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ORIGINAL PAPER

Effectiveness of antipsychotic maintenance therapy with quetiapine in comparison with risperidone and olanzapine in routine schizophrenia treatment: results of a prospective observational trial

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Abstract Objective of this observational trial is to examine the effects of quetiapine in comparison with olanzapine and risperidone on clinical outcomes and quality of life in patients with schizophrenia and schizoaffective disorder in routine care. 374 adult persons with schizophrenia or schizoaffective disorder prescribed antipsychotic maintenance therapy with quetiapine, olanzapine, or risperidone at discharge from inpatient treatment were included. Clinical and psychosocial outcomes were assessed before discharge and at 6, 12, 18, and 24 months. Statistical analyses were conducted by mixed-effects regression models for longitudinal data. The propensity score method was used to control for selection bias. Patients discharged on olanzapine had significantly lower hospital readmissions than those receiving quetiapine or risperidone. The average chlorpromazine equivalent dose of quetiapine was higher than in patients treated with olanzapine or risperidone. No further significant differences between treatment groups were found. Quetiapine and risperidone are less effective in preventing the need for psychiatric inpatient care than olanzapine, and higher chlorpromazine equivalent doses of quetiapine are needed to obtain clinical effects similar to those of olanzapine and risperidone.

Keywords Schizophrenia · Antipsychotic maintenance therapy · Quetiapine · Olanzapine · Risperidone · Observational trial

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Introduction

Quetiapine was introduced as an atypical antipsychotic drug for the treatment of schizophrenia in 1998. Results of clinical trials suggest that quetiapine may produce fewer extrapyramidal side effects than risperidone and less weight gain than olanzapine but that it may be less effective in reducing psychotic symptoms [1, 2]. However, the evidence from RCTs is considered to be limited due to high drop-out rates [1].

The effectiveness of quetiapine and other atypical antipsychotics was compared in several pragmatic trials, and study results are mixed [3–9]. In the CATIE study, olanzapine and risperidone were found superior to quetiapine with regard to treatment discontinuation, while for other outcomes including safety, no significant differences were

found [8]. Stroup et al. [7] reported results from the second CATIE study phase indicating that, in a sample of patients who had discontinued perphenazine treatment, quetiapine and olanzapine were superior to risperidone in preventing treatment discontinuation. In a naturalistic multi-site study, Dossenbach et al. [3] found that olanzapine was superior to quetiapine with regard to continuation of initial antipsychotic treatment and median response time. In a recent publication, Johnsen et al. [10] found that quetiapine was superior to olanzapine, risperidone, and ziprasidone in reducing psychopathological symptoms and severity of illness and in improving functional capacity during a 24-month follow-up period. In this pragmatic randomized trial, 50 % of study participants were lost to follow-up beyond the first follow-up assessment. High panel attrition rates as reported by Johnsen et al. are a common problem in RCTs which exclude a switch of medication unless participants drop out. In some large studies, patients whose initial treatment had been discontinued were re-randomized for the next follow-up interval to address this issue [7]. However, this is not what happens under real-world treatment conditions, where persons (a) switch between medication regimens and (b) receive several additional psychoactive drugs including antipsychotic combination therapy or other types of polypharmacy. Therefore, even pragmatic randomized trials fail to provide the full picture of routine care. As an alternative, well-designed observational cohort studies can contribute to filling the gap between randomized trials and post-marketing studies [11].

Aim of the present study is to examine if under real-world treatment conditions an antipsychotic maintenance therapy with quetiapine is more effective than a therapy with olanzapine or risperidone with regard to the prevention of inpatient admissions (primary endpoint) and with regard to several clinical and social criteria (secondary endpoints).

Materials and methods

Study design

The ELAN (***E***ffects of ***L***ong-term ***A***typical ***N***euroleptic Treatment under Routine Conditions) Study is a multicentre prospective observational trial following up persons with schizophrenia and schizoaffective disorder under routine psychiatric treatment conditions over 2 years after discharge from psychiatric inpatient treatment. 374 study participants were recruited from January 2005 to December 2006, and data collection continued until November 2008. Baseline assessments were conducted during the last week before hospital discharge, and follow-up assessments were performed at 6, 12, 18, and 24 months.

