Management of obsessive-compulsive disorder in adults

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive thoughts, images, or urges that cause anxiety or distress (obsessions), and by repetitive mental or behavioral acts (compulsions) that the individual feels driven to perform. Compulsions are done in response to the obsession (ie, to decrease distress or prevent a feared consequence from occurring, or according to rules that must be applied rigidly). Almost all individuals with OCD have both obsessions and compulsions.

OCD typically starts in childhood or adolescence, often persists throughout life if not successfully treated, and produces substantial impairment in functioning due to the severe and chronic nature of the illness.

OCD can be treated with cognitive-behavioral therapy using exposure and response prevention (CBT/ERP), serotonergic antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or clomipramine, or a combination of the two. Frequently, patients experience a partial response to treatment and warrant augmentation strategies.

This topic discusses the initial treatment choice and subsequent management of OCD in adults. Psychotherapy for OCD is discussed elsewhere. Other topics related to OCD in adults, children, adolescents, pregnancy, postpartum, and treatment of refractory OCD are found elsewhere.

- (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis".)

- (See "Obsessive-compulsive disorder in adults: Psychotherapy".)
- (See "Obsessive-compulsive disorder in pregnant and postpartum patients".)
- (See "Deep brain stimulation for treatment of obsessive-compulsive disorder".)

- (See "Obsessive-compulsive disorder in children and adolescents: Treatment overview".)
- (See "Obsessive-compulsive disorder in children and adolescents: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)

CHOOSING INITIAL TREATMENT

For most individuals with obsessive-compulsive disorder (OCD), we favor initiating treatment with cognitive-behavioral therapy using exposure and response prevention (CBT/ERP). Limited data suggest that CBT/ERP may be more effective than pharmacotherapy and does not expose the patient to side effects of medication. Treatment of OCD with CBT/ERP is discussed elsewhere. (See "Obsessive-compulsive disorder in adults: Psychotherapy".)

However, we do consider several factors in determining the choice of initial treatment. These include the severity of symptoms, presence of comorbidity, past treatment history, level of insight, willingness and ability to participate in CBT/ERP, the availability of CBT/ERP, cost of appropriate treatment, health insurance coverage, and patient preference.

Alternative initial treatment, depending on clinical scenario, include pharmacotherapy combined with CBT/ERP or pharmacotherapy only. Additionally, as treatment with both medication and CBT/ERP has consistently shown greater efficacy than pharmacotherapy alone, our preference is initiating treatment with combined, multimodal treatment [1-6]. Unfortunately, practical limitations (eg, greater cost, frequency of appointments, availability of therapists with the necessary expertise) typically limit this option.

- **Severe symptoms** – We initiate treatment with combined modality (CBT/ERP plus pharmacotherapy) for individuals with severe symptoms. We typically assess clinical severity with the Clinical Global Impressions Scale (CGI) scale (5 or above), or the Yale-Brown Obsessive Compulsive Scale (Y-BOCs; score >24). However, if the severity of symptoms precludes participation in CBT/ERP, we begin with pharmacotherapy, as this can lessen symptoms sufficiently for the individual to engage in CBT/ERP, if needed. (See 'SSRIs: First pharmacotherapeutic option' below.)

- **Unwilling/unable to participate in CBT/ERP; no response to past CBT/ERP** – We initiate pharmacotherapy (eg, selective serotonin reuptake inhibitor [SSRI] or clomipramine) for individuals who are unwilling or unable to participate in CBT/ERP, or who have previously

not responded to CBT. For example, we would treat an individual who has a strong preference against CBT/ERP, or is unwilling or unable to do the work required to benefit from CBT/ERP, with pharmacotherapy. Additionally, for individuals with limited ability to critically examine thoughts or feelings or who have a cognitive impairment, we choose pharmacotherapy as our first choice. (See 'SSRIs: First pharmacotherapeutic option' below.)

- **Co-occurring psychiatric disorder** – We initiate treatment with a combined modalities (CBT/ERP and SSRI) for individuals with a co-occurring psychiatric disorder (eg, major depression or social anxiety disorder) that is typically responsive to SSRI treatment, and who are willing to participate in CBT/ERP. The vast majority of patients with OCD have at least one comorbid depressive or anxiety disorder and are therefore likely to benefit most from the combination of pharmacotherapy and CBT/ERP. (See "Unipolar major depression in adults: Choosing initial treatment" and "Pharmacotherapy for social anxiety disorder in adults", section on 'Selective serotonin reuptake inhibitors'.)

- **Individuals with past response to pharmacotherapy (eg, SSRI, clomipramine)** – For individuals with favorable response to a particular medication (with or without CBT/ERP) in the past, we typically begin treatment with the same medication (with or without CBT). For example, if an individual has successfully responded to clomipramine in the past, we would use clomipramine as our first choice again.

