

Adjunctive quetiapine for serotonin reuptake inhibitor-resistant obsessive-compulsive disorder: a meta-analysis of randomized controlled treatment trials

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Small studies have shown positive effects from adding a variety of antipsychotic agents in patients with obsessive-compulsive disorder who are unresponsive to treatment with serotonin reuptake inhibitors. The evidence, however, is contradictory. This paper reports a meta-analysis of existing double-blind randomized placebo-controlled studies looking at the addition of the second-generation antipsychotic quetiapine in such cases. Three studies fulfilled the inclusion criteria. Altogether 102 individuals were subjected to analysis using Review Manager (4.2.7). The results showed evidence of efficacy for adjunctive quetiapine (<400 mg/day) on the primary efficacy criterion, measured as changes from baseline in total Yale-Brown Obsessive Compulsive Scale scores ($P=0.008$), the clinical significance of which was limited by between-study heterogeneity. The mechanism underlying the effect may involve serotonin and/or

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Introduction

Although serotonin reuptake inhibitors (SRIs) effect satisfactory improvements in obsessive-compulsive disorder (OCD) for many individuals, residual symptoms remain. Even after switching to a second SRI, approximately 30% cases do not respond (March *et al.*, 1997; Eddy *et al.*, 2004). Compared with data supporting first-line treatments for OCD (Fineberg and Gale, 2005), the evidence base for second-line treatments is slim and based on small numbers of small studies. Reports on placebo-controlled studies of SRI augmentation using haloperidol, risperidone, olanzapine and quetiapine support further exploration of the efficacy of this approach in resistant OCD, although negative and positive findings have been reported (Fineberg *et al.*, 2006).

Quetiapine, administered as an adjunct to SRIs, has been the subject of recent investigation. The drug is reported to be associated with a favourable adverse effect profile compared with other second-generation antipsychotics, with reduced propensity for extrapyramidal side effects, prolactin and sexual dysfunction (Toren *et al.*, 2004). Preliminary open-label studies showed benefits in up to 50% treated cases of OCD (Denys *et al.*, 2002; Sevincok and Topuz, 2003; Bogan *et al.*, 2005) although one study showed little benefit (Mohr *et al.*, 2002). A single-blind

study by Atmaca *et al.* (2002) found a clinical response in 14 of 27 (64%) cases. Three double-blind, randomized placebo-controlled studies of quetiapine have been recently completed and show contradictory results. In the first, Denys *et al.* (2004a) showed significant and robust efficacy for quetiapine augmentation in a sample of 40 SRI-unresponsive cases. More recent studies, however, by Carey *et al.* (2005) and Fineberg *et al.* (2005), which investigated 42 and 21 individuals, respectively, reported no statistically significant between-group differences on any of the outcome measures.

Given the relatively small effect sizes seen for quetiapine in these studies and the variability in placebo-response rates, it seems clear that larger randomized controlled trials are needed to confirm efficacy. At present, the prospect of such large-scale studies being conducted is not promising. Meta-analyses cannot substitute for high-quality head-to-head comparator trials but may compensate for small study size by combining data from separate studies using specific rules. In this paper, the authors of the three published randomized controlled trials of adjunctive quetiapine pooled their study data to produce the first meta-analysis of adjunctive antipsychotic treatment for resistant OCD. Quetiapine has a distinct pharmacological profile compared with other second-generation antipsychotics. Therefore, it

was decided not to include other antipsychotic trials within this analysis.

Method

A search of the major bibliographic databases (EMBase, Medline, Psychinfo, Cochrane Library) confirmed the existence of just three published double-blind placebo controlled randomized treatment studies investigating adjunctive quetiapine in SRI-treated cases of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders – Fourth edition) OCD. All three studies were critically appraised for methodological quality and fulfilled the following criteria: double-blind random allocation, intention-to-treat analysis and the mean and standard deviation for continuous outcomes reported. Outcome data were extracted directly from the studies by one independent reviewer (PP) and entered into Review Manager 4.2.7 (Cochrane Collaboration, 2004). Meta-analysis was then used to synthesize the evidence using Review Manager. Efficacy outcomes were calculated on an intention-to-treat basis. The following key comparisons between quetiapine and placebo were performed:

