EXPERT REVIEWS

Commonly asked questions in the treatment of obsessive-compulsive disorder

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Obsessive-compulsive disorder (OCD) is a common and often a highly disabling condition that was considered untreatable before the 1960s. The advent of serotonin reuptake inhibitors and exposure and response prevention revolutionized the treatment of OCD. Although they are still the first line treatments for OCD, new treatments like augmentation strategies, brain stimulation techniques, psychosurgery, newer forms of psychotherapy (like cognitive therapy, acceptance and commitment therapy) have been added to the armamentarium. With the available treatment strategies, many patients can achieve at least partial remission of symptoms. Nevertheless, the plethora of information gives rise to many questions on their application for practicing clinicians. We provide evidence-based responses to these questions and suggest a broad guideline for treatment of OCD.

KEYWORDS: augmentation • behavior therapy • cognitive-behavior therapy • obsessive-compulsive disorder • psychosurgery • repetitive transcranial magnetic stimulation • selective serotonin reuptake inhibitor • treatment

Obsessive-compulsive disorder (OCD) is a common and often a highly disabling condition that was considered untreatable before the 1960s. Long-term studies show that many patients have persistent symptoms up to 40 years of follow-up [1]. Earlier psychological (e.g., psychodynamic therapy) and somatic treatments (e.g., non-specific tricyclic antidepressants [TCAs], electroconvulsive therapy [ECT]) were ineffective in the treatment of OCD [2–4]. In the later part of 20th century, it was recognized that OCD responds preferentially to drugs that have powerful serotonin reuptake inhibiting activity, namely, selective serotonin reuptake inhibitors (SSRIs) and clomipramine [4]. Around the same time, behavior therapy (BT), in the form of exposure and response prevention (ERP), was also found to be effective [2]. New treatments like augmentation strategies [5], novel psychotherapies like acceptance and commitment therapy (ACT) [6], novel brain stimulation techniques like repetitive transcranial magnetic stimulation (rTMS) [7] and neurosurgery [8] have been added to the armamentarium.

The plethora of information gives rise to many questions on their application for practicing clinicians. We encounter many such questions when discussing treatment of OCD in academic fora and from well-informed patients. Here, we provide evidence-based responses to these questions and suggest broad guidelines for treatment of OCD. Recent systematic reviews and guidelines have discussed extensively on treatment of OCD [4,9]. We augment this valuable literature by providing evidence-based recommendations on specific aspects of implementation of various interventions for OCD and the relative place of each intervention. This review takes into consideration recent literature on a range of pharmacological augmenting agents, evidence supporting the use of cognitive behavior therapy (CBT) in partial responders and non-responders to SSRIs, brain stimulation techniques and neurosurgical interventions. Additionally, the review also briefly addresses management of OCD comorbid with schizophrenia and bipolar disorder (BPD).

What is the first-line treatment of OCD?

Randomized controlled trials (RCTs) and meta-analyses have consistently demonstrated the efficacy of SSRIs and clomipramine and behaviorally oriented therapies (BT and CBT) in the treatment of OCD [4,6,10,11]. Most

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treatment guidelines recommend either or both of them as first-line treatments in OCD [9,12].

Behavioral therapy using ERP has been consistently found to be one of the most effective forms of treatment of OCD [11,13]. Cognitive therapy with or without ERP has also been found to be effective [6,13]. A recent meta-analysis has demonstrated an effect size of 1.35 for ERP (Hedge's g, 95% CI: $p < 0.001$) compared with controls, which signifies a large effect size [14]. As there is widespread variability across different studies, it is difficult to determine an adequate 'dose' of therapy [12]. Recent meta-analyses have found that intensity of treatment in the form of number and frequency of treatment sessions are unrelated to treatment outcome [13,14]. Most of the studies in these meta-analyses carried out 10–15 sessions per patient. In the meta-analysis by Olatunji *et al.*, 11 of the 16 studies fall within this range [14]. The lack of relationship could be due to insufficient variability in these studies to allow a relationship to be detected. In a more inclusive meta-analysis, treatment intensity in the form of number of therapist hours predicted treatment efficacy [12]. The effect of number of therapist hours on treatment efficacy was stronger for interventions with less than 10 therapist hours per patient as compared with interventions with more than 10 therapist hours per patient [12], suggesting some evidence of dose–response relationship. Recent large RCTs have employed at least 15–22 sessions of exposure [15–17]. Therefore, it seems reasonable to assume that 15–20 sessions over 8–12 weeks may be required for most patients.