- **Patient preference for combined treatment** – We initiate treatment with both pharmacotherapy and CBT/ERP in individuals who express a preference for combined treatment and stand to benefit from the combined treatment.

Meta-analyses and individual trials have found both CBT/ERP and pharmacologic management with serotonin reuptake inhibitor medications (eg, clomipramine or SSRIs) to be effective treatments for OCD [1,7-16]. Some data comparing them have suggested that while either are effective, CBT/ERP may be superior to pharmacotherapy [2]. As an example, in a 12-week trial, 122 individuals with OCD were randomized to treatment with ERP (provided intensively for 4 weeks followed by 8 weeks weekly maintenance sessions), clomipramine (200 to 250 mg/day), ERP plus clomipramine, or placebo [2]. At 12 weeks, a greater percentage of individuals responded (ie, CGI ≤2) to ERP compared with clomipramine or placebo (62 versus 42 versus 8 percent, respectively). Furthermore, individuals in the ERP group had a greater number of individuals “very much improved” at 12 weeks (ie, CGI = 1) than did those in either the clomipramine or placebo groups (41 versus 14 versus 0).

Combined therapy with medication and CBT/ERP has consistently been found to be more effective than pharmacotherapy alone for patients with OCD [1-6]. The dose of medication, the frequency and duration of treatment with CBT, and the timing of the treatments (eg, if they begin together or sequentially) can influence the effectiveness of this strategy. For example, in the 12-week trial above [2], individuals randomized to receive ERP alone had similar rates of both response (ie, CGI ≤2) and excellent response (ie, CGI = 1) as those randomized to ERP plus clomipramine (response rate: 62 and 60 percent respectively; excellent response rate: 41 and 43 percent respectively). However, ERP and clomipramine were started at the same time, such that the full effects of clomipramine may not have been fully realized. This contrasts with trials in which CBT was added to individuals already treated with 12 weeks of medications in which the addition of ERP appears to improve rates of response [4-6]. (See 'Augmentation with CBT/ERP' below.)

Further discussion of psychotherapy for OCD, including specifics on administering psychotherapy, can be found elsewhere. (See "Obsessive-compulsive disorder in adults: Psychotherapy".)

SSRIS: FIRST PHARMACOTHERAPEUTIC OPTION

For most individuals with obsessive-compulsive disorder (OCD) who are starting pharmacotherapy instead of or in addition to cognitive-behavioral therapy using exposure and response prevention (CBT/ERP), we prefer to use a selective serotonin reuptake inhibitor (SSRI) rather than other antidepressants (ie, clomipramine) as the initial pharmacologic option. Our preference for SSRIs rather than other antidepressants comes from the superior side effect profile and ease of use for SSRIs [7,17-25]. (See 'Choosing initial treatment' above and 'Efficacy of serotonin reuptake inhibitors' below and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

Choosing among SSRIs — We choose from among the SSRIs based on each medication's side effect profile, drug-drug interactions, and the individual's prior treatment response. In cases where the individual has successfully responded to an agent in the past, we often choose that agent again. We also consider patient preference. (See 'Choosing initial treatment' above.)

For example, in an individual who is concerned about medication-related weight gain, we would choose escitalopram and avoid paroxetine, as paroxetine is associated with more weight gain. Side effects of commonly used antidepressants are found in the table (table 1).

Indirect comparisons of effectiveness suggest that while SSRIs tested have similar efficacy for symptom reduction in treatment of OCD, they differ in terms of adverse effects [7]. (See 'Efficacy of serotonin reuptake inhibitors' below and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

Starting and titrating SSRIs — To avoid side effects and increase tolerability, we start individuals at the lowest initial starting dose recommended for the individual medication. We typically titrate at weekly or twice monthly intervals to the maximum tolerated dose within the therapeutic range; however, the pace of dose titration depends on several factors, including the patient's sensitivity to side effects, frequency of visits, treatment setting, and patient adherence. As an example, in an individual who has tolerated treatment with fluoxetine in the past, we typically begin at 20 mg and titrate every four to five days. However, for an individual with no prior history of treatment with SSRIs, in those with reported sensitivity to side effects, or in those with co-occurring anxiety disorders (ie, generalized anxiety disorder, illness anxiety disorder, panic disorder), we typically start at a lower starting dose (eg, fluoxetine 10 mg) and titrate in 10 mg increments every 7 to 10 days, as tolerated.

Starting doses and dose titration increments for SSRIs in the treatment of OCD are found in the table (table 2).

Prescribing and titrating SSRIs are discussed further elsewhere. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Administration' and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Dose' and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Side effects'.)

