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Patterns of Quetiapine Use in Psychiatric Inpatients: An Examination of Off-Label Use

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Background. *Despite emerging recognition that off-label use of atypical antipsychotics is widespread, there is little data concerning patterns of such use. To investigate such usage of quetiapine, we evaluated prescribing practices of this drug at our acute-care psychiatric hospital.*

Methods. *Inpatient orders for quetiapine were obtained from October 2004 to March 2006 and divided into standing or prn (as needed) dose regimens. For patients receiving standing dose regimens, diagnosis, total daily dose, and dosing adequacy were ascertained. For patients receiving prn dosing, diagnosis, behavioral indication, dose, and frequency were determined.*

Results. *The most common diagnoses in patients receiving standing dose quetiapine were depressive disorders, followed by substance-related, bipolar, and psychotic disorders. Mean dose was 169 ± 154 mg/day (median = 200 mg/day), with 29.8% of patients receiving ≥ 300 mg/day. Only 28.5% of patients had one of the diagnoses for which quetiapine is approved; in these patients, 46.4% received ≥ 300 mg/day. Patients receiving prn dosing had a similar distribution of diagnoses. The most common prn dose was 50 mg, given for agitation or insomnia.*

Conclusion. *We found extensive off-label use of quetiapine. Further research is needed on the safety and efficacy of quetiapine in non-approved doses and diagnoses.*

Keywords Quetiapine, Off-label, Antipsychotic, Atypical, Drug usage

INTRODUCTION

"Off-label" use involves use of a marketed drug, biologic, or medical device for an indication or at a dosage not approved by the U.S. Food and Drug Administration (FDA). Two systematic reviews (1,2) and several other reports (3–5) have recently addressed off-label use of atypical antipsychotics. This reflects an emerging recognition that the indications and dosing regimens in which these drugs are currently being used in clinical practice differ substantially from those approved. Off-label use of these medications has been attributed to the fact that they are generally well-tolerated and have a low incidence of acute extrapyramidal side effects and tardive dyskinesia (6).

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Quetiapine is an atypical antipsychotic approved by the FDA for use in adults with schizophrenia and mania, and recently approved for the depressed phase of bipolar disorder (7). Its investigational use has been reported in a number of conditions, including autism (8), anxiety, social anxiety disorder (9), and borderline personality disorder (10). Studies have examined its efficacy in psychosis (11) and mania (12) in children and adolescents and in psychosis-related behaviors in the elderly (13). There have also been descriptions of quetiapine's use as an adjunctive agent in the treatment of depression, depression with anxiety (14,15), obsessive-compulsive disorder (16), delirium (17), and substance use disorders (18).

Quetiapine's mechanism of action involves antagonism at dopamine D_2 and serotonin 5-HT_2 receptors, and its receptor binding profile also includes histaminic H_1 and α_1/α_2-adrenergic antagonist properties, with no appreciable binding at muscarinic M_1 and M_2 receptors (19). In general, the drug is well-tolerated. However, metabolic side effects of quetiapine may

include weight gain and dyslipidemia (20–22), and the long-term morbidity resulting from these side effects is still unclear.

We observed extensive use of quetiapine at our facility, consistent with claims that this is the most commonly prescribed atypical antipsychotic (23). Our impression was that much of this use was off-label and at low doses. The manufacturer recommends starting quetiapine at 25 mg three times a day, titrating up in 25–50 mg increments to therapeutic doses (24). This gradual titration schedule may have led to the clinical practice of low-dose quetiapine use, although other investigators have described higher than approved dosing in some clinical settings (25).

To clarify these issues, we evaluated two-year trends in quetiapine prescribing at our freestanding psychiatric hospital. Our aim was to identify the frequency of off-label use, indications for such use, and the diagnoses commonly associated with off-label prescribing. We hypothesized that quetiapine was being used for the treatment of agitation, anxiety, and insomnia in patients with a wide variety of diagnoses, and in low-dose regimens.

METHODS

Data for this study were obtained from the Butler Hospital pharmacy dispensing database. Butler Hospital is a 145-bed freestanding private nonprofit psychiatric hospital that serves as the major psychiatry training site for Brown Medical School. In addition to the full-time attending medical staff, psychiatry fellows, general psychiatry residents, and medical students provide care. The patient population includes individuals with private, public, and no insurance. The Butler Hospital Institutional Review Board (IRB) approved this study on drug utilization.

