Abstract
Schizophrenia is a severe illness with substantial effects on individual and social functioning. First-line treatment in these patients is the use of atypical antipsychotics. The atypical antipsychotic quetiapine was approved in 1997 by the US Food and Drug Administration (FDA), and has been available since 2007 as an extended-release (quetiapine XR) formulation. This formulation has the advantage of once-daily application and achieves an effective dose within two to three days without compromising tolerability. Several trials conducted with quetiapine XR have demonstrated effectiveness in patients with acute schizophrenia and in preventing relapse in long-term treatment. Switching from quetiapine immediate-release (quetiapine IR) or other antipsychotics to quetiapine XR was feasible in a short time and maintained effective treatment. The safety and tolerability profile was similar to that of quetiapine IR. The results of these studies anticipate quetiapine XR to be a promising new treatment option that may lead to an increase in medical adherence.

Key words
Schizophrenia, atypical antipsychotic, quetiapine, quetiapine XR, extended release

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Correspondence: Richard Musil, Psychiatric Clinic, University of Munich, Nußbaumstrasse 7, 80336 Munich, Germany E: richard.musil@med.uni-muenchen.de

Pharmacological Formulation and Chemical Structure
Quetiapine XR is available as quetiapine hemifumarate in 50, 200, 300 and 400mg tablets. All tablets are film-coated. The drug has the same chemical structure as quetiapine immediate-release (quetiapine IR). The galenic structure of quetiapine XR involves a polymeric gel matrix of hydroxypropylmethylcellulose (HPMC). Quetiapine is interlinked with the polymeric structure of HPMC in a net-like structure. HPMC widens its structure in the presence of water to form a smaller hard core and a softer outer cellulose gel membrane. Thus, the tablet can release the active drug continuously over a period of 20 hours.

Indication
Quetiapine XR is approved for the treatment of schizophrenia and for the prevention of exacerbations of disease in stable schizophrenic patients.

Mechanism of Action
Quetiapine XR displays the same receptor profile as quetiapine IR. Quetiapine and its active metabolite N-desalkyl-quetiapine have high affinities to dopaminergic D1- and D2 receptors, 5-HT2 receptors, histaminergic and alpha-1-adrenergic receptors and to alpha-2 and 5-HT1A receptors. The active metabolite N-desalkyl-quetiapine has high affinities to 5-HT2A receptors, and low affinities to DA1 and DA2 receptors. Quetiapine is supposed to account for the “atypical” properties of second-generation antipsychotics, and thus SGAs induce much fewer extra-pyramidal motor symptoms (EPS).

Quetiapine XR displays the same receptor profile as quetiapine XR.
affinity to the norepinephrine transporter. Quetiapine IR shows only transient D2-receptor occupancy of 58–64% D2 occupancy two to three hours after a single dose, decreasing to 0–27% D2 occupancy 12 hours after the last dose. This transient D2 occupancy is thought to account for the low incidence of EPS and prolactin rise, while still being potent enough to exhibit antipsychotic effects. To determine whether the extended-release formulation shows similar central receptor occupancy to the immediate-release formulation, Mamo et al. performed a positron emission tomography (PET) study using [11C]-raclopride, a radiolabelled D2/D3-receptor antagonist. In 12 schizophrenic subjects in three dose groups, namely 300, 600 or 800mg/day, they found that the mean plasma levels in all dose groups were significantly higher at peak levels than trough levels for quetiapine XR, and the mean plasma levels did not differ significantly between formulations. The mean D2-receptor occupancy was significantly higher at peak than at trough for both formulations and for all dose groups except for quetiapine IR 800mg/day. The binding profile and the D2-receptor occupancy did not differ between the two formulations. Furthermore, quetiapine XR displayed a dose-occupancy relationship.

**Pharmacokinetics**

Quetiapine is well absorbed after oral intake and maximum plasma peak levels (t\text{max}) are reached about six hours after administration. For quetiapine IR, maximum plasma peak levels are reached one and a half hours after application (see Figure 1). The once-daily dosing of quetiapine XR reaches similar overall plasma concentrations to the twice-daily dosing of quetiapine IR. Plasma levels for quetiapine and its active metabolite are linear and proportional to the administered dosing up to a dose of 800mg/day. Comparing quetiapine XR with the IR formulation, the plasma concentration time area under the curve (AUC) is equivalent, but the mean maximum plasma concentration (C\text{max}) in steady-state is about 13% lower, and for the active metabolite N-desalkyl-quetiapine 18% lower (495.3 versus 568.1ng/ml). The bioavailability of quetiapine once daily is influenced by high-fat food (approximately 800–1,000 calories), showing elevations of t\text{max} and AUC of 42–52% and 20–22%, respectively. However, Juckel et al. showed that the pharmacokinetics seem not to be affected by a light meal (approximately 300 calories). The plasma protein binding of quetiapine is approximately 83%. It is widely distributed throughout the body.