Despite its efficacy, BT is not widely practiced because of lack of awareness, insufficient training and time intensive nature of the treatment. Modifications have been made to BT to make it more accessible and cost-effective. The therapist contact time can be decreased by administering patient-controlled ERP with supervision by a therapist. Meta-analyses have found therapist-guided exposure superior to therapist-assisted self-exposure [13,18]. A recent study by van Oppen *et al.* showed that there was no significant difference in efficacy between patient-controlled and therapist-controlled ERP, conducted either by experienced behavior therapists or clinically inexperienced master's students in clinical psychology [19]. But the finding of this study may have to be interpreted in the context of modest sample size. ERP has also been adapted to group format, which has generally been found to be equally effective to individual therapy [14]. A computer-guided BT self-help system (BT STEPS) was more effective than relaxation training, but less effective than therapist-guided exposure [20,21]. Such less intensive forms of BT may be tried in patients with mild-to-moderate OCD and intensive treatments with more therapist contact time can be reserved for severe and treatment-resistant patients.

Among the pharmacotherapies, serotonin reuptake inhibitors (SRIs) have the best evidence [11]. These include SSRIs and clomipramine. According to a recent meta-analysis, the relative risk of treatment response of SSRIs versus placebo is 1.84 (95% CI: 1.56–2.17) with a number needed to treat (NNT) of 6 [10]. In this meta-analysis, response was defined as 25% or greater reduction in Yale–Brown Obsessive Compulsive Scale (Y-BOCS) [10]. It is generally recommended that people with OCD require a higher dose of SSRIs than that used in depression and other anxiety disorders [9,22]. Fixed-dose comparison studies have shown a dose–response relationship for fluoxetine, paroxetine and escitalopram, but not for other SSRIs [4]. A recent meta-analysis of nine RCTs on SSRIs showed that high dose of SSRIs (60–80 mg fluoxetine equivalents) is more effective than low (20–30 mg fluoxetine equivalents) or medium dose (40–50 mg fluoxetine equivalents) of SSRIs [23]. High-dose SSRIs was associated with higher dropouts due to side effects, although the proportion of 'all-cause' dropouts did not differ based on SSRI dose [23]. There is some preliminary evidence to suggest that higher than recommended dose of SSRIs (e.g., 250–400 mg/day of sertraline) may be useful in non-responders to standard doses [24]. Improvement with SSRIs may start occurring at around 4–6 weeks, but there may be a delay in treatment onset up to 12 weeks, with increasing improvement observed up to 1 year after treatment initiation [9,12,22,25,26]. There is some recent evidence to suggest that early improvement in OC symptoms (at 4 weeks) predicts subsequent treatment response (at 12 week) [27]. In the above study, early improvement predicted subsequent treatment response with 76% sensitivity and 62% specificity [27]. In summary, a high dose of SSRIs should be considered as the first-line pharmacological treatment for OCD. Medications have to be continued for at least 12 weeks for adequate treatment response.

Which is better – BT or SSRI?

As both BT and SSRI treatment have been found to be effective, often the question arises which should be tried first in a given patient. There have been few head-to-head comparison trials comparing the relative efficacy of these treatments. Foa *et al.* compared the efficacy of clomipramine, ERP and their combination with a pill placebo [15] in a randomized multi-site study. ERP, either alone or in combination with clomipramine was superior to clomipramine treatment. ERP was provided quite intensively in this study (daily 2-h therapist-guided exposure sessions 5 days a week along with 2 h a day of ERP home work for initial 3 weeks followed by 8 weekly maintenance sessions including 2 home visits by therapist in the 4th week), which may not be replicable in many clinical settings. Less-intensive ERP (weekly sessions) has not been found to be superior to fluoxetine [28]. Meta-analyses have usually revealed a larger effect-size for BT compared with pharmacotherapy [11,29], but the difference was not statistically significant, after controlling for methodological variables [29]. According to a recent meta-analysis, 62% of patients entering ERP improve with treatment while 53% starting SSRIs improve with treatment [11]. The definition of improvement varied across studies included in this meta-analysis, limiting their comparability. Foa *et al.* found a significantly higher response rate for ERP (Clinical Global Impression – Improvement scale ≤2) compared with clomipramine in treatment completers, but the difference was not significant in the treated group [15]. The percentage of

excellent responders (Clinical Global Impression – Improvement scale = 1) was significantly higher in the ERP group in both the treated group and the completer group [15]. Post-treatment Y-BOCS scores have been found to be lower in BT/CBT-treated patients compared with SSRI-treated patients [11,15,30]. In a clinical effectiveness trial mimicking 'real-world' scenario, patients receiving group CBT and SSRI had similar post-treatment total Y-BOCS scores and responder rates [31]. This study had broader inclusion criteria compared with traditional RCTs, resulting in an increased comorbidity profile in the sample. Hence, the superiority of BT/CBT over SSRI seen in RCTs may not be apparent in the clinical setting.

Patients treated with medications have a higher relapse rate on treatment discontinuation compared with those treated with BT [32]. Although psychotherapies are considered to have no adverse effects, ERP is associated with significant anxiety as a part of treatment, which leads to dropout rate as high as 30%. In fact, the dropout rate has not been found to be different between ERP and SRIs [15,29]. Patients with psychiatric comorbidity have a higher chance of dropout from either treatment [33]. Existing international guidelines recommend CBT in mild illness and either CBT or SSRI or their combination in people with more severe illness considering factors like patient preference, comorbidity, previous treatment response, etc. [9,12].

