Treatment Resistance in Obsessive-Compulsive Disorder

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11.1 Introduction

Obsessive-compulsive disorder (OCD) is characterized by obsessions (recurrent thoughts, images, or urges that typically provoke anxiety and distress) and compulsions (repetitive behaviors that the individual feels driven to perform, often to alleviate distress or prevent feared consequences). To warrant a diagnosis of OCD, obsessions and/or compulsions must be time-consuming (e.g., present for more than 1 hour per day) and cause significant distress or impairment in an individual's daily functioning [1]. The severity of symptoms can be assessed using the Yale-Brown Obsessive Compulsive Scale (YBOCS) [2].

OCD has an estimated lifetime prevalence rate of 2–3% in the population, making it more than twice as common as schizophrenia. OCD typically starts in childhood or adolescence (with a median onset of 19 years old) and persists throughout a person's life, with symptoms typically following a chronic waxing and waning course. OCD produces substantial impairment in functioning due to the severe and chronic nature of the illness. Earlier age of onset can disrupt normal developmental trajectories and thus lead to greater impairment. Males often have an earlier OCD onset age, but by adulthood, OCD is estimated to affect equal numbers of men and women [3].

Practice guidelines from the American Psychiatric Association (APA) [4] recommend beginning treatment with either pharmacotherapy with serotonin reuptake inhibitors (SRIs), cognitive-behavioral therapy (CBT), or their combination. SRIs include the selective serotonin reuptake inhibitors (SSRIs, i.e., fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram) as well as the nonselective SRI clomipramine; which have been shown in large, multisite, randomized controlled trials (RTCs) to outperform placebos in reducing OCD symptoms [5]. The recommended form of CBT is that consisting of Exposure and Ritual (Response) Prevention (ERP), a structured psychotherapy that involves two major components: systematic confrontation with feared situations and stimuli (i.e., exposures) and voluntary restriction from engaging in compulsive rituals (i.e., ritual prevention component). SRIs and ERP, either on their own, or used together, will help

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Y.-K. Kim (ed.), *Treatment Resistance in Psychiatry*, https://doi.org/10.1007/978-981-10-4358-1_11

many patients reduce their OCD symptoms and about half achieve minimal symptoms [6–9].

However promising, these results indicate that these treatment options are not universally effective, as up to 40–60% of individuals fail to respond to these first-line treatments [10, 11]. A "treatment response" in OCD clinical trials has historically been operationalized as a decrease of 25–35% in OCD symptoms, typically assessed with the YBOCS, and often combined with a rating of "improved" or "very much improved" on the Clinical Global Impressions-Improvement Scale (CGI-I) [12]. Individuals who fail to achieve a sufficient response, and those who continue to experience clinically significant symptoms despite a 25–35% decrease, are often referred to as "treatment-resistant" [13]. When a first-line treatment is not enough, several alternatives are available, depending on the type and degree of treatment resistance (i.e., resistance to SSRIs, ERP, or both), as discussed below.

11.2 Treatment Resistance with Pharmacotherapy

11.2.1 Predictors of SRI Response

In the Cochrane review [14] meta-analysis of 17 RCTs (comprising more than 3000 participants), researchers found SRIs to be associated with significant reductions in OCD symptoms, with an average YBOCS reduction for patients who respond to SRIs to be 30–60% from baseline. In this analysis, no individual medication emerged as more efficacious. However, because the side effects associated with clomipramine can be more severe [5, 14, 15], treating clinicians typically begin with an SSRI.

Ineffective dosages or insufficient duration may be responsible for poor response to SRI treatment, the so-called technical failure. Studies show that higher doses yield, on average, higher rates of improvement in symptoms [16]. Similarly, data suggest that doses should be maintained for at least 8–12 weeks for maximum therapeutic effects [17]. However, higher doses of SSRIs produce more side effects, leading some patient to prematurely discontinue the medication [18]. Therefore, it is recommended that patients begin at low doses and increase their dose to the maximum tolerated. The maximally tolerated dose should be maintained for a minimum of 6 weeks to be considered an adequate therapeutic trial [3, 16].