Quetiapine is mainly metabolised in the liver with a mean terminal half-life (t\text{1/2}) of seven hours for quetiapine and nine to 12 hours for N-desalkyl-quetiapine. Steady-state concentrations are reached within two days after initialising treatment. Only about 1% of quetiapine is excreted as unchanged drug. Within the liver, quetiapine is metabolised by sulphoxidation to a sulphoxide metabolite and by oxidation to the parent acid metabolite. These metabolites are pharmacologically inactive. The inactive and active metabolites are formed via the P450 isoenzyme 3A4. 7-hydroxy quetiapine, another active metabolite, is formed via CYP2D6. Pharmacokinetics are not influenced by gender, ethnicity or smoking; however, dose adjustments have to be performed in certain clinical subpopulations such as elderly patients or those with hepatic impairment.

**Interaction Potential**

Data from in vitro enzyme inhibition suggest little inhibitory or stimulatory potential of quetiapine and its metabolites on cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4. Orally administered quetiapine clearance is increased by cytochrome P450 3A4 inducers and decreased by enzyme inhibitors.

**Clinical Efficacy Trials**

**Overview**

To date, 20 trials have been completed to determine quetiapine XR pharmacokinetic data (seven trials), clinical pharmacology (six trials), efficacy and tolerability (five trials) and other data (two trials). In total 3,231 patients have been recruited; 1,677 of these patients were diagnosed with schizophrenia, 951 patients took part in short-term trials over six weeks, 327 patients took part in a relapse-prevention trial and 808 patients took part in switching studies. To evaluate clinical status, usual psychometric instruments were used in all trials on quetiapine XR efficacy, including the Positive And Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI)-Scale. Inclusion criteria of all studies were age between 18 and 65 years and a diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria, including catatonic, disorganised, paranoid or undifferentiated type. Exclusion criteria included diagnosis of any other axis I condition, substance abuse or clinically relevant somatic diseases among others. Statistical analyses were typically performed in three patient populations, the (modified) intention-to-treat population (MIT; all patients receiving study medication and with at least one post-baseline PANSS rating), the per-protocol population (all patients lacking major protocol deviations) and the safety population (all randomised patients given at least one dose study medication).

**Short-term Clinical Efficacy**

In three trials, the tolerability and efficacy of quetiapine XR were studied in acutely ill schizophrenic patients. The primary end-point of all three trials was change in PANSS total scores from baseline to week six. All trials were randomised, double-blind, double-dummy, multicentre and placebo-controlled. In the first published study, by Kahn et al. (the short-term 132-trial), 588 patients were recruited in 39 centres. Of these, 573 patients were included in the MITT-analysis. Additional inclusion criteria were CGI-S scores ≥4 and PANSS-total scores ≥70 and ≥4 in the single items of delusions, conceptual disorganisation, hallucinatory behaviour or suspiciousness/persecution. The patients were randomised to one of the five treatment arms. Quetiapine XR began at 300mg and then increased on day two to 400 or 600mg/day, with only one group reaching 800mg on day three. The fourth group began on 50mg quetiapine IR and gradually titrated up to 400mg on day five. The last group received placebo. All four active treatment arms showed statistically significant changes in total PANSS scores.
Peuskens et al. investigated long-term efficacy in a randomised, double-blind, multicentre study with a fixed-dose regimen conducted over six weeks in 74 centres worldwide (the switching 146-trial).23 After four weeks of treatment with stable doses of quetiapine IR (400, 600 or 800mg/day) twice daily in the run-in phase, patients were randomised to continue quetiapine IR or were switched in one day to the same dose of quetiapine XR. In total, 630 patients were enrolled in the study, and 497 were randomised to treatment. All patients included were outpatients displaying a CGI-S score ≥3. The primary outcome variable was non-inferiority of quetiapine XR in efficacy compared with quetiapine IR. Secondary objectives were stability in PANSS scores and data on safety and tolerability. Non-inferiority was shown for the per-protocol population (p=0.0017) with a non-inferiority margin of 6% (see Figure 4), but not for the MITT population. For all secondary objectives, results were similar in both treatment groups.

