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Pharmacological treatment for schizoaffective disorder

A comparison with schizophrenia and bipolar disorder

Although quite different from one another, schizophrenia, schizoaffective disorder, and bipolar disorder share many commonalities regarding their psychopathology, progression, and biological features—thus making clear distinctions between them difficult.

The group of schizophrenias whose biological basis exhibits an imbalance among dopaminergic, serotonergic, and glutamatergic systems is very heterogeneous [2]. There are various subtypes—paranoid, catatonic, disorganized, residual, simple, or undifferentiated schizophrenia—all requiring individualized and differentiated therapies. National and international guidelines [3–5] outline the treatment of schizophrenia, recommending monotherapy with antipsychotics. However, clinical reality reveals a growing tendency toward antipsychotic combination therapy, including combination strategies consisting of different antipsychotics and augmentation strategies consisting of an antipsychotic combined with another psychopharmacological substance class [6, 7]. Although this trend has been confirmed by both clinical and trial data exhibiting greater efficacy for combined medication [8–12], in a recently conducted systemic review and meta-analysis Galling et al. demonstrated that high-quality evidence is lacking for the efficacy of combination therapies consisting of two antipsychotics [13]. Furthermore, no high-quality studies have addressed multi-pharmaceutical combination therapies (augmentation strategies) to date.

To treat bipolar disorder in the acute phase, the national and international guidelines [14, 15] recommend mood stabilizers (e.g., lithium, valproate) or antipsychotics (e.g., olanzapine, risperidone, quetiapine) in mono- or combination therapy, while clear recommendations for the treatment of bipolar depression are lacking, because (a) the administration of antidepressants for bipolar depression is controversial, although the tendency is to recommend selective serotonin reuptake inhibitors (SSRIs) [16], (b) the use of mood stabilizers as acute monotherapy has yielded inconsistent findings [12, 16–18], and (c) the multi-pharmaceutical treatment of bipolar depression has not been adequately investigated so far. The use of antipsychotics in monotherapy to treat bipolar depression also has diverse effects [19–21]. Mood stabilizers such as carbamazepine, lamotrigine (only for depressive episodes), and lithium are approved for the prevention of bipolar episodes [22]. Furthermore, antipsychotics such as aripiprazole, olanzapine, or risperidone have proven effective in the prophylactic treatment of manic episodes and are therefore favored. A widespread strategy in clinical practice to prevent the depressive and manic episodes characteristic of bipolar disorders is combination therapy, despite the fact that only a few controlled studies have demonstrated its efficacy. There is substantial evidence that in addition to the mood stabilizers, atypical antipsychotics have positive effects [23]. According to the DGPPN ("Deutsche Gesellschaft für Psychiatrie, Psychotherapie, Psychosomatik und Nervenheilkunde") S3 Guidelines on bipolar disorders [14], pharmacological combination therapies are prescribed in clinical routine because of high numbers of patients responding insufficiently to monotherapy, a somewhat surprising recommendation considering the lack of convincing data from controlled investigations of polypharmaceutical strategies.

Schizoaffective disorder (SAD) is characterized by symptoms of schizophrenia and bipolar disorder; however, there is controversy about the existence of this disorder. No guidelines have been developed for the treatment of SAD, and only a few controlled studies have examined the pharmacological treatment of this disorder. Baethge et al. [24] suggested treating primarily affective symptoms with lithium and using carbamazepine to prevent relapses; they recommend treating primarily psychotic features with clozapine.

Because (a) data on the therapy of bipolar disorders are very inconsistent, and (b) the only drug certified for the treatment of SAD is paliperidone (which also encompasses therapy for manic episodes), the question remains on which level of evidence psychiatrists can base their therapeutic decisions

when trying to help patients with these disorders.

In the present study we compared the prescription patterns in cases of diagnosed SAD, schizophrenia, and bipolar disorder to identify similarities and differences in the pharmacological treatment of these disorders.

