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Study 33: Analysing a cross-over study. Statistical work and challenges related to planning, conducting and analysing a clinical trial with cross-over design.

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Abstract

Conducting a trial according to Good Clinical practice requires input from a statistician (ICH, E9 http://www.ich.org/). The statistician plays an important role in the study throw the different stages of the study: Study planning, study conduction, study analysis and study reporting. This report will describe the author's statistical contribution during the conduction of a clinical trial named study 33. This study has been published, see section 7: Appendix 1, but the published paper have a clinical focus and will therefore not fully account of the statistical work in the study. Therefore the report also contains more general and more detailed sections describing relevant statistical aspects. Study 33 was carried out as a double blinded, randomized crossover study in healthy volunteers with the primary objective:"The primary objective for this study will be to compare sedation, one hour after first dose in each period, between qutiapine immediate release formulation (SEROQUEL®) and qutiapine extended release formulation (SEROQUEL XR®) during initial dose escalation."The crossover design, where all patients receive both treatment options, allows a within patient comparison. But it also introduces statistical challenges such as period effect and possible interaction between treatment and period. This report describes how these risks were handled in study 33. Furthermore this report includes the results from study 33 as presented in a publication of study 33 (section 7).

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Contents

1. Introduction

The main purpose of this report is to describe the statistical work that was carried out for study 33 (section 3, 4.2, 5 and 7) Furthermore, the report has the ambition to give a more general introduction to clinical trials and how they are conducted (section 2). Thus, section 2-6 are intended to provide a suitable background to reading the Study 33 article (section 7).

The result from study 33 was presented in a publication, Self-Reported Sedation Profile of Immediate-ReleaseQuetiapine Fumarate Compared With Extended-Release Quetiapine Fumarate During Dose Initiation: A Randomize Double-Blind, Crossover Study in Healthy Adult Subjects a copy is found as section 7. My role in study 33 was to act as the study statistician during the planning, conduction and analysis phases of the study, described in more details in section 2. For the publication, my main responsibility was to provide the analyses of study data and together with the other authors to participate in the interpretations of the results. My role also included to provide advises, comments and performing review of numbers, conclusions and text the publication. To write a publication is a true team effort where the statistician plays a key role.

All information, numbers and conclusions other than found in the publication are my own responsibility. AstraZeneca and Stockholm's University cannot be hold accountable for the content of this report.

2. Clinical trail

2.1 What is a clinical trial?

Clinical trials are a crucial part in all medical drug development. The purpose of a clinical trial is to assess efficacy, safety or mechanisms associated with a new or established drug in humans. All clinical trials are closely regulated by the medical authorities around the world. The main focus is to perform the clinical trial in the most ethical, safe and scientific way possible. This is ensured by conducting the study in line with the guidelines and regulations provided by Good Clinical Practice (GCP). The most commonly used GCP-system is the one defined by International Committee of Harmonisation (ICH, http://www.ich.org/), the ICH committee consists of the regulatory authorities and pharmaceutical industry of Europe, Japan and the US. In order to be compliant with GCP the statistician plays an important role all the way from study planning and designing to analyzing the study and to the final interpretation and conclusion of the results (ICH E9, http://www.ich.org/). This section will describe in short the different steps in a clinical trial from a statistician's perspective.

2.2 Study planning

A clinical study is designed to answer a specific unresolved clinically important question (the main purpose), this is ***the primary objective*** of the study . The primary objective is assessed by measuring and evaluating one or more primary endpoints and is often expressed in terms of reduced mortality or other measures of efficacy, always in comparison with standard care or placebo. To support the primary objective the study often also includes different secondary objectives. Sometimes the clinical endpoints are differences in certain laboratory variables or in caring procedures. Such endpoints are regarded as surrogate endpoints as they might not alter the clinical course even if the changes are theoretically favourable and might explain the results.

There are several designs possible to answer the clinical question. They might be regarded in a hierarchical order with the large multicenter, placebo controlled, randomized, and double blinded study regarded as the most conclusive. Certain questions are not possible to answer with such design. It is not always possible to perform blinding procedures due to obvious differences in preparation, colour, immediate effects etc. Lower levels of evidence originate from less rigorously designed studies like cohort studies and case series. From a statistical point of view, large metadata studies of published data and case reports or register studies might provide a good clinical background for the study planning, but are usually (with very few exceptions for extremely rare indications) not considered as studies providing conclusive evidence for a submission. In addition this is a globally rapidly evolving field of gaining knowledge of actual effects in every day practice and adherence to guidelines. Such studies are called effectivity studies, as opposed to efficacy studies, and provide useful information for already approved drugs. Another good source for post marketing data is data base studies, they are necessary to show overall health effects in the general population and the effect change over time. Thus, the appropriate design chosen must always depend on the clinical question posed and the development state of the drug.

All the study objectives need to be specified and the primary outcome defined prior to the study is started. In addition the analyses planed for the primary outcome should also be pre –specified. Often are pre-specified subgroups included in the design. The randomization, concealment and blinding

procedures must all be thoroughly documented. Exclusion and inclusion criteria must be precisely defined. In this way the design must ensure the integrity of the analyses and minimize the risks of different biases and over interpretation. In order for the study results to be considered valid the preplanning of the design, conduction and end points appropriately of the study needs to be properly documented. Also, all statistical methods to be used to analyze the results should be defined and described in detail in advance. An important part of the statistical planning is the power calculation. The sample size needed to gain the pre specified answers must be thoroughly calculated. The power calculation is based on an assumption of the expected results. This assumption might be derived from previous studies and laboratory results or from meta analyses of literature.

Today, larger clinical trials are often registered in different open official data bases (i e www.clinicaltrails.gov) in order to evaluate publication biases and interrupted studies. Similarly, the design of some large trails is presented as a scientific paper of its own. In this way the conduct and planning of the trail is fully translucent. Also, this approach is a guarantee against scientific fraud. However, for confidentiality reasons this approach is not always possible in commercially sponsored trails. In all phases of this complicated planning process statistical expertise is fundamental.

Also, all clinical trials must have an ethical approval from an official ethical national or regional board before starting. The application for ethical approval must contain all relevant aspects of the trail: the study plan, risks and benefits for the patient and the patient information form. It must clearly be stated that consent to participate in the trail is completely voluntary and that denied consent will not affect care in general. In most cases written informed consent is mandatory.

At AstraZeneca Pharmaceutical Company there are two main documents outlining the design and analyses planed for a study: the Study Design Concept (SDC) and the Clinical Study Protocol (CSP). The SDC is a first high-level overview used in the initial planning phase of the study. The CSP is a more detailed documentation of the study and how it will be performed. Designing a study will start with creating a SDC and the CSP will then be created based on the concept outlined in the CSP. This CSP needs to be approved by the regulating authorities in the countries where the study will be preformed. All study related procedures then need to be strictly conducted according to the protocol. Deviations from the protocol need to be reported and documented in the study report as a protocol violation. Any major changes in the protocol after the finalized will be provided in an amendment. The amendment, outlining the changes, needs to be submitted to the appropriate authorities for approval.

The statistician is closely involved in the work of developing both the SDC and the CSP, especially the sample size estimation and the statistical analysis plan (SAP). The SAP can be either a part of the CSP or a document on its own (depending on the size and complexity of the study) and includes detailed information about how study data will be handled and analysed.

2.2.1 Study conduction

After the planning phase of the study the next phase, study conduction, will follow. Patients or healthy volunteers (from now on referred to as subjects) will be recruited at the centres selected for the study. The selection will be done according to the selection criteria specified in the CSP. The subject will be informed about the study, the investigational product, possible risks and benefits. The

subject must sign an informed consent form before entering the study. No study procedures may be started before the informed consent has been signed. Large clinical studies usually require a large number of sites in order to facilitate the recruitment of the subjects in a timely manner. As the external validity requires multiple centres in different countries as well as a large number of subjects, the logistic challenges are demanding. This makes the coordination complicated and requires dedicated and close monitoring.

The subject will then be started on study treatment including the investigational drug and if applicable placebo or active controls depending on study design (see more about study designs in section1.3.4).

In larger trails there is often an additional safety measure with an independent safety monitoring board, with the task to stop the trail if intermediary analyses or monitoring of adverse events show significant inferiority of study intervention.

The progress of the study in the individual subject will be documented in a specific Case Report Form (CRF). Usually, the CRF includes all relevant background information concerning the subject, demographic information (age, baseline height, baseline weight, sex, race etc), different safety parameters (vital signs, weight, laboratory findings, adverse event information etc) as well as dose information. In studies designed to measure efficacy endpoints it is also the means to capture effect information. The CRF information will be the source data for all the analyses performed within the study framework. After completion of study the information captured in the CRFs will be entered in a database.

2.2.2 Study analysis and interpretation

After completion of the study the analysis and result interpretation will start. Data will be analysed *per protocol* or according to the *intention to treat principle*. The *intention to treat principle* means that the patient always is analysed in the stratum allocated even if he or she interrupted the treatment or received the wrong treatment or in any other way did not fulfil the protocol. *Per protocol* means that only patients fulfilling the protocol in each stratum will be analysed. The *intention to treat principle* will create the most reliable clinical results and is not biased for drop-outs or protocol violations. However in laboratory settings with specific questions the *per protocol* is to prefer. Ideally, these two principles coincide.

The statistician is (according to AstraZeneca procedures) responsible for creating the output as well as contributing to the interpretation of the results. Results from the study will be reported in the clinical study report (CSR) as well as in publications (if applicable). The main findings in the study will be made public this way. Other results will be kept as data on file and is not available publicly. These unpublished results cannot be discussed and scrutinized in the scientific society, but are readily available upon request from authorities and if applicable included in submissions. For study 33 an abbreviated CSR was used since the main goal was to present the results in a publication (see the publication in section 7) other data will be referred to as data on file.

2.3Aim of study 33

2.3.1 What is Seroquel®?

The active substance of Seroquel® is qutiapine, a dibenzothiazepine derivate. It is a classified as an atypical antidepressant and antipsychotic medication. The mechanism of action is inhibition of the dopamine2 -receptor in the central nervous system. . It was first approved for treatment of schizophrenia (United states food and drug administration, FDA www.fda.gov , in 1997) and bipolar disorders (the treatment of acute manic episodes, FDA in 2004, and depressive episodes, FDA in 2006). In addition qutiapine was recently approved for major depressive disorder (FDA, in 2009) as an add-on treatment to first line antidepressants. There are two different approved oral formulations of the drug, Seroquel (immediate release formulation) and Seroquel XR (extended release formulation).

2.3.2 Rational for conducting study 33

The most commonly reported adverse drug reaction for qutiapine includes somnolence and sedation. Besides having dopamin2receptor inhibitory activity, qutiapine has high affinity to the histamine H_1 receptor site. This interaction might explain the sedative effect. The safety and tolerability profile is similar between the two formulations of qutapine, but it has been observed that the commonly reported adverse event of initial sedation varies by formulation. The study hypothesis is that the intensity of sedation follows the plasma concentration time curve for each formulation, immediate release vs extended release. Hypothesizing that earlier and higher peak concentration increases somnolence.

In study 33 healthy volunteers were selected in order to determine if the extended release formulation of qutiapine causes a different sedation pattern then immediate release formulation of qutiapine when given at a starting dose of 50 mg in the morning.

2.3.3 Study objectives

Primary objective for study 33 (as described in the CSP) was:

“The primary objective for this study will be to compare sedation, one hour after first dose in each period, between qutiapine immediate release formulation (SEROQUEL®) and qutiapine extended release formulation (SEROQUEL XR®) during initial dose escalation.”

The secondary objectives for study 33 (as described in the CSP) were:

- To characterize the difference in sedation profile for qutiapine IR and XR over the period of initial dose escalation as measured by the Visual Analog Scale. The sedation profile includes measures such as maximum intensity of somnolence, time to maximum intensity of somnolence, and area under the curve (AUC) over the following time periods after dose: 0 to 4 hours, 8 to 14 hours, 0 to 24 hours, on all dosing days.

- To characterize the pharmacokinetics of qutiapine and one of its metabolites (neuroqutiapine) on Day 5 over an 11 hour interval by measuring C_{max}, t_{max} and AUC_{0-t}.
- To explore the relationship between systematic exposure to qutiapine and one of its metabolites (neuroqutiapine) and measures of sedation

2.3.4 Study design

Study 33 was a phase I, double blind, double-dummy, randomized, 2-period crossover study conducted in one center in the United States (US). The study is conducted in healthy volunteers.

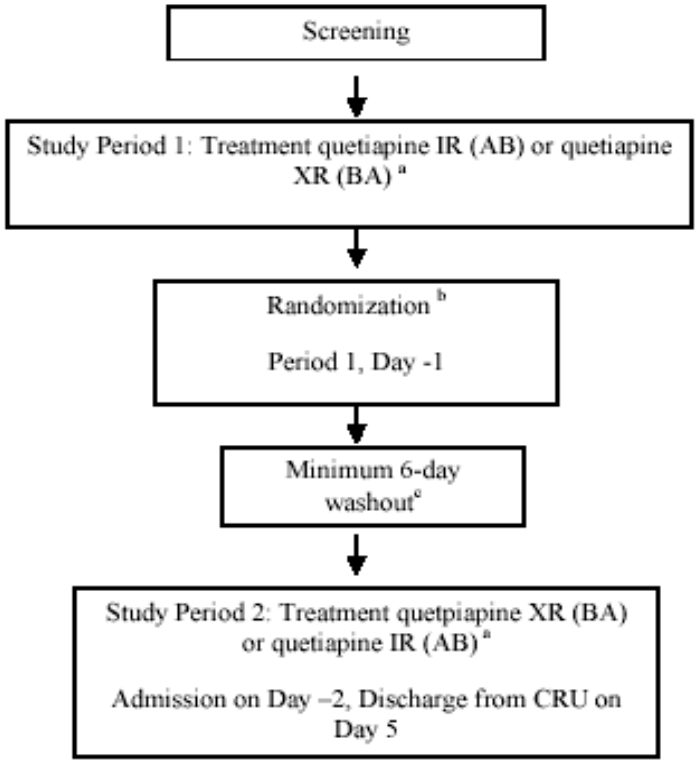
A crossover study is a special form of a controlled double blind randomized trial. In a controlled double blind randomized parallel group trial the subject will be randomized to one of two or more treatment arms. After randomization the patient will receive the randomized treatment in a double blind setting (both the subject and the investigator is blinded, the subjects ID and the treatment will not be linked together until after the end of the study when all results are unblinded in order to be analysed). The crossover design is similar but instead of randomizing the subject to one treatment the subject will be randomized to a treatment sequence. The treatment sequence consists of one or more treatments applied in a fixed sequence of periods.

Study 33 was a two-period crossover were the subjects were either randomized to sequence AB (Seroquel IR followed by Seroquel XR) or sequence BA (Seroquel XR followed by Seroquel IR). In order to keep the blinding the study used double dummy. This means that the patients received two sets of tablets each day one set of active Seroquel tablets (IR or XR) and one set of placebo tablets matching IR or XR. The active tablet and the matching placebo tablet is then switched for the second part of the study. In the end the subject will have received active tablets for both Seroquel IR and XR as well as placebo tablets matching both Seroquel IR and XR.

The major benefit of the crossover design is that it will allow within patient comparison, which is not possible in a conventional parallel group design. In addition a crossover design usually requires a smaller sample size in order to reliably estimate the magnitude of the treatment effect. However there are a number of disadvantages with a crossover design (Clinical trials- A Practical Approach, Stuart J Pocock). One of the major issues with the crossover design is that the patient needs to be part of the study long enough for the switch between treatment periods. Therefore crossover designs are primarily suitable for short term studies. Since somnolence is known primarily to be a short term risk with Seroquel the objective of study 33 was to look at sedation during the initial dose titration. Thus, the short term nature of the study is compatible with the crossover approach. Another issue with crossover trails is the stability of the disease. The disease state might fluctuate over time irrespective of treatment given. Also, it is important that normal within patient variability is small and does not change over time and that the disease symptoms are stable over study periods. This is a prerequisite for within patient comparisons and the cross over design. In our study we measured Seroquels sedative effect in healthy volunteers. Therefore we did not have to account for disease fluctuations. However, there was still a risk of carry over effect from one period to another. This was addressed by including a wash out period of 6 days between the two periods (see figure 1).

Both the period effect (see section 2.3.1) and the interaction between period and treatment (see section 2.3.2) will be analyzed.

Figure 1



a Treatment as follows:

On Days 1 – 5 of period 1, subjects will receive either Treatment AB or Treatment BA . During Period 2, subject will crossover to opposite treatment.

Treatments AB and BA:

- Day -1 – matching placebo dose
- Day 1 – 50 mg XR or 50 mg IR
- Day 2 - 100 mg XR or 100 mg IR
- Day 3 – 200 mg XR or 200 mg IR
- Day 4 – 300 mg XR or 300 mg IR
- Day 5 – 300 mg XR or 300 mg IR

b Randomize to either quetiapine XR or quetiapine IR.

c Minimum 6 day washout is between doses of active treatment (e.g., Period 1, Day 5 to Period 2, Day – 1 must be at least 6 days)

2.3.5 Study 33 publication

The result of study 33 was presented in a publication, see section 7, as well as in a Clinical Study Report (AstraZeneca data on file).

3. Statistical methods and considerations

3.1Sample size calculations

The sample size calculation was performed as described in the CSP, (see below)

The hypothesis to be tested was:

$$H_0 : VAS_{DIFF} = 0$$

versus

$$H_1 : VAS_{DIFF} \neq 0$$

The estimate of the delta and standard deviation (SD) is based on data from 2 healthy volunteer crossover studies (D1448C00008 and D1448C00013) evaluating tolerability of the XR formulation which utilized the Bond-Lader VAS scale for Alert-Drowsy assessment.

Based on the pharmacokinetic profile for IR and XR and on the VAS data in studies D1448C00008 and D1448C00013, the magnitude of difference between IR and XR at 1 hour post the first 50 mg dose is estimated to be 10 mm. This was estimated based on an estimation of peak sedation from the above studies. for quetiapine XR. The maximum observed difference between XR and placebo occurred at the 8 AM assessment (11 hours after dosing) and the expected level of sedation at peak concentration (6 hours after dosing) was estimated. For the quetiapine IR formulation this was multiplied by 2 to account for expected differences due to the know differences in C_{max} for the 2 formulations.

This calculation resulted in an estimated level of sedation at peak for quietiapine IR of approximately 16.6 mm. Since it is expected that the 1-hour VAS assessment for quetiapine IR may not be at peak (average time to peak is 90 minutes) and the 1-hour VAS assessment for quetiapine XR may not be at placebo level, a difference of 10 mm was considered to be a reasonable approximation to the expected difference between the two treatments at 1 hour after dosing. This was used as the delta for calculation of sample size.

The estimate of variability, to be conservative, was taken as the maximum SD from the 11-hour evaluation in the 2 studies, which was 22.2.

Sample size was estimated for a 2-sided t-test at a = 0.05 with 90% Power assuming delta =

10 mm and SD = 22.2 mm. It was assumed that about 10% of subjects would not complete the entire study and thus not included in the primary analysis set (i.e. the PP analysis set), so the sample size was set at 60 to ensure at least 52 fully evaluable subjects. The sample for a 2-sided t-test was calculated using Kraemer, (1987):

$$n = \frac{2(Z_{1-\alpha/2} + Z_{1-\beta})^2\sigma^2}{\delta^2}$$

For the crossover design we only need ½ the sample size since one subject will contribute to both arms. This gives us (Kraemer 1987):

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2\sigma^2}{\delta^2}$$

3.2Statistical methods

3.2.1 Analysis of primary objectives

The statistical analyses preformed on the primary objective (as described in the CSP):
The primary objective is to compare the sedative effect, as measured by the Bond-Lader Visual Analogue Scale (VAS), of IR and XR 1 hour after dose administration at the first dosing day (i.e. Day 1) of each period.

Denote the VAS value on IR by VAS_{IR} and the corresponding value for XR by VAS_{XR}. For each patient the difference between VASXR and VASIR will be calculated (VAS_{XR}-VAS_{IR}=VAS_{DIFF}). The hypothesis that VAS_{DIFF}=0 will be tested by means of the Student's paired t-test and a p-value less than, or equal to, 0.0500 will be regarded statistically significant. As a robustness analysis the hypothesis will be tested by means of the Wilcoxon signed rank test as well.

This analysis approach makes two main assumptions (in addition to the normality assumption for the Student's paired t-test): no period effect and no treatment-period interaction. These assumptions will be tested using the methods presented in Pocock (1983). If the period effect is significant (i.e. the p-value is less than or equal to 0.0500) the test presented above will be adjusted in order to take the period effect into consideration (Pocock, 1983). If the interaction between treatment and period is significant (i.e. the p-value is less than or equal to 0.0500) only the first period will be used.

3.2.2 Statistical analysis of secondary objectives

Secondary objectives will be analysed according to the same principal as for the primary objective described above except for the robustness analyze and the test for period effect and the test of treatment period interaction.

3.3Statistical considerations

As described in section 2.2.1 the relatively straightforward analysis of the primary objective makes two main assumptions, no period effect and no treatment-period interactions. The sections 2.3.1 and 2.3.2 describes how these effects was analysed and handled in study 33.

3.3.1 Period effect

As discussed earlier the crossover design is only feasible in a setting where the condition of interest, in this case the sedation, remains stable during the study. If the condition changes during the study it will affect the results. The level of somnolence or sedation is naturally not stable over hours or days. Therefore it is very important to test for period effect. The treatment effect in study 33 was examined by comparing the mean differences for the two treatment orders and test it with a t-test (under the hypotheses that the difference is equal to 0, no period effect) with $n_{(A-B)}+n_{(B-A)}-1$ degrees of freedom. The test statistic t can be calculated as:

$$t = \frac{VAS_{DIFF(A-B)} - VAS_{DIFF(B-A)}}{\sqrt{\frac{SD_{(A-B)}{}^2}{n_{(A-B)}} + \frac{SD_{(B-A)}{}^2}{n_{(B-A)}}}}$$

Where $VAS_{DIFF(A-B)}$ is the mean difference in VAS score after A – mean difference in VAS score after B. The $SD_{(A-B)}$ is the standard deviation of the difference and $n_{(A-B)}$ is the number of patients in the treatment sequence A followed by B. The same parameters but with a subscript B-A donates the mean difference, standard deviation and numbers of patients for the sequence B followed by A.

If the period effect test is non-significant we use the test statistic (as described in section 2.2.1):

$$t = \frac{VAS_{DIFF}}{\sqrt{\frac{SD^2}{n}}}$$

Where the mean difference (VAS_{DIFF}) and standard deviation of the difference (SD) is calculated based on the difference between Seroquel XR and Seroquel IR regardless of treatment sequence.

If the period effect test is significant there is evidence for a period effect and we need to adjust the results according to Pocock (1983). This gives us the slightly modified test statistic:

$$t = \frac{VAS_{DIFF(A-B)} + VAS_{DIFF(B-A)}}{\sqrt{\frac{SD_{(A-B)}{}^2}{n_{(A-B)}} + \frac{SD_{(B-A)}{}^2}{n_{(B-A)}}}}$$

Note that $VAS_{DIFF}=(VAS_{DIFF(A-B)}- VAS_{(B-A)})/2$ if the number of patients are the same (e.i. the two equations above are equivalent). Caution should still be made when interpreting the results since the presence of a period effect can have a medical meaning that will not be captured in the adjusted test of the primary objective.

3.3.2 Interaction between treatment and period

The study design for study 33 included a 6 day washout between the two treatment periods. The purpose of the washout period was to minimize the risk of a carryover of the drug effect from the drug in period 1 into period 2. Still there might be a carryover effect present or other interactions between period and treatment. Therefore a test of interaction between treatment and period was preformed.

The interaction between treatment and period was examined by comparing the mean within patient with means between the arms. The mean within patient means can be calculated as:

$$VAS_{Patient\ mean\ (A-B),i} = \frac{VAS_{after\ A\ in\ arm\ (A-B),i} + VAS_{after\ B\ (in\ arm\ A-B),i}}{2}$$

Where $VAS_{\text{after A in arm (A-B),}}$ corresponds to the VAS score after treatment A for patient i in arm A-B. This gives the mean over patient means:

$$VAS_{Mean\ (A-B)} = \frac{\sum_{i=1}^{n(A-B)} VAS_{Patient\ mean\ (A-B),i}}{n_{(A-B)}}$$

Comparison between the two treatments arms performed with a two-sample t-test (Pocock (1983)):

$$t = \frac{VAS_{Mean\ (A-B)} - VAS_{Mean\ (A-B)}}{\sqrt{\frac{SD(VAS_{Mean\ (A-B)})^2}{n_{(A-B)}} + \frac{SD(VAS_{Mean\ (B-A)})^2}{n_{(B-A)}}}}$$

If a treatment-period effect is present it is hard to interpret such an interaction but one common reason is the carry-over effect. If a significant interaction is found Pocock (1983) recommend to abandon the planed within patient analyse and instead analyse the between patient comparison using the first period only. This is the same approach as described for this study in section 2.2.1.

It is also important to note in the interpretation of the results that the test for treatment-period effect described above has low sensitivity. Especially for small crossover trials one may fail to detect an interaction even if present.

4. Results

The main results from study 33 are described in the published paper *Self-Reported Sedation Profile of Immediate-Release Quetiapine Fumarate Compared With Extended-Release Quetiapine Fumarate During Dose Initiation: A Randomized, Double-Blind, Crossover Study in Healthy Adult Subjects* (Clinical Therapeutics Volume 31, Number 3, March 2009), see section 7 for the full article.

Results not included in the publication are not yet public (AstraZeneca data on file) and therefore not included here.

4.1 Summary of main efficacy results

Sixty-three subjects was enrolled and received at least one dose of study medication and fifty-eight subjects was eligible for the per-protocol population that was used in the efficacy analyze. The difference in VAS one hour after first dose on day 1, a significant greater intensity of sedation with quetiapine IR then with quetiapine XR (mean VAS score, 33.2 vs 11.3, respectively; P<0.001). The difference was also significant at 1.5, and 2 hours after dosing (P<0.001) and at 3 hours after dosing (P<0.01); on day 2 at 1 hour after dosing (P<0.01), at 1.5 and 2 hour after dosing (P<0.001) and at 3, 4, and 5 hours after dosing (P<0.001) ; on day 3 at 0.5 an 1 hour after dosing (P<0.05), at 1.5, 2, 3, and 4 hours after dosing (P<0.001), and at 5 and 6 hours after dosing (P<0.05); on day 4 at 1 hour after dosing (P<0.01), at 1.5, 2, 3, and 4 hours after dosing (P<0.001), and at 5 hours after dosing (P<0.01); and on day 5 at 1.5, 2, and 3 hours after dosing (P<0.001), and at 4 hours after dosing (P<0.05). **Figures and more details can be found in section 7.**

4.2 Statistical considerations

The test of period effect and of interaction between treatment and period was conducted according to the analysis described in section 2.3.1 and 2.3.2. The result of the analysis was not statistically significant (AstraZeneca, data on file) on the pre-specified significance level of 0.05. It is still important to note, for the interpretation of the results, that the test for interaction between treatment and period has a low sensitivity and one may fail to detect an interaction even if present.

The robustness analysis (for more details see section 2.2.1) of the primary hypothesis confirmed the results of the primary analyze (AstraZeneca, data on file).

No correction for multiplicity was done.

