

Antipsychotics for obsessive-compulsive disorder: Weighing risks vs benefits

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Mr. E, age 37, has a 20-year history of obsessive-compulsive disorder (OCD), with comorbid generalized anxiety disorder and hypertension. His medication regimen consists of lisinopril, 40 mg/d, to control his blood pressure, and escitalopram, 40 mg/d, for OCD and anxiety symptoms, which he started taking 12 weeks ago. Mr. E also has completed cognitive-behavioral therapy (CBT) with Exposure Response Prevention (ERP) therapy for his OCD symptoms. Although escitalopram and CBT have reduced Mr. E's OCD symptoms, he still exhibits obsessions, such as fear of contamination, and compulsions, including handwashing, that are time-consuming and cause significant social and occupational distress. His Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score is 24. Mr. E asks his psychiatrist if there is anything else that may provide benefit. He is started on risperidone, 0.5 mg at bedtime, in addition to his existing medications. After 8 weeks of treatment with risperidone, Mr. E's Y-BOCS score decreases to 21.

OCD, a chronic illness with a prevalence of approximately 1% to 2%, is characterized by

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uncontrollable, recurrent thoughts or urges (obsessions) as well as actions (compulsions) in response to those thoughts and/or urges. OCD symptom severity is commonly measured using the Y-BOCS, a 10-item clinician-rated scale. The Y-BOCS score ranges from 0 to 40, with higher scores indicating greater severity of symptoms. First-line treatment for OCD includes selective serotonin reuptake inhibitors (SSRIs) and CBT. The use of antipsychotics for treating OCD is indicated in treatment guidelines (*Box*,¹⁻³ page 48) and has been the subject of multiple studies.¹⁻⁴

Efficacy


The 2013 National Institute for Health Care and Excellence Evidence Update included a 2010 Cochrane Review of 11 randomized controlled trials (RCTs) of

Practice Points

- In patients with a partial response to selective serotonin reuptake inhibitors (SSRIs) and/or cognitive-behavioral therapy (CBT), **American Psychiatric Association guidelines recommend that augmentation may be preferable to switching treatments.**
- **Assessing the potential harms related to the use of antipsychotics in treating obsessive-compulsive disorder (OCD) is complicated, because this information is not always assessed in trials.**
- Although most evidence supports using Exposure Response Prevention (ERP) over antipsychotics for treating OCD symptoms that have not responded to SSRIs, **ERP poses its own challenges that may limit clinical utility.**



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Box

Antipsychotics for OCD: What the guidelines recommend

The 2013 American Psychiatric Association (APA) obsessive-compulsive disorder (OCD) treatment guidelines include recommendations regarding the use of antipsychotics in patients who do not respond to first-line treatment with selective serotonin reuptake inhibitors (SSRIs) and/or cognitive-behavioral therapy (CBT). The APA recommends evaluating contributing factors, including comorbidities, family support, and ability to tolerate psychotherapy or maximum recommended drug doses, before augmenting or switching therapies.¹

In patients with a partial response to SSRIs and/or CBT, the APA suggests that augmentation may be preferable to switching treatments. Augmentation strategies for SSRIs include antipsychotics or CBT with Exposure Response Prevention (ERP); augmentation strategies for CBT include SSRIs. Combining SSRIs and CBT may decrease the chance of relapse when

medication is discontinued. If the patient has a partial response to ERP, intensification of therapy also can be considered based on patient-specific factors. In non-responders, switching therapies may be necessary. Alternative treatments including a different SSRI; an antidepressant from a different class, such as clomipramine or mirtazapine; an antipsychotic; or CBT.

The 2006 National Institute of Health and Clinical Excellence guidelines for OCD recommend additional high-intensity CBT, adding an antipsychotic to an SSRI or clomipramine, or combining clomipramine with citalopram in non-responders. There is no guidance regarding the order in which these treatments should be trialed. Antipsychotics are recommended as an entire class, and there are no recommendations regarding dosing or long-term risks. These guidelines are based on limited evidence, including only 1 trial of quetiapine and 1 trial of olanzapine.^{2,3}

Clinical Point

In patients with a partial response to SSRIs and/or CBT, the APA suggests that augmentation may be preferable to switching treatments

antipsychotics as adjunctive treatment to SSRIs.⁵ All trials were <6 months, and most were limited regarding quality aspects. Two trials found no statistically significant difference with olanzapine in efficacy measures (Y-BOCS mean difference [MD] -2.96; 95% confidence interval [CI] -7.41 to 1.22; effect size $d = -2.96$ [-7.14, 1.22]). Among patients with no clinically significant change (defined as $\leq 35\%$ reduction in Y-BOCS), there was no significant difference between groups ($n = 44$, 1 RCT, odds ratio [OR] 0.76; 95% CI 0.17 to 3.29; effect size $d = 0.76$ [0.17, 3.29]). Studies found increased weight gain with olanzapine compared with antidepressant monotherapy.

