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ASCP Corner

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Pharmacotherapy for Treatment-Resistant Obsessive-Compulsive Disorder

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Obsessive-compulsive disorder (OCD) is a disabling illness affecting approximately 2%–3% individuals worldwide that is marked by recurrent, distressing intrusive thoughts (obsessions) and repetitive behaviors (compulsions).[1,2] The underlying pathophysiology is incompletely understood, but OCD symptoms are thought to emerge partly from aberrant functionality in cortico-striato-thalamo-cortical neural circuits.[3] Though OCD is a major cause of functional disability and impairment,[4] the only medications currently approved by the US Food and Drug Administration (FDA) are serotonin reuptake inhibitors (SRIs, ie, the selective SRIs [SSRIs] and clomipramine).[5] Extensive evidence supports that SRIs are effective for treating OCD symptoms, and with a favorable side effect profile relative to clomipramine, SSRIs are currently the first-line pharmacotherapy.[6] However, around half of patients will respond incompletely to SSRIs,[7] and at least 8 weeks of sustained treatment are typically needed before meaningful clinical improvement is seen.[6] SSRI treatment is associated with dose-dependent side effects including gastrointestinal upset and sexual dysfunction, which may be particularly problematic given that patients with OCD tend to require treatment with higher doses to achieve symptomatic relief compared to those with anxiety and depressive disorders.[8]

When patients do not respond to or cannot tolerate SSRIs, the evidence supports several next steps. Here, I briefly review options for pharmacologic management of treatment-resistant OCD, summarizing the evidence supporting each. What constitutes "responsiveness" to OCD treatment remains controversial, though improvement from baseline of 25%–35% on the Yale-Brown Obsessive Compulsive Scale is a commonly used definition. Experts similarly disagree on the definition of "treatment resistance," but have generally quantified it based on the number of failed treatment trials.[9] A comprehensive review of this topic, including a review of psychotherapeutic and somatic treatment approaches, is beyond the scope of this article; for more detailed discussions, see references 6, 9, 10, and 11.

Medication Options for Treatment-Resistant OCD

Optimize dose and trial duration. When SSRI treatment produces little response, optimizing the dose is a reasonable first step. Doses exceeding the typical maximum set by manufacturers have been shown to be effective, and the current American Psychiatric Association practice guidelines recommend occasional prescribing of doses as high as escitalopram 60 mg/d, fluoxetine 120 mg/d, fluvoxamine 450 mg/d, paroxetine 100 mg/d, and sertraline 400 mg/d.[5] Whereas high-dose SSRIs have been linked to increased side effect burden without increased efficacy for major depressive disorder (MDD), a 2010 meta-analysis found that for patients with OCD, higher SSRI doses were associated with greater efficacy than low or medium doses.[8] For example, in a trial of nonresponders to sertraline 200 mg/d, dose titration up to 400 mg/d led to greater symptomatic improvement and similar tolerability compared to maintaining the original dose.[10] However, higher SSRI doses are also linked to increased rates of treatment discontinuation due to adverse effects (such as initial gastrointestinal upset or sexual side effects), making careful monitoring for side effects essential.[8] Among the SSRIs, citalopram in particular is associated with QT interval prolongation. The FDA now recommends avoiding doses greater than 40 mg/d (and 20 mg/d in elderly patients), which makes citalopram a potentially problematic choice for treating OCD given that doses of up to 120 mg may be required to achieve clinical efficacy. It is less clear whether escitalopram, a therapeutically active enantiomer of citalopram, can prolong QT interval, but nonetheless at doses above the FDA maximum this agent should be used carefully. Electrocardiographic (ECG) monitoring may be required in elderly individuals or those with a cardiac history when using citalopram or escitalopram at any dose.[9]

Compared to MDD, longer periods of SSRI monotherapy are often required before OCD symptoms respond, leading experts to recommend SSRI trials lasting at least 8–12 weeks (and at least 4–6 weeks at the maximum tolerable dose).[5,11] There is no evidence that plasma SSRI levels correlate with OCD treatment efficacy, though they may help to confirm adherence.[12]

Switch to a different agent. If SSRI response is insufficient despite a trial of adequate dose and duration, switching to an alternative agent is a valid strategy. Options include another SSRI, a serotonin-norepinephrine reuptake inhibitor (SNRI), or clomipramine, with the strongest evidence favoring an additional SSRI trial.[6,11] Controlled trials of the SNRIs venlafaxine and duloxetine suggest that both may have some efficacy for treating OCD symptoms, though results were mixed.[6,9] There remains a dearth of trials investigating the effects of SNRIs.[13] Given results from a prior trial which suggested that augmenting fluoxetine with buspirone (a 5-HT_{1A} agonist) may have some benefit for treatment-resistant OCD, newer serotonergic drugs with 5-HT_{1A} activity such as vortioxetine and vilazodone could theoretically be useful.[11] However, the data here are even scarcer. Two case reports[14,15] describe successful treatment of refractory OCD with vortioxetine (as monotherapy in one case, combined with aripiprazole in another), while the effects of vilazodone in OCD have yet to be documented at all.

