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ORIGINAL PAPER

Quetiapine Dosage Across Diagnostic Categories

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Abstract *Objective* The aim of the current study was to evaluate quetiapine doses used across diagnosis categories in a sample of psychiatric inpatients. *Methods* Discharge letters of all adult inpatients who had received quetiapine between 1999 and 2005 were retrospectively reviewed. Logistic regressions were carried-out to assess links between quetiapine discharge dosage ($\geq$800 mg/day vs. <800 mg/day), diagnostic categories, substance abuse or dependence, benzodiazepine discharge doses, age and sex. *Results* The data of 231 patients were included. Five hundred and for discharge documents were analyzed: 113 for psychotic disorders, 190 for personality disorders, 134 for bipolar and schizoaffective bipolar disorders, 29 for unipolar depression or anxiety disorders, and 35 for mental retardation. Considering psychotic disorders as a reference group, patients with personality disorders were statistically significantly less likely to be in the high quetiapine dosage group at discharge ($P = 0.007$, OR = 0.1 and CI [0.03; 0.6]). *Conclusions* Quetiapine seems to be used in a variety of clinical situations, with a wide range of doses and a lower dosage in patients treated for personality disorders.

Keywords Quetiapine · Antipsychotic drugs · Bipolar disorder · Schizophrenia · Borderline personality disorder

Introduction

Quetiapine is a novel antipsychotic drug labeled for the treatment of patients with schizophrenia [1], bipolar mania [2] and bipolar depression [3].

The registration studies of quetiapine suggest a target dose of quetiapine ranging from 300 to 500 mg/day for schizophrenia, and a maximum dosage up to 800 mg/day [4].

Quetiapine has been tried across multiple diagnosis categories and seems to be used, among other atypical antipsychotics, in clinical practice for an expanding range of disorders [5].

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Several recent studies have demonstrated quetiapine's clinical benefits in patients with depression, impulsivity, aggression, and substance abuse disorders [6–10].

Preliminary works suggest interest of quetiapine in monotherapy or augmentation strategy for a wide range of other psychiatric disorders such as antisocial personality disorder (600–800 mg/day) [11], borderline personality disorders (175–400 mg/day) in one study [12] and at higher dosage in a recent one (400–800 mg/day, with average daily dosage: 540 mg/day) [13], resistant depression (mean dosage: 166.67 ± 211.69 mg/day) [14], post traumatic stress disorders [15] (mean dosage: 216 mg/day), resistant obsessive compulsive disorders (quetiapine dosages titrated upward to 300 mg/day, mean dose: 215 ± 124 mg/day) [16]. Controversial data, for example, on the lack of efficacy of quetiapine at dosage lower than 150 mg/day highlights the importance of a precise determination of the potentially effective dosage [17].

Whereas most validation studies on the efficacy of quetiapine used up to a maximum dosage of 800 mg/day, naturalistic reports show a current use in higher dosage in a variety of clinical situations [4, 18, 19]. Due to this gap between validation studies (quetiapine used up to 800 mg/day) and naturalistic reports (quetiapine frequently used at higher doses than 800 mg/day), the aim of the current retrospective study was to evaluate prescription of quetiapine in dosage $<$800 mg/day and $\geq$800 mg/day across diagnostic categories in a naturalistic sample of psychiatric inpatients.

Methods

All patients described in this retrospective cross-sectional descriptive study had been treated in the Psychiatric hospital of the University Hospital of Vaud, Lausanne, Switzerland. Discharge letters of all adult inpatients who had received a prescription for quetiapine during at least one hospitalization (during the stay in the hospital and/or at discharge) between December 1999 (introduction of quetiapine in Switzerland) and September 2005 were retrospectively reviewed. Discharge letters are the official and final medical document, signed by a resident in psychiatry and a senior psychiatrist, which summarize events, diagnosis, symptoms evolution and treatment during hospitalization and contains systematic reporting of all treatments at discharge. Discharge letters containing the word quetiapine were identified through a computerized research. Letters that did not contain this word were not checked. Letters in which quetiapine was not reported at discharge were excluded from the analysis.

The following information was recorded from the discharge letter: baseline demographic characteristics, psychiatric diagnostic including active substance abuse or dependence, number of previous hospitalization, medication including benzodiazepine dosage at discharge (in lorazepam equivalent), quetiapine dose at discharge, duration of hospitalization, civil compulsory hospitalizations. Diagnoses were established according to DSM-IV criteria by the residents in psychiatry and senior psychiatrists.

