PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Differential use of extended and immediate release quetiapine: A retrospective registry study of Finnish inpatients with schizophrenia spectrum and bipolar disorders
AUTHORS	Taru Hallinen, Erkki J. Soini, Yrjö Ovaskainen, Esa Leinonen, Hannu J. Koponen and Kari Hänninen

VERSION 1 - REVIEW

REVIEWER	Erik Johnsen, M.D., PhD Senior Consultant Haukeland University Hospital Assoc. Professor University of Bergen. I declare to have received honoraria for lectures given in meetings arranged by Bristol-Myers Squibb, Eli Lilly, and AstraZeneca, and for a contribution to an information brochure by Eli Lilly. I have been reimbursed by the Eli Lilly Company and the Janssen Cilag Company for attending conferences.
REVIEW RETURNED	25/02/2012

GENERAL COMMENTS	In my opinion this is a clearly written paper on a topic that should be of broad interest to clinicians The main limitation which I think should be further discussed in the manuscript, is the fact that the data are obtained in one local hospital in which only 4 psychiatrists have been responsible for the drug choices made. The authors correctly state that the results might not be inferrable to other contries, or to out-patient settings. Indeed the evidence shows that there are marked differences between different regions even in the same country (see for instance Bitter et al. Pharmacopsychiatry 2003;36:143-149 and Kroken et al. BMC Psychiatry 2009;9:24). The generalizability from this single-site sample from a rather small hospital does accordingly, in my opinion, come with limitations also in a national perspective. Another issues concerns the interpretations of the dosing. Higher rates of concomitant use of antipsychotics were found for the IR group together with lower mean doses and the authors interpret these findings to reflect that the XR formulation is used as the main antipsychotic drug and that the IR formulation is used as an add-on to treat other symptom domains. This interpretation is in my opinion sound. There might also, however, be other explanations related to dosing the I would challenge the authors to elaborate some further on. For instance, the optimal dosing of quetiapin is in my opinion not fully established. Interestingly, the dose-response study by Arvanitis (Arvanitis et al. Biol Psychiatry 1997;42:233-46) found the doses of 150 mg and 300 mg to be the most efficacious, indicating an inverse

	U shape of the dose-response curve.

REVIEWER	Leila Ben Amor MD MSc Associate Professor Dept Psychiatry Laval University (Quebec, Canada)
REVIEW RETURNED	25/04/2012

THE STUDY	This is an interesting retrospective naturalistic study comparing quetapine IR vs quetiaine XR use in schizophrenia and bipolar disorder, during hospitalisation. The paper is well written and data are clearly presented. However there are some points that need to be addressed in order to have better interpretation of the results: 1-There is no indication if these patients are drug naïve or not, at leat for Antipsychotics (data are given only for prior use of quetiapine). 2- During the period of the study, it is interesting to mention which proportion of patients with schizophrenia or bipolar disorder was on quetiapine among all those on antipsychotics. 3- The severity of symptoms (the GAF is not enough to describe the severity of the disorder) and the subtype of disorder (negative vs. positive, bipolar I or II, etc..) had to be described and also to see if there is a different use of quetiapine form in function of these clinical data. 4- There is no indication on the duration of treatments 5- In North America, quetiapine IR is significantly cheaper than quetiapine XR, so indications should take in account efficacy of treatment but also the economic impact. It is important to add information in this point when comparing these two forms of quetiapine.

VERSION 1 – AUTHOR RESPONSE

Our responses to the comments by the editor and the reviewers are given below.

Question: Can you confirm that this is a 'naturalistic study'? The Methods describe the study as a retrospective register study, which may be a more appropriate term for use, e.g. in the title. In the key messages and the introduction what is meant by a 'naturalistic inpatient setting'? Does this just mean 'routine'? What makes this inpatient setting 'naturalistic' rather than anything non-naturalistic? Can you assess whether this is the correct term at every point it is used?