Method

The present study was approved by the local ethics committee. For this retrospective, explorative study we gained access to the patient files of 300 patients from ten German adult psychiatric clinics in the "Landschaftsverband Westfalen-Lippe" (LWL Psychiatry Network), thereby covering a region of approx. 8.3 million inhabitants. Patients included in the study had been diagnosed with schizophrenia (F20), bipolar disorder (F31), or SAD (F25) from 2004 to 2011, classified according to the ICD-10 (International Classification of Diseases, 10th version). Exclusion criteria were (a) concurrent presentation of more than one of the aforementioned disorders, (b) another mental illness, or (c) epilepsy. After applying these exclusion criteria, records from 287 patients were analyzed. Our data set comprised 99 patients with schizophrenia, 101 with SAD, and 87 with bipolar disorder diagnosis. After inpatient treatment, the diagnoses and medication(s) at the time point of discharge were analyzed.

Statistical analysis was performed using the SPSS program (IBM, Böblingen, Germany). The homogeneity of distribution was subjected to Levene's test, demographic data to the chi-square test, and group differences to the Kruskal–Wallis test (in the case of no normal distribution) or one-way ANOVAs (analysis of variance in the case of normal distribution) followed by post hoc tests.

Results

Sociodemographic data

The sociodemographics of the patients included in this study are shown in **Table 1**. Using chi-square tests analyzing the demographic data, we observed no differences among the three diagnostic groups in gender or educational level. Significant differences were also noted in: (a) the school-leaving qualification between patients with schizophrenia and patients bipolar disorders ($p = 0.017$) and furthermore between patients with SAD and patients with bipolar disorders ($p < 0.0001$), while the maximum educational level attained was as follows: schizophrenia ≥ bipolar disorder > SAD; (b) employment status (schizophrenia vs. bipolar disorder $p < 0.0001$; schizophrenia vs. SAD $p = 0.031$; SAD vs. bipolar disorder $p < 0.0001$), with the percentage of jobless patients highest in the schizophrenia group; and (c) marital status, with a significant lower percentage of patients "in a steady relationship" in the schizophrenia group than in the SAD ($p = 0.001$) and bipolar disorder groups ($p < 0.0001$).

Regarding the age of the patients, we found significant differences between the three diagnosis groups: $F(2.284) = 28.473$, $p < 0.0001$. Post hoc tests showed that patients with schizophrenia (M = 38.4 years, SD = 11.218) were of significantly younger age than patients with SAD (M = 46.7 years, SD = 10.807, $p < 0.0001$) and bipolar disorder (M = 49.6 years, SD = 12.044, $p < 0.0001$).

Table 1 Sociodemographic data of patients

	F20 (%)	F25 (%)	F31 (%)
Gender			
Male	52.5	52.5	39.0
Female	47.5	47.5	61.0
School-leaving qualification			
No graduation	6.1	4.0	2.3
Special needs school	2.0	4.0	1.1
Lower secondary school-leaving certificate	21.2	29.7	8.0
General secondary school-leaving certificate	10.1	13.9	24.1
Vocational diploma	4.0	1.0	5.7
General qualification for university entrance	18.2	6.9	14.9
Not specified	38.4	40.6	43.7
Training status			
No vocational training	31.3	15.8	16.1
Vocational training	3.0	3.0	4.4
Completed academic studies	0.0	0.0	0.0
Not specified	65.7	81.2	79.3
Professional status at the last inpatient stay			
Unemployed	35.4	24.8	29.9
Employment contract	8.1	5.9	25.3
Disability pension	20.2	32.7	12.7
Job in a work center	2.0	2.0	0
Retirement pension	0	5.0	11.5
Not specified	34.3	29.7	20.7
Marital status at the last inpatient stay			
In a steady relationship	22.2	38.6	54.0
No relationship	54.5	31.7	29.9
Not specified	23.3	29.7	16.1

