Dosing of Quetiapine in Schizophrenia: How Clinical Practice Differs From Registration Studies

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Background: A substantial number of patients with psychosis receive quetiapine in amounts that are greater than what is recommended in the product labeling approved by drug regulatory agencies. The purpose of this article is to review the past and present dosing patterns of quetiapine for the treatment of schizophrenia.

Method: A PubMed search for the period January 1, 1990, to July 1, 2005, was conducted to identify English-language articles related to quetiapine dose in schizophrenia using the search terms *quetiapine*, *dose*, and *schizophrenia*. Trends in dosing of quetiapine in a large, state-operated psychiatric hospital system and the anecdotal evidence describing the use of quetiapine in excess of 800 mg/day were also reviewed.

Results: The registration studies of quetiapine suggest a target dose range of 300 to 500 mg/day for schizophrenia. In contrast, among inpatients hospitalized in New York State in the period of April 1, 2004, to June 30, 2004, the mean dose of quetiapine prescribed was 620 mg/day, with 33.6% receiving doses in excess of 750 mg/day. Patients with nonwhite ethnicity, length of stay of at least 1 year, or history of prior state hospital admission were more likely to receive doses greater than 750 mg/day. Patients receiving quetiapine as antipsychotic monotherapy or in combination with other antipsychotics were equally likely to receive doses greater than 750 mg/day. Published anecdotal reports describe the use of quetiapine in excess of 800 mg/day and up to 2400 mg/day among patients not responding to lower doses, but currently there are no published reports from double-blind randomized clinical trials establishing the utility of this high-dose treatment strategy.

Conclusions: Dosing of quetiapine in clinical practice is higher than what has been established in the registration program for schizophrenia. Although there is anecdotal evidence describing the use of quetiapine in excess of 800 mg/day, double-blind randomized clinical trials are needed.

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Quetiapine is a second-generation antipsychotic that has demonstrated clinical efficacy for the treatment of schizophrenia[1–3]; however, there is much uncertainty as to optimal dose. The product label suggests achieving a dose between 300 and 500 mg/day.[4] Maximum doses in the published double-blind randomized studies evaluating quetiapine[1–3] do not exceed 800 mg/day, including an 8-week study of treatment-resistant schizophrenia in which quetiapine 600 mg/day was compared to haloperidol 20 mg/day.[5] The doses used in these studies are in contrast to the observation that clinicians prescribe quetiapine at substantially higher doses, particularly among inpatients hospitalized in state-operated psychiatric facilities.[6] This article will review the doses of quetiapine in the registration studies for schizophrenia, provide new data about the use of quetiapine in New York State in 2004, review results from studies using higher doses of quetiapine, and, finally, summarize future directions for research.

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METHOD

A PubMed search for the period January 1, 1990, to July 1, 2005, was conducted to identify English-language articles related to quetiapine dose in schizophrenia. Search terms were *quetiapine*, *dose*, and *schizophrenia*. Additional sources were obtained from the reference lists in the identified articles. Posters and abstracts were identified by attendance at the scientific meetings in question and queries to AstraZeneca Medical Resources in both the United States and United Kingdom in 2005.

In New York State, data on current antipsychotic utilization and dosing were collected using the Integrated Research Database (IRDB) created by the Information Sciences Division of the Nathan S. Kline Institute for Psychiatric Research. The IRDB contains patient information (demographic characteristics, dates of admission/transfer/discharge, and diagnosis) and drug prescription information for every inpatient within the adult civil facilities of the New York State psychiatric hospital system.

REGISTRATION STUDIES

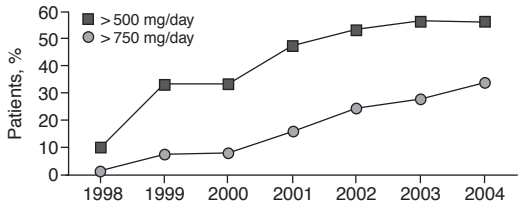
In the commercial development of quetiapine, only 2 randomized clinical trials specifically addressed dose response within the study design.[1,2] In the first study, among 356 patients with schizophrenia, fixed-dose regimens of quetiapine 75, 150, 300, 600, and 750 mg/day were compared with haloperidol 12 mg/day and placebo in a 6-week study.[1] Quetiapine at all doses above 75 mg/day was significantly superior to placebo. Attempts at dose-response modeling using several rating-scale scores showed significant quadratic functions of log-dose, indicating maximal efficacy at 300 mg/day and slight attenuation of efficacy at higher doses (600 and 750 mg/day). Plasma levels of quetiapine did not appear to have any relationship to efficacy measures.

