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Anxiety, Obsessive Compulsive, and Related Disorders (CB Nemeroff, Section Editor)

Management of Treatment-Resistant Obsessive-Compulsive Disorder

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Opinion Statement

Purpose of review Many individuals with obsessive-compulsive disorder (OCD) do not fully respond to first-line treatments (psychotherapy consisting of exposure and response prevention [EX/RP] and serotonin reuptake inhibitor [SRI] pharmacotherapy). These cases are often considered "treatment-resistant" OCD. In this article, we offer a heuristic guide for treating clinicians for such cases.
Recent findings Clinical options for treatment-resistant OCD include augmenting first-line treatments with medications, psychotherapy, and neuromodulatory approaches. These augmentation and novel monotherapy interventions offer promise in allowing more patients to improve. For the most refractory cases, neurosurgery may be considered, though only as a last resort after less invasive treatments have been given adequate trials.
Summary In the future, advances in our understanding of OCD and its brain mechanisms may refine existing interventions and yield new treatment options. Ultimately, these efforts may lead to a precision medicine approach to treating OCD by allowing clinicians to match optimal treatment strategies to each individual patient.

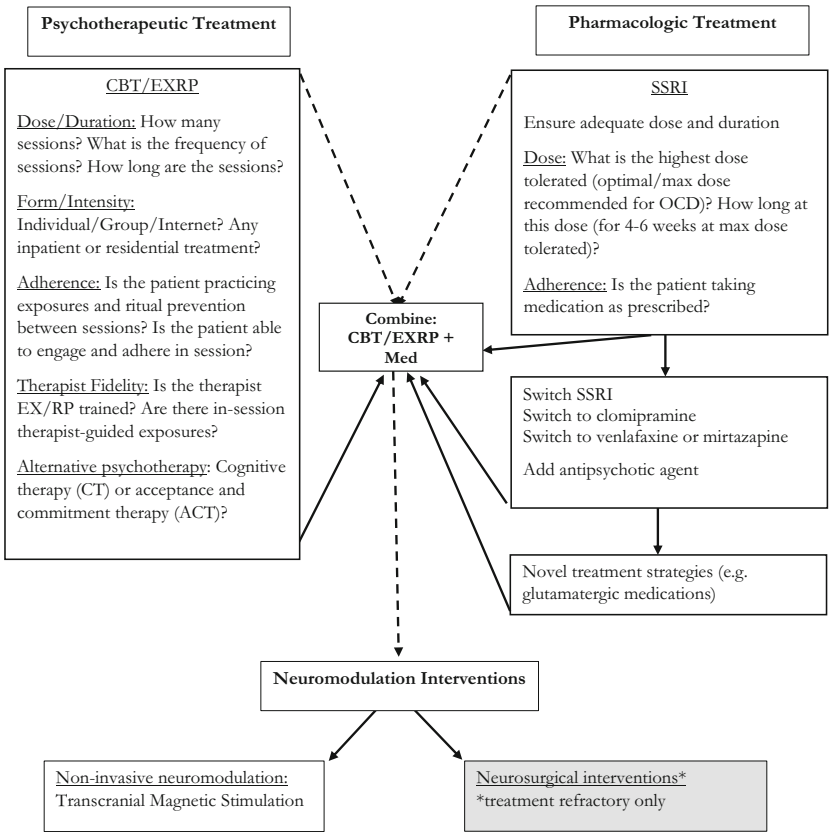

Fig. 1. Treatment strategies for treatment-resistant OCD.

Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent and intrusive thoughts, images or urges, as well as repetitive behaviors [1]. OCD affects approximately 2% of the population and can be disabling when severe [2]. Fortunately, effective interventions exist for OCD, allowing some sufferers to achieve minimal symptoms and restoration of functioning. First-line treatment options include pharmacotherapy with serotonin reuptake inhibitors (SRIs) and/or cognitive behavioral therapy (CBT) consisting of exposure and response prevention (EX/RP) [3••]. It is estimated, however, that 40–60% of individuals do not respond or only partially respond to these initial treatments. Given the number of patients who continue to experience impairing OCD symptoms after trying a recommended treatment, a great deal of attention has been paid to "treatment-resistant" OCD.

In this paper, we review treatment options for addressing treatment-resistant OCD, including augmentation of first-line treatments with medication, psychotherapy, and neuromodulation. A treatment algorithm is presented to guide clinicians in selecting the next appropriate intervention to facilitate response (Fig. 1). Of note, the strategies with the highest base of empirical evidence are recommended first in this decision tree, followed by more experimental treatments. In conjunction with these guidelines, we also encourage the treating clinician to consider individual factors and preferences that may influence patients' adherence and response, including the presence of comorbid psychiatric or medical conditions and readiness for treatment.