Inclusion and exclusion criteria

Inclusion criteria were a first-line diagnosis of schizophrenia or schizoaffective disorder based on the International Diagnosis Checklists for ICD-10, an age of 18 or older, and a clinical recommendation of antipsychotic maintenance treatment with quetiapine, olanzapine, or risperidone for a minimum of 12 months. At study onset any combinations between the three study medications were excluded, but all other types of combination, both with other antipsychotics and antidepressants, mood stabilizers, and benzodiazepines, were allowed according to individual clinical judgment. Further exclusion criteria comprised a first-line diagnosis of substance dependence, organic psychiatric disorder, or developmental/learning disability. Persons who were eligible according to these criteria were selected on the basis of inpatient admission files in nine psychiatric hospitals located in South Germany. The participating hospitals provide the full range of psychiatric in- and outpatient services for catchment areas with a total population of about 3-million people. Two of the nine hospitals are university clinics while the others are psychiatric hospitals providing in- and outpatient psychiatric care for regional catchment areas.

In the recruitment process, compatibility with inclusion criteria was established by study workers using a standardized screening procedure. Eligible persons were only included in the study after signing an informed consent form. The study protocol was approved by the Ethical Committees of Tübingen University, Ulm University, and of the State Medical Chamber of Baden-Württemberg.

Assessments

All assessments were conducted by study workers trained for use of the study instruments. Rater training for the PANSS and the side effects scales was performed by clinical experts.

Psychopathological symptoms were assessed by means of the Positive and Negative Syndrome Scale PANSS [12]. Functional capacity was measured by the Global Assessment of Functioning (GAF) scale from the DSM-IV [13]. Medication side effects were rated using the Simpson-Angus Scale for extrapyramidal motor side effects (SAS) [14] and the Abnormal Involuntary Movement Scale (AIMS) for tardive dyskinesia [15]. Quality of life (QOL) was measured using the Lancashire Quality of Life Profile LQoLP [16]. Adherence to drug treatment was assessed with the Medication Adherence Rating Scale for Psychosis (MARS) [17]. Cognitive processing speed (CPS) was assessed using the Digit Symbol Coding subtest from the Wechsler Adult Intelligence Scale WAIS [18]. Information about psychiatric service use including consumption of

psychotropic medication was obtained by means of the Client Sociodemographic and Services Receipt Interview (CSSRI) [19]. Total chlorpromazine equivalent (CPZeq) doses of antipsychotic drugs were computed from CSSRI data using recent recommendations by Andreasen et al. [20]. For substances not included in the analysis of Andreasen et al., the recommendations by Gardener et al. [21] were used.

Statistical analyses

Bias control

The propensity score method [22–24] was applied to control for selection bias in all statistical analyses. Propensity scores for the conditional probability of receiving olanzapine or risperidone rather than quetiapine at baseline were computed by means of a multinomial logistic regression model [23, 25] including the following independent variables: antipsychotic drug at hospital admission; outpatient treatment setting before hospital admission; a primary diagnosis of schizoaffective disorder; a comorbid diagnosis of substance abuse or personality disorder; a history of bipolar affective disorder, post-schizophrenic depression, or anxiety disorder from clinical records; involuntary admission at index hospitalization; number of previous inpatient episodes, number of suicide attempts; self-rated compliance with medical treatment before admission (yes/no), GAF score at baseline; body weight at baseline; age, gender; employment status before admission; education; living in own apartment; having a partner; nationality; occupational training, job status, and foreign mother language.

Primary outcome

The rehospitalization of patients after discharge from index hospitalization was regarded as the primary outcome. As indicated by post hoc power analysis with the program GPower 3.1.3 [26], a positive odds ratio of 2.0 or a negative odds ratio of 0.41 could be detected with a power of 0.95 at a significance level of $p = 0.05$ with the given sample size of 374 cases.

A random-effects logistic regression model was computed for the effects of antipsychotic treatment type on hospital readmission during the four follow-up periods. To take into account the causal order of the effects, antipsychotic medication group and additional psychotropic medication were included as $t-1$ time-lagged variables. In addition, the propensity scores for the probability of receiving olanzapine or risperidone rather than quetiapine at baseline were included in the regression equation. Random-effects logistic regression analysis was conducted by means of the xtlogit module of STATA 11 for Windows. The multinomial logistic regression analysis was conducted by means of the mlogit module of STATA 11 for Windows.

Secondary outcomes

Time to change of antipsychotic medication

A Cox regression model was computed for the number of days patients stayed on their initial antipsychotic drug. The propensity scores for olanzapine and risperidone were included as covariates. Cox regression analysis was computed by SPSS 18 for Windows.

Dosage of antipsychotic medication

A random-effects regression model with robust standard error was computed for the effects of antipsychotic medication on chlorpromazine equivalent antipsychotic dose. Additional psychotropic medication, PANSS total score, and propensity scores for the probability of receiving olanzapine or risperidone rather than quetiapine at baseline were included in the model. Random-effects regression analyses were performed by means of the xtreg module of STATA 11 for Windows.

