Drug Prescription Patterns in Schizophrenia Outpatients: Analysis of Data from a German Health Insurance Fund

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Abstract
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Introduction: The aim of this study was to investigate routine administrative data from a major German health insurance fund, Techniker Krankenkasse, which covers 5.4 million insured individuals. Using a retrospective cohort design, this study analysed data collected from patients with a hospital diagnosis of schizophrenia in 2003 (index hospitalisation) in order to evaluate prescription patterns of antipsychotic drugs.

Methods: Patients with an ICD-10 diagnosis of schizophrenia, at least one year prior membership with the insurance fund and a follow-up period of one year were identified. Results were standardised by age and stratified by the severity of their illness, defined by the number of hospital bed days during the three years preceding the index hospitalisation.

Results: A total of 3 121 patients with schizophrenia (male 56.4%, female 43.6%) received 56 692 single prescriptions of antipsychotics. Of these, 35.4% of the prescriptions were for typical and 64.6% for atypical antipsychotics; 55% were for high-potency, 45% for low-potency typical antipsychotics. The most frequently prescribed drugs were olanzapine (26.6%), clozapine (21.3%) and risperidone (19%). There were no relevant gender differences concerning prescription patterns. During a 12-month follow-up period after the first hospitalisation, 1 372 patients (43.9%) were treated exclusively with an atypical antipsychotic, another 499 patients (16%) had a combination of an atypical plus a low-potency typical antipsychotic. Thus, basal therapy with an atypical was observed in 59.9% of our study population. Only 327 patients (10.5%) were treated exclusively with a typical antipsychotic. A total of 645 patients (20.7%) were treated with a combination of atypical plus typical antipsychotic. Changes of medication within one substance group occurred more often with typical antipsychotics (50%) as compared to atypical antipsychotics (25%).

Discussion: At 60%, the proportion of patients in this study treated with atypical antipsychotics was surprisingly high. Of significant interest is the frequent prescription of clozapine (14%). The results are discussed in comparison to comparable studies from other countries.

Introduction
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Despite the fact that the lifetime prevalence of schizophrenia accounts only for about 0.7–1.0% of cases in industrialised countries [5,27], the WHO Global Burden of Disease Study ranked schizophrenia fifth amongst the diseases leading to permanent disability [17,26].

Schizophrenia affects a broad range of mental, psychological and social functions and thus has a very strong impact on many aspects of daily living for the patients themselves as well as for their relatives and society [12]. Keeping in mind that every episode of schizophrenia worsens the patient's quality of life, overall responsiveness to antipsychotic drug treatment and lifetime prognosis and treatment adherence is extremely important [15]. Thus, prevention of relapse and avoidance of a chronic course of illness are major therapeutic goals [7,9].

One of the major causes of relapse is the discontinuation of drug therapy which is frequently linked to either insufficiently controlled symptoms of schizophrenia or specific side effects of antipsychotic medication.

Antipsychotic drugs may cause a variety of side effects, some of them indistinguishable from disease symptoms themselves [19]. The most common symptoms especially with typical antipsychotic medication drugs are extrapyramidal

symptoms (EPS). Current evidence suggests that atypical antipsychotic drugs are superior to typical antipsychotics concerning negative symptoms and side effects and therefore more acceptable to patients [7, 8, 16, 24]. This might in turn result in improved therapy adherence and better health outcomes. Accordingly, atypical neuroleptics have gained a leading position in treatment recommendations for schizophrenia during recent years [1, 4]. However, recommendations are inconsistent [8].

Haro et al. [12] reported prescription ratios for atypical compared to typical antipsychotic drugs for France (20.2%) and Italy (22.3%) similar to those reported for Germany (20.7%), however the respective rates in other European countries like Denmark (33.3%), the Netherlands (35.6%) and the UK (27.5%) were substantially higher. Nevertheless, these data must be interpreted with caution, as 1) the study populations in the latter countries were significantly smaller, 2) these were not based on routine data analyses but collected from ambulatory care doctors, and 3) they were from the year 2001.

Against this background, we investigated the routine prescription data available for patients insured with the German health insurance fund – "Techniker Krankenkasse (TK)" – in view of claims that atypical antipsychotic drugs are less often prescribed in Germany as compared to other countries. This is allegedly due to higher costs of atypical antipsychotic drugs and drug budgets imposed on ambulatory care doctors in Germany [6].

