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Differential use of extended and immediate release quetiapine: a retrospective registry study of Finnish inpatients with schizophrenia spectrum and bipolar disorders

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ABSTRACT

Objective: Extended release (XR) and immediate release (IR) quetiapine have differing dosing, titration and plasma concentration profiles. The authors assessed whether the use of quetiapine XR and IR in schizophrenia spectrum disorders (SCZ) and bipolar disorder (BD) differ.

Design: Retrospective non-interventional registry study.

Setting: Secondary healthcare.

Participants: All SCZ and BD (ICD-10 codes F20–F29, F30–F31) patients discharged between June 2008 and June 2010 from a Finnish psychiatric hospital with any use of quetiapine during their inpatient stay.

Primary and secondary outcome measures: Differences in patient characteristics between quetiapine XR and IR users were tested. To assess the profile of XR versus IR patients, logistic regressions were performed.

Results: 43 patients used quetiapine XR, 58 used quetiapine IR and 55 used both formulations (n=156). 102 patients were diagnosed with SCZ and 54 with BD, with no significant differences between the quetiapine formulations. The mean daily dose of quetiapine XR was significantly higher than that of quetiapine IR (542 mg vs 328 mg; $p<0.001$). This was also true for the SCZ subgroup (XR: 593 mg vs IR: 338 mg; $p<0.001$) and the BD subgroup (XR: 466 mg vs IR: 308 mg; $p=0.009$). 48% of all quetiapine IR patients used a mean dose of ≤200 mg compared with 2% of XR patients. Injectable antipsychotics were combined with quetiapine IR but not with quetiapine XR (12% vs 0%; $p=0.019$). At discharge, quetiapine XR was used as monotherapy to a greater extent than IR (79% vs 44%; $p=0.003$). The odds for quetiapine XR use in hospital were lower with advancing age, substance abuse diagnosis and prior IR use.

Conclusions: Among SCZ and BD inpatients, quetiapine XR was more often used as monotherapy and in significantly higher doses than quetiapine IR. Differential use of the quetiapine formulations appears to depend, at least in part, on patient characteristics.

ARTICLE SUMMARY

Article focus

- Quetiapine exists in an extended (XR) and an immediate release (IR) formulation with different dosing, titration and plasma concentration profiles.
- This study assesses whether these differences lead to differential use of the two quetiapine formulations when treating schizophrenia spectrum disorders and bipolar disorder in a routine inpatient care setting.

Key messages

- Use of quetiapine XR and IR differs in a routine inpatient care setting: quetiapine XR was used in higher doses and more often as monotherapy when compared with quetiapine IR.
- Certain patient characteristics differ between quetiapine XR and IR users: the odds for being treated with quetiapine XR in hospital were lower for older patients, patients with a substance abuse diagnosis, and prior IR use.

Strengths and limitations of this study

- The study depicts real-life use patterns of quetiapine XR and IR in an unrestricted patient population: all patients with schizophrenia spectrum disorder or bipolar disorder and any use of quetiapine during their inpatient stay were included.
- The results may not be generalisable to other settings as the use of quetiapine may differ in other countries and in the outpatient clinical setting in Finland.

INTRODUCTION

Schizophrenia spectrum disorders (SCZ) and bipolar disorder (BD) are severe psychiatric disorders that coaggregate[1] and overlap.[2 3]

Atypical antipsychotic (AAP) medications are the first-line treatment of SCZ and commonly used in BD. Guidelines advocate the use of AAP monotherapy for SCZ[4 5] and as one treatment option in BD, particularly bipolar mania.[6 7]

Treatment of these disorders in clinical practice is complex. Individualising drug treatments for SCZ and BD with respect to side effects, adherence challenges and patient preferences, is crucial for treatment success.[8 9] Therefore, different patient and drug characteristics are likely to determine the psychiatrist's drug choice in clinical practice. Randomised controlled clinical trials (RCTs), on the other hand, usually include a strictly defined subgroup of patients. As a result, RCT populations are likely to be a subset of the patient populations that are treated with different antipsychotics in naturalistic, routine care settings with respect to attributes such as age, gender, comorbidities and polypharmacy.

Currently used antipsychotics differ considerably in their pharmacological properties.[10] Indeed, antipsychotics (including AAPs) may differ in efficacy on positive and other symptoms as well as on comorbid symptoms (eg, depression and anxiety) and in terms of side effects (eg, somnolence, extrapyramidal symptoms and weight gain). Therefore, an individualised drug therapy would be preferable, as it would reflect how different drug characteristics respond to the needs of each patient.

Quetiapine is an established therapy for SCZ and BD. It exists in two formulations: an immediate release formulation (quetiapine IR) and an extended release formulation (quetiapine XR). Quetiapine XR was developed to provide patients and physicians with a more convenient dosage and a simpler dose administration regimen.[11] Quetiapine XR is characterised by once-daily dosing, faster dose titration and different pharmacological and tolerability profiles compared with quetiapine IR.[11–14] The different properties of the two quetiapine formulations may influence how these medications are used in inpatient and outpatient settings. For instance, the possibility for faster titration and once-daily dosing could facilitate the use of quetiapine XR in an inpatient setting.