1. Responder rates (defined according to study criterion).
2. Changes from baseline Yale–Brown Obsessive Compulsive Scale (Y-BOCS, Goodman *et al.*, 1989) total scores (chosen as the a priori primary efficacy criterion).
3. Changes from baseline depression scores: Hamilton Depression Scale (Ham-D, Hamilton, 1967) or Montgomery Asberg Depression Rating Scale (MADRS, Montgomery and Asberg, 1979).
4. Changes from baseline Sheehan Disability Scale scores (Leon *et al.*, 1992).
5. Number of patients leaving the study early.
6. Number of patients leaving the study early owing to adverse events.
7. Number of serious adverse events.

Dichotomous outcomes were presented as relative risks (RRs) (ratio of the treatment event rate to the control event rate; an RR of 1 indicates no difference between treatment and control) with the associated 95% confidence

interval (CI). Continuous outcomes were analysed as standardized mean difference (SMD). To check for heterogeneity between studies, we used χ^2 tests ($P < 0.1$) and visual inspection of the plots. If heterogeneity was established, an attempt was made to explain the variation.

Results

Individual studies are summarized in Table 1. In the first, Denys *et al.* (2004a) showed significant efficacy for quetiapine augmentation in a sample of 40 patients who had previously failed to respond to at least two SRIs. An intent-to-treat analysis for the 20 quetiapine-treated cases showed a significant advantage over placebo from 4 weeks onwards on the Y-BOCS and an average improvement of 32% from baseline Y-BOCS scores, compared with 6.8% improvement in the placebo group at the 8-week endpoint. In the study by Carey *et al.* (2005), 42 individuals who had responded inadequately to open-label treatment with an SRI for 12 weeks were randomized to either placebo or flexible doses of quetiapine added into their treatment. Both quetiapine and placebo-treated groups improved to a similar extent (26.9 and 26% post-baseline reduction in Y-BOCS scores, respectively) at the end of the 6-week treatment period. In the study by Fineberg *et al.* (2005), 21 patients with OCD who had failed to respond to at least 6 months of SRI treatment were randomized to 16 weeks of treatment with SRI and quetiapine or SRI and placebo. The quetiapine group's reduction in baseline Y-BOCS scores averaged 13.8% at week 16 compared with 5.8% under placebo. No statistically significant between-group differences were observed on any of the outcome scores.

The results of the meta-analysis are presented in Fig. 1 as forest plots. Altogether, 102 cases were analysed. Each forest plot displays the effect size and CI for each study as well as the summary statistic. The graphs are organized so that the display of data to the left of the 'line of no effect' indicates a favourable outcome for quetiapine.

