Schizophrenia Research 248 (2022) 35–41

Contents lists available at ScienceDirect

Schizophrenia Research

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

Overactive, aggressive, disruptive and agitated behavior associated with the use of psychotropic medications in schizophrenia

Maria Fagerbakke Strømme [a,b,c,*], Christoffer Bartz-Johannesen [a,c], Rune Andreas Kroken [a,b,c], Lars Mehlum [d], Erik Johnsen [a,b,c]

[a] Division of Psychiatry, Haukeland University Hospital, Postboks 1400, 5021 Bergen, Norway
[b] Department of Clinical Medicine, University of Bergen, Haukeland University Hospital, Postboks 1400, 5021 Bergen, Norway
[c] NORMENT, Centre of Excellence, Haukeland University Hospital, Postboks 1400, 5021 Bergen, Norway
[d] National Centre for Suicide Research and Prevention, Institute of Clinical Medicine, University of Oslo, Sognsvannsveien 21, Bygg 12, 0372 Oslo, Norway

ARTICLE INFO

Keywords:
Schizophrenia
Aggression
Antipsychotics
Antidepressants
Mood stabilizers
Benzodiazepines

ABSTRACT

Background: Evidence is limited for the associations between use of psychotropic medications and overactive, aggressive, disruptive or agitated behavior (OADA)[1] in clinical practice.
Aims: To investigate the associations between risk of readmission with OADA and use of antipsychotics, antidepressants, mood stabilizers and benzodiazepines in patients with schizophrenia.
Method: A consecutive total cohort diagnosed with schizophrenia ($N = 663$) after admission to the Haukeland University Hospital psychiatric acute unit in Bergen, Norway, was followed from discharge over 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 non-use of antipsychotics, antidepressants, mood stabilizers and benzodiazepines were recorded as time-dependent variables in each patient and compared using 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 (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.

1. Introduction

Overactive, aggressive, disruptive or agitated behavior (OADA) can pose major challenges to some patients with schizophrenia, their families and carers. These behaviors represent obvious risks of injury, and even death, and an odds ratio close to 20 for homicide has been found in patients with psychosis compared to the general population (Fazel et al., 2009). A systematic review and meta-analysis by Whiting et al. (2021) also found that the risk of perpetrating intrapersonal violence, including homicide, was significantly higher in patients with schizophrenia compared to the general population. Adding to this, acts of violence in the psychiatric population also significantly increase the stigma of mental illness (Torrey, 2011). Perhaps less obvious is that physical aggression has also been identified as a risk factor for sudden cardiac death in people with schizophrenia (Hou et al., 2015) and that agitation is associated with risk of suicide in this population (Stephens et al., 1999; McGirr and Turecki, 2008; Pompili et al., 2009). OADA may, accordingly, be highly pertinent as a contributor to the premature mortality in people with severe mental illness. The etiology behind OADA in people with schizophrenia is heterogeneous, and aggressive

* Corresponding author at: Haukeland universitetssjukehus, Psykiatrisk klinikk, Sandviken, Postboks 1400, 5021 Bergen, Norway.
E-mail addresses: maria.stromme@helse-bergen.no (M.F. Strømme), christoffer.andreas.bartz-johannessen@helse-bergen.no (C. Bartz-Johannesen), rune.andreas.kroken@helse-bergen.no (R.A. Kroken), lars.mehlum@medisin.uio.no (L. Mehlum), erik.johnsen@helse-bergen.no (E. Johnsen).
[1] OADA: overactive, aggressive, disruptive or agitated behavior.

https://doi.org/10.1016/j.schres.2022.07.014
Received 2 February 2022; Received in revised form 23 June 2022; Accepted 24 July 2022
Available online 4 August 2022

behavior 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 medications, and clozapine in particular, remain the treatment of choice for the management of persistent aggression in schizophrenia (Correll et al., 2017; Serper, 2011; Frogley et al., 2012). Although some studies have indicated that the drug adherence is slightly better in users of clozapine compared to users of other antipsychotic medications (Takeuchi et al., 2020; Kroken et al., 2014), non-adherence to antipsychotic medications remain a major challenge, with non-adherence rates of 50–75 % reported (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 accompanies antipsychotic drug use, may contribute to agitation (Lohr et al., 2015).