F20 schizophrenia, *F25* schizoaffective disorder, *F31* bipolar disorder

Compliance of patients

Data regarding the compliance rely on the subjective accounts of patients. Of the patients analyzed in this study, 97.5% had experience taking medication, but only 21.8% of them displayed consistent medication intake prior to their inpatient stay (**Fig. 1**). In this regard, the group of patients with schizophrenia (13.1%) exhibited the least, and significantly lower, reliability compared with the patients with bipolar disorder (27.6%) or those with SAD (24.8%): schizophrenia vs. SAD $\chi^2(1, N = 200) = 2.45$, $p = 0.117$; schizophrenia vs. bipolar disorder $\chi^2(1, N = 186) = 4.37$, $p = 0.036$; SAD vs. bipolar disorder $\chi^2(1, N = 188) = 0.390$, $p = 0.532$. No reliable data on medication intake were available for 26.4% of the patients.

Prescription patterns

Only 24.4% of the patients included in this study were given monotherapy, while about three quarters were dispensed combinations of two or more psychopharmacological drugs (**Fig. 2**). These data reveal a mean of 2.27 drugs per patient. The proportion of patients on monotherapy was the largest in the schizophrenia group (44.4%), followed by bipolar disorder (16.1%) and SAD (11.9%; **Fig. 2**). Statistical analysis using the Kruskal–Wallis test showed significant differences between the groups: $H(2) = 36.19$, $p < 0.0001$. Subsequent post hoc tests identified a significant smaller number of psychopharmacological agents prescribed in the schizophrenia ($M = 1.81$) than in the bipolar disorder ($M = 2.43$, $p < 0.0001$) and SAD groups ($M = 2.53$, $p < 0.0001$). Medications prescribed were antipsychotics, mood stabilizers, and antidepressants (**Fig. 3**). All patients in the schizophrenia group received antipsychotics: in 44.4%, they were administered as monotherapy, in 35.4% in combination with various antipsychotics, and in 20.2% augmented with mood stabilizers (50%) or antidepressants (50%). In the group of patients with SAD and bipolar disorder, antipsychotics were part of the medication in 97% and 88.5% of cases, respectively.

Abstract · Zusammenfassung

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Pharmacological treatment for schizoaffective disorder. A comparison with schizophrenia and bipolar disorder

Abstract

Background. Bipolar disorder and schizophrenia are severe mental illnesses, each with a prevalence of approximately 1–2% in the general population. There is considerable controversy about differentiating schizophrenia from schizoaffective or bipolar disorder owing to many similarities in psychopathology, progression, and biological factors. The aim of this study was to identify similarities and differences in the pharmacological treatment of these disorders by comparing the prescription patterns.

Method. In this retrospective, explorative study we analyzed the prescribed medication of 300 patients with bipolar, schizophrenic, or schizoaffective disorders from data obtained from ten German adult psychiatric clinics of the LWL ("Landschaftsverband Westfalen-Lippe") psychiatric network.

Results. Only 21.8% of patients analyzed were consistently compliant in taking their medication before hospitalization. Polypharmacy was applied in 75.6% of cases, whereby 2.27 psychopharmacological agents were prescribed at discharge. Briefly, we observed greater similarity between prescription patterns associated with bipolar and schizoaffective disorders than with schizophrenia prescription patterns.

Conclusion. Polypharmacy tends to be more the rule than the exception, especially when patients present with affective psychotic features. Bipolar and schizoaffective disorders cannot be differentiated according to their prescription patterns.

Keywords

Antidepressants · Lithium · Antipsychotics · Psychopharmacology · Polypharmacy

Pharmakologische Behandlung schizoaffektiver Störungen. Ein Vergleich mit schizophrenen und bipolaren Störungen

Zusammenfassung

Hintergrund. Bipolare und schizophrene Störungen sind sehr schwere und bei einer Prävalenz von 1–2% in der Allgemeinbevölkerung auch häufige psychische Erkrankungen. Aufgrund zahlreicher Gemeinsamkeiten zwischen Schizophrenien, schizoaffektiven und bipolaren Störungen hinsichtlich der Psychopathologie, dem Verlauf sowie der biologischen Grundlage wird eine klare Trennung dieser Entitäten kontrovers diskutiert. Der im Rahmen dieser Studie durchgeführte Vergleich der Verordnungsgewohnheiten in verschiedenen Kliniken hatte das Ziel, Hinweise auf eine differenzielle Pharmakotherapie dieser Störungen aufzudecken.