Defining "treatment resistance"

There has been debate among researchers about how to operationally define treatment response and non-response [4, 5••, 6]. Yet, consensus in the field is important to allow comparisons across research studies and to inform treatment guidelines. In an effort to establish consensus, Mataix-Cols and colleagues [5••] surveyed OCD experts (both psychologists and psychiatrists) about their agreement with a set of conceptual and operational criteria of response, remission, recovery, and relapse. Although there was broad consensus for all definitions at the conceptual level, operational criteria evidenced some disagreement. The criteria with the highest degree of consensus (> 82% agreement) defined response as follows: a 35% reduction on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS [7]) and a Clinical Global Impression-Improvement (CGI-I [8]) rating of 1 ("very much improved") or 2 ("much improved") for the duration of at least 1 week. Partial response was defined by ≥ 25% but < 35% reduction in Y-BOCS scores plus CGI-I rating of at least 3 ("minimally improved"), lasting for at least 1 week. Importantly, definitions of response belie the fact that many "responders" continue to experience mild-to-moderate OCD symptoms [6] which may continue to cause substantial interference in one or more life domain.

Non-response has often been defined as the opposite of response. Whereas non-response is specific to a trial of a given intervention, "treatment-resistant" OCD refers to cases of OCD in which the individual had minimal or no response to at least two SRI trials [9]. Other definitions include response to not just SRIs but also to cognitive behavioral treatments [10]. "Treatment-refractory" OCD has typically indicated a higher degree of resistance and has been reserved for those who do not respond to "all available treatments." We propose a pragmatic way for a clinician to determine treatment-resistance to first-line treatments: The patient has not achieved minimal OCD symptoms after: (1) at least two SRI trials, (2) an adequate trial of CBT (specifically EX/RP), and/or (3) the combination of an SRI with CBT.

In evaluating "treatment-resistance," we recommend the treating clinician carefully determine whether a given trial of intervention was sufficiently administered prior to moving to the next line of treatments. In evaluating response, it is recommended that symptoms be assessed with validated measures such as the Y-BOCS, and that patients' course of symptoms is well documented including the details of each trial (dose, duration, side effects) and degree of improvement.

Treatment

American Psychiatric Association treatment guidelines recommend that treatment begins with either an SRI medication and/or CBT consisting of EX/RP; both of which have strong empirical support [3••]. Depending on treatment response to this initial intervention, augmentation and alternative strategies are presented.

Pharmacologic treatment

Serotonergic antidepressants (SRIs) are the only class of medications that have been shown to be effective for treatment of OCD in large multi-site randomized controlled trials. The recommended SRIs include selective SRIs (SSRIs; fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram) and a tricyclic antidepressant (clomipramine). These SRIs have the highest empirical support or grade A evidence (Guidelines of the World Federation of Societies of Biological Psychiatry [11]) and are approved by the Food and Drug Administration (FDA) for the treatment of OCD in both children and adults. According to the Cochrane review and other meta-analyses of placebo-controlled SSRI trials in OCD, there were no statistical differences in efficacy among SSRIs [12, 13]. In terms of side effect profile, the SSRIs are typically better tolerated than clomipramine and for this reason are recommended as the starting point for pharmacological treatment. Clomipramine is typically reserved for those with who have not had an adequate response to an SSRI [14, 15]. Although all SSRIs appear to be equally effective, there may be differences in response with individual patients. The prescribing physician should consider the safety and acceptability of specific side effects, presence of other psychiatric or general medical conditions, and potential drug interactions when choosing a particular SRI.

Few individuals (< 25%) however achieve remission after the initial treatment with SRIs [6]. Importantly, the provider should be cognizant of possible contributing factors to suboptimal outcomes, including co-occurring psychiatric and medical conditions and external stressors. After addressing contributing factors, the following strategies are recommended after a partial or non-response to a first SRI trial:

(*1) Ensure adequate dose and duration of SRI.* In some cases, non-response may be due to "technical failure," that is patients may not have received an adequate dose or duration of a given treatment [16]. Higher SSRI dosing guidelines are typically recommended for treating OCD as compared to depression (see [17] for optimal and maximum doses for specific SRIs). It is recommended that optimal doses be achieved and maintained for 8–12 weeks (at least 4–6 weeks at maximally tolerated dose) prior to evaluating response. Higher SSRI doses than are FDA approved may produce a higher response rate in some individuals and should be considered when the medication is well tolerated by the patient [18]. However, "off-label" doses require careful monitoring of potential adverse effects by a physician. OCD symptom reduction with SSRIs tends to be gradual; a recent meta-analysis indicated a logarithmic response curve with 75% of response occurring within 6 weeks of being on a stable dose [19•]. For partial responders, a longer duration for an additional 12 weeks may be recommended before altering treatment, to prevent premature changes to a treatment that could be effective.

(*2a)Augment with CBT, specifically EX/RP.* Adding EX/RP to unsuccessful SRIs has demonstrated efficacy with higher response rates than SRIs alone [20–22] and also superior to antipsychotic augmentation (discussed below [23]). In deciding between augmenting an SRI with either EX/RP or an antipsychotic

medication, treating clinicians often incorporate patient preferences and might not recommend an EX/RP trial to medication-preferring patients, despite evidence that EX/RP outperformed risperidone in a head-to-head randomized controlled trial (RCT) [23]. However, secondary results from that trial suggest that patients who preferred to be randomized to risperidone had equivalent outcomes to EX/RP-preferring patients [24]. Thus, clinicians might consider recommending a trial of EX/RP even to patients who prefer medication augmentation. Combined treatment may also decrease relapse when medication is discontinued. EX/RP may serve as a protective factor, a consideration for those patients who may wish to reduce the duration of their pharmacological treatment once symptoms have remitted. The effects of EX/RP have been shown to be long-lasting with treatment gains maintained at 6-month follow-up [25, 26••].

