Impact of extended-release quetiapine fumarate on hospitalization length and cost in schizophrenia and bipolar disorder patients: a retrospective, hospital-based, US-cohort analysis

Aim: The aim was to evaluate the impact of quetiapine extended release (XR) on hospitalization length and cost in schizophrenia or bipolar disorder, versus quetiapine immediate release (IR), using Premier Perspective™ inpatient hospital database data. Methods: Inpatient discharges classified within diagnosis-related group 430 (psychoses), prescribed quetiapine XR or IR, were identified. Patients had International Classification of Disease-9 diagnosis of schizophrenia or bipolar disorder. The impact of the XR formulation on hospitalization length and costs was assessed using generalized linear model analyses. Results: A total of 30,429 discharges between 1 January 2008 and 30 June 2009 were analyzed. Patients who received quetiapine XR had significantly reduced hospitalization length (10.73% estimated reduction; \( p = 0.001 \)) and cost (9.52% estimated reduction; \( p < 0.001 \)), versus IR. This corresponds to a 1.0-day reduction in hospitalization (10.73% of 9.2 days) and US$532 reduction in hospitalization cost (9.52% of US$5588) per patient, based on least squares mean estimations. Evaluation of patient subpopulations suggested the reduction in length of hospitalization for quetiapine XR versus IR was driven mainly by patients with bipolar disorder, whereas cost reduction was driven mainly by patients with schizophrenia. Conclusion: Inpatient use of quetiapine XR in schizophrenia or bipolar disorder is associated with reduced hospitalization length and cost, possibly due to the faster titration schedule versus quetiapine IR.

Keywords: bipolar disorder • cost • hospitalization • quetiapine XR • schizophrenia
disorder, and as an adjunctive treatment for the maintenance of bipolar I disorder. In addition, quetiapine XR is also licensed in the USA and EU as an adjunctive treatment for patients with major depressive disorder who have had an inadequate response to antidepressant treatment alone. In some countries, including Australia and Canada, quetiapine XR has also been approved as monotherapy for the treatment of major depressive disorder.

The XR formulation of quetiapine has demonstrated efficacy in two out of three randomized, double-blind, placebo-controlled trials in patients with acute schizophrenia [7–9], and quetiapine IR is well established for the treatment of schizophrenia [10–12]. In bipolar disorder, quetiapine XR and quetiapine IR have demonstrated efficacy in patients with manic or depressive symptoms [13–20].

The recommended dosing frequency for quetiapine IR in schizophrenia and bipolar mania is twice daily. Qetiapine XR is a once-daily formulation that reduces the time needed to achieve the target therapeutic dose and has potential advantages in patient convenience, compliance and tolerability. Both quetiapine XR and quetiapine IR are dosed once daily in bipolar depression.

In pharmacokinetic studies, once-daily quetiapine XR resulted in a similar overall exposure (area under the curve) to that of twice-daily quetiapine IR administered at the same daily dose level [21].

Table 1 presents the initial dose titration schedules for quetiapine XR and quetiapine IR, as reported in the prescribing information for schizophrenia and bipolar disorder. The more rapid titration schedule of quetiapine XR, compared with quetiapine IR, means that patients with schizophrenia and bipolar mania may receive an effective dose sooner than with quetiapine IR [22–26]. Based on the conclusions of Agrawal and Agell from a small retrospective study of prescription charts from inpatients who received clozapine, we hypothesize that rapid titration schedule is one factor that may contribute to a reduction in the length of hospitalization [27].

Randomized controlled trials may be of limited use in measuring healthcare resource utilization and costs, due to the relatively short duration of exposure to treatment, the controlled environment and the limited patient numbers studied [28]. Observational studies, including administrative data, are an important supplement to randomized controlled trials, providing data from real-world clinical practice. The Premier Perspectives™ inpatient hospital database is a large, nationally representative, administrative, hospital billing database, which includes nonfederal, short-stay hospitals in the USA.

This study evaluates the impact of quetiapine XR on the length and cost of hospitalization in patients with schizophrenia or bipolar disorder, compared with quetiapine IR, using data from this database.

