

FEATURE REVIEW

A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder

MH Bloch¹, A Landeros-Weisenberger², B Kelmendi³, V Coric³, MB Bracken⁴ and JF Leckman¹

¹Child Study Center, Yale University School of Medicine, New Haven, CT, USA; ²Universidad Nacional Autónoma de México and Hospital Español, Mexico City, Mexico; ³Connecticut Mental Health Center, New Haven, CT, USA and ⁴Yale School of Epidemiology and Public Health, New Haven, CT, USA

As many as half of obsessive-compulsive disorder (OCD) patients treated with an adequate trial of serotonin reuptake inhibitors (SRIs) fail to fully respond to treatment and continue to exhibit significant symptoms. Many studies have assessed the effectiveness of antipsychotic augmentation in SRI-refractory OCD. In this systematic review, we evaluate the efficacy of antipsychotic augmentation in treatment-refractory OCD. The electronic databases of PubMed, PsychINFO (1967–2005), Embase (1974–2000) and the Cochrane Central Register of Controlled Trials (CENTRAL, as of 2005, Issue 3) were searched for relevant double-blind trials using keywords ‘antipsychotic agents’ or ‘neuroleptics’ and ‘obsessive-compulsive disorder’. Search results and analysis were limited to double-blind, randomized control trials involving the adult population. The proportion of subjects designated as treatment responders was defined by a greater than 35% reduction in Yale Brown Obsessive-Compulsive Scale (Y-BOCS) rating during the course of augmentation therapy. Nine studies involving 278 participants were included in the analysis. The meta-analysis of these studies demonstrated a significant absolute risk difference (ARD) in favor of antipsychotic augmentation of 0.22 (95% confidence interval (CI): 0.13, 0.31). The subgroup of OCD patients with comorbid tics have a particularly beneficial response to this intervention, ARD=0.43 (95% CI: 0.19, 0.68). There was also evidence suggesting OCD patients should be treated with at least 3 months of maximal-tolerated therapy of an SRI before initiating antipsychotic augmentation owing to the high rate of treatment response to continued SRI monotherapy (25.6%). Antipsychotic augmentation in SRI-refractory OCD is indicated in patients who have been treated for at least 3 months of maximal-tolerated therapy of an SRI. Unfortunately, only one-third of treatment-refractory OCD patients show a meaningful treatment response to antipsychotic augmentation. There is sufficient evidence in the published literature, demonstrating the efficacy of haloperidol and risperidone, and evidence regarding the efficacy of quetiapine and olanzapine is inconclusive. Patients with comorbid tics are likely to have a differential benefit to antipsychotic augmentation.

Molecular Psychiatry advance online publication, 4 April 2006; doi:10.1038/sj.mp.4001823

Keywords: obsessive-compulsive disorder; antipsychotic agents; systematic review; meta-analysis; tics

Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder characterized by either obsessions (recurrent or persistent unwanted thoughts, images or impulses) or compulsions (repetitive behaviors or mental acts often performed to relieve anxiety or distress). The obsessions and compulsions of OCD cause significant distress to the afflicted individual. Once believed to be rare, OCD is now estimated to affect between 2 and 3% of the general population and is the fourth most common psychiatric illness (after specific phobias, substance abuse and major

depression). Patients with OCD have a poorer overall quality of life, and experience significant impairment in academic functioning, work performance and interpersonal relationships.^{1–3} In fact, OCD is estimated to be the 10th leading cause of disability in the world.^{4–8}

Before the introduction of clomipramine and serotonin reuptake inhibitors (SRIs) in the mid-1980s,^{9,10} OCD was considered to be a poorly treated disorder with a chronic and unremitting course.¹¹ Even after implementation of SRIs for the treatment of OCD, a follow-up study of 144 in-patients treated for OCD in Sweden revealed only a 20% complete recovery rate 40 years after initial treatment.¹¹ Although a substantial proportion (83%) experienced a decline in symptom severity from the point of their initial hospitalization, over half (52%) continued to have clinically significant OCD symptoms 40 years

Correspondence: Dr MH Bloch, Child Study Center, Yale University School of Medicine, 230 South Frontage Road, New Haven, CT 06520, USA.

E-mail: michael.bloch@yale.edu

Received 9 January 2006; accepted 6 February 2006

later. Other retrospective studies from the same time period estimate that clinical improvement is experienced only by 32–74% of OCD patients who were followed up at time intervals of 5 years or longer.^{12–18}

The introduction of SRIs and behavioral therapy techniques have certainly improved clinical outcome in many patients. Serotonin reuptake inhibitors are considered the most effective and well-established pharmacotherapy for the treatment of OCD.^{19–21} However, 40–60% of OCD patients do not respond adequately to SRI therapy^{22–24} and an even greater proportion of patients fail to experience complete remission of their symptoms.²⁵ Even those patients who are judged to be clinical responders based on stringent response criteria (i.e., typically a greater than 25 or 35% decline in Y-BOCS rating) continue to experience significant impairment from their residual OCD symptoms. Furthermore, as many as 25% of patients fail to experience any improvement from initial SRI monotherapy.²⁶

Approximately one-third of non-responders to initial SRI monotherapy respond when switched to a second, different SRI.¹⁹ Two additional pharmacological augmentation strategies have been implemented to aid patients non-responding to SRI monotherapy. The first category of augmentation strategies involves the use of serotonin-enhancing agents (such as lithium, clonazepam and buspirone) to maximize treatment response. The results from clinical studies of such agents yielded uniformly discouraging results.^{27,28} The second category of augmentation strategies has involved the addition of low-dose dopamine antagonists to SRI medications. Open-label studies of antipsychotic augmentation agents have yielded very promising results compared to the use of serotonin-enhancing agents.^{29–32} This systematic review examines the efficacy and safety of antipsychotic agents as an augmentation strategy for treatment-refractory OCD in recently conducted, double-blind, randomized control clinical trials.