Clinical and psychosocial outcomes

Mixed-effects regression models were fitted for each outcome variable including a random linear time effect, and fixed-effects for the initial treatment groups and treatment × time interaction effects using quetiapine as reference category. All models were controlled for the interaction between the baseline measure of the dependent variable, the effects of additional atypical and typical antipsychotics, antidepressants, benzodiazepines, mood stabilizers, and the propensity scores of receiving olanzapine or risperidone rather than quetiapine at baseline. Missing values were assumed as random. Mixed-effects regression models were computed by the xtmixed module of STATA 11 for Windows.

As physicians and patients were free to change treatment regimens in any direction, the following six medication groups were included in the mixed-effects models: (a) quetiapine; (b) olanzapine; (c) risperidone; (d) other atypical antipsychotics; (e) typical antipsychotics; and (f) no antipsychotics. Mixed-effects regression models were computed by the xtmixed module of STATA 11 for Windows.

Results

Study sample and study flow

530 persons were found to be eligible for inclusion and asked for study participation. 374 patients (71 %) agreed to participate and gave informed consent. Patients who refused to participate, in comparison with those who participated, were significantly younger and had fewer inpatient episodes and a lower rate of schizoaffective disorder diagnoses. The sociodemographic and clinical characteristics of study participants are presented in Table 1.

Table 1 Sample description

	Treatment group			Sig. dif.[a]
	1 Quetiapine	2 Olanzapine	3 Risperidone	
N (%)	183 (48.93)	91 (24.33)	100 (26.74)	
Female *n* (%)	99 (54.10)	37 (40.66)	42 (42.00)	1>2,3[b]
Age m (SD)	39.24 (12.6)	41.1 (12.4)	40.3 (12.7)	ns[c]
Having a job *n* (%)	73 (39.9)	29 (31.9)	36 (36.0)	ns[b]
Own apartment *n* (%)	111 (60.7)	62 (68.1)	67 (67.0)	ns[b]
Living with a partner *n* (%)	61 (33.3)	27 (29.7)	23 (23.0)	ns[b]
Foreign nationality *n* (%)	18 (9.8)	5 (5.5)	6 (6.0)	ns[b]
Higher education *n* (%)	92 (50.3)	50 (55.0)	41 (41.0)	ns[b]
Schizoaffective disorder *n* (%)	49 (26.8)	30 (33.0)	27 (27.0)	ns[b]
Involuntary admitted *n* (%)	35 (19.1)	21 (23.1)	28 (28.0)	ns[b]
Body mass index m (SD)	33.0 (6.9)	30.1 (5.6)	33.6 (6.8)	2<1,3
Number of inpatient admissions m (SD)	7.3 (9.3)	6.1 (6.7)	6.8 (7.7)	ns[c]
GAF score m (SD)	55.8 (12.9)	56.9 (12.3)	53.8 (11.5)	ns[c]
PANSS total score m (SD)	55.0 (13.3)	55.2 (16.2)	54.4 15.0)	ns[c]
Total CPZ dosage m (SD)	599.62 (395.64)	514.18 (394.34)	532.20 (376.60)	1>2,3[c]

[a] Significance of group differences $p \leq 0.05$

[b] χ^2 test

[c] Anova with Bonferroni or Scheffé multiple comparison test

A total of 257 patients (69 %) were assessed at all follow-up assessments. 29 persons (8 %) left the study after the baseline assessment. 323 (86 %) participated in the first follow-up at 6 months, 314 (84 %) patients participated in the second follow-up at 12 months, 302 (81 %) participated in the third follow-up at 18 months, and 300 (80 %) patients participated in the fourth follow-up at 24 months.

Pharmacological treatment

At baseline, 33 (18.0 %) patients treated with quetiapine, 25 (27.5 %) patients receiving olanzapine, and 19 (19.0 %) patients treated with risperidone received no other psychotropic medication.

As indicated in Table 2, 101 (55.2 %) patients treated with quetiapine, 45 (49.5 %) of those on olanzapine, and 56 (56.0 %) patients receiving risperidone were prescribed at least one additional typical or atypical antipsychotic drug, and a substantial number of participants received other psychotropic drugs such as antidepressants, benzodiazepines, mood stabilizers, or anti-Parkinsonian medications in addition to their principal antipsychotic drug.