Overall, it appears that CBT involving ERP may have some advantages compared with SSRIs in the form of greater symptom improvement and lower relapse rate. However, the choice of treatment is dictated by severity of illness, availability of trained therapist, feasibility, ability to tolerate initial anxiety, motivation of the patient and patient preference. In most developing countries, there is severe shortage of mental health professionals, and in such situations SSRIs may become the preferred choice of treatment over CBT alone or a combination of SSRI and CBT.

What is the role of other psychotherapies like cognitive therapy or mindfulness-based techniques?

Although ERP is considered '*one of the success stories in behavior therapy*', it has its own limitations which include: refusal to undergo BT; early dropout and poor response to BT; persistence of residual symptoms, which may need additional treatment; relapse in a sizable minority; doubtful efficacy in pure obsessives without overt compulsions, hoarding, etc. and poor motivation, non-compliance [34]. There was a need felt for innovations in psychotherapy for OCD. The primarily cognitive nature of obsessions makes cognitive therapy the obvious choice. It was hypothesized that cognitive interventions may also help people with poor insight to facilitate exposure [35]. Most cognitive therapies for OCD are variations of the original Salkovskis model [36]. The cognitive model posits that obsessions arise because of faulty appraisal of normally occurring innocuous mental intrusions as highly significant and potentially threatening [34]. The treatment consists of identification and correction of these misinterpretations and underlying obsessive beliefs. There is a high degree of overlap between BT and cognitive interventions. Most protocols that employ cognitive techniques also employ behavioral techniques in the form of ERP, often referred to as CBT. Cognitive interventions are often used to facilitate ERP and behavioral experiments used in cognitive therapy are similar to exposure strategies in that they provide opportunity to disconfirm distorted beliefs and also encourage habituation [37]. Most studies use the term CBT as it often involves a combination of both techniques.

Most of the head-to-head comparison studies and meta-analyses have found similar efficacy for CBT and ERP [6,11,13,14]. CBT may be preferred in patients with pure obsessions [38,39]. However, purely cognitive intervention without behavioral component may be less effective [11,37]. The role of cognitive interventions in poor-insight OCD has not been studied adequately. New forms of cognitive interventions like Danger Ideation Reduction Therapy and cognitive coping therapy have been found to be superior to BT/CBT in a few trials with methodological limitations [40–42]. But the findings have not been replicated by independent research groups. ACT and satiation therapy are other new therapies that have been found effective in single trials [43,44]. Psychodynamic therapy, stress management and other behavioral interventions like systematic desensitization, aversion therapy, thought stopping techniques are of little use in OCD [2,6].

Mindfulness has been demonstrated as an alternate way of handling unwanted intrusions in a non-clinical student population with OC symptoms [45]. In contrast to cognitive therapy which encourages patients to actively analyze the content of obsessions to understand their irrationality, mindfulness encourages non-judgmental observation, awareness and acceptance of these intrusions to decrease their significance [45,46]. It has been suggested that mindfulness techniques may be less anxiety provoking compared with ERP [46] and especially useful in managing thought-action fusion and thought suppression [47]. Despite the interesting premise, mindfulness has not been rigorously tested in controlled trials in OCD. Available evidence is in the form of case series and one non-RCT in a non-clinical population [45,47]. Further mindfulness is usually provided as a component of a package as in mindfulness-based cognitive therapy and ACT [43,46]. Whether mindfulness is an active component in these treatments needs to be studied. A small RCT (n = 22) found *kundalini* yoga meditation protocol superior to relaxation response plus mindfulness meditation technique in reducing OC symptoms [48]. Larger studies are needed to confirm the efficacy of these interventions.

Overall, CBT is the only treatment that has been found to be as effective as ERP. Cognitive strategy along with ERP may be tried in patients who do not cooperate or respond to ERP. The role of new forms of therapy like mindfulness-based techniques, ACT and purely cognitive interventions has to be studied further.

Is combination of psychotherapy & SSRI/clomipramine better than either treatment alone?

Given the efficacy of SSRIs and BT/CBT in OCD, it is natural to assume that a combination of these two treatments may work better than either of them alone. Early controlled trials

were not able to find any advantage of combination of drugs and CBT over either of them alone [49]. Combination treatment was found to be helpful only in people with comorbid severe depression [50,51]. However, three recent multi-center RCTs have shown that combination of SSRI/clomipramine and CBT may be superior to the medications alone [15,52,53]. In the Pediatric OCD Treatment Study trial, combination of sertraline and CBT was found to be superior to either treatment alone in children [52]. A subsequent study, Pediatric OCD Treatment Study II too demonstrated that a combination of medication and CBT was superior to medication alone in children with partial response to SRI [53]. A study in adults demonstrated that a combination of ERP + clomipramine and ERP alone were superior to clomipramine, but there was no significant difference between ERP alone and ERP plus clomipramine [15].

The studies on augmentation strategy have been more consistent. Many RCTs have shown that adding BT/CBT improves the treatment outcome in partial/poor responders to SSRI/clomipramine treatment [16,53–55]. In a recent SSRI augmentation study, CBT was superior to risperidone and risperidone was no better than pill placebo [17]. The effectiveness of CBT augmentation in partial responders to SRIs has been demonstrated in a naturalistic setting in a multi-center trial [56]. There is also some evidence that the effect of CBT may persist up to 1 year post-treatment in well-characterized SSRI non-responders [57]. Albert *et al.* recently reviewed the efficacy of combination treatments and found that combination is consistently effective as augmentation strategy for SSRIs, while it has yielded conflicting results when started together [49].

Which SSRI to choose?

Clomipramine was the first pharmacological agent found to be efficacious in OCD. The strong serotonin reuptake inhibiting property of clomipramine is hypothesized to be responsible for its anti-obsessive action [4]. Other non-selective TCAs have been found to be ineffective in OCD [11,58]. Clomipramine also acts on other neurotransmitter systems (like acetylcholine, histamine and norepinephrine), which leads to unwanted side effects. It can also cause some serious adverse events like seizures and prolongation of QT interval. SSRIs are selectively serotonergic with negligible effects on other neurotransmitters and have less severe adverse effects. Over the years, evidence has accumulated for the efficacy of all available SSRIs in OCD including fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram and escitalopram [4].

There have been a few head-to-head comparison studies comparing different SSRIs. In a double-blinded RCT comparing fluoxetine (n = 73) and sertraline (n = 77), patients on sertraline showed a significantly greater improvement at earlier assessments (up to 12 weeks), which disappeared at the end of the study (24 weeks). The apparent difference in early response was not significant in Kaplan–Meier analysis. Further, the study was not powered to detect between-group differences in early treatment response [59]. In a study by Stein *et al.*, escitalopram (20 mg/day) was associated with earlier treatment response compared with paroxetine (40 mg/day), but there was no difference at end point [60]. No significant difference in efficacy was found in two other small head-to-head comparison studies [61,62]. Meta-analyses of RCTs in adults and children could not find any significant difference in efficacy between the individual SSRIs [10,63]. Overall, there is little evidence to support the use of any particular SSRI over the other in OCD. The choice of SSRI will ultimately depend upon previous response, drug interactions and adverse-effect profile.

Meta-analyses of RCTs in adults and children comparing clomipramine and SSRIs have shown that clomipramine may be superior in terms of efficacy [11,63]. A systematic analysis of published and unpublished data by the UK National Institute for Health and Clinical Excellence has negated this finding [12]. Head-to-head trials have consistently shown that clomipramine has similar efficacy to comparator drugs (fluoxetine, sertraline, fluvoxamine, citalopram and paroxetine), but poor tolerability [64–67]. Given the questionable superiority and poor tolerability of clomipramine, SSRIs should be considered the first choice of medications in OCD and clomipramine should be tried if patients do not show satisfactory response to initial trials of SSRIs [12,22].

What is the optimum duration of pharmacotherapy?

The question often arises on how long to continue treatment after a successful SSRI trial. Treatment guidelines recommend continuation of medications for at least 1–2 years to prevent relapse and to allow further improvement [9,12]. Ongoing improvement with SSRIs has been observed both over short term (20–24 weeks) and long term (1 year) in treatment continuation studies [25,26,59,60,68]. A meta-analysis of the RCTs found a statistically significant superior efficacy of SSRIs compared with placebo in relapse prevention (relative risk of relapse: 0.52; 95% CI: 0.41–0.66; $p < 0.00001$) [69]. Patients who improve with pharmacotherapy have a higher chance of relapse on treatment discontinuation [70]. In most studies, SSRIs were continued in the same therapeutic dose. A small study (n = 30) with a relatively brief follow-up duration (102 days) showed that dose reduction does not affect the efficacy in the relapse prevention phase [71]. Without replication from larger studies with longer follow-up duration, this strategy may not be advisable. Taken together, the available evidence suggests that SSRIs should be continued for relapse prevention for at least 1–2 years after remission. Treatment discontinuation should be decided considering various factors such as severity and duration of the illness, number of previous episodes, history of relapse upon discontinuation, presence of residual symptoms and concurrent psychosocial difficulties [12]. It should be emphasized that discontinuation of SSRIs should be carefully considered and in most patients continued treatment may be necessary in view of high rates of relapse upon discontinuation [69].

What is the role of other antidepressants in OCD?

Venlafaxine has been found to be effective in one double-blinded [72] and one single-blinded active comparator study [73]. Other serotonin norepinephrine reuptake inhibitors like

duloxetine and milnacipran have not been studied adequately. Mirtazapine was found to be effective in an open-label trial followed by double-blinded discontinuation [74]. Mirtazapine has also been found to accelerate the response to citalopram in a single-blinded placebo-controlled trial, although there was no difference in the response rate at the end of treatment [75]. TCAs (except clomipramine), monoamine oxidase inhibitors and benzodiazepines have not been found to be effective [5,11]. Venlafaxine may be tried if SSRIs/clomipramine are not tolerated or are found ineffective.