Ganesan et al. conducted a 12-week open-label worldwide study in 65 centres (the switching 147-trial).22 Patients were switched from previous antipsychotic medications (due to a lack of efficacy or adverse events) to quetiapine XR in a flexible-dose regimen.22 The switching regimen followed the same method as the long-term study. Of the 533 patients enrolled, 477 were switched to quetiapine XR. The primary end-point was the percentage of patients with a clinical benefit, defined as an improvement in the CGI-Clinical Benefit (CGI-CB) score at week 12. Of those who took part, 295 patients (62.8%) met this criterion (p<0.0001 for the overall patient population). Patients switching from first-generation antipsychotics experienced most clinical benefit and patients switching due to lack of efficacy showed greater decreases in PANSS scores compared with patients switching due to insufficient tolerability.

Tolerability
Tolerability measures included the recording of spontaneous reported adverse events, laboratory measures, electrocardiogram, vital signs, weight, recording of extra-pyramidal symptoms with the Barnes-Akathisia Scale (BAS)21 and Simpson-Angus Scale (SAS)20 and the use of anticholinergic medication. Data were analyzed from the safety population.

Adverse Events
Overall, the incidence of recorded adverse events (AEs) in the performed studies varied from 31.9 to 72.5% of patients reporting on AEs. Details of
two acute trials were not available, but pooled data from one were provided by AstraZeneca.15 The AE rate in the study by Kahn et al. was higher in the active treatment groups than the placebo group, but similar between quetiapine XR and quetiapine IR. Quetiapine XR showed no dose effect to any of the AEs reported except for somnolence. Five AEs were considered serious and related to drug treatment. One death occurred in the quetiapine IR group, but it was not considered to be related to treatment.20

In the switching study by Möller et al., 13 serious AEs were reported and 11 led to discontinuation during the run-in phase, but none of these were regarded as related to treatment. None of the reported AEs occurred at a frequency of 5%, and only two serious AEs (agression and psychotic disorder) were considered to be related to treatment.23 The most common reasons for AEs leading to discontinuation in the study were sedation, dizziness, psychotic disorder and schizophrenia. Three patients had a serious AE that was considered to be related to treatment (EPS, psychosis and exacerbation of psychosis). Two deaths occurred during this study but were not related to study medication.22

The long-term tolerability trial by Peuskens et al. revealed 49.8% of patients reporting 214 treatment-related AEs during the open-label stabilisation phase. No serious AEs were reported in this treatment period. During the randomisation phase, three AEs of the quetiapine XR group were considered to be severe – insomnia, anxiety and hyperhidrosis – and one patient in the placebo group committed suicide; this was not considered to be treatment-related.21

Figure 4: Data on Discontinuation – Quetiapine Immediate-release versus Extended-release

The proposed rapid titration of quetiapine XR formulation led to the specific question of rate of adverse events in the first week of treatment. In the 132 study, quetiapine was well tolerated in the rapid titration phase with a higher incidence of somnolence and dizziness in the active treatment groups. Overall, four patients withdrew due to AEs in the first week, but none withdrew in the three-day dose escalation period. In the switching 147 study, eight patients withdrew due to AEs in the first four days of dose titration. The most common AEs in the switching phase were sedation (12.4%), somnolence (11.3%), dizziness (10.1%) and dry mouth (9.0%).

Extra-pyramidal Motor Symptoms

Patients in the acute study by Kahn et al. showed a reduction or no change in BAS and SAS scores at week six compared with baseline in all treatment groups. Accordingly, the use of anticholinergic medication was low in all arms and even lower in the quetiapine XR groups compared with the two other groups (0.9, 0.9 and 1.7% for quetiapine XR 400, 600 and 800mg, respectively, versus 4.1% for quetiapine IR and 2.5% for placebo).22

The switching 146-trial displayed similar frequencies of AEs related to EPS in both study groups. Changes in SAS scores in the quetiapine XR group showed an improvement in 20.7% and no change in 69.3% of patients. In the quetiapine IR group, results were 21.1% improvement and 76.5% no change. Over 90% of patients had no change in BAS global assessment scores. The use of anticholinergic medication was very low in both treatment groups (0.9% in quetiapine XR versus 0.6% in quetiapine IR).

Similar to the results of the 132-study, the patients switched to quetiapine XR in the 147-study showed reductions in SAS and BAS scores that were statistically significant. Patients switched from conventional antipsychotics or due to EPS experienced the greatest benefit. The use of anticholinergic medication dropped from 20.8% of patients at baseline to 9.1% at week 12. The incidence of EPS in the long-term 004-trial was similar to that seen with placebo during the randomisation phase. The use of anticholinergic medication was low throughout the long-term trial.