Antipsychotic medicines are 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 medications, 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 people 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. (2016) reported no increased aggression in adults using antidepressants, and another review by Walsh and Dinan (2001) actually reported a negative association between the use of antidepressants and aggression/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. (2016) reported no significant association. It is well known that lithium reduces impulsive-aggressive behavior 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 behavior and the need for urgent pharmacological tranquilization. The scientific evidence behind the use of benzodiazepines as an add-on medication is limited and of poor quality, but so far such treatment has not been associated with any major advantages, only the risk of adverse events when the use extends beyond the acute situation (Zaman et al., 2018).

Taken together, OADA is a major problem in the treatment of schizophrenia and may contribute to premature mortality. However, evidence is limited for associations between the use of psychotropic medications and OADA in clinical practice. Accordingly, in a consecutive total cohort of all patients with schizophrenia admitted to a psychiatric acute unit, the study aimed to explore how the use and non-use of antipsychotic medications, antidepressants, mood stabilizers and benzodiazepines might be related to increased risk of psychiatric readmission with OADA.

2. Material and methods

The material and methods have been partly described in two previous papers by Stromme et al. (2021, 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 1 May 2005 and 15 June 2014 and met the ICD-10 criteria (https://icd.who.int/browse10/2019/en) for schizophrenia (F20.0–F20.9) (Uysal, 2019). The follow-up ended on 1 May 2015, which is the period of available data. 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 over the 10-year period (Fig. 2) but 99 could not be included because they were discharged after the end of the study period or post-discharge data on psychotropic medication use were missing. The net sample therefore comprised 663 patients.

2.2. Procedure

The first admission for each patient during the study period was termed the index admission. Follow-up started at discharge of the index admission and ended on 1 May 2015 or at the date of first psychiatric readmission with the presence of OADA (the primary endpoint) or the date of censoring. Missing OADA assessment at 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. carried out 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 were not registered as terminations 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 the Health of the Nation Outcome Scale (HoNOS) (Wing et al., 1998); is a clinician-rated instrument that measures the level of OADA on a five-point scale from ‘no problems’ to ‘severe to very severe problems’. The scale is presented in Fig. 1. The level of OADA was assessed for all patients at every readmission to the psychiatric acute unit. We defined the presence of OADA as a score of 2 (mild problem) or higher.

In individual patients, to capture periods with and without the use of each psychotropic drug, respectively, a dichotomous time-dependent variable was applied, separating ‘use’ from ‘non-use’. The category ‘non-use’ of psychotropic medications included both patient non-adherence 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 antidepressants included 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 benzodiazepines included were alprazolam, diazepam, flunitrazepam, nitrazepam, oxazepam, zolpidem and zopiclone.

The Alcohol Use Scale (AUS) and Drug Use Scale (DUS) are single-

	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 overactivity or agitation
3	Problem of moderate severity	Physically aggressive to others or animals (short of rating 4), threatening manner, more serious overactivity 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

Fig. 1. Health of the Nation Outcome Scale (HoNOS); first item: overactive, aggressive, disruptive or agitated behavior (Wing et al., 1998).

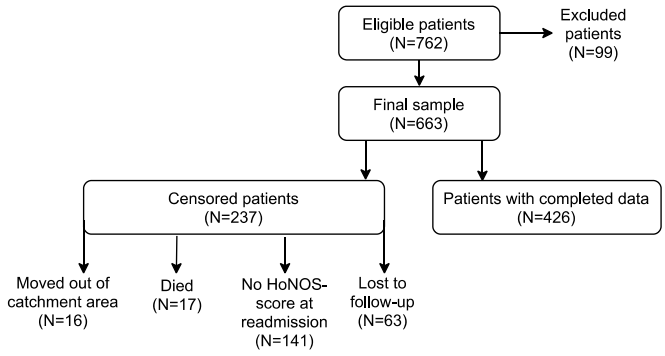

Fig. 2. Flow of patients through the study.

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 and B., 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 the AUS and DUS in the analyses. If values were missing, the AUS ($N = 77$) and DUS ($N = 69$) scores were set to zero by default.

