**Review**
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# Clinical Advances in Treatment Strategies for Obsessive-compulsive Disorder in Adults

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In the present article, we provide a comprehensive review of the treatment strategies for obsessive-compulsive disorder (OCD), a common, chronic, and often debilitating disorder, characterized by overwhelming obsessions and compulsions. OCD typically starts in childhood or adolescence and persists throughout life, causing functional impairment across multiple domains. The article begins by describing the historical concepts of OCD from religious and guilt-based explanations to psychoanalytic perspectives, and then explores the changing understanding of OCD as a treatable condition. Recent advances include the development of evidence-based psychological treatments, such as exposure and response prevention, and pharmacological treatments, such as selective serotonin reuptake inhibitors. The latest version of the Diagnostic and Statistical Manual of Mental Disorders, and the International Classification of Diseases, has removed OCD from the anxiety disorder grouping and regrouped it into obsessive-compulsive and related disorders. We conclude by highlighting the current state of knowledge and development in the clinical management of OCD, including recommendations for first- and second-line treatments, alternative, or augmentative strategies for and novel agents under investigation for OCD. In future, the latest advances in neuroimaging, electrophysiology, digital technology, and data-driven analysis will help elucidate the pathophysiology of OCD and develop personalized intervention strategies.

**KEY WORDS:** Obsessive-compulsive disorder; Treatment; Pharmacotherapy; Psychotherapy; Transcranial magnetic stimulation; Neurosurgery.

## INTRODUCTION

Obsessive-compulsive disorder (OCD) is a relatively common, often chronic, and time-consuming disorder characterized by unwanted and distressing obsessions (repetitive thoughts, images, or urges) or compulsions (repetitive behaviors or thoughts), often accompanied by phobic-like avoidance. The lifetime prevalence of OCD in the general population is estimated to range from 1% to 3.2% [1]. Accordingly, the World Health Organization (WHO) has reported that OCD is one of the leading cause of illness-related disability [2]. OCD commonly starts in childhood or adolescence, often persists in adulthood, and causes functional impairment across multiple domains owing to its severe and chronic nature. Early detection and proper intervention for OCD can reduce individual suffering and alleviate the public health burden of the disease. Recent advances include the revised diagnostic criteria for OCD in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) published by the American Psychiatric Association (APA) and the International Classification of Diseases, 11th Revision approved by the WHO [3]. Additionally, clinical guidelines for managing OCD require an update because clinical practice has made significant progress in many areas. These areas include new pharmacological therapies and augmentation strategies for treatment-refractory OCD patients, advances in invasive and noninvasive neuromodulations and rapid progress in genomics for precision medicine and technology-based approaches. The goal of

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this article was to review the current state of knowledge and development of the clinical management of OCD.

## CHANGING CONCEPTS OF OCD

Described since antiquity, the earlier historical descriptions of obsessive-compulsive behaviors were often explained in a religious context [4]. By the early 17th century, the obsession and compulsive washing that Shakespeare's Lady Macbeth suffered were regarded as a result of her feelings of guilt, for which no medical treatment was available. At the beginning of the twentieth century, Raymond and Janet [5] described the development of OCD symptoms through a sense of incompleteness and indecisiveness, and a strong urge for uniformity. Freud believed that obsessive-compulsive behavior was a defense against unconscious conflicts and urges, especially related to libido. He isolated obsessive neurosis from neurasthenia and called the obsessive and compulsive disorder 'Zwangsneurose' in his paper in 1895 [6].

Despite no scientific reports on their efficacy published prior to the 1970s and 1980s, interventions for OCD consisted largely of psychodynamically oriented therapies derived from psychoanalytic perspectives on unconscious conflicts. Solomon *et al.* [7] demonstrated an experimental paradigm of exposure and response prevention (ERP) in an animal behavioral model of OCD. Adapting similar treatment paradigms, behaviorally oriented clinician, Meyer [8], first reported the successful application of ERP in OCD patients. Contemporary ERP involving systematic, repeated, and prolonged exposure with abstinence from compulsion has been found and proven to be highly effective in the treatment of OCD. The generally-held belief was that individuals with OCD are refractory to pharmacotherapy [9]. However, Spanish psychiatrists [10] made a seminal accidental discovery that the tricyclic antidepressant (TCA), clomipramine, alleviated also "obsessional" symptoms in depressed patients. Thereafter, extensive studies confirmed the effectiveness of pharmacotherapy for OCD with or without comorbid psychiatric disorders.