Objectives

- To identify and systematically review evidence of the efficacy of augmentation with antipsychotic agents compared to placebo in inducing clinical remission among treatment-resistant adult OCD patients who are concurrently receiving SRI monotherapy.
- To evaluate the efficacy of augmentation with antipsychotic agents compared to placebo in reducing OCD and depression symptom severity among treatment-resistant adult OCD patients who are concurrently receiving SRI monotherapy.
- To determine if choice of particular antipsychotic agent used affected treatment outcome. Antipsychotic agents were classified individually and in typical versus atypical categories for this analysis. Outcome measure will be proportion of treatment responders and mean difference in Y-BOCS ratings.
- To determine if the proportion of treatment responders and mean difference in Y-BOCS ratings are influenced by length of time therapy with antipsychotic augmentation is followed.
- To determine if the proportion of treatment responders and mean difference in Y-BOCS ratings after antipsychotic augmentation differed based on minimum inclusion criterion for studies of OCD non-responsiveness (treatment-resistant versus treatment-refractory OCD).
- To determine whether adult OCD patients with comorbid tic disorders respond preferentially to SRI augmentation with antipsychotic agents compared to treatment-resistant OCD patients without comorbid tics.
- To evaluate the tolerability of antipsychotic agents compared to placebo when added as an augmentation agent to SRI monotherapy in treatment-resistant OCD patients. Tolerability of antipsychotic agents will be measured through proportion of subjects who drop-out, and experience sedation, increased appetite or extrapyramidal side effects in the antipsychotic versus placebo groups.

Methods

Search strategy for the identification of studies

The electronic databases of PubMed, PsychINFO (1967–2005), Embase (1974–2000) and the Cochrane Central Register of Controlled Trials (CENTRAL – as of 2005, Issue 3) were searched for relevant trials. PubMed was searched using the medical subject headings (MeSH) ‘obsessive-compulsive disorder’ and ‘antipsychotic agents’. The search results were limited to adults (over age 18) and clinical trials. PsychINFO and Embase were searched using the MeSH ‘obsessive-compulsive disorder’ and ‘neuroleptic agents’. The search results in PsychINFO were further limited to the adulthood age group (over age 18) and the ‘treatment outcome/randomized controlled trial’ methodology requirement. The search results in Embase were limited to the adult (ages 18–64) and aged (>65) age groups. CENTRAL was searched using the MeSH terms ‘obsessive-compulsive disorder’ and ‘antipsychotic agents’ for relevant trials. The reference lists of yielded papers were also scanned for additional published reports and citations of unpublished research. There were no language limitations for this review.

Study selection

Only randomized clinical trials that were conducted in a double-blind manner were included in the study analysis. Quasi-randomized and non-randomized trials as well as open-label studies were excluded from this systematic review. Trials were included if (1) the primary study population were patients with a primary Axis I psychiatric diagnosis of OCD who had not responded to at least 2 months of treatment with traditional SRI therapy, (2) the study compared antipsychotic and placebo augmentation in addition

to SRI monotherapy and (3) the study used the Y-BOCS as a measure of OCD severity before and following adequate augmentation with an antipsychotic augmentation agent. Two reviewers (MHB and ALW) independently identified and selected the studies to be included in this review by using the selection criteria discussed above.

Outcome measures

Our primary outcome measure was the proportion of treatment responders (as defined by a 35% decline in Y-BOCS scores) in the antipsychotic augmentation group compared to the placebo group. A 35% decline in Y-BOCS rating was chosen as the threshold for treatment response based on the definition of full treatment response suggested by the International Treatment Refractory OCD Consortium.³³ Secondary outcome measures were the mean difference in Y-BOCS and Hamilton Rating Scale for Depression (HAM-D) ratings before and after pharmacological intervention in antipsychotic augmentation and placebo augmentation groups, and the proportion of subjects who dropped out and experienced sedation or extrapyramidal side effects in the antipsychotic group compared to the placebo group.

Subgroup analysis

The following subgroup comparisons were analyzed in antipsychotic treatment responders:

- Stratification by antipsychotic augmentation agent studied.
- Stratification by length of antipsychotic augmentation therapy. Trials were stratified according to study length in the following groups: (1) less than 4 weeks; (2) greater than or equal to 4 weeks but less than 6 weeks; (3) greater than or equal to 6 weeks but less than 8 weeks; (4) greater than or equal to 8 weeks but less than 12 weeks and (5) greater than or equal to 12 weeks.
- Stratification by minimum length of failed SRI monotherapy at maximal dose before antipsychotic augmentation. Trials were stratified by (1) less than 12 weeks of SRI monotherapy on a single agent or (2) greater than or equal to 12 weeks of failed SRI monotherapy on one or more agents.
- Stratification by the presence or absence of comorbid tic disorders.

Systematic review and meta-analysis methods

Specially designed forms/coding sheets were used by two independently working reviewers (MHB and ALW) to collect data on methods, participants, intervention and outcome measurements, and other relevant attributes and results of the studies. In order to assure that variation was not caused by systematic errors in the design of a study in this analysis, the methodological quality of each potentially eligible trial was assessed by two reviewers (MHB and ALW) independently. Critical appraisal of studies will combine the standard approach described in the Cochrane Handbook,³⁴ which considers randomiza-

tion, allocation concealment and intention to treat, with quality scores from the Cochrane Collaboration Depression, Anxiety and Neurosis Group endorsed Quality Ratings Scale, a 23-item scale, relating to important elements of trial design and conduct.³⁵ Any disagreement between reviewers was resolved through discussion and obtaining more information from the study investigators when possible. Missing data were obtained from study investigators whenever possible. For drop-outs, the measurements of outcome variables were treated with last observation carried-forward analysis.

For all binary outcome measures of interest, proportion of treatment responders and proportion of subjects who dropped out or experienced particular side effects were analyzed using pooled absolute risk difference (ARD). The number needed to treat (NNT) was also reported for these outcome measures as this statistic is the most clinically relevant when considering antipsychotic augmentation use in treatment-resistant OCD patients. For all outcome measures, 95% confidence intervals (CIs) were reported.

Publication bias was analyzed by entering data from included trials into a funnel plot (trial effect size plotted against sample size).³⁶ Heterogeneity of between-trials was assessed visually from the forest plot of ARD and mean differences of individual studies. If the studies were found to be clinically too heterogeneous, then quantitative synthesis of the results was not carried out. Also, stratification of results by our various subgroup comparisons examined various obvious sources of heterogeneity within our study sample. Statistical estimates of heterogeneity were also assessed using the I^2 heterogeneity statistic in RevMan. Sensitivity analysis was conducted to determine the robustness of the reviewers' conclusions to methodological assumptions made in conducting this systematic review. In particular, sensitivity analyses were conducted to determine the effects of subject drop-out. This was determined through a 'worst-case/best-case' scenario with regard to treatment response. In this method, a negative and a positive response was substituted for all missing data (i.e., drop-outs) in the treatment and control groups, respectively.³⁷ In a second comparison, the type of outcome for these two groups was reversed. Should the conclusions regarding treatment efficacy not differ between these two comparisons, it can be assumed that missing data in trial reports do not have a significant influence on outcome. For all statistical analyses, RevMan version 4.2.8 was used in analysis. A final copy of this manuscript was submitted to all corresponding authors of included studies in order to ensure, proper treatment of their individual studies in the overall meta-analysis.