In another study (N = 286), 2 dose ranges of quetiapine were compared with placebo.[2] The "high" dose (up to 750 mg/day, mean 360 mg/day, mean for completers 488 mg/day), but not the low dose (up to 250 mg/day, mean 209 mg/day, mean for completers 248 mg/day), showed significantly better efficacy than placebo. Again, no significant relationship was found between plasma levels and efficacy of quetiapine.

Although not specifically designed to assess dose response, flexible-dose studies can illustrate preferred doses. For example, in a double-blind study comparing chlorpromazine with quetiapine (N = 201), doses were determined by clinical titration within specified ranges.[3] The range for quetiapine was set at 100 to 750 mg/day; the mean dose was 407 mg/day.

Thus, the initial recommendations for dosing in patients with schizophrenia stemmed from the observation that the fixed-dose and flexible-dose studies converge at the optimal dose of 300 to 400 mg/day for general antipsychotic efficacy in patients not selected for treatment resistance. The product labeling for schizophrenia states that efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day, and that, in 1 study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300-mg/day dose, but that, in other studies, doses in the range of 400 to 500 mg/day appear to be needed.[4] Reduced dosage schedules are recommended in special populations. The label further states that the safety of doses above 800 mg/day has not been evaluated in clinical trials.

Figure 1. Percentage of Patients Receiving Quetiapine at Doses Above 500 or 750 mg/day (among all patients receiving quetiapine)[a]



[a]Data for the > 500-mg/day group, 1998 through 2003 only, from Citrome et al.[6] Data extracted from April 1 to June 30 for each calendar year.

TRENDS IN DOSING IN NEW YORK STATE

In contrast to the product labeling, substantially higher doses of quetiapine are prescribed by clinicians, and quetiapine is used in combination with other antipsychotics, particularly among inpatients hospitalized in state-operated psychiatric facilities.[6]

In hospitals operated by the New York State Office of Mental Health, during the reporting period of April 1, 2004, through June 30, 2004, 4809 patients were receiving antipsychotic medication. Of these, 1086 (22.6%) were receiving quetiapine at a weighted mean dose of 620 mg/day (calculated by summing the daily dose for each day for each patient and dividing by the number of all medication days during the reporting period, producing a mean daily patient dose weighted by days), compared with 314 mg/day in 1998.[6]

Examining mean daily dose by unique patients, mean daily patient dose (unweighted) was 573 mg, with 244 (22.5%) of the patients receiving doses greater than 500 and up to 750 mg/day, 227 (20.9%) receiving doses greater than 750 and up to 900 mg/day, 105 (9.7%) receiving doses greater than 900 and up to 1200 mg/day, and 33 (3.0%) receiving doses in excess of 1200 mg/day. Figure 1 describes the percentage of patients taking quetiapine who received greater than 500 mg/day or greater than 750 mg/day from 1998 to 2004. The proportion receiving

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Table 1. Characteristics of Patients Receiving Quetiapine During the Period of April 1, 2004, to June 30, 2004, by Dose Range in the New York State Psychiatric Hospital System