Although the Diagnostic and Statistical Manual of Mental Disorders was published in 1953, the diagnostic entity of OCD was not included in the DSM until the second edition in 1968 under the category Neurosis, along with anxiety neurosis and phobic neurosis [11]. In DSM-5 and ICD-11, OCD was removed from Anxiety Disorders and Anxiety and Fear-Related Disorders, respectively, and added to the new category, Obsessive Compulsive and Related Disorders (OCRD) [12]. Although anxiety is often a prominent feature of OCD, the affective experiences of OCD may include shame, disgust, sense of "incompleteness," or "just right." The heterogeneity of affective components and subsequent research evidence of distinct neurobiological mechanisms contributes to the rationale for separate OCRD groupings.

## PATHOPHYSIOLOGY

The etiological hypotheses for OCD are currently involve a combination of vulnerability factors and lifetime stressor exposures. Adverse lifetime experiences may induce neurobiological and behavioral adaptations of the central nervous system within a genetic window of vulnerability. According to a review of family data, the genetic contribution to OCD ranges from 35 to 50% [13,14]. Dysfunctional neurotransmitter systems most likely implicated in the neurobiological pathology of OCD include serotonin, dopamine, and possibly glutamate. Disruption of the "cortico-striato-thalamo-cortical" (CSTC) circuits which include the orbitofrontal cortex (OFC), caudate nucleus, and thalamus, is the main pathological basis of OCD. Neuroimaging studies have repeatedly reported dysregulation of the CSTC circuit. This dysfunction can be modulated after successful treatment of OCD. Altered immune systems due to modulated brain mechanisms have also been observed in neuroimaging studies.

## ADVANCES IN TREATMENT FOR OCD IN ADULTS

This overview primarily focuses on the therapeutic strategies for OCD and does not cover other specific disorders in OCRDs. A treatment algorithm for OCD is summarized in Figure 1. It is based on a review of pertinent scientific literature, including recent reports [15,16] and existing guidelines for the treatment of OCD [17-19]. After a thorough review of the literature, this guideline was revised from the previous version published by the Korean Treatment Algorithm Project for OCD 2007 [20]. Although general principles of practice guidelines have been suggested, they need to be tailored individually. A