Primary outcome measure

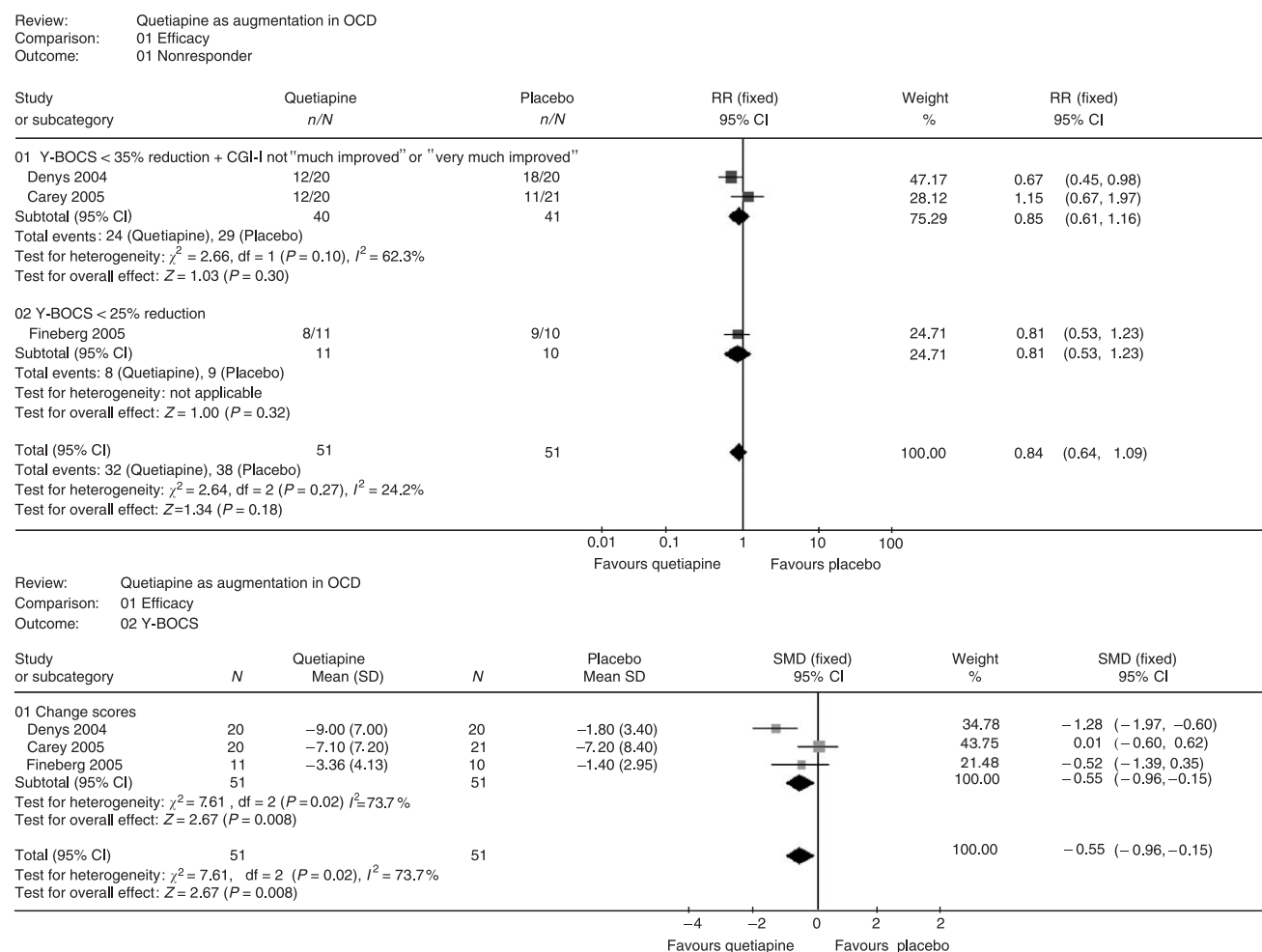
The second forest plot (Fig. 1) shows evidence of a clinically significant effect favouring quetiapine

Table 1 Characteristics of included studies

Study	Failure to	Condition	Duration (weeks)	Patients	Female/male	Age (years) (SD)	Maximum dose (mg/day)	Baseline Y-BOCS (SD)	Endpoint Y-BOCS (SD)	Mean percentage decrease in Y-BOCS (%)
Denys <i>et al.</i> (2004a)	2 SRIs	Placebo	8	20	14/6	34 (10)	300	26.4 (6.3)	24.6 (6.7)	6.8
		Quetiapine	8	20	16/4	36 (14)	300	28.2 (4.3)	19.2 (6.4)	32
Carey <i>et al.</i> (2005)	1 SRI	Placebo	6	21	13/8	31.8 (12.1)	300	27.7 (3.9)	20.5	26
		Quetiapine	6	20	9/11	33.8 (9.7)	300	26.4 (4.6)	19.3	26.9
Fineberg <i>et al.</i> (2005)	1 SRI	Placebo	16	10	4/6	37.9 (10.7)	400	24.1 (4.3)	22.7 (5.5)	5.8
		Quetiapine	16	11	8/3	37.4 (11.4)	400	24.5 (4.6)	21.1 (6.4)	13.8

SRI, serotonin reuptake inhibitor.

Fig. 1



Forest plots showing results of the meta-analysis.