The presented data are drawn from a study protocol approved by the local Ethical committee and the institutional review board.

Analyses

Statistical analyses were carried out using SPSS for Windows (version 11.0).

An initial exploratory analysis involved calculation of means, standard deviation and median for age and discharge quetiapine and benzodiazepine (in lorazepam equivalent) dosages.

Diagnostic categories are regrouped in 5 categories as follows:

(1) Bipolar spectrum including: bipolar disorder and schizoaffective bipolar disorder in manic or mixed states (with exclusion of bipolar depression due to small sample size: 6 discharge letters), (2) Psychotic disorders including: schizophrenia and schizoaffective disorders depressive type, psychotic disorders not otherwise specified, delusional disorders, (3) Unipolar depression and anxiety disorders, (4) Personality disorders (cluster B), (5) Mental retardation.

Schizoaffective disorder, bipolar type and bipolar disorder were in the same category "Bipolar spectrum" in accordance with previous results [19] showing that higher quetiapine dosage is rather related to the mood episode type than to the category of bipolar disorder or schizoaffective bipolar disorder.

When co-morbidity was mentioned, the categorization was considered in consideration of the diagnosis linked to the hospitalization as reported in the discharge letter. Substance abuse or dependence was considered as, a co-morbidity.

Quetiapine doses between diagnostic categories were studied in consideration of high ($\geq$800 mg/day) vs. low (<800 mg/day) quetiapine dosage repartition, in consideration to the 800 mg cut-off of validation studies and the frequency of prescription of doses higher than 800 mg/day in clinical practice.

Analyses were conducted on the sample of patients, taking the mean quetiapine dose over all the hospitalizations made by each patient (the average of the different daily discharge dose prescribed for each patient). The mean quetiapine doses as the dependent variable of age, benzodiazepine discharge doses, diagnostic categories, sex, as well as substance abuse variables as predictors were tentatively analyzed through a multiple linear regression. Because of strong deviance from normality and non-constant variance, the data were finally analyzed by a logistic regression model providing a better fit. The mean quetiapine discharge dose was categorized into high dose: $\geq$800 mg vs. low dose: <800 mg/day. Goodness of fit of the model was assessed through the logarithm of the likelihood and the Nagelkerke R^2 statistics. Leverage values were also analyzed for detecting cases that have a large impact on the predicted values. For all analyses, a significance level of $P \leq 0.05$ was used.

Results

Five hundred and four discharge letters were analyzed after exclusion of 38 discharge letters of patients who were not discharged with quetiapine (refusal of treatment, switch, to another antipsychotic agent, quetiapine side effects, considering no reason for quetiapine maintenance treatment). The data of 231 patients [female (59%)], were included into the analyses. During the studied period the included patients totalized 504 hospitalizations: 113 hospitalizations for psychotic episodes, 190 for personality disorders (cluster B), 137 for bipolar and schizoaffective bipolar disorder, 29 for unipolar depression [15] or anxiety disorder [14] and 35 for mental retardation. Only three patients (7 hospitalizations) received quetiapine for two different diagnoses in successive hospitalizations, the last diagnosis was considered for each of these patients because it was considered as more accurate by the clinicians. Forty-three percent of the study sample had a co-morbidity of

substance abuse or dependence to one or more substances, most frequently alcohol (50%), marijuana (40%), cocaine (15%) and opiate (4%).

The socio-demographic and clinical characteristics of the patients and the hospitalizations are shown in Table 1. The logistic regression performed well with an overall percentage of 85% of the cases correctly classified (high: ≥800 mg/day vs. low: <800 mg/day quetiapine dosage category). The R^2 Nagelkerke statistics show that about 67% of the variation in the outcome variable is explained by the logistic regression model. The variables, age and diagnosis, are statistically significant ($P < 0.0005$ and $P = 0.002$ respectively) while benzodiazepine dosage, sex and substance abuse or dependence are not. Compared to those with psychotic disorders (Table 2), patients with personality disorders were significantly less likely to be in the high dose category ($P = 0.007$, OR = 0.1 and CI [0.03; 0.6]). Considering age variable, an increase of 1 year decreases the likelihood to be in the high quetiapine dose group ($P < 0.0005$, OR = 0.96 and CI [0.93; 0.98]).