5. Discussion and conclusions

5.1 Study design

All study designs have their specific advantages and disadvantages. The choice of design is highly dependent on the scientific question to be answered. The crossover design was chosen for study 33 primarily to address the between subject variability in sedation. Due to studying healthy volunteers and thus controlling for the setting and the specific design of the study (including a washout period to minimize carry-over effect) the risk of period effect and carry-over effect could be minimized (see section 3.2 for more details). However conducting the study in healthy volunteers induces inevitable bias in the translation of the study results to patients for which qutiapine IR and XR are approved. The possibility of a difference in sedation profile and tolerability between healthy volunteers and a patient population cannot be neglected and further studies are needed to assess the clinical validity of the results in the present study.

Furthermore the study was only designed to investigate sedative effects (as measured by the VAS scale) and not quality of sleep, ability to perform tasks, impact on disease state or other related consequences of sedation that might have significance in the clinical setting. This limits the direct clinical application of the study. Larger studies with patients are needed to evaluate the clinical impact of qutiapine induced sedation. In such studies additional measures of sedation and its consequences can be included.

To conclude, the design of study 33 was appropriate given the scope of the study. To further characterize the sedation profiles of qutiapine IR and XR in the clinical setting, additional studies are needed.

5.2 Study results

Study 33 was designed to compare sedation profiles between qutiapine IR and qutiapine XR during initial dose escalation in healthy subjects. The results of the study showed a statistically significant difference in sedation (VAS score) 1 hour after first dose on day one and subsequent separation between the sedation profiles (based on VAS scores) as described in the publication (section 7) and in section 3.1.

5.3 Concluding remarks

No statistical correction for multiple calculations was performed for secondary endpoints or additional time points (not covered by the primary analysis). Bonferroni or other corrections might be used for this purpose. Therefore caution should be taken when interpreting the results. Significant p-values might be due to chance as multiple different variables and time points are analysed independently. However, the result seems to be consistent between different study days and over other types of measurements (i.e. number of patients at sleep and VAS categorical shifters). These consistent clinical observations support the interpretation of the results.

In order to gain more knowledge concerning the sedative profile of quitiapine IR and qutiapine XR a larger clinical study in patients was needed. Subsequently, a clinical study along these intentions has

been performed. This study was designed as a controlled two armed double blinded study to compare sedation during the initial dose titration between Seroquel IR and Seroquel XR in bipolar depression patients (http://clinicaltrials.gov/ct2/show/record/NCT00926393).

6. List of references

Clinical trials.gov homepage, study NCT00926393
http://clinicaltrials.gov/ct2/show/record/NCT00926393

FDA homepage www.fda.gov

International Committee of Harmonisation (ICH) homepage http://www.ich.org/

Kraemer, H.C. and Theimann, S. (1987). How many subjects? Statistical power analysis in research. Newbury Park, CA: Sage

Stuart J. Pocock (1984). Clinical Trials- a practical approach. John Wiley & Sons Ltd.

Self-Reported Sedation Profile of Immediate-Release Quetiapine Fumarate Compared With Extended-Release Quetiapine Fumarate During Dose Initiation: A Randomized, Double-Blind, Crossover Study in Healthy Adult Subjects

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ABSTRACT

Objectives: The primary study objective was to assess the time course and intensity of sedation after administration of immediate-release (IR) and extended-release (XR) quetiapine fumarate in healthy subjects during dose initiation. The tolerability of the 2 formulations was also evaluated.

Methods: This was a randomized, double-blind, double-dummy, 2-period crossover study in healthy adult (age 18–50 years) subjects. It employed the dose-initiation schedule used in studies of the 2 quetiapine formulations in patients with bipolar depression: 50 mg on day 1, 100 mg on day 2, 200 mg on day 3, and 300 mg on days 4 and 5. Doses were administered in the morning. The primary end point was the level of sedation 1 hour after dosing on day 1, as rated by subjects using a visual analog scale (VAS) ranging from 0 = alert to 100 = drowsy. Secondary VAS end points included sedation over a 14-hour period on day 1, and on days 2 through 5. Blood was drawn on day 5 of both periods for determination of plasma drug concentrations by a liquid chromatography method with tandem mass-spectrometric detection. Adverse events (AEs) were recorded throughout the study.

Results: Sixty-three subjects were enrolled in the study, comprising the safety population. The per-protocol population consisted of 58 subjects (79.0% male, 21.0% female; 67.2% black, 24.1% white; mean age, 31.8 years; mean weight, 80.7 kg). One hour after dosing on day 1, sedation was significantly greater with quetiapine IR than with quetiapine XR (mean VAS score, 33.2 vs 11.3, respectively; $P < 0.001$). There were no significant differences in sedation between formulations at 7 hours after dosing (64.5 and 53.6), 8 hours after dosing (46.9 and 50.8), or 14 hours after dosing (both, 12.7). On day 1, numerically more subjects had a VAS score >75 (substantial sedation) 1 hour after dosing in the quetiapine IR group than in the quetiapine XR group (14 vs 4 subjects). On day 5, the mean (95% CI) quetiapine C_{max} for the IR and XR formulations was 689.19 (605.83–784.02) and 381.70 (341.40–426.76) ng/mL; the mean AUC_{0-11} was 2835.89 (2517.92–3194.02) and 2515.21 (2281.76–2772.55) ng · h/mL; and the median T_{max} was 2.0 and 5.0 hours. The incidence of any AEs was 21.7% with quetiapine IR and 9.8% with quetiapine XR.

Conclusion: In these healthy subjects, quetiapine XR was associated with a lower intensity of self-reported sedation compared with quetiapine IR. ClinicalTrials.gov Identifier: NCT00702676; Astra Zenecaclinicaltrials.com Identifier: D1443C00033. (*Clin Ther.* 2009;31:492–502) © 2009 Excerpta Medica Inc.

Key words: bipolar depression, atypical antipsychotic, extended release, quetiapine, sedation.

INTRODUCTION

Bipolar disorder is a highly prevalent, chronic, recurrent, and disabling condition.[1] Although there are several well-established pharmacotherapies for the treatment of bipolar mania,[2,3] there is little evidence to support the efficacy of agents for the treatment of bipolar depression.[3,4] Current options include combination olanzapine–fluoxetine, lithium, valproate, lamotrigine, quetiapine, and the combination of an anti-

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depressant (eg, selective serotonin reuptake inhibitor, serotonin–norepinephrine reuptake inhibitor) and a mood stabilizer.[5]

Quetiapine fumarate is the only approved monotherapy for bipolar depression and the only atypical antipsychotic approved as monotherapy for the treatment of both poles of this disorder. Both the immediate-release (IR) and extended-release (XR) formulations of quetiapine are approved for the treatment of schizophrenia, bipolar mania, and bipolar depression in the United States and several European countries. In the United States, quetiapine IR and quetiapine XR are approved as adjunctive treatment to lithium or divalproex for the maintenance treatment of bipolar I disorder.[6,7] Evidence from 5 published studies supports the efficacy of the 2 quetiapine formulations in bipolar depression.[8–13]

Whereas the IR formulation provides rapid drug release, quetiapine XR is formulated to provide gradual release of quetiapine. At equivalent total daily doses, quetiapine IR given twice daily and quetiapine XR given once daily have similar AUC_{0-24} and $t_{1/2}$ values. However, the T_{max} is longer with quetiapine XR dosed once daily than with quetiapine IR dosed twice daily (~6.0 vs ~1.5 hours, respectively); this, along with gradual drug release over the day, produces a smoother pharmacokinetic profile with quetiapine XR, allowing attainment of more stable plasma concentrations than with quetiapine IR.[14]

Examination of tolerability data from the quetiapine XR clinical trial program,[13,15–18] including adverse events (AEs) and longitudinal laboratory data, and indirect comparison with the quetiapine IR database (N = 25,359) suggests that the overall tolerability profile of quetiapine XR, including events related to sedation, is consistent with that of quetiapine IR for each indication studied. The occurrence of AEs related to sedation during clinical trials is a relatively crude measure of the sedation that may occur during treatment, particularly during dose initiation. The first scheduled postbaseline visit in clinical studies often occurs at week 1, and any information regarding AEs is likely to be less detailed than if it had been recorded daily. Also, there are methodologic difficulties associated with formal comparisons of patients treated during separate clinical trial programs (eg, possible bias due to timing and geographic location), which may be considered "nonrandomized" cohorts. In countries where quetiapine XR is currently licensed, observations from clinical practice suggest that there may be some tolerability differences between quetiapine IR and quetiapine XR, particularly with respect to the onset and characteristics of sedation. These differences may be important, as registration studies do not generally capture tolerability variables on a daily basis, and evidence of a drug's tolerability is based largely on AE reporting. It is also possible that there may be meaningful differences between the XR formulations of some drugs compared with the corresponding IR formulation in terms of tolerability; for example, less nausea and dizziness were reported with venlafaxine XR than with venlafaxine IR.[19]

This study (AstraZeneca clinical trial number D1443C00033) examined the time course and intensity of self-reported sedation with quetiapine IR and quetiapine XR during dose initiation in healthy adult subjects, using the approved dose-initiation schedule for patients with a depressive episode associated with bipolar disorder.[6,7] The hypothesis was that the time course and intensity of sedation would correspond to the pharmacokinetic profiles of the 2 formulations. The tolerability of quetiapine IR and quetiapine XR was also evaluated.