(2b) *Augment with antipsychotic agents.* For those with a partial SRI response, one of the most common strategies is augmentation with neuroleptic agents (or antipsychotics), such as aripiprazole, haloperidol, olanzapine, quetiapine, or risperidone [27, 28]. Antipsychotic agents have been shown to produce a response in approximately 30% of treatment-resistant patients with the strongest evidence for haloperidol and risperidone [29, 30•, 31]. This strategy may also be especially effective for patients with comorbid tics [29]. It is recommended that atypical antipsychotic medication is added after at least 12 weeks of a maximally tolerated SRI trial. Given the potential side adverse effects of this class of medications (including metabolic syndrome, tardive dyskinesia, and neuroleptic malignant syndrome), they should be discontinued if no benefit is achieved after an adequate trial. The effect of antipsychotic agents is typically more rapid than SRIs and should be assessed within 2–4 weeks after initiation.

(3) *Switch SRI.* If there is no response to the initial trial with an SRI, another trial switching either to a different SSRI or clomipramine is recommended. Venlafaxine or duloxetine, serotonin and norepinephrine inhibitors, are other potential options to consider, although the evidence for these medications is less strong. Up to 50% of individuals may benefit from switching SRIs, though the rate of response however decreases with each failed trial [15, 32]. It is recommended to attempt two to three trials of SRIs including clomipramine before switching to a different class of medication [3••].

(4) *Novel and experimental agents.* Alternative pharmacological agents have been explored for their ability to facilitate treatment response either on their own or as an SRI augmentation strategy. The novel agents garnering the most excitement have been medications modulating the glutamatergic system. Glutamate modulators may tap a new mechanism different from the first-line medications (i.e., serotonergic system). These agents include N-acetylcysteine, memantine, riluzole, lamotrigine, topiramate, and minocycline. In a small study, a single dose of IV ketamine led to the rapid reduction in OCD symptoms in unmedicated adults with OCD [33], raising the exciting possibility that rapid resolution of OCD symptoms might be possible. The problem with ketamine however is that its therapeutic effects appear to be temporary and the safety of repetitive doses is unclear. Other potential augmentation agents may include

addition of pregabalin, celecoxib, and dextroamphetamine [3••]. Of note, the evidence base for these agents remains limited and requires more research. Given their preliminary promise but limited available evidence, these agents should be reserved for those patients who have had limited to no response to the recommended medications and a legitimate reason for not trying EX/RP (e.g., cost, lack of therapist availability). Importantly, we only recommend these medications as a promising strategy for patients for whom other treatments have not worked and not as a replacement for existing treatments.

Psychotherapeutic treatment

CBT consisting of exposure and response prevention (EX/RP) as monotherapy or in combination with SRIs is the first-line treatment for OCD. EX/RP consists of behavioral techniques that involve exposure to feared stimuli while refraining from compulsive behaviors. EX/RP has the strongest evidence base for treating OCD and has been shown to be superior to other psychotherapeutic interventions [15].

Most of the currently available research on treatment-resistant OCD has focused on non-response to initial treatment with pharmacological treatment (vs. initial trial with CBT). "Technical failure" may also extend beyond pharmacological trials, that is, lack of treatment response may be due to adequacy of dose/duration/type of delivered treatment. If patients demonstrate partial or no response to EX/RP, the following strategies are recommended:

(1) *Evaluate/increase the dose and duration of treatment.* In considering the nature of the initial EX/RP trial, it is important to consider the length and frequency of sessions. An adequate duration of an EX/RP trial is typically considered to be 13 to 20 sessions delivered weekly or twice weekly. Treatment manuals for EX/RP suggest that twice weekly 90-min sessions are preferable to weekly 45-min sessions [34]. There seems to be a dose limit, however, as five sessions per week may not add additional benefit beyond what is offered by twice weekly sessions [35]. Therapist-guided exposures appear to be more effective than therapist-assigned self-exposures, presumably because the therapist can ensure patient adherence [36]. The combination of in vivo and imaginal exposures also tends to be associated with greater gains than in vivo exposures alone [34]. To promote generalization of learning, home and out-of-the office exposure sessions (in naturalistic settings) may be beneficial (vs. exposures occurring solely in the therapy office).
If the response to the initial trial of EX/RP is limited, an increase in the intensity of treatment may be warranted, including increasing the level of care. Inpatient hospitalization or residential treatment may offer unique advantages to implementing EX/RP on daily basis. Some research supports the added benefit of an inpatient treatment for treatment-resistant OCD [37, 38].

(2) *Ensure and improve patient adherence* (*and therapist fidelity*). In evaluating response to EX/RP, the clinician is encouraged to evaluate patient adherence to both in-session exposures and between-session homework assignments. The Patient EX/RP Adherence Scale (PEAS [39]) is recommended for this purpose. The PEAS provides a standardized measure for clinicians to quantify patients' efforts during exposure and ritual

prevention practices. PEAS scores have been shown to significantly predict symptom reduction at post-treatment and OCD severity at 6-month follow-up [40, 41, 42•]. If the patient is not able to fully participate in exposures or if ritual prevention remains limited, ways of increasing adherence should be explored. These include incorporating of motivational interviewing techniques and/or including family members in treatment, particularly in cases with high levels family accommodation [43, 44].