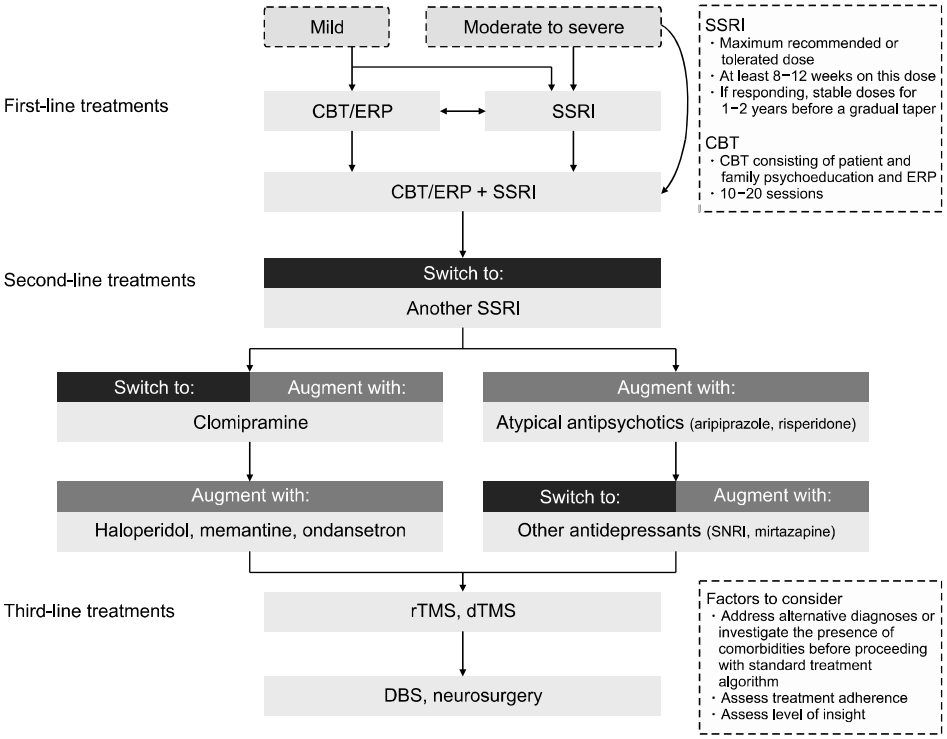


**Fig. 1.** A treatment algorithm for OCD.
OCD, obsessive-compulsive disorder; CBT, cognitive behavioral therapy; ERP, exposure and response prevention; SSRI, selective serotonin reuptake inhibitor; rTMS, repetitive transcranial magnetic stimulation; dTMS, deep transcranial magnetic stimulation; SNRI, serotonin–norepinephrine reuptake inhibitors; DBS, deep brain stimulation.

therapist may make a clinical judgement based on available evidence considering other clinical correlates including the age of the patient, psychiatric and other medical comorbid conditions, medication history, side-effect profile, and the individual's readiness to adhere to the treatment recommendations.

The treatment of OCD comprises several components, starting with recognition and accurate diagnosis with the initial assessment of symptom severity. Consistent evidence obtained from multiple randomized trials suggests the use of cognitive behavioral therapies and selective serotonin reuptake inhibitors (SSRIs) for the treatment of OCD. Given the proven efficacy of SSRIs and ERP, a gold-standard CBT, they are commonly used in combination in clinical practice. However, even after adequate trials of standard treatment have been attempted, only 40–60% of patients achieve a partial response [21]. Therefore, further investigation is required to develop augmentation strategies, novel pharmacological agents, and neuromodulation and neurosurgical approaches.

## Pharmacotherapy

### Selective serotonin reuptake inhibitor (SSRI)

SSRIs (escitalopram, fluoxetine, sertraline paroxetine and fluvoxamine) are first-line therapies for OCD based on their evidence of effectiveness, tolerability, safety, and the absence of abuse potential. As there are no noticeable differences in the efficacy between specific SSRIs [22], the adverse effects of SSRIs could be one of the main considerations in the choice of a specific SSRI. In general, the maximum tolerable dose of SSRIs is often recommended for OCD, as compared to other anxiety or depressive disorders. At least 8 to 12 weeks of treatment are often needed to determine responsiveness to a particular medication. If treatment with an SSRI fails, switching to another SSRI is preferred over the augmentation strategy. When the response is not sufficient after changing SSRIs, switching to clomipramine or augmentation strategies, including clomipramine or atypical antipsychotics, is recommended.

### Clomipramine

Clomipramine, a serotonin-selective TCA, was the first medication to show the efficacy in the treatment of OCD. It has long been the gold standard for pharmacological treatment; however, it remains unclear whether clomipramine is more effective than SSRIs. A meta-analysis of head–to–head trials directly comparing clomipramine with SSRIs indicated equivalent efficacies [22]. Clomipramine has a less favorable side-effect profile than SSRIs [23].

Thus, clomipramine has been suggested as a second-line agent for patients who are not responsive to SSRIs. Despite the lack of well-controlled trials, low doses of clomipramine are sometimes used as an augmentation strategy for SSRIs.

### Augmentation strategies

Estimates suggest that approximately 40−60% of patients with OCD do not satisfactorily respond to an initial trial of SSRI, with a remission rate of 10−40% [24]. The addition of antipsychotics is the most widely studied augmentation strategy. Antipsychotic augmentation is based on the hypothesis that dopaminergic hyperactivation contributes to the etiology of OCD. While antipsychotic agents remain off-label for OCD, the prevalence of antipsychotic prescriptions is currently increasing [25]. Further augmentation treatment strategies have been attempted with other various add-on medications.