There is little research on how different formulations of the same antipsychotic are used in real-life treatment settings. To our knowledge, no previous study has evaluated the clinical use of quetiapine XR and IR with respect to, for instance, patient characteristics, dosing and add-on medication. This study assesses whether there are differences in the use of quetiapine XR and IR in a routine inpatient care setting. Using logistic regression analysis, we also assess the factors associated with the use of quetiapine XR versus IR.

METHODS

Study design

A local, non-interventional, retrospective register study (study code NIS-NFI-SER-2009/1) was designed to evaluate the current clinical treatment practices with quetiapine XR and quetiapine IR in one Finnish psychiatric hospital. The South Karelia Central Hospital in Lappeenranta in Southeast Finland (with four treating physicians and 63 beds in service at the time of the study) has a population catchment area of 130 000. All patients using quetiapine XR or IR during their inpatient stay and having SCZ (ICD-10 codes F20–F29) or BD (F30–F31) diagnosis were included in the study population. No exclusion criteria were applied.

The patient population consisted of patients who were discharged from the South Karelia Central Hospital between June 2008 and June 2010. There was no need for patient informed consent as this retrospective study was based solely on patient records (ie, hospital databases) and no intervention in routine care took place. The data collected consisted of basic sociodemographic information (age, gender, living circumstances, employment) and information related to the patient's treatment and characteristics at hospital admission (use of antipsychotics at admission, history of psychosis, voluntary/involuntary hospitalisation, global assessment of functioning (GAF) score), during hospitalisation (drug use, diagnoses) and at discharge (use of antipsychotics, GAF). Data were collected systematically by a trained study nurse, using a structured format and at two separate time points: August 2009 and July 2010. To increase the sample size of the study population, the original patient data (n=98) from June 2008 to August 2009 were extended in July 2010 to cover patients discharged between September 2009 and June 2010. The study design and its extension were approved by the South Karelia Central Hospital Research Ethics Board.

Statistical analysis

Similarities and differences among the patients using the two different quetiapine formulations were assessed. Variables with normal distributions were tested using t tests on the equality of means, whereas variables with non-normal distributions (normality tested with the Shapiro–Wilk W test) were tested with a non-parametric test (Wilcoxon rank sum test). A p value ≤ 0.05 was considered to indicate statistical significance.

The factors that were associated with the use of quetiapine XR versus IR during inpatient stay and at hospital discharge were assessed using logistic regression models. Logistic regression analysis allowed us to test multiple correlations and significances simultaneously. An exploratory approach was chosen for the modelling because we had no solid prior belief about the factors that would determine the use of quetiapine XR and IR. In the primary model (ie, exhaustive model, given the data available), all known characteristics were included as explanatory variables. The final model was obtained by dropping explanatory variables in a stepwise manner until the value of the Akaike information criterion (AIC) was minimised. The AIC provides a tool for model selection that rewards goodness of fit and penalises

overfitting. In essence, the AIC was used to find the set of variables that best explain the choice between quetiapine XR and IR. In addition, the validity of the model predictions was assessed on the basis of the proportion of patients classified correctly (see, eg, Soini and colleagues[15]). In a sensitivity analysis, we analysed the use of quetiapine during the inpatient stay in a patient subgroup with a hospital stay of 7 or more days (results available upon request).

All analyses were performed with Stata (R) statistical software, V.11.1.

RESULTS

Patient and drug use characteristics

The study population consisted of 156 patients (90 men and 66 women), with a mean age of 45.4 years (SD 16.6 years). Of all patients with SCZ and BD (n=399), 39.1% were treated with quetiapine. Approximately one-third of the study patients (n=54) were diagnosed with BD and the remainder (n=102) with SCZ. The mean GAF score at hospital admission was 34.3 (SD 8.4). Forty-three patients used quetiapine XR, 58 patients used quetiapine IR and 55 patients used both formulations (XR and IR) either concomitantly or sequentially during their hospital stay.

Antipsychotic polypharmacy (66.0% of all patients) and switches between antipsychotics (46.8%) were common during the inpatient stay. There were altogether 78 different antipsychotic drug sequences (ie, concomitant or sequential drug use) among the 156 patients. Use of antidepressants (n=40), antiepileptics (n=38) or anxiolytics (n=39) was found in approximately one-quarter of the patients. The detailed characteristics of the study patients are shown in table 1.

Use of quetiapine XR and IR

There were significant differences in the patient groups using quetiapine XR and IR (table 1). Compared with quetiapine XR, quetiapine IR was used in older patients (mean age 48.2 vs 40.5; p=0.022) and was more frequently combined with injectable antipsychotics (12.1% vs 0% of patients; p=0.019).

Considerable differences were found in the way the two quetiapine formulations were used. The mean daily dose of quetiapine was higher for XR than for IR patients: 584 versus 341 mg (p<0.001) during the inpatient stay and 630 versus 394 mg at discharge (p=0.002). The pattern of significantly higher quetiapine XR doses holds across various subgroups (table 2).

Almost half (48.3%) of the patients in the IR group were using quetiapine in daily doses ≤200 mg, whereas such low doses were observed in only 2.3% of the patients in the XR group (table 3). Consequently, there was a statistically significant difference in the use of quetiapine doses ≥400 mg/day during the inpatient stay between the XR and IR groups: 65.1% of patients in the XR group and 39.7% of patients in the IR group (p=0.011).