Materials and Methods
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In order to minimise potential bias, the results were standardised by age and stratified by severity of illness using the direct method of standardisation. The distribution of the whole study population was taken as the standard population and five different age groups were defined (<25; 25–35; 35–45; 45–55; >55 years). To stratify by severity, hospital bed days in the 12 months prior to the index hospitalisation were used as a proxy for illness severity.

Routine prescription data of neuroleptic drugs and other psychopharmacological medication of patients insured with the social health insurance fund "Techniker Krankenkasse (TK)" were analysed. TK covers approximately 5.4 million individuals across all German regions. Due to its history the TK population has an above average socio-economic status as compared to the German population as a whole and other social health insurance funds.

From all TK insured persons those patients with at least one hospitalisation in 2003 due to a diagnosis of schizophrenia (ICD-10, F20) were identified. Data of this group were analysed with respect to the inclusion criteria of our study.

Thus a total of 3 397 patients were identified and the following inclusion criteria were applied (○ **Fig. 1**): (i) time of membership prior to the index hospitalisation in the calendar year 2003 of sufficient length to build up the severity index (at least 365 days), and (ii) follow-up period of at least 365 days after the index hospitalisation.

112 patients (3.3%) were excluded due to TK membership being shorter than 365 days prior to the index hospitalisation. 164 patients (4.8%) were lost to follow-up due to a change of insurance fund.

Ambulatory routine prescription data for the years 2003 and 2004 from the TK insured population were collected and analysed. We analysed prescription rates of antipsychotic drugs with an emphasis on the comparison of typical versus atypical antipsychotics. Special attention was given to the variables; age, gender, co-medication and therapy adherence. Prescriptions for depot medication were also taken into account.

To control for potential confounding by indication in the absence of clinical classification tools, a severity index was constructed using data on prior hospitalisations with the main diagnosis of schizophrenia for each of 2000, 2001 and 2002 (○ **Fig. 2**). Thus our severity index is based on average days in hospital per year. Prescription data were analysed with respect to basic antipsychotic medication, adjuvant psychotropic drugs and other neuropsychopharmacological pharmaceuticals. Data were analysed by gender, age and severity based on prior hospitalisations. Statistical analysis was performed with SAS version 9.1 for Windows.

Originally, we aimed to analyse patients with schizophrenia but excluding patients with schizoaffective disorder indicated by the prescription of an antidepressive or anticonvulsive drugs as the ICD-10 diagnosis of schizoaffective disorder is not always applied. Thus, from the remaining 3 121 patients, 1 270 patients (40.7%) were analysed, separately, due to co-medication with antidepressive drugs (34.6%), anticonvulsive drugs (10.0%) or
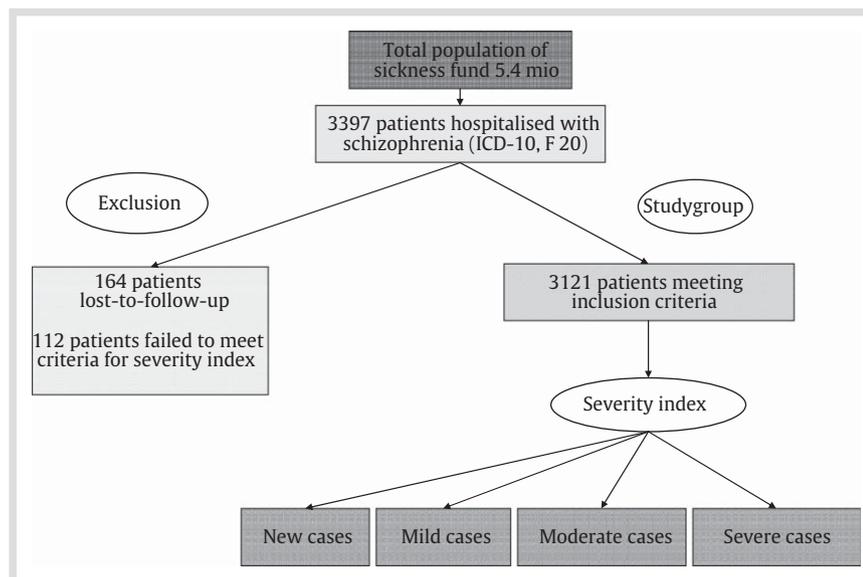
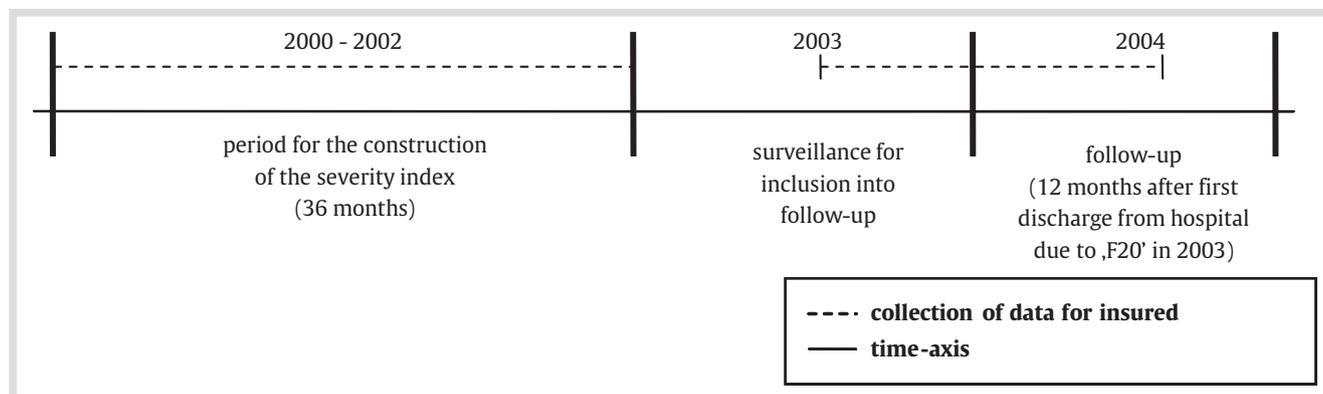**Fig. 1** Process of patient selection.