Included studies

All nine trials included in this review were true double-blind, randomized, placebo-controlled studies that examined the efficacy of augmentation with a

single, specific antipsychotic agent compared to placebo (Table 1).^{38–46} All studies used Y-BOCS ratings as the primary measure of OCD symptom severity and defined treatment response as the primary outcome measure. Four of these nine studies used a greater than 35% reduction in Y-BOCS score as their criteria for treatment response.^{40,41,44,45} Five of these studies used a greater than 25% reduction in Y-BOCS score as their criteria for treatment response.^{37,38,41,42,45} Through a combination of personal communications with the authors^{37,41,42} and available manuscript data,^{39,46} the number of responders at the 35% reduction threshold was available for all these trials. Seven of the nine traditional antipsychotic augmentation versus placebo studies tested HAM-D ratings for depression, whereas two used the

Montgomery–Asberg Depression Ratings Scale (MADRS).^{39,42} Seven of these nine studies examined antipsychotic augmentation in OCD subjects who had failed at least 12 weeks of SRI monotherapy on a single agent or 16 weeks on a combination of two agents SRI. Two studies examined antipsychotic augmentation in OCD patients who had failed SRI monotherapy at maximal doses of less than 12 weeks duration.^{39,46} The range of follow-up interval after initiation of antipsychotic augmentation ranged from 4 weeks⁴⁴ to 16 weeks,⁴² with the majority of studies settling on 6 or 8 weeks. Five studies included OCD patients with comorbid tic disorders.^{39,43–46} Five of the nine studies were primarily industry funded.^{38–40,42,43} A full description of the nine included studies in this review are available in Table 1.

Table 1 Characteristics of included studies

Study	Methods	Participants	Intervention
Bystritsky <i>et al.</i> ³⁸	Double-blind, placebo-controlled trial	26 OCD subjects who failed to respond to 12-week treatment with SRI at maximum level with tolerable side effects	6 weeks of olanzapine (mean 11.2 ± 6.5, max. 20 mg/day)
Carey <i>et al.</i> ³⁹	Multi-center (<i>n</i> = 5), double-blind, placebo-controlled trial	41 OCD subjects who failed to respond to 12 weeks of open-label SRI treatment (at least 6 weeks at maximum-tolerated dose)	6 weeks of quetiapine (mean 169 ± 121, max 300 mg/day)
Denys <i>et al.</i> ⁴⁰	Double-blind, placebo-controlled trial	40 OCD subjects who failed to respond to courses of treatment with at least 2 different SRIs at maximal dose for 8 weeks	8 weeks of quetiapine (max. 300 mg/day)
Erzegovesi <i>et al.</i> ⁴¹	Double-blind, placebo-controlled trial	20 OCD subjects out of 45 who failed to respond to 12 weeks of open-label fluvoxamine	6 weeks of risperidone (dosage equal to 0.5 mg/day)
Fineberg <i>et al.</i> ⁴²	Double-blind, placebo-controlled trial	21 OCD subjects who failed to respond to at least 12 weeks of consistent SRI treatment at maximum-tolerated dose (actual minimum was 6 months)	16 weeks of quetiapine (mean 215 ± 124, max. 400 mg/day)
Hollander <i>et al.</i> ⁴³	Double-blind, placebo-controlled trial	16 OCD subjects with CGI score > 2 after trials with at least 2 SRIs of 'adequate dose and duration'	8 week of risperidone (mean 2.3 ± 0.9, max. 3 mg/day)
Mcdougale <i>et al.</i> ⁴⁴	Double-blind, placebo-controlled trial	34 OCD subjects out of 62 who failed to respond to 8 weeks of open-label fluvoxamine. All patients failed treatment with at least one prior pharmacological agent before entering into study	4 weeks of haloperidol (6.2 ± 3.0, max. 10 mg/day)
Mcdougale <i>et al.</i> ⁴⁵	Double-blind, placebo-controlled trial	36 OCD subjects who failed to respond to at least 12 weeks of open-label SRI treatment and had symptoms present for at least 1 year in duration	6 weeks of risperidone (mean = 2.2 ± 0.7, max. 6 mg/day)
Shapira <i>et al.</i> ⁴⁶	Double-blind, placebo-controlled trial	44 OCD subjects with Y-BOCS > 19 and CGI score > 2 after 8 weeks of open-label fluoxetine	6 weeks of olanzapine (mean = 6.1 ± 2.1, max. 10 mg/day)

CGI = Clinical Global Impression Scale; OCD = obsessive-compulsive disorder; SRI = serotonin reuptake inhibitor. Studies were included in this systematic review if they were double-blind, placebo-controlled trial studying augmentation of traditional SRI monotherapy with a Food and Drug Administration-approved antipsychotic agent in subjects with a primary Axis I disorder of OCD. Studies were eligible for inclusion if subjects were entered into the trial after failing to respond adequately to at least 8 weeks of pretreatment with an SRI agent. Other exclusion criteria were comorbid bipolar disorder and schizophrenia. Comorbid depressive, tic and substance abuse disorders were not exclusion criteria.

All trials included in this review were of moderate or high quality. High-quality trials use central randomization, double-blinding and follow-up of a large proportion of trial participants. Eight of our nine trials were judged to be of high quality.^{39–46} Bystritsky *et al.* trial was judged to be of only moderate quality owing to the high rate of drop-outs (31%) in this trial. Besides the high drop-out rate, the Bystritsky *et al.* trial was indistinguishable from the other included trials in methodological quality. Randomization techniques are unclear for all papers, except for the Carey *et al.* trial, which describes a centralized, computerized randomization technique stratified by site in this multi-center trial. No studies tested the integrity of the blinding technique among raters' measuring outcome. There was a significant risk of unblinding occurring owing to medication side effects (mainly sedation) in two quetiapine studies, Denys *et al.* and Carey *et al.*, where the rate of sedation reported in the treatment group was 95 and 75%, respectively, compared to less than 33% in the placebo groups. All trials included in this systematic review employed intent-to-treat analysis.

We excluded one study from the analysis.⁴⁷ This study used an elegant crossover design to compare OCD symptom severity after 2 weeks of SRI augmentation with haloperidol, risperidone or placebo. If treatment response data had been available for the first 2-week augmentation period (before crossover), we would have included this manuscript in our analysis.