2.4. Statistics

In each patient, periods of use versus non-use of antipsychotic medications, antidepressants, mood stabilizers and benzodiazepines were recorded as time-dependent variables, reflecting periods on and off psychotropic drugs. The Cox regression model can handle time-dependent variables and, accordingly, was used in our main statistical analysis. We analyzed associations between the use of different classes of psychotropic medications and the risk of readmission with OADA, which is the primary outcome. Use and non-use were compared in a between-individual analysis, and non-use was used as reference. Univariate and multivariate analyses were conducted, mutually adjusted for the use of antipsychotic medications, antidepressants, mood stabilizers and benzodiazepines, as well as gender, age at index admission and excessive use of alcohol and illicit substances. In the models, censored patients contributed with time from inclusion until the date of censoring. Furthermore, a multivariate sensitivity analysis was carried out, where patients with missing AUS/DUS scores were excluded instead of having the AUS/DUS score set to zero, and also a sensitivity analysis, where multiple imputation was used to estimate the missing AUS/DUS scores. Moreover, we conducted a sensitivity analysis where we distinguished between short-term (<4 weeks) and long-term (≥4 weeks) use of benzodiazepines.

Chi-square and *t*-tests were conducted, comparing clinical and socio-demographic 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 also conducted between the total group and the group with the 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.

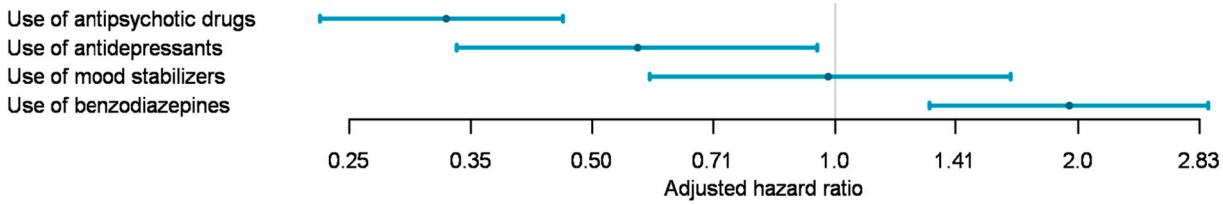

Fig. 3. Use of psychotropic drugs and risk of unplanned psychiatric readmission with overactive, aggressive, disruptive or agitated behavior (OADA).
The forest plot from the multivariate Cox regression analysis, displaying the adjusted hazard ratio and the corresponding 95%CI bounds. For reference: non-use of antipsychotic medications, antidepressants, mood stabilizers and benzodiazepines = 1.

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), which also authorized the use of patient information without informed consent.

3. Results

Clinical and sociodemographic characteristics at 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 on 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 Fig. 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 non-use, the risk of readmission with OADA at any timepoint was reduced by 67 % and 43 % for the use of antipsychotics and antidepressants, respectively. A significant negative association was found 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 the 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 or 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 analyses (one where missing AUS/DUS scores were excluded 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 the sensitivity analysis where patients with missing AUS/DUS scores were excluded (p = 0.06). The complete results of these sensitivity analyses are presented in Tables A.1 and A.2 in the Appendix. In the sensitivity analysis, where short-term and long-term use of benzodiazepines were analyzed separately, we found a positive association between readmission with OADA and both short-term (AHR = 2.92, p < 0.01, CI = 1.51–5.63) and long-term use of benzodiazepines (AHR = 1.82, p = 0.01, CI = 1.15–2.89). This means that compared to periods of non-use, short-term (<4 weeks) and long-term (≥4 weeks) use of benzodiazepines are associated with 192 % and 82 % increased risk of readmission with OADA, respectively. The complete results of this sensitivity analysis are presented in Table A.3 in the Appendix.

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

Table 1
Characteristics of the sample at first discharge (N = 663).[a]

	n	Percentage
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

N = number; SD = standard deviation; AUS = Alcohol Use Scale; DUS = Drug Use Scale.
ICD-10 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] Where values are missing, the total n is presented in parentheses.

Table 2
Risk of unplanned psychiatric readmission with overactive, aggressive, disruptive or agitated behavior (N = 663).