Response: We have used the term “naturalistic” in the meaning that the drug has been used in the real-life setting as opposed to clinical trial setting and because of this “routine” would be equally appropriate. We have changed the term “naturalistic” in the title to “retrospective registry”. We also changed the term in the manuscript text.

Comment:In my opinion this is a clearly written paper on a topic that should be of broad interest to clinicians The main limitation which I think should be further discussed in the manuscript, is the fact that the data are obtained in one local hospital in which only 4 psychiatrists have been responsible for the drug choices made. The authors correctly state that the results might not be inferrable to other contries, or to out-patient settings. Indeed the evidence shows that there are marked differences between different regions even in the same country (see for instance Bitter et al. Pharmacopsychiatry 2003;36:143-149 and Kroken et al. BMC Psychiatry 2009;9:24). The generalizability from this single-

site sample from a rather small hospital does accordingly, in my opinion, come with limitations also in a national perspective.

Response: We fully agree that the generalizability of our results is the biggest limitation of our study. We have now further emphasized this in the discussion section and article summary. We have also used the references that were kindly given by the reviewer. However, one recent study (Eriksson et al. 2011) in 14 Swedish inpatient clinics and 178 schizophrenia patients suggests that our differential use results may actually be generalizable to other settings. That study documents differential use of quetiapine IR and XR in clinical practice with respect to e.g. mean doses and add-on medication. We have added this reference to the discussion section and we present its main results.

Comment: Another issues concerns the interpretations of the dosing. Higher rates of concomitant use of antipsychotics were found for the IR group together with lower mean doses and the authors interpret these findings to reflect that the XR formulation is used as the main antipsychotic drug and that the IR formulation is used as an add-on to treat other symptom domains. This interpretation is in my opinion sound. There might also, however, be other explanations related to dosing the I would challenge the authors to elaborate some further on. For instance, the optimal dosing of quetiapin is in my opinion not fully established. Interestingly, the dose-response study by Arvanitis (Arvanitis et al. Biol Psychiatry 1997;42:233-46) found the doses of 150 mg and 300 mg to be the most efficacious, indicating an inverse U shape of the dose-response curve.

Response: We acknowledge that our interpretation of the result that quetiapine XR is used in higher mean doses and with less add-on antipsychotic medication than quetiapine IR is one interpretation, and that there could be alternative interpretations.

The reviewer points out that he considers our interpretation to be sound. We agree with him and also consider this to be a more plausible explanation than the “U-shaped dose-response curve” for quetiapine. The study by Arvanitis et al. (1997) was a small scale study comparing different quetiapine doses to placebo and haloperidol. It did not compare the inter-dosage efficacy of quetiapine. Almost half of the patients did not complete the 6 week trial reflecting the difficulties in treating patients with schizophrenia and keeping them to a given drug regimen. In our opinion, it is not possible to conclude based on Arvanitis et al. (1997) that the dose-response relationship would be U-shaped for quetiapine. Smaller improvements in the BPRS, CGI and SANS could be caused, for example, by differing times to treatment discontinuation in the studied dose groups. The analyses in Arvanitis et al. (1997) were based on the last observation carried forward (LOCF) technique. As pointed out by Molnar et al. (2009), LOCF analysis relies on the assumption that the subjects’ responses would have remained constant after the last observed value and that the missing values are missing at random (and are therefore not caused by e.g. drug side effects, group assignment, disease severity or symptoms). Molnar et al. (2009) also state that “study results may also be biased against the drug under study (i.e., underestimating effectiveness) if there are earlier dropouts or greater dropout rates in the control group or if there are subjects whose disease progresses more rapidly among those who drop out of the control group”. In the study by Arvanitis et al. (1997) more patients dropped out of the groups using lower doses of quetiapine due to inefficacy (42-51% for doses 75-300mg and 31-35% for doses 600-750mg).