Several clinical factors can also predict poor response to SRIs. Higher levels of symptoms at baseline have been associated with lower levels of SRI response in multiple trials [12, 19, 20]. Comorbid tic disorders, such as Tourette's, have also been linked to poorer SRI outcomes. For example, in a study of 33 OCD patients on fluvoxamine, 52% of OCD patients without a history of tic disorders achieved a significant decrease in symptoms (assessed by the YBOCS), compared to only 21% of OCD patients in the comorbid tic group [21]. These findings have been replicated in children and adolescents with the SSRIs sertraline and paroxetine [22, 23]. However, in a small pilot study, comorbid tics did not appear to adversely impact response to clomipramine [21]. One issue complicating the interpretation of these data is that higher rates of comorbid tic disorders have been linked to earlier OCD onset [24]. Early age of OCD onset has also been linked to treatment nonresponse across several SRIs [25–29], including fluvoxamine, paroxetine, citalopram, and clomipramine [28, 29].

Patients with OCD often present with comorbid psychiatric conditions, most frequently anxiety disorders (e.g., panic disorder, social anxiety disorder, generalized anxiety disorder, specific phobias), which appear in about 75% of OCD patients [30]. However, the impact of comorbid anxiety disorders on SRI response remains unclear. Most OCD studies have not found comorbid anxiety disorders to interfere with SRI response [17, 31], though an earlier review of this literature came to a different conclusion [32]. Unexpectedly, some reports have found that comorbid PTSD predicts better responses in individuals with certain OCD symptoms (hoarding, contamination fears, illness concerns, mental rituals, and/or superstition) [33]. A "post-traumatic" OCD subtype has been proposed as a potential explanation for these findings, though further

research on this area is warranted [34]. Although panic disorder has not been shown to impact SSRI response in OCD, higher doses of SSRIs in these individuals have been linked to increases in panic attacks in multiple studies [17].

Medication adherence has also been linked to the likelihood of responding to SRI treatment, with nonadherent patients at risk for treatment failure [28]. Unwanted medication effects are a barrier to adherence for many patients. Common side effects with SRIs include gastrointestinal problems (nausea, constipation, and diarrhea), weight gain, tremors, apathy, sleep disturbances (insomnia and/or vivid dreams), fatigue and somnolence, dry mouth, and sexual dysfunction (decreased libido, trouble ejaculating, anorgasmia) [16, 35], the latter three of which have been found to be the most predictive of medication discontinuation for patients beginning pharmacotherapy [35]. Other patients may have difficulty with adherence to medication due to particular aspects of their presentation of OCD (e.g., those with contamination fears may be concerned about what they ingest, making them more hesitant to take medicine [36]).

A patient's degree of insight may also impact his or her adherence to medication. Insight can be defined as the degree to which an individual recognizes the maladaptive nature of their symptoms. Several studies have reported poor insight as a significant predictor of poor SRI response [37, 38].

11.2.2 Management of Resistance with SRIs

Patients who do not experience an adequate response to SSRIs may explore several different options. If they do not have dose-limiting side effects, a practical first step is to increase their dose. The FDA has approved the following SSRI dose ranges for OCD: fluoxetine 20–60 mg/day, fluvoxamine 100–300 mg/day, paroxetine 40–60 mg/day, sertraline 50–200 mg/day, citalopram up to 40 mg/day (20 mg/day in patients older than 60), and escitalopram 10–20 mg/day [39]. However, higher doses are recommended in practice guidelines and are commonly used in clinical practice (e.g., fluoxetine up to 120 mg/day, fluvoxamine up to 450 mg/day, paroxetine up to 100 mg/day, sertraline up to 400 mg/day, citalopram up to 120 mg/day, and escitalopram up to 60 mg/day) [17]. As noted above, since higher SRI doses may increase the risk for side effects in some patients, dosing should begin on the lower end after which dosages can be increased every 1–2 weeks to determine the maximally tolerated dose. Only following 6 weeks at this dose should a patient be considered treatment-resistant [16].

Switching SSRIs or exploring monotherapy with clomipramine are both alternatives for patients who have experienced little to no response to an initial SSRI trial. It has been estimated that less than 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 [16, 25]. Switching to clomipramine, a tricyclic antidepressant that inhibits the reuptake of both serotonin and norepinephrine, is often tried after two different SSRIs have not produced a significant relief from symptoms. Although not typically a first-line agent due to its side effect profile (e.g., sedation, dry mouth, constipation, urinary delay, orthostatic hypotension, and cardiac conduction delay), some meta-analyses find that clomipramine can lead to larger effects than SSRIs [39].

