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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]

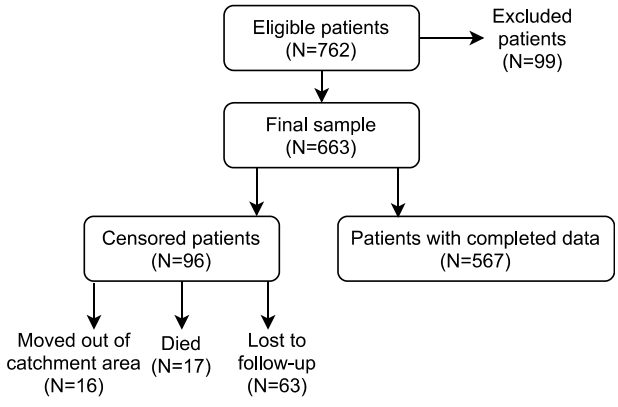

FIGURE 1. Flow of patients through the study.

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

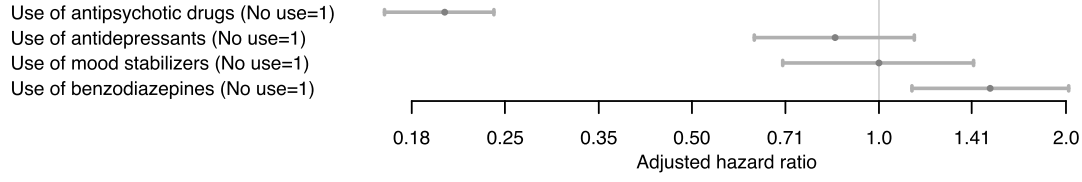

FIGURE 2. Pharmacological predictors of acute psychiatric readmission. The forest plot from the multivariate Cox regression analysis displays the AHR and the corresponding 95% CI bounds.

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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