Hospital pharmacy profiles were obtained for all quetiapine use on adult inpatient units from October 2004 to March 2006, with each profile anonymized through the assignment of a random numerical designation. Only patients between the ages of 18 and 65 years were included in the study, and patients were excluded if they were currently in the hospital so that all data could be considered definitive as of the time of discharge. Data analyses were based on the last dose regimen ordered by the treating physician and the treating physician's primary discharge diagnosis. Pharmacy profiles were grouped by unique admission number, rather than by unique patient, so that multiple admissions of the same patient were each counted separately.

From these profiles, quetiapine orders were categorized as to whether they reflected standing dose or *prn* (as needed) administration. For those patients receiving quetiapine as a standing dose, total daily dose at discharge was obtained. For those patients receiving a *prn* regimen, last ordered dose and dose frequency and indication for use were recorded. The percentage of patients receiving both standing dose and *prn* quetiapine was also recorded.

Specific primary diagnoses were aggregated into the DSM-IV-TR Axis I major diagnostic classes. Mood disorders were subdivided into depressive and bipolar disorders because of differences in the FDA-approved uses of quetiapine for these conditions; no patients in this sample received a primary discharge diagnosis of cyclothymic disorder. "Psychotic disorders" hereafter refers to all those listed in DSM-IV-TR under schizophrenia and other psychotic disorders.

Based on the manufacturer's FDA-approved recommendations, we defined adequate antipsychotic/antimanic dosing of quetiapine as at least 300 mg/day. Since we were primarily interested in the phenomenon of lower-than-recommended dosing with quetiapine, we did not consider higher-than-recommended dosing (i.e., greater than 800 mg/day) as off-label for the purposes of this study. Psychotic and bipolar disorder groups were combined to determine the percentage of patients receiving adequate dosing. The percentage of patients without psychotic or bipolar disorders receiving at least 300 mg/day of quetiapine was also determined.

Subsequent to the observation period of this study, quetiapine received FDA approval for treatment of the depressed phase of bipolar disorder (7). To clarify usage in this group, we identifed all patients with a diagnosis of bipolar I, most recent episode depressed, and all bipolar II patients, given that the latter suffer primarily from frequent depressive phases (26,27) and are almost always admitted to our inpatient facility during this phase (there is not a depressive specifier for bipolar II). Adequate dosing for this group was also defined as at least 300 mg/day (28).

Groups were subdivided by age and sex to evaluate relationships between these variables and quetiapine doses. Data were analyzed with standard parametric and nonparametric tests using SPSS software (SPSS for Windows version 11.5, SPSS, Inc. Chicago, IL). All statistical tests were two-tailed, with significance set at $p < .05$.

RESULTS

Sample Characteristics

A total of 1,912 patients (989 (52%) male, 923 (48%) female) were included in the study. Mean age of the sample was 39 ± SD 11 years. The most frequent primary diagnoses were depressive (50.5%, N = 965), substance-related (20.4%, 390), bipolar (11.8%, 225), psychotic (9.6%, 183), anxiety (2.0%, 39), and adjustment disorders (2.0%, 38). Infrequent primary diagnoses included impulse-control disorders (0.6%, 11), cognitive disorders (0.4%, 7), eating disorders (0.2%, 4), mental disorders due to a general medical condition (0.2%, 4), disorders usually first diagnosed in childhood (0.2%, 3), somatoform disorders (0.05%, 1), and dissociative disorders (0.05%, 1). Diagnoses were unavailable for 0.9% (18) of patients.

Quetiapine Use by Dose Regimen

A total of 738 (35.6%) patients (362 (49%) male, 376 (51%) female; mean age = 39 ±11 years) received standing dose quetiapine. Of these, 7.8% (161) received mixed standing and *prn* dose regimens; these patients were included in the analyses of both standing and *prn* dose groups. The most common total daily dose in the standing dose group was 100 mg (25.6% of patients) (Table 1), with only 29.8% (220) of patients receiving at least 300 mg/day. The mean total daily dose at discharge was 169 ± 154 mg (range, 25–1200 mg/day; median = 200 mg/day). Most of these patients (64.2%) received quetiapine as an evening or bedtime dose. The most common diagnoses of patients receiving standing dose quetiapine were depressive disorders, followed by substance-related, bipolar, and psychotic disorders (Table 2). Only 28.5% of patients had one of the two diagnoses for which quetiapine is indicated.