	Multivariate analysis			Univariate analysis		
	AHR	95 % CI	p	AHR	95 % CI	p
Age at index admission, per year	1.00	0.99–1.01	0.76	1.00	0.99–1.01	0.56
Gender	0.59	0.41–0.84	<0.01	0.57	0.40–0.81	<0.01
Use of antipsychotic medications	0.33	0.23–0.46	<0.01	0.31	0.22–0.43	<0.01
Use of antidepressants	0.57	0.34–0.95	0.03	0.47	0.28–0.77	<0.01
Use of mood stabilizers	0.98	0.59–1.65	0.95	0.82	0.49–1.35	0.42
Use of benzodiazepines	1.95	1.31–2.90	<0.01	1.75	1.19–2.55	<0.01
Excessive use of alcohol[a]	0.97	0.58–1.63	0.91	1.35	0.83–2.18	0.22
Excessive use of illicit substances[b]	1.59	1.02–2.45	0.04	2.09	1.41–3.11	<0.01

AHR = adjusted hazard ratio. The multivariate analysis is mutually adjusted for all the listed variables.
For reference: male gender = 1; and non-use of psychotropic medications, alcohol and illicit substances = 1.
[a] The Alcohol Use Scale (AUS) score is ≥3.
[b] The Drug Use Scale (DUS) score is ≥3.

total group and the group with the presence of OADA ($n = 161$) showed that the proportion of men in the group with the presence of OADA was significantly higher ($p = 0.01$) than in the total group. Otherwise, no differences in clinical and sociodemographic characteristics were found between the groups. The complete results of the sensitivity analyses are presented in Tables A.4 and A.5 in the Appendix.

4. Discussion

We found that the use of antipsychotic medications and antidepressants was associated with 67 % and 43 % lower risk of readmission with OADA, respectively. Use of benzodiazepines was, in contrast, associated with a 95 % increased risk of readmission with OADA, whereas no association was found between the use of mood stabilizers and the risk of readmission with OADA. As far as we know, this is the first study to analyze the association between 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 admitted to a university hospital's general psychiatric acute unit.

Antipsychotic medications remain an important ingredient in the treatment of persistent aggression in patients with schizophrenia (Correll et al., 2017; Serper, 2011; Frogley et al., 2012). A review by Volavka (2013) reported that clozapine was the most effective treatment of aggressive behavior in patients with schizophrenia and suggested that olanzapine may be the second-line treatment. In line with these findings, large nationwide studies from Sweden have found that compared to non-use, use of antipsychotics is associated with reduced risk of violent crime (Fazel et al., 2014; Sariaslan et al., 2021), and that clozapine, olanzapine and risperidone were associated with lower arrest and conviction risks than other antipsychotics (Sariaslan et al., 2021). 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 medications. In a study by Wu et al. (2018) it was reported that non-adherence to antipsychotic medications was the most important risk factor for aggression, with an odds ratio of 2.92. Thus, our finding of an association between the use of antipsychotic medications 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 (Puranen et al., 2020; Ballon and Stroup, 2013; Baandrup, 2020). However, the role of antidepressants in the 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 the use of antidepressants in adults has been reported in systematic reviews (Sharma et al., 2016) or in large studies based on nationwide registry data (Bouvy and Liem, 2012). As mentioned above, a review by Walsh and Dinan (2001) found a negative association between the 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 behavior. In accordance with these findings, we found a significantly lower risk of readmission with OADA in periods with the use of antidepressants.

Mood stabilizers, and lithium in particular, are important in the treatment of impulsive–aggressive behavior 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. (2016) found no significant association between aggression and the use of mood stabilizers. In line with this, we found no significant association between the use of mood stabilizers and risk of readmission with OADA in the present study.

Benzodiazepines can provide urgent pharmacological tranquilization and are often used in acutely agitated and aggressive patients (Wlodarczyk et al., 2017). A recent systematic review by Zaman et al. (2018) aimed to examine whether benzodiazepines are an effective treatment for psychosis-induced aggression. They concluded that the 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. (2016) reported that patients who received benzodiazepines had higher aggressiveness scores than patients who did not, and a large observational study by Tiihonen et al. (2015) found that the use of benzodiazepines was associated with increased risk of homicide in patients with schizophrenia. Corresponding well with these previous studies, we found that the use of benzodiazepines was associated with a higher risk of readmission with OADA. In the sensitivity analysis, where short-term (<4 weeks) and long-term (≥4 weeks) use of benzodiazepines were analyzed separately, we found that both short-term and long-term use were significantly associated with increased risk of readmission with OADA. However, an important limitation in the interpretation of our results is that it is not possible to determine the causal direction of the association between the use of different classes of psychotropic drugs and the risk of readmission with OADA. 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 behavior as a consequence of addiction and withdrawal symptoms.