In addition to patient adherence, the therapist fidelity to the EX/RP protocol needs to be assessed. Specifically, the clinician should ensure that the EX/RP that the patient received was delivered by an EX/RP-trained therapist and incorporated the necessary components and procedures of the treatment. Some of the proposed factors in defining an adequate trial of CBT include [10]: therapy delivered by a CBT specialist, defined as having engaged in supervised CBT with at least 10 but preferably 20 OCD cases; at least 40 h of intensive exposure in relevant naturalistic settings; daily homework assigned and monitored regularly; treatment-inferring behaviors are identified and addressed. If access to an EX/RP-trained professional is limited, technology-facilitated therapy including Internet-based EX/RP programs may be ex plored, as these have been demonstrated to produce significant treatment gains in OCD [45, 46].

(3) *Alternative psychotherapies*. EX/RP can be anxiety-provoking for some patients to initially engage in. For those who find EX/RP difficult to adhere to, psychotherapy incorporating cognitive or acceptance-based techniques may offer an alternative or augmentation strategy. Cognitive therapy involves identifying and modifying distorted thoughts and dysfunctional beliefs. Acceptance and Commitment Therapy (ACT) integrates mindfulness and acceptance-based processes with values-connected behaviors, and may be especially useful as a transdiagnostic approach for patients with comorbid mood and anxiety disorders. Alternative CBT variants have demonstrated positive effects in treating OCD, although these trials have not been as extensive or well supported as EX/RP [36, 47]. Thus, although EX/RP is the recommended first-line treatment, other variants of CBT (i.e., CT/ACT) may be helpful for some individuals when EX/RP is not available. Alternatively, these interventions may also provide a way of increasing motivation and addressing any barriers to engaging EX/RP, with the eventual goal of proceeding to an adequate trial of EX/RP.

(4) *Augment with SRI* (*as reviewed above*). In combined treatments, the SRI may reduce OCD symptoms to a degree that allows patients to engage in the therapy. Combined SRI and EX/RP treatment is also recommended for patients who have comorbid disorders responsive to SRI treatment (e.g., depression).

(5) *Novel strategies under research.* Pharmacological agents that enhance fear extinction learning (an underlying mechanisms of exposure-based treatment) could offer novel augmentation strategies by strengthening treatment response within EX/RP. For example, although the literature is mixed, some data suggest that D-cycloserine (DCS) may be used to accelerate EX/RP response, but not necessarily increase the overall reduction in symptoms [48, 49]. Ketamine's rapid effects have also been studied in

conjunction with EX/RP. In an open-label trial, Rodriguez and colleagues [50] investigated the effect of a single administration of IV ketamine followed by an abbreviated course of EX/RP. They found that 63% of patients demonstrated and maintained treatment response with this novel pairing. These pharmacological agents are still in their infancy but show great potential in enhancing or accelerating EX/RP response. Non-pharmacological strategies to augment exposure-based interventions, based on basic science work, are also being studied and generating excitement in the field [51].

Neuromodulation and neurosurgical interventions

For those who have limited response to pharmacological and psychotherapeutic treatments, the following interventions focusing directly on modulating neurological pathways may be considered.

(1) *Non-invasive neuromodulation.* Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive stimulation procedure that modules neural transmission. The targets of most promise have been the orbitofrontal cortex and supplemental motor area. Review of small trials suggests that rTMS may be beneficial for some individuals, with response rates of 35% (compared to 14% sham condition) [52, 53]. In a more recent meta-analysis of 20 studies with 791 patients, both low and high frequency rTMS appeared to outperform the control condition [54]. Of note, larger effects were observed in individuals who were non-treatment resistant and did not have comorbid major depressive disorder, limiting rTMS' potential as secondary treatment option. In addition, extant rTMS trials are characterized by heterogeneity in stimulation parameters (including the intensity, frequency, duration of treatment), which limits conclusions and underscores the need for more research [55]. Another non-invasive neuromodulation treatment with promise involves transcranial direct current stimulation (tDCS), which applies direct current to the scalp rather than using magnets (e.g., [56]). The combination of tDS and SSRI may be helpful for some individuals although the data supporting its use remains limited [57].

(2) *Neurosurgical interventions.* Neurosurgery should be reserved for the most treatment-refractory cases, who have not responded to any of the strategies discussed above, and are continuing to experience severe and debilitating level of symptoms. The neurosurgical field has agreed on the following guidelines for defining refractory cases [58•]: (1) at least three SRI trials (one of which must have included clomipramine), all at a minimum duration of 12 weeks at maximally tolerated dose; (2) at least two augmentation strategies (including antipsychotic augmentation, another SRI, benzodiazepine, lithium carbona, or buspirone); (3) at least 20 h of EX/RP (of sufficient dose, duration and exposure quality); and (4) Y-BOCS score reduction less than 25% after adequate pharmacological and psychotherapeutic trials with CGI ratings of less than "minimally improved." Candidacy for the following treatment options should be evaluated by a specialist with expertise in OCD and in these neurosurgical approaches. Although seemingly promising in its

effects, more research is needed to identify target areas and to investigate long-term effects of these strategies. These treatments are generally considered as options of last resort.