SUBJECTS AND METHODS

Subjects

The study included healthy men and women aged 18 to 50 years. Other key inclusion criteria were weight ≥50 kg and normal findings (or deviations from normal that were not considered clinically significant by the investigator) on a complete physical examination that included vital signs, clinical laboratory tests, and an electrocardiogram. Subjects were excluded if they had (or had a history of) neurologic, hematologic, psychiatric, gastrointestinal, hepatic, pulmonary, cardiovascular, or renal disease, or another condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs. Other exclusions were a history of significant alcohol, drug, or substance abuse within the past year; use of prescription medication for an acute or chronic medical condition within 4 weeks of the first day of period 1 (day 1); and receipt of an investigational drug within 4 weeks of day 1. Pregnant or lactating women were also excluded. Use of drugs that induce or inhibit the cytochrome P450 3A4 isozyme was not permitted within 4 weeks of day 1, and use of over-the-counter medications (with the exception of acetaminophen) was not permitted within 7 days of day 1.

Study Design and Treatment

This randomized, double-blind, double-dummy, 2-period crossover study was conducted at a single center in the United States. The dose-initiation schedules were those approved for quetiapine IR and quetiapine XR in bipolar depression.[6,7] A computerized scheme was used to randomize subjects to treatment sequence AB or BA. Subjects initiated treatment with either quetiapine IR or quetiapine XR, given as a single dose in the morning (with ~240 mL of water), in the following order: 50 mg on day 1, 100 mg on day 2, 200 mg on day 3, and 300 mg on days 4 and 5. Medication was given in the morning to enable accurate assessment of the intensity and time course of sedation. Each treatment period lasted 7 days and 6 nights. After a washout period of at least 6 days, subjects were switched to the alternative formulation and repeated the treatment sequence. A matching placebo was used to maintain blinding. Compliance was assessed by supervised administration of study medication, including inspection of the oral cavity and hands. In each period, subjects were admitted to the study center on day −2 and discharged on day 5. A light breakfast was served ~1 hour before dosing on all study days.

Written informed consent was obtained from all subjects. The study was performed in accordance with the ethical principles of the Declaration of Helsinki[20] and the Good Clinical Practice guidelines,[21] applicable regulatory requirements, and the AstraZeneca policy on bioethics and human biological samples. Local institutional review board approval was obtained.

Study End Points and Assessments

Sedation

To evaluate the primary end point—the intensity of sedation with the 2 quetiapine formulations 1 hour after administration on the first day of dosing (day 1)—subjects rated their level of alertness using a 100-mm visual analog scale (VAS), with responses ranging from 0 = alert to 100 = drowsy. Such self-reported rating scales of sedation may be used in clinical practice, as well as in clinical trials.[22] Secondary VAS end points included sedation over a 14-hour period on day 1, and on days 2 through 5. The 14-hour time point was chosen as reasonable for a "late evening" assessment and was expected to provide information pertinent to levels of sedation that might occur in the morning in actual use.

Subjects were given standardized verbal instructions for completing the VAS. Each day from day −1 through day 4 of both study periods, they were to complete the VAS before dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 11, and 14 hours after dosing. On day 5, subjects completed the VAS before dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 11 hours after dosing. Mean VAS scores were calculated at each time point on each day. If a subject was asleep at the time of a scheduled assessment, the VAS score was recorded as 100. To facilitate comparisons and add clinical relevance, VAS scores were categorized as >75 (substantial sedation), 50–75 (marked sedation), 25–49 (moderate sedation), and <25 (alert).

Pharmacokinetics of Quetiapine and Norquetiapine

The pharmacokinetics of quetiapine and norquetiapine, the major active metabolite of quetiapine in humans, were characterized over an 11-hour period on day 5 (although steady state would not have been achieved).

Blood was drawn by individual venipuncture or through an indwelling catheter for determination of plasma concentrations before dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 11 hours after dosing on day 5 of each study period. Venous blood samples (2 mL) were collected into K_2EDTA spray-coated tubes; for samples obtained from a catheter, the first 1 mL of blood was discarded, and the catheter was flushed with 2 mL of normal saline after sampling to keep it patent. Blood samples were placed on ice and centrifuged (10 minutes at 1500*g*) within 30 minutes of collection; the resulting plasma was frozen at or below −70°C within 15 minutes of plasma preparation and kept frozen until transported to the laboratory.

Plasma drug concentrations of quetiapine were determined by Bioanalytical Systems, Inc. (West Lafayette, Indiana), using fully validated bioanalytic methods. In brief, quetiapine was extracted from human plasma by liquid/liquid extraction at alkaline pH with methyltert-butyl ether using isotope-labeled internal standards for each analyte; the organic layer was collected and evaporated to dryness, and the residue was reconstituted with an ammonium formate buffer. The samples were injected into a liquid chromatography system with tandem mass-spectrometric detection (LC-MS/MS) multiplexed with 2 Luna C18 columns (Phenomenex, Inc., Torrance, California) using ammonium formate/methanol mobile phases.

The C_{max}, T_{max}, and AUC_{0-11} were determined for quetiapine. Plasma concentrations of norquetiapine were also determined using liquid extraction and LC-MS/MS methodology, and the same pharmacokinetic parameters were determined as for quetiapine.

Adverse Events

AEs, whether spontaneously reported by subjects, elicited by open questioning, or observed by study personnel, were assessed and recorded throughout the study. Because sedation was assessed using the VAS, it was not recorded as an AE.

A full physical examination was conducted at screening and at the end of the study. At screening and on days −2, −1, and 5 of both study periods, blood pressure and heart rate were recorded (preferably before administration of any scheduled dose) after the subject had been seated for at least 5 minutes. Clinical chemistry tests (nonfasting creatinine, bilirubin, glucose, and thyroid function) and hematology tests (hemoglobin, platelet count, and complete blood count) were performed at screening and at day −2 of the first study period and day 5 of the second study period.

Statistical Analysis

Based on the pharmacokinetic profiles of quetiapine IR and quetiapine XR and VAS data from previous unpublished studies in healthy subjects, the magnitude of difference between quetiapine IR and quetiapine XR at 1 hour after dosing on day 1 was estimated to be 10 mm. The sample size was estimated for a 2-sided *t* test at $\alpha = 0.05$ with 90% power, assuming $\delta = 10$ mm and SD = 22.2 mm. It was assumed that ~10% of subjects would not complete the entire study, so the sample size was set at 60 to ensure at least 52 fully evaluable subjects.

The primary analytic set, which was used for all analyses, was the per-protocol (PP) population, which consisted of all subjects who completed both periods and thus provided information for both formulations of quetiapine. Results of the 2 study periods were pooled, allowing direct intrasubject comparison of the tolerability of quetiapine IR and quetiapine XR.

The paired *t* test was used to analyze the primary and secondary objectives related to sedation. A *P* value ≤0.05 was considered statistically significant.[23] The Wilcoxon signed rank test was also used as a measure of the robustness of the primary objective. No correction was made for multiplicity.

Pharmacokinetic parameters were derived by noncompartmental methods using WinNonlin Enterprise edition version 4.1 (Pharsight Corporation, Mountain View, California) and summarized using descriptive statistics. C_{max} and AUC_{0-t} were summarized using geometric means (95% CIs). T_{max} was recorded as a median (range). AUC_{0-t} was calculated using the linear trapezoidal rule. For the comparison of the quetiapine IR and XR formulations, geometric mean ratios (90% CIs) for C_{max} and AUC_{0-t} were determined (with the IR formulation as the reference) using a mixed-effect model, with treatment sequence, treatment period, and treatment as fixed effects and subject nested in sequence as a random effect. Log-transformed AUC_{0-11} and C_{max} were analyzed using an analysis-of-variance model; least squares means (95% CI) were calculated for each treatment group, and the geometric mean ratios (90% CIs) were calculated for the difference between treatment groups. The least squares means and corresponding CIs were antilog-transferred back to the original scale to obtain the geometric means and CIs for each treatment group and the geometric mean ratios and 90% CIs for the difference between treatment groups. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

AEs were analyzed in the safety population (those who received at least 1 dose of study medication) using descriptive statistics.

RESULTS

Sixty-three subjects were enrolled and received at least 1 dose of medication (safety population). Four subjects decided to discontinue the study, and 1 discontinued for personal reasons. Thus, the PP population consisted of 58 subjects (79.0% male, 21.0% female; 67.2% black, 24.1% white; mean age, 31.8 years; mean weight, 80.7 kg).

Sedation

On day −1, when no active drug was given, mean VAS scores for sedation over 14 hours ranged from 0.9 to 25.2. One hour after dosing on day 1, VAS scores indicated a significantly greater intensity of sedation with quetiapine IR than with quetiapine XR (mean VAS score, 33.2 vs 11.3, respectively; $P < 0.001$) (**Figure 1**). The difference in mean VAS scores between treatments was significant on day 1 at 1, 1.5, and 2 hours after dosing ($P < 0.001$) and at 3 hours after

dosing ($P < 0.01$); on day 2 at 1 hour after dosing ($P < 0.01$), at 1.5 and 2 hours after dosing ($P < 0.001$), and at 3, 4, and 5 hours after dosing ($P < 0.05$); on day 3 at 0.5 and 1 hour after dosing ($P < 0.05$), at 1.5, 2, 3, and 4 hours after dosing ($P < 0.001$), and at 5 and 6 hours after dosing ($P < 0.05$); on day 4 at 1 hour after dosing ($P < 0.01$), at 1.5, 2, 3, and 4 hours after dosing ($P < 0.001$), and at 5 hours after dosing ($P < 0.01$); and on day 5 at 1.5, 2, and 3 hours after dosing ($P < 0.001$) and at 4 hours after dosing ($P < 0.05$) (**Figure 2**).