Methodik. In dieser retrospektiven, explorativen Studie wurde das medikamentöse Verordnungsverhalten bei bipolaren, schizophrenen bzw. schizoaffektiven Störungen bei insgesamt 300 Patienten aus 10 Kliniken des LWL-Psychiatrieverbunds untersucht.

Ergebnisse. Nur 21,8% der insgesamt in die Studie eingeschlossenen Patienten zeigten eine befriedigende Compliance in der Medikamenteneinnahme vor dem stationären Aufenthalt. Polypharmazie lag bei 75,6% der Patienten vor, im Mittel bestand eine Verordnung für 2,27 psychotrope Medikamente bei Entlassung. Zusammenfassend ähnelt das Verschreibungsverhalten bei bipolaren Störungen eher demjenigen bei schizoaffektiven Störungen als dem bei Schizophrenie.

Schlussfolgerung. Polypharmazie ist eher die Regel als die Ausnahme, besonders beim Vorliegen affektiver und psychotischer Merkmale. Im klinischen Verordnungsverhalten sind bipolare Störungen und schizoaffektive Störungen kaum zu unterscheiden.

Schlüsselwörter

Antidepressiva · Lithium · Antipsychotika · Psychopharmakologie · Polypharmazie

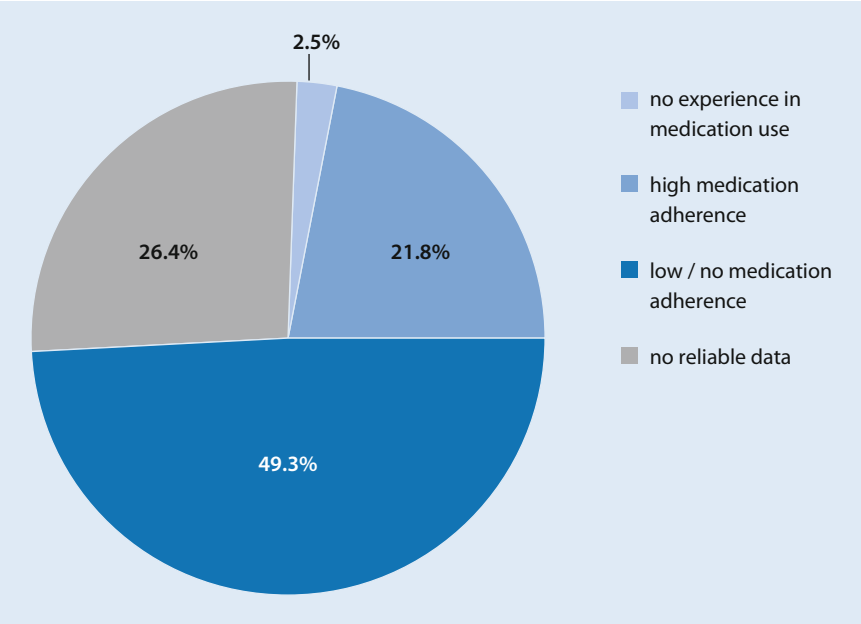

Fig. 1 ▲ Patient compliance. The percentage of patients with no experience in medication use, with high medication adherence, with low or no medication adherence, and of cases where no reliable data were available at the time of the last inpatient stay

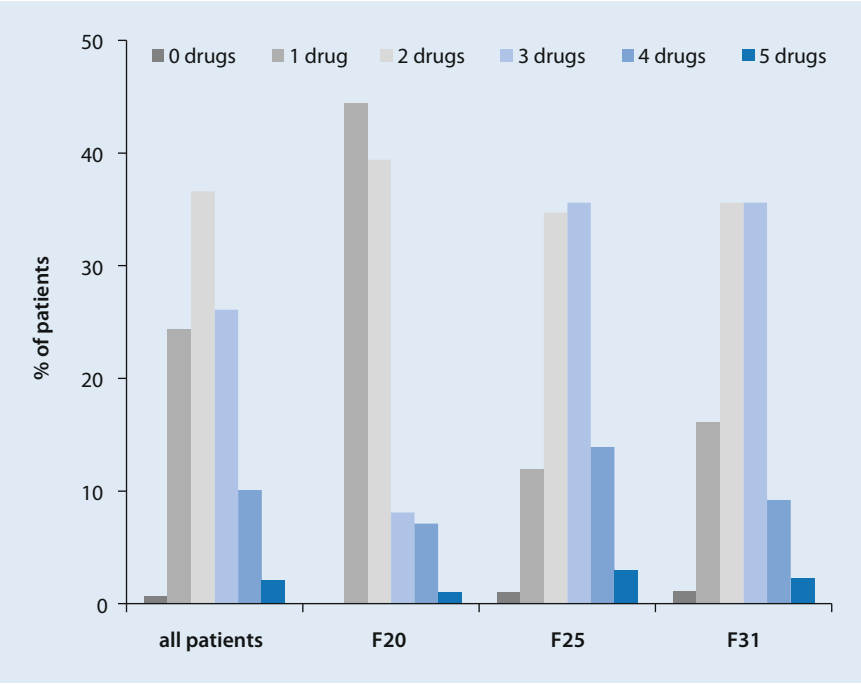

Fig. 2 ▲ Number of prescribed antipsychotic drugs. The proportion of patients receiving no drugs, one drug, two drugs, three drugs, four drugs, and five drugs is demonstrated in percent based on the total of patients included or on the number of patients with schizophrenia (*F20*), schizoaffective disorder (*F25*), and bipolar disorder (*F31*) classified using the ICD-10 classification system (International Statistical Classification of Diseases and Related Health Problems).

Notably, they were used as monotherapy (SAD 11.9%, bipolar disorder 8%) or combination therapy consisting of various antipsychotics (SAD 13.95%, bipolar disorder 4.6%) in only a few patients. Thus, in contrast to schizophrenia, in the majority of SAD and bipolar disorder patients, antipsychotics were used in augmentation therapy. In 54.5% of patients with an SAD diagnosis and in 52.9% of those with bipolar disorder, antipsychotics were augmented with mood stabilizers. Polypharmaceutical therapy including all three substance classes—antipsychotics, antidepressants, and mood stabilizers–was administered in none of the schizophrenia patients, in 5.9% of the SAD patients, and in 18.4% of the bipolar disorder patients. No relevant differences were observed in the prescription of first- (FGA) and second-generation antipsychotics (SGA) among the three diagnostic groups (data not shown). Long-acting injections (LAI) were administered to 18% of the patients with schizophrenia, 18% of those with SAD, and 3.5% of those with bipolar disorder.

Frequencies of prescriptions

In all, 66.8% of patients were treated with antipsychotics, 21.9% of whom received FGA and 44.9% SGA (**Fig. 4a**). Flupentixol was the most often prescribed FGA, followed by haloperidol > pipamperone > chlorprothixene > zuclopenthixol > levomepromazine > melperone > promethazine (**Fig. 4b**). The order of frequency of prescribed SGA was as follows: quetiapine > olanzapine > risperidone > aripiprazole > amisulpride > clozapine > ziprasidone > paliperidone (**Fig. 4c**). Mood stabilizers were dispensed to 23.6% of the patients (**Fig. 4a**). Valproate was the most frequently prescribed mood stabilizer (61.4%), followed by lithium (21.6%), lamotrigine (11.8%), and carbamazepine (5.2%; **Fig. 4d**). In cases of mood stabilizer prescription, valproate was the only mood stabilizer used for schizophrenia patients, and it was given to 63.3% of the SAD and to 55.4% of the bipolar disorder patients (data not shown). Other mood stabilizers dispensed in these diagnostic

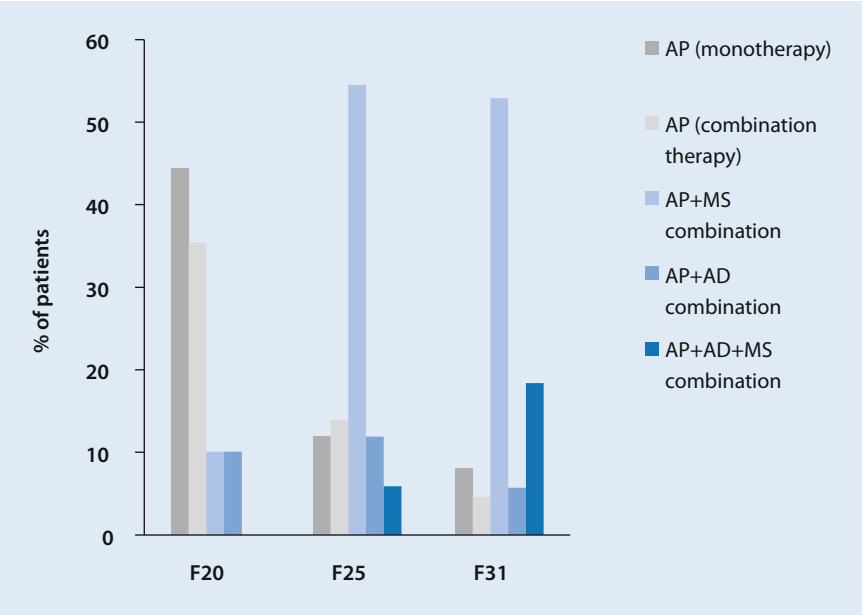

Fig. 3 ▲ Prescription patterns of the different pharmaceutical substance groups. The percentage of patients in the different diagnosis groups receiving: antipsychotics as monotherapy; antipsychotics as combination therapy; antipsychotics and mood stabilizers; antipsychotics and antidepressants; or antipsychotics, antidepressants, and mood stabilizers. *AD* antidepressants, *AP* antipsychotics, *MS* mood stabilizers. *F20* schizophrenia, *F25* schizoaffective disorder, *F31* bipolar disorder

groups were carbamazepine, lamotrigine, or lithium (data not shown). No differences were observed in the dosages.

Antidepressants were given to 9.6% of our study patients (**Fig. 4a**). The order of frequency of the antidepressants prescribed was as followed: escitalopram > venlafaxine > citalopram > agomelatine > mirtazapine > sertraline > trimipramine > amitriptyline > bupropion > doxepin > duloxetine > fluoxetine > fluvoxamine > maprotiline > paroxetine (**Fig. 4e**). The first three drugs listed here comprised 45.1% of the prescribed antidepressants.

Discussion

The present study shows that in daily clinical practice the vast majority of patients diagnosed with schizophrenia, SAD, or bipolar disorder receive polypharmacy consisting of two or more psychotropic drugs rising from schizophrenia to SAD to bipolar disorder. Only 23.7% of these patients were given monotherapy (according to the first-line recommendation in treatment guidelines). These findings are in line with results of a meta-analysis of treatment options in schizophrenia in German clinics [9] and studies examining prescription patterns of antipsychotics [25], antidepressants [26], and mood stabilizers [27]. Combination therapy has proven to be beneficial in daily clinical practice and can be justified by the high comorbidity rates and the need for rapid and efficient progress of inpatient therapy.

In the present study valproate was prescribed three times as often as lithium. While valproate was the only mood stabilizer given to schizophrenia patients, it was given to 63.3% of the SAD and to 55.4% of the bipolar disorder patients compared with lithium used in 19.7% of SAD and 25.7% of bipolar disorder patients. A significant positive effect of valproate augmentation therapy was shown in meta-analysis providing an argument for this strategy of therapy in schizophrenia or SAD practiced worldwide despite lacking high-quality evidence [28]. However, only a few published studies focused on evaluating pharmacological combination therapies, a factor probably attributable to the high standard of trial design required.

Therapeutic efforts fail when patients are incompliant. In the present study, only 13.1% of the patients with schizophrenia reported consistent medication intake. Patients with diagnosed SAD and bipolar disorder were somewhat more compliant (24.8 and 27.6%, respectively) before hospitalization. However, these percentages are too low to reflect a satisfactory compliance rate. It is well known that the risk of relapse rises when patients' compliance is poor, just as the risk of a non-response or therapy resistance increases. In line with our results that patients with schizophrenia in our study setting were younger than the patients with SAD and bipolar disorder and were less compliant, in many studies young age was identified as a predictor of poor adherence in patients with schizophrenia and bipolar disorder [29–32].

In accordance with a previous study [33], patients of all three diagnostic entities were treated with antipsychotics, the most frequently prescribed psychopharmacological agents. The approval of antipsychotics for treating acute depressive or manic symptoms (as well as for relapse prevention) broadens the spectrum of efficacy, probably the reason for their broad application and frequent prescription. This may also explain the higher number of antipsychotics prescribed in bipolar disorder reported in this study. It is noteworthy that the majority of patients with schizophrenia in our study received an antipsychotic monotherapy in contrast to the majority of patients with a bipolar disorder who were given antipsychotics augmented with mood stabilizers.

LAI are the primary medication of choice for poorly compliant patients [34]. It is thus unsurprising that 21.2% of patients with schizophrenia received LAI treatment, as did 26.2% of those with schizoaffective disorders. In line with the better compliance we observed among the study patients with bipolar disorders, only 7.7% of the bipolar disorder patients received depot neuroleptics.

The aim of this study was to give insight into pharmacotherapy used to stabilize patients with schizophrenia, SAD, and bipolar disorder under natural conditions to identify distinctions in the prescription patterns of psychopharmacological