Results

Proportion of treatment responders in antipsychotic versus placebo augmentation groups

All nine trials included in this review contributed to this outcome measure. There were a total of 278 OCD patients (143 receiving antipsychotic augmentation and 135 receiving placebo augmentation) included in

these analyses. A treatment response was significantly more likely in the antipsychotic augmentation than in the placebo augmentation group ($z = 4.52$, $P < 0.00001$). The ARD in treatment response was 0.22 (95% CI: 0.13, 0.31, range among individual studies 0.05–0.40) in antipsychotic augmentation versus placebo. A forest plot depicting the ARD differences in individual augmentation studies and the cumulative meta-analysis is depicted in Figure 1. The rate of treatment response in the antipsychotic augmentation group was 32% (46 of 143) compared to 11% (15 of 135) in the placebo group. This result sets the NNT to benefit from antipsychotic augmentation among treatment-resistant OCD patients at 4.5 (95% CI: 3.2, 7.7).

In sensitivity analysis, under the worst-case scenario, when all drop-outs in the antipsychotic augmentation arm were judged as treatment non-responders and all drop-outs in the placebo arm were judged as treatment responders, antipsychotic augmentation was still associated with a positive treatment response (ARD = 0.13, 95%: 0.03, 0.23). Under the best-case scenario, when all drop-outs in the antipsychotic augmentation arm were judged as treatment responders and all drop-outs in the placebo arm were not, the ARD was 0.31 (95% CI: 0.22, 0.41). No publication bias on funnel plot or heterogeneity either graphically or through the I^2 statistic in RevMan were observed in this result.

Proportion of treatment responders stratified by antipsychotic agent

Figure 2 is a forest plot demonstrating the absolute mean difference in proportion of treatment responders stratified by antipsychotic agent utilized. All nine studies involving 278 subjects were included for this outcome measure. One study involving 34 subjects (17 receiving antipsychotic augmentation and 17 controls) contributes to the haloperidol strata.⁴⁴ Three studies involving 72 subjects (40 receiving antipsychotic augmentation and 32 receiving placebo

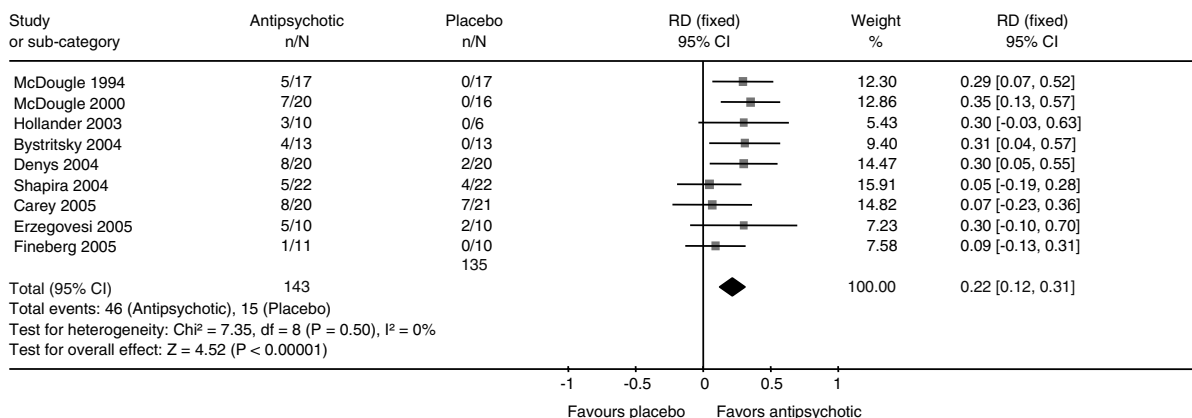


Figure 1 Proportion of treatment responders comparing antipsychotic augmentation to placebo among all treatment-resistant OCD patients. A forest plot comparing absolute risk difference (ARD) between proportion of treatment responders in the antipsychotic augmentation versus placebo group in individual treatment studies and cumulative meta-analysis. Treatment response is characterized by a greater than a 35% reduction in Y-BOCS rating from baseline at the end of augmentation. A positive ARD favors antipsychotic augmentation.

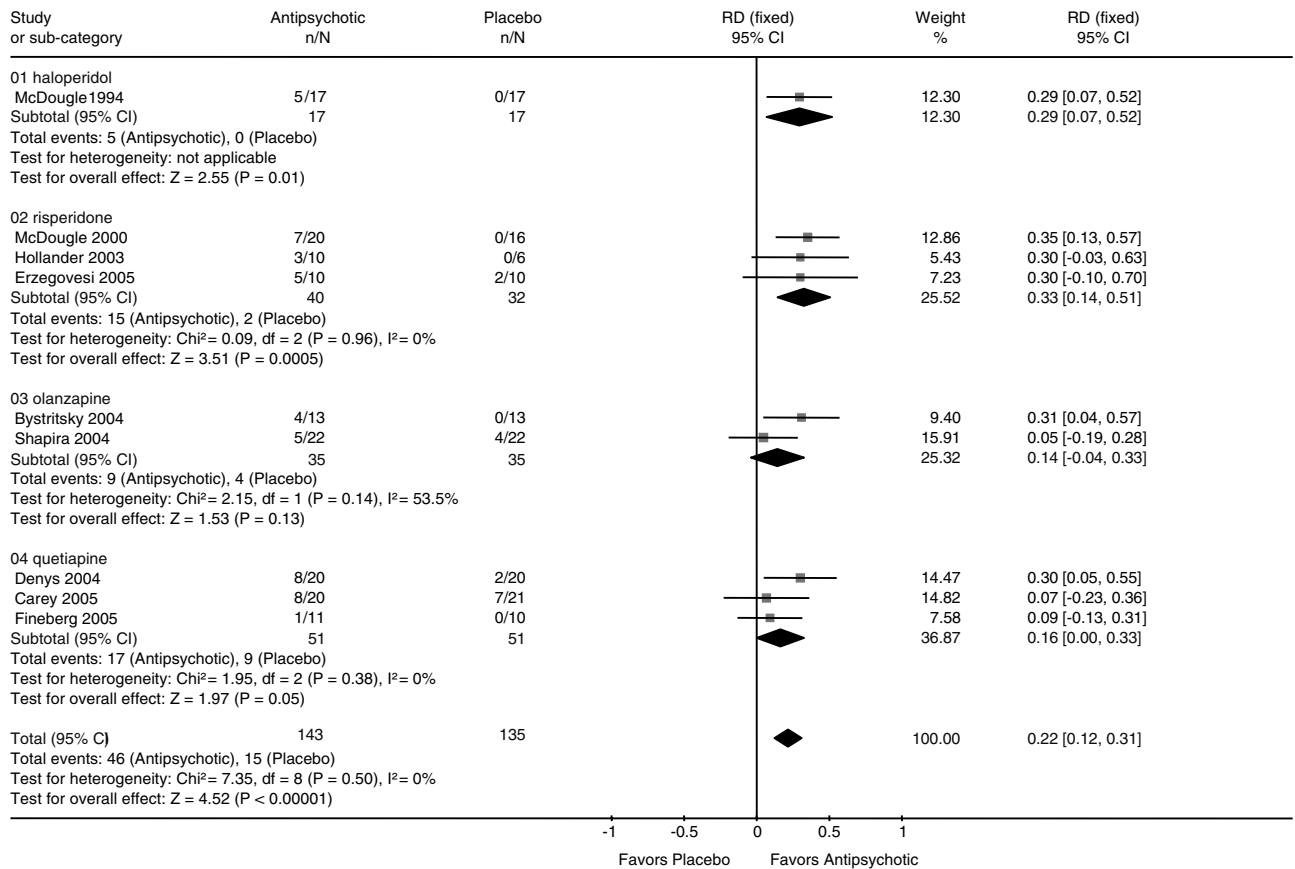


Figure 2 Stratification by antipsychotic agent utilized. A forest plot comparing absolute risk difference (ARD) between proportion of treatment responders in the antipsychotic augmentation and placebo group in individual treatment studies and cumulative meta-analysis as stratified by antipsychotic agent utilized. Treatment response is characterized by a greater than a 35% reduction in Y-BOCS rating from baseline at the end of augmentation. A positive ARD favors antipsychotic augmentation. There have not been a sufficient number of studies to definitively compare the relative efficacy of each agent. However, quetiapine and olanzapine appear to be less efficacious than the other agents, including haloperidol and risperidone.

augmentation) contributed to the risperidone strata.^{41,43,45} Two studies involving 70 subjects (evenly divided between treatment arms) contributed to the olanzapine strata.^{38,46} Three studies involving 102 subjects (evenly divided between treatment arms) contributed to the quetiapine strata.^{39,40,42} Haloperidol (ARD in proportion of treatment responders = 0.29 (95% CI: 0.07, 0.52) and risperidone (ARD = 0.33 (95% CI: 0.14, 0.51)) demonstrated significant efficacy as compared to placebo. Quetiapine augmentation (ARD = 0.16 (95% CI: 0.00, 0.33)) and olanzapine augmentation (ARD = 0.14 (95% CI: -0.04, 0.33)) failed to demonstrate efficacy as compared to placebo based on the totality of evidence in currently published studies.

Proportion of treatment responders and length of time on antipsychotic augmentation

Stratification based on length of antipsychotic augmentation (Figure 3) revealed no evidence that length of antipsychotic augmentation over 4 weeks improved the proportion of treatment responders

on mean reduction in Y-BOCS rating. All nine trials involving 278 subjects contributed to this analysis.

Proportion of treatment responders and minimum length on SRI treatment before antipsychotic augmentation

All nine studies including 278 subjects contributed to this analysis. Two studies involving 83 subjects (42 antipsychotic augmentation, 41 placebo augmentation) followed OCD patients who were treated with less than 12 weeks of SRI monotherapy before antipsychotic augmentation.^{39,46} The other seven studies involving 193 subjects followed subjects who had been treated with at least 12 weeks of SRI monotherapy at the maximum-tolerated dose before augmentation. Subjects in the McDougle *et al.*⁴⁴ study were assigned to the later strata even though the minimum inclusion criterion for double-blind augmentation in this study was only treatment failure after 8 weeks of open-label fluvoxamine therapy, because all subjects in this study had, in fact, failed