Fig. 2   Time frame of severity index and data collection.

Table 1   Study population by gender and age.

	<25 years	25–35 years	35–45 years	45–55 years	>55 years	Total	Percent
female	166	292	470	250	183	1,361	43.6%
male	451	474	520	195	120	1,760	56.4%
total	617	766	990	445	303	3,121	–
percent	19.8%	24.5%	31.7%	14.3%	9.7%	–	100%

both of them (4.0%). When comparing data of these two groups we did not find any relevant differences, thus data of all patients with schizophrenia were analysed together.

Results

In 2003 and 2004, from a total of 5.4 million insured; 3 121 patients with schizophrenia met our inclusion criteria. 56.4% of our study population were male and 43.6% were female. 19.8% of patients were younger than 25 years of age, 24.5% were 25–35 years old, 31.7% were 35–45 years old and another 14.3% were 45–55 years old, while only 9.7% were older than 55 years. Thus, around 56% of our patients were between 25 and 45 years of age representing the typical peak of illness in this age bracket (⊙ **Table 1**).

In 2004, 3 121 patients received 28 026 prescriptions for neuroleptic drugs. 9 916 prescriptions (35.4%) were for typical neuroleptic drugs. 55% of these were for high-potency and 45% for low-potency drugs. Another 18 110 prescriptions (64.6%) were for atypical neuroleptics. Olanzapine was the most frequently prescribed atypical (26.6%), followed by clozapine (21.3%), risperidone (19%), quetiapine (14.2%), amisulpride (12.1%), ziprasidone (6.17%) and zotepine (0.6%). Data for the year 2003 were quite similar.

With respect to gender there were no significant differences in prescription patterns. Typical antipsychotic drugs were prescribed for 10.5% of women compared to 10.4% of male patients. However, atypical antipsychotic drugs as single therapy were prescribed less frequently in women (42.5%) compared to 45.1% in men. Atypical antipsychotic drugs plus an adjuvant low-potency typical antipsychotic were prescribed in 17.0% of female patients compared to 15.2% in male patients. A combination of both high-potency typical and atypical antipsychotics was found in 20.9% of females compared to 20.5% of males. 9.0% of females and 8.8% of males did not receive prescriptions for antipsychotic drugs in ambulatory care.
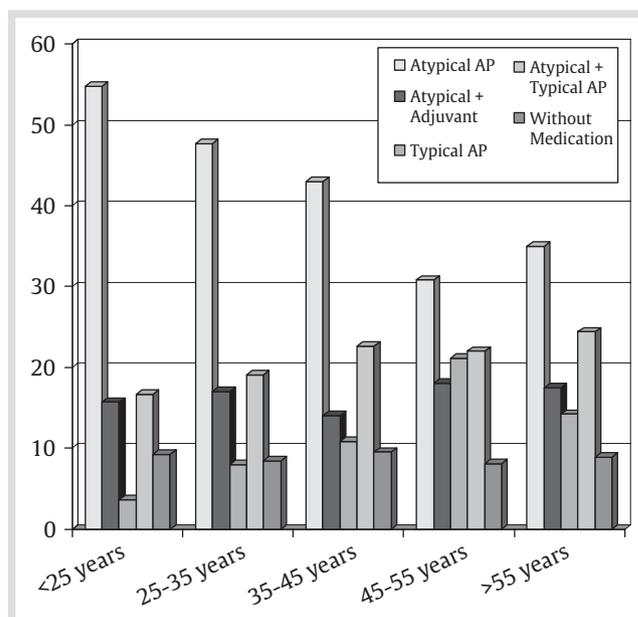