The mean reported intensity of sedation was numerically greater with quetiapine IR than with quetiapine XR over 7 hours after dosing on day 1 (mean VAS scores at 7 hours, 64.5 and 53.6, respectively); the intensity of sedation on day 1 did not differ significantly between formulations at 8 (46.9 and 50.8), 11 (15.8 and 12.8), and 14 (both, 12.7) hours after dosing (**Figure 2**). A similar pattern was seen on each subsequent day.

On day 1, the highest mean VAS score was 73.0 with quetiapine IR (observed 3 hours after dosing) and 53.9 with quetiapine XR (observed 3 and 6 hours after dosing). On day 5, the highest VAS scores were a respective 56.6 (3 hours after dosing) and 37.8 (6 hours after dosing). Consistent with these results, the mean area under the VAS score–time curve for each day suggested more overall sedation with quetiapine IR than with quetiapine XR, with significant differences between formulations on days 1 ($P = 0.004$), 3 ($P < 0.001$), 4 ($P = 0.029$), and 5 ($P = 0.001$) (**Table I**).

No relationship was found between the level of sedation and the dose during dose initiation with either quetiapine formulation, as indicated by similar area under the VAS score–time curve values on days 1 to 4 (50- to 300-mg doses).

On day 1, numerically more subjects had a VAS score >75 (substantial sedation) 1 hour after dosing in the quetiapine IR group than in the quetiapine XR group (14 vs 4 subjects, respectively) (**Table II**). Of the 52 subjects who had a VAS score <25 (alert) 1 hour after dosing with quetiapine XR on day 1, 15 (28.8%) had a VAS score ≥50 (marked sedation) 1 hour after dosing with quetiapine IR on day 1. Of the 36 subjects who had a VAS score <25 at 1 hour after dosing with quetiapine IR on day 1, 2 (5.6%) had a VAS score ≥50 at 1 hour after dosing with quetiapine XR on day 1.

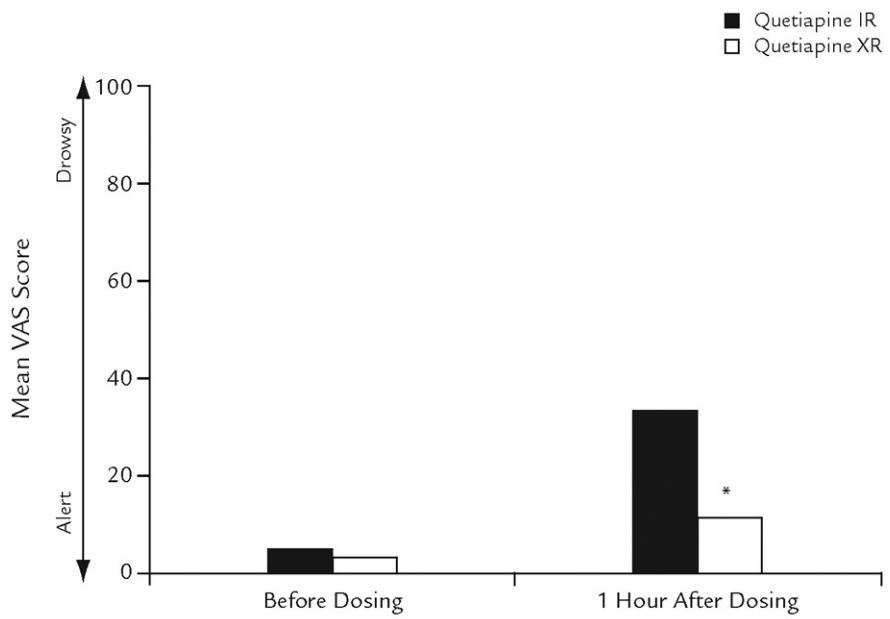

Figure 1. Visual analog scale (VAS) scores for quetiapine immediate release (IR) and quetiapine extended release (XR) before dosing and 1 hour after dosing on the first day of active medication in 58 healthy subjects (per-protocol population). *$P < 0.001$ versus quetiapine IR, paired t test.

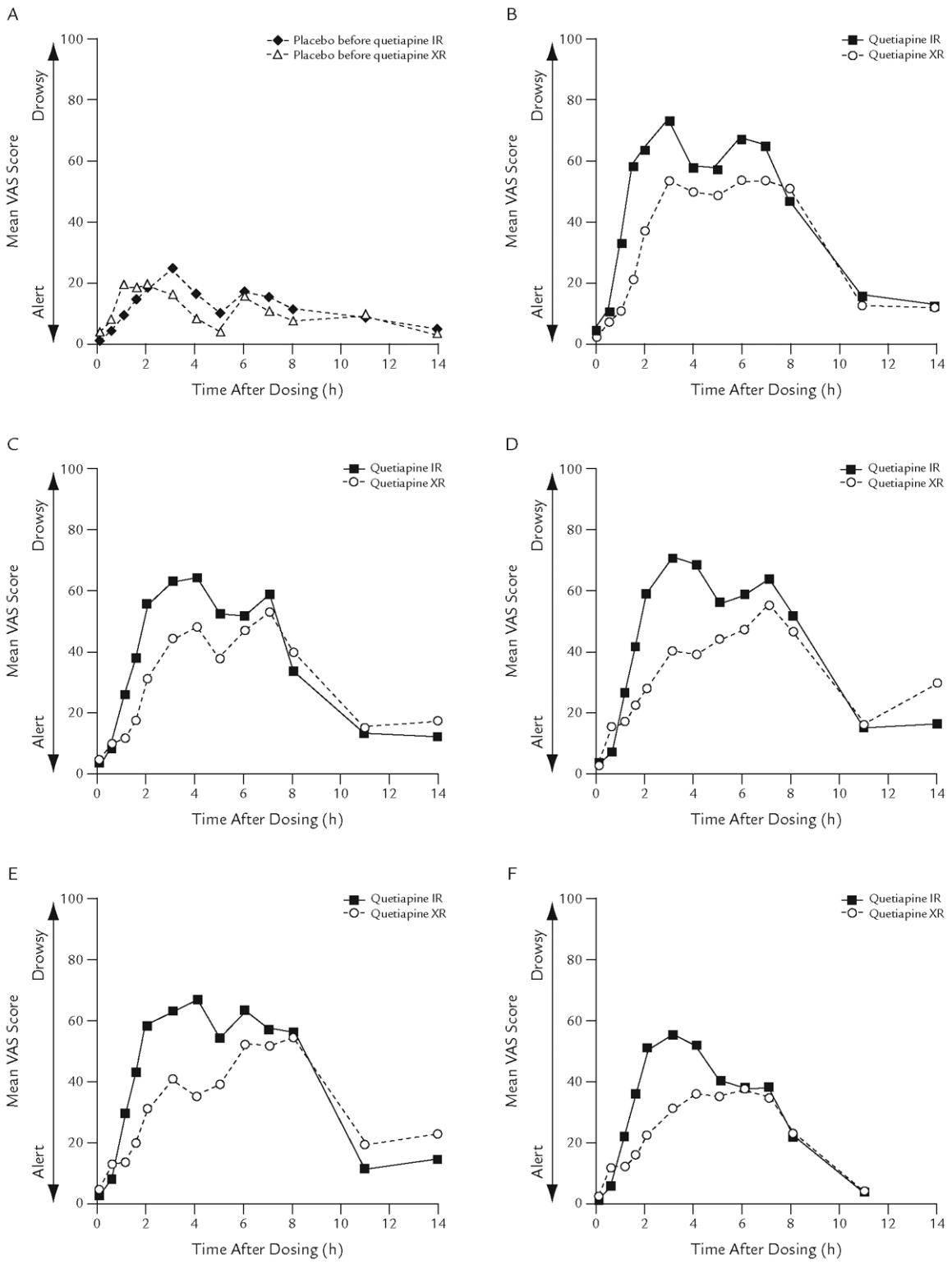

Figure 2. Visual analog scale (VAS) scores for quetiapine immediate release (IR) and quetiapine extended release (XR) on (A) day –1, (B) day 1, (C) day 2, (D) day 3, (E) day 4, and (F) day 5 of dose initiation in 58 healthy subjects (per-protocol population).

Table I. Mean area under the visual analog scale score–time curve from 0 to 14 hours, by day, in 58 healthy subjects (per-protocol population).

Day (Dose)	Quetiapine IR	Quetiapine XR	*P*
Day –1 (no active drug)	168.0	133.0	–
Day 1 (50 mg)	579.3	467.1	0.004
Day 2 (100 mg)	480.7	414.9	0.067
Day 3 (200 mg)	572.6	445.9	<0.001
Day 4 (300 mg)	565.9	470.0	0.029
Day 5 (300 mg)*	348.8	268.3	0.001

IR = immediate release; XR = extended release.
*Based on the period from 0 to 11 hours.