### Augmentation with antipsychotics

Aripiprazole and risperidone have been consistently reported as effective augmenting agents. Risperidone has consistent evidence of efficacy in resistant OCD. Meta-analysis [26] found that the add-on strategy with antipsychotics was providing benefits to approximately one-third of patients and risperidone was confirmed as a potential first choice augmenting agent. In a crossover study, both add-on risperidone and haloperidol were effective on obsessive symptomatology [27]. According to a recent meta-analysis, low doses of add-on aripiprazole had an important overall effect size and was the most effective short-term option [28]. Low doses of augmented aripiprazole (10 mg/day) were confirmed to be effective and well-tolerated in treatment-refractory OCD by several RCTs [29,30]. Unlike other antipsychotics, aripiprazole is associated with fewer adverse effects such as sedation, weight gain, cholesterol and prolactin increase [31]. Haloperidol significantly reduced the total Y-BOCS score while risperidone was more tolerable and led to significant improvements in depressive symptoms. A meta-analysis for augmentation strategies suggested that risperidone and aripiprazole appear to be the most robust evidence-based options for patients with treatment-resistant OCD [32]. The evidence for haloperidol was insufficient to draw conclusions as it was based on a single trial. Studies have shown that other antipsychotics, such as quetiapine, olanzapine, and paliperidone, are less effective than aripiprazole [26,30]. Given that antipsychotic augmentation is effective in less than half of patients with SSRI-resistant OCD, antipsychotics should be administered at low doses for a limited period. The use of antipsychotics carries a significant risk of adverse effects, including weight gain and metabolic dysregulation [33]. Thus, continuous monitoring of the risks and benefits for long-term use is required in patients undergoing antipsychotic augmentation strategies.

### Alternative augmentation or switching agents

Several promising pharmacological augmentation strategies have been proposed and tested for treatment-resistant OCD. Several lines of research, and converging evidence from neuroimaging to genetics, suggest that glutamate signaling dysfunction may be important in OCD pathogenesis. Thus, augmentation with glutamatergic modulating agents, such as memantine and lamotrigine, has demonstrated some evidence of adequate safety profiles and efficacy in open-label or small RCTs [34].

N-Acetylcysteine modulates glutamatergic transmission in subcortical brain regions via the cystine-glutamate antiporter. Despite promising findings in placebo-controlled trials for both trichotillomania and excoriation disorder [35], its usefulness for OCD patients is inconsistent including most recent negative finding in a phase III, double-blind, randomized, placebo-controlled trial [36].

Ketamine, as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, has been the subject of much attention in recent years due to its rapid-onset antidepressant effect for treatment-resistant depression. To date, a few open-label trials and a randomized cross-over trial have demonstrated anti-obsessional effects of intravenous ketamine infusion [37]. Further well-controlled trials with larger clinical samples are needed to confirm the anti-obsessional effects of ketamine using different methods of administration and multiple sessions.

Troriluzole is a new drug that is a prodrug formulation of riluzole, a glutamate modulating agent. Although the drug is currently undergoing phase 2−3 controlled trials, no meaningful results have been reported yet [38]. The efficacy of ondansetron, a 5-HT3 serotonin receptor antagonist, in the treatment of refractory OCD was significant in several RCTs with add-on to SSRIs [39]. Although further studies are necessary to confirm its long-term safety and

efficacy, ondansetron was rated with the level of evidence A and recommendation level 2 as a potential augmenting agent [15].

BDZs are not mentioned or recommended as a potential treatment option for OCD in recent treatment guidelines due to the lack of reliable efficacy data. A randomized and double-blind crossover study that included 28 patients found that clonazepam was significantly effective in 40% of patients who did not respond to clomipramine [40].

Switching to serotonin–norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine was demonstrated to be as effective as paroxetine; paroxetine may be more effective than venlafaxine in refractory cases [41]. According to WFBSP guidelines, venlafaxine, noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine were rated with the level of evidence B and recommendation level 2 due to the lack of placebo-controlled trials [15].

Tolcapone is a catechol-O-methyl-transferase (COMT) enzyme inhibitor that enhances dopamine signaling in the cortex. It was effective in a randomized, placebo-controlled crossover trial [42] and further evaluation as a candidate medication for OCD is needed.

## Psychotherapy

### Psychoeducation

Psychoeducation is an educational method aimed at providing the necessary information and training to psychiatric patients and their families. This forms part of an overall clinical management plan for OCD patients and their family members working together with mental health professionals. Knowledge about symptoms, prognosis, stigma, prejudice, and family accommodation should be provided, so that a strong emphasis on psychoeducation may lay the groundwork for subsequent treatment success. Recent studies targeting family accommodation, particularly in younger patients, suggest that it is more effective in reducing OC symptoms; thus, it has been suggested as a fundamental component of psychoeducation [32].