Therapeutic trial — If a given medication is tolerated by the patient, we ensure that a full therapeutic trial at a therapeutic dose of that medication is completed before it can be considered to be ineffective, and before considering further titration to supratherapeutic doses or augmentation strategies (table 2). (See 'Inadequate response to initial treatment' below.)

We consider a therapeutic trial to be 8 to 12 weeks, with at least 4 to 6 weeks at the maximum tolerated dose within the therapeutic range. We explain this to the individual so that they do not prematurely stop the medication before a full therapeutic trial has been completed. The treatment response curve appears to follow a logarithmic shape, with the greatest incremental benefits occurring on average by week 6 [17].

Most fixed-dose trials of the serotonergic antidepressants studied in OCD suggest that higher doses led to greater probability of response and/or greater mean degree of improvement, compared with lower doses [26-30]. However, a meta-analysis that supported this dose-

response relationship also found that higher doses are associated with a higher proportion of dropouts due to side effects [31]. (See 'Efficacy of serotonin reuptake inhibitors' below and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

Defining response and frequency of monitoring — We define response as a minimum of 35 percent decrease in the Yale-Brown Obsessive Compulsive scale (Y-BOCS) score. We define remission as Y-BOCS score <12 [32]. However, response to treatment of OCD has been variably defined.

In a standard outpatient treatment setting, we typically monitor individuals who have been started on pharmacotherapy twice monthly for one month and then approximately monthly thereafter. The frequency of the visits depends on the severity of the individual's symptoms, whether suicidal ideation is present, the complexity introduced by comorbid conditions, and the presence of side effects. We see individuals with any of these factors more frequently (ie, once per week or more often).

At each visit, we review symptoms and their effect on the individual's functioning, progress in treatment, side effects of medications, and reinforce the need for completion of a full therapeutic trial. Additionally, we administer a Y-BOCS monthly or more frequently. If time does not permit, we typically monitor with the Obsessive-Compulsive Inventory-Revised, a quick self-report measure that patients can complete in 5 to 10 minutes.

Efficacy of serotonin reuptake inhibitors — Our goal is elimination of symptoms of OCD; however, monotherapy typically leads to only partial amelioration of symptoms. In clinical trials, treatment with serotonin reuptake inhibitors (ie, SSRI, clomipramine) generally leads to clinically significant improvement in 40 to 60 percent of participants. On average, individuals experience a 20 to 40 percent reduction in symptoms within 12 weeks of treatment with monotherapy [25,33]. Therefore, adding CBT/ERP and/or augmenting with adjunctive medications is frequently necessary to achieve fuller response.

Data from clinical trials support the use of serotonin reuptake inhibitors in the treatment of OCD [1,7,17,25,33]. As an example, in a meta-analysis of 17 randomized trials with a total of 3097 patients with OCD, SSRIs as a group were more effective than placebo in reducing symptoms of OCD at 6 to 13 weeks posttreatment (Y-BOCS weighted mean difference 3.21, 95% CI -3.84 to -2.57) [7]. Furthermore, in a meta-analysis of 13 studies including 2697 participants with OCD, individuals in the SSRI treatment group had a higher rate of response (variably defined as 25 to 35 percent reduction in Y-BOCS or a Clinical Global Impressions Scale [CGI] score of 1 or 2) than individuals in the placebo arm (relative risk 1.84, 95% CI 1.56-2.17) [7]. The weighted mean difference for the individual SSRI medications included (citalopram, fluoxetine,

fluvoxamine, paroxetine, and sertraline) were similar to one another, indicating that they appear to be similarly effective versus placebo in treating symptoms of OCD.

Direct and indirect comparisons between clomipramine and SSRIs have not shown either to be superior to the other for the treatment of OCD [1,8,18-24]. Meta-analysis of randomized trials that did not directly compare SSRIs with clomipramine have suggested that clomipramine has a greater effect size than SSRIs [34]. However, studies of SSRIs generally occurred in a later era than those for clomipramine, and likely included more individuals who had previously had an inadequate response to another agent.

RESPONSE TO INITIAL TREATMENT

Good response

Response to cognitive-behavioral therapy using exposure and response prevention — Psychotherapy for obsessive-compulsive disorder (OCD), including frequency and duration, is discussed elsewhere. (See "Obsessive-compulsive disorder in adults: Psychotherapy", section on 'Frequency and duration'.)

Response to selective serotonin reuptake inhibitors — We continue medications for at least one year in individuals who achieve remission with pharmacotherapy. However, the severity of comorbid disorders often plays a role in this decision. In individuals with a comorbid disorder that is being treated with the medication, we consider the possibility of worsening comorbidity with decreased medications. Our treatment plan is individualized to address these differences.

The decision to taper off medications after successful treatment is based on several clinical factors, including response to medications, level of psychosocial impairment, history of prior exacerbations upon discontinuation of medications, severity of symptoms, severity of comorbid disorders, and whether the patient has done cognitive-behavioral therapy using exposure and response prevention (CBT/ERP). For example, in an individual with OCD who has responded to treatment, but who had significant psychosocial impairment due to the disorder, or in an individual who has had recurrence with tapering medications in the past, we would continue medications for a longer period of time (eg, two or more years).

If the decision is made to taper medications, we attempt a gradual taper [35]. We typically taper medications by up to 25 percent every month while monitoring for recurrence of symptoms. For example, in an individual who has responded to 300 mg/day of fluvoxamine, we would lower by 50 mg each month to 50 mg/day, then by 25 mg every month before discontinuing fluvoxamine. Most clinical trials of medications for OCD are short-term trials. Extended trials of

selective serotonin reuptake inhibitors (SSRIs), which randomly assigned individuals who respond to medication to continued medication treatment or to placebo, have generally found that patients who continue medication have a lower rate of relapse than patients on placebo [27,36-38]. Relapse rates have varied widely, in part due to methodological differences among studies. OCD patients who have completed a course of CBT/ERP have a significantly lower rate of relapse after medications are discontinued than do patients treated with pharmacotherapy alone [39].

Inadequate response to initial treatment

Potential causes — For individuals with an inadequate response (either minimal/nonresponse or partial response) to initial treatment, our first steps are to confirm adherence to medication, review factors that may be affecting pharmacotherapy and/or psychotherapy, review for potential co-occurring disorders (eg, substance abuse, bipolar disorder, personality disorder, posttraumatic stress disorder [PTSD], tic disorder), and address factors that may be exacerbating or maintaining the individual's OCD symptoms.

- **Confirm adherence to medications** – We assess adherence to medication by directly asking the individual. In some cases, side effects to medications may be limiting adherence. In cases where there is questionable adherence, we typically involve family members or other supports to try to enhance adherence. We stress the need to remain on medication for a full therapeutic trial to adequately assess response to the medication. (See 'Therapeutic trial' above.)

- **Factors affecting psychotherapy** – We review the individual's level of motivation, the length and frequency of therapy sessions, and the capacity for introspection. Additionally, we confirm that the individual is practicing exposures and resisting rituals in-between sessions. Adherence to ERP is one of the most robust predictors of both acute and long-term outcomes [40-42]. (See "Obsessive-compulsive disorder in adults: Psychotherapy".)

- **Inaccurate diagnosis or comorbid disorders affecting treatment response** – We confirm the current diagnosis by review of history and symptoms and assess for the presence of overlooked comorbid conditions (mood disorders, anxiety disorders, personality disorders, PTSD, substance use disorders, tic disorders) or other psychosocial stressors that might be affecting treatment response. (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis", section on 'Comorbidities'.)

Addressing inadequate response to initial treatment — For individuals with inadequate response to initial management, after addressing potential causes (see 'Potential causes'

above), as indicated, our next steps are:

For inadequate response to CBT/ERP monotherapy — We add a serotonergic medication as augmentation to CBT/ERP in individuals who have inadequate response to initial treatment with CBT/ERP monotherapy. In most cases this is an SSRI; however, for individuals that have responded to another agent in the past (eg, clomipramine) we would choose the same medication.

Additionally, in more severe cases, we refer the individual for intensive CBT/ERP at a higher level of care (eg, intensive outpatient program, partial hospitalization program, or residential treatment center). Intensive CBT/ERP, administered several hours/day, several days/week, has been found to be effective for many individuals with severe, treatment-refractory OCD. (See 'Choosing initial treatment' above and 'Choosing among SSRIs' above.)

For inadequate response to initial pharmacologic management — For individuals with inadequate response to initial pharmacotherapy, our next steps include augmentation with CBT/ERP while simultaneously increasing the SSRI to a supratherapeutic dose, as tolerated:

Augmentation with CBT/ERP — After addressing potential causes of inadequate response (see 'Potential causes' above), we encourage all individuals who have had an inadequate response to initial pharmacologic management to begin augmentation with CBT/ERP if they have not already done so. A detailed discussion of psychotherapy including CBT/ERP for OCD can be found elsewhere. (See 'Choosing initial treatment' above and "Obsessive-compulsive disorder in adults: Psychotherapy".)

Randomized trials have demonstrated the benefit of adding CBT/ERP to medication treatment of patients with OCD who have partially responded to a serotonergic antidepressant [4-6].