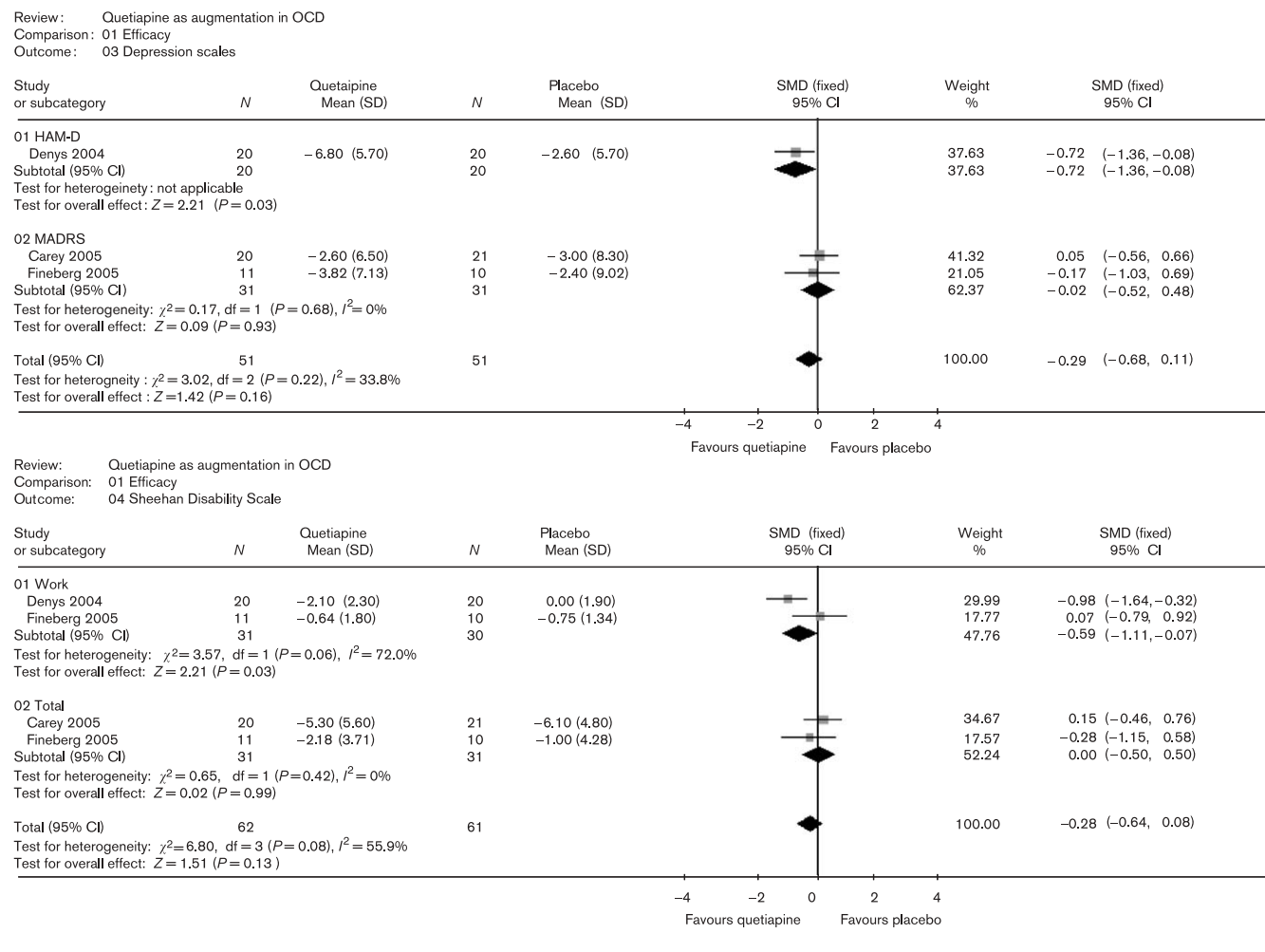
augmentation over placebo in improving obsessive-compulsive symptoms measured as changes from baseline in total Y-BOCS scores ($P = 0.008$). From the three studies (Denys *et al.*, 2004a; Carey *et al.*, 2005, Fineberg *et al.*, 2005, $n = 102$), the SMD between the quetiapine group and the placebo group on the change in Y-BOCS score from baseline was statistically significant, favouring the quetiapine group (SMD = -0.55, 95% CI, -0.96 to -0.15). We cannot be confident about efficacy, however, because the effect edges towards the 'line of no effect' and overlaps with the region of uncertainty. Therefore, the result indicates 'limited clinical significance', that is, a point intermediate between 'strong' and 'insufficient' clinical significance where the CI includes values other than clinically important effects. Of the three individual studies, only the study by Denys *et al.* (2004a) produced a statistically significant result. The degree of heterogeneity between the studies reached statistical significance ($P = 0.02$). Heterogeneity was removed when the study by Denys *et al.* was excluded from the analysis, suggesting

that this study was mainly responsible for the overall effect.