4.1. Limitations and strengths

In the present study, readmission with OADA was the primary endpoint but OADA was only measured on 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 behavior 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 also censoring patients if doubt remained regarding medication use. Information on doses was not registered, which is a limitation of 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 medications is through a 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 medications was lower than that 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, the differences found between use and non-use of the different psychotropic medications are probably conservative estimates. Studies such as ours are always limited by residual confounding and it is likely that other environmental factors, such as living conditions, psychosocial strains and conflicts, may be associated with both risk of OADA and non-use of antipsychotic medications. However, these data were not available.

Our study benefits from the large and clinically representative

sample. Results of antipsychotic drug trials in general, and randomized controlled trials specifically, have been accused of limited generalizability because of risk 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, primarily representing those in need of at least one hospitalization. To what extent the results might be applicable to patients with schizophrenia treated on an outpatient basis remains unknown. Generalizability is further strengthened by the real-life data acquisition, mirroring the usual experience of patients using psychotropic medications in some periods but not in others. 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 medications and antidepressants was associated with 67 % and 43 % lower risk of readmission with OADA, respectively. Use of benzodiazepines was, on the contrary, associated with a 95 % increased risk of readmission with OADA, whereas no association was found between the use of mood stabilizers and risk of readmission with OADA. These findings emphasize the importance of the use of antipsychotic medications and antidepressants, and may indicate the need for more restrictive use of benzodiazepines in patients with schizophrenia after hospital discharge.

Funding

The study was funded by the Division of Psychiatry, Haukeland University Hospital, and received additional support in the form of research grants from the Western Norway Regional Health Authority (grant numbers: 911209/HV and 911671/HV). The funders were not involved in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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. R.A.K. contributed to the study design and revised the manuscript. 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.

Declaration of competing interest

None.

Acknowledgments

The authors thank the research nurses and scientists in the Bergen Psychosis Research Group for their contribution, which ensured the high quality of the data. In particular, we thank Liv Solrunn Mellesdal for invaluable contributions to this work, as the founder and principal investigator of SIPEA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.07.014.