Pharmacokinetics

The plasma concentration–time curves on day 5 indicated that concentrations of quetiapine were numerically higher in the first 4 hours after dosing with the IR formulation than with the XR formulation (**Figure 3**). As expected, higher plasma concentrations of quetiapine were reached and the T_{max} was shorter after dosing with the IR formulation than after dosing with the XR formulation, as supported by the geometric mean values for C_{max} (689.19 ng/mL [95% CI, 605.83–784.02] and 381.70 ng/mL [95% CI, 341.40–426.76], respectively) and the median T_{max} (2.0 hours [95% CI, 0.5–5.0] and 5.0 hours [95% CI, 1.5–11.0]) on day 5 (**Table III**). For C_{max}, the geometric mean ratio of quetiapine XR to IR was 0.55 (90% CI, 0.49–0.62). The geometric mean AUC_{0-11} for quetiapine IR and quetiapine XR was 2835.89 ng · h/mL (95% CI, 2517.92–3194.02) and 2515.21 ng · h/mL (95% CI, 2281.76–2772.55). The geometric mean ratio of quetiapine XR to IR was 0.89 (90% CI, 0.82–0.96).

The pharmacokinetic variables for norquetiapine after doses of quetiapine XR and quetiapine IR followed a similar pattern to those for the parent compound (**Table III**).

The pattern of sedation for the 2 quetiapine formulations appeared to follow the respective plasma concentration–time curves measured on day 5.

Adverse Events

No serious AEs, deaths, or AEs leading to discontinuation occurred during the study. The most common AEs (occurring at an incidence of ≥5% with either formulation) are summarized in **Table IV**. The incidence of any AEs was numerically greater in the quetiapine IR group than in the quetiapine XR group (21.7% vs 9.8%, respectively). The most commonly reported AEs for quetiapine IR were dry mouth and dizziness (11.7% each), followed by headache and nausea (8.3% each). The most commonly reported AEs for quetiapine XR were dry mouth and nausea (6.6% each).

Table II. Ratings of sedation 1 hour after dosing on day 1, showing the correspondence between the number of subjects in each visual analog scale (VAS) score category when they received quetiapine immediate release (IR) and quetiapine extended release (XR) (N = 58; per-protocol population).*

VAS Score Category When Subjects Received Quetiapine IR	VAS Score Category When Subjects Received Quetiapine XR			
	<25	25–49	50–75	>75
<25	33	1	0	2
25–49	4	0	0	0
50–75	4	0	0	0
>75	11	0	1	2

*Subjects rated their level of sedation using a 100-mm VAS, with responses ranging from 0 = alert to 100 = drowsy. VAS scores were categorized as >75 (substantial sedation), 50–75 (marked sedation), 25–49 (moderate sedation), and <25 (alert).

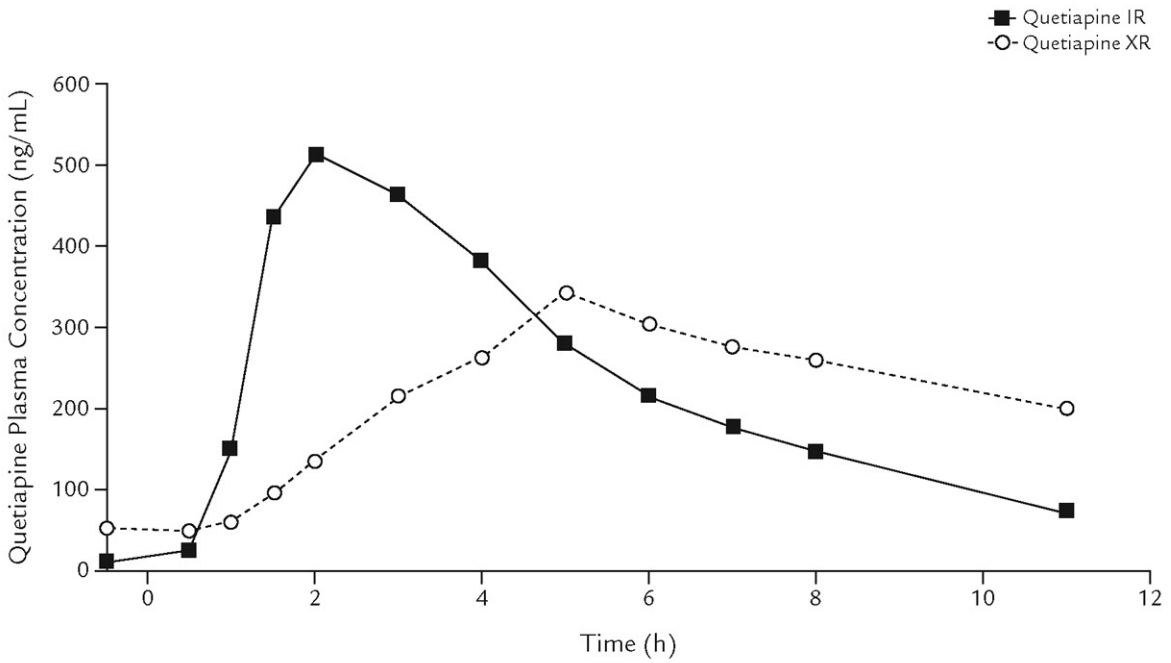

Figure 3. Plasma concentration–time curves for quetiapine on day 5 after administration of the quetiapine immediate-release (IR) and quetiapine extended-release (XR) formulations (day 1, 50 mg; day 2, 100 mg; day 3, 200 mg; days 4 and 5, 300 mg) in healthy subjects (per-protocol population).

Table III. Pharmacokinetic parameters of quetiapine and norquetiapine on day 5 after administration of the quetiapine immediate-release (IR) and quetiapine extended-release (XR) formulations in 58 healthy subjects (per-protocol population).

Analyte/Parameter	Quetiapine IR, Geometric Mean (95% CI)	Quetiapine XR, Geometric Mean (95% CI)	Geometric Mean Ratio, XR/IR (90% CI)*
Quetiapine			
C_{max}, ng/mL	689.19 (605.83–784.02)	381.70 (341.40–426.76)	0.55 (0.49–0.62)
AUC_{0-11}, ng · h/mL	2835.89 (2517.92–3194.02)	2515.21 (2281.76–2772.55)	0.89 (0.82–0.96)
T_{max}, h†	2.0 (0.5–5.0)	5.0 (1.5–11.0)	–
Norquetiapine			
C_{max}, ng/mL	153.47 (137.94–170.74)	107.69 (99.65–116.38)	0.70 (0.66–0.75)
AUC_{0-11}, ng · h/mL	1074.42 (985.29–1171.62)	880.22 (820.27–944.55)	0.82 (0.78–0.86)
T_{max}, h†	3.0 (1.0–8.0)	6.0 (3.0–11.0)	–

*For comparison of quetiapine XR and IR, geometric mean ratios of C_{max} and AUC_{0-t} and 90% CIs were determined (with IR as the reference) using a mixed-effect model with treatment sequence, treatment period, and treatment as fixed effects, and subject nested in sequence as a random effect.

† Median (range).

DISCUSSION

Results for the primary study objective—VAS scores for sedation 1 hour after dosing on the morning of day 1—indicated that the initial intensity of sedation was significantly greater with quetiapine IR than with quetiapine XR ($P < 0.001$). Quetiapine IR and quetiapine XR appeared to have different sedation profiles during dose initiation, with the XR formulation associated with a lower intensity of sedation. In these healthy subjects, the level of sedation with quetiapine XR was numerically lower than with quetiapine IR during the first 7 hours after dosing on each day of active treatment, but became similar in the 2 groups by 8 to 14 hours after dosing. In addition, maximum levels of sedation appeared to occur later with quetiapine XR than with quetiapine IR. Although evening dosing was not directly assessed in this study, clinicians should follow the prescribing information for quetiapine XR with regard to evening dosing to minimize potential sedation.[6]

The low level of sedation with both quetiapine formulations between 8 and 14 hours after dosing corresponds to the approximate time patients would awaken after taking an evening dose. Throughout day –1, when subjects were not receiving medication, mean VAS scores were low (range, 0.9–25.2). VAS scores were higher after dosing on day 1: the maximum score for quetiapine IR was higher than that for quetiapine XR (73.0 vs 53.9, respectively). However, maximum VAS scores had decreased by day 5 (56.6 and 37.8). The greatest differences in the level of sedation between the 2 formulations generally occurred between 1 and 4 hours after dosing. Over the entire dose-initiation period (days 1–5), sedation was lower with quetiapine XR than with quetiapine IR, as indicated by the area under the VAS score–time curve, with significant differences between formulations on days 1 ($P = 0.004$), 3 ($P < 0.001$), 4 ($P = 0.029$), and 5 ($P = 0.001$). The area under the VAS score–time curve also indicated that the level of sedation was decreased with both formulations on day 5. The amount of sedation had no relationship with the dose during dose initiation with either formulation, as indicated by the similar area under the VAS score–time curve values on days 1 to 4 (50- to 300-mg doses). The pattern of sedation appeared to follow the plasma concentration–time curves for the 2 formulations, as measured on day 5. Overall, the differences in sedation profiles may be attributable to differences in the pharmacokinetic profiles of quetiapine after administration of the 2 formulations.[14] In fact, based on the plasma concentration–time curves and pharmacokinetic variables for quetiapine after administration of the IR and XR formulations on day 5 (300-mg dose), quetiapine plasma concentrations appeared to be higher and the T_{max} shorter for the IR formulation relative to the XR formulation. The AUC_{0-11} values for quetiapine after dosing with the IR and XR formulations were similar, and, although it was not possible to characterize the AUC over an entire dosing interval (the full time course—up to 48 hours—was not evaluated for the 300-mg dose), the similarity in AUC_{0-11} values suggests that the 2 formulations may produce comparable exposure. The pharmacokinetics of the major active human metabolite of quetiapine, norquetiapine, showed a similar pattern to that of the parent compound.