Another pivotal study for quetiapine IR, in acute schizophrenia, found high dose quetiapine (up to 750 mg/day) to be superior to low dose quetiapine (up to 250 mg/day) and placebo (Small et al. 1997). Significant differences were identified between patients receiving high-dose quetiapine and placebo for both primary efficacy variables, with endpoint differences in the BPRS positive-symptom cluster score. Furthermore, 58% of patients in the high-dose group completed the 6 week study, compared to 43% in the low-dose group and 41% in the placebo group (Small et al. 1997). Later quetiapine studies in schizophrenia seem to confirm these findings. For example, Zhong et al. (2006) compare

quetiapine IR to risperidone in a randomized 8-week trial with flexible doses. The mean dose of quetiapine achieved was 574 mg/day for responders and was 626 mg/day for completers. Zhong et al. (2006) state that this is in line with other studies suggesting that the optimal therapeutic dose of quetiapine for the treatment of schizophrenia is about 600 mg/day. Furthermore, Kahn et al. (2007) showed a numerical difference in efficacy of 600 to 800 mg quetiapine XR over and above that of 400 mg quetiapine XR or 400 mg quetiapine IR (however, neither this trial was designed to show differences among doses). The trial by Kahn et al. (2007) had a high completion rate, approximately 75%, compared to approximately 50% in the trial by Arvanitis et al. (1997).

The antipsychotic effect of quetiapine is believed to be mediated through a combination of dopamine type 2 (D2) and serotonin type 2A (5HT2A) antagonism (McIntyre et al. 2007). By modeling time-related neuro-receptor occupancy based on available pharmacokinetic data and in-vitro receptor binding data for Seroquel XR and quetiapine IR, Nyberg (2010) shows differences in the receptor binding properties when comparing various doses of Seroquel XR with the same doses for quetiapine IR. Nyberg (2010) states that: “The receptor occupancy at different doses may help to explain why Seroquel XR 150–300 mg/day has demonstrated antidepressant efficacy, while higher doses (i.e. >400 mg/day) of quetiapine are required for antipsychotic and antimanic efficacy”.

Clinical and expert guidelines also recommend quetiapine doses above 400 mg for psychosis (Gardner et al. 2010). Stahl (2006) points out that a quetiapine dose of 400-800 mg should be reached to optimize the success when treating acute psychosis or mania. Expert consensus guidelines on the acute treatment of patients with schizophrenia indicate 500-800 mg for multiple-episode patients (Kane et al. 2003).

Because we feel that addressing this issue in full would require a substantially expanded “Discussion” section, we have not included the explanation above to the manuscript text. We have, however, revised the “Discussion” section to acknowledge that our interpretation of the differential dosing and add-on medication results is one interpretation of these results. Moreover, we have expanded a sentence so that it now also states that doses above 400 mg of quetiapine are likely to be required for maximal antipsychotic efficacy and we have added another clinical guidelines reference.

References:

Eriksson L et al. 2011, Use of quetiapine XR and quetiapine IR in clinical practice for hospitalized schizophrenic patients – a retrospective study, Poster presented at ICNPTG, November 24-27, Thessaloniki, Greece.

Gardner DM, Murphy AL, O’Donnell H, et al. International consensus study of antipsychotic dosing. Am J Psychiatry 2010;167:686-93.

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Kane JM., Leucht S, Carpenter D et al. 2003, Expert consensus guideline series. Optimizing pharmacological treatment of psychotic disorders: medication selection, dosing and dose equivalence. J Clin Psychiatry 2003; 64 (suppl 12): 21-51.

Molnar FJ, Man-Son-Hing M, Hutton B, Fergusson DA. Have last-observation-carried-forward analyses caused us to favour more toxic dementia therapies over less toxic alternatives? A systematic review. Open Medicine 2009;3(2).

Nyberg S. 2010, Predictive modeling - impact of varying doses and different formulations on receptor occupancy profile for quetiapine. 23rd ECNP Congress 28 August 2010 - 01 September 2010 Eur Neuropsychopharmacology Vol 20, Suppl 3, Page S264.

Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG 1997, Seroquel Study Group, Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. Arch Gen Psychiatry. 1997 Jun;54(6):549-57.