Variable	N	Mean ± SD Dose, mg/d	Patients in Dose Range, %			Relative Risk (95% CI) for Receiving Dose > 750 mg/d
			0 to 500 mg/d	> 500 to 750 mg/d	> 750 mg/d	
Total	1086	620 ± 359	44.0	22.5	33.6	
Gender						Male vs female: 1.17 (0.98 to 1.40)
Male	674	635 ± 367	42.5	22.0	35.4	
Female	412	594 ± 344	46.4	23.3	30.2	
Ethnicity						Nonwhite vs white: 1.24 (1.04 to 1.47)*
White	519	585 ± 337	47.6	22.5	29.8	
Black	398	666 ± 348	40.7	21.4	38.0	
Hispanic	131	632 ± 436	39.7	25.2	35.1	
Other	36	532 ± 390	47.3	22.2	30.6	
Length of stay						≥ 1 Year vs < 1 year: 1.18 (1.00 to 1.40)*
< 30 d	66	550 ± 333	48.5	18.2	33.3	
30–90 d	167	613 ± 367	46.2	22.2	31.8	
91–180 d	154	599 ± 447	43.5	26.5	29.9	
181–364 d	147	599 ± 322	43.5	26.5	29.9	
1–5 y	284	636 ± 336	37.0	25.7	37.3	
> 5 y	268	629 ± 351	45.5	18.7	35.9	
Prior state admission						Prior history vs none: 1.23 (1.02 to 1.49)*
Yes	744	638 ± 348	41.6	22.8	35.7	
No	342	578 ± 380	49.4	21.6	29.0	
Diagnosis						Schizophrenia vs nonschizophrenia: 1.01 (0.85 to 1.20)
Schizophrenia	448	611 ± 332	46.3	20.1	33.7	
Schizoaffective	378	651 ± 388	39.7	24.2	36.2	
Bipolar	109	623 ± 349	43.1	21.1	35.7	
Other	130	555 ± 370	50.0	26.9	23.0	

*p < .05.

doses in excess of 500 mg/day increased from 10.1% in 1998 to 56.1% in 2004. Using a higher threshold of 750 mg/day, the proportion of patients exceeding that amount increased from 0.7% in 1998 and 7.1% in 1999 to 33.6% in 2004.

Two conclusions can be drawn from these data: (1) mean quetiapine dosage has significantly increased over the span of time between 1998 and 2004, and (2) the mean dose during the 2004 reporting period is much higher than the dose recommended by the manufacturer.

The first observation may relate to the facts that clinicians initially were not familiar with the range of effective doses of quetiapine and that, with more experience and the absence of high rates of adverse events, clinicians became more comfortable with higher dosages. The second observation may relate to the severity of illness commonly found among patients hospitalized in state institutions. This observation raises the possibility that, in subgroups of patients with prior partial response, quetiapine may need to be dosed at higher than the product-label maximum of 800 mg/day.

Comparing patients receiving lower and higher doses of quetiapine reveals differences in gender, ethnicity (race), and chronicity of illness (as measured by history of prior admission and length of stay), seen in Table 1. The relative risk of receiving a dose of quetiapine greater than 750 mg/day was 1.24 (95% CI = 1.04 to 1.47) for nonwhites compared with whites, 1.18 (95% CI = 1.00 to 1.40) for lengths of stay of at least 1 year compared with less than 1 year, and 1.23 (95% CI = 1.02 to 1.49) for a prior history of state hospital admission compared with no such history. There was a trend for men to be prescribed doses in excess of 750 mg/day (p = .078). No significant differences were found when comparing diagnosis of schizophrenia versus bipolar disorder or schizophrenia versus nonschizophrenia.

The finding that higher doses of quetiapine were more frequently administered to nonwhites, men, patients with a prior history of state hospital admission, or patients with a longer length of stay may not be unique to quetiapine. The above findings of a higher quetiapine dose being administered to patients with a prior history of state hospital treatment, or longer length of stay, are consistent with the idea that these patients may be more chronically ill. The observation of a higher dose being administered to nonwhites (statistically significant) or men (trend) is not consistent with a contemporary study of 167 inpatients in which no ethnic or gender differences in the use of second-generation antipsychotics were found.[7]

Dosing of quetiapine among patients receiving more than 1 antipsychotic was also examined. There were 758 unique patients receiving quetiapine on calendar day May 15, 2004, of whom 471 (62%) were also receiving another antipsychotic. This coprescribing percentage did not differ significantly for those patients receiving quetiapine 25 to 300 mg/day (63% of 172), 325 to 500 mg/day (63% of 134), 525 to 750 mg/day (59% of 153), or more than 750 mg/day (62% of 299). Results were unchanged when this

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analysis was repeated for calendar days April 1, 2004, and June 20, 2004.