During the inpatient stay, a trend was observed for more common use of quetiapine XR monotherapy compared with IR monotherapy (44% vs 28% of patients; p=0.08). At discharge, monotherapy with quetiapine XR was more common than with IR (79% vs 44% of patients; p=0.003). The mean number of other antipsychotics used during the inpatient stay was higher in the IR than the XR group (1.4 vs 1.1), although this difference was not statistically significant. At discharge, patients in the XR and IR groups used on average 0.4 and 0.8 other antipsychotics, respectively; the difference is statistically significant (p=0.022). More quetiapine IR than XR patients used atypical as well as typical

Table 1 Characteristics of the study patients

Variable	Study population, n=156	XR population, n=43	IR population, n=58	XR and IR population, n=55
Mean age, years (SD)	45.4 (16.6)	40.5 (16.1)* †	48.2 (17.7)*	46.2 (15.3)†
Gender, male, %	57.7	58.1	51.7	63.6
Lives alone, %	51.9	58.1	46.6	52.7
Employed, %	23.5	23.8	21.4	25.5
History of psychosis, %	76.9	83.7†	84.5‡	63.6‡ †
Personality disorder, %	12.2	4.7	15.5	14.5
Substance abuse, %	10.3	7.0	17.2	5.5
Involuntary hospitalisation, %	37.2	44.2	41.4	27.3
Mean GAF score at admission (SD)	34.3 (8.4)	33.2 (9.1)	34.2 (8.0)	35.4 (8.3)
Mean GAF score at discharge (SD)	55.3 (8.2)	55.4 (7.7)	55.6 (8.4)	54.9 (8.6)
SCZ diagnosis, %	65.4	65.1	75.9‡	54.5‡
BD, %	34.6	34.9	24.1‡	45.5‡
Use of any antipsychotic at admission, %	52.6	46.5	58.6	50.9
Mean length of inpatient stay, days (SD)	59.3 (70.4)	54.4 (52.8)	64.0 (92.5)	58.2 (54.8)
Duration of quetiapine treatment, days (SD)	43.5 (56.7)	39.0 (33.7)	38.0 (77.1)	52.9 (44.3)

*Statistically significant (p<0.05) difference between IR and XR group.
†Statistically significant (p<0.05) difference between XR and XR and IR group.
‡Statistically significant (p<0.05) difference between IR and XR and IR group.
BD, bipolar disorder; GAF, global assessment of functioning; IR, immediate release quetiapine; SCZ, schizophrenia spectrum disorder; XR, extended release quetiapine.

Table 2 Comparison of quetiapine doses in different subgroups of patients (XR and IR group not shown)

	XR group			IR group			
	Mean	95% CI	N	Mean	95% CI	N	p Value
Mean doses during inpatient stay							
All patients	583.7	499.7 to 667.6	43	341.0	267.9 to 414.1	58	<0.001
Women	579.1	472.4 to 685.8	18	295.1	185.7 to 404.5	28	<0.001
Men	587.0	458.1 to 715.9	25	383.9	282.3 to 485.5	30	0.013
SCZ	622.0	508.4 to 735.6	28	328.1	244.4 to 411.8	44	<0.001
BD	512.1	389.4 to 634.8	15	381.6	212.2 to 551.0	14	0.186
Patients aged >45 years*	535.3	427.1 to 643.5	13	295.6	207.8 to 383.3	30	0.002
Patients aged ≤45 years*	604.6	490.8 to 718.5	30	389.7	267.6 to 511.8	28	0.011
Maximum dose during inpatient stay	672.1	580.9 to 763.3	43	459.1	352.8 to 565.3	58	0.004
Mean dose at discharge†	630.3	527.5 to 733.1	33	394.1	290.1 to 498.2	34	0.002

*Mean age in the study population.
†Among patients who were discharged with the study drug.
BD, bipolar disorder; SCZ, schizophrenia spectrum disorder.

antipsychotics, although these differences were not statistically significant. There were numerical differences in the use of specific antipsychotics between the XR and IR groups, but the only significant difference was in the use of risperidone, which was used at some point during their stay by 19.0% of IR and 4.7% of XR patients (p=0.03). Detailed information about the drug use is found in table A1 in the supplementary material.

In the XR and IR groups, 76.7% and 58.6% of patients (p=0.058), respectively, were discharged with the study drug. When studying those patients discharged with either quetiapine XR or IR, significant differences in the dose intensity were observed. Among patients discharged with quetiapine monotherapy, the daily doses were ≤200 mg in 3.8% and 60.0% of the patients (p<0.001) in the XR and IR groups, respectively. Similarly, quetiapine daily doses were ≥400 mg in 75.8% and 47.1% of the discharged patients (p=0.016) in the XR and IR groups (either monotherapy or combination therapy with other antipsychotics), respectively. Daily doses ≥600 mg were used by 73.1% and 26.7% of discharged patients (p=0.003) on quetiapine XR and IR monotherapy, respectively. Antipsychotic polypharmacy at discharge was observed in 21.2% of patients in the XR group and 52.9% in the IR group (p=0.004).