As examples, in one trial, 108 individuals with a partial response to 12 weeks of treatment with a serotonergic antidepressant medication (SSRI or clomipramine) continued the medication and were randomly assigned to ERP or stress management training (17 90-minute sessions over eight weeks) [5]. After eight weeks, patients in the ERP plus medication group, as compared with the stress management plus medication group, experienced a greater decrease in OCD symptoms (mean decline in Yale-Brown Obsessive Compulsive Scale [Y-BOCS] 11.2 versus 3.6, respectively), a higher rate of treatment response (74 versus 22 percent), and a greater proportion with mild to minimal symptoms (33 versus 4 percent). In another trial, 100 individuals with OCD who had obtained some benefit from at least 12 weeks of a serotonergic antidepressant treatment were randomly assigned to receive eight weeks of additional ERP, risperidone, or pill placebo [6]. A greater percentage of individuals in the ERP group responded to treatment (Y-BOCS score decrease ≥25 percent) than those in the risperidone or placebo

groups (80 versus 23 versus 15 percent). Additionally, more patients receiving ERP reached remission (Y-BOCS score of ≤12) than those in the risperidone or placebo group (43 versus 13 versus 5 percent).

Increasing the SSRI medication to supratherapeutic dose — After addressing potential causes of inadequate response (see 'Potential causes' above), we increase the dose of medication to a supratherapeutic dose, as tolerated, in individuals who have had an inadequate response to SSRI medication.

We do this at the same time we encourage the individual to begin CBT/ERP. For example, for an individual who has tolerated fluoxetine for a total of 12 weeks, with 6 weeks at 80 mg/day (maximum therapeutic dose), we would attempt to increase to 100 mg/day for 2 weeks, and then 120 mg/day if necessary and tolerated. We monitor response and side effects at the supratherapeutic range for a minimum of 6 to 8 weeks, if tolerated, before determining it to be effective or ineffective.

Data supporting the efficacy of higher than normal dosing of SSRIs are limited [31,43]. One trial randomly assigned patients with OCD who had not responded to 16 weeks of sertraline (titrated from 50 mg/day to 200 mg/day) to continue sertraline at 200 mg/day or to continue at an increased dose (averaging 357 mg/day) [43]. After 12 weeks of treatment, the higher dose group showed greater average improvement than the lower dose group. However, the difference was clinically modest. Both groups continued to have clinically significant symptoms and similar rates of adverse events. This strategy is not recommended for citalopram, because higher doses of citalopram have been associated with greater risk of QTc prolongation (table 2) [44,45].

SUBSEQUENT TREATMENT

Our subsequent pharmacotherapy for individuals who have not responded to treatment to this point (initial management, addressing potential causes, combined modality, increasing to supratherapeutic doses), is based on the level of response to the treatment (eg, minimal/no response or partial response). (See 'Response to initial treatment' above and 'Inadequate response to initial treatment' above.)

Minimal or nonresponse — For individuals with minimal or no response to this point, or in those who could not tolerate the side effects of medication, we recommend switching to a different selective serotonin reuptake inhibitor (SSRI), preferably one with a different side effect profile. If this is ineffective, we switch to either clomipramine or venlafaxine. While data support

clomipramine, some practitioners are reluctant to use it due to side effects and need for monitoring.

- **Change to a different SSRI** – Our preferred method is to stop the initial medication and immediately start an equivalent dose of the new medication. Overlap in mechanisms of action between SSRIs typically prevents discontinuation symptoms that might otherwise occur when an SSRI is suddenly stopped. However, some clinicians prefer cross-titration, lowering the ineffective medication while simultaneously introducing the new medication. This can usually be accomplished over one to two weeks and may avoid idiosyncratic side effects or discontinuation/withdrawal symptoms from particular SSRIs. SSRI dose equivalents are on the associated table (table 3). (See "Switching antidepressant medications in adults", section on 'Between SSRIs' and "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome'.)

  It has been estimated that less than one-half of patients will benefit from switching from one SSRI to another, and the likelihood of response diminishes as the number of failed adequate trials increases [35].

- **Switch to clomipramine** – We treat individuals who have not responded to at least two therapeutic trials of SSRIs with clomipramine (see 'Therapeutic trial' above). Clomipramine appears to have similar efficacy to SSRIs in the treatment of obsessive-compulsive disorder (OCD) [1,8,18-24]. However, due to necessary safety monitoring, toxicity in overdose, and unfavorable side effect profile, some practitioners may be more comfortable prescribing venlafaxine than clomipramine. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

  - **Prior to starting clomipramine** – Prior to starting treatment with clomipramine, we review the individual's past medical history with attention to a prior history of heart disease (including congenital or acquired long QT syndrome or conduction system disease). A detailed discussion about baseline testing and periodic monitoring for safety in individuals being treated with clomipramine can be found elsewhere. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Baseline testing and monitoring for safety' and "Acquired long QT syndrome: Clinical manifestations, diagnosis, and management" and "Congenital long QT syndrome: Epidemiology and clinical manifestations".)