Secondary outcome measures

Responder rates were defined as > 35% improved baseline Y-BOCS and 'much' or 'very much improved' on the Clinical Global Impressions Improvement Scale (Guy, 1976) in the studies by Denys *et al.* (2004a) and Carey *et al.* (2005), or as > 25% improved baseline Y-BOCS in the study by Fineberg *et al.* (2005). From the three studies, the number of non-responders was 32 out of 51 patients in the quetiapine group and 38 out of 51 patients in the placebo group. The likelihood of non-response in the quetiapine group relative to the placebo group was not significantly different (RR = 0.84, 95% CI, 0.64 to 1.09). No evidence showed efficacy on the meta-analysis for any of the secondary outcome measures, apart from a significant advantage favouring quetiapine on the Work Subscale score of the Sheehan Disability Scale ($P = 0.03$). From two studies (Denys *et al.*, 2004a;

Fig. 1 (Continued)



Fineberg *et al.*, 2005; $n = 61$), the SMD between the quetiapine group and the placebo group on the Sheehan Disability Scale-Work Subscale was statistically significant (SMD = -0.59, 95% CI, -1.11 to -0.07), although we cannot be confident about the clinical significance of this difference because the SMD approaches the 'line of no effect'. This effect did not, however, extend to the total Sheehan Disability Scale score ($P = 0.99$). From the three studies (Denys *et al.*, 2004a; Carey *et al.*, 2005; Fineberg *et al.*, 2005), the number of participants discontinuing from the study was four out of 51 patients in the quetiapine group and one out of 51 in the placebo group. No significant difference was observed between the quetiapine group and the placebo group on the likelihood of discontinuing from the study (RR = 2.43, 95% CI, 0.5 to 11.69).

Discussion

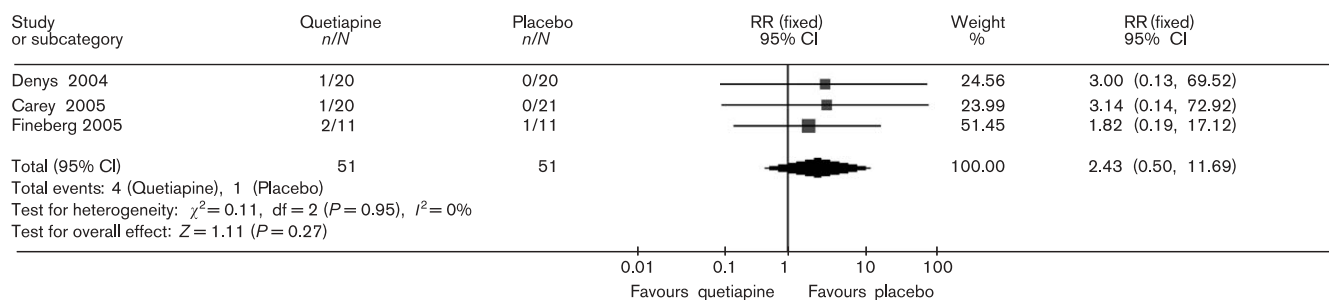
This is the first meta-analysis to be reported and the largest cohort of resistant cases of OCD, augmented with antipsychotic under double-blind conditions, to have

been analysed. Notwithstanding statistical limitations, the results of the analysis are positive and show evidence supporting efficacy for quetiapine using the primary efficacy criterion. To find a significant difference in relatively small numbers suggests that the finding is robust. Moreover, the finding of a significant difference on one of the domains on the Sheehan Disability Scale is an argument for clinical relevance.