These results are counterintuitive because the use of other antipsychotics together with quetiapine should have obviated the need to dose quetiapine as high, if one assumes that higher quetiapine dosing is used in order to achieve sufficient inhibition of dopaminergic (D_2) transmission in mesolimbic dopaminergic pathways. Patients with only a partial prior antipsychotic response may need at least 65% or more D_2 occupancy levels in order to achieve a therapeutic response. It has been demonstrated that quetiapine has overall low D_2 occupancy levels (0%–27%) at dosages of 300 to 600 mg daily,[8] although occupancy levels could be transiently much higher, and the so-called fast dissociation hypothesis has been used as an explanation for the antipsychotic action of quetiapine.[9]

Nonetheless, one would expect coprescribed antipsychotics to increase D_2 receptor occupancy levels, so why would this not lead to the expected observation of lower quetiapine doses when used with other antipsychotics? Perhaps the answer lies in other receptor-binding affinities that may be associated with therapeutic effect, which varies from antipsychotic to antipsychotic, and whose importance varies according to the individual patient's clinical profile.[10] Clinicians using higher doses of quetiapine, with or without other antipsychotics, may be seeing improvements related to these receptor-binding affinities. Further research is required to identify and test this possibility.

REVIEW OF QUETIAPINE DOSING IN EXCESS OF 800 MG/DAY

Although there are currently no published randomized controlled studies of quetiapine at doses that exceed 800 mg/day, several case reports[11–14] and case series[15,16] are available that describe the potential benefits and drawbacks of higher dosing in schizophrenia. For example, Bobes et al.[12] describe the tolerability and efficacy of quetiapine 1600 mg/day in a 34-year-old woman. The medication was well tolerated, with only temporary dizziness at initiation of treatment. A retrospective record review of 7 patients with treatment-resistant schizophrenia revealed mild to moderate improvements with doses of quetiapine ranging from 1200 to 2400 mg/day among patients hospitalized at a forensic hospital.[15] Side effects of sedation, orthostasis, and dysphagia were seen but were responsive to reductions in the dose of quetiapine. The pattern of weight gain or loss was not consistent—1 patient lost 40 lb in 14 months, and 1 patient gained 64 lb in 14 months.

Additional work has been presented as posters, but these reports were not subject to peer review.[17–20] One report on plasma levels of quetiapine and their relationship to efficacy and safety[21] deserves special mention. There was a significant correlation between serum quetiapine levels and clinical improvement (according to the Clinical Global Impressions scale) ($p = .005$). There were no correlations found between serum quetiapine levels and side effects (according to the UKU side effect rating scale).

Expert consensus guidelines recommend dosing of quetiapine within a target range of 650 to 1100 mg/day before switching antipsychotic medication because of lack of efficacy.[22] However, these recommendations are based on clinical impressions. Whether higher or lower doses are helpful or not cannot be answered by the observation that higher or lower doses of certain agents are routinely used or recommended. To answer this question, more systematic dose-finding studies are needed.[23]

FUTURE DIRECTIONS

Although outpatients responsive to treatment may benefit from a dose range of quetiapine between 300 and 500 mg/day as recommended in the product label,[4] there remains an urgent need to conduct well-designed clinical trials that would address the question of whether or not there is an efficacy advantage when exceeding this recommended range and address the safety and efficacy of quetiapine when exceeding the product label maximum of 800 mg/day.

One such study, among state hospital patients with schizophrenia who have a poor history of response to treatment, is currently under way by 2 of the authors (L.C. and J.-P.L.). In this protocol, subjects undergo a lead-in period of 4 weeks taking quetiapine 600 mg/day. If the patient does not improve by at least a 15% change on the Positive and Negative Syndrome Scale,[24] he or she is randomly assigned to receive, double-blind, quetiapine at either 600 mg/day or 1200 mg/day for 8 weeks. This design mirrors clinical practice in which dose of quetiapine is increased beyond 800 mg/day in patients not responding to lower doses.

CONCLUSIONS

Registration studies of quetiapine have led to dosage recommendations that differ from clinical practice. Initial recommendations for a target range of 300 to 500 mg/day for patients with schizophrenia have been superseded by clinical practice in which doses in excess of 500 mg/day and 750 mg/day are routinely used among hospitalized patients with serious and persistent mental illness, either alone or, at times, in combination with other antipsychotics. Anecdotal reports have provided preliminary indications that doses in excess of 800 mg/day and up to 2400 mg/day may be safe and efficacious. However, double-blind randomized clinical trials are required to clarify this use of quetiapine. Such studies are currently under way.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), haloperidol (Haldol and others), quetiapine (Seroquel).

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