(a) *Deep brain stimulation* (*DBS*). DBS involves reversible surgical implantation of electrodes in specific brain circuits. The focus of DBS research has been on the cortico-striatal-thalamic-cortical (CSTC) circuits implicated in OCD [59]. In 2009, the FDA approved the use of DBS for treatment-refractory OCD. Research suggests that it may be helpful in 50 to 75% of individuals [60, 61] , though response may vary depending on specific targets. In a multi-site study of DBS targeting the ventral anterior limb of the internal capsule and adjacent ventral striatum (VC/VS), Greenberg et al. [61] demonstrated an overall improvement in symptoms with significant Y-BOCS reductions (ranging from 34.0 to 53.8% change). Risks associated with DBS include brain hemorrhage, infection, onset of seizures, hypomanic symptoms, and an increase in depression [62].

(b) *Ablative neurosurgery*. In ablative neurosurgery, lesions are created using either stereotactical guidance or radiosurgical techniques ("gamma-knife"). The four lesioning procedures are anterior cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy. A small but growing body of research supports these techniques with estimates of 30–70% patients responding with at least minimal improvement [63–65]. In a recent systematic review of 10 neurosurgical studies involving 193 participants, cingulotomy (54% met response criteria at last follow-up) and capsulotomy (41%) procedures were shown to be efficacious [64]. Most of the evidence so far however has been limited to case series, unblinded cohort studies, and uncontrolled trials. In the first double-blind, placebo-controlled RCT of ablative surgery [58•], patients with intractable OCD (n = 16) were randomized to receive gamma ventral capsulotomy (n = 8) or sham procedure (n = 8). Those who underwent the active procedure demonstrated greater reduction in OCD symptoms than those in the sham condition, though this result only reached trend-level statistical significance (p = .11). These findings highlight the need for replication with larger samples to better understand the efficacy and safety profile of these neurosurgical interventions. Given the irreversible nature of this procedure, RCTs are also needed to evaluate long-term outcomes (including at 6 months to 3 years after the procedure). Of note, improvement with these procedures may take several weeks to months to become evident. Most individuals will continue to experience some level of OCD symptoms that could require additional treatment with medication and/or psychotherapy. Post-surgical reduction in symptoms may increase the patient's ability to engage and adhere to treatments described above, perhaps allowing for a full response.

The field has also focused its efforts on identifying predictors of response in ablative neurosurgery. In a recent retrospective analysis of patients who underwent capsulotomy, researchers were able to identify specific parameters of the lesion that were associated with clinical response [66]. Variability in response may also be due to individual neuroanatomical differences and may ultimately be used to preoperatively predict which patients are most likely to respond to these procedures [67•, 68•]. As our understanding of

predictive markers continues to evolve and clinical precision of ablative procedures continues to improve, personalized treatments may allow pro viders to consider invasive treatments only with those who are expected to respond.

Conclusions

Many individuals with OCD do not respond or only partially respond to first-line treatments and these non-responders may be considered to have "treatment-resistant" OCD. Suboptimal treatment outcomes may be related to inadequacy of the treatment trial (i.e., "technical failure") due to insufficient dose, duration, or type of treatment. To prevent prematurely declared treatment failures, it is imperative for clinicians to conduct comprehensive evaluations of the attempted treatments with specific details regarding each trial. When treatment trials do not succeed, it is also important for the provider to consider possible contributing factors to treatment resistance, such as comorbidity, external stressors, and difficulty adhering to treatment. Clinical options for treatment-resistant OCD include augmenting first-line treatments with medications, psychotherapy, and neuromodulatory approaches. These augmentation and novel monotherapy interventions offer promise in allowing more patients to experience significant improvement. Some interventions such as neurosurgery should be considered only as a last resort after more empirically supported treatments have been given adequate trial. The appropriate treatment for most patients is one that is not only efficacious but also safe and a good match for individual (i.e., one that they will adhere to). Factors impacting response, such as empirical evidence, availability/access to specific treatments, and treatment preference, need to be balanced. Advances in our understanding of the neural processes involved in OCD and individual differences of clinical responses (via neurological/genetic factors) will enable the field to optimize our current treatments and aid clinicians in selecting the treatment that is predicted to work best for each individual patient.

Compliance with Ethical Standards

Conflict of Interest

Dr. Gershkovich declares that she has no conflict of interest. Dr. Wheaton declares that he has no conflict of interest. Dr. Simpson has received research support from the National Institutes of Health (NIH), New York Presbyterian Youth Anxiety Center, and New York State Office of Mental Health.

Human and Animal Rights and Informed Consent

With regard to the authors' research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders 5th Edition (DSM-5). Washington, DC: American Psychiatric Publishing; 2013.
2. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15:53–63.
3.•• Koran LM, Simpson HB: Guideline Watch (2013): Practice guideline for the treatment of obsessive-compulsive disorder. Arlington: American Psychiatric Association; 2013.

Most recent APA treatment guidelines for OCD.