Among the 55 patients using both quetiapine XR and IR during their inpatient stay, 67.3% had a switch between XR and IR, whereas 32.7% used both products simultaneously (at least at some point during their inpatient stay). The mean daily dose of IR was lower compared with the mean quetiapine XR dose within the XR and IR group: 313 versus 509 mg (p<0.001). In this group, 29.1% of patients were discharged using quetiapine IR, 45.5% were discharged with quetiapine XR, 12.7% were discharged with both quetiapine formulations and the remaining patients were discharged with other or no antipsychotics.

Use of quetiapine XR and IR according to diagnosis

Among all 102 study patients with SCZ diagnosis, the average daily doses of XR and IR were 593 mg (95% CI 523 to 664) and 338 mg (95% CI 274 to 402; p<0.001), respectively (table 2). Mean daily doses were lower in BD patients: 466 mg (95% CI 386 to 547) for XR patients compared with 308 mg (220–396; p=0.009) for IR patients. In the subgroup of SCZ patients using only quetiapine XR (n=28) or IR (n=44) during their inpatient stay, the daily doses were 622 mg (95% CI 508 to 736) and 328 mg (95% CI 244 to 412; p<0.001), respectively. Among BD patients using only quetiapine

Table 3 Quetiapine doses in the XR and IR groups during hospitalisation and at discharge

	Patients treated with quetiapine XR or IR during hospitalisation (%)		Patients treated with quetiapine XR or IR at discharge (%)		Patients discharged with quetiapine XR or IR as the only antipsychotic (%)	
Quetiapine dose (mg)	XR (n=43)	IR (n=58)	XR (n=43)	IR (n=58)	XR (n=26)	IR (n=15)
≤200	2.3	48.3	2.3	24.1	3.9	60.0
201–400	32.6	12.1	16.3	6.9	15.4	0
401–600	23.3	17.2	4.7	12.1	7.7	13.3
601–1000	32.6	19.0	41.9	12.1	53.9	20.0
≥1000	9.3	3.4	11.6	3.4	19.2	6.7
Not discharged with study drug	–	–	23.3	41.4	–	–

IR, immediate release; XR, extended release.

XR (n=15) or IR (n=14) during their inpatient stay, the average daily dose of quetiapine XR was 512 mg (95% CI 389 to 635) and the average dose of IR was 382 mg (95% CI 212 to 551; p=0.19). The daily doses of quetiapine XR were higher than doses of IR also among patients in XR and IR group during their inpatient stay, regardless of their diagnosis (SCZ: 567 vs 352 mg; p=0.003; BD: 439 vs 267 mg; p=0.02).

The characteristics of SCZ patients who used either quetiapine XR or IR during their inpatient stay were broadly similar. The only statistically significant differences between XR and IR patients were observed for age (39.3 vs 47.7 years; p=0.03), prior use of study drugs (IR use in 12.0% vs 55.0%; p<0.001; XR use in 36.0% vs 0%; p<0.001) and use of injectable antipsychotics (0% vs 15.9%; p=0.03). Similarly, the only statistically significant difference between BD patients using either quetiapine XR or IR during their inpatient stay was the use of antiepileptic medication, which was more common among XR patients (53.3% vs 14.3%; p=0.03).

Exploratory analysis of factors affecting quetiapine XR and IR use

The factors affecting the choice of quetiapine formulation were analysed among the 77 patients using either quetiapine XR or IR and are presented in table 4. In the exhaustive model, the odds for being treated with quetiapine XR (as compared with IR, holding all other variables constant) were lower with advancing age (OR=0.93; 95% CI 0.88 to 0.99), substance abuse problems (OR=0.02; 95% CI 0.00 to 0.25), quetiapine IR use prior to admission (OR=0.09; 95% CI 0.01 to 0.58) and SCZ (OR=0.12; 95% CI 0.02 to 0.80 as compared with patients with BD). The odds for XR treatment were higher for patients using antiepileptic drugs (OR=5.22; 95% CI 1.03 to 26.56).

The AIC-minimising model instead focused on the most important explanatory variables, excluding 'unnecessary' variables from the analysis. Here, the odds for being treated with XR were lower with advancing age (OR=0.93; 95% CI 0.89 to 0.98), in patients with substance abuse problems (OR=0.03; 95% CI 0.00 to 0.34) and in patients with quetiapine IR use prior to admission (OR=0.10; 95% CI 0.02 to 0.49). However, SCZ diagnosis and use of antiepileptics no longer had statistically significant coefficients (OR=0.22; 95% CI 0.05 to 1.01 (p=0.052) and OR=4.11; 95% CI 0.91 to 18.59 (p=0.066), respectively). Previous use of quetiapine XR was always associated with use of XR during inpatient stay, and having a disorder that affects mental abilities was always associated with the use of quetiapine IR during inpatient stay; as a result, the modelling procedure dropped patients with these characteristics from the analysis.

In the exhaustive logistic regression model (table 4) that assesses factors associated with being discharged with quetiapine XR as opposed to IR, statistically significant differences were observed for use of quetiapine IR at admission (OR=0.14; 95% CI 0.04 to 0.47) and use of anxiolytic medication during inpatient stay (OR=0.15; 95% CI 0.04 to 0.59). In the model that minimises AIC, the odds for being discharged with quetiapine XR were lower for patients using quetiapine IR at admission (OR=0.16; 95% CI 0.04 to 0.47), having higher GAF scores at admission (OR=0.94; 95% CI 0.88 to 0.99) and patients using anxiolytics during inpatient stay (OR=0.17; 95% CI 0.05 to 0.62).