Methods

Study design & data source

This study was a retrospective database analysis using the Premier Perspectives inpatient hospital database. All analyses were performed on data for patients discharged from hospital who were classified as diagnosis-related group (DRG) 430 (psychoses; accounting for the majority of psychiatric admissions and including major personality disorders such as schizophrenia, catatonia, manic disorders, bipolar affective disorders and paranoia), collected between 1 January 2008 and 30 June 2009. DRGs are classification systems that are assigned to patients by physicians on their admission to hospital, in order to group patients according to their clinical characteristics and the resource utilization required for their treatment.

Study population

Eligible patients were inpatients aged 18–65 years with an International Classification of Disease 9th Revision diagnosis of schizophrenia or bipolar disorder (Table 2), receiving either quetiapine XR or quetiapine IR. A patient could have more than one diagnosis during hospitalization.

Cost measures

Cost analyses included pharmacy, laboratory, and room and board costs. Patients were included in the analyses if hospitalization cost records were complete, and excluded if one of the items in the particular department being analyzed was zero. The reference year for costs was 2008 and adjustments for 2009 costs were made using a discount rate of 3%.

Statistical analysis

All statistical analyses were performed with SAS® Version 8.2 for Windows® (SAS Institute, Inc., NC, USA), a general statistical modeling tool that fits generalized linear models to data. Descriptive statistics were used to examine patient demographics and clinical characteristics associated with the use of quetiapine XR or quetiapine IR.

A generalized linear model was used to evaluate differences between quetiapine XR and quetiapine IR, with regard to length and cost of hospitalization, and provide least squares mean (LSM) estimations.

The length and cost of hospitalization data from the eligible population were not normally distributed. Therefore, given the skewed distribution of these data,
all cost variables were log-transformed before the model was applied, and the parameter estimates in the output were also log-transformed for the length of hospitalization analysis. To control for potential confounding effects, the following parameters were included as covariates in the analysis: patient gender; patient age; all-patient-refined-DRG defined disease severity; hospitalization in a teaching hospital; hospital type; and type of insurer.

Data were analyzed using the GENMOD procedure in SAS. This procedure also provides a facility for fitting generalized estimating equations to correlated response data that are categorical, such as repeated dichotomous outcomes. The antilogarithms for all parameter estimates, together with a 95% confidence interval, are presented together with a p-value. A ratio of <1 relates to shorter length of stay and reduced cost of hospitalization, and a p-value of <0.05 is considered statistically significant.

The percentage reduction in length and cost of hospitalization for quetiapine XR, compared with quetiapine IR, was calculated as the percentage reduction, multiplied by the antilogarithms of LSM estimations, for patients treated with quetiapine IR.

The data used in the study had no patient identifiers and complied with the Health Insurance Portability and Accountability Act. Consequently, the analysis protocol was not submitted to an institutional review board.

Results
In total, 30,429 patients were admitted into hospital with a primary diagnosis of schizophrenia (14,275) or bipolar disorder (17,228) (Table 3). As patients could have more than one diagnosis during hospitalization, the sum of patients with a primary diagnosis of schizophrenia or bipolar disorder is greater than the total number of discharges. Of these patients, a total of 1292 were treated with quetiapine XR and 29,137 were treated with quetiapine IR (Table 3).

The demographic and clinical characteristics of patients treated with quetiapine XR and quetiapine IR are presented in Table 4. Overall characteristics were comparable for quetiapine XR and quetiapine IR:
the mean age of patients was 39.4 years for quetiapine XR and 40.9 years for quetiapine IR; and a large proportion of patients treated with quetiapine XR and quetiapine IR were classified as having 'moderate' disease (57.1 and 58.0%, respectively), as defined by the all-patient-refined-DRG system.

Length of hospitalization
Table 5 summarizes the difference in the length of hospitalization for patients treated with quetiapine XR compared with quetiapine IR, according to the generalized linear model analyses. LSM estimations of length of hospitalization for patients treated with quetiapine XR and quetiapine IR are presented in Figure 1.

Overall, in patients with schizophrenia or bipolar disorder, the length of hospital stay for quetiapine XR was 8.2 days \((n = 1292)\), compared with 9.2 days \((n = 29,137)\) for quetiapine IR. In patients with schizophrenia only, the length of stay was 10.1 days, compared with 11.1 days for quetiapine IR; in bipolar disorder, the length of stay was 6.9 days for quetiapine XR, compared with 8.0 days for quetiapine IR.