  - **Starting and titrating clomipramine** – We typically start clomipramine at 25 mg QHS. If tolerated, we then increased by 25 mg every four to seven days to a target dose of 150 to 250 mg nightly. We check levels of clomipramine and its active metabolite,

desmethylclomipramine, when we reach 100 mg and then at 200 mg total daily dose. We keep combined plasma levels below 500 mg/dl to minimize the risk of cardiac conduction delay or seizures.

Clomipramine is associated with side effects including anticholinergic effects (eg, dry mouth, constipation, urinary hesitancy), sedation, weight gain, cardiac conduction delay, and lowering of the seizure threshold. Seizures can occur in individuals treated with higher than maximum doses and in those with previous seizure disorder or underlying condition predisposing to a seizure disorder. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Seizures'.)

Meta-analyses and randomized trials have found clomipramine to be superior to placebo in the treatment of OCD [8,34,46-48]. In a meta-analysis of seven trials including 392 individuals with OCD, treatment with clomipramine led to greater improvement as measured by a decrease in the 40-point Yale-Brown Obsessive Compulsive Scale (Y-BOCS) compared with placebo (pooled difference -8.2, 95% CI -10.5 to -5.9) [8]. Additional evidence comes from a collaboration of two studies totaling 520 individuals with OCD. In each of these studies, individuals treated with clomipramine had greater declines in Y-BOCS scores compared with individuals treated with placebo (38 versus 3 percent in one study and 44 versus 5 percent in the other) and higher rates of response with clomipramine compared with placebo (51 versus 8 percent and 60 versus 7 percent) [47].

- **Switch to venlafaxine** – Treatment with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine is another option after two unsuccessful trials of SSRIs.

  Limited data support the use of SNRIs in the treatment of OCD [49-54]. However, despite this, some practitioners may be more comfortable prescribing venlafaxine than clomipramine, due to greater adverse effects and the need for more monitoring with clomipramine.

  In a trial, 150 individuals with OCD were randomly assigned to receive either venlafaxine 300 mg daily or paroxetine 60 mg daily [50]. Similar improvements (as measured by the mean decrease in the Y-BOCS) and response rate (>35 percent decrease in Y-BOCS) were noted for each. Additionally, the incidence of adverse effects was comparable. Another trial including 47 individuals with OCD compared venlafaxine 350 mg daily with clomipramine up to 225 mg daily. Similar efficacy was found for each agent while those treated with venlafaxine had fewer side effects [51]. Larger, placebo-controlled trials are needed to establish the efficacy or venlafaxine in the treatment of OCD.

Duloxetine, another SNRI, has shown promise in case reports and open trials [55]. In one randomized trial, it has been shown to be as effective as sertraline as an agent of augmentation for individuals with refractory OCD [56]. To our knowledge, there is no published study of the SNRI desvenlafaxine for OCD, but it is often prescribed as an off-label alternative to SSRIs.

Side effects associated with SNRIs are discussed elsewhere. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

Partial response — For individuals with a partial response (ie, continue to have clinically significant symptoms of OCD) to initial treatment despite cognitive-behavioral therapy with exposure and response prevention (CBT/ERP) augmentation and supratherapeutic dosing (see 'Addressing inadequate response to initial treatment' above) we typically augment the SSRI with another medication. Our choice of the agent is based on several factors, including the quality of the evidence in support of the treatment, side effects of the medication, past history, and patient preference. For most patients, we augment with antipsychotic medication as a first option and if not effective, we typically try the medication sequentially (as listed by bulleted section directly below). However, for those with significant nausea we often begin with adding a 5HT-3 antagonist.

- **Antipsychotic augmentation** – In most cases, augmentation with a second-generation antipsychotic is our first choice in augmentation. Our preference is based on this strategy having the strongest evidence from randomized trials [57-66] and their favorable side effect profile, including lower likelihood of extrapyramidal symptoms. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

  We typically start with a very low dose of an atypical antipsychotic and titrate as tolerated. As examples, we often start augmentation with aripiprazole at 2 mg/day and titrate to 5 to 10 mg per day over one month. When using risperidone, we begin at 0.5 mg per day and titrate to 2 to 4 mg over one month. Effective target doses of adjunctive antipsychotics are generally lower than when these medications are used for treatment of psychotic disorders or bipolar disorder. For example, doses of adjunctive aripiprazole 5 to 10 mg/day, risperidone 2 to 4 mg/day, and olanzapine 5 to 10 mg/day have been found to be effective for serotonin reuptake inhibitor-refractory OCD in placebo-controlled trials [58,59,61]. For individuals with sensitivity to weight gain, we typically begin with adding adjunctive ziprasidone, an antipsychotic medication that is not associated with weight gain.