The validity of the models can be considered acceptable: in predictions of the sample, the models classified 68%−79% of the cases correctly and produced balanced positive and negative predictive values. In addition, other model fitness measures including Bayesian information criteria and Pseudo R^2 were in line with the AIC measure.

In the sensitivity analysis of quetiapine XR and IR use during the inpatient stay among patients with an inpatient stay ≥7 days, the model predictions improved slightly (results available upon request). In the AIC-minimising logistic regression model, the odds for being treated with quetiapine XR were higher for patients living alone (OR=5.03; p=0.04) and lower for patients having substance abuse problems (OR=0.06; p=0.03), using quetiapine IR at admission (OR=0.07; p=0.004), and having SCZ diagnosis (OR=0.08; p=0.02). There was a trend for increased odds of being treated with quetiapine XR for patients with a history of previous psychosis (OR=8.36; p=0.08) and antipsychotic non-adherence prior to hospitalisation (OR=5.81; p=0.07) and lower odds for patients with increasing age (OR 0.94; p=0.052).

DISCUSSION

We investigated the clinical use of long-acting quetiapine XR and short-acting quetiapine IR in 156 hospitalised SCZ and BD patients in one Finnish psychiatric hospital. Our study documents differential use of quetiapine XR and IR with respect to factors such as dosing, add-on medication and discharge medication. Using logistic regression analysis, we also explored the patient characteristics associated with quetiapine XR and IR use. Five important findings merit further comment.

The first key finding was the complexity of treatments given to SCZ and BD patients. There were 78 different treatment sequences reported in the study, which means that at least one in two patients had a unique drug treatment sequence. This illustrates the requirement to tailor the drug treatment to the needs of the patients in order to achieve treatment response and, ultimately, remission. Indeed, a survey of European psychiatrists has suggested that a mean of 2.5 changes in antipsychotics (excluding titration adjustments) is needed in order to stabilise patients with a newly diagnosed or acute-phase SCZ.[8] In our study, a mean of 2.5 different antipsychotics were used during the inpatient stay. Similarly, antipsychotic polypharmacy was observed in 33% of the patients at discharge and 66% during inpatient stay. Other

Table 4 Results of the logistic regression analysis of factors associated with the use of quetiapine XR versus IR during inpatient stay (excluding patients in the XR and IR group) and at discharge (excluding patients using both XR and IR at discharge)

	Drug at hospital (XR=1, IR=0), n=77				Drug at discharge (XR=1, IR=0), n=92			
	Full model		AIC minimising model		Full model		AIC minimising model	
Variable	OR (SE)	P>z	OR (SE)	P>z	OR (SE)	P>z	OR (SE)	P>z
Age	0.93 (0.03)*	0.025	0.93 (0.02)*	0.011	1.01 (0.02)	0.56		
Gender	2.42 (1.98)	0.279			1.00 (0.55)	1.00		
Lives alone	3.04 (2.06)	0.102	2.98 (1.89)	0.086	2.75 (1.54)	0.07	2.61 (1.31)	0.06
Employed	0.26 (0.22)	0.119	0.29 (0.24)	0.136	1.73 (1.21)	0.43	1.15 (0.62)	0.80
History of psychosis	3.07 (3.13)	0.270	3.46 (2.97)	0.147	1.94 (1.46)	0.38	2.48 (1.56)	0.15
Personality disorder	0.32 (0.48)	0.449			1.29 (0.94)	0.73		
Substance abuse	0.02 (0.02)**	0.003	0.03 (0.04)**	0.004	0.75 (0.62)	0.73		
Disability	(Omitted)		(Omitted)		0.43 (0.49)	0.46		
Involuntary hospitalisations	0.20 (0.17)	0.063	0.30 (0.21)	0.087	1.04 (0.70)	0.96		
Non-adherence†	3.35 (3.36)	0.228	3.52 (2.77)	0.110	0.46 (0.41)	0.38		
Quetiapine IR use†	0.09 (0.09)*	0.012	0.10 (0.08)**	0.004	0.14 (0.09)**	<0.001	0.16 (0.09)**	0.001
Quetiapine XR use†	(Omitted)		(Omitted)		(Omitted)		(Omitted)	
Other antipsychotic use†	1.93 (1.51)	0.400			1.59 (0.96)	0.44		
GAF score at admission	1.00 (0.05)	0.958			0.93 (0.04)	0.08	0.94 (0.03)*	0.03
SCZ diagnosis	0.12 (0.12)*	0.028	0.22 (0.17)	0.052	1.81 (1.19)	0.37		
Use of antidepressants	0.32 (0.30)	0.224			0.70 (0.46)	0.59		
Use of anxiolytics (N05B)	0.49 (0.40)	0.382			0.15 (0.11)*	0.01	0.17 (0.11)*	0.01
Use of hypnotics and sedatives (N05C)	0.67 (0.71)	0.705			1.27 (1.03)	0.77		
Use of antiepileptics	5.22 (4.33)*	0.046	4.11 (3.17)	0.066	0.93 (0.63)	0.91		
Pseudo R^2	0.34		0.28		0.21		0.19	
AIC	103.7		95.1		138.2		117.5	
BIC	145.9		120.9		186.1		135.1	
Default class	62.3%		62.3%		50.0%		50.0%	
Correctly predicted	79.2%		77.9%		71.7%		68.5%	
Positive predictive value	74.1%		75.0%		70.0%		66.7%	
Negative predictive value	82.0%		79.3%		73.8%		77.7%	