In patients with schizophrenia or bipolar disorder, treatment with quetiapine XR, compared with quetiapine IR, was associated with a significant reduction in the length of hospitalization.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Quetiapine XR (n = 1292)</th>
<th>Quetiapine IR (n = 29,137)</th>
<th>Overall (n = 30,429)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia; n (%)</td>
<td>665 (51.5)</td>
<td>13,610 (46.7)</td>
<td>14,275 (46.9)</td>
</tr>
<tr>
<td>Bipolar disorder; n (%)</td>
<td>690 (53.4)</td>
<td>16,538 (56.8)</td>
<td>17,228 (56.6)</td>
</tr>
</tbody>
</table>

*One invalid code in the ‘gender’ field (for quetiapine IR).
Four invalid codes in the ‘admission’ field (all for quetiapine IR).
APR: All-patient-refined; DRG: Diagnosis-related group; IR: Immediate release; SD: Standard deviation; XR: Extended release.
of hospitalization (antilogarithm of generalized estimating equation parameter estimates = 0.89269; \( p = 0.001 \)) (Table 5). The percentage reduction in the length of hospitalization was 10.73\% \((1 - 0.89269 \times 100)\), corresponding to approximately 1.0 inpatient day (10.73\% of 9.2 days) (Figure 1).

In patients with schizophrenia only, treatment with quetiapine XR, compared with quetiapine IR, was associated with an 8.70\% shorter length of hospitalization, corresponding to approximately 1.0 inpatient day (8.70\% of 11.1 days) (Figure 1); however, the difference between the treatment groups was not statistically significant \(( p = 0.11 \)) (Table 5). In patients with bipolar disorder only, treatment with quetiapine XR, compared with quetiapine IR, was associated with a significantly shorter length of stay: days of hospitalization were reduced by 13.64\%
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Table 6. A summary of the generalized linear model analysis for the difference in cost of hospitalization for the treatment of the diagnosis-related group 430 patients with schizophrenia or bipolar disorder with quetiapine extended release compared with quetiapine immediate release.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Quetiapine XR vs quetiapine IR: antilogarithms of GEE parameter estimates</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia or bipolar disorder (n = 30,429)</td>
<td>0.90485</td>
<td>0.86209–0.94973</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Schizophrenia (n = 14,275)</td>
<td>0.87172</td>
<td>0.80988–0.93829</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bipolar disorder (n = 17,228)</td>
<td>0.94526</td>
<td>0.88934–1.00471</td>
<td>0.07</td>
</tr>
</tbody>
</table>

GEE: Generalized estimating equations from the generalized linear model analysis; IR: Immediate release; XR: Extended release.

Cost of hospitalization

Table 6 summarizes the difference in the cost of hospitalization for patients treated with quetiapine XR, compared with quetiapine IR, according to the generalized linear model analyses. LSM estimations of the cost of hospitalization in patients treated with quetiapine XR and quetiapine IR are presented in Figure 2.

In the combined analysis of patients with schizophrenia or bipolar disorder, the cost of hospitalization for quetiapine XR was US$5056, compared with US$5588 for quetiapine IR. In patients with schizophrenia only, the cost of hospitalization for quetiapine XR was US$5269 compared with US$6045 for quetiapine IR, and US$4807 compared with US$5085 in patients with bipolar disorder only, respectively (Figure 2).

In patients with schizophrenia or bipolar disorder, treatment with quetiapine XR, compared with quetiapine IR, was associated with a significant reduction in the cost of hospitalization by 9.52% (p < 0.001) (Table 6), corresponding to approximately US$532 (9.52% of US$5588) (Figure 2).

In patients with schizophrenia only, treatment with quetiapine XR was associated with a significant reduction in the cost of hospitalization of 12.83% (p < 0.001) (Table 6), compared with quetiapine IR, which corresponds to approximately US$776 (12.83% of US$6045) (Figure 2).

In patients with bipolar disorder only, treatment with quetiapine XR was associated with a 5.47% reduction in the cost of hospitalization, compared with quetiapine IR, which corresponds to approximately US$278 (5.47% of US$5085) (Figure 2); however, the difference here was not statistically significant (p = 0.07) (Table 6).

