High- v. low-dose quetiapine in schizophrenia: meta-analysis

Nitesh Painuly¹

Aims and method  To study the difference between high- and low-dose quetiapine in acute treatment of schizophrenia. Data available from published double-blind fixed-dose trials were combined and analysed.

Results  There was no statistically significant difference between high- (750–800 mg/day) and low-dose (300–400 mg/day) quetiapine in terms of the response rate, change in positive symptoms score and the discontinuation rates either as a result of lack of response or adverse effects.

Clinical implications  Combined evidence from fixed-dose trials does not support the prevalent practice of targeting the higher dose of quetiapine for optimal treatment response in schizophrenia.

Declaration of interest  None.

There is uncertainty around the optimal dose of quetiapine in the treatment of schizophrenia. Clinicians in practice prescribe quetiapine at substantially higher dose than that established in clinical trials.¹ In a recent comprehensive review,² the authors concluded that the balance of evidence does not support the belief that higher dosages are required

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for a full therapeutic response. The present meta-analysis is an attempt to answer this dilemma through combining data available from fixed-dose double-blind controlled studies, which are taken as the most robust evidence in such a dose–response relationship scenario. The aim was to look for any definitive and categorical significant differences in efficacy and effectiveness between low- and high-dose quetiapine in the acute treatment of schizophrenia.

**Method**

In August 2007, the following databases were searched: PubMed, EMBASE, PsycINFO, AMED (Allied and Complementary Medicine), CINHAL and SSCI (Social SciSearch), with the search terms ‘quetiapine AND schizophrenia’. For this meta-analysis, only fixed-dose, double-blind, randomised controlled trials in the acute treatment of schizophrenia were included. Cross-references of identified articles were checked manually and AstraZeneca in the UK was contacted to access any missing data. The search identified a total of seven fixed-dose published trials. Single fixed-dose trials and the studies with clearly subtherapeutic dosage of quetiapine (50 mg/day) were excluded from the analysis. A pilot study (n = 21) that included participants with schizoaffective disorder was also excluded. This ultimately led to the inclusion of only two studies. Quality analysis of the included studies was carried out as per the protocol of the Centre for Reviews and Dissemination (CRD). Individual and pooled effects of studies were expressed in the form of odds ratio and standardised mean difference with 95% confidence intervals. A fixed or random effect model was chosen according to the level of heterogeneity within the studies, for which the chi-squared method was used.

**Results**

Tables 1 and 2 show the descriptive and pooled results.

**Publication bias**

As only two studies were included, funnel chart statistics were not feasible.

**Heterogeneity of studies**

No significant heterogeneities were found between the studies with regard to the response rate, discontinuation as a result of lack of response or as a result of adverse effects, but heterogeneity existed for positive symptoms scores (P < 0.05).

**Pooled results**

There was no statistically significant difference between high- and low-dose quetiapine in terms of the response rate and the discontinuation due to lack of response or due to adverse effects. An alternate analysis was done for the response rate after excluding those individuals who had dropped out from the total number of participants. Again, the odds ratio in favour of high-dose quetiapine was not statistically significant (OR = 1.40, 95% CI 0.80–2.44). There was no statistically significant difference between high- and low-dose quetiapine in terms of the response rate and the discontinuation due to lack of response or due to adverse effects. An alternate analysis was done for the response rate after excluding those individuals who had dropped out from the total number of participants. Again, the odds ratio in favour of high-dose quetiapine was not statistically significant (OR = 1.40, 95% CI 0.80–2.44).
low-dose quetiapine for improvement in positive symptoms score (Fig. 1).

**Discussion**

Findings of this meta-analysis are in line with those of Sparshatt et al.\(^2\) and Buckley.\(^{11}\) Buckley\(^{11}\) undertook a combined analysis of three randomised, placebo-controlled trials and divided participants into two groups – those receiving quetiapine < 400 mg/day and those receiving > 400 mg/day. Although differences in the Brief Psychiatric Rating Scale positive symptom cluster scores was numerically greater in the higher dosage group it was not statistically significant. The possibility of this difference becoming significant is raised if the study by Kahn et al.\(^9\) (which shows a statistically significant relationship between increasing dosage and therapeutic effect) is included.\(^2\) Present meta-analysis shows that this is not the case as standardised mean difference on positive symptoms score is not significantly different in both groups (Fig. 1). It is possible that high-dose quetiapine might prove to be superior in the long term as these trials were only 6 weeks long. Also, certain participants with treatment resistance or comorbid substance misuse, who are not represented in these trials, might respond only to the high-dose quetiapine. From the effectiveness prospective, high- and low-dose quetiapine do not show very different discontinuation rates, but the small number of participants included in the analysis and the very wide range of the confidence interval raises the question of the validity of these results.