4. Pallanti S, Hollander E, Bienstock C, Koran L, Leckman J, Marazziti D, et al. Treatment non-response in OCD: methodological issues and operational definitions. Int J Neuropsychopharmacol. 2002;5:181–91.
5.•• Mataix-Cols D, de la Cruz FL, Nordsletten AE, Lenhard F, Isomura K, Simpson HB. Towards an international expert consensus for defining treatment response, remission, recovery, and relapse in obsessive-compulsive disorder. World Psychiatr. 2016;15(1):80–1.

This article provides expert definitions of treatment response.

6. Simpson HB, Huppert JD, Petkova E, Foa EB, Liebowitz MR. Response versus remission in obsessive compulsive disorder. J Clin Psychiatry. 2006;67:269–76.
7. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown obsessive compulsive scale, I: development, use, and reliability. Arch Gen Psychiatry. 1989;46:1006–11.
8. Guy, W.(Eds.) Assessment manual for psychopharmacology—revised. US Dept Health, Education and Welfare Publication (ADM), National Institute of Mental Health, Rockville; 1976; 76–338.
9. Goodman WK, Ward HE, Kablinger AS, Murphy TK. Biological approaches to treatment-resistant obsessive compulsive disorder. In: Goodman WK, Rudorfer MV, Maser JD, editors. Obsessive-compulsive disorder: contemporary issues in management. Lawrence Erlbaum Associates: London; 2000. p. 333–69.
10. Sookman D, Steketee G. Specialized cognitive behavior therapy for treatment resistant obsessive–compulsive disorder. In: Sookman D, Leahy R, editors. Treatment resistant anxiety disorders: resolving impasses to symptom remission. New York: Routledge; 2010. p. 31–74.
11. Bandelow B, Zohar J, Hollander E, Kasper S, Moller HJ, Allgulander C, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders—first revision. World J Biol Psychiatry. 2008;9(4):248–312.
12. Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive–compulsive disorder (OCD). (Electronic publication) Cochrane Database Systematic Review. 2008;23:1.
13. Skapinakis P, Caldwell D, Hollingworth W, Bryden P, Fineberg N, Salkovskis P, et al. A systematic review of the clinical effectiveness and cost-effectiveness of pharmacological and psychological interventions for the management of obsessive compulsive disorder in children/adolescents and adults. Health Technol Assess 2016; 20(43).
14. National Institute for Health and Clinical Excellence: Obsessive compulsive disorder: core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder [NICE Guideline]. Clinical guideline No. 31. London, UK, National Institute for Health and Clinical Excellence, 2005.
15. Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB, American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. Am J Psychiatry. 2007;164(7 suppl):5–53.
16. Fineberg N, Reghunandanan S, Simpson HB, Phillips KA, Richter MA, Matthews K, et al. Obsessive–compulsive disorder (OCD): practical strategies for pharmacological and somatic treatment in adults. Psychiatry Res. 2015;1:114–25.
17. Stein DJ, Koen N, Fineberg N, Fontenelle LF, Matsunaga H, Osser D, et al. A 2012 evidence-based algorithm for the pharmacotherapy for obsessive-compulsive disorder. Curr Psychiatry Rep. 2012;14(3):211–9.
18. Bloch MH, McGuire J, Landeros-Weisenberger A, et al. Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. Mol Psychiatry. 2010;15:850.
19.• Issari Y, Jakubovski E, Bartley CA, Pittenger C, Bloch MH. Early onset of response with selective serotonin reuptake inhibitors in obsessive-compulsive disorder: a meta-analysis. J Clin Psychiatry. 2016;77(5):e605–11.

This meta-analysis examines trajectory of treatment response to SSRIs.

20. Foa EB, Liebowitz MR, Kozak MJ, Davies S, Campeas R, Franklin ME, et al. Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine,

and their combination in the treatment of obsessive-compulsive disorder. Am J Psychiatry. 2005;162:151–61.

21. Tenneij NH, van Megen HJ, Denys DA, Westenberg HG. Behavior therapy augments response of patients with obsessive–compulsive disorder responding to drug treatment. J Clin Psychiatry. 2005;66:1169–75.
22. Simpson HB, Foa EB, Liebowitz MR, Ledley DR, Huppert JD, Cahill S, et al. A randomized, controlled trial of cognitive-behavioral therapy for augmenting pharmacotherapy in obsessive-compulsive disorder. Am J Psychiatry. 2008;165:621.
23. Simpson HB, Foa EB, Liebowitz MR, Huppert JD, Cahill S, Maher MJ, et al. A randomized controlled trial of cognitive behavioral therapy versus risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder. JAMA Psychiatry. 2013;70:1190–9.
24. Wheaton MG, Carpenter JK, Kalanthroff E, Foa EB, Simpson HB. Augmenting SRIs for obsessive-compulsive disorder: patient preference for risperidone does not limit effectiveness of exposure and ritual prevention. Psychother Psychosom. 2016;85(5):314–6.
25. Foa EB, Simpson HB, Liebowitz MR, Powers MB, Rosenfield D, Cahill SP, et al. Six-month follow-up of a randomized controlled trial augmenting serotonin reuptake inhibitor treatment with exposure and ritual prevention for obsessive compulsive disorder. J Clin Psychiatry. 2013;74(5):464–9.
26.•• Foa EB, Simpson HB, Rosenfield D, Liebowitz MR, Cahill SP, Huppert JD, 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):440–6. https://doi.org/10.4088/JCP.14m09044.