What are the options in a person who has shown partial or poor response to a SSRI trial?

Non-response and partial response are quite common with SSRI treatment. A significant proportion of patients continue to have clinically significant symptoms despite improving with treatment. A meta-analysis showed that average post-treatment Y-BOCS score was 17.9, suggesting significant residual symptoms [11]. The initial SSRI should be tried for at least 12 weeks for assessing treatment response. Delayed response has been seen, especially in trials with fluoxetine [59,76]. Switching over to a different SSRI is recommended for people with non-response, while augmentation strategies are generally recommended for people with partial response. In people with non-response to initial SSRI, switching to a different SSRI has been found to be useful in around 40% of patients [77]. Switching over to venlafaxine and clomipramine are other options [22,78,79].

Augmentation refers to the process of adding medications with a different mechanism of action to the primary drug to boost its therapeutic efficacy. BT/CBT and rTMS are also used as augmentation strategies. We recently reviewed augmentation strategies in OCD and found that antipsychotic and CBT augmentation have the best evidence for efficacy [5]. Among antipsychotics, risperidone has the best evidence followed by aripiprazole and haloperidol [5,80]. A recent multi-center randomized controlled study found augmentation of SSRIs with CBT to be much superior to augmentation with risperidone and risperidone was no better than placebo [17]. In view of this important observation, it is recommended that CBT should be considered as a first-line augmenting strategy in those who do not show satisfactory response to SSRIs. Other promising augmentation strategies include clomipramine, 5HT-3 antagonists like ondansetron and granisetron, memantine, lamotrigine and topiramate [25,81–87]. The evidence for these augmenting agents is based on few RCTs involving small sample sizes; therefore, larger studies are required to confirm their efficacy. Preliminary evidence exists for psychostimulants, pregabalin and glutamatergic agents [5]. *N*-Acetyl cysteine, a *N*-methyl-D-aspartate (NMDA) modulator has shown positive result in a recent RCT [88].

Other innovative strategies have been tried in treatment non-responders. Few studies suggest that higher than recommended dose of SSRIs (e.g., 250–400 mg of sertraline) may be efficacious and tolerated well in people not responding to usual doses [24,89]. Intravenous citalopram [90] and clomipramine [91] have been shown to be useful in treatment-resistant patients, but one study demonstrated equal efficacy for oral and intravenous pulse loading clomipramine regimens [92]. High-dose and intravenous SSRI treatment have not been studied adequately and should be tried only when other measures fail.

How to boost the efficacy of CBT?

Augmentation strategies have also been tried to boost the efficacy of CBT. One interesting strategy is augmentation of BT sessions with D-cycloserine, a NMDA partial agonist, which has been shown to promote extinction of conditioned fear and consolidation of learning associated with extinction training. Small placebo-controlled trials have demonstrated the efficacy of adding D-cycloserine 1–2 h before therapy sessions [93–95]. However, in a study by Storch *et al.*, D-cycloserine was not superior to placebo when given 4 h before the exposure session [96]. Large well-controlled trials are needed to confirm the efficacy of this strategy. Adding motivational interviewing to improve patient adherence to CBT has yielded mixed results [97–99]. Strategies for BT non-responders have not been studied adequately. van Balkom *et al.* found fluvoxamine to be superior to cognitive therapy in non-responders to BT [100]. Although controlled trials show that a combination of SRIs and BT may not be superior to BT alone [15], the strategy of augmenting BT/CBT with SSRIs in those who are not responding to BT/CBT has not been studied systematically. As SSRIs are one of the effective treatments for OCD and probably have a different mechanism of action, it may be worthwhile trying them in BT/CBT non-responders.

How to manage a drug-induced manic switch or comorbid BPD?

Recent epidemiological studies show that the prevalence rate of BPD in OCD is markedly higher than expected [101]. SSRIs, the drugs of choice in OCD, can induce switch to mania/hypomania in BPD patients and may cause cycle acceleration and suicidal behavior [102]. Clinicians often face the dilemma of treating this rather complex but common comorbidity. The safest option would be to treat BPD with mood stabilizers and/or atypical antipsychotics and OCD with BT/CBT. But this is not always a viable option when SSRIs are indicated or unavoidable for various reasons. Some case series have demonstrated that treatment of patients with comorbid BPD and OCD with standard mood stabilizers like lithium or antipsychotics lead to improvement in both OC and mood symptoms, without the need for SSRIs [103–105]. This is in keeping with other lines of evidence which suggest that OCD in people with BPD share many features with primary mood disorders than OCD including episodic course of illness, and high family loading of mood disorders [101,106]. Hence, some recommend withholding SSRIs and suggest mood stabilization as the first priority [103]. There are no controlled studies to support this strategy. The need for SSRI has to be assessed on a case-by-case basis. SSRIs can be used in patients with persistent OC

symptoms only under the cover of mood stabilizers after the acute control of manic symptoms.