The data presented here provide valuable information for prescribers regarding the timing of dosing of quetiapine XR and quetiapine IR. Evening dosing is recommended for quetiapine XR,[6] whereas bedtime dosing is recommended for quetiapine IR.[7] In the healthy subjects in the present study, the onset of sedation was later with quetiapine XR than with quetiapine IR. Therefore, to help manage potential evening

Table IV. Most commonly reported (≥5% with either formulation) adverse events (AEs) (safety population). Data are number (%) of subjects.*

Variable	Quetiapine IR (n = 60)	Quetiapine XR (n = 61)
Any AE	13 (21.7)	6 (9.8)
Specific AEs		
Dry mouth	7 (11.7)	4 (6.6)
Dizziness	7 (11.7)	1 (1.6)
Headache	5 (8.3)	2 (3.3)
Nausea	5 (8.3)	4 (6.6)
Abnormal dreams	3 (5.0)	1 (1.6)
Nasal congestion	3 (5.0)	1 (1.6)
Dysarthria	3 (5.0)	0

IR = immediate release; XR = extended release.
*Subjects with multiple events were counted only once.

or next-day sedation, administration of quetiapine XR in the evening—for example, a few hours before bedtime—may be beneficial.

This study in healthy subjects was conducted to examine the sedation profiles of the 2 quetiapine formulations over 14 hours after dosing using the same dose-initiation schedule as in studies of quetiapine IR and quetiapine XR in bipolar depression.[8,9,11–13] The intention was to provide data to supplement any indirect comparisons of AE data from such studies. This small but focused study allowed more in-depth investigation of the sedation profiles of the 2 formulations of quetiapine than can be derived from AE reporting in registration studies.

Examination of the data from published studies in patients with bipolar depression suggests similarities in the overall incidence and type of AEs observed at equivalent doses of quetiapine IR[8,9,11,12] and quetiapine XR.[13] In a randomized, double-blind, placebo-controlled study in patients with schizophrenia, the median time to the onset of sedation with quetiapine IR and quetiapine XR was <3 days.[18] In addition, a retrospective analysis of the quetiapine IR safety database found that the onset of sedation typically occurred within the first week of treatment and that sedation was generally mild in intensity.[24]

Somnolence and sedation are AEs associated with the atypical antipsychotics.[25] It has been suggested that the receptor-binding profiles of the atypical agents, including blockade of histamine H_1 receptors, may be responsible for this sedation.[25,26] Along with other aspects of patient management, a favorable tolerability profile, particularly early in the course of treatment, may improve patients' adherence to medication. Approximately half of patients prescribed antipsychotic medication for bipolar disorder are partially adherent or completely nonadherent to medication,[27] and patients cite AEs as one of the reasons for their reluctance to comply with treatment.[28] Adherence to medication is essential for reducing symptoms and improving outcomes.

This study was specifically designed to evaluate the time course and intensity of sedation associated with the 2 quetiapine formulations over 5 days; the use of a crossover design, with sufficient washout (≥6 days) between phases, ensured that the data for the 2 formulations could be compared. Other strengths of the study included its randomized, double-blind, double-dummy design and the measurement of sedation using a self-rated VAS, making the findings applicable to the real-world setting. However, the inclusion/exclusion criteria preclude extrapolation of the study findings beyond the healthy subjects studied. Other potential study limitations include daytime administration of medication and the lack of a placebo arm. Furthermore, the study design required the performance of pharmacokinetic assessments during dose initiation (day 5); therefore, the results did not reflect steady-state exposure and bioequivalence could not be determined. Finally, because sedation was not assessed as an AE and subjects who were asleep were unable to provide VAS ratings, AEs may have been underestimated.

CONCLUSIONS

In this small study in healthy subjects, a difference was observed in the sedation profiles of quetiapine XR and quetiapine IR when administered according to the dose-initiation schedule for the treatment of patients with bipolar depression. Sedation was lower with quetiapine XR than with quetiapine IR in the first few hours after dosing. By 8 to 14 hours after dosing, sedation levels were similarly low with the 2 formulations.

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REFERENCES

1. Huxley N, Baldessarini RJ. Disability and its treatment in bipolar disorder patients. *Bipolar Disord.* 2007;9:183–196.
2. Gajwani P, Kemp DE, Muzina DJ, et al. Acute treatment of mania: An update on new medications. *Curr Psychiatry Rep*. 2006;8:504–509.
3. Keck PE Jr, McElroy SL. New approaches in managing bipolar depression. *J Clin Psychiatry.* 2003;64(Suppl 1):13–18.
4. Kemp DE, Muzina DJ, McIntyre RS, Calabrese JR. Bipolar depression: Trial-based insights to guide patient care. *Dialogues Clin Neurosci*. 2008;10:181–192.
5. Yatham LN, Kennedy SH, O'Donovan C, et al, for the Guidelines Group, CANMAT. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: Update 2007. *Bipolar Disord*. 2006;8:721–739.
6. Seroquel XR (quetiapine fumarate) extended-release tablets [US prescribing information]. http://www.astrazeneca-us.com/pi/seroquelxr.pdf. Accessed January 26, 2009.

7. Seroquel (quetiapine fumarate) [US prescribing information]. http://www1.astrazeneca-us.com/pi/seroquel.pdf. Accessed January 26, 2009.
8. Calabrese JR, Keck PE, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162:1351–1360.
9. Thase ME, Macfadden W, Weisler RH, et al, for the BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: A double-blind, placebo-controlled study (the BOLDER II study) [published correction appears in *J Clin Psychopharmacol*. 2007;27:51]. *J Clin Psychopharmacol*. 2006;26:600–609.
10. Weisler RH, Calabrese JR, Thase ME, et al. Efficacy of quetiapine monotherapy for the treatment of depressive episodes in bipolar I disorder: A post hoc analysis of combined results from 2 double-blind, randomized, placebo-controlled studies. *J Clin Psychiatry*. 2008;69:769–782.
11. McElroy S, Young AH, Carlsson A, et al. A double-blind, placebo-controlled study with acute and continuation phase of quetiapine and paroxetine in adults with bipolar depression (EMBOLDEN II). *Bipolar Disord*. 2008;10(Suppl 1):59. Abstract.
12. Young AH, McElroy S, Chang W, et al. A double-blind, placebo-controlled study with acute and continuation phase of quetiapine and lithium in adults with bipolar depression (EMBOLDEN I). *Int J Neuropsychopharmacol*. 2008;11:187. Abstract.
13. Suppes T, Datto C, Minkwitz M, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. Poster presented at: 48th Annual New Clinical Drug Evaluation Meeting; May 27–30, 2008; Phoenix, Ariz.
14. Figueroa C, Brecher M, Hamer-Maansson JE, Winter H. Pharmacokinetic profiles of extended release quetiapine fumarate compared with quetiapine immediate release. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33:199–204.
15. Ganesan S, Agambaram V, Randeree F, et al. Switching from other antipsychotics to once-daily extended release quetiapine fumarate in patients with schizophrenia. *Curr Med Res Opin*. 2008;24:21–32.
16. Möller JH, Johnson S, Mateva T, et al. Evaluation of the feasibility of switching from immediate release quetiapine to extended release quetiapine fumarate in stable outpatients with schizophrenia. *Int Clin Psychopharmacol*. 2008;23:95–105.
17. Peuskens J, Trivedi JK, Malyarov S, et al. Prevention of schizophrenia relapse with extended release quetiapine fumarate dosed once daily: A randomized placebo-controlled trial in clinically stable patients. *Psychiatry*. 2007;4:34–50.
18. Kahn RS, Schulz SC, Palazov VD, et al, for the Study 132 Investigators. Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: A randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68:832–842.
19. Entsuah R, Chitra R. A benefit-risk analysis of once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. *Psychopharmacol Bull*. 1997;33:671–676.
20. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/e/policy/b3.htm. Accessed January 28, 2009.
21. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) adopts Consolidated Guideline on Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. *Int Dig Health Legis*. 1997;48:231–234.
22. Bond A, Lader M. The use of analogue scales in rating subjective feelings. *Br J Med Psychol*. 1974;47:211–218.
23. Pocock SJ. *Clinical Trials: A Practical Approach*. Chichester, UK: John Wiley & Sons Ltd; 1983.
24. Goldstein J. Tolerance to somnolence with quetiapine: A review of the evidence. *World J Biol Psych*. 2005;6(Suppl 1):280. PO-021.
25. Miller DD. Atypical antipsychotics: Sleep, sedation, and efficacy. *Prim Care Companion J Clin Psychiatry*. 2004;6(Suppl 2):3–7.
26. Kane JM, Sharif ZA. Atypical antipsychotics: Sedation versus efficacy. *J Clin Psychiatry*. 2008;69(Suppl 1):18–31.
27. Sajatovic M, Valenstein M, Blow FC, et al. Treatment adherence with antipsychotic medications in bipolar disorder. *Bipolar Disord*. 2006;8:232–241.
28. Fleck DE, Keck PE Jr, Corey KB, Strakowski SM. Factors associated with medication adherence in African American and white patients with bipolar disorder. *J Clin Psychiatry*. 2005;66:646–652.

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