Six-month follow-up outcomes of an RCT comparing SRI augmentation strategies (EX/RP vs. risperidone).

27. Fineberg NA, Gale TM, Sivakumaran T. A review of antipsychotics in the treatment of obsessive compulsive disorder. J Psychopharmacol. 2006, 1:97–103.
28. Fineberg NA, Brown A, Reghunandanan S, Pampaloni I. Evidence-based pharmacotherapy of obsessive-compulsive disorder. Int J Neuropsychopharmacol. 2012;15(8):1173–91.
29. Bloch MH, Landeros-Weisenberger A, Kelmedi B, Coric V, Bracken MB, Leckman JF. A systematic review: antipsychotic augmentation with treatment-refractory obsessive-compulsive disorder. Mol Psychiatry. 2006;11:622–32.
30.• Dold M, Aigner M, Lanzenberger R, Kasper S. 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):pyv047.

An updated meta-analysis of antipsychotic augmentation.

31. Komossa K, Depping AM, Meyer M, Kissling W, Leucht S. Second-generation antipsychotics for obsessive compulsive disorder. Cochrane Database of Systematic Reviews 2010, (12). No.: CD008141. DOI: https://doi.org/10.1002/14651858.CD008141.pub2.
32. March JS, Frances A, Carpenter D, Kahn DA. The expert consensus guideline series: treatment of obsessive-compulsive disorder. J Clin Psychiatry. 1997;58(suppl 4):3–72.
33. Rodriguez CI, Kegeles LS, Levinson A, Feng T, Marcus SM, Vermes D, et al. Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. Neuropsychopharmacology. 2013;38(12):2475–83.
34. Foa EB, Yadin E, Lichner TK. Exposure and response (ritual) prevention for obsessive-compulsive disorder: therapist guide (treatments that work), 2nd ed. Oxford University Press: 2012.
35. Abramowitz JS, Foa EB, Franklin ME. Exposure and ritual prevention for obsessive-compulsive disorder: effects of intensive versus twice-weekly sessions. J Consult Clin Psychol. 2003;71:394–8.
36. Rosa-Alcazar AI, Sanchez-Meca J, Gomez-Conesa A, Marin-Martinez F. Psychological treatment of obsessive-compulsive disorder: a meta-analysis. Clin Psychol Rev. 2008;28(8):1310–25.
37. Boschen MJ, Drummond LM, Pillay A. Treatment of severe, treatment-refractory obsessive-compulsive disorder: a study of inpatient and community treatment. CNS Spectr. 2008;13(12):1056–65.
38. Bjorgvinsson T, Wetterneck CT, Powell DM, Chasson GS, Webb SA, Hart J, et al. Treatment outcome for adolescent obsessive-compulsive disorder in a specialized hospital setting. J Psychiatr Pract. 2008;14(3):137–45.
39. Simpson HB, Maher M, Page JR, Gibbons CJ, Franklin ME, Foa EB. Development of a patient adherence scale for exposure and response prevention therapy. Behav Ther. 2010;41(1):30–7.
40. Simpson HB, Maher MJ, Wang Y, Bao Y, Foa EB, Franklin M. Patient adherence predicts outcome from cognitive behavioral therapy in obsessive-compulsive disorder. J Consult Clin Psychol. 2011;79(2):247–52. https://doi.org/10.1037/a0022659.
41. Simpson HB, Marcus SM, Zuckoff A, Franklin M, Foa EB. Patient adherence to cognitive-behavioral therapy predicts long-term outcome in obsessive-compulsive disorder. J Clin Psychiatry. 2012;73(9):1265–6. https://doi.org/10.4088/JCP.12l07879.
42.• Wheaton MG, Galfalvy H, Steinman SA, Wall MM, Foa EB, Simpson HB. Patient adherence and treatment outcome with exposure and response prevention for