Discussion

Schizophrenia and bipolar disorder are chronic and debilitating mental illnesses, which often result in patients being hospitalized and are associated with high medical costs [1,4]. In this study, the impact of treatment with quetiapine XR, compared with quetiapine IR, on the length and cost of hospitalization was analyzed, using real-world data from the Premier Perspective™ inpatient hospital database.

The use of quetiapine XR was associated with significantly shorter length and lower cost of hospitalization compared with quetiapine IR, in a combined sample of patients classified within DRG 430 (psychoses) and diagnosed with schizophrenia and/or bipolar disorder.

The quetiapine XR formulation is based on gel matrix technology using a soluble polymer to control the release of quetiapine fumarate from the tablet [29]. Pharmacokinetic profiling reveals that the quetiapine XR formulation demonstrates a slower rise in plasma level compared with the equivalent quetiapine IR dose and a more gradual decline over a 24-h period, allowing for a faster titration schedule [21,30]. The rapid titration schedule of quetiapine XR for schizophrenia or bipolar disorder means that an effective dose can be reached by day 2 in schizophrenia and bipolar mania, and by day 4 in bipolar depression [22–26]. The shorter length of hospitalization among patients receiving quetiapine XR may be partly due to the faster titration schedule, as a reduction in the time taken to reach therapeutic drug levels may positively impact the length of hospitalization. Shorter length of hospitalization, in turn, contributes to a reduction in cost.

Previous studies comparing hospitalization in patients treated with antipsychotics have reported lower annual risks for hospitalization and shorter length of stay in patients treated with quetiapine, compared with risperidone, olanzapine, ziprasidone, aripiprazole and haloperidol [31,32]. Strutton et al. [32] reported that in all patients with schizophrenia from the Premier Perspective™ inpatient hospital database, the length of hospitalization was 10.0 days. Patients receiving monotherapy had shorter lengths of hospitalization (8.4 days) and drug switching was associated with longer lengths of hospitalization (12.3 days). When specific antipsychotic drugs were considered, quetiapine and risperidone were associated with the shortest mean length of hospitalization (8.4 days,
standard deviation 6.6 days), compared with 8.6 (7.1) days with haloperidol and 8.9 (7.2) days with olanzapine, ziprasidone and aripiprazole [32].

When the data in the current study were examined by diagnosis, quetiapine XR was associated with a significantly shorter duration of hospitalization in patients with bipolar disorder versus those receiving quetiapine IR. However, in patients with schizophrenia, although quetiapine XR was associated with a directional shorter duration of hospitalization, the estimate was not significantly different between the two treatment groups. In contrast, patients with schizophrenia who received quetiapine XR accrued significantly lower costs of hospitalization compared with those receiving quetiapine IR; however, in bipolar disorder, the difference between the quetiapine formulations did not reach statistical significance with regard to the cost of hospitalization.

These analyses by diagnosis suggest that the overall significant reduction in length of hospitalization associated with quetiapine XR appears to be mainly driven by patients with a diagnosis of bipolar disorder, whereas the significant reduction in costs appears to be driven by patients with a diagnosis of schizophrenia.

Generic versions of quetiapine IR became available in 2012, resulting in lower drug costs in patients where treatment with quetiapine IR is appropriate. Drug costs represent around 25% of the total national expenditure for mental health services in the USA [4]. Despite reductions in the cost of quetiapine IR, quetiapine XR provides a valuable treatment option for patients with schizophrenia or bipolar disorder, resulting in cost offsets due to shorter length and reduced costs of hospitalization. Any potential impact of revised drug costs on the results presented here would be minimal due to the relatively short time period being analyzed (i.e., drug costs during the hospitalized period only). Indeed, access to a broad range of therapeutic agents is essential for the effective treatment of patients with schizophrenia or bipolar disorder according to individual patient’s needs [33].

Figure 2. Antilogarithms of least squares mean estimations of the cost of hospitalization for the diagnosis-related group 430 patients with schizophrenia or bipolar disorder, treated with quetiapine extended release or quetiapine immediate release.

*p-values are from generalized linear model analyses presented in Table 6.