†Prior to admission.
*Statistically significant at $p<0.05$, **Statistically significant at $p<0.01$.
AIC, Akaike information criterion; BIC, Bayesian information criterion; GAF, global assessment of functioning; IR, immediate release; SCZ, schizophrenia spectrum disorder (dummy variable: 1=SCZ, 0=bipolar disorder); XR, extended release.

studies have reported antipsychotic polypharmacy in 20%–50% of the patients.[16–19]

The second important finding was that, on average, quetiapine XR was used in significantly higher daily doses than quetiapine IR. The mean daily quetiapine XR dose was 584 mg compared with a quetiapine IR daily dose of 341 mg—a difference that widened in discharged patients. In fact, almost half of the patients in the IR group in this study had daily doses below the suggested clinical trial-based optimal quetiapine dose of ≥250 mg.[20] A consensus dosing study for psychotic disorders recommend daily quetiapine doses of 400–800 mg[21] and expert guidelines indicate doses of 500–800 mg for multiple-episode patients with acute schizophrenia.[22] Other evidence stresses that a quetiapine dose ≥400 mg is required to maximise efficacy in acute psychosis or mania.[23 24] In discharged patients, for example, quetiapine XR was significantly more often given in daily doses ≥600 mg compared with quetiapine IR (in 73% vs 27% of patients, respectively). One interpretation of the high mean daily doses of quetiapine XR is therefore that this quetiapine formulation is used as the main antipsychotic to treat the primary symptoms of SCZ and BD. The low daily doses of quetiapine IR suggest that this formulation is used to treat comorbid symptoms, such as anxiety, and that an additional antipsychotic medication was required specifically to treat SCZ and BD.

The pattern of high quetiapine XR and rather low quetiapine IR daily doses also held in the subgroups with SCZ (n=102) and BD (n=54). We observed that the average daily dose was lower in BD patients than in SCZ patients. Around half of the BD patients in this study were treated with antidepressants. The effective quetiapine doses are lower in bipolar depression than bipolar mania (see the summary of product characteristics for quetiapine). Moreover, the experience of many Finnish clinicians is that optimal symptom control is obtained with lower antipsychotic doses in patients who use antidepressants and antipsychotics concomitantly.

A third finding was that the number of concomitant medications was higher in quetiapine IR-treated patients. At discharge, patients on quetiapine IR used a mean 0.8 add-on antipsychotics, whereas XR patients used a mean 0.4, a difference that was statistically significant. Quetiapine IR was also sometimes combined with injectable antipsychotics, whereas quetiapine XR was not. Considering the low average doses of quetiapine IR, it is not surprising that its use was more often associated with antipsychotic polypharmacy. For instance, among patients discharged using the study drug, 53% and 21% of IR and XR patients, respectively, were also prescribed other antipsychotics. This finding supports the interpretation that quetiapine XR is more commonly used as the primary antipsychotic medication, whereas quetiapine IR is more often used as an add-on medication in these severe mental disorders.

A fourth and rather interesting finding is the existence of a patient group using both XR and IR. The concomitant use of both quetiapine formulations strongly suggests that short-acting and long-acting quetiapine differ in ways that have therapeutic value. Quetiapine XR and IR were used simultaneously in 12% of patients during at least some period of their inpatient stay, and around 5% of patients were discharged with both quetiapine XR and IR. The mean dose of quetiapine XR in the XR and IR group was significantly higher than that of quetiapine IR. This is in line with the clinical experience that in these cases, quetiapine XR is used as the main antipsychotic, whereas quetiapine IR serves as supportive medication for insomnia, anxiety, restlessness, confused behaviour, for example. This practice is supported by a clinical study by Datto and colleagues,[12] which showed that quetiapine IR had a stronger sedative effect than the XR formulation 1 h after drug intake.

Our fifth finding was that certain patient characteristics increase the odds of being treated with quetiapine XR rather than IR in the inpatient setting. In particular, increasing age was consistently associated with decreased odds of being treated with quetiapine XR compared with IR. Concomitant substance abuse problems also decreased the odds of being treated with quetiapine XR, probably because IR is preferred over benzodiazepines in these patients. There was a trend for lower odds of being treated with quetiapine XR in patients with SCZ diagnosis compared with BD patients, when controlling for previous psychoses. As history of psychosis was associated with increased odds of being treated with quetiapine XR, this finding, although not statistically significant, suggests that patients without a history of psychosis but having SCZ diagnosis during the inpatient stay were more likely to be treated with quetiapine IR. Similarly, the odds for being discharged with quetiapine XR as compared with IR were lower when (holding other things constant) the GAF scores at admission were higher, perhaps suggesting that quetiapine XR was used to treat more severe cases.