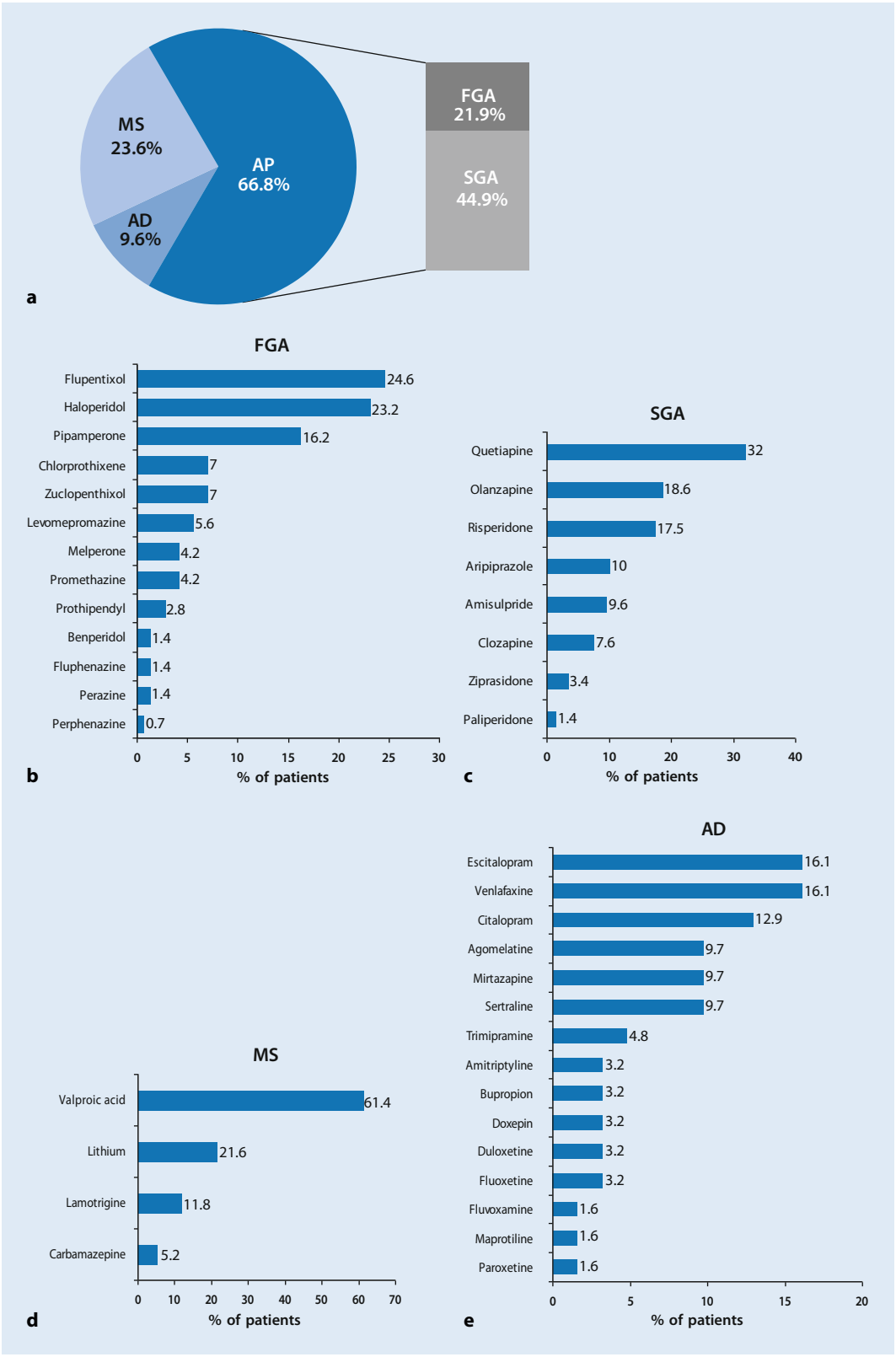

Fig. 4 ◄ Frequencies of prescribed medication. **a** The percentage of prescribed antipsychotics (*AP*), also divided into first-(*FGA*)/second-generation antipsychotics (*SGA*), mood stabilizers (*MS*), and antidepressants (*AD*), is calculated on the totality of patients included in this study. **b**–**e** The frequencies of dispensed drugs of the different pharmaceutical substance groups—FGA (**b**), SGA (**c**), MS (**d**), and AD (**e**)—is demonstrated as percentage on the basis of all patients

agents among the three diagnostic entities.

In our study cohort, pharmacological treatment of schizophrenia (antipsychotics in monotherapy) was remarkably different from that of SAD or bipolar disorder (antipsychotics and mood stabilizers), while SAD and bipolar disorder displayed no such relevant differences. SAD and bipolar disorder are primarily characterized by their affective symptoms, which strongly influence their treatment strategies and are probably the reason for the similarities we observed in prescription patterns.

Systematic reviews of clinical studies comparing demographic and clinical characteristics of patients with SAD, schizophrenia, and bipolar disorder indicated that SAD is not a schizophrenia or bipolar disorder comorbidity or an independent disorder [1, 35]. Instead it has to be ranked somewhere between schizophrenia and bipolar disorder, being constituted by patients with characteristics of schizophrenia and bipolar disorder. The treatment behavior of clinicians observed in our investigation certainly seems to support this assumption.

Limitations

Finally, it should be noted that a limitation of this study is the study cohort consisting of only hospitalized patients at the time point of possible relapses and readmission. Stable patients with a successful (combination of) medication regimen are not included.

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Compliance with ethical guidelines

Conflict of interest. H.-J. Assion, A. Schweppe, H. Reinbold, and U. Frommberger declare that they have no competing interests.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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