Fig. 3   Study group by medication and age in % (N = 3 121).

Atypical antipsychotics were the most commonly prescribed drugs across all age groups accounting for approximately 54.8% in patients aged under 25 years, 47.7% for patients between 25 and 35 years of age, 43% for patients between 35 and 45 years, 30.8% for those between 45 and 55 years of age and for 35% of patients being older than 65 years (⊙ **Fig. 3**). The rising share of combination treatments increasing with age (from 16.7% for patients aged under 25 to 24.4% for patients older than 55 years) probably corresponds to the growing severity during the course of illness.

According to average hospital days per year in 2000–2002 we defined four severity grades: New cases (no days spent in hospi-
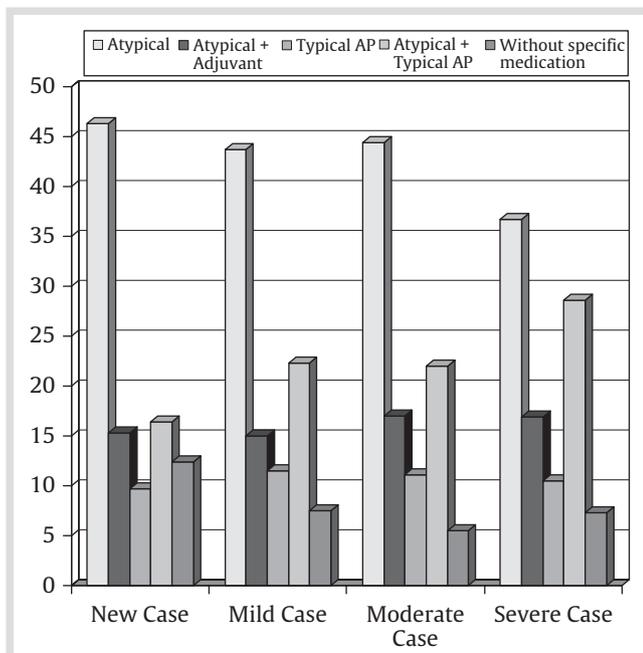
Fig. 4   Study population by medication and severity grade (based on prior hospitalisations) in % (N = 3 121).

Fig. 5   Patients receiving specific co-medication by antipsychotic medication (in %, N = 3 121).

tal), mild cases (0–14 days per year spent in hospital per year), moderate cases (14–61 days per year) and severe cases (>61 days per year). 1 301 patients (41.7 %) were assigned to the category new cases, 453 patients were assigned to mild cases (14.5 %), 912 (29.2 %) to moderate cases and 455 (14.6 %) to severe cases. With respect to the low incidence of schizophrenia it must be acknowledged that the share of new cases accounting for 41.7 % of the study population is quite high. Within each severity group we analysed the share of patients receiving typical or atypical antipsychotic medication (○ **Fig. 4**).

Atypical antipsychotics were the most frequently prescribed medication, irrespective of severity grade (prior hospitalisations). 602 (46.3 %) of new cases, 198 (43.7 %) of mild cases, 405 (44.4 %) of moderate cases, and 167 (36.7 %) of severe cases, respectively, were prescribed atypical antipsychotics. The next frequently prescribed medication was a combination therapy consisting of an atypical plus a high-potency typical antipsychotic accounting for 16.4 % of new cases, 22.3 % of mild cases, 22.0 % of moderate cases and 28.6 % of severe cases. The rise in prescriptions through the severity groups is most likely a reflection of the increasing complexity of treating patients with a chronic course of schizophrenia. In the third place, an atypical antipsychotic drug is combined with a low-potency (adjuvant) typical antipsychotic drug accounting for approximately 15–17 % of prescriptions across all severity grades.