When patients experience a partial response to serotonergic medication but continue to have clinically impairing symptoms, SRI augmentation is often considered. In general, augmentation strategies involve the addition of either psychotherapy (ERP) or an antipsychotic medication such as risperidone. In our recent trial, we found ERP augmentation to be more efficacious than risperidone, even among patients who preferred medication over ERP [7, 40]. Given this result, as well as the side effect profile of antipsychotics, augmentation with ERP is the best to try first [41, 42].

However, ERP is not available to all patients, and not all are willing to try it. Therefore, antipsychotic augmentation remains a viable strategy for some patients. Haloperidol, risperidone, quetiapine, olanzapine, and aripiprazole have all been shown in RCTs to enhance response to

SRIs, though not all trials with these agents have had positive results [41–43]. It is unclear if mixed responses found across antipsychotic trials reflect true differences in efficacy between these agents or methodological issues with specific trials. Meta-analyses across all of these trials [42, 44, 45] suggest that around one third of OCD patients on an SRI will have a treatment response when an antipsychotic medication is added. Some data suggest that OCD patients with comorbid tics are more likely to respond, particularly, to risperidone and haloperidol [44]. Although effective for some, antipsychotics are associated with weight gain, metabolic syndrome, and a variety of extrapyramidal side effects including acute dyskinesias and dystonic reactions, tardive dyskinesia, parkinsonism, akinesia, akathisia, and neuroleptic malignant syndrome [44]. Patients starting an antipsychotic should be monitored closely for side effects, and the medication should be discontinued if no benefits are observed after an adequate therapeutic trial of 1 month [16].

There is some evidence from case studies to support augmentation with other pharmacological agents such as lithium, buspirone, and clonazepam. However, none were found to outperform placebo in small clinical trials, which may suggest that these drugs are only effective for a subset of patients [46].

Monotherapy with other medications has also been explored, including venlafaxine and mirtazapine. Venlafaxine had robust effects on OCD symptoms in both open-label and double-blind comparator studies. However, these effects were not replicated in a placebo-controlled trial [47]. In one small study, mirtazapine was shown to be effective in patients who have had no more than one failed SSRI trial [48].

11.3 Treatment Resistance with ERP

11.3.1 Predictors of Treatment Resistance

Although the evidence supporting ERP is substantial [17], not all patients benefit. Some patients discontinue treatment prematurely, and of those who complete, a subset does not respond [8]. Substantial effort has been made to describe predictors of ERP outcomes in order to identify patients at risk for poor outcomes. Both patient factors (e.g., patient adherence, comorbidity, degree of insight) and treatment factors (e.g., treatment intensity and duration) can influence outcome [49].

Patient adherence is the strongest predictor of ERP outcome. ERP requires patients to confront fears and refrain from compulsive rituals, both in therapy sessions (under therapist supervision) and between therapy sessions (as homework assignments). Several studies have shown that the degree to which patients adhere to ERP assignments robustly predicts acute outcomes [50], and also outcomes 6 months later [51]. Monitoring patient adherence, particularly adherence to ritual prevention instructions, has also been shown to prospectively forecast who will benefit from treatment, allowing treating clinicians to make individualized treatment predictions [40].

Some studies have found that higher initial OCD symptom severity and severe comorbid depression can also predict poor ERP outcomes [52]. However, other studies have not replicated these findings, and a recent meta-analysis found no relationship between either baseline OCD severity or depression severity and ERP effect size [53]. One potential explanation for these mixed results is that it may only be severe depression that predicts ERP response, which has been excluded in many ERP trials. Severe depression can also impact patient adherence to treatment, which may mediate the link with poor outcomes. Similarly, other common comorbid disorders found in OCD populations (e.g., obsessive-compulsive personality disorder and comorbid anxiety disorders) warrant clinical attention when they impact a patient's ability to adhere to treatment [17].

Some studies have reported that patients with poor insight are less likely to experience an ERP treatment response compared to patients with good or fair insight [30, 54]. However, other studies have found no association between insight

and treatment response [17, 50, 55]. One possible explanation for these different outcomes is restriction in range of insight, as few patients with the poorest insight present for treatment. The link between insight and outcome may also be via patient adherence. For example, early studies found that approximately 25–30% of patients who begin ERP drop out due to the nature of ERP (i.e., ERP requires the patient to confront their anxiety [56]). Thus, the APA recommends that clinicians gauge patient insight as a preliminary step to the establishment of a treatment plan [17]. Assessing insight before treatment selection can inform the clinician of their patient's motivation and willingness to adhere; this information can in turn be factored into the patient's treatment plan.

