EXPERT REVIEWS

Augmentation strategies in obsessive–compulsive disorder

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Around 40–60% of patients with obsessive–compulsive disorder do not show adequate response to selective serotonin reuptake inhibitors (SSRIs). Augmentation strategies are recommended in people who show partial response to SSRI treatment or poor response to multiple SSRIs. In this article, the authors review the evidence for augmentation strategies. The available evidence is predominantly based on small-scale, randomized controlled trials, open-label trials and case series. Antipsychotic augmentation, especially risperidone, haloperidol, aripiprazole and cognitive-behavior therapy have shown the best evidence. Ondansetron, memantine, riluzole, clomipramine, mirtazapine and repetitive transcranial magnetic stimulation over supplementary motor area show some preliminary evidence. Ablative neurosurgery or deep brain stimulation may be tried in carefully selected treatment refractory patients.

Keywords: antidepressants • antipsychotics • augmentation • cognitive-behavior therapy • glutamate antagonists • obsessive–compulsive disorder • repetitive transcranial magnetic stimulation • SSRI • treatment-resistant • psychosurgery

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Obsessive–compulsive disorder (OCD) is a common psychiatric illness with a lifetime prevalence of 2–2.5% [1]. It affects individuals in the most productive period of life. It usually has an onset in childhood or early adulthood [2], and more commonly runs an unremitting course persisting into adulthood [3]. Disability and quality-of-life impairment in people suffering from OCD have been comparable with that of serious mental illness like schizophrenia [4]. Despite this, it is a highly under-recognized condition and conservative estimates suggest that more than half of patients do not receive any treatment [5]. Even among those receiving treatment, a large proportion receive inadequate or improper treatment [6].

Prior to the 1960s, OCD was considered an untreatable condition. The demonstration that an antidepressant with a more selective serotonergic action, namely clomipramine, was more effective in controlling the symptoms revolutionized the treatment of OCD. Since then, the efficacy of clomipramine in the treatment of OCD has been demonstrated in several randomized controlled trials (RCTs) [7]. Due to the adverse effects commonly observed in people treated with clomipramine, selective serotonin reuptake inhibitors (SSRIs) have taken over clomipramine as the first-line agents in the treatment of OCD. Several RCTs have consistently demonstrated the efficacy of SSRIs in the treatment of OCD [8], albeit at a higher than usual antidepressant dosage and a longer time (8–12 weeks) for improvement [9].

It has been observed that all SSRIs are equally efficacious in OCD [8], and the choice of SSRI is usually made based on other factors like adverse effect profile, comorbidity, and so on. People who do not respond to one SSRI may respond to a second one [9]. Clomipramine is generally recommended when treatment with at least two SSRIs have failed [9]. The other effective treatment is cognitive-behavior therapy (CBT) [10], which along with SSRIs are considered to be first-line treatments for OCD [11]. But considering the time constraints and requirement of highly skilled professionals, this effective treatment may not be easily accessible to everyone. Hence, SSRIs are often the first-line treatments for OCD.

Nearly 40–60% of patients treated with SSRIs do not respond to treatment or only respond partially [12]. It is generally recommended that augmentation with other treatments, either medications or CBT, is suitable for people with partial response, while switching over to a different SSRI is recommended for people who do not respond.

What is augmentation?

Augmentation refers to the process of adding medications with a different mechanism of action to the primary drug to boost its therapeutic efficacy. Evidence from basic science research suggests that multiple neurotransmitters may be relevant in the pathophysiology of OCD. Hence using a combination of medications with different mechanisms of action has a theoretical rationale. In this article, the authors review efficacy and tolerability of different augmentation strategies in the treatment of OCD.

The treatment literature in OCD is marred by varied definitions of treatment response outcome, making it hard to interpret the findings of published studies. The terms like 'response', 'remission', 'treatment resistance' and 'treatment refractory' may not convey the same meaning in different studies. Nevertheless, most of the studies either use the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) [13], either alone or along with the Clinical Global Impression (CGI) scale. The term 'treatment-resistant' is sometimes used to describe patients who do not respond satisfactorily to any first-line therapy, and the term 'treatment-refractory' is used to describe patients who do not respond satisfactorily to all available therapeutic alternatives [14,15]. Some authors have tried to differentiate 'drug resistance' from 'treatment resistance'; the former referring to patients who have not responded to SSRIs and the latter to both SSRIs and behavior therapy [16]. There is no clear consensus on the definition of treatment refractory OCD. For example, Denys *et al.*,

for their study on deep brain stimulation, defined treatment refractory OCD as nonresponse or insufficient response to at least two treatments with SSRIs at maximum dosage for at least 12 weeks, plus one treatment with clomipramine at maximum dosage for at least 12 weeks, plus at least one augmentation trial with an atypical antipsychotic for 8 weeks in combination with a SSRI, plus at least one CBT trial for a minimum of 16 sessions [17]. In another study that examined the efficacy of bilateral capsulotomy, patients were considered refractory to treatment if medications, psychotherapy or CBT administered for more than 5 years did not result in clinical improvement or led to worsening [18]. This study included patients who were refractory to medications alone.

In an effort to clear this confusion, expert consensus-based outcome criteria have been proposed by Pallanti *et al.* [12]. They defined various stages of treatment response from Stage I to VII. Stage I, termed as recovery, includes those who score <8 on Y-BOCS after treatment. Remission (Stage II) is defined as <16 score on Y-BOCS. A 35% reduction in the Y-BOCS score or CGI-I of 1 or 2 suggest full response to treatment (Stage III), while a Y-BOCS reduction of 25–35% suggests partial response (Stage IV). Less than 25% reduction in the Y-BOCS total score and a CGI-I of 4 suggests nonresponse to treatment (Stage V), while relapse (Stage VI) is defined as CGI-I 6 or 25% increase in Y-BOCS from remission score. Refractory (Stage VII) patients include those who show no change or worsening with all available therapies. Pallanti *et al.* [12] also suggest levels of nonresponse to treatment, based on the number and types of treatment, which range from level 1 (SSRI or CBT) to level 10 (which include all available treatments including neurosurgery). These are not widely used in the treatment literature.

Augmentation strategies may be useful in three groups of patients. The first group includes those who respond partially to SSRI treatment. The authors define this group as patients who show 25–35% reduction in Y-BOCS score after adequate treatment with an SSRI. The second group includes those who have shown response to medications (greater than 35% reduction on the Y-BOCS), but have not achieved remission of symptoms (i.e., <16 on Y-BOCS). The third group includes those who do not respond to at least adequate trials of two SSRIs. For the third group, clomipramine may be considered before augmentation as there is some evidence that clomipramine may be superior to SSRIs in treatment of OCD [7].

With this background, the authors review the literature on the efficacy of augmentation strategies in OCD and provide a recommendation for the use of augmenting strategies based on the available literature.

Method

A MEDLINE literature search using PUBMED was conducted for all studies up to August 2012 using the search strategy (OCD) AND (augmentation) OR (adjunctive) OR (refractory) OR (resistant). The individual treatments obtained using this strategy were used as key words along with the keyword 'obsessive–compulsive disorder' (e.g., 'cognitive behavior therapy' AND 'obsessive–compulsive disorder', 'risperidone' AND 'OCD', and so on). In addition, the reference sections of major articles and reviews (systematic reviews and meta-analyses) were also screened. The authors included all types of studies including case series, open-label studies, controlled studies and systematic reviews and meta-analyses.

Augmentation strategies in OCD

Antipsychotic medications

Antipsychotics were one of the first medications to be tried for treatment of OCD. The earlier use of antipsychotics as monotherapy for obsessive-compulsive symptoms was prompted by the effectiveness of these agents in Tourette's syndrome, which has phenomenological similarities with OCD. There are very few if any well designed studies on antipsychotic monotherapy for OCD. Clozapine monotherapy was found to be ineffective in an open-label trial in treatment refractory OCD patients [19]. An open-label study on aripiprazole has shown some positive response [20]. However, these studies are too preliminary for clinical application. By far, the majority of antipsychotic studies in OCD have been as an augmentation strategy for SSRIs. Thirteen double-blind, randomized, placebo-controlled trials (Table 1) and three active comparator studies (Table 2) have been published to date on the efficacy of augmentation with antipsychotics in treatment-resistant OCD. Most of the RCTs have been conducted with atypical antipsychotics. All these studies have a modest sample size (10–20 patients in each arm) and are heterogeneous in methodology, including the dosage, inclusion criteria and outcome measurements. Hence the results of these studies should be interpreted with caution.

Efficacy of antipsychotic augmentation

A recent meta-analysis of 12 placebