point scale from “no problems” to “severe to very severe problems”. The scale is presented in Figure 1. We defined presence of OADA as a score of 2 (mild problem) or higher.

To capture, in the individual patients, periods with and without use of each psychotropic drug, respectively, a dichotomous time dependent variable was applied, separating “use” from “no use”. The category “no use” of psychotropic drugs included both patient nonadherence and clinician-guided drug discontinuation. We classified the medications according to the Anatomical Therapeutic Chemical (ATC) system, and counted only antipsychotics primarily given and indicated for psychosis: amisulpride, aripiprazole, clozapine, flupentixol, haloperidol, olanzapine, paliperidone, perphenazine, pimozide, quetiapine, risperidone, sertindole, ziprasidone, and zuclopenthixol. The included antidepressants were amitriptyline, bupropion, citalopram, clomipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, mianserin, mirtazapine, moclobemide, nortriptyline, paroxetine, phenelzine, reboxetine, sertraline, trimipramine, and venlafaxine. The group of mood stabilizers included carbamazepine, gabapentin, lamotrigine, lithium, and valproic acid. The included benzodiazepines were alprazolam, diazepam, flunitrazepam, nitrazepam, oxazepam, zolpidem, and zopiclone.

The Alcohol Use Scale (AUS) and Drug Use Scale (DUS) are single-item clinician-rated indexes of alcohol and drug use that measure use on a five-point scale from “no problems” to “extremely severe problems” (Drake et al., 1996). Referring to previous literature (Van Wormer, 2009), excessive use was defined as a score of 3 or higher. If a patient had more than one readmission before censoring or the end of the study, we used the highest given score on AUS and DUS in the analyses. If values were missing, the AUS (N=77) and DUS (N=69) scores were set to 0 by default.

2.4. Statistics

In each patient, periods of use versus non-use of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines were entered as time-dependent variables into the cox

multiple regression to analyze associations to readmission with OADA, the primary outcome. Univariate analyses and multivariate analyses adjusting for the use of antipsychotic drugs, antidepressants, mood stabilizers, and benzodiazepines, as well as gender, age at index admission, and excessive use of alcohol and illicit substances were conducted. Furthermore we did a multivariate sensitivity analysis where patients with missing AUS/DUS scores were censored instead of having the score of AUS/DUS set to 0, and also a sensitivity analysis where multiple imputation was used to estimate the missing AUS/DUS scores.

Chi-square tests and t-tests were conducted, comparing clinical and sociodemographic characteristics between the total group (n=663) and the group that was censored because the level of OADA was not reported at readmission (n=141). Corresponding analyses were conducted also between the total group and the group with presence of OADA (n=161).

We used R. 4.0.2 (https://www.r-project.org/) for the statistical analyses, and checked the Cox-proportional hazard assumption by using the cox.zph() function.

2.5. Ethics

The study was approved by the Norwegian Directorate of Health, the Norwegian Centre for Research Data, and the Regional Committee for Medical Research Ethics (Approval No. REK 46004). The use of patient information without informed consent was authorized by these authorities.

3. Results

Clinical and sociodemographic characteristics at the baseline are presented in Table 1. A total of 410 patients (61.8%) were readmitted at least once during the follow-up period. Of these, 161 were readmitted with OADA, and the mean (SD) and median times in years to readmission with OADA were 2.8 (2.6) and 2.1, respectively. Throughout the follow-up period, 17 (2.6%) patients died, 16 (2.4%) moved out of the hospital's catchment area, 63 (9.5%) were censored due to post-discharge missing data about psychotropic drug use and 141 (21.3%) were censored because the level of OADA was not reported at readmission.

The main results are presented in Figure 3, and the complete results of the Cox multivariate and univariate analyses are presented in Table 2. In the multivariate analyses, there were statistically significant negative associations between readmission with OADA and the use of

antipsychotic medications (Adjusted hazard ratio (AHR) =0.33, p<0.01, CI: 0.24-0.46) and antidepressants (AHR=0.57, p=0.03, CI: 0.34-0.95), meaning that compared to periods of no-use, the risk of readmission with OADA at any timepoint was reduced by 67% and 43% for use of antipsychotics and antidepressants, respectively. A significant negative association was found also between readmission with OADA and female gender (AHR=0.59, p<0.01, CI: 0.41-0.84), meaning that the risk of readmission with OADA at any timepoint was 41% lower for women compared to men. A significant positive association was found between readmission with OADA and the use of benzodiazepines (AHR=1.95, p<0.01, CI: 1.31-2.90), and excessive use of illicit substances (AHR=1.59, p=0.04, CI: 1.02-2.45). This means that compared to periods of non-use, the risk of readmission with OADA at any timepoint was increased by 95% and 59% for use of benzodiazepines and excessive use of illicit substances, respectively. No significant associations were found between readmission with OADA and age, use of mood stabilizers and excessive use of alcohol. Results of the univariate analyses were in accordance with those in the main analysis. Moreover, the results from the two sensitivity analysis, one where missing AUS/DUS scores were censored and one where multiple imputation was used to estimate the missing AUS/DUS scores, were also similar to those in the main analysis. However, although the effect sizes were unchanged, use of antidepressants was no longer significantly associated with readmission with OADA in both the sensitivity analyses (p=0.06 in both analyses).

A total of 141 patients were censored because the level of OADA was not reported at readmission. However, analyses comparing clinical and sociodemographic characteristics at first discharge found no differences between the total group (n=663) and the censored group (n=141). In accordance with our main results, corresponding analyses between the total group and the group with presence of OADA (n=161) showed that the proportion of men in the group with presence of OADA was significantly higher (p=0.01) compared to in the total group. Otherwise, no differences in clinical and sociodemographic characteristics were found between the groups.

4. Discussion

We found that use of antipsychotic drugs and antidepressants were associated with 67% and 43% lower risk of acute readmission with OADA, respectively. Use of benzodiazepines was, in contrast, associated with 95% increased risk of acute readmission with OADA, while no association was found between use of mood stabilizers and risk of acute readmission with

OADA. As far as we know, this is the first study to analyze the association between acute readmission with OADA and use versus non-use of different psychotropic drug classes in a time dependent manner and a clinically relevant setting, representing patients with schizophrenia acutely admitted to a university hospital's general psychiatric acute unit.

Antipsychotic drugs remain an important ingredient in the treatment of persistent aggression in patients with schizophrenia (Correll et al., 2017; Frogley et al., 2012; Serper, 2011). A review by Volavka et al. (Volavka, 2013) reported that clozapine was the most effective treatment of aggressive behaviour in patients with schizophrenia, and suggested that olanzapine may be the second line treatment. A high level of positive symptoms is associated with increased risk of aggression (Wu et al., 2018), and this may at least partly explain the anti-aggressive effect of antipsychotic drugs. In a study by Wu et al. (Wu et al., 2018) it was reported that non-adherence to antipsychotic drugs was the most important risk factor for aggression, with an odds ratio at 2.92. Thus, our finding of an association between use of antipsychotic drugs and reduced risk of OADA is in line with previous literature.

Antidepressants are commonly used as an adjuvant medication in schizophrenia in cases of depression or persistent negative symptoms (Ballon and Stroup, 2013; Baandrup, 2020; Puranen et al., 2020). However, the role of antidepressants in treatment of OADA is rather controversial. Most antidepressants contain warnings to clinicians and patients about the possibility of aggressive or violent acts, and antidepressants have previously been reported to be disproportionally involved in violent incidents (Moore et al., 2010). Despite this, no association between aggression and use of antidepressants in adults have been reported in neither systematic reviews (Sharma et al., 2016), nor in large studies based on nationwide registry data (Bouvy and Liem, 2012). As mentioned above, a review by Walsh et al. (Walsh and Dinan, 2001) found a negative association between use of antidepressants and aggression, suggesting that the anti-aggressive effect is caused by positive effects on the serotonergic dysfunction that is implicated in aggressive behaviour. In accordance with these findings, we found a significant lower risk of readmission with OADA in periods with use of antidepressants.

Mood stabilizers, and lithium in particular, are important in the treatment of impulsive-aggressive behaviour in patients with bipolar disorder (Benard et al., 2016). However, the scientific evidence for the effect of mood stabilizers on aggression is sparse (Huband et al., 2010; Wang et al., 2016). Studies have suggested that anticonvulsants, such as valproate, may

reduce aggression in schizophrenia (Huband et al., 2010; Wang et al., 2016). Although there is no firm evidence to support this, the use of mood stabilizers were recently recommended as augmentation in cases of clozapine-resistant aggression in schizophrenia in an international expert survey (Wagner et al., 2020). A cross-sectional study by Fond et al. (Fond et al., 2016) found no significant association between aggression and the use of mood stabilizers. In line with this, we found no significant association between use of mood stabilizers and risk of readmission with OADA in the present study.

Benzodiazepines can provide urgent pharmacological tranquillisation, and are often used in acutely agitated and aggressive patients (Wlodarczyk et al., 2017). A recent systematic review by Zaman et al. (Zaman et al., 2018) aimed to examine whether benzodiazepines are an effective treatment for psychosis-induced aggression. They concluded that use of benzodiazepines as an add-on medication did not seem to confer clear advantages, and underlined the potential for adding unnecessary adverse effects. Moreover, a cross-sectional study by Fond et al. (Fond et al., 2016) reported that patients who received benzodiazepines had higher aggressiveness scores than patients who did not. Corresponding well with these previous studies, we found that use of benzodiazepines was associated with higher risk of acute readmission with OADA. However, it is impossible to conclude on the causal direction between use of benzodiazepines and risk of readmission with OADA in our data. Theoretically, the use of benzodiazepines may be a direct reflection of high levels of OADA. On the other hand, the use of benzodiazepines may induce agitation and aggressive behaviour as a consequence of addiction and withdrawal symptoms.

Limitations and strengths

In the present study, readmission with OADA was the primary endpoint. OADA was only measured at the first day of every readmission. Hence, episodes with OADA in-between readmissions were not recorded if they did not lead to rehospitalization. However, it is a common clinical experience that episodes of severe aggression or violent behaviour very often lead to readmission. A total of 141 patients (21.3%) were censored because the level of OADA was not reported at readmission. However, analyses comparing clinical and sociodemographic characteristics at first discharge found no differences between the total group (n=663) and the censored group (n=141).

Although data collection always involves elements of subjectivity, we ensured transparent and rigorous methods of data collection by using predefined algorithms in cases of doubt, and censored patients if doubt remained regarding medication use. Information about doses were not registered, which is a limitation in the study. Furthermore, we were not able to distinguish between periods of non-use related to non-adherence or drug discontinuation guided by a clinician, respectively. If discontinuation of antipsychotic drugs is through supervised taper, the risk of OADA and readmission may theoretically be lower, but based on our data we are unable to elaborate any further on this. It is possible that the adherence to antipsychotic drugs was lower than what we registered in patients using oral medications. In these cases, "use" is actually a mix of use and non-use, and the differences found between use and non-use may represent underestimations. Periods of non-use of medication lasting up to two weeks, were not registered as discontinuations, as long as the drug was restarted thereafter. (Mullins et al., 2008). Accordingly, differences found between use and non-use of the different psychotropic drugs are probably conservative estimates. Studies like ours are always limited by residual confounding. It is likely that other environmental factors, such as for example living conditions, psychosocial strains and conflicts, may be associated with both risk of OADA and non-use of antipsychotic drugs.

Our study benefits from the large and clinically representative sample. Result of antipsychotic drug trials in general, and RCTs specifically, have been accused of limited generalizability because of risks of selection bias, short durations, and restricted sample sizes (Leucht et al., 2008). In the present study, due to its design and authorizations, all patients admitted with schizophrenia were eligible, securing the representation of even the most gravely ill. To this end, the sample is skewed towards patients with relapsing courses and previous readmissions, and primarily represent those in need of at least one hospitalization. To what extent the results might be applicable to patients with schizophrenia treated ambulatory, remains unknown. Generalisability is further strengthened by the real-life data acquisition, mirroring the usual experience of patients using psychotropic drugs in some periods but not in other. Confounding factors, such as alcohol and substance abuse, of high relevance to the primary outcome, were accounted for.

5. Conclusion

In the present study, we have provided evidence that the use of antipsychotic drugs and antidepressants were associated with 67% and 43% lower risk of acute readmission with

OADA, respectively. Use of benzodiazepines was, on the contrary, associated with 95% increased risk of acute readmission with OADA, while no association was found between use of mood stabilizers and risk of acute readmission with OADA. These findings emphasize the importance of use of antipsychotic drugs and antidepressants, and may indicate the need for a more restrictive use of benzodiazepines in patients with schizophrenia after hospital discharge.

Conflicts of interest and financial disclosures:

None

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Figure 1: Health of The Nation Outcome Scale (HoNOS); First item: Overactive, aggressive, disruptive or agitated behavior(Wing et al., 1998)

	Level of severity	Description
0	No Problem	No problems of this kind during the period rated
1	Minor problem requiring no formal action	Irritability, quarrels, restlessness etc. Not requiring action
2	Mild problem	Includes aggressive gestures, pushing or pestering others, threats or verbal aggression, lesser damage to property (e.g. broken cup or window), marked over-activity or agitation
3	Problem of moderate severity	Physically aggressive to others or animals (short of rating 4), threatening manner, more serious over-activity or destruction of property
4	Severe to very severe problem	At least one serious physical attack on others or on animals, destruction of property (e.g. fire-setting), serious intimidation or obscene behavior

Figure 2: Flow of patients through the study

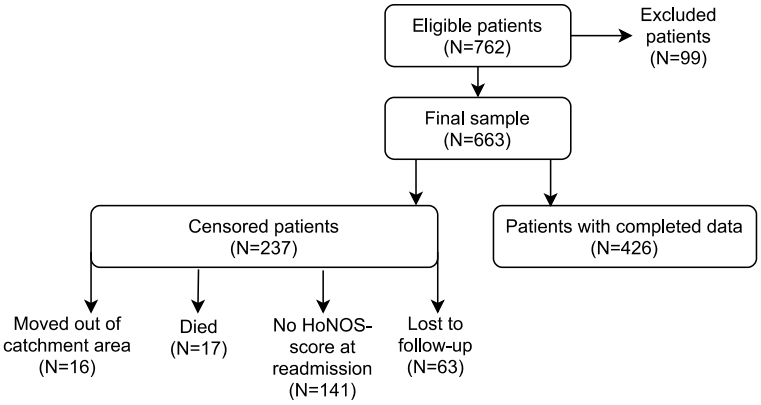

*Table 1: Characteristics of the sample at first discharge (N=663)**

	n	Percent
Gender		
Male	411	62.0%
Female	252	38.0%
Receiving social benefits at index admission *(n = 644)*	564	87.6%
Non-Norwegian ethnicity	80	12.1%
Highest completed education *(n = 587)*		
Primary school, 7-9 years	317	54.0%
Secondary school, 12 years	199	33.9%
University or college	71	12.1%
Previous treatment contact		
Outpatient care only	40	6.0%
Inpatient care	591	89.1%
No previous treatment contact	32	4.8%
Schizophrenia diagnosis at discharge from index admission		
F20.0	503	75.9%
F20.1	49	7.4%
F20.2	7	1.1%
F20.3	38	5.7%
F20.4-9	66	10.0%
Comorbid alcohol or drug problem at index admission		
AUS score ≥ 3 *(n = 586)*	64	10.9%
DUS score ≥ 3 *(n = 594)*	90	15.2%
Comorbid ICD-10 diagnosis, F10.0-F19.9	94	14.2%
Use of medications		
Antipsychotics	618	93.2%
Antidepressants	128	19.3%
Mood stabilizers	90	13.6%
Benzodiazepines	112	16.9%
	Mean (Range)	**SD**
Age at index admission	40.8 (16-92)	14.4

*If values are missing, the total *n* is presented.

N = Number

SD = Standard deviation

AUS = Alcohol Use Scale

DUS = Drug Use Scale

ICD10 diagnoses:

F20.0 = Paranoid schizophrenia

F20.1 = Hebephrenic schizophrenia

F20.2 = Catatonic schizophrenia

F20.3 = Undifferentiated schizophrenia

F20.4-9 = Post-schizophrenic depression, residual schizophrenia, simple schizophrenia, other schizophrenia, and unspecified schizophrenia

F10.0-F19.9 = Mental and behavioral disorders due to psychoactive substance abuse

Table 2: Predictors of unplanned psychiatric readmission with overactive, aggressive, disruptive or agitated behavior (OADA)

	Multivariate analysis			Univariate analyses		
	AHR	**95% CI**	**P-value**	**HR**	**95%CI**	**P-value**
Age at index admission, per year	1.00	0.99-1.01	.76	1.00	0.99-1.01	.56
Gender (male gender =1)	0.59	0.41-0.84	<.01	0.57	0.40-0.81	<.01
Use of antipsychotic drugs (No use =1)	0.33	0.23-0.46	<.01	0.31	0.22-0.43	<.01
Use of antidepressants (No use =1)	0.57	0.34-0.95	.03	0.47	0.28-0.77	<.01
Use of mood stabilizers (No use=1)	0.98	0.59-1.65	.95	0.82	0.49-1.35	.42
Use of benzodiazepines (No use =1)	1.95	1.31-2.90	<.01	1.75	1.19-2.55	<.01
Excessive use of alcohol[1] (no=1)	0.97	0.58-1.63	.91	1.35	0.83-2.18	.22
Excessive use of illicit substances[2] (no=1)	1.59	1.02-2.45	.04	2.09	1.41-3.11	<.01

AHR= Adjusted hazard ratio

[1] = AUS ≥ 3

[2] = DUS ≥ 3

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