Selection bias

Results of the multinomial logistic regression model (not shown) revealed that the likelihood of receiving olanzapine in comparison with quetiapine at baseline was higher for patients already on olanzapine before index admission (RR 3.18; p 0.000) and lower for patients on quetiapine (RR 0.02; p 0.000) before index admission. Patients who had a post-schizophrenic depression episode in their illness history had an increased chance of receiving olanzapine rather than quetiapine (RR 20.06; $p = 0.050$). While the probability of receiving olanzapine versus quetiapine decreased with increasing body weight (RR 0.95; p 0.001), it increased with age (RR 1.04; $p = 0.003$). Female patients had a lower chance of receiving olanzapine rather than quetiapine compared with their male counterparts (RR 0.28; p 0.002).

The likelihood of receiving risperidone rather than quetiapine was higher for patients who already received risperidone before index admission (RR 4.31, p 0.000) and lower for patients who received quetiapine (RR 0.07; p 0.000) before index admission. With increasing GAF score, patients had a declining probability of receiving risperidone (vs. quetiapine) (RR 0.96; p 0.011). Patients who lived in an own apartment had a higher chance of receiving risperidone (vs. quetiapine) than those who lived in sheltered accommodation (RR 2.73; p 0.027). The chance of receiving risperidone rather than quetiapine was lower in patients who received a disability pension (RR 0.23; p 0.000) and for those who lived with a partner (RR

Table 2 Additional psychotropic medication at baseline

	Quetiapine	Olanzapine	Risperidone	Total	Sig.
Atypical antipsychotic *n* (%)	26 (14.2)	8 (8.8)	16 (16.0)	50 (13.4)	0.308
Typical antipsychotic *n* (%)	75 (41.0)	37 (41.0)	40 (40.0)	152 (40.6)	0.987
Antidepressant *n* (%)	49 (26.8)	23 (25.3)	29 (29.0)	101 (27.0)	0.842
Benzodiazepines *n* (%)	57 (31.2)	20 (22.0)	24 (24.0)	101 (27.0)	0.200
Mood stabilizer *n* (%)	29 (15.9)	15 (16.5)	21 (21.0)	65 (17.4)	0.532
Anti-Parkinsonian *n* (%)	19 (10.4)	3 (3.3)	9 (9.0)	31 (8.3)	0.128

0.68; p 0.023) compared with those who received no disability pension or lived alone.

The pseudo R^2 of 0.29 indicates that the model variables explain about 29 % of the variance in the probability of patients starting into the study with one of the three antipsychotics.

Hospital readmission

At each follow-up period, an average of 28 % of study participants was admitted to psychiatric inpatient treatment at least once. As indicated in Fig. 1, the average 6-month hospital readmission rate was lowest among patients prescribed olanzapine at the beginning of each follow-up period. Results of a logistic random-effects regression analysis (not shown) confirm that the average readmission rate of study participants who received olanzapine as principal antipsychotic agent was significantly lower in comparison with patients treated with quetiapine (OR = 0.40; p 0.017) and compared with those on risperidone (OR 0.25; p 0.000) at $t-1$ (Fig. 1).

Antipsychotic medication dose

The mean daily dose of quetiapine was 588 mg (SD 268 mg), the average daily olanzapine dose was 15 mg (SD 6.5 mg), and the average dose for risperidone was 3.9 mg (SD 1.8 mg) per day. Dosages of all antipsychotics were higher during inpatient stays than during outpatient treatment, and all dosages decreased in the course of the study (Fig. 2).

As indicated by the results of the random-effects regression model (not shown), patients treated with olanzapine (b −92.35; p 0.023) or risperidone (b −120.75; p 0.001) received significantly lower chlorpromazine equivalent medication dosages compared to those on quetiapine. In addition, total CPZeq dosage was higher for patients who received additional atypical antipsychotics (b 171.10; p 0.000) or typical antipsychotics (b 374.51; p 0.000) but lower for participants who received additional antidepressants (b −58.59; p 0.004). CPZeq dosage was also significantly positively related to the total PANSS score (b 2.38; p 0.000).