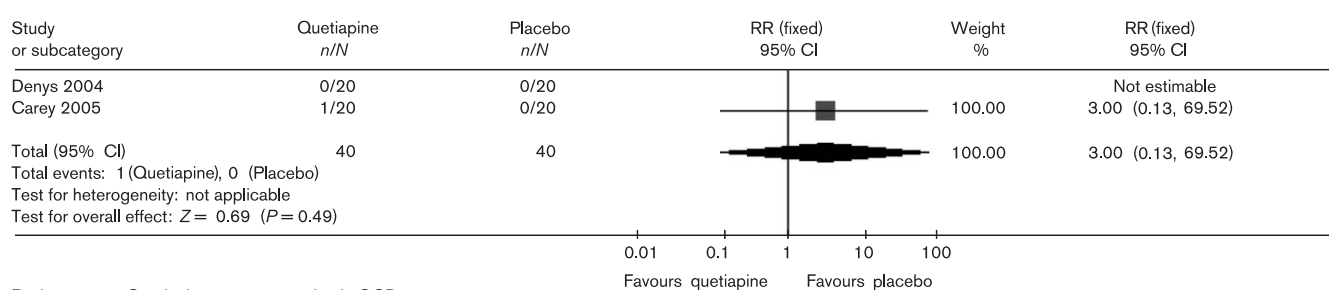
Meta-analyses are subject to various methodological shortcomings, often attributable to between-study differences that diminish the validity of combining their data under a single analysis. In our case, the included studies shared important features such as the diagnostic classification of cases (DSM-IV), primary efficacy parameter and pivotal rating scales. The ages and sex ratio of the cases and dose range of quetiapine (maximum 300 mg/day or 400 mg/day) were also similar (Table 1). Clear differences, however, were observed between the three studies in terms of (1) entry criteria, (2) duration and (3) sample sizes.

Fig. 1 (Continued)

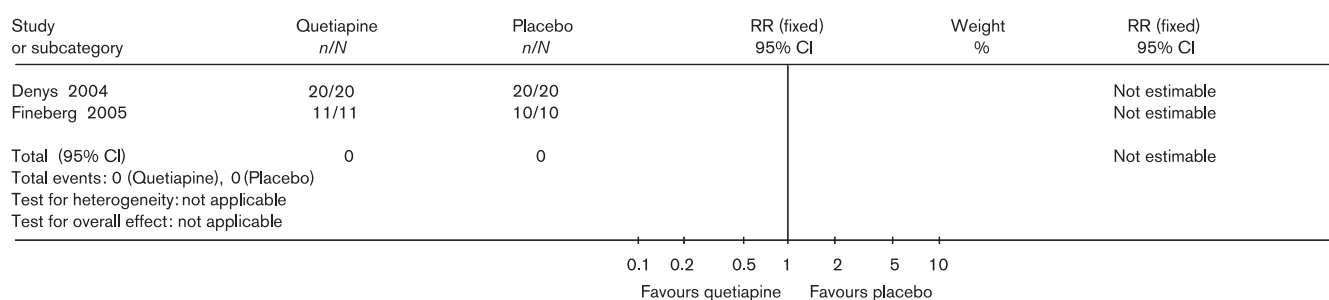
Review: Quetiapine as augmentation in OCD
 Comparison: 02 Tolerability
 Outcome: 01 Leaving the study early



Review: Quetiapine as augmentation in OCD
 Comparison: 02 Tolerability
 Outcome: 02 Leaving the study early due to adverse events



Review: Quetiapine as augmentation in OCD
 Comparison: 02 Tolerability
 Outcome: 03 Adverse events