The major limitation of this meta-analysis is that only two studies\(^{3,9}\) could be included in the meta-analysis, which not only adds a significant publication bias but also limits the power of the study to give any definitive answer. Regarding heterogeneity, both studies used different preparations of quetiapine and different scales for measuring outcome. Kahn et al.\(^9\) excluded people with treatment resistance, substance misuse and a hospital stay > 1 month; whereas in the study by Arvanitis et al.\(^3\) all the participants were in-patients. Also, it should be remembered that limitations inherent to individual studies are carried over in meta-analyses; and meta-analyses tend to neglect the specifications of the individual studies.

In conclusion, this meta-analysis does not prove the therapeutic superiority of high-dose quetiapine in acute treatment of schizophrenia; both in terms of efficacy and effectiveness. From a clinical practice point of view, in general, 300–400 mg/day seems to be the optimal dose of quetiapine and the common practice of targeting quetiapine dosage to 600 mg/day or above is not supported by the evidence from fixed-dose trials.

**Acknowledgements**

Sincere thanks to Dr Subodh Dave (Consultant Psychiatrist and Clinical Teaching Fellow, Derby City General Hospital) for his valuable suggestions in revision of the manuscript.

**About the author**

Nitesh Painuly is a Consultant Psychiatrist at Derby City General Hospital, Derbyshire Mental Health Services NHS Trust.

**References**


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**Table 2** Pooled results for meta-analysis

<table>
<thead>
<tr>
<th>Results</th>
<th>Response rate</th>
<th>Discontinuation due to lack of response</th>
<th>Discontinuation due to adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio (95% CI)</td>
<td>Odds ratio (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arvanitis et al(^3)</td>
<td>0.93 (0.43–1.99)</td>
<td>0.74 (0.34–1.62)</td>
<td>7.12 (0.14–359.12)</td>
</tr>
<tr>
<td>Kahn et al(^9)</td>
<td>1.63 (0.97–2.74)</td>
<td>0.85 (0.37–1.94)</td>
<td>0.47 (0.12–1.77)</td>
</tr>
<tr>
<td>Test of heterogeneity,(^a) Q (P)</td>
<td>1.44 (0.22)</td>
<td>0.05 (0.82)</td>
<td>1.66 (0.19)</td>
</tr>
<tr>
<td>Pooled effect (95% CI),(^b)</td>
<td>1.36 (0.88–2.10)</td>
<td>0.78 (0.44–1.39)</td>
<td>0.64 (0.19–2.17)</td>
</tr>
</tbody>
</table>

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**Fig 1** Change in positive symptoms score (forest plot). IV, inverse variance.

\(\text{a. Chi-squared distribution. } d.f=1 \text{ for all. No heterogeneity present for all.} \)

\(\text{b. Fixed effect model.} \)

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Olive Tree community treatment centre for individuals with personality disorder: naturalistic service evaluation

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The Department of Health 2003 policy implementation guideline Personality Disorder: No Longer a Diagnosis of Exclusion set out to the UK’s National Health Service (NHS) trusts the government’s intentions for the delivery of personality disorder services within general mental health and forensic settings. In this document, the government built on standards four and five in the National Service Framework for Mental Health and set out specific guidance on the development of services for people with personality disorder. It made explicit that all trusts delivering general adult mental health services need to consider how to meet the needs of individuals with a personality disorder who experience significant distress or difficulty as a result of their disorder. Later in 2003, a further National Institute for Mental Health in England publication indicated that new funds would be made available to help stimulate the development of improved and new services to support users with personality disorders. The Olive Tree community treatment centre for individuals with personality disorder, created by the Coventry Primary Care Trust, became one of the pilots of this government initiative. At a time of change in the field of personality disorders, possible changes in classification and
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The Psychiatrist Online 2010, 34:9-12.
Access the most recent version at DOI: 10.1192/pb.bp.108.022277

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