Table 1 Sociodemographic and clinical characteristics (the reported diagnosis is the diagnosis linked to the hospitalization)

Patients (*n*)	231
Female (%)	59%
Age, years (mean ± SD; median)	36.3 ± 11.3; 35
Numbers of previous hospitalization (mean ± SD; median)	7.4 ± 11.3; 4
Daily mean quetiapine dosage	393.8 ± 320.2
Mean quetiapine dosage by episode	
(1) Psychotic disorders	557.3 ± 277.5
(2) Bipolar disorders and schizoaffective, bipolar type	435 ± 395.4
(3) Personality disorders	251.6 ± 211.7
(4) Depressive and anxiety disorders	279.2 ± 279.9
(5) Mental retardation	414.2 ± 223
Number of subjects by episode type (*n*)	
(1) Psychotic disorders	58
(2) Bipolar disorders and schizoaffective, bipolar type	69
(3) Personality disorders	74
(4) Depressive and anxiety disorders	18
(5) Mental retardation	12
Hospitalizations (*n*)	504
Number of hospitalizations during the studied period (mean ± SD)	1.9 ± 1.6
Actual comorbidity with a substance abuse or dependence (%)	216, 43%
Bipolar disorders and schizoaffective, bipolar type (*n*, %)	137, 27.2%
Personality disorders (*n*, %)	190, 37.7%
Psychotic disorders (*n*, %)	113, 22.4%
Depressive and anxiety disorders (*n*, %)	29 (5.8%)
Mental retardation (*n*, %)	35 (6.9%)
Duration in days (mean ± SD; median)	19.3 ± 22.8; 10
Civil compulsory hospitalization (%)	22%
Quetiapine discharge dosage in mg/day (mean ± SD; median)	427.6 ± 316.2; 400
Doses ≥800 mg/day at discharge (*n*, %)	73 (14.5%)

Table 2 Odds ratio to receive quetiapine at dosage ≥800 mg/day at discharge (for diagnostic variable, psychotic disorders is the reference group)

Variable	OR	95% CI	*P*-value
Age	0.96	0.93–0.98	<0.0005
Benzodiazépine dosage	1.07	0.98–1.16	0.1
Substance abuse/dependence	0.6	0.2–1.3	0.2
Gender	1.003	0.44–2.27	0.9
Diagnostic	–	–	0.002
Psychotic disorders	1	–	–
Bipolar disorder spectrum	2.3	0.9–5.8	0.09
Unipolar depression and anxiety disorders	0.3	0.03–2.7	0.3
Personality disorders	0.1	0.03–0.6	0.007
Mental retardation	0.3	0.03–2.7	0.3

Discussion

In accordance with previous naturalistic studies [5], it seems that quetiapine is given commonly in off-label as well as in labeled indication for the treatment of a large range of psychiatric disorders. The main finding of this study is that the use of quetiapine discharge doses (<800 vs. ≥800 mg/day) is clearly influenced by diagnostic categories whereas benzodiazepine discharge dosage, co-morbid substance abuse or dependence did not contribute significantly to the final model. Personality disorders are less likely than psychotic disorders to need quetiapine dosage at discharge higher than 800 mg/day. Clinical differences across diagnostic categories could explain the finding, however one could hypothesize that clinicians are more likely to dose above licensed doses for licensed indications but not for unlicensed indications. Interestingly, the study found a link between age and quetiapine discharge doses. This may be due to differences of symptomatology between younger and older people or to a poorer tolerance of higher dosage in older patients. We excluded only 38 discharge letters of patients who were not discharged with quetiapine. Whereas all discharge letters are expected to mention all treatments used during a hospitalization, it is possible that discharge letters may have failed to mention a quetiapine administration.

Some limitations have to be considered when interpreting the results of the present study. Especially, its open-label retrospective design, lack of prospective outcome measures, and the observation limited to the discharge period.

The result suggests the need for conducting prospective randomized controlled trials (with flexible or with multiple fixed doses including dosage higher than 800 mg/day) in order to assess efficacy and optimal doses of quetiapine in various psychiatric disorders such as unipolar depression, anxiety disorders, personality disorders, bipolar disorders and schizophrenia.

Conclusion

Quetiapine is used in a variety of clinical situations, in a wide range of doses, with a lower dosage for patients treated for a personality disorder.

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