References

Baandrup, L., 2020. Polypharmacy in schizophrenia. Basic Clin Pharmacol Toxicol. 126 (3), 183–192.
Ballon, J., Stroup, T.S., 2013. Polypharmacy for schizophrenia. Curr Opin Psychiatry. 26 (2), 208–213.
Benard, V., Vaiva, G., Masson, M., Geoffroy, P.A., 2016. Lithium and suicide prevention in bipolar disorder. Encéphale 42 (3), 234–241.
Bouvy, P.F., Liem, M., 2012. Antidepressants and lethal violence in the Netherlands 1994–2008. Psychopharmacology 222 (3), 499–506.
Correll, C.U., Yu, X., Xiang, Y., Kane, J.M., Masand, P., 2017. Biological treatment of acute agitation or aggression with schizophrenia or bipolar disorder in the inpatient setting. Ann. Clin. Psychiatry 29 (2), 92–107.
Drake, R.E., Rosenberg, S.D., Mueser, K.T., 1996. Assessing substance use disorder in persons with severe mental illness. New Dir. Ment. Health Serv. 70, 3–17.
Fazel, S., Gulati, G., Linsell, L., Geddes, J.R., Grann, M., 2009. Schizophrenia and violence: systematic review and meta-analysis. PLoS Med. 6 (8), e1000120.
Fazel, S., Zetterqvist, J., Larsson, H., Langstrom, N., Lichtenstein, P., 2014. Antipsychotics, mood stabilisers, and risk of violent crime. Lancet 384 (9949), 1206–1214.
Fond, G., Boyer, L., Favez, M., et al., 2016. Medication and aggressiveness in real-world schizophrenia. Results from the FACE-SZ dataset. Psychopharmacology (Berl) 233 (4), 571–578.
Frogley, C., Taylor, D., Dickens, G., Picchioni, M., 2012. A systematic review of the evidence of clozapine's anti-aggressive effects. Int. J. Neuropsychopharmacol. 15 (9), 1351–1371.
Hou, P.Y., Hung, G.C., Jhong, J.R., Tsai, S.Y., Chen, C.C., Kuo, C.J., 2015. Risk factors for sudden cardiac death among patients with schizophrenia. Schizophr. Res. 168 (1–2), 395–401.
Huband, N., Ferriter, M., Nathan, R., Jones, H., 2010. Antiepileptics for aggression and associated impulsivity. Cochrane Database Syst. Rev. 2, CD003499.
Kroken, R.A., Kjelby, E., Wentzel-Larsen, T., Mellesdal, L.S., Jorgensen, H.A., Johnsen, E., 2014. Time to discontinuation of antipsychotic drugs in a schizophrenia cohort: influence of current treatment strategies. Ther. Adv. Psychopharmacol. 4 (6), 228–239.
Leucht, S., Heres, S., 2006. Epidemiology, clinical consequences, and psychosocial treatment of nonadherence in schizophrenia. J. Clin. Psychiatry 67 (Suppl. 5), 3–8.
Leucht, S., Heres, S., Hamann, J., Kane, J.M., 2008. Methodological issues in current antipsychotic drug trials. Schizophr. Bull. 34 (2), 275–285.
Lohr, J.B., Eidt, C.A., Abdulrazzaq Alfaraj, A., Soliman, M.A., 2015. The clinical challenges of akathisia. CNS Spectr. 20 (Suppl. 1), 1–14 quiz 15–16.
McGirr, A., Turecki, G., 2008. What is specific to suicide in schizophrenia disorder? Demographic, clinical and behavioural dimensions. Schizophr. Res. 98 (1–3), 217–224.
Moore, T.J., Glenmullen, J., Furberg, C.D., 2010. Prescription drugs associated with reports of violence towards others. PLoS One 5 (12), e15337.
Mullins, C.D., Obeidat, N.A., Cuffel, B.J., Naradzay, J., Loebel, A.D., 2008. Risk of discontinuation of atypical antipsychotic agents in the treatment of schizophrenia. Schizophr. Res. 98 (1–3), 8–15.
Pompili, M., Lester, D., Grispini, A., et al., 2009. Completed suicide in schizophrenia: evidence from a case-control study. Psychiatry Res. 167 (3), 251–257.
Puranen, A., Koponen, M., Tanskanen, A., Tiihonen, J., Taipale, H., 2020. Use of antidepressants and mood stabilizers in persons with first-episode schizophrenia. Eur. J. Clin. Pharmacol. 76 (5), 711–718.
Sariaslan, A., Leucht, S., Zetterqvist, J., Lichtenstein, P., Fazel, S., 2021. Associations between individual antipsychotics and the risk of arrests and convictions of violent and other crime: a nationwide within-individual study of 74 925 persons. Psychol. Med. 1–9.
Serper, M.R., 2011. Aggression in schizophrenia. Schizophr. Bull. 37 (5), 897–898.
Sharma, T., Guski, L.S., Freund, N., Gotzsche, P.C., 2016. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ 352, i65.
Stephens, J.H., Richard, P., McHugh, P.R., 1999. Suicide in patients hospitalized for schizophrenia: 1913–1940. J. Nerv. Ment. Dis. 187 (1), 10–14.
Stromme, M.F., Mellesdal, L.S., Bartz-Johannesen, C., et al., 2021. Mortality and non-use of antipsychotic drugs after acute admission in schizophrenia: a prospective total-cohort study. Schizophr. Res. 235, 29–35.
Stromme, M.F., Mellesdal, L.S., Bartz-Johannesen, C.A., et al., 2022. Use of benzodiazepines and antipsychotic drugs are inversely associated with acute readmission risk in schizophrenia. J. Clin. Psychopharmacol. 42 (1), 37–42.
Takeuchi, H., Borlido, C., Sanches, M., et al., 2020. Adherence to clozapine vs. Other antipsychotics in schizophrenia. Acta Psychiatr. Scand. 142 (2), 87–95.
Tiihonen, J., Lehti, M., Aaltonen, M., et al., 2015. Psychotropic drugs and homicide: a prospective cohort study from Finland. World Psychiatry 14 (2), 245–247.
Torrey, E.F., 2011. Stigma and violence: isn't it time to connect the dots? Schizophr. Bull. 37 (5), 892–896.
Uysal, S., 2019. ICD-10-CM diagnosis coding for neuropsychological assessment. Arch. Clin. Neuropsychol. 34 (5), 721–730.
Van Wormer, K.T., B., 2009. Evidence-based Practice in the Field of Substance Abuse. A Book of Readings, 1 ed. SAGE Publications, Thousand Oaks, California.
Volavka, J., 2013. Violence in schizophrenia and bipolar disorder. Psychiatr. Danub. 25 (1), 24–33.