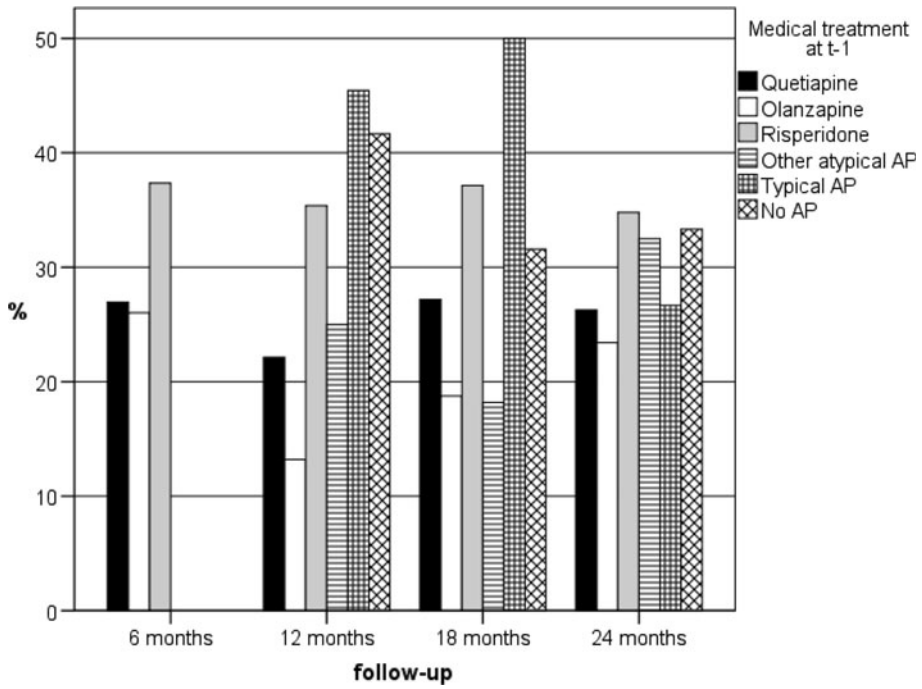

Fig. 1 Psychiatric hospital admissions (%) at each follow-up period by medication at the beginning ($t-1$) of the follow-up period

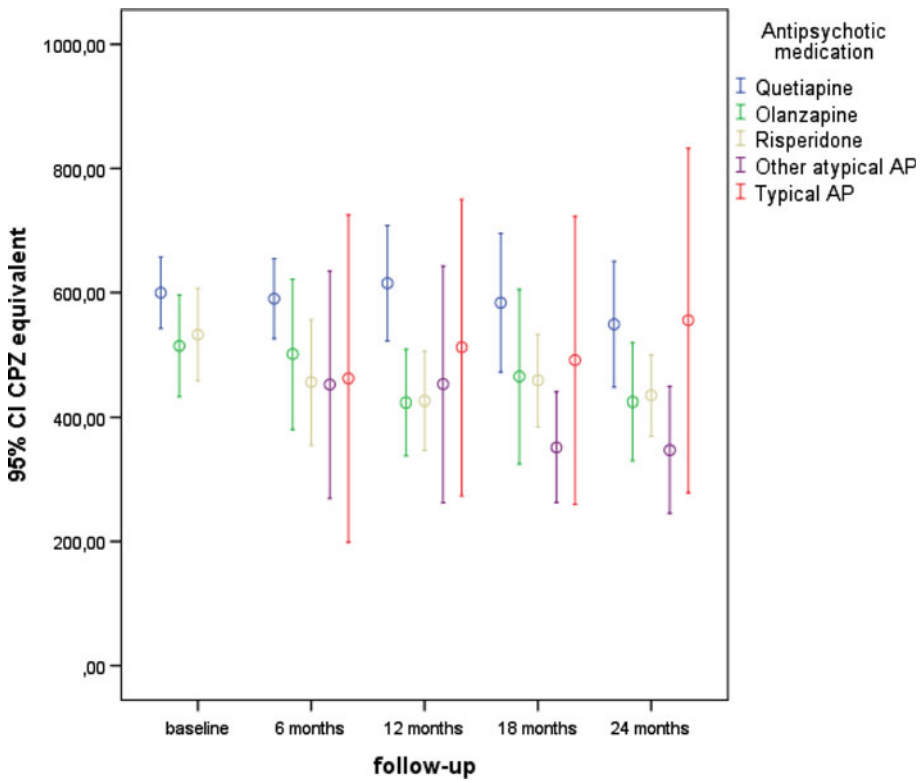

Fig. 2 Chlorpromazine equivalent dosages of antipsychotic medication

Time to change of initial antipsychotic treatment

The average time to any change of the initial antipsychotic treatment was 466 days (SD 264 days) for participants who started on quetiapine, 441 days (SD 259 days) for participants prescribed olanzapine at baseline, and 442 days (SD 266 days) for participants who initially received risperidone (Fig. 3).

Results of the Cox regression model adjusted for propensity scores (Fig. 3) revealed that participants who started on quetiapine did not differ significantly with regard to time to treatment discontinuation from participants receiving olanzapine (OR 1.158; p 0.525) or risperidone (OR 0.796; p 0.315) at discharge.

Effects of medication on clinical and psychosocial outcomes

The effects of quetiapine in comparison with the other antipsychotic drugs on the clinical and psychosocial outcomes are presented in Table 3.