Statistically significant differences were demonstrated with the addition of quetiapine to antidepressant monotherapy as shown in Y-BOCS score at endpoint (Y-BOCS MD -2.28; 95% CI -4.05 to -0.52; effect size $d = -2.28$ [-4.05, -0.52]). Quetiapine also demonstrated benefit for depressive and anxiety symptoms. Among patients with no clinically significant change (defined as $\leq 35\%$ reduction in Y-BOCS),

there was a significant difference between groups ($n = 80$, 2 RCTs, OR 0.27; 95% CI 0.09 to 0.87; effect size $d = 0.27$ [0.09, 0.87]).

Adjunctive treatment with risperidone was superior to antidepressant monotherapy for participants without a significant response in OCD symptom severity of at least 25% with validated measures (OR 0.17; 95% CI 0.04 to 0.66; effect size $d = 0.17$ [0.04, 0.66]), and in depressive and anxiety symptoms. Mean reduction in Y-BOCS scores was not statistically significant with risperidone (MD -3.35; 95% CI -8.25 to 1.55; effect size $d = -3.35$ [-8.25, 1.55]).⁵

A 2014 meta-analysis by Veale et al³ included double-blind, randomized trials that examined atypical antipsychotics compared with placebo for adults with OCD that used an intention-to-treat analysis. Unlike the Cochrane Review, these studies used the Y-BOCS as a primary outcome measure. Participants had a Y-BOCS score of ≥ 16 ; had at least 1 appropriate trial of an SSRI or clomipramine (defined as the maximum dose tolerated for at least 8 weeks);



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and had to continue taking the SSRI or clomipramine throughout the trial, which was a duration of at least 4 weeks. Of 46 published antipsychotic papers that were identified, 20 were excluded and 12 were duplicates. The primary reason for trial exclusion was open-label study design.

Fourteen articles were included in the meta-analysis, but all had small sample sizes and no long-term follow-up data.³ Antipsychotics in the meta-analysis included risperidone (4 studies), quetiapine (5 studies), olanzapine (2 studies), aripiprazole (2 studies), and paliperidone (1 study).

The overall difference in Y-BOCS score change between drug and placebo groups was 2.34 points, which had an overall effect size of $d = 0.40$. Those taking antipsychotics had approximately a 10% reduction in Y-BOCS score over time. The overall difference was statistically significant with risperidone (overall mean reduction of 3.89 points on the Y-BOCS; 95% CI 1.43 to 5.48; effect size of $d = 0.53$) and aripiprazole (difference in Y-BOCS outcome 0.1 scores of 6.29 points; effect size of $d = 1.11$). One trial of risperidone used a low dose (0.5 mg) and had a larger effect size than the studies that used moderate doses. The overall difference was not statistically significant for quetiapine (difference of Y-BOCS outcome scores of 0.81 points) or olanzapine (difference in Y-BOCS outcome scores of -0.19 ; indicating <1 point difference on the Y-BOCS).³

Studies included in the meta-analysis ranged in durations from 6 to 16 weeks; duration of ≥ 4 weeks did not make a difference in response. One study demonstrated a worsening of symptoms in the quetiapine group between weeks 4 and 12. Only 4 studies included most patients that had a previous trial of CBT. One study with an additional treatment arm evaluating CBT found that adding CBT was superior to adjunctive risperidone or placebo. Another study found that adding clomipramine or placebo to fluoxetine was superior to treatment with quetiapine. All study participants had Y-BOCS scores that indicated moderate

OCD severity (16 to 23). Those with higher baseline Y-BOCS scores had a larger effect size for risperidone and quetiapine.³

Two studies included in the meta-analysis classified OCD symptoms by subtype, such as by dimensions of checking; symmetry, ordering, counting, and repeating; contamination and cleaning; and hoarding. Currently, no clinically significant predictor of outcome of antipsychotic therapy has been identified. Two studies included in the meta-analysis assessed patients with comorbid tic disorders and found no difference by treatment. One study demonstrated benefit of haloperidol in patients with comorbid tic disorders compared with those without comorbid tic disorders. Of note, none of the studies included in the meta-analysis excluded patients with hoarding characteristics, which generally indicate a worse prognosis with treatment.³