Volavka, J., Citrome, L., 2008. Heterogeneity of violence in schizophrenia and implications for long-term treatment. Int. J. Clin. Pract. 62 (8), 1237–1245.
Wagner, E., Kane, J.M., Correll, C.U., et al., 2020. Clozapine combination and augmentation strategies in patients with schizophrenia -recommendations from an international expert survey among the treatment response and resistance in psychosis (TRRIP) working group. Schizophr. Bull. 46 (6), 1459–1470.
Walsh, M.T., Dinan, T.G., 2001. Selective serotonin reuptake inhibitors and violence: a review of the available evidence. Acta Psychiatr. Scand. 104 (2), 84–91.
Wang, Y., Xia, J., Helfer, B., Li, C., Leucht, S., 2016. Valproate for schizophrenia. Cochrane Database Syst. Rev. 11, CD004028.
Whiting, D., Lichtenstein, P., Fazel, S., 2021. Violence and mental disorders: a structured review of associations by individual diagnoses, risk factors, and risk assessment 8 (2), 150–161. https://doi.org/10.1016/S2215-0366(20)30262-5.
Wing, J.K., Beevor, A.S., Curtis, R.H., Park, S.B., Hadden, S., Burns, A., 1998. Health of the nation outcome scales (HoNOS).Research and development. Br J Psychiatry 172, 11–18.
Wlodarczyk, A., Szarmach, J., Cubala, W.J., Wiglusz, M.S., 2017. Benzodiazepines in combination with antipsychotic drugs for schizophrenia: GABA-ergic targeted therapy. Psychiatr. Danub. 29 (Suppl. 3), 345–348.
Wu, Y., Kang, R., Yan, Y., et al., 2018. Epidemiology of schizophrenia and risk factors of schizophrenia-associated aggression from 2011 to 2015. J. Int. Med. Res. 46 (10), 4039–4049.
Zaman, H., Sampson, S., Beck, A., et al., 2018. Benzodiazepines for psychosis-induced aggression or agitation. Schizophr. Bull. 44 (5), 966–969.

Maria Fagerbakke Strømme: MD from 2016 and PhD-candidate at the University of Bergen from 2018. Fields of interest include psychosis, clinical psychopharmacology and sleep disorders.

Christoffer Bartz-Johannesen: Master degree at NTNU Trondheim in civil engineering, working with extreme value statistics in his master thesis. He has worked as a biostatistician at the orthopaedic department at Haukeland University Hospital before he started working at the Division of Psychiatry at Sandviken.

Rune Andreas Kroken: MD from 1989, worked in general practice before entering psychiatry, specialist of psychiatry in 1998. Has been working in clinical psychiatry in several positions, from 2012 as head of the psychosis department at Haukeland university hospital in parallel with conducting research. Completed PhD in 2013, and is currently engaged in several clinical research projects with themes including effects of antipsychotic treatment, effect of prednisolon on psychosis/schizophrenia and more broadly psychosis and inflammation/immunity.

Lars Mehlum is the founding director of the National Centre for Suicide Research and Prevention at the Institute of Clinical Medicine, University of Oslo, Norway. The past president of the International Association for Suicide Prevention (IASP), the International Academy of Suicide Research (IASR) and the European Society for the Study of Personality Disorders (ESSPD), he has a conducted numerous clinical and epidemiological studies of suicidal behavior and associated mental health problems and the efficacy of interventions. He has published >200 scientific papers and has received several national and international awards.

Erik Johnsen MD PhD is psychiatrist and head of the Bergen Psychosis Research Group and in the leader group of the Norwegian Centre for Mental Disorders Research (NORMENT) Centre of Excellence. He is head consultant at Haukeland University Hospital, professor at the University of Bergen, and is the principal investigator of several researcher initiated clinical drug trials in schizophrenia and related disorders. Fields of interest include translational psychosis research and clinical psychopharmacology.