How to treat OC symptoms in patients with psychotic disorders?

Obsessive-compulsive symptoms (OCS) are frequently comorbid with schizophrenia. The term schizo-obsessive disorder is sometimes used to denote this comorbidity [107]. Epidemiological studies show that around 8–26% of patients of schizophrenia suffer from OCD and 10–60% have comorbid OC symptoms [108]. This is much higher than the prevalence of 2–2.5% seen in the general population [109]. OC symptoms occur in schizophrenia in different contexts. OC symptoms precede the onset of schizophrenia in 49–76% of patients and succeed schizophrenia onset in 23–25% of patients [108]. Atypical antipsychotics may also induce *de novo* OC symptoms in people with psychosis [110]. Hence, OC symptoms in schizophrenia have been variably conceptualized as a manifestation of the disease process or as a comorbid illness or as an adverse effect of medication. Different strategies have been tried depending on the conceptualization [111].

Very few studies have examined the treatment strategies for OC symptoms in schizophrenia. There is some evidence to suggest that continuing antipsychotics alone may decrease OC symptoms in a subset of patients [111,112]. This strategy has been recommended when OC symptoms appear to be secondary to the psychotic process [111]. It has been seen that OC symptoms in schizophrenia are phenomenologically similar to that seen in 'pure OCD' and hence may share similar pathogenic mechanisms [113]. Therefore, treatment strategies used in routine care of OCD has been recommended by some authors [114]. Few open-label trials [115–117] support the efficacy of SSRIs in the treatment of OCS in schizophrenia. The SSRIs with less drug interactions like citalopram, escitalopram and sertraline are generally recommended [118]. There is some evidence to support the use of CBT in this population [119,120]. For patients with antipsychotic-induced OC symptoms, either a dose reduction [111] or shifting to a drug with less antiserotinergic action like amisulpride may be helpful [121]. Lamotrigine augmentation to an antipsychotic regimen has been found to be effective decreasing OC symptoms in an open-label trial [122].

There is insufficient evidence to definitively guide treatment of OC symptoms in schizophrenia. A trial with an antipsychotic alone can be tried as an initial strategy for people who have OC symptoms only during the course of psychosis, particularly in acute psychotic conditions. OC symptoms may be persistent in many patients with schizophrenia. In such patients, SSRIs and CBT may be indicated. Dosage reduction or shift to a different antipsychotic can be tried in people with clear history of antipsychotic-induced OC symptoms. More stringent and larger studies are needed test these recommendations.

What is the role of brain stimulation techniques like ECT and rTMS?

ECT is a well-established treatment for severe depression. The efficacy of ECT in OCD is still unproven and the available evidence in the form of case reports and case series has shown mixed results [3]. The improvement observed in some reports has been attributed to comorbid illnesses like depression, schizophrenia, etc. [3]. The available evidence does not support the use of ECT targeting OCD alone, but may be tried for a comorbid illness like depression or schizophrenia.

rTMS involves application of rapidly changing electromagnetic fields over the scalp to modulate activity in specific brain regions. Application of high-frequency rTMS (≥5 Hz) increases cortical excitability in specific regions, while low-frequency rTMS (≤1 Hz) decreases cortical excitability [7]. rTMS using standard coils can modulate cortical excitability up to a maximum depth of 1.5–2.5 cm from the scalp [123]. The neural regions implicated in OCD consist of deeper structures (orbitofrontal cortex, thalamus, basal ganglia), which are difficult to access directly using standard TMS coils. Other easily accessible regions which have connections with these structures are usually targeted in the treatment of OCD. Despite some encouraging results from open-label trials, RCTs have shown that rTMS applied to the right or left dorsolateral prefrontal cortex is not effective in OCD [7]. Two double-blind RCTs have demonstrated the efficacy of low-frequency rTMS over bilateral supplementary motor area (SMA) in resistant OCD [124,125]. The extensive connections of SMA with other deeper brain regions like thalamus and basal ganglia may explain the efficacy of this target [125]. However, sequential administration of low-frequency rTMS over right dorsolateral prefrontal cortex and bilateral SMA was not effective in a sham controlled trial [126]. A single-blind RCT demonstrated the efficacy of low-frequency rTMS applied over orbitofrontal cortex in drug-resistant OCD patients [127]. An earlier meta-analysis of three RCTs did not find rTMS effective in OCD [128]. A recent meta-analysis including 10 sham-controlled RCTs found a medium effect size of 0.59 ($z = 2.73$; $p = 0.006$) for active rTMS [129]. Subgroup analysis revealed promising results for low-frequency rTMS and rTMS over SMA and OFC [129]. Current evidence suggests that low-frequency rTMS over SMA or OFC may have a role in OCD, but the evidence is not convincing enough to recommend rTMS in the routine management of OCD. Larger sham-controlled RCTs are required to establish the efficacy of rTMS in OCD.