A total of 1,335 (64%) patients, (710 (53%) male, 625 (47%) female; mean age = 39 ±11 years) received *prn* dose quetiapine. In patients receiving a *prn* dose regimen, the most commonly utilized dose was 50 mg, followed by 25 mg and 100 mg (Table 3), and the most common dose interval was every 1 hour, followed by every 2 hours and bedtime dosing (Table 4). When an indication was given, the most common reason for ordering *prn* dose quetiapine was agitation (75%, N = 463), followed by agitation/anxiety (8%, 50) and anxiety (8%, 50). Insomnia, either alone or in combination with agitation or anxiety, was given as an indication in 9% (53) of patients. Paralleling findings with the standing dose regimen, the most common diagnoses of patients receiving *prn* quetiapine were depressive disorders, followed by substance-related, bipolar, and psychotic disorders (Table 5). Only 17.4% of patients had one of the two diagnoses for which quetiapine is indicated.

There was no significant difference in mean dose between males and females for *prn* regimens (males, 61 ± 50 mg vs. females, 67 ± 76 mg), but females received a higher dose than males for standing regimens (males, 154 ± 142 mg/day vs. females, 183 ± 163 mg/day; $t = 2.54$, $df = 729$, $p = .011$). There was a trend for males to be more likely than females to receive *prn* regimens ($\chi^2 = 3.2$, df = 1, $p = .071$). Patients receiving *prn* regimens were slightly younger (39 ± 11 years) than those receiving standing regimens (40 ± 11 years) ($t = 2.16$, $df = 1533$, $p = .031$).

Quetiapine Use by Diagnosis

In those patients with psychotic or bipolar disorders, the mean daily dose for standing regimens was 242 ± 185 mg/day. Of these patients, 46.4% (97) received a standing dose of at

Table 1 Distribution of Total Daily Doses in Patients Receiving Standing Dose Quetiapine (N = 738)

Total Daily Dose (mg/day)	Frequency	Percentage
25	22	3.0
50	59	8.0
75	37	5.0
100	189	25.6
125–150	59	8.0
200–250	152	20.6
300–375	87	11.8
400–450	73	9.9
500–600	44	6.0
≥ 700	16	2.2

Table 2 Major Diagnostic Classes in Patients Receiving Standing Dose Quetiapine (N = 738)

Disorders by Major Diagnostic Class	Frequency	Percentage
Depressive	346	46.9
Substance-related	128	17.3
Bipolar	108	14.6
Psychotic	102	13.8
Adjustment	15	2.0
Anxiety	15	2.0
Impulse-control	5	0.7
Eating	4	0.5
Cognitive	4	0.5
Childhood-onset	2	0.3
Due to medical condition	2	0.3
No diagnosis	7	0.9

Table 3 Distribution of *prn* Unit Doses in Patients Receiving *prn* Dose Quetiapine (N = 1,335)

mg Ordered	Frequency	Percentage
25	240	18.0
50	834	62.5
75	9	0.7
100	194	14.5
150–200	32	2.4
250–300	13	1.0
400–500	6	0.4
600–≥700	7	0.5

Table 4 Distribution of *prn* Dosing Time Intervals in Patients Receiving *prn* Dose Quetiapine (N = 1,335)

Time Interval	Frequency	Percentage
Q1 hr	857	64.2
Q2 hr	171	12.8
Q3–4 hr	55	4.1
Q6–8 hr	5	0.4
Once	9	0.7
QAM/Daily	10	0.7
QHS/QPM	137	10.3
BID	58	4.3
TID	25	1.9
QID	8	0.6

Table 5 Major Diagnostic Classes in Patients Receiving *prn* Dose Quetiapine (N = 1,335)

Disorders by Major Diagnostic Class	Frequency	Percentage
Depressive	700	52.4
Substance-related	316	23.7
Bipolar	136	10.2
Psychotic	96	7.2
Anxiety	32	2.4
Adjustment	26	1.9
Impulse-control	7	0.5
Cognitive	4	0.3
Due to medical condition	2	0.1
Somatoform	1	0.1
Dissociative	1	0.1
Childhood-onset	1	0.1
No diagnosis	13	1.0

least 300 mg/day. Of those patients categorized as bipolar depressed (35 bipolar I, 15 bipolar II), 38% (19) received a standing dose of at least 300 mg/day. In psychotic or bipolar patients meeting this criterion of adequate dosing, the mean daily dose was 440 ± 172 mg/day. For *prn* regimens in patients with psychotic or bipolar disorders, the mean dose was 73 ± 88 mg.

In patients who did not have psychotic or bipolar disorders, the mean daily dose for standing regimens was 141 ± 128 mg. Of these patients, 23.7% (123) received a standing dose of at least 300 mg/day. The mean daily dose in patients who were not psychotic or bipolar, but who met the criterion of adequate antipsychotic/antimanic dosing, was 404 ± 161 mg/day. For *prn* regimens in patients who were not psychotic or bipolar, the mean dose was 61 ± 56 mg.