In 2015, Dold et al⁶ provided an update to a 2013 meta-analysis⁷ assessing antipsychotic augmentation of SSRIs in treatment-resistant OCD. This update included 2 new RCTs. The 2013 analysis⁷ concluded that risperidone should be considered first-line and is preferred over olanzapine and quetiapine. However, the update found the highest effect size for aripiprazole ($d = -1.35$), followed by haloperidol ($d = -0.82$), risperidone ($d = -0.59$), quetiapine ($d = -0.50$), olanzapine ($d = -0.49$), and paliperidone ($d = -0.21$).^{6,7}

The 2015 update⁶ concluded that the antipsychotic doses used in trials were moderate and that there was no association between dose and treatment response, indicating that high doses of antipsychotics may not be more effective. Dold et al⁶ postulated that the antipsychotic doses required for treating OCD are similar to those used in treating major depressive disorder and lower than doses used in treating schizophrenia. The 2013 meta-analysis demonstrated that moderate doses of antipsychotics resulted in statistically significant efficacy (relative risk [RR] = 3.99, 95% CI 1.92 to 8.27), while low

Clinical Point

A 2015 study found no association between antipsychotic dose and treatment response, suggesting higher doses may not be more effective

Clinical Point

Consider the potential physical risks of long-term antipsychotic use, such as weight gain and extrapyramidal side effects

doses did not demonstrate statistical significance (RR = 1.06, 95% CI 0.45 to 2.53).^{6,7}

The 2015 subgroup analysis update evaluated the duration of SSRI treatment prior to the antipsychotic augmentation phase, but did not demonstrate statistically significant efficacy for studies with <8 weeks' duration of SSRI treatment, further highlighting the need for extended duration of treatment with an SSRI prior to augmentation.⁶

The 2013 meta-analysis discussed populations with comorbid tic disorders, including a study that found that patients with OCD and comorbid tic disorders benefit more from adjunctive antipsychotic therapy than those without the comorbidity. The 2015 update excluded trials that included patients with comorbid tic disorders to reduce bias, which did not affect the overall effect sizes of the data.^{6,7}

In summary, efficacy has been demonstrated for risperidone and aripiprazole. There has been no benefit demonstrated with olanzapine and limited benefit with quetiapine. One study suggested worsening of symptoms with quetiapine the longer that treatment persisted.^{3,5-7}

Safety

Assessing potential harms related to the use of antipsychotics in treating OCD is complicated, because this information is not always assessed in trials. Instead, researchers often focus on exploring potential benefits because long-term effects of antipsychotics, including sedation, weight gain, metabolic syndrome, and extrapyramidal side effects, are well documented.³

Trials included in the meta-analysis by Veale et al³ had a maximum duration of 16 weeks, so it is likely that many of the potential harms of antipsychotic use would not yet have been measurable. The authors cautioned that, although aripiprazole and risperidone demonstrated benefit, their benefit must be weighed against the potential physical risks of long-term antipsychotic use.³

One study that was not included in the meta-analysis by Veale et al³ evaluated individuals who did not respond to a SSRI, and randomly assigned them to quetiapine, olanzapine, or risperidone plus CBT. At 1-year follow-up, 50% of participants receiving an antipsychotic had an increase of >10% in body mass index (BMI) and had higher fasting blood sugars compared with only 15.2% of participants with increased BMI in the comparison group (SSRI responders).³

Foa et al⁸ investigated long-term outcomes (ie, 6 months) of SSRI augmentation with ERP or risperidone in patients with OCD. Forty patients were randomized to receive risperidone, and 9 were considered responders. Only 8 chose to enter the maintenance phase, and of those participants, 5 did not complete the study. Two withdrew due to worsening depression, 2 withdrew due to intolerable adverse effects, and 1 was lost to follow-up. Unfortunately, there was no further discussion of what the intolerable adverse effects were.⁸

Patients with comorbid schizophrenia and OCD face additional risks. Lifetime prevalence rates of OCD are greater in persons with schizophrenia compared with the general population (26% vs 8%, respectively). Most studies have demonstrated poor prognosis and medication adherence among patients with comorbid schizophrenia and OCD. Fonseka et al⁹ assessed the risk of antipsychotic induction and exacerbation of OCD symptoms in patients with schizophrenia. Induction and exacerbation of OCD symptoms with clozapine was evident in several case reports, series, and retrospective reviews. A dose-dependent relationship is demonstrated in the literature as well. It is thought that this risk is related to clozapine's action at the 5-HT₂ receptor. Although evidence is limited, it appears that compared with other antipsychotics, clozapine is associated with the greatest risk of induction and exacerbation of OCD symptoms, with 20% to 28% of clozapine-treated patients exhibiting induction of OCD symptoms and 10% to

18% exhibiting an exacerbation of existing OCD symptoms.

Evidence of olanzapine induction and exacerbation of OCD symptoms is also limited to case reports and retrospective studies. However, some studies have estimated induction of OCD symptoms with olanzapine in 11% to 20% of patients.⁹ There is insufficient evidence to form conclusions regarding other antipsychotics. Fonseka et al⁹ recommends switching to an antipsychotic with lower 5HT-2 binding affinity or adding an SSRI, such as fluvoxamine, if induction or exacerbation of OCD symptoms occurs.

Consider long-term risks

The evidence for benefits with antipsychotics in treatment-resistant OCD is limited by different populations recruited, small sample sizes, and lack of long-term follow-up. Most evidence supports using ERP over antipsychotics for treating OCD symptoms that have not responded to SSRIs. However, ERP poses its own challenges that may limit clinical utility, such as economic and time restraints. Therefore, benefits with antipsychotics, such as risperidone and aripiprazole, must be weighed against potential long-term risks of treatment, including sedation, weight gain, metabolic syndrome, and extrapyramidal side effects.

Regarding Mr. E's case, because he had been maximized on SSRI therapy for an adequate duration (escitalopram, 40 mg/d, for 12 weeks) and completed CBT with ERP with a partial response, adding risperidone, 0.5 mg at bedtime, was an appropriate treatment option that is supported by the available guidelines and evidence. The risperidone dose is reflective of the initial dosing strategies used in clinical trials. It is recommended to assess efficacy of treatment at 8 weeks with a validated measure, such as the Y-BOCS. A dose increase may be needed to achieve clinically significant symptom improvement, because moderate doses of risperidone have demonstrated efficacy in

Related Resource

- Schatzberg AF, Nemeroff CB. The American Psychiatric Association Publishing textbook of psychopharmacology. 5th ed. Arlington, VA: American Psychiatric Association Publishing; 2017.

Drug Brand Names

Aripiprazole • Abilify	Lisinopril • Prinivil, Zestril
Citalopram • Celexa	Mirtazapine • Remeron
Clomipramine • Anafranil	Olanzapine • Zyprexa
Clozapine • Clozaril	Paliperidone • Invega
Escitalopram • Lexapro	Quetiapine • Seroquel
Fluoxetine • Prozac	Risperidone • Risperdal
Haloperidol • Haldol	

trials; however, high doses of risperidone are unlikely to provide additional benefit and increase the risk of adverse effects. If risperidone does not provide a clinically favorable risk–benefit ratio for Mr. E, aripiprazole is a potential alternative.

References

- American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/ocd.pdf. Published July 2007. Accessed December 11, 2017.
- National Institute for Health and Care Excellence (NICE). Obsessive compulsive disorder. <http://arms.evidence.nhs.uk/resources/hub/1028833/attachment>. Updated September 18, 2013. Accessed December 11, 2017.
- Veale D, Miles S, Smallcombe N, et al. Atypical antipsychotic augmentation in SSRI treatment refractory obsessive-compulsive disorder: a systematic review and meta-analysis. *BMC Psychiatry*. 2014;14:317.
- Diagnostic and statistical manual of mental disorders, 5th ed. Washington, DC: American Psychiatric Publishing; 2013.
- Komossa K, Depping AM, Meyer M, et al. Second-generation antipsychotics for obsessive compulsive disorder. *Cochrane Database Syst Rev*. 2010;12:1-44.
- Dold M, Aigner M, Lanzenberger R, et al. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: an update meta-analysis of double-blind, randomized, placebo-controlled trials. *Int J Neuropsychopharmacol*. 2015;18(9). doi: 10.1093/ijnp/pyv047.
- Dold M, Aigner M, Lanzenberger R, et al. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. *Int J Neuropsychopharmacol*. 2013;16(3):557-574.
- Foa EB, Simpson HB, Rosenfield D, et al. Six-month outcomes from a randomized trial augmenting serotonin reuptake inhibitors with exposure and response prevention or risperidone in adults with obsessive-compulsive disorder. *J Clin Psychiatry*. 2015;76(4):440-446.
- Fonseka TM, Richter MA, Muller DJ. Second generation antipsychotic-induced obsessive-compulsive symptoms in schizophrenia: a review of the experimental literature. *Curr Psychiatry Rep*. 2014;16(11):510.

Clinical Point

Compared with other antipsychotics, clozapine is associated with the greatest risk of induction and exacerbation of OCD symptoms