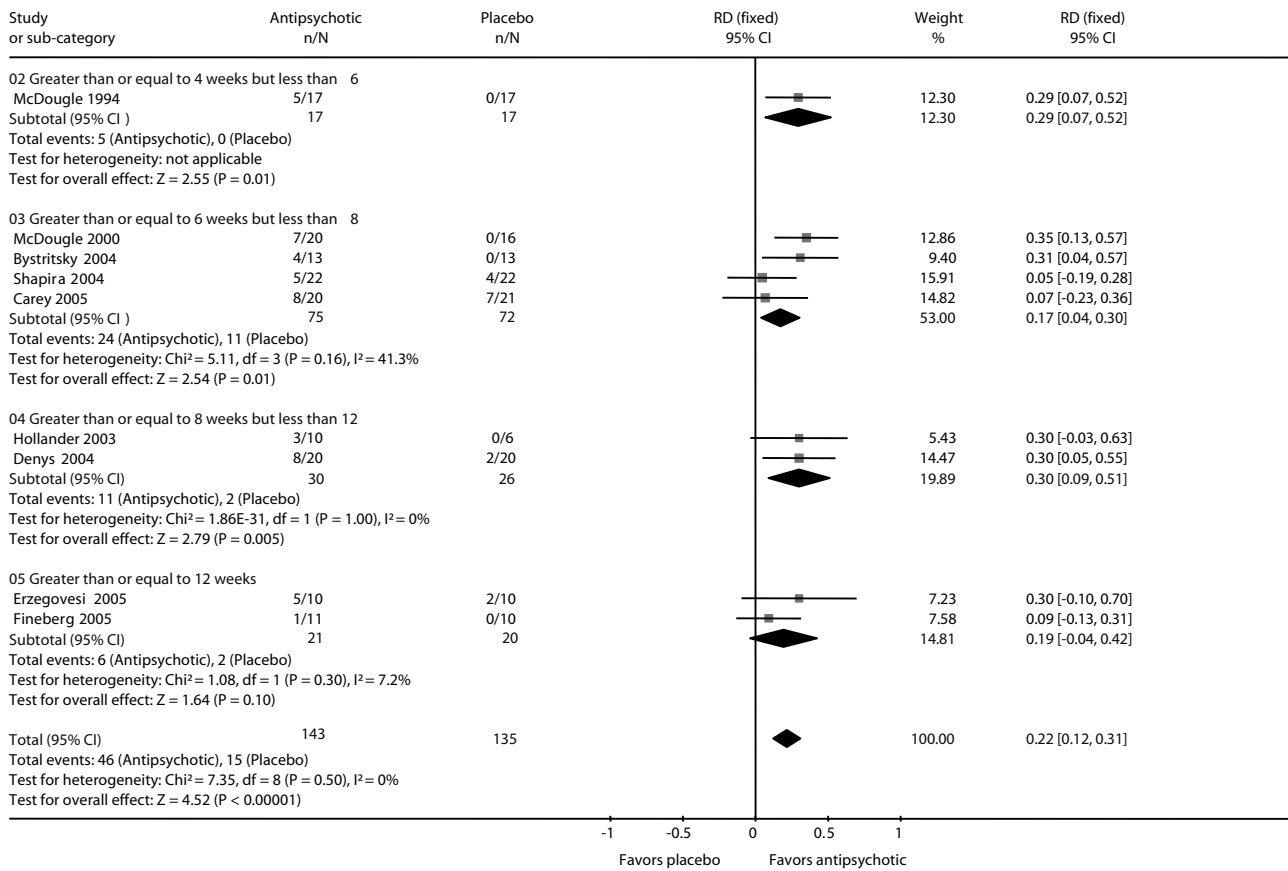


Figure 3 Stratification by duration of antipsychotic augmentation. A forest plot comparing absolute risk difference (ARD) between proportion of treatment responders in the antipsychotic augmentation and placebo group in individual treatment studies, and cumulative meta-analysis as stratified by length antipsychotic augmentation was followed. Treatment response is characterized by a greater than a 35% reduction in Y-BOCS rating from baseline at the end of augmentation. A positive ARD favors antipsychotic augmentation.

treatment with at least one additional agent before enrollment in this study.

There was no evidence suggesting a treatment effect of antipsychotic augmentation in OCD patients who received less than 12 weeks of maximal SRI treatment. The ARD of a treatment response in the group of OCD patients receiving less than 12 weeks of maximal SRI monotherapy was 0.06 (95% CI: -0.13, 0.24) (Figure 4). This lack of efficacy was attributable to the high rate of treatment response to continued SRI monotherapy among these subjects (25.6%) as compared to 4.3% in those receiving maximal SRI monotherapy for 12 weeks or greater.

Proportion of treatment responders and comorbid tic disorder

All nine studies involving 278 contributed to the analysis, with five studies^{39,43–46} including OCD subjects with comorbid tic disorders. McDougle *et al.*⁴⁴ reported a significantly increased rate of response to antipsychotic augmentation in the OCD patients with comorbid tics compared to those without. None of the four subsequent studies were able to confirm this study owing to small sample sizes. The results from the Hollander *et al.* trial were excluded

from meta-analysis because all three of the subjects with comorbid tic disorders were randomized to the antipsychotic augmentation group (one of three responded) and thus it was impossible to calculate ARD and weighted mean difference.

In our meta-analysis, OCD patients with comorbid tic disorders appeared to demonstrate a favorable response as compared to OCD patients without comorbid tics. The ARD for treatment-resistant OCD patients with comorbid tics was 0.43 (95% CI: 0.19, 0.68), making the NNT in this subpopulation 2.3 (95% CI: 1.5, 5.2). Among OCD patients without comorbid tics, the NNT was 5.9 (ARD=0.17 (95% CI: 0.07, 0.27)). The forest plot of this subgroup comparison is shown in Figure 5.

Proportion of treatment responders and comorbid depression symptoms

Out of the nine included trials in this systematic review, only Denys *et al.*⁴⁰ and McDougle *et al.*⁴⁵ reported mean change in HAM-D score before and after augmentation in both the antipsychotic and placebo augmentation groups. Both Denys *et al.*⁴⁰ (6.8 point decline in antipsychotic augmentation group compared to 2.6 in the placebo group) and McDougle

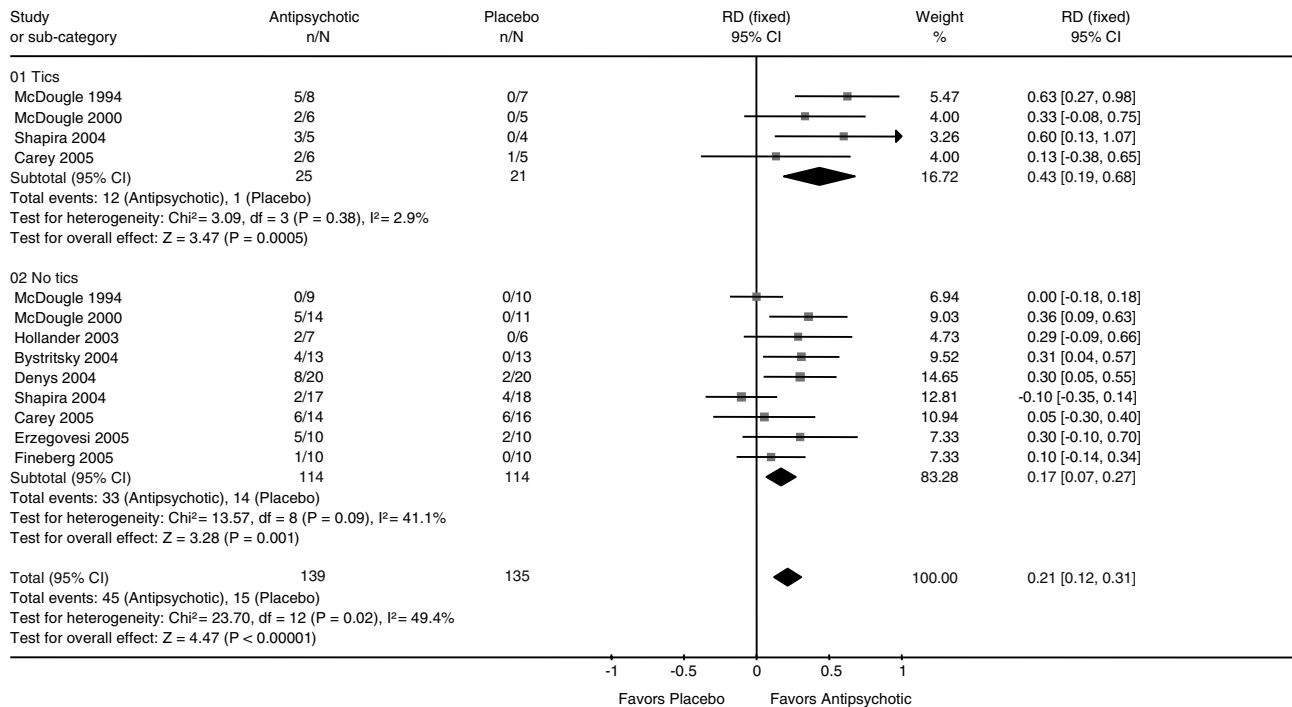


Figure 4 Stratification by minimum length of maximal dose serotonin reuptake inhibitor (SRI) monotherapy before augmentation. A forest plot comparing absolute risk difference (ARD) between proportion of treatment responders in the antipsychotic augmentation and placebo group in individual treatment studies and cumulative meta-analysis as stratified by length of maximal dose SRI monotherapy before augmentation. Treatment response is characterized by a greater than a 35% reduction in Y-BOCS rating from baseline at the end of augmentation. A positive ARD favors antipsychotic augmentation.

*et al.*⁴⁵ (4.1 point decline in antipsychotic augmentation group compared to 3.0 point increase in the placebo group) reported significant improvements in HAM-D scores from antipsychotic augmentation. Four of the remaining studies reported no significant change in HAM-D ratings in the antipsychotic augmentation versus placebo groups, although no data were available from these studies.^{38,41,43,44} The remaining studies did not report HAM-D as an outcome measure.^{39,42,46} No meta-analysis was performed on the available data as the missing data were not missing at random, that is, there was a bias toward presenting actual numeric data for changes in HAM-D score within individual studies when these results were significant.

Proportion of treatment drop-outs in antipsychotic versus placebo augmentation groups

All nine studies including 278 total subjects contributed to this analysis. There was no difference in the number of drop-outs in the antipsychotic augmentation versus placebo augmentation arms of included randomized-control clinical trials (ARD = 0.01, 95% CI: -0.06, 0.08). There were 14 drop-outs (out of 143 subjects) in the antipsychotic augmentation arm and 11 drop-outs (out of 135 subjects) in the placebo augmentation arm. More than half ($N=6$) of the placebo augmentation drop-outs were contributed by one study.³⁷

Proportion of subjects reporting sedation in antipsychotic versus placebo augmentation groups

Only four of the nine included studies reported on rates of sedation in both the antipsychotic versus placebo augmentation group.^{39,40,43,45} Three of these studies reported a significant increased risk of sedation in the antipsychotic versus placebo augmentation groups (McDougle *et al.*⁴⁵ (risperidone) – ARD = 0.35, 95% CI: 0.06, 0.64; Carey *et al.* (quetiapine) – ARD = 0.42, 95% CI: 0.14, 0.69; and Denys *et al.* (quetiapine) – ARD = 0.60, 95% CI: 0.37, 0.83). The fourth demonstrated a borderline significant result (Hollander *et al.* (risperidone) – ARD = 0.30, 95% CI: -0.03, 0.63). Of the five remaining studies, two studies, Fineberg *et al.* (eight of 11) and Erzegovesi *et al.* (seven of 20), mentioned sedation rates in the antipsychotic augmentation group only. As all of these published studies included a paragraph documenting examining side-effect profile, it was judged that missing results in the literature were not missing at random. This was because there was a proper publication bias to report only significantly different side-effect results in the literature. For this reason, a meta-analysis was not conducted on this outcome measure.

Proportion of subjects reporting increased appetite in antipsychotic versus placebo augmentation groups

Only three of eight included studies reported rates of increased appetite reported by subjects in the anti-

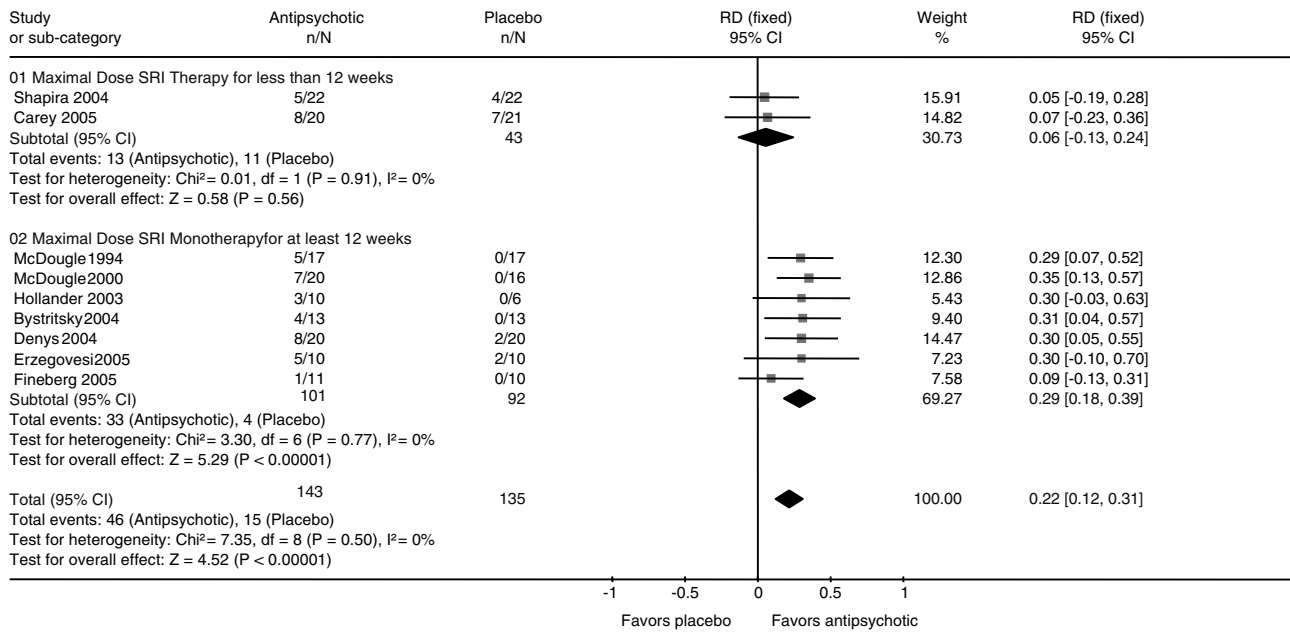


Figure 5 Stratification by the presence or absence of comorbid tic disorder. A forest plot comparing absolute risk difference (ARD) between proportion of treatment responders in the antipsychotic augmentation and placebo group in individual treatment studies and cumulative meta-analysis as stratified by the presence or absence of comorbid tic disorder. Treatment response is characterized by a greater than a 35% reduction in Y-BOCS rating from baseline at the end of augmentation. A positive ARD favors antipsychotic augmentation.

psychotic augmentation and placebo groups.^{39,40,45} Denys *et al.* (quetiapine) reported a significant rate of increased appetite in the antipsychotic augmentation versus the placebo group (ARD=0.20, 95% CI: 0.01, 0.39). McDougle *et al.*⁴⁵ reported a higher but non-significant rate of increased appetite in the antipsychotic augmentation than in the placebo group (ARD=0.11, 95% CI: -0.16, 0.39). Carey *et al.* reported a lower rate of increased appetite in the antipsychotic augmentation group than in placebo (ARD=-0.05, 95% CI: -0.20, 0.11). Among the other six studies included in this review, only Erzegovesi *et al.* reported on the rate of increased appetite – three of 10 subjects in the risperidone augmentation group but did not report the rate of this side effect in the placebo group. Shapira *et al.* reported a higher amount of weight gain of 2.8 ± 3.1 kg during the 6-week olanzapine augmentation phase than 0.5 ± 1.8 kg in the placebo group, but did not report rate of increased appetite. Again, as non-reported results in the literature were judged not to be missing at random, with a publication bias to report clinically meaningful differences in side effects, a meta-analysis was not conducted on these data.

Proportion of extrapyramidal side effects (acute dystonia, akathisia or restlessness) in the antipsychotic versus placebo augmentation groups

Only two of nine published studies reported on the rate of extrapyramidal symptoms – defined as acute dystonia, akathisia or restlessness – in both the placebo and antipsychotic augmentation groups. McDougle *et al.*⁴⁵ (risperidone – restlessness, ARD=-0.08, 95% CI: -0.39, 0.24) reported a decreased rate

of extrapyramidal-like symptoms in the risperidone augmentation compared to the control group and Hollander *et al.* reported observing no extrapyramidal symptoms in either treatment groups. Of the remaining studies, Fineberg *et al.* reported a rate of akathisia of four of 11 subjects in the quetiapine augmentation group and McDougle *et al.* reported nine of 31 subjects receiving haloperidol augmentation experienced akathisia (this result included 14 patients who received open-label haloperidol at the end of the double-blind phase), but neither study reported rates in the placebo group. As non-reported results were believed not to be missing at random from the literature, no meta-analysis was conducted for this outcome measure.

Discussion

This systematic review demonstrates that antipsychotic augmentation is an effective treatment intervention for OCD patients who fail to exhibit a treatment response after 12 weeks of maximal therapy with at least one SRI agent. The NNT for antipsychotic augmentation is 4.5 (95% CI: 3.2–7.7) when treatment response is defined by a 35% decline in Y-BOCS ratings. Nearly one-third of treatment-refractory OCD patients exhibited a treatment response to antipsychotic augmentation.

Stratification by specific antipsychotic agent demonstrated strong evidence of efficacy for haloperidol or risperidone augmentation compared to placebo augmentation; however, data analysis did not prove efficacy for quetiapine or olanzapine. Two

possible explanations for the difference in efficacy between antipsychotic agents seem plausible. First, haloperidol and risperidone may simply be more effective augmentation agents for treatment-refractory OCD than olanzapine or quetiapine. A possible pharmacological rationale for this hypothesis could be the greater D2-dopamine receptor affinity of haloperidol and risperidone than of other antipsychotic agents. Another possible explanation for the observed antipsychotic medication difference may also be that it is a product of the study heterogeneity used in evaluating the efficacy of these agents. For this reason, comparison between pharmacological agents across different placebo-controlled studies is often erroneous. The differences between the study designs of some trials comparing different antipsychotic augmentation agents to placebo could explain the discrepancy in efficacy. The Shapira *et al.* study of olanzapine and Carey *et al.* study of quetiapine included OCD patients who had been treated with 8 weeks or less of maximal SRI monotherapy before augmentation and thus these trials experienced a much higher response to continued SRI monotherapy in their placebo augmentation group than other trials. Additionally, the Bystritsky *et al.* study of olanzapine was plagued by a high drop-out rate compared to other studies. Additional studies of olanzapine and quetiapine are needed to prove efficacy as augmentation agents for treatment-refractory OCD. Head-to-head trials between antipsychotic augmentation agents (such as the Li *et al.* trial) are needed to show which antipsychotic agents are most effective.⁴⁷

Stratification by the length of antipsychotic augmentation did not reveal any difference in the number of treatment responders beyond 4-week duration. This result suggests that this intervention works relatively quicker in treating OCD, and patients are unlikely to improve if they have not responded after 1 month of intervention. On the other hand, stratification by length of maximal dose on SRI therapy before augmentation suggested that there remains a high treatment response rate even 2–3 months after initiation of SRI agents and that antipsychotic augmentation should only be implemented after an OCD patient has failed to respond to maximal dose SRI monotherapy for a full 3 months.

The subgroup of OCD patients with comorbid tics (NNT = 2.3) appeared to have a particularly beneficial response to treatment with antipsychotic augmentation. Current evidence supports using risperidone or haloperidol for this sub-population as these medications have proven efficacy for both Tourette syndrome^{48,49} and antipsychotic augmentation for treatment refractory OCD.

Antipsychotic agents were generally well tolerated in these double-blind, placebo-controlled trials with similar drop-out rates in the antipsychotic augmentation and placebo groups. The only very pronounced side effect was that of sedation in the quetiapine-augmentation studies. It should be noted that the short follow-up intervals of these studies prevented

the assessment of weight gain, which is another important side effect of antipsychotic agents.

This systematic review combines nine double-blind, randomized controlled clinical trials involving 278 subjects in the published literature to demonstrate that antipsychotic augmentation is a more effective intervention than placebo for treatment-refractory OCD at the $P < 0.00001$ level. There was also no evidence of publication bias based on the funnel plot of published data. However, publication bias in this literature cannot be ruled out. Requiring pre-registration of clinical trials as a requirement of acceptance into major psychiatric journals would help eliminate this potential limitation of further systematic reviews in the area and add greatly to the credibility of the current psychiatric drug treatment literature. Given the strong effect size and statistical significance of this finding, further research efforts should be focused on additional crossover studies to distinguish which antipsychotic augmentation agent is actually most effective in treating treatment-refractory OCD, in determination of which types of OCD patients (i.e., which comorbid conditions and OCD symptom dimensions predict favorable response) and in developing novel treatment interventions for the roughly two-thirds of treatment-refractory OCD patients who do not respond to antipsychotic augmentation.

Acknowledgments

We thank Bryann Baker BA, Alexander Bystritsky MD, Paul Carey MD, Damiaan Denys MD, Stefano Erzegovesi MD, Naomi Fineberg MD, Eric Hollander MD, Nathan Shapira MD and Thanusha Sivakumaran BA for conducting data analysis and answering questions related to their respective studies and to Christopher McDougale MD for leaving the individual patient data necessary to conduct this meta-analysis within his manuscript. Without their generosity and openness with regard to their study data and spirit of collegiality, this analysis would not have been possible. Dr Michael Bloch was supported through a Tourette Syndrome Association Research Award, the NIH Loan Repayment Program and an institutional NIMH T32 training grant.

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