IR: Immediate release; XR: Extended release.
Our study was a retrospective database analysis and, as such, this should be acknowledged as a limitation; such analyses are potentially associated with a number of methodologic limitations related to nonrandomization. Far fewer patients were treated with quetiapine XR (n = 1292) than quetiapine IR (n = 29,137) and the study does not account for selection bias or sample imbalances. Furthermore, the analyses reported here are limited to the relatively short time period that the patients were hospitalized and may not be generalizable to the entire disease course. In addition, the Premier Perspectives™ inpatient hospital database does not include data from psychiatric and rehabilitation hospitals. Despite these limitations, this analysis did control for potential confounding effects.

Conclusion
Consideration of the available evidence leads to the conclusion that the use of quetiapine XR, compared with quetiapine IR, is associated with a shorter length of stay and reduced cost of hospitalization in patients with schizophrenia and bipolar disorder. Therefore, where treatment with quetiapine XR is appropriate, it provides an alternative treatment option to quetiapine IR and its generic formulations due to hospital cost savings in patients.

Financial & competing interests disclosure
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Executive summary
- Mental illness can be chronic and debilitating, and is often associated with cognitive dysfunction and significantly impaired quality of life.
- Despite psychopharmacologic and psychotherapeutic advances, many newly diagnosed patients, and those who relapse, require hospitalization.
- Quetiapine is an atypical antipsychotic, available as an extended release (XR) or immediate release (IR) formulation for the treatment of schizophrenia, acute depressive and manic episodes associated with bipolar disorder, and as an adjunctive treatment for the maintenance of bipolar I disorder.
- Quetiapine XR is also licensed in the USA and EU as an adjunctive treatment for patients with major depressive disorder who have had an inadequate response to antidepressant treatment alone. In some countries, including Australia and Canada, quetiapine XR has also been approved as monotherapy for the treatment of major depressive disorder.
- The recommended dosing frequency for quetiapine IR is twice daily. Quetiapine XR is a once-daily formulation that reduces the time needed to achieve a target therapeutic dose.
- The aim of this study was to evaluate the impact of quetiapine XR on hospitalization length and cost in schizophrenia or bipolar disorder, versus quetiapine IR, using Premier Perspective™ inpatient hospital database data.
- Analysis of data from the Premier Perspective™ inpatient hospital database demonstrated that inpatient use of quetiapine XR in patients with schizophrenia or bipolar disorder is associated with reduced length and cost of hospitalization, possibly due to the faster titration schedule for quetiapine XR versus quetiapine IR.
- Where treatment with quetiapine XR is appropriate, it provides an alternative treatment option to quetiapine IR and its generic formulations due to hospital cost savings in patients.

References
Papers of special note have been highlighted as:
• of interest
• Full paper describing a study that showed superior efficacy of quetiapine extended release 600 mg/day versus placebo in patients with schizophrenia.
• Full paper describing a study in which quetiapine demonstrated superior efficacy to placebo in patients with bipolar mania.
• Full paper describing a study in which quetiapine monotherapy was shown to be efficacious and well tolerated for the treatment of bipolar depression.
• Full paper describing a 3-week study, which suggests that quetiapine extended release (400–800 mg) once-daily monotherapy is efficacious (from day 4) and generally well tolerated in patients with manic or mixed episodes of bipolar I disorder.
• Full paper describing a study in which quetiapine (300 or 600 mg/day), but not paroxetine, was more effective than placebo for treating acute depressive episodes in bipolar I and II disorder.
• Full paper describing a study in which quetiapine extended release (300 mg) once-daily monotherapy was significantly more effective than placebo for treating episodes of depression in bipolar I disorder, throughout the 8-week study, with significance observed as early as day 7.
• Full paper describing a study, that demonstrates that quetiapine monotherapy is an effective and well-tolerated treatment for depressive episodes in bipolar disorder, confirming the results observed from a previous study (BOLDER I).
• Full paper describing a study that demonstrated that quetiapine (300 or 600 mg/day) was more effective than placebo for the treatment of episodes of acute depression in bipolar disorder, and that lithium did not significantly differ from placebo on the main measures of efficacy.
23 AstraZeneca Pharmaceuticals LP. Seroquel (quetiapine fumarate) Prescribing Information. www1.astrazeneca-us.com/pi/seroquel.pdf
24 AstraZeneca Pharmaceuticals LP. Seroquel XR (quetiapine fumarate) extended release tablets Prescribing Information. www1.astrazeneca-us.com/pi/seroquelxr.pdf


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