The coefficients for the random linear time effects in the mixed-effects regression models in Table 3 indicate that, at the Bonferroni corrected significance level of 0.006, coefficients for the GAF (b 1.350; $p = 0.000$), for quality of life (b 0.628; $p = 0.006$), and for cognitive performance (b 0.270 $p = 0.000$) indicated a significant improvement of patients who were treated with quetiapine.

The lack of significant treatment × time interactions for these variables indicates that clinical improvement in patients who received olanzapine or risperidone did not positively or negatively differ from change among patients treated with quetiapine.

The only significant treatment × time interaction effects indicate that AIMS scores decreased more (b −0.370; p 0.002) among participants who were treated with other atypical antipsychotics after baseline in comparison with those who were treated with quetiapine. No other significant interaction effects between time and medication group were found.

The effects of the variables for polypharmaceutical treatment indicate that additional treatment with typical antipsychotic drugs was related to higher average PANSS values (b 6.077; p 0.000), lower average GAF scores (b −4.922; p 0.000), lower overall quality of life (b −3.267; p 0.017), higher SAS scores (b 0.080; p 0.005), and higher AIMS scores (b 0.642; p 0.001). Additional treatment with antidepressants was related to lower overall quality of life (b −1.504; p 0.003) and higher SAS scores (b 0.055; p 0.000). Additional treatment with benzodiazepines was related to higher average PANSS total score (b 5.415; p 0.000), lower average GAF score (b −3.611; p 0.000), lower overall quality of life (b −1.850; p 0.001), and lower medication adherence (b −0.446; p 0.000). Additional use of anti-Parkinsonian drugs was related with higher SAS side effects (b 0.150; p 0.000) and higher AIMS scores (b 1.251; p 0.000).

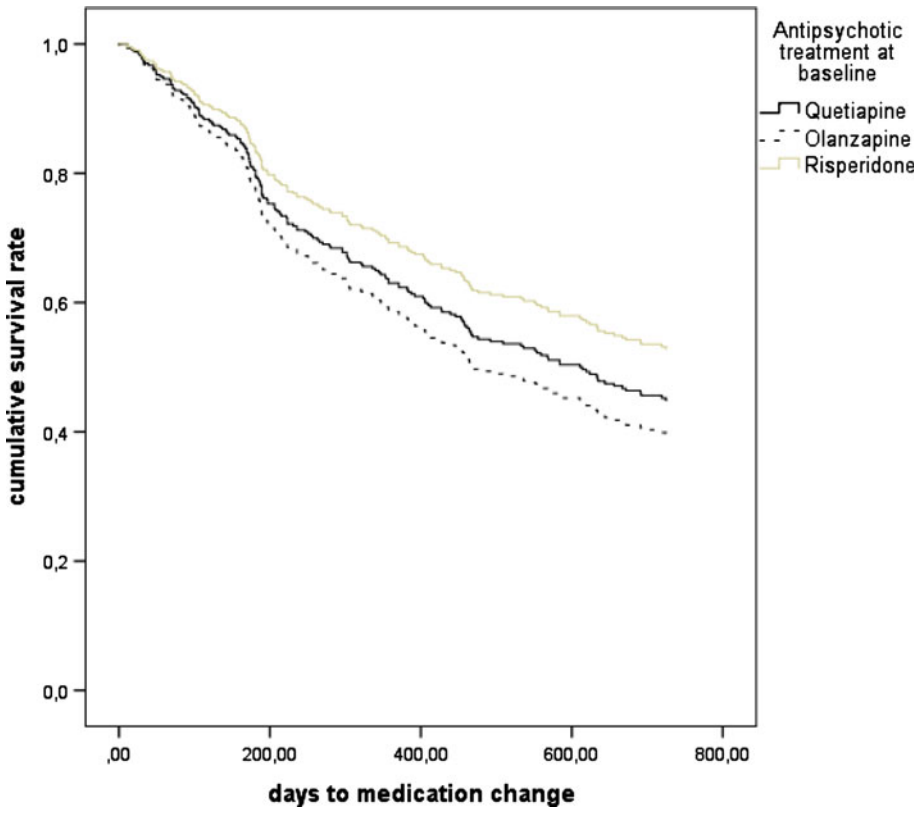

Fig. 3 Survival function for days to treatment discontinuation adjusted for propensity scores

The coefficients for baseline differences indicate that patients who were treated with typical antipsychotics after baseline had higher SAS scores (b 0.433; p 0.000) at baseline and that patients who were treated with other atypical antipsychotics had higher baseline AIMS scores (b 1.389; p 0.000). MARS scores indicate that patients who discontinued antipsychotic medication (b −2.308; p 0.005) were less treatment adherent at baseline.

