Short-term benefits of higher-dose quetiapine (up to 1600 mg/day) are maintained long term

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Abstract

Introduction: Quetiapine (‘Seroquel’) is an established treatment for schizophrenia currently approved at doses up to 750 mg/day (800 mg/day in the USA); however, some patients may benefit from treatment with higher doses.

Methods: This open-label study of 35 hospitalised patients with schizophrenia, schizoaffective disorder, bipolar disorder or alcohol-induced psychosis investigated the efficacy and tolerability of quetiapine at doses up to 1600 mg/day during a 4-week acute phase and at doses up to 1000 mg/day during a 14-month follow-up after discharge. All patients had stopped their previous antipsychotic medication due to extrapyramidal symptoms (EPS). The Clinical Global Impression of Improvement (CGI-I) scale was the primary efficacy evaluation.

Results: Eleven patients (31.4%) received 1000-1600 mg/day quetiapine during the acute phase, 15 (42.9%) received 600-800 mg/day and 9 (25.7%) received ≤400 mg/day. Of the 11 patients on ≥1000 mg/day, 5 (14.3%) continued on 800-1000 mg/day after discharge. Quetiapine was well tolerated with a low incidence of side effects and no EPS were observed with dose elevation. After 4 weeks’ hospitalisation, CGI-I scale results showed that quetiapine improved symptomatology in 33 (94.3%) patients: 13 (37.1%) ‘very much improved’; 13 (37.1%) ‘much improved’ and 7 (20.0%) ‘minimally improved’. No change was observed in 2 (5.7%) patients, and no patient experienced symptom deterioration.

Conclusions: This study demonstrates that short-term treatment with quetiapine at doses up to 1600 mg/day is well tolerated and effective in patients with psychoses and that these benefits can be maintained for up to 14 months with doses up to 1000 mg/day.

Objectives

► The aim of this study was to assess the efficacy, safety and tolerability of short-term (4 weeks) quetiapine therapy at doses up to 1600 mg/day in hospitalised patients, and the clinical efficacy of doses up to 1000 mg/day during a 14-month follow-up after discharge.

Methods

Study design

► An open-label study carried out over a period of 15 months.
► The study consisted of a 4-week hospitalisation period (acute treatment phase) and a 14-month follow-up period after discharge (maintenance phase).

Patients

► Male or female patients aged 18-65 years with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or other psychotic disorder were recruited.
► Patients had previously received and responded to conventional or atypical antipsychotics other than quetiapine but stopped medication due to EPS.
► Exclusion criteria included antipsychotic-naïve patients, those with cardiac, renal or hepatic dysfunction, known or suspected allergy to quetiapine, aged >65 years, pregnancy or concomitant alcohol abuse.

Treatment

► Quetiapine was initiated from Day 1 at 100-400 mg/day (50-200 mg bid).
► Patients experiencing florid symptoms had their dose increased by 50-100 mg/day every 1-2 days, up to a maximum of 1600 mg/day, until symptom relief was obtained.
► Patients received quetiapine at the higher dose for 1-4 weeks depending on response, before proceeding to the maintenance phase.
► Before discharge, quetiapine doses were reduced where possible by 50-100 mg/day to a level that allowed control of psychotic symptoms (maintenance phase).
► During the study, concomitant sedatives and antidepressants were permitted, but other antipsychotic agents were not.

Introduction

► Patients taking antipsychotic medication frequently discontinue treatment due to distressing adverse events (AEs), in particular extrapyramidal symptoms (EPS).1 This is a concern with conventional antipsychotics (eg haloperidol) and some atypicals which have dose-related EPS (eg risperidone, olanzapine).2
► Quetiapine (‘Seroquel’) is an atypical antipsychotic that is effective at improving the positive, negative and cognitive symptoms of schizophrenia at doses up to 750 mg/day.3-6 The incidence of EPS (including akathisia) and prolactin levels are no different than placebo across the dose range.3
► Recent studies and clinical experience suggest the target dose of quetiapine is 600 mg/day.7-10 However, some patients may require higher doses of quetiapine to achieve optimal control of symptoms.
Efficacy assessments

The primary efficacy measure was the Clinical Global Impression of Improvement (CGI-I) scale to assess psychiatric symptomatology. Assessments were made daily during hospitalisation and monthly following discharge.

Tolerability assessments

AEs were monitored and recorded daily during hospitalisation and monthly during the maintenance phase.

Electrocardiography (ECG), routine haematological and laboratory tests were performed prior to study entry, before quetiapine dose reduction and at discharge.

Data analysis

The data are summarised using descriptive statistical methods.

Results

Patients

A total of 35 patients enrolled in the study and received quetiapine (Table 1).

Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female, n</td>
<td>24:11</td>
</tr>
<tr>
<td>Mean age (range), years</td>
<td>44.6 (25-64)</td>
</tr>
<tr>
<td>DSM-IV diagnosis, n</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>31</td>
</tr>
<tr>
<td>(paranoid/catatonic/hebephrenic)</td>
<td>(29/1/1)</td>
</tr>
<tr>
<td>Bipolar disorder, manic</td>
<td>1</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>2</td>
</tr>
<tr>
<td>(mixed/manic symptoms)</td>
<td>(1/1)</td>
</tr>
<tr>
<td>Alcohol-induced hallucinosis</td>
<td>1</td>
</tr>
<tr>
<td>Previous treatment, n</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>17</td>
</tr>
<tr>
<td>Chlorprothixene</td>
<td>10</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
</tr>
<tr>
<td>Chlorprothixene + haloperidol</td>
<td>2</td>
</tr>
<tr>
<td>No previous treatment</td>
<td>1*</td>
</tr>
<tr>
<td>EPS as the reason for stopping medication, n</td>
<td>35**</td>
</tr>
</tbody>
</table>

*Not on treatment prior to study, but had previously received haloperidol.

**Two patients had a previous history of neuroleptic malignant syndrome.

Patients with schizophrenia had symptoms for 2-20 years. Two patients with schizoaffective disorder had symptoms for 2 and 3 years, respectively.

The patient with bipolar disorder had symptoms for 30 years. One patient had alcohol-induced psychosis (although the patient was no longer dependent on alcohol) and had experienced three hallucinations.

One patient was lost to follow-up and two patients withdrew during maintenance treatment due to no improvement in catatonic or paranoid symptoms (although there was a decrease in excitement and hostility).

Dose

Acute phase treatment:

- the modal dose of quetiapine was 800 mg/day (range 200-1600 mg/day) (Figure 1).
- the majority of patients received 800 mg/day or higher (Figure 1).

Maintenance phase treatment:

- daily doses were decreased to 200-600 mg/day in 27 patients; 4 patients received 800 mg/day; 1 patient required 1000 mg/day (Figure 2). The modal dose was 600 mg/day.

Efficacy

CGI-I measurements showed 94% of patients experienced an improvement in global symptoms after 4 weeks of quetiapine treatment, with the majority classified as ‘very much improved’ or ‘much improved’ (Figure 3).

- A rapid improvement or elimination was observed in symptoms of hostility (within 2-3 days), restlessness (1-3 days) and insomnia (1-2 days). This was achieved with doses <800 mg/day.

- Hallucinations improved after 1 week of quetiapine therapy (600-1400 mg/day).

- Delusions became milder or disappeared after 3 weeks of quetiapine at doses ≥800 mg/day. This is similar to that observed with the other atypical antipsychotics.

Safety and tolerability

Quetiapine was well tolerated at all doses with no increase in AEs following dose elevation. There was no evidence of EPS even at the highest dose studied (1600 mg/day).

The only AEs reported during acute treatment were orthostatic hypotension, daytime somnolence and dry mouth (Table 2).

Table 2. AEs occurring in ≥5% of patients during acute treatment

<table>
<thead>
<tr>
<th>AE</th>
<th>No. (%) patients (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime somnolence</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>5 (14.2)</td>
</tr>
</tbody>
</table>

AEs quickly resolved in all patients experiencing orthostatic hypotension (resolved within 1-2 days) and one patient with daytime somnolence (resolved spontaneously). The other patient with daytime somnolence benefited from quetiapine’s calming properties and experienced considerable reductions in stress and anxiety symptoms.

No AEs were reported during follow-up.

ECG values and routine laboratory tests were within the normal ranges and there were no clinically significant (>1 kg) changes in body weight.
Figure 1. Distribution of maximal dose of quetiapine during acute treatment (Weeks 1-4; n=35).

![Figure 1: Distribution of maximal dose of quetiapine during acute treatment](image)

Figure 2. Distribution of quetiapine dose during follow-up (n=32).

![Figure 2: Distribution of quetiapine dose during follow-up](image)

Figure 3. CGI-I scale scores in hospitalised patients following acute treatment with quetiapine (n=35).

![Figure 3: CGI-I scale scores](image)
Conclusions

- Quetiapine is effective and well tolerated at doses up to 1600 mg/day in patients with psychoses who had stopped previous antipsychotic therapy due to EPS.

- These beneficial effects are maintained for up to 14 months with doses up to 1000 mg/day.

- No evidence of EPS (including akathisia) or weight gain was seen during the study. This dose-independent tolerability allows the dose of quetiapine to be increased to optimise efficacy during acute and long-term treatment.

References


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