Sedation and Dizziness

In the acute study by Kahn et al., somnolence and sedation were the most frequent adverse events, occurring in 7.1, 8.8 and 11.6% of the quetiapine XR 400, 600 and 800mg groups, respectively, and in 7.3% of the quetiapine IR group versus 1.7% of the placebo group. AEs associated with somnolence occurred to a lesser extent in the 146-switching study, but were higher in the 147-switching study and the long-term 004-trial. However, during the randomisation phase of the long-term trial, two patients treated with placebo reported somnolence, but none of the quetiapine XR-treated patients did. The authors concluded that the withdrawal of quetiapine XR resulted in reported somnolence. The rates of all AEs related to somnolence are listed in Table 2.

The clinical advantage of sedation might be fewer patients reporting on insomnia or needing additional medication for sleep-disturbances. Accordingly, in the 132-trial the percentage of patients needing medication for insomnia was higher in the placebo group than in the quetiapine groups.23 The frequency of patients in the placebo group reporting on insomnia was twice as high compared with the active treatment group in the long-term 004-trial. Dizziness occurred most often in the 147-switching trial, and the frequency of dizziness was similar between quetiapine XR and IR in the acute 132- and the switching 146-trial.

Weight Gain

Weight gain is among the most important adverse events of second-generation antipsychotics, and is a common reason for medical non-adherence in schizophrenic patients.11,24 Weight gain associated with quetiapine XR treatment ranged from a small decrease in the quetiapine XR group of the 146-switching study to 1.09 and 1.80kg weight gain in the quetiapine XR treatment groups of the 132-trial. Weight gain in the quetiapine IR formulation groups was slightly higher in the 132-and 146-trials. Patients switching due to weight gain from their previous medication in the 147-switching study
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lost 1.6kg over 12 weeks. Patients randomised to placebo in the long-term 004-trial lost weight, whereas patients remaining on quetiapine XR mildly gained weight (see Table 3).

Prolactin

Prolactin levels dropped in all treatment groups in the acute 132-trial (-24.11ng/ml in the placebo group versus -24.37, -19.83 and -14.18ng/ml in the quetiapine XR 400, 600 and 800mg groups, respectively, versus -24.09ng/ml in the quetiapine IR group). The same result was achieved in the switching 147-trial, with a mean decrease of 529.1mIU/l (24.96ng/ml) prolactin at week 12, and 90.5% of patients with high baseline values shifted to the normal range. Data on prolactin levels during the 146-switching trial were provided by AstraZeneca, showing a mild increase in prolactin levels in both treatment arms.

Hyperglycemia, New-onset Type 2 Diabetes

Changes in glucose levels and the development of type II diabetes in schizophrenic patients are dependent on type of treatment, and constitute a major challenge in the treatment with SGAs. In the 132-trial, glycated haemoglobin (HbA1c) and glucose levels remained unchanged in all treatment groups. Changes in glucose, insulin or HbA1c levels were small and similar in both treatment groups of the switching 146-trial. In the 147-trial, 96.4% of patients had high baseline values shifted to the normal range. Data on prolactin levels during the 146-switching trial were provided by AstraZeneca, showing a mild increase in prolactin levels in both treatment arms.

Haematological and Blood Chemistry Changes

Overall changes in blood chemistry were low in the acute 132-trial and interindividual variation high. Patients treated with the active component showed an increase in cholesterol and triglyceride levels compared with those treated with placebo. The changes were highest in the group receiving quetiapine IR. The triglycerides increased mildly in the switching 147-study over 12 weeks. The 004-trial revealed no patients with clinically meaningful shifts of serum lipoprotein levels. The trial also revealed a total of 11 patients with low neutrophil counts during the stabilisation phase. All neutrophil counts increased to normal following the randomisation phase. No agranulocytosis was reported during the long-term trial. No other study reported on changes in neutrophil counts and none of the trials reported on increase in liver enzymes.

Cardiovascular System

Orthostatic hypotension was reported in one patient in the quetiapine XR 800mg group and two patients in the quetiapine IR 400mg group of the six-week 132-trial. Tachycardia was reported in 1.2% of patients in both groups of the randomisation phase of the switching 146-trial. No syncope occurred in either group and orthostatic hypotension was reported by one patient in both groups. Pulse rates slightly increased during the randomisation phase of the long-term 004-trial in the active treatment group. No AEs were reported on QTc changes, orthostatic hypotension or syncope.