Denys *et al.* (2004a) and Fineberg *et al.* (2005) excluded comorbid axis 1 pathology including tic disorders, whereas Carey *et al.* (2005) did not. In addition, Denys *et al.* (2004a) and Fineberg *et al.* (2005) only included patients who had failed at least 4 months before SRI treatment, thereby limiting the sample to truly SRI-resistant cases. This was supported by low placebo-response rates amounting to a mean reduction of around 6% from baseline Y-BOCS scores in both studies. In contrast, the study by Carey *et al.* (2005) showed an unusually high placebo-response rate (26%) that the authors attributed to the possible inclusion of non-resistant cases that went on to respond to treatment with SRI extended beyond the 6-week entry criterion. The studies also differed in terms of duration (see Table 1) but it is unlikely that this would have affected the results. Most

studies have found positive effects of antipsychotic addition develop within 4 weeks and last for several months (Maina *et al.*, 2003). The endpoints of our studies at 6, 8 and 16 weeks fall within that time frame. On the other hand, there are no controlled research trials on the efficacy of antipsychotic addition over the long term. Finally, there are differences with regard to sample size. Studies of both Denys *et al.* (2004a) and Carey *et al.* (2005) were conducted on samples comprising 40 patients, which should be sufficient to detect a mean difference in Y-BOCS score of ≥ 3.6 between quetiapine and placebo. The study by Fineberg *et al.* (2005) was conducted on a smaller sample of 21 patients which requires a mean difference in Y-BOCS scores between quetiapine and placebo of at least 5.3 to reach a power of 0.8.

Although limited, our analysis shows evidence of efficacy for quetiapine for SRI-resistant OCD patients. The beneficial effect of adding quetiapine to SRIs in OCD is intriguing as it is generally accepted that antipsychotics in monotherapy lack efficacy in OCD (McDougle *et al.*, 1995; Connor *et al.*, 2005). Several possible explanations exist for the efficacy of quetiapine addition. The first is a pharmacokinetic interaction between quetiapine and SRIs. Quetiapine and its metabolites are weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 enzymes, although at concentrations 10 to 50-fold higher than used in these studies (maximum 400 mg/daily). Therefore, it is unlikely that quetiapine would enhance the efficacy of SRIs by inhibiting their metabolism. On the other hand, SRIs such as paroxetine, fluvoxamine and fluoxetine might inhibit the CYP3A4 system, which is primarily responsible for metabolizing quetiapine. Then again, there is no evidence that higher doses of quetiapine are more effective than lower doses in treating OCD, although dose-ranging studies have yet to be performed. Next, a number of pharmacodynamic hypotheses may be advanced. The enhanced therapeutic response may be caused by a specific synergistic quality of the combination of SRIs with antipsychotics. Marek *et al.* (2003), for example, suggested that the clinical efficacy of SRIs with atypical antipsychotics resulted from blockade of 5-HT_{2A} coincident with activation of non-5-HT_{2A} serotonergic receptors. This appealing hypothesis may account for the efficacy of risperidone, olanzapine or quetiapine but not for the efficacy of haloperidol (McDougle *et al.*, 1994), which is 30-fold more potent at the D₂ than at the 5-HT_{2A} receptor. The efficacy of haloperidol and pimozide (McDougle *et al.*, 1990) as adjuncts to SRIs favours the significance of dopaminergic antagonism. Although preliminary, preclinical studies suggest that the combination of an SRI with an atypical antipsychotic results in a unique synergistic effect on extracellular dopamine levels in the prefrontal cortex. For example, the combination of olanzapine with fluoxetine resulted in a robust and sustained increase of extracellular dopamine and noradrenaline levels in the prefrontal cortex (Zhang *et al.*, 2000). These increases were significantly higher than the increases achieved with either drug in monotherapy. Denys *et al.* (2004b) found similar increases of extracellular dopamine levels in the prefrontal cortex following co-administration of fluvoxamine with quetiapine. This synergistic effect on dopamine levels did not apply to changes in extracellular serotonin, nor was it observed in other brain areas such as the striatum or the nucleus accumbens. Changes in dopamine activity within the prefrontal cortex may be critical for OCD, as it is suggested that dopamine coordinates the long-term extinction of fear conditioning and modulates neural interactions between the prefrontal cortex, hippocampus and amygdala. Further research is needed to determine whether changes in extracellular dopamine levels account for the clinical efficacy of

addition strategies with antipsychotic agents such as quetiapine in treatment-resistant OCD.

Conclusions

This meta-analysis of three double-blind, randomized placebo-controlled studies reports limited evidence of efficacy of adjunctive quetiapine in SRI-unresponsive cases. The mechanism underpinning the therapeutic effect remains poorly understood and may involve neurotransmitters other than serotonin.

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