### Cognitive behavioral therapy (CBT)/exposure and response prevention (ERP)

In psychotherapy for OCD, CBT is the most effective evidence-based form of treatment and is suggested as a first-line treatment strategies by all treatment guidelines. CBT/ERP monotherapy is recommended for patients with OCD with mild or moderate symptom severity.

Despite the limitation that most psychotherapeutic trials included patients were prescribed stable doses of SSRIs [22], meta-analyses of RCTs have consistently demonstrated that CBT/ERP therapy significantly improves OCD symptoms [43,44].

CBT involves several components: cognitive reappraisal, restructuring, and behavioral intervention. The latter, typically in the form of ERP, is the most frequently used psychological treatment of choice for OCD. ERP for OCD is a structured, manualized psychological intervention that involves gradual and repeated systematic confrontation with external and internal obsessional cues (exposure) and abstaining from compulsive rituals (response prevention).

However, there are some barriers to CBT trials, including the lack of availability of practitioners trained in OCD-specific CBT, time and financial requirements, and participants' motivation to engage in ERP [17]. Moreover, even among those who engaged in an adequate trial, a substantial proportion of patients endorsed the impairment of residual symptoms.

### Internet-based cognitive behavioral therapy (iCBT)

Another adaptation of CBT with innovative delivery formats which has been examined in recent years, is mobile application-based CBT and iCBT.

Recent evidence from a meta-analysis suggested a significant difference between iCBT and active controls and iCBT rates at level of evidence A and recommendation level 1 [15]. Another meta-analysis reported that iCBT was significantly more effective than passive controls but did not differ from active controls [45].

Although the evidence for iCBT remains preliminary, active online interventions using digital platforms may potentially facilitate treatment adherence in certain environments where regular face-to-face CBT is not viable [46].

### Acceptance and commitment therapy (ACT)

ACT aims to foster psychological flexibility through the practice of acceptance and mindfulness in addition to behavioral commitment with values-based methods. ACT can help OCD patients embrace their experiences and

strive toward meaningful areas of life, despite the presence of obsessions, anxiety, and compulsions. Although a recent meta-analysis, including a small number of studies, reports the applicability of ACT for OCD [47], it needs to be tested with more extensive RCTs in larger samples.

### Inhibitory learning theory (ILT)-based approaches

The inhibitory learning framework provides a novel foundation for understanding how ERP can be maximized to overcome a sizeable percentage of non-responders. According to ILT, ERP is effective to the extent that it facilitates the development of new safety-based learning that is strong enough to inhibit older fear-based learning [48]. Although robust clinical value is believed to exist in optimizing ILT, empirical testing of the treatment efficacy of ILT-based ERP for OCD remains lacking. One controlled trial showed that ILT-based ERP added to SSRI was more effective than SSRI alone at a longer follow-up [49].

### Inference-based therapy (IBT)

IBT has been shown to be an effective therapeutic approach for OCD, with a focus on the inference process that generates obsessive beliefs and assumptions [50]. IBT directly addresses the content of obsessive beliefs using imaginative intervention techniques and contrasting inference processes from normal and pathological suspicions [51]. Randomized controlled trials have demonstrated that IBT is effective in reducing symptoms of OCD [52]. Currently, it is evolving into inference-based CBT through its combination with CBT [53].

## Neuromodulation and Neurosurgery

Approximately 20−25% of patients with OCD are resistant to standard pharmacological and psychological interventions. Neuromodulatory and neurosurgical treatments generally target the major nodes in the cortico-striato-thalamo-cortical (CSTC) circuits implicated in OCD. Neuromodulation incldudes both noninvasive and invasive interventions, including transcranial electric stimulation (tES), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS). Neurosurgical procedures are used to treat refractory OCD.

### Repetitive transcranial magnetic stimulation (rTMS)

rTMS induces noninvasive stimulation of major cortical nodes in the CSTC pathways, thereby modulating their excitability or inhibition based on the frequency of magnetic stimulation. A growing body of evidence supports the efficacy of rTMS for OCD, targeting cortical regions, including the supplementary motor area (SMA) and OFC, mostly with low-frequency stimulation [54]. However, evidence has been inconsistent, and long-term follow-up results are still lacking. Deep TMS, a novel type of rTMS using different H-coils, is more likely to directly modulate deeper areas such as the anterior cingulate cortex (ACC). Deep TMS achieved US FDA indications for OCD in 2018, and its long-term durability of response was recently demonstrated [55].