Table 1: Percentage of Patients Presenting Different Adverse Events

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Placebo</th>
<th>Quetiapine XR</th>
<th>Quetiapine IR</th>
<th>Quetiapine XR</th>
<th>Quetiapine IR</th>
<th>All patients</th>
<th>Placebo</th>
<th>Quetiapine XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>6.6</td>
<td>12.7</td>
<td>15.7</td>
<td>1.8</td>
<td>3.6</td>
<td>15.1</td>
<td>3.4</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1.3</td>
<td>12.1</td>
<td>9.2</td>
<td>4.2</td>
<td>1.2</td>
<td>14.0</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3.8</td>
<td>12.1</td>
<td>13.3</td>
<td>3.9</td>
<td>2.4</td>
<td>17.8</td>
<td>19.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.8</td>
<td>9.8</td>
<td>8.9</td>
<td>2.4</td>
<td>3.0</td>
<td>14.0</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14.7</td>
<td>9.7</td>
<td>10.1</td>
<td>0.6</td>
<td>0.6</td>
<td>5.7</td>
<td>4.9</td>
<td>7.4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14.4</td>
<td>7.5</td>
<td>6.8</td>
<td>0</td>
<td>1.2</td>
<td>5.0</td>
<td>0.3</td>
<td>17.5 (10.7)</td>
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</tbody>
</table>

Table 2: Adverse Events Associated with Somnolence MedDRA Terms

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Placebo</th>
<th>Quetiapine XR</th>
<th>Quetiapine IR</th>
<th>Quetiapine XR</th>
<th>Quetiapine IR</th>
<th>All patients</th>
<th>Placebo</th>
<th>Quetiapine XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>10.0</td>
<td>24.7</td>
<td>29.5</td>
<td>25.4</td>
<td>26.3</td>
<td>22.6</td>
<td>1.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4.7</td>
<td>6.4</td>
<td>6.0</td>
<td>1.2</td>
<td>1.8</td>
<td>8.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>5.6</td>
<td>8.5</td>
<td>10.1</td>
<td>0.3</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MedDRA (Medical Dictionary for Regulatory Activities) terms = somnolence, sedation, lethargy and sluggishness or orthostatic disturbances.
Table 3: Weight Change

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Placebo (n=319)</th>
<th>Quetiapine XR (n=951)</th>
<th>Placebo (n=414)</th>
<th>Quetiapine XR (n=331)</th>
<th>Placebo (n=166)</th>
<th>Quetiapine XR (n=168)</th>
<th>All patients (n=477)</th>
<th>Open-label Quetiapine XR (n=327)</th>
<th>Placebo (n=103)</th>
<th>Quetiapine XR (n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change (kg)</td>
<td>0.2</td>
<td>1.3</td>
<td>1.4</td>
<td>-0.2</td>
<td>0.30</td>
<td>1.0</td>
<td>0.89</td>
<td>-0.88</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>% weight gain (%)</td>
<td>5.4</td>
<td>9.9</td>
<td>12.5</td>
<td>1.5</td>
<td>2.4</td>
<td>8.1</td>
<td>1.1</td>
<td>5.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adherence to Medication

The once-daily dosing of quetiapine XR is supposed to result in a higher rate of medical adherence. Unfortunately, not all performed trials recorded data on medical adherence. Based on pool counts, 95% of patients of the switching 147-study took at least 70% of their medication. The same results were achieved in the long-term 004-trial.1

Conclusion

Several trials have been conducted to evaluate the new extended release formulation of quetiapine in clinical practice. The rapid titration regimen used over three days in the studies was well tolerated and did not result in many withdrawals due to AEs. Similarly, the rapid discontinuation of quetiapine XR over four days did not reveal early rebound phenomena or higher incidence of rebound psychosis during the first two weeks after withdrawal, as reported with other antipsychotics.21,31-33

Switching without cross-titration by the next day from quetiapine IR to quetiapine XR did not reveal a greater proportion of reported AEs in patients switched to quetiapine XR. Regarding clinical efficacy, quetiapine XR was shown to be an effective treatment in acute schizophrenic patients22 and superior in preventing relapse compared with placebo in placebo-controlled trials.21 Switching stable patients from quetiapine IR to quetiapine XR is not a disadvantage in terms of maintaining an effective treatment.23 The results of a PET study also revealed comparable D2 receptor occupancy, predicting similar clinical efficacy.16

For all AEs, pattern, type and intensity seem to be similar with quetiapine XR and IR.21,33,35 No unexpected AEs were reported. The incidence of AEs related to EPS was on placebo level. Weight gain and changes in lipid metabolism were mild in magnitude; the most prominent side-effects were sedation, somnolence and dizziness.

In conclusion, quetiapine XR is a well-tolerated and efficacious new treatment option in the psychopharmacological treatment of schizophrenic patients. The once-daily dosing of this new formulation may result in better adherence to treatment. Whether quetiapine XR will be established also in the treatment of bipolar disorder, like quetiapine IR, needs to be investigated in further studies.