The coefficients for the contrast between olanzapine and the other antipsychotic drugs are shown in Table 3a in the online addendum. The only significant treatment × time interaction indicates that the AIMS scores decreased more (b −0.383; $p = 0.003$) among patients who received other atypical in comparison with those who received olanzapine.

Discussion

The principal objective of this observational study was to examine real-world differential effects on clinical and psychosocial outcomes of quetiapine as compared with olanzapine and risperidone in patients with schizophrenia or schizoaffective disorder. Our results suggest that patients treated with olanzapine had a lower risk of hospital readmission than patients treated with quetiapine or risperidone. Otherwise, quetiapine, olanzapine, or risperidone had few differential effects during a two-year follow-up period after psychiatric inpatient treatment.

The average daily doses of quetiapine and risperidone, in our study, were similar to those reported in the CATIE study [8] but higher than those reported by the SOHO study group [3]. In contrast, the average olanzapine dose was lower than mean doses reported in CATIE but higher than dosages reported in the SOHO study. In spite of the chlorpromazine equivalent dose adjustment for quetiapine to the higher dosage regimens that are currently used [20], the total average chlorpromazine equivalent dose in participants receiving quetiapine was still significantly higher than average dosages in persons treated with olanzapine or risperidone. This finding held after controlling for additional antipsychotic medication and the severity of psychotic symptoms.

Neither the inferiority of quetiapine regarding time to treatment discontinuation found in the CATIE study [8] nor the superiority of quetiapine over other second-generation antipsychotic drugs reported by Johnson et al. [10] could be confirmed in the ELAN study. These differences in findings could have been due to the fact that participants, in our study, were not randomly allocated to treatment groups. As is the rule in routine care, antipsychotic treatment decisions in the ELAN study were made jointly by patient and psychiatrist. Thus, it could be hypothesized that antipsychotic medication, in this observational trial, may have better

Table 3 Results of the mixed-effects regression models (Quetiapine = reference category)

	PANSS total		GAF		QOL total score		SAS side effects		AIMS side effects		BMI		MARS		Cognitive performance		Waist circumference	
	b	*p*	*b*	*p*	*b*	*p*	*b*	*p*	*b*	*p*	*b*	*p*	*b*	*p*	*b*	*p*	*b*	*p*
Time[a]	−0.865	0.015	1.350	0.000	0.628	0.006	−0.016	0.016	0.047	0.325	0.212	0.006	0.102	0.020	0.270	0.000	0.460	0.019
Quetiapine[b]	Reference category																	
Olanzapine[b]	1.792	0.236	0.689	0.627	−1.825	0.062	0.012	0.709	−0.115	0.609	−0.108	0.752	0.103	0.608	0.137	0.629	−0.743	0.419
Risperidone[b]	−0.712	0.624	0.054	0.997	−0.194	0.838	0.061	0.057	0.273	0.206	−0.438	0.174	−0.052	0.787	−0.093	0.733	−0.267	0.760
Other atypical AP[b]	−1.153	0.690	1.517	0.554	0.762	0.651	0.100	0.091	1.389	0.000	−0.059	0.901	−0.193	0.607	−0.373	0.448	−0.897	0.488
Typical AP[b]	4.073	0.298	−3.253	0.348	−5.404	0.020	0.433	0.000	1.383	0.008	−0.236	0.705	−1.363	0.008	0.726	0.265	1.116	0.538
No Medication[b]	5.515	0.168	−3.876	0.275	−2.288	0.330	−0.038	0.674	0.158	0.786	−1.176	0.076	−2.308	0.005	0.445	0.512	−0.918	0.617
Quetiapine × time[c]	Reference category																	
Olanzapine × time[c]	−0.279	0.651	−0.420	0.458	0.145	0.712	−0.008	0.515	0.013	0.876	0.147	0.251	−0.093	0.226	−0.001	0.991	0.647	0.055
Risperidone × time[c]	0.781	0.158	−0.627	0.217	−0.514	0.150	−0.018	0.088	−0.024	0.749	0.026	0.822	0.023	0.743	0.030	0.765	0.008	0.979
Other atyp. × time[c]	0.285	0.746	−0.728	0.357	−0.384	0.471	−0.257	0.152	−0.370	0.002	−0.123	0.428	0.142	0.218	0.061	0.684	−0.069	0.865
Typical × time[c]	1.647	0.171	−1.068	0.321	0.226	0.758	−0.071	0.005	0.211	0.191	0.122	0.543	0.228	0.153	−0.343	0.091	−0.234	0.676
None × time[c]	−0.961	0.482	1.631	0.178	−0.345	0.670	0.004	0.889	0.049	0.808	0.090	0.711	0.294	0.270	0.056	0.806	−0.642	0.324
Baseline × time[d]	−0.067	0.000	−0.020	0.105	−0.020	0.024	0.000	0.120	0.005	0.007	0.006	0.065	−0.002	0.113	−0.006	0.019	−0.022	0.008
Atypical AP[e]	2.222	0.207	−3.510	0.025	−0.733	0.483	0.026	0.426	0.442	0.052	−0.082	0.783	−0.161	0.457	−0.311	0.306	0.336	0.681
Typical AP[e]	6.077	0.000	−4.922	0.000	−3.267	0.000	0.080	0.005	0.642	0.001	0.100	0.703	−0.329	0.080	−0.375	0.164	1.505	0.035
Antidepressant[e]	2.048	0.014	−1.140	0.130	−1.504	0.003	0.055	0.000	0.046	0.679	−0.001	0.993	0.050	0.622	−0.167	0.252	−0.031	0.941
Benzodiazepine[e]	5.415	0.000	−3.611	0.000	−1.850	0.001	0.026	0.142	0.195	0.105	−0.099	0.516	−0.446	0.000	−0.399	0.009	0.124	0.771
Anti-epileptic[e]	−1.421	0.187	0.224	0.817	0.881	0.176	0.026	0.195	0.104	0.461	0.069	0.738	0.110	0.399	−0.097	0.609	0.751	0.190
Anti-Parkinsonian[e]	−0.342	0.824	0.103	0.941	−0.166	0.859	0.150	0.000	1.251	0.000	−0.215	0.439	−0.111	0.569	−0.286	0.287	−0.878	0.246