### Transcranial direct current stimulation (tDCS)

tDCS, a kind of tES, involves the application of a weak electrical current to the scalp to induce focal and cortical modulation. Despite inconsistent stimulation protocols, encouraging evidence from both small open-label and sham-controlled RCT has supported that tDCS has potential efficacy in patients with OCD. Future research should include larger representative samples of OCD to identify optimal stimulation parameters.

### Deep brain stimulation (DBS)

DBS is a potentially reversible and adjustable procedure involving neurosurgical implantation of an electrode that can induce electrical stimulation in specific subcortical regions of the neuronal circuitry. The potential DBS targets for OCD are striatal areas, including the anterior limb of the internal capsule/nucleus accumbens or thalamus/subthalamic nucleus [56]. Recent meta-analyses have shown that DBS is superior to sham stimulation [57] and as effective as ablative surgery [58]. DBS should be reserved for carefully selected patients with chronic (> 5 years) refractory OCD after an independent review by a multidisciplinary team.

### Neurosurgery

'Traditional' neurosurgery involves producing irreversible focal tissue ablation in specific regions of the CSTC circuit which require skull opening. Accurate targeting of the lesion is possible with the help of "invasive" stereotactic surgery or "less-invasive" ablation with the help of image-guided gamma radiation or focused ultrasound. Adverse effects may vary depending on the surgical procedure, including headache, nausea/vomiting, weight-gain/

loss, personality changes, seizures, and reduced cognitive function, although the rates are not high. Given the invasive nature of the neurosurgical approach, 'traditional' neurosurgery should be reserved to the most severe treatment-refractory cases. Some newer less invasive methods without skull opening include gamma knife radiosurgery and magnetic resonance-guided focused ultrasound surgery (MRgFUS). The former potentially has adverse effects related to radiation dose, while the latter offers the potential for safer and more cost-effective surgical approaches in recent open trials [59].

## DISCUSSION

Prior to the 1960s, OCD was considered rare, of psychological origin, and intractable. In the 1970s and the 1980s, the findings of serotonergic drugs such as clomipramine and SSRIs paved the way for changes in the perception of OCD as a treatable condition [60]. This led to the development of contemporary psychological treatment (ERP) which replaced the psychodynamic approach and focused on serotonergic pathways that underpin the neuropathology of OCD. Due to advances in research on neurocircuitry and endophenotypes, OCD has been removed from the anxiety disorder grouping in the DSM-5 and ICD-11 and regrouped into OCRDs.

CBT/ERP is the first-line therapy for mild-to-moderate OCD. A combination of SSRI and CBT is recommended for patients with moderate-to-severe OCD. Considering the limited resources available for delivering CBT, prescribing SSRIs could be the preferred first-line treatment option for OCD. For partial responders and non-responders to first-line treatments, even after switching to another SSRI, augmentation strategies including atypical antipsychotics, mainly risperidone and aripiprazole, or changing to clomipramine are recommended. Although novel agents under investigation for OCD include glutamatergic modulators and ondansetron, long-term data is still lacking. Further alternative or augmentative strategies for ERP, the inhibitory learning approach, and acceptance-focused interventions are often recommended empirically. Increasing evidence supporting the safety and efficacy of brain-circuit-based neuromodulatory interventions provides alternatives for OCD patients who are resistant to first-line therapy. DBS and less invasive ablative neurosurgery may be considered in chronic, carefully selected patients with severe, chronic, treatment-refractory OCD. In future, digital technology may offer new opportunities for improving treatment dissemination by creating cost-effective alternatives to traditional face-to-face psychotherapy. A multimethod approach that employs the latest advances in neuroimaging, electrophysiology, data-driven analysis, and parallel behavioral models will continue to clarify the pathophysiology of OCD and develop personalized intervention strategies.

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No potential conflict of interest relevant to this article was reported.

### ■ Author Contributions

Writing—Original draft & editing: Daeyoung Roh. Writing—Review & editing: Ki Won Jang. Conceptualization & Supervision: Chan-Hyung Kim.

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