The difference in mean daily standing dose between patients with and without psychotic or bipolar disorders was highly significant (t = 8.44, df = 551, p = .001). There was a trend towards significance in the difference in mean *prn* dose between the two groups (t = 1.898, df = 291, p = .059). The proportion of patients receiving a standing dose of at least 300 mg/day was higher in psychotic or bipolar patients than in other patients (χ^2 = 20.36, df = 1, p = .01). In patients who received a standing dose of at least 300 mg/day, there was no difference in mean dose between psychotic or bipolar patients and other patients.

DISCUSSION

Data from this retrospective chart review indicate that quetiapine is being utilized in a variety of off-label dosing regimens and indications. Only a third of the patients in this study were receiving quetiapine in a standing dose regimen, and of those, just over a quarter were receiving the minimum established antipsychotic/antimanic dose of 300 mg/day. Consistent with this is our finding that only a quarter of the patients receiving standing dose quetiapine had a psychotic or bipolar disorder diagnosis, the two conditions for which the drug is currently approved. While the proportion of psychotic or bipolar patients on standing dose quetiapine who received minimum established dosing was double that of patients without these diagnoses, it was still less than half of the sample. These findings in a socioeconomically diverse sample of psychiatric inpatients broadly parallel recently published observations in outpatient Medicaid enrollees (29). The majority of patients receiving standing dose quetiapine in our sample had either depressive or substance use disorders.

Most of the quetiapine orders in our sample reflected *prn* usage, generally for agitation, anxiety, or insomnia, again most commonly for patients with depressive or substance use disorders. These data, and our extensive discussions with treating physicians, suggest to us that quetiapine is being utilized as a treatment for agitation when clinicians are reluctant to use benzodiazepines or typical antipsychotics, such as in patients with a history of intolerance or contraindication to these drugs. This is of interest given previous work comparing oral quetiapine and haloperidol in agitated schizophrenic patients (30) and in the treatment of anxiety in substance-related disorders (18). Whether the efficacy and safety of quetiapine warrant its replacement of older drugs as a *prn* agent in these conditions is not established.

A striking amount of quetiapine administration in this sample occurred in the evening or at bedtime, suggesting that even though the indication may not always have been made explicit, quetiapine was frequently used for its sedative-hypnotic properties. A prior study noted the use of quetiapine for phenelzine-associated insomnia in depressed patients (31). Again, the risks and benefits of quetiapine relative to more traditional agents used in this context are unclear. Of note in this regard, there have been several recent anecdotal reports on the illicit use of quetiapine, including intranasal and intravenous abuse, particularly within correctional facilities (32–36). This raises the possibility that exposure to quetiapine use for anxiolysis or other off-label uses may have unanticipated social ramifications.

There are several limitations to this study. This was a retrospective chart review, so that information about the rationale for use was limited to indication order and diagnosis. The sample was restricted to adult psychiatric inpatients, so these results may not reflect outpatient prescription practices or practices in pediatric and geriatric age groups. Only orders were available, so actual quantities of drug administered on a *prn* basis could not be determined. The data were grouped by unique admission, so that admission of some patients on multiple occasions may have led to inflation of some prevalence rates. Since only diagnostic classes were used, we were not able to identify patients with specific diagnoses in which use of quetiapine as an antipsychotic might have seemed more appropriate (e.g., psychotic depression). Since there are no DSM code specifiers for the phase of bipolar II patients, we could only identify the total number, rather than phase, of these patients (we assumed them to be depressed). Lastly, no

information on either safety or efficacy could be gleaned from our data, and side effects and reasons for discontinuation were not reported.

CONCLUSIONS

In summary, we found extensive use of quetiapine in dosing regimens and for indications in which the safety and efficacy of the drug have not been established; indeed, in considering both dosage levels and diagnoses, in our setting the majority of quetiapine medication orders were off-label. While treating physicians commonly offer a variety of rationales for their off-label use of quetiapine (e.g., well-tolerated, low abuse potential, mildly sedating but with low risk of confusion, low risk of extrapyramidal symptoms, modest cardiovascular effects), it is difficult to quantify these potential benefits against possible risks (e.g., excessive sedation, hypotension, tachycardia, hyperglycemia, constipation, seizures). Risk-benefit considerations of off-label use are particularly fraught with respect to possible longer-term risks (e.g., dyslipidemia, obesity, diabetes), and since the dose-dependence of such risks is unclear, even seemingly modest *prn* doses may be of concern, especially given emerging data on possible illicit use. Research into the safety and range of efficacy of quetiapine in non-approved doses and diagnoses is urgently needed to guide clinicians in their use of this drug.

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