For individuals who respond to antipsychotic augmentation, we typically continue the medication for at least 6 to 12 months before attempting a gradual taper over one month to six weeks. If symptoms recur or worsen during the taper, we increased the medication back to the dose that was effective and continue for another six months provided that the individual is not experiencing long-term adverse effects to the antipsychotic (eg, extrapyramidal symptoms, tardive dyskinesia, weight gain, sedation). In individuals with evidence of extrapyramidal symptoms, dyskinesias, or metabolic dysregulation, we consider other options for augmentation. (See 'Pharmacologic options with limited supporting data' below.)

If the individual does not show a clear and clinically significant benefit to treatment with the antipsychotic, we discontinue it after one month to six weeks to limit exposure to the known risks of antipsychotic medications. It may then be useful to switch to a different adjunctive antipsychotic.

Efficacy trials of antipsychotic augmentation for OCD have generally examined short-term use only. In one trial, 82 individuals with OCD who were treated with SSRIs were randomized to the addition of either risperidone, ERP, or pill placebo for eight weeks. Individuals were then monitored for six months. Individuals who acutely responded to risperidone and remained on risperidone were likely to maintain their treatment gains out to six months [67]. In one small retrospective study, 13 out of 15 patients had a return of OCD symptoms within two months of their antipsychotic being stopped [68].

Meta-analyses and individual trials investigating augmentation methods for individuals with OCD treated with serotonin reuptake inhibitors have generally shown efficacy for adjunctive antipsychotics [57-66,69-72]; however, not all trials have supported this [73,74]. It is unclear whether varying responses found across antipsychotic trials reflect true differences in efficacy or methodologic issues specific to the trials.

In a meta-analysis of 14 trials, 491 individuals with OCD were treated with first- or second-generation antipsychotics as augmentation (quetiapine, risperidone, aripiprazole, olanzapine, paliperidone, haloperidol) versus placebo [65]. The primary outcome was mean change in the Y-BOCS total score. Pooled effect size for antipsychotic treatment was superior to placebo (Hedges' g -0.64, 95% CI -0.87 to -0.41). Aripiprazole, risperidone, and haloperidol showed the strongest evidence for effect compared with placebo; however, the results for haloperidol are based on one trial only. Olanzapine, paliperidone, and quetiapine showed similar effect to placebo. Furthermore, response rate (defined as Y-BOCS reduction ≥35 percent) was higher in the treatment versus placebo group (pooled response rate 30 versus 13 percent). Methodologic differences limit the interpretation of

data supporting antipsychotic augmentation of SSRIs for OCD. However, a systematic review concludes that augmentation with some antipsychotics is supported by clinical trials, and that antipsychotics as a group appear to benefit approximately one-third of individuals with serotonin reuptake inhibitor-refractory OCD [63].

Despite evidence supporting antipsychotic augmentation of individuals with partial response to serotonin reuptake inhibitor medications, some practitioners may be reluctant to begin treatment with an antipsychotic due to metabolic dysregulation and other side effects associated with them. Treatment with other augmenting agents may be an acceptable alternative to antipsychotic agents in individuals with existing metabolic disturbances [35].

Side effects and other considerations when prescribing antipsychotic medications are discussed elsewhere. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)

- **Augment with clomipramine** – In individuals with partial response to initial treatment with an SSRI, we typically augment with clomipramine (up to 50 to 75 mg/day) as a next choice.

  When we use this approach, we typically add 25 mg nightly of clomipramine to the SSRI and increase by 25 mg per week to 50 to 75 mg nightly. We check an electrocardiogram (ECG) prior to beginning clomipramine and upon reaching maximum dose of clomipramine. We check plasma levels of clomipramine upon reaching 75 mg daily and monthly thereafter. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Baseline testing and monitoring for safety'.)

  Augmentation of SSRIs with clomipramine has been found to be effective for treatment of OCD in case series and open trials [70,75,76]. Combining clomipramine with some SSRI medications increases the risk of serotonin syndrome, QTc prolongation, and other side effects due to each interacting with cytochrome p450 metabolic enzymes and subsequent increasing levels of each. Symptoms of toxicity include tremor, dry mouth, tachycardia, myoclonic jerks, QTc prolongation, seizures and serotonin overstimulation. (See "Serotonin syndrome (serotonin toxicity)" and "Acquired long QT syndrome: Clinical manifestations, diagnosis, and management".)

- **Augmentation with a glutamate modulator** – Our preference from among glutamate modulators is based on the quality of the evidence in support of the agent, avoidance of

side effects (weight gain, metabolic syndrome, extrapyramidal symptoms) and clinical level of comfort. For example, in an individual sensitive to weight gain we might try topiramate.

Altered glutamate neurotransmission in cortico-striatal-pallidal-thalamic brain circuits may contribute to symptoms of OCD. In many but not all studies, glutamate modulators appear to be effective as augmenting agents for those individuals with OCD without response to serotonin reuptake inhibitors. However, the studies are small and further research is warranted.