Therapist fidelity to ERP is another factor that may play a role in treatment outcomes. If ERP is not administered effectively, patients may not respond [57]. Effective ERP administration involves exposing patients to distress-provoking stimuli and then persisting in the exposure for a sufficient amount of time in order for the patient to learn that the situation can be managed without giving into compulsive rituals [52]. Therapist failure to follow these treatment procedures during sessions may interfere with patients' ability to benefit from ERP. Some data also suggest that the frequency of sessions also can affect treatment outcomes, as reviewed below.

Finally, other factors have also been identified in individual studies to affect ERP outcomes, including gender, marital status, and baseline quality of life/functioning. For example, some studies have reported that females have poorer ERP response as compared to males [58], while others have found that married/partnered patients fare better than single patients [59]. Similarly, Maher et al. reported that individuals with worse quality of life at baseline had poorer ERP responses [58], while Wheaton et al. found that greater problems in functioning at baseline predicted poorer ERP response [60]. However, for each of these variables, multiple other studies have reported null results [61]. It may be that many factors each play a small role in ERP outcomes which can vary from sample to sample in terms of strength, with patient adherence to the ERP playing a major role and showing a consistent relationship with ERP outcomes [58]. Given how effective ERP is for individuals with OCD, further study is warranted and should include both therapist and patient factors as well as biological, psychological, behavioral, and sociocultural variables.

11.3.2 Management of Treatment Resistance with ERP

When a trial of ERP does not yield a sufficient treatment response, therapists should consider increasing exposure intensity (i.e., utilize stimuli that induce higher levels of anxiety) and/or increasing the duration and frequency of sessions before considering a different type of therapy or exploring pharmacological options. There is some evidence that ERP sessions are more effective when administered intensively (at least twice weekly); however, this benefit may plateau at five sessions per week in outpatient treatment [10, 17]. Increasing dose and intensity may be particularly helpful for patients who need extra support in adherence outside of session ERP assignments, including those with poor insight [10, 62].

Residential treatment is another option when outpatient ERP does not succeed. In the United States, several specialty residential programs have been established focusing on OCD, including programs at Rogers Memorial Hospital and the McLean Institute at Massachusetts General Hospital. Even though these programs tend to enroll patients with high illness severity, who often also have multiple comorbidities, both programs have reported positive results in terms of reducing OCD and depressive symptoms [63–65]. Residential programs allow patients to receive multiple hours per day of ERP work, delivered in both group and individual formats.

When ERP does not succeed as a monotherapy, it can be combined with either medications or other techniques from other forms of psychotherapy. For example, psychotherapy incorporating cognitive therapy may offer an alternative or an augmentation strategy to

standard ERP [66]. Cognitive therapy involves identification and modification of distorted or dysfunctional beliefs, and some trials have found it to be effective at reducing OCD symptoms, although these trials have not been as extensive those for ERP [46, 67].

11.4 Treatment Resistance to Both SRIs and ERP

SRIs and ERP alone, or in combination, can help up to 50% of OCD patients become well [7, 9]. However, any of the aforementioned factors can interfere with achieving wellness, and thus many continue to suffer. After thoroughly exploring the treatment options outlined above, the use of more experimental therapies may be warranted. These include neuromodulatory treatments and even neurosurgery.

Transcranial magnetic stimulation (TMS) is a noninvasive method for either stimulating or inhibiting neural transmission. Greenberg et al. (1997) found that a single session of stimulation of the right lateral prefrontal cortex (PFC) led to a decrease in compulsive urges that lasted for 8 hours. Since then, there have been several trials of repetitive TMS (rTMS) targeting different brain regions [46]. Meta-analyses of existing trials of rTMS studies suggest that rTMS of prefrontal regions (specifically the dorsolateral PFC) may not be effective in OCD, but low-frequency rTMS targeting the supplemental motor area appears to be promising [68–70].

Patients deemed treatment refractory (i.e., failed at least three adequate SRI trials, several augmentation trials (e.g., with an antipsychotic or clonazepam), and at least one adequate CBT trial) are potential candidates for neurosurgical interventions. These interventions include either making targeted lesions in cortico-striatal-thalamic-cortical (CTSC) circuits or altering activity within these circuits using deep brain stimulation (DBS).