Our study has some important strengths in relation to the real-world use of antipsychotic medication. First, by avoiding the selected and arguably unrepresentative patient populations associated with many RCTs, this naturalistic study describes SCZ and BD patients treated by psychiatrists in clinical practice. Often clinical practice differs substantially from RCTs with respect to, for instance, dosage, patient characteristics (eg, comorbidities) and drug exposure (eg, monotherapy vs polypharmacy). Second, since patient informed consent was not needed due to the retrospective design of our study, there was no bias in patient selection. All the hospital's inpatients who had used quetiapine at any time during the 2-year period studied were included in the study. Third, we observed differential use and large dose differences between the quetiapine formulations in both SCZ and BD patients. Fourth, our retrospective analysis of medical records ensured that the psychiatrist's treatment choice was not influenced by the study. By comparison, in RCTs, there is a risk of compromising the

patient–doctor relationship due to factors such as intensified monitoring.

This study also has its limitations. First, we lack information about each patient's specific symptoms that were treated with the study drugs. The patient cohort in our study was also too small to allow separate analyses according to different subtypes of SCZ and BD. Because of this, SCZ was defined with ICD-10 codes F20–F29 and BD with ICD-10 codes F30–F31. More detailed information regarding the symptoms and disorder subtypes would have further improved our ability to explain the differential use of quetiapine XR and IR in the study. Second, as the results are based on healthcare professionals' reports, they may not be fully accurate due to a possible lack of reporting and a risk for misreporting. Third, the study included only hospitalised patients with SCZ and BD in one treatment centre. Regional differences have been previously observed in the use of antipsychotics,[19] and therefore, the results may not be representative for all inpatient and outpatient clinical settings in Finland. Fourth, as the study presents a Finnish psychiatric inpatient setting, its findings cannot necessarily be generalised to other countries (see eg, the study by Bitter and colleagues[25]). However, a recent study on 178 schizophrenia patients in 14 Swedish inpatient clinics confirms our results that quetiapine XR is used in significantly higher mean doses and with significantly less concomitant psychiatric medication than quetiapine IR.[26] In that study, the mean daily dose of quetiapine XR was 494 mg compared with 345 mg for quetiapine IR, and quetiapine XR patients used 27% less concomitant psychiatric medications. These findings show that the differential use of quetiapine XR and IR in routine care is not confined to our study.

Generic versions of quetiapine IR have been available in Finland since 2007. As a consequence, the drug cost of quetiapine IR is lower than for quetiapine XR (although the exact cost difference is unknown due to hospital tender of antipsychotic drugs). This price difference means that there are no economic incentives for an inpatient clinic to use quetiapine XR rather than quetiapine IR. The use of quetiapine XR in this setting should thus be medically—not economically—motivated. In fact, the differential use of the two quetiapine formulations is likely to be explained by the different properties of quetiapine XR and IR. Quetiapine XR is dosed once daily, whereas quetiapine IR is dosed twice daily (except in bipolar depression, where quetiapine IR is dosed once daily). Remington and colleagues[27] and Diaz and colleagues[28] have shown once-daily dosing to improve adherence in SCZ patients. Moreover, quetiapine XR allows for faster titration to target dose than quetiapine IR,[11] which makes it possible to stabilise acutely ill patients more rapidly. Quetiapine XR also displays a smoother plasma concentration profile compared with quetiapine IR. One study showed that the steady-state plasma concentration was lower and occurred several hours later with quetiapine XR compared with IR.[13] This is one potential explanation for the faster titration of quetiapine XR. Another study found peak D_2 dopamine receptor occupancy to be significantly higher with the IR than with the XR formulation.[29] Differences in receptor occupancy properties between quetiapine XR and IR could translate into clinically meaningful differences, for instance related to the tolerability profile. Compared with quetiapine IR, quetiapine XR has been associated with less orthostatic dizziness[30] as well as less daytime sedation.[12]

Our findings highlight the individual tailoring of drug treatments in patients with SCZ and BD. Even though the patients in our study were using different formulations of the same atypical antipsychotic, the real-life treatment patterns differed considerably between the two formulations of quetiapine. There were also differences in characteristics between patients treated with either quetiapine XR or IR. These findings have implications as to the broader interpretation of RCTs as well as register-based studies. First, they suggest that many RCTs do not capture the individualisation of drug treatments that occur in psychiatric clinical practice, where two formulations of the same antipsychotic may be used differently. Second, our findings can be of importance when conducting register-based studies of antipsychotics where information on patient characteristics and treatment patterns may be missing. Based on our findings, it seems that such studies may be at risk of comparing two or more divergent patient groups as well as different treatment patterns (eg, doses, add-on medication).

We have shown that among SCZ or BD inpatients, quetiapine XR was used more often as monotherapy and in significantly higher daily doses than quetiapine IR. These results suggest that quetiapine XR is used as the main antipsychotic to a larger extent than IR, whereas quetiapine IR appears to be more commonly used as an add-on medication. This differential use of quetiapine formulations seem, at least in part, to depend on patient characteristics. Further research on the determinants of antipsychotic drug choices, and how therapies are individualised to meet the needs of the individual patient, is warranted.

CONCLUSIONS

Among SCZ and BD inpatients, quetiapine XR was used in significantly higher doses than quetiapine IR. Compared with quetiapine XR, quetiapine IR was more often combined with other antipsychotics. Differential use of the quetiapine formulations appears to depend, at least in part, on patient characteristics.

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Contributors YO, TH, EJS and KH contributed to the study design. TH contributed to data management. TH, EJS and OG designed the statistical analyses which TH carried out. TH and OG drafted the first version of the manuscript. All authors contributed to the interpretation of the results and provided input on drafts of this paper. All authors approved the final version of the manuscript.

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Competing interests TH and EJS are consultants and shareholders of ESiOR Oy, and EJS is also the CEO of ESiOR Oy, the company commissioned by AstraZeneca to help perform this study. ESiOR Oy also carries out studies, consultancy, education, reporting and health economic evaluations for several pharmaceutical, food industry, diagnostics and device companies, hospitals and academic institutions. OG and YO are employees of AstraZeneca. HJK has received consulting fees from AstraZeneca and payment for lectures from AstraZeneca and GlaxoSmithKline. EL has received consulting fees and payment for lectures from AstraZeneca. EL and HJK are members of AstraZeneca's advisory board for Seroquel. KH declares no conflict of interests.

Ethics approval The ethics approval was provided by the South Karelia Central Hospital Research Ethics Board.

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Supplement 1.

Table A1. Detailed information about drug use among the study patients

Variable	**Study population, n=156**	**XR population, n=43**	**IR population, n=58**	**XR&IR population, n=55**
Drug use prior to admission:				
Use of any antipsychotics, %	52.6	46.5	58.6	50.9
Antipsychotic non-adherence among current and previous users, %	23.3	35.5^	26.2˜	6.7˜^
Quetiapine IR use, %	38.9	15.0*^	51.9*	43.6^
Quetiapine XR use prior, %	10.1	27.5*^	0.0*˜	7.3˜^
Other[1] antipsychotic use, %	35.6	47.5^	44.4˜	18.2˜^
Use of drugs during the inpatient stay:				
Number of other[1] antipsychotics, mean (SD)	1.1 (1.3)	1.1 (1.3)	1.4 (1.2)˜	0.9 (1.3)˜
Switches between antipsychotics, %	46.8	25.6^	27.6˜	83.6˜^
Polypharmacy, antipsychotics , %	66.0	72.1	67.2	60.0
Typical, %	39.1	32.6	46.6	36.4
Atypical, %	39.7	41.9	48.3˜	29.1˜
Injectable depot antipsychotics, %	5.8 (23.4)	0.0*	12.1*	3.6
Number of different individual drug sequences[2]	78	22	35	21
Lithium, %	16.0	20.9	17.2	10.9
Antidepressants (N06A), %	25.6	23.3	20.7	32.7
Anxiolytics (N05B), %	25.0	20.9	25.9	27.3
Hypnotics and sedatives (N05C), %	12.2	7.0	15.5	12.7
Antiepileptics (N03A), %	24.4	27.9	17.2	29.1
Drug use at discharge:				
Quetiapine IR at discharge, %	36.5	-	58.6	41.8
Quetiapine XR at discharge, %	42.3	76.7*	1.7*˜	58.2˜
Any use of other[1] antipsychotics, %	55.1	53.5	70.7˜	40.0˜
Number of other[1] antipsychotics, mean	0.6 (0.7)	0.4 (0.7)*	0.8 (0.7)*˜	0.4 (0.6)˜

(SD)				
Other[1] atypicals, %	26.9	23.3	37.9~	18.2~
Typicals, %	23.7	16.3	31.0	21.8
Injectable depot antipsychotics, %	4.4	0	8.6	3.6

[1]"Other" refers to antipsychotics other than quetiapine IR and XR. [2]For example if the patient used IR and risperidone during the inpatient stay, IR+risperidone was considered to be one treatment sequence regardless of whether the drugs were used as monotherapy or in combination. Quetiapine IR and XR as well as oral and depot injections of the same active ingredient were counted as two different drugs. GAF=global assessment of functioning, IR=immediate release, XR=extended release. *=statistically significant difference between IR and XR group, ~=statistically significant difference between IR and XR&IR group, ^=statistically significant difference between XR and XR&IR group.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract *Checked (We used the term "registry study", if "cohort study" is preferred, we can change the title e.g. "…naturalistic cohort study…")*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found *Checked.*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported *Checked.*
Objectives	3	State specific objectives, including any prespecified hypotheses *Checked. (We did not have any prespecified hypotheses)*
Methods		
Study design	4	Present key elements of study design early in the paper *Checked.*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection *Checked.*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed *Checked*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. *Checked.*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. *Checked.*
Bias	9	Describe any efforts to address potential sources of bias. *Checked (we included all patients and due to the exploratory nature of our study, there is no risk of bias).*
Study size	10	Explain how the study size was arrived at. *Checked*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. *Checked.*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses *Checked.*
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram *Checked*

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) *Checked*
Outcome data	15*	Report numbers of outcome events or summary measures over time *Checked*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period *Checked*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses *Checked*
Discussion		
Key results	18	Summarise key results with reference to study objectives *Checked*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias *Checked*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence *Checked*
Generalisability	21	Discuss the generalisability (external validity) of the study results *Checked*
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based *Checked*

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.