This study also investigated the influence of primary medication on the stability of drug prescriptions with respect to the main medication groups namely typical versus atypical antipsychotics. Patients on atypical antipsychotic medication switched less often to other drugs. The share of switchers increased through severity grades beginning at 21.6 % of new cases, 25.3 % of mild cases, 26.2 % of moderate cases, and 29.9 % of severe cases. Interestingly, the lowest share of switchers using typical antipsychotics was recorded in the new cases group, at 38.1 %. This is higher than the highest share recorded for atypicals. The proportion of switchers among patients receiving typicals increased further,

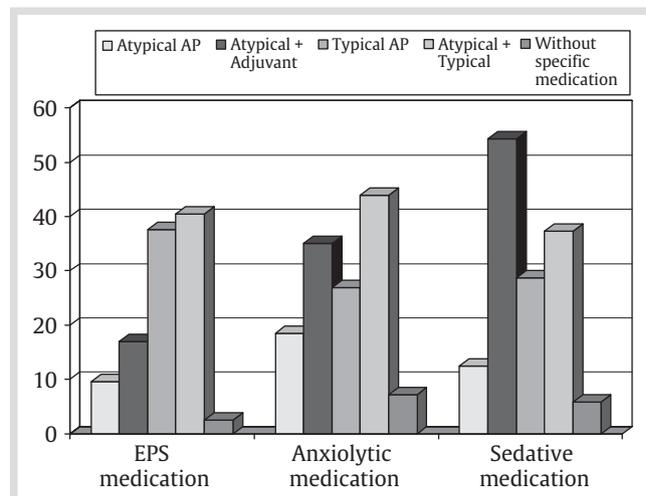amounting to 44.2 % of mild cases, 52.5 % of moderate cases and 60.4 % of severe cases.

Because adherence to depot medication is undeniably higher when compared to oral medication, this study also analysed the share of patients receiving antipsychotic depot medication. Within the group of typical neuroleptics the percentage of patients receiving depot medication was substantially higher (26.6 %) compared to atypicals (1.8 %). Keeping in mind that the share of switchers was nevertheless higher within the group of typicals our results seem to underline the preferably higher compatibility of atypical neuroleptic drugs.

For patients who did not switch their medication, the study analysed data with respect to specific co-medication, i.e., drugs against extrapyramidal symptoms (EPS), against anxiety and against agitation.

Medication against EPS was prescribed significantly less often for patients receiving atypical antipsychotics. Just 7.8 % of patients on atypicals received drugs against EPS. In contrast, 30.5 % of patients being treated with a typical antipsychotic drug received prescriptions for anticholinergic drugs or tiaprid. Thus, the relative risk for patients on atypicals receiving treatment against EPS compared to patients on typical antipsychotics was 0.26 (95 % CI 0.18–0.38). Prescriptions for other neuropsychopharmacological medication were also analysed. There were no relevant differences with respect to hypnotic and sedative drugs (RR 0.66; 95 % CI 0.43–1.02) or anxiolytics (RR 0.83; CI 0.56–1.24). Both medication groups were also less frequent in patients receiving atypical antipsychotics (○ **Fig. 5**). However differences diminished when the data were standardised by age (○ **Table 2**).

19.5 % of all cases were prescribed drugs against EPS. The highest share was in patients aged between 45 and 55 years (24.8 %), whereas the lowest share was seen in patients aged between 25 and 35 years (16.2 %). Patients between 35 and 45 years of age and between 45 and 55 years of age received medication against EPS in 20.9 and 21.6 % of cases, respectively. With respect to the fact that susceptibility for EPS increases with age, this finding is striking. However, in summary the results most likely reflect that an increase of illness severity (based on prior hospitalisations) during the course of illness seems to correspond with a decrease in the ability to find satisfactory therapeutic options.

Table 2 Percentage of patients with side-effects according to medication and severity group (based on prior hospitalisations), standardised by age.