DBS involves delivering electrical impulses to various areas of the brain via surgically implanted electrodes. Recent literature has focused on the CSTC circuit as a target for this treatment modality [71], with a double-blind trial and several case reports/series focusing on the anterior limbs of the internal capsules (ALIC) and the subthalamic nucleus. A case series investigation in which the ALIC was targeted using DBS found a greater than 25% decrease in YBOCS scores in 73% of participants. Studies using the subthalamic nucleus as a target have not reported significant decreases in YBOCS scores [72, 73]. While DBS is reversible (in the sense that the stimulation can be turned off and the electrodes removed from the brain), risks include brain hemorrhage, infection, and new onset of seizures. For these reasons, DBS is only used in treatment-refractory populations [17].

Neurosurgical lesions can be produced either surgically or using radiosurgical ("Gamma Knife") techniques. Different lesions have been tried: subcaudate tractotomy, capsulotomy, cingulotomy, and limbic leucotomy [74, 75]. Case series find that 30–70% of patients have at least minimal improvement symptoms following these procedures [10, 76]. The first RTC of gamma knife capsulotomy was conducted in 2014. The final report found that two of the eight patients who received the procedure responded at the 12-month follow-up and an additional two responded at the 54-month follow-up [77]. A second report during an open phase of the same study found significant improvement in two out of four patients who were elected to undergo the procedure after initial randomization to the sham condition. No patients in the sham condition of either phase reported an improvement in symptoms [78]. Ablative procedures are irreversible and can lead to serious adverse events (SAEs) including seizures, increased executive dysfunction, apathy, disinhibition, suicide, weight gain, brain hemorrhage, stroke, edema, hydrocephalus, and personality change [75, 79]. Thus, ablation is only used in treatment-refractory populations.

11.5 Biological Predictors of Treatment-Resistant OCD: Current Research

Current research continues to examine the mechanisms underlying obsessions and compulsions as well as how our current treatments work. These data may help explain why some individuals respond to current treatments and others do not, and may lead to novel targets for treatment development and markers of disease that can guide treatment choice.

One approach has been to study the basic neural processes that may lead to obsessions and compulsions. For example, some have investigated whether dysfunction in the learning or extinction of fear contributes to OCD [80], and impairment in fear extinction has been demonstrated in laboratory studies in patients with OCD [81]. Others have examined whether abnormalities in goal-directed versus habitual behavior explain the compulsions seen in OCD. For example, Gillan et al. (2011) found evidence of disruption in goal-directed action control among OCD patients [82], and these findings have been replicated in other samples [80, 83]. However, whether any of these abnormalities predict treatment response remains to be tested.

Another approach has been to identify brain signatures of obsessions and compulsions using neuroimaging [84]. While abnormalities have been identified in CSTC circuits as well as in other areas [80] linked to compulsivity [85], it is not clear whether these brain abnormalities cause OCD or result from it. In addition, it remains unclear the extent to which neural functioning can be used to predict treatment outcome. A recent study by Fullana et al. (2017) found a significant association between decreased connectivity in the basolateral amygdala–ventromedial prefrontal cortex and better ERP treatment outcomes [86]. However, these findings yielded a relatively small effect size, similar to many other imaging studies conducted with the OCD population [87].

Neuroinflammatory markers are a third area of interest. One theory holds that neuroinflammation may cause obsessions and compulsions in a subset of OCD patients, and research on pediatric autoimmune neuropsychiatric disease (PANS/PANDAS) has highlighted this connection [36]. In addition, a recent paper found evidence for neuroinflammation in CSTC circuits in unmedicated OCD patients [88]. Thus, neuroinflammatory markers might identify a subset of individuals that are potentially resistant to existing treatments. The role of neuroinflammation in OCD deserves further study as it opens up a new pathway for treatment development.

Finally, researchers are interested in using genetic studies to identify which treatments will work best for individual patients. Genome-wide association studies (GWAS) offer one approach to identifying common genetic risk factors, but the studies in OCD are still underpowered, and no findings with genome-wide significance have yet been identified [89, 90]. An alternative is to search for rare or de novo (DN) mutations using whole-genome or exome sequencing in select samples. This approach has been applied in two studies [91, 92] utilizing parent-child trios (i.e., children with OCD and their parents). In one of these studies, researchers identified two risk genes, SCUBEI and CHD8, in the children. Both of these genes contained significant clusters of damaging DN variants [91]. The long-term goal of this line of research is to identify gene variants that might explain why certain individuals developed OCD and might guide more precise treatment selection.