As examples:

- Lamotrigine [77]
- Memantine [78-80]
- Topiramate [81,82]
- Pregabalin [83]
- Amantadine [84]
- N-acetylcysteine [85,86]
- Riluzole [87,88]
- IV ketamine [89,90]

- **Augmentation with a 5HT-3 antagonist** – We occasionally use a 5HT-3 antagonist in individuals with excessive gastrointestinal disturbances such as nausea. In clinical trials, serotonin 5HT-3 receptor antagonists (eg, ondansetron, granisetron, tropisetron) have been found to be superior to placebo as augmentations for serotonin reuptake inhibitor-refractory OCD [91-95].

Pharmacologic options with limited supporting data — We use these agents only after inadequate response to the above treatments. We seek expert consultation in the management of individuals who are refractory to treatment or in whom we are considering use of the following agents.

These agents have shown promise in the treatment of OCD as monotherapy or augmentation. However, data are limited to small, randomized trials, case reports, or open trials. Further trials with greater numbers of individuals are needed to establish efficacy.

- Stimulants (ie, caffeine, dextroamphetamine, methylphenidate ER [96-100]
- Anti-inflammatory agents (ie, celecoxib [101], tramadol [102], minocycline [103,104])
- D-Cycloserine [105-108]

Surgical and neuromodulatory treatments — Discussion of deep brain stimulation, transcranial magnetic stimulation, and other potential treatments for individuals that have not responded to several prior treatments is found elsewhere. (See "Deep brain stimulation for treatment of obsessive-compulsive disorder".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Obsessive-compulsive disorder and related disorders".)

SUMMARY AND RECOMMENDATIONS

- **Preferred initial treatment**
  - **Most patients** – For most individuals with obsessive-compulsive disorder (OCD), we suggest initiating treatment with cognitive-behavioral therapy using exposure and response prevention (CBT/ERP) rather than pharmacologic management (**Grade 2C**). (See 'Choosing initial treatment' above.)

    We consider clinical presentation, past response to treatment, and patient preference in initial management decisions. Other initial treatments are reasonable in individuals with the following presentation:

    - **Patients with severe symptoms** – We suggest treating individuals with severe symptoms with the combination of pharmacotherapy and CBT/ERP rather than either treatment alone (**Grade 2C**). However, for individuals whose severe symptoms preclude participation in CBT/ERP we begin with pharmacotherapy. (See 'Choosing initial treatment' above.)

    - **Patients with co-occurring psychiatric disorder** – We initiate treatment with a combined modalities (CBT/ERP and selective serotonin reuptake inhibitors [SSRIs]) for individuals with a co-occurring psychiatric disorder (eg, major depression or social anxiety disorder) that is typically responsive to SSRI treatment. (See 'Choosing initial treatment' above.)

    - **Patients unwilling/unable to participate in CBT/ERP** – We initiate treatment with pharmacotherapy (eg, SSRI) for individuals who are unwilling or unable to

participate in CBT/ERP, or who have previously not responded to CBT.

- **Alternative initial treatment** – CBT/ERP may not be available for some patients, and some patients may be unwilling to participate in CBT/ERP. For such individuals, we suggest initial treatment with an SSRI rather than other pharmacotherapeutic options (**Grade 2C**). SSRIs are also our first choice when choosing to combine pharmacotherapy with CBT/ERP. (See 'SSRIs: First pharmacotherapeutic option' above.)

  We treat all individuals for 8 to 12 weeks with at least four to six weeks at the maximum tolerated dose within the therapeutic range before determining whether a given SSRI medication has been effective for their OCD (table 2). (See 'Therapeutic trial' above.)

- **Patients with inadequate response to initial treatment** – For individuals with inadequate response to initial therapeutic trial, we first address potential causes, including poor adherence to medication, limited ERP, and inaccurate diagnosis or the presence of undiagnosed comorbid disorders. (See 'Potential causes' above.)

  After addressing these, we suggest combined modality therapy with CBT/ERP and SSRI (**Grade 2C**). In these cases, we simultaneously titrate the medication to supratherapeutic dose, as tolerated. The intensity of CBT/ERP can also be increased as needed. (See 'Addressing inadequate response to initial treatment' above.)

- **Subsequent pharmacotherapy options**

  - **Patients with minimal to no response** – For individuals with minimal or no response to pharmacotherapy with or without CBT/ERP, we switch to a different SSRI. If this is ineffective, we switch to either clomipramine or venlafaxine. (See 'Minimal or nonresponse' above.)

  - **Patients with partial response** – For individuals who have a had partial response to treatment, we typically augment the SSRI with a second-generation antipsychotic. However, augmentation with either clomipramine, glutamate modulator, or 5HT-3 antagonist are reasonable choices depending on clinical scenario. (See 'Partial response' above.)

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