OCD: which components of adherence matter and who becomes well? Behav Res Ther. 2016;85:6–12.
This article highlights the significance of patient adherence for treatment outcome.
43. Simpson HB, Zuckoff A, Page JR, Franklin ME, Foa EB. Adding motivational interviewing to exposure and ritual prevention for obsessive-compulsive disorder: an open pilot trial. Cogn Behav Ther. 2008;37(1):38–49.
44. Thompson-Hollands J, Abramovitch A, Tompson MC, Barlow DH. A randomized clinical trial of a brief family intervention to reduce accommodation in obsessive compulsive disorder: a preliminary study. Behav Ther. 2015;46(2):218–29.
45. Andersson E, Enander J, Andrén P, et al. Internet-based cognitive behaviour therapy for obsessive–compulsive disorder: a randomized controlled trial. Psychol Med. 2012;42(10):2193–203. https://doi.org/10.1017/S0033291712000244.
46. Patel S, Wheaton M, Schmidt A, LaLima C, Pascucci O, Andersson E, Ruck C, Myers R, Dixon L, Simpson HB: Implementing Internet based cognitive behavioral therapy for OCD in the United States. Behavior Therapy. In press.
47. Olatunji BO, Davis ML, Powers MB, Smits JAJ. Cognitive-behavioral therapy for obsessive-compulsive disorder: a meta-analysis of treatment outcome and moderators. J Psychiatr Res. 2013;47:33–41.
48. Kushner MG, Kim SW, Donahue C, Thuras P, Adson D, Kotlyar M, et al. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. Biol Psychiatry. 2007;62(8):835–8.
49. Wilhelm S, Buhlmann U, Tolin DF, Meunier SA, Pearlson GD, Reese HE, et al. Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. Am J Psychiatr. 2008;165(3):335–41.
50. Rodriguez CI, Wheaton M, Zwerling J, Steinman SA, Sonnenfeld D, Galfalvy H, et al. Can exposure-based CBT extend the effects of intravenous ketamine in obsessive-compulsive disorder? An open-label trial. J Clin Psychiatry. 2016;77(3):408–9.
51. Mathes BM, Van Kirk N, Elias JA. Review of psychotherapeutic approaches for OCD and related disorders. Curr Treat Options Psych. 2015;2:284–96.
52. Jaafari N, Rachid F, Rotge JY, Polosan M, El-Hage W, Belin D, et al. Safety and efficacy of repetitive transcranial magnetic stimulation in obsessive compulsive disorder: a review. World J Biol Psychiatry. 2012;13:164–77.
53. Berlim MT, Neufeld NH, Van den Eynde F. Repetitive transcranial magnetic stimulation (rTMS) for obsessive–compulsive disorder (OCD): an exploratory meta-analysis of randomized and sham-controlled trials. J Psychiatr Res. 2013;47:999–1006.
54. Zhou DD, Wang W, Wang GM, Li DQ, Kuang L. An updated meta-analysis: short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder. J Affect Disord. 2017;215:187–96.
55. Kumar N, Kumar S, Gupta R. An update of the application of repetitive transcranial magnetic stimulation (rTMS) in patients with obsessive compulsive disorder. Neuropsychiatry. 2016;6:10–4.
56. Dinn WM, Aycicegi-Dinn A, Goral F, Karamursel, Yildirim EA, Hacioglu-Yildirim M, et al. Treatment-resistant obsessive-compulsive disorder: insights from an open trial of transcranial direct current stimulation (tDCS) to design a RCT. Neurol Psychiatry Brain Res. 2016;3-4:146–54.
57. Bation R, Poulet E, Haesebaert F, Saoud M, Brunelin J. Transcranial direct current stimulation in treatment-resistant obsessive-compulsive disorder: an open-label pilot study. Prog Neuro-Psychopharmacol Biol Psychiatry. 2016;65:153–7.
58.• Lopes AC, Greenberg BD, Canteras MM, Batistuzzo MC, Hoexter MQ, Gentil AF, et al. Gamma ventral capsulotomy for obsessive-compulsive disorder: a randomized clinical trial. JAMA Psychiatry. 2014;71:1066–76.
First double-blind placebo-controlled RCT of neurosurgical ablation.
59. Bourne SK, Eckhardt CA, Sheth SA, Eskandar EN. Mechanisms of deep brain stimulation in for obsessive compulsive disorder: effects upon cells and circuits. Front Integr Neurosci. 2012;6:29.
60. de Koning PP, Figee M, Van den Munckhof P, Schuurman PR, Denys D. Current status of deep brain stimulation for obsessive–compulsive disorder: a clinical review of different targets. Curr Psychiatry Rep. 2011;13:274–82.
61. Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, et al. Three-year outcomes in deep brain stimulation for highly resistant obsessive–compulsive disorder. Neuropsychopharmacology. 2006;31:2384–93.
62. Greenberg BD, Nahas Z, Carpenter LL. Current status of deep brain stimulation. Primary Psychiatry. 2005;12:59–64.
63. Dougherty DD, Baer L, Cosgrove GR, Cassem EH, Price BH, Nierenberg AA, et al. Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive-compulsive disorder. Am J Psychiatry. 2002;159:269–75.
64. Brown LT, Mikell CB, Youngerman BE, Zhang Y, McKhann GM, Sheth SS. Dorsal anterior cingulotomy and anterior capsulotomy for severe, refractory obsessive-compulsive disorder: a systematic review of observational studies. J Neurosurg. 2016;124:77–89.

65. Sheth SS, Neal J, Tangherlini F, Mian MK, Gentil A, Cosgrove GR, et al. Limbic system surgery for treatment-refractory obsessive-compulsive disorder: a prospective long-term follow-up of 64 patients. J Neurosurg. 2013;118:491–7.
66. Nanda P, Banks GP, Pathak Y, Paulo DK, Horga G, Hoexter MQ, et al. Tractography characterizing lesions differentiating responders to stereotactic capsulotomy for obsessive-compulsive disorder. Neurosurgery. 2016;63:180–1.
67.• Banks GP, Mikell CB, Youngerman BE, Henriques B, Kelly KM, Chan AK, Herrera D, Dougherty DD, Eskandar EN, Sheth SS. Neuroanatomical characteristics associated with response to dorsal anterior cingulotomy for obsessive-compulsive disorder. JAMA Psychiatry, 2015: 127–25.
This paper presents a retrospective analysis of neuroanatomical characteristics that differentiated responders from non-responders to neurosurgery.
68.• van den Heuvel OA. Toward brain-based guidance of clinical practice. JAMA Psychiatry. 2015;72(2):108–9.
This paper provides commentary on neuroimaging predictors of treatment response to neurosurgery.