Controlled for propensity scores of receiving olanzapine or risperidone rather than quetiapine at baseline (coefficients not shown)

[a] Random linear time effects

[b] Main effects of antipsychotic medication

[c] Interaction effect between time and antipsychotic medication

[d] Interaction effects between baseline values of outcome variables and time

[e] Main effects of additional medication

matched participants' individual needs and preferences. This is in line with the finding that average time to drug discontinuation for all antipsychotics was considerably longer in the ELAN study than discontinuation times reported in most RCTs of quetiapine [1].

The current observational trial of routine care reveals that only a small proportion of participants were treated with a single antipsychotic while the majority received either combinations of different antipsychotics or combinations of antipsychotics with other psychotropic drugs. These results are consistent with findings of several other studies [27–33] showing similar rates of polypharmacy, and they underline the necessity of conducting further observational studies under real-world treatment conditions. We addressed the problem of polypharmacy in our regression models by controlling for any type of additional psychotropic drug. Thus, effects of the principal antipsychotic drug under conditions of no additional psychotropic drugs could be estimated for all participants.

Strengths of the ELAN study include the long duration of follow-up assessments of 24 months, the inclusion of a typical routine treatment sample, and a low panel attrition rate. Limitations result from the observational design of the study, the lack of rater blinding, and the lack of clinical drug monitoring. The propensity score method including clinical and socio-demographic variables was used to control for drug selection bias. The multinomial logistic regression model for the estimation of the propensity scores indicated that the prescription of antipsychotic drugs was mainly influenced by prior treatment decisions and by a small number of clinical and sociodemographic characteristics. The model explained a third of the variance in antipsychotic prescription at baseline which suggests that selection bias could be controlled for to a substantial degree (but not fully). Despite the large number of clinical and sociodemographic variables included in the propensity score model, additional variables may have had an impact on the selection of initial antipsychotic drug (and on clinical outcomes). The development of more comprehensive models for the control of selection bias is therefore an important task for future research.

Implications

In routine care, treatment of patients with schizophrenia or schizoaffective disorder with olanzapine is related to a lower risk of psychiatric inpatient readmission when compared with quetiapine or risperidone. Otherwise, treatment regimens with quetiapine, olanzapine, or risperidone as the principal antipsychotic agent have no differential effects on clinical outcomes or quality of life. However, on the basis of our results on adverse effects, we hypothesize that in observational trials adverse effects of antipsychotics may be less prominent than in clinical studies. Patients who develop severe adverse effects such as weight gain or motor symptoms may convince (or prompt) their psychiatrist to switch to an alternative drug or discontinue treatment. Thus, differential adverse effects may disappear due to clinical management efforts. Further analyses of these processes are necessary to improve our understanding of factors affecting the outcome of schizophrenia treatment under real-world conditions.

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