11.6 Alternative Treatment Modalities: Current Research

Given that first-line treatments fail in up to half of OCD patients (as reviewed above), new and alternative treatments are needed. In terms of alternative psychotherapies, recent work has investigated acceptance and commitment therapy (ACT), which integrates mindfulness and

acceptance-based processes with values-connected behaviors [93]. Initial data supports the use of ACT as an OCD treatment, but further research on this method is warranted [94]. Similarly, mindfulness therapy is currently being explored in the literature. This approach focuses on creating awareness and subsequent detachment between an individual and their symptoms. A recent review of this approach has suggested that it may be useful for some OCD patients [95, 96].

With regards to medications, glutamatergic agents have garnered much attention because of data from genetic and neuroimaging studies implicating the glutamate system in OCD. Many different glutamatergic agents have been investigated in the last 5 years, including N-acetylcysteine, memantine, and riluzole [78–81]. These medications have been shown to benefit some OCD patients in both open-label and placebo-controlled trials, although there have also been failed trials [97–101]. In a proof-of-concept crossover study, a single dose of IV ketamine (an antagonist at the N-methyl-D-aspartate receptor [NMDA] receptor) led to the rapid resolution of obsessions in unmedicated adults with OCD [82], introducing the exciting possibility of developing rapidly acting medications for OCD.

The potential role of the endocannabinoid (eCB) system in the treatment of OCD has attracted new interest. Studies in mice have linked activity within the eCB system to altered functionality within frontal-striatal circuits that regulate the balance between goal-directed and habitual action strategies [102]. Exogenously delivered cannabinoids can reduce marble-burying, a repetitive behavior thought to be a proxy for compulsions in OCD [103–107]. Both mouse models and human studies suggest that cannabidiol (CBD, a non-psychoactive constituent of the marijuana plant) can enhance fear extinction, suggesting that agents targeting the eCB system may be beneficial when combined with exposure-based treatments [99]. However, to date, human studies involving cannabinoid agents in OCD populations are limited to two case reports. Both describe patients with treatment-resistant OCD who experienced an improvement in symptoms after dronabinol was added to ongoing treatment with an SRI [108].

The potential role of neuroinflammation in OCD has led some to reconsider the effects of drugs like N-acetylcysteine (NAC) and celecoxib. The efficacy of NAC, a glutamate-modulator with anti-inflammatory properties, has been supported in an RTC, with further evidence from prior case studies [109]. Similarly, celecoxib has found support as an adjunctive treatment to fluvoxamine and fluoxetine in two RTCs [110].

Finally, studies are investigating how to combine different types of noninvasive neuromodulation (i.e., rTMS and tDCS) with pharmacotherapy [111, 112] or with ERP [80, 113]. In addition, new targets for interventions are being examined. For example, several case studies have found positive results targeting the inferior thalamic peduncle in treatment-resistant OCD patients, and results were maintained at a 1-year follow-up [63].

Conclusion

While there is substantial evidence for effective first-line treatments for OCD, many individuals fail to sufficiently respond. These individuals are considered treatment-resistant. Many factors have been shown to predict treatment resistance. Suboptimal response has been linked to "technical failures." These include insufficient dose, duration, and/or type of treatment, as well as clinical factors such as symptom severity, comorbidities, age of onset, insight, and patient adherence. To avoid these issues, treatment guidelines recommend thorough evaluation and treatment planning to ensure appropriate progression of treatment types.

Management options for treatment-resistant OCD should be evaluated based on the level of response the individual demonstrates. Management of partial response to initial first-line treatments can include increasing dose and duration, or augmentation of SRIs with ERP, or vice versa. For patients with minimal to no response, options include switching medications or augmenting with an antipsychotic. Patients who continue to see an

inadequate response to these treatments can explore novel treatment strategies including new glutamate medications. Only in the most severe cases should neurosurgical approaches (e.g., DBS or ablation) be considered.

Recent advances in genetic, neuroimaging, and neurobehavioral studies may allow future research to uncover what causes OCD while also aiding in the development of new treatment options. Ideally, treatment will one day be tailored to each individual, and as a result, treatment outcomes and quality of life will improve for these individuals, and for the patients of the future.

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