What is the role of neurosurgery in OCD?

There has been a resurgence of interest in neurosurgical procedures for treatment refractory psychiatric disorders, especially depression and OCD [130]. With the help of modern-day neurosurgical procedures using MRI, stereotactic instruments, radiosurgery, etc., reliable lesions can be produced non-invasively in specific brain regions. Deep brain stimulation (DBS) allows us to place electrodes in specific brain regions and alter functioning of the regions in a flexible and reversible manner [8].

It has been estimated that around 20% of patients are refractory to available pharmacological and psychological treatments [8]. Converging evidence suggest the involvement of

medial and orbital frontal–basal ganglia–thalamic circuits in the pathogenesis of OCD [8]. Lesioning procedures (also known as ablative neurosurgery) targeting various regions in this circuit have been tried in refractory OCD. The common ablative procedures practiced include anterior cingulotomy, capsulotomy, subcaudate tractotomy and limbic leucotomy. There are no controlled studies on the efficacy of ablative procedures. Uncontrolled studies suggest that 45–65% of patients improve with these procedures [131]. The improvement is usually observed after 6 months to 2 years post-surgery. A recent review suggests that capsulotomy may be a more effective procedure for OCD [132]. Stereotactic surgery is associated with minimal adverse effects. There are reports of isolated post-operative convulsions. Occasional cases of intra-cerebral hemorrhage and infection have been reported with traditional open surgeries [133]. Such complications can be prevented by the use of radiosurgery. Gamma knife surgeries may lead to radiation-induced edema and delayed cyst formation. Late cyst formation has been observed in 1.6–3.6% of patients after radiosurgery for arterio-venous malformations [134]. Long-lasting personality alterations, weight gain, incontinence and cognitive disturbances have been reported in less than 10% of patients [133].

The most common target for DBS in OCD is the ventral capsule/ventral striatum, which includes the nucleus accumbens. Other targets include bed nucleus of the stria terminalis, inferior thalamic peduncle and subthalamic nucleus. A few double-blind crossover studies have been conducted. A review of the 90 patients who received DBS in internal capsule/ventral striatum showed around 50% improvement occurs in OCD, depressive and anxiety symptoms [135]. It has been suggested that DBS over this region enhances extinction of conditioned fear [136]. Hence, DBS could augment the effectiveness of BT for OCD. In 2009, the US FDA approved a humanitarian device exemption for DBS for severe and treatment-resistant OCD [137].

How to select patients for surgery?

Despite the availability of safe procedures, psychosurgery remains a contentious area. This is partly fallout of overzealous use of procedures of doubtful efficacy in the past. Further, producing irreversible changes in the brain without knowing the exact mechanism of action raises ethical concerns. Nevertheless, neurosurgical procedures have a role in contemporary psychiatric practice, provided patients are carefully selected based on predetermined criteria.

Most centers use similar criteria for selecting OCD patients for surgery. The criteria includes patients with a primary diagnosis of OCD, with a duration of ≥5 years, with severe symptoms (Y-BOCS ≥28) causing functional impairment. Treatment resistance is usually defined as insufficient improvement with at least 3 SRIs (one of which should be clomipramine), 1–2 augmentation strategies and at least 20 h of BT/CBT. Patients with clearly documented intolerance to BT/CBT and clomipramine are also included. Patients with comorbid psychosis, recent manic episode, current substance dependence, major neurological/medical illness, significant abnormalities in MRI and other physical contraindications for surgery are excluded [131,135,138]. Ideally, an independent review committee consisting of independent psychiatrists, neurosurgeons and neurologists should assess each patient regarding suitability for surgery.

Table 1. Recommended dose of anti-obsessive agents.

Drug	Anti-obsessive dosage/day (mg)
Fluoxetine	40–80
Sertraline	150–200
Fluoxamine	200–300
Paroxetine	40–60
Escitalopram	20–40
Clomipramine	150–250
Venlafaxine	225–300

Expert commentary

Current evidence suggests that either SSRI or BT/CBT is the first-line treatment of OCD. There is not enough evidence to support the use of combination of BT/CBT and SSRI at the beginning of treatment, especially in adults. However, this treatment strategy is effective in non-responders. Both treatments seem to be equally effective, though BT may have some advantages in the form of greater reduction of symptoms and better relapse prevention. Guidelines recommend use of CBT alone in mild to moderately ill patients. Nevertheless, due to pragmatic considerations, pharmacotherapy is more widely practiced. If pharmacotherapy is the chosen modality, SSRIs are the drugs of choice. All SSRIs are equally effective and the choice is made based on adverse effects, drug interactions and previous treatment response. SSRIs should be given at a higher dose (Table 1) and continued for at least 12 weeks to assess treatment response. Patients with partial response may continue to improve on extending the treatment further. If psychotherapy is the chosen modality, BT using ERP has the best evidence. Cognitive interventions in combination with behavioral techniques are also effective. In people who respond to SSRI treatment, medications should be continued for at least 1–2 years after remission of symptoms. Many patients need longer treatment. The duration of treatment should be decided on individual case basis considering chance of relapse, severity of illness and adverse effects. For non-responders to one SSRI, another SSRI may be tried in an adequate dose for adequate duration. Clomipramine may be tried if a person does not respond to two SSRIs. For partial responders and non-responders, augmentation strategies may be tried. Low dose of atypical antipsychotics, especially ripseridone are the preferred augmenting agents. They should be tried for at least 4–8 weeks to assess their effectiveness [5]. CBT augmentation of a SSRI is also a highly effective intervention and should be tried early on, if

facilities are available. Other potentially effective augmenting agents include ondansetron, clomipramine, memantine, riluzole, *N*-acetyl cysteine, lamotrigine and topiramate. Patients may respond to a particular SSRI despite poor response to others. In patients who do not respond to initial trials of SSRIs, clomipramine or standard augmenting strategies, other SRIs including venlafaxine may be tried in tandem. High-dose SSRIs or intravenous SRIs may be tried if the first-line treatments and augmenting strategies fail, but evidence supporting their efficacy is limited. ECT does not have any role unless the patient has comorbid severe depression that interferes with treatment. rTMS over SMA may be tried if facilities are available, but more evidence is required to recommend it as a routine treatment. A substantial minority of patients do not respond to all available pharmacotherapy and psychotherapy. If such patients are highly dysfunctional for long periods, surgery may be considered in the form of gamma ventral capsulotomy or anterior cingulotomy or DBS.

Five-year view

There have been hardly any paradigm shifts in the treatment of OCD after the introduction of SSRIs and CBT. The other interventions studied till date, are useful as augmentation strategies, but have not been consistently found to be effective as stand-alone treatments. A considerable proportion of patients do not respond adequately to both BT and SSRIs, including clomipramine. Hence, there is a need for alternate first-line treatments.

Cognitive interventions have been hailed as a major innovation in OCD treatment. However, clinical trials have not found it to be superior to ERP. Cognitive therapy may be more effective in a subset of patients where ERP is less effective like compulsive hoarders, primary obsessive slowness, people with pure obsessions without compulsions and people with poor insight OCD [34]. This has to be studied systematically. New age therapies like those using mindfulness techniques (e.g., ACT) have a different way of handling intrusive thoughts compared with traditional CBT. Their efficacy in comparison with CBT should be studied.

From the traditional serotonin hypothesis, there has been a shift to other neurobiological mechanisms. Several lines of evidence including genetic studies, magnetic resonance spectroscopy studies, CSF analysis and animal studies, point to a glutamatergic dysfunction in OCD [139]. Current evidence of drugs acting on glutamatergic system (e.g., memantine, riluzole, *N*-acetyl cysteine) have focused on NMDA receptors and have shown promising results as augmenting agents. Their role as stand-alone interventions has to be studied. Drugs acting on other glutamate receptors like the metabotropic receptors are currently being patented and tested [139]. Agents targeting 5HT-1D and 5HT-2A/2C receptors which are currently implicated in the pathogenesis of OCD have to be studied [140]. In this regard, there have been open-label studies on agomelatine and mirtazapine [74,141]. Well-designed controlled trials on these and other serotonergic agents have to be conducted. The other need is to decrease the time lag in therapeutic response for SSRIs. Mirtazapine has shown some promise in this regard [75], but it has to be replicated.

Current treatment algorithms are based on trial-and-error basis and there are no clear indicators on choosing treatment for a particular patient. OCD is a heterogeneous condition. Many different subtypes have been proposed based on symptom dimensions, age of onset and comorbidity pattern [142]. Efficacy of treatments on different subtypes of illness has seldom been studied. These may help in individualizing the treatment process.

There is likely to be changes in other biological treatments too. Development of deep rTMS coils for rTMS may help in targeting areas particularly involved in OCD. The targets for DBS and ablative surgeries are currently being refined. These have to be to be studied more extensively, particularly regarding their long-term safety and benefits.

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Key issues

- The first-line treatment of obsessive-compulsive disorder (OCD) is either selective serotonin reuptake inhibitors (SSRI) or behavior therapy/cognitive behavior therapy (CBT).
- Combination of SSRI and CBT is recommended for severely ill and SSRI non-responsive patients.
- Both behavioral and cognitive interventions are effective and can complement each other.
- A second SSRI can be tried in those who do not show response to first trial. Clomipramine can be tried in patients not responding to ≥2 SSRIs.
- Augmentation with CBT or atypical antipsychotics has the best evidence base and therefore is recommended in partial responders and non-responders to SSRIs.
- Other potential augmentation strategies include *N*-methyl-D-aspartate antagonists, 5HT-3 antagonists, clomipramine, lamotrigine and topiramate.
- Ablative neurosurgery or deep brain stimulation may be tried in carefully selected treatment refractory patients.

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