	New cases (%)	Mild cases (%)	Moderate cases (%)	Severe cases (%)
at least one prescription for EPS medication				
atypical (non-switcher)	10.4	7.9	7.9	9.7
typical (non-switcher)	29.6	26.4	40.7	22.5
at least one prescription for hypnotics/sedatives				
atypical (non-switcher)	8.6	16.6	14.2	11.1
typical (non-switcher)	15.7	18.3	19.7	13.7
at least one prescription for anxiolytics				
atypical (non-switcher)	13.3	19.7	19.6	20
typical (non-switcher)	17.2	12.9	20.2	25.2

Discussion

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60% of all schizophrenia outpatients in this study received an antipsychotic drug regimen based primarily on atypical drugs. This means that atypical antipsychotics with and without other adjuvant medication are the most commonly prescribed psychotropics in this routine care study population. This proportion is substantially higher than previous reports on the prescription rate for atypical antipsychotics in Germany from Clade [6] and Haro [12] and higher than reports from some studies in other European countries. Nevertheless, Ballerini et al. reported a prescription rate of 59% for atypical antipsychotics at discharge in a study from Italy [3]. In Turkey, Atik et al. reported that 75.1% of patients were treated with atypical antipsychotics versus 24.9% with typical antipsychotics. This data was based on a retrospective chart review of 1 606 university clinic patients and not limited to schizophrenia. According to a study using routine care data from the Finnish National Hospital Discharge Register, initial use of clozapine, perphenazine depot and olanzapine were associated with the lowest rates of medication discontinuation when compared with oral haloperidol and associated with the lowest risk of rehospitalisation [23].

In this study we analysed the data of outpatients with a hospital (inpatient) diagnosis of schizophrenia. To control for two main confounding variables, patients were standardised by age and stratified by severity of illness based on prior hospitalisations. With respect to gender we did not find relevant differences in the treatment procedure within our study sample, whereas age had a relevant impact on the prescription pattern corresponding to the course of schizophrenic disorder. Within the group of atypical antipsychotics, clozapine and olanzapine are frequently prescribed agents [4]. Clozapine has convincing efficacy and an advantageous side-effect profile in respect to tardive dyskinesia and EPS. However, serious side effects in the form of a metabolic syndrome and agranulocytosis limit its use. Clozapine was prescribed considerably more frequently (14%) in our study population compared to the SOHO study group [12] which reported atypical prescription rates of 5.5% for Italy, 3.6% for the Netherlands, 4.9% for the UK and 2.7% for Germany. Our findings confirmed the relevance of clozapine as a therapeutic option in clinical routine care. The American College of Psychiatrists and the British National Institute for Health and Clinical Excellence (NICE) recommend the use of clozapine as a second- or third-line treatment option only. Nevertheless, according to current research from Asia, clozapine is widely used for a number of psychiatric disorders in China. Approximately 25–60% of all treated patients with schizophrenia in China are treated with clozapine, which is a fundamentally higher rate compared to our data analysis [22, 28].

One possible explanation for the frequent use of clozapine in our study compared to other European studies may be attributed to the fact that we required a hospital diagnosis of schizophrenia in the index year 2003 as ICD coding in ambulatory care is incomplete. This might have caused a selection bias towards more severe cases. On the other hand, 41.7% of patients in our study population were classified as being new cases with no hospital stay recorded in their medical history during the three years prior to the index hospitalisation. This probably reflects some misclassification in our severity index because we could not access data prior to the year 2000 and thus some patients with previous hospitalisations might have been erroneously included in the new cases severity category.

Despite the fact that most depot medications were prescribed within the group of typical antipsychotics (26.6% versus 1.8% for atypicals), 40–60% of patients on depot medication switched within their medication category compared to 20–30% of patients receiving atypical antipsychotics. This most likely reflects the higher illness severity of patients on depot medication.

As expected patients on atypical antipsychotics received significantly less anticholinergic medication, and this is in accordance with the literature [7]. In addition, hypnotic and anxiolytic drugs were prescribed less often in patients receiving atypical antipsychotics, well in accordance with previous research [8,16,24]. Nevertheless, differences in prescriptions for co-medication were statistically not significant after age standardisation. Our data did not permit us to analyse the relationship between compliance with antipsychotic medication and the risk of hospitalisation, previously shown to be significantly correlated in a sample of 4 325 outpatients [25].

In addition, our data must be interpreted with some caution. A limitation is the nature of the study sample being extracted from the routine administrative database of one social health insurance fund and as such the study results from this sample may not be entirely representative of the whole German population. On the positive side, our study reflects real world clinical practice in the treatment of schizophrenia outpatients in Germany without suffering from the selection biases associated with clinical trials and other observational study designs.

To sum up, this study contributes to the knowledge about routine care prescription patterns for schizophrenia outpatients in Germany. At 60%, the proportion of patients treated with atypical antipsychotic drugs was substantially higher than expected, as was the high proportion of patients treated with clozapine (14%). With respect to adherence (switching of antipsychotic medication) and EPS (using anti-EPS medication as a proxy), atypical antipsychotics demonstrated better compatibility.

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