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Clomipramine, a tricyclic antidepressant that inhibits serotonin reuptake and binds several other receptor targets, was the first agent to show efficacy in treating OCD. Meta-analyses suggest that clomipramine may be more efficacious than SSRIs.[9,11] However, more recent head-to-head trials comparing clomipramine to SSRIs have challenged the idea that clomipramine is truly superior. Moreover, compared to SSRIs, clomipramine is associated with greater side effect burden, including anticholinergic effects (eg, dry mouth, constipation), antihistaminergic effects (eg, sedation, weight gain), anti–alpha-adrenergic effects (eg, hypotension), arrhythmogenic potential (necessitating ECG monitoring), and reduction of the seizure threshold. To reduce the risk for toxicity, clomipramine doses exceeding the FDA maximum of 250 mg should be avoided, and plasma levels should be obtained with the goal of keeping combined levels of clomipramine and its metabolite desmethylclomipramine below 500 ng/mL.[5] Considering these challenges, SSRIs remain the first-line agents of choice.

Augment with another medication. When monotherapy does not yield an adequate response, a reasonable next step is to treat with an adjunct medication. Antipsychotic augmentation is supported by the most and highest-quality evidence. Though several different antipsychotics have been studied, a recent meta-analysis found that risperidone had the greatest efficacy,[16] while another also found comparable efficacy for aripiprazole.[17] Low antipsychotic doses (eg, risperidone up to 3 mg/d, aripiprazole up to 15 mg/d) are recommended given their associated adverse effects, which include weight gain, metabolic syndrome, and tardive dyskinesia (the last of which occurs less frequently with atypical than with typical antipsychotics).[6,9,11,18] Approximately one third of treatment-resistant patients with OCD will respond to antipsychotic augmentation; this rate may be somewhat higher in patients with co-occurring motor tics or Tourette syndrome.[5,19]

Recent evidence of abnormal glutamate neurotransmission in OCD generated a series of trials evaluating glutamate modulators as augmentation agents for treatment-resistant OCD. *N*-acetylcysteine (NAC) has the greatest body of support. Of 5 randomized, placebo-controlled trials in which it was added to SSRI monotherapy, 3 showed greater efficacy for reducing OCD symptoms compared to placebo.[6] NAC between 600 mg/d to 3,000 mg/d was delivered in the above trials, typically in divided doses. It should be noted that NAC is not currently regulated by the FDA. There are not currently enough data to recommend any commercially available NAC brand over another, though 600 mg effervescent capsules were used in the above trials and in several case reports. Randomized, double-blind, placebo-controlled trials of the glutamate modulators lamotrigine (2 trials, up to 100 mg/d), topiramate (3 trials, up to 400 mg/d), riluzole (3 trials, up to 100 mg/d), memantine (3 trials up to 20 mg/d), and intravenous ketamine (1 trial, single dose of 0.5 mg/kg) have all yielded preliminary evidence of efficacy when added to SRIs in patients with treatment-resistant OCD.[6,11,20] Smaller open-label studies also support memantine (2 trials) and intravenous ketamine (1 trial) augmentation of SSRIs.[21] To date, only case reports describe the effects of intranasal ketamine on OCD symptoms.[22,23]

Though beyond the scope of this review, evidence supports the efficacy of psychotherapy and somatic treatments as well. Cognitive behavioral therapy is a first-line treatment for OCD and an alternative to SSRIs. CBT can also effectively augment SSRI monotherapy in patients with treatment-resistant OCD, with a recent trial showing larger effect sizes for CBT compared to risperidone augmentation.[24] There is evidence supporting the use of repetitive transcranial magnetic stimulation (rTMS) as well.[25,26] Surgical options, reserved for the most severe treatment-refractory cases, include deep brain stimulation.[27]

Conclusion and Future Directions

SSRIs remain the first-line medications for treating OCD. When SSRI treatment fails to control symptoms, the current literature supports the following algorithm: First, optimize the SSRI dose, and ensure an adequate trial length, checking plasma SSRI levels to confirm adherence if appropriate. Second, switch to an alternative agent (initially another SSRI or clomipramine, after which an SNRI could be tried). Third, augment with an additional medication (eg, an antipsychotic or glutamate modulator). ERP and somatic treatments (eg, rTMS and in extreme cases, neurosurgery) should also be considered and can effectively be combined with medications.

Though the evidence base favoring the above strategy is strongest, results from small studies are beginning to reveal possible new medication approaches. For example, in 49 treatment-naive patients with OCD, mirtazapine (an α_2-adrenergic receptor antagonist) accelerated the initial treatment response when added to citalopram, though it did not improve overall efficacy.[11] Two small studies suggested possible benefits from stimulants, including *d*-amphetamine and, interestingly, caffeine (which one trial included as an active placebo), though these results need replication.[9] Anti-inflammatories have also garnered interest given hypothesized associations between OCD symptoms and inflammatory or autoimmune abnormalities. Results from small trials augmenting fluvoxamine with celecoxib (a nonsteroidal anti-inflammatory drug that inhibits cyclooxygenase-2) and minocycline (a tetracycline-derived antibiotic that may also have glutamate-modulating and anti-inflammatory properties) were promising, though problematic design aspects (eg, suboptimal fluvoxamine doses) limit their generalizability.[28]

There remains an urgent need for more effective, faster-working, and more acceptable medications to help individuals with OCD achieve wellness. To that end, researchers are investigating several novel pharmacotherapies. According to the ClinicalTrials.gov database, agents tested in ongoing or recently completed trials include tolcapone, BHV-4157 (troriluzole, a riluzole precursor), rapastinel, probiotics (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175), psilocybin (2 trials), rituximab, nitrous oxide, ketamine, vitamin C, D-cycloserine, nabilone, cannabis, and ondansetron. Testing these agents, which span a variety of classes, may help to identify novel pharmacologic targets and yield new treatments for patients who suffer from OCD.

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