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

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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

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.[2] 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 Complementry 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.[3–9] Single fixed-dose trials[6,8] and the studies with clearly sub-therapeutic dosage of quetiapine (50 mg/day),[4,5] were excluded from the analysis. A pilot study[7] ($n = 21$) that included participants with schizoaffective disorder was also excluded. This ultimately led to the inclusion of only two studies.[3,9] Quality analysis of the included studies was carried out as per the protocol of the Centre for Reviews and Dissemination (CRD).[10] 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

Table 1 Details of studies included in meta-analysis

			High-dose quetiapine					Low-dose quetiapine				
Study	Description[a]	Quality analysis[b]	*n*	Dosage mg/day	Response rate, *n* (%)	Discontinuation due to lack of response, *n*	Discontinuation due to adverse effects, *n*	*n*	Dosage, mg/day	Response rate, *n* (%)	Discontinuation due to lack of response *n*	Discontinuation due to adverse effects *n*
Arvanitis *et al*[3]	Multiple fixed dosage of quetiapine (75, 150, 300, 600 mg/day) and haloperidol (12 mg/day)	Level 1	54	750 (IR)	26 (49)[c]	19	1	52	300 (IR)	26 (51)[c]	22	0
Kahn *et al*[9]	Multiple fixed dosage of quetiapine XR (400, 600 and 800 mg/day) and quetiapine IR 400 mg/day	Level 1	121	800 (XR)	66 (56.4)[d]	12	6	113	400 (XR)	49 (44.1)[d]	13	3

IR, immediate release; XR, extended release.
a. Both trails: 6 weeks, multicentric randomised double-blind, placebo-controlled.
b. Hierarchy of study designs for studies of effectiveness.[10]
c. Reduction in total Brief Psychiatric Rating Scale score ⩾30%.
d. Reduction in total Positive and Negative Syndrome Scale score ⩾30%.

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Table 2 Pooled results for meta-analysis

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

a. Chi-squared distribution. d.f = 1 for all. No heterogeneity present for all.
b. Fixed effect model.

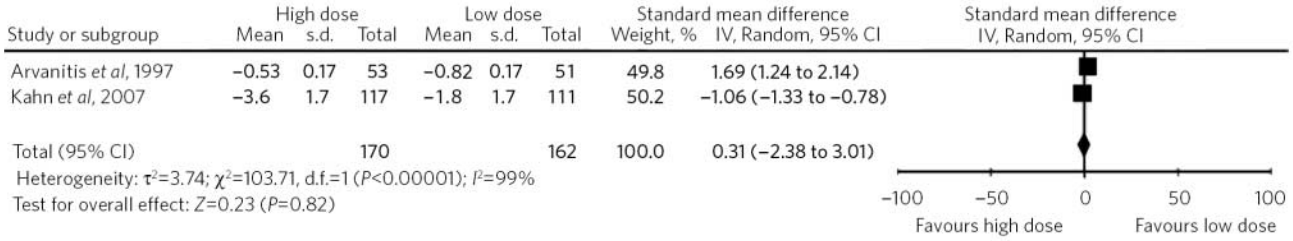

Fig 1 Change in positive symptoms score (forest plot).
IV, inverse variance.

low-dose quetiapine for improvement in positive symptoms score (Fig. 1).

Discussion

Findings of this meta-analysis are in a 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.

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

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Aims and method Community treatment for individuals with personality disorder is a fast developing field. We report here on the effectiveness of one such approach. We examine the referral pathway of all clients between January 2005 and April 2008, including the mean days spent in our unit, the days spent in a psychiatric hospital before and after admission to our unit, and the results of changes in the rating scales we routinely use.

Results Drop-out rates and the mean duration of therapy were acceptable. There has been a clear reduction of in-patient bed use and a small but significant improvement of most psychometric test results.

Clinical implications This study provides further evidence for the effectiveness of community treatment for individuals with personality disorder.

Declaration of interest None.

The Department of Health 2003 policy implementation guideline *Personality Disorder: No Longer a Diagnosis of Exclusion*[1] 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*[2] 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[3] 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.[4,5] At a time of change in the field of personality disorders, possible changes in classification and