Stahl S.M. 2006, Essential Psychopharmacology: The Prescriber's Guide, Cambridge University Press, New York.

Zhong K, Sweitzer D, Hamer R., Lieberman J. 2006, Comparison of quetiapine and risperidone in the treatment of schizophrenia: a randomized, double-blind flexible-dose, 8-week study, J Clin Psychiatry 2006; 67: 1093-1103.

Comment: This is an interesting retrospective naturalistic study comparing quetapine IR vs quetiaine XR use in schizophrenia and bipolar disorder, during hospitalisation.The paper is well written and data are clearly presented. However there are some points that need to be addressed in order to have better interpretation of the results:There is no indication if these patients are drug naïve or not, at leat for Antipsychotics (data are given only for prior use of quetiapine).

Response: Unfortunately we do not know whether the patients in our study were antipsychotic naïve or not as we did not collect this data. However, we do know if they had been prescribed any antipsychotic (also other than quetiapine) at the time of hospital admission. We have now added this information in table 1. There were no statistically significant differences in the use of any antipsychotic at the time of admission.

Comment: During the period of the study, it is interesting to mention which proportion of patients with schizophrenia or bipolar disorder was on quetiapine among all those on antipsychotics.

Response: We are thankful for this suggestion. We have now added this information in the "Results" section: "Of all patients with SCZ and BD (n=399), 39.1% were treated with quetiapine".

Comment: The severity of symptoms (the GAF is not enough to describe the severity of the disorder) and the subtype of disorder (negative vs. positive, bipolar I or II, etc..) had to be described and also to see if there is a different use of quetiapine form in function of these clinical data.

Response: We acknowledge that the GAF is not sufficient to describe the severity of the disorder. Because our study was retrospective in nature, we had to base our assessment on information that is always recorded in the patient files, such as GAF. In our discussion section we point out that we did not have information regarding the exact symptom(s) of the patient that was targeted with quetiapine IR or XR. Although it would have been interesting to see whether there are differences in the doses of quetiapine IR and XR within the subtypes of schizophrenia and bipolar disorder, our data did not enable such comparisons as the number of patients within each subtype would have been very small (e.g. in our comparison for bipolar disorder there were only 15 patients in the XR group and 14 in the IR group). In our logistic regression analyses we aimed to control for potential differences by adjusting for the use of other drugs among the patient cohort. We have now emphasized this as a limitation of our study in the "Discussion" section.

Comment: There is no indication on the duration of treatments

Response: Thank you for pointing this out. We have now added the duration of drug treatment to

table 1. There were no significant differences.

Comment: In North America, quetiapine IR is significantly cheaper than quetiapine XR, so indications should take in account efficacy of treatment but also the economic impact. It is important to add information in this point when comparing these two forms of quetiapine.

Response: We thank the reviewer for this remark and agree that this is a topic worth discussing. Also in Finland quetiapine IR is cheaper than quetiapine XR due to generic competition; in Finnish pharmacies the price of e.g. quetiapine IR 200 mg is at around 25% of the price of Seroquel Prolong (quetiapine XR) 200mg. In the studied inpatient setting the cost difference is smaller compared to the outpatient setting, but the exact prices are not known due to hospital tender of drugs. We have now commented on this issue in the “Discussion” section. Our interpretation is that, since the price of quetiapine XR is higher than for IR, there are no economic incentives for the hospitals to use quetiapine XR and therefore the use is likely to be based on a clinical assessment only.

Although not included in the manuscript text, we would also like to point out that, from the patient perspective, the cost per inpatient day in Finland is equal regardless of the drugs that are being used during the inpatient stay. In Finland the drug choice during the inpatient stay is also not likely to be motivated by the patients’ ability to afford the drug after discharge. In the Finnish social insurance system, 100% societal reimbursement is granted for the treatment of severe mental illnesses (including ICR 10 codes F20-F25, F28, F29, F30.1, F30.2, F31, F32.3) and therefore the patient copayment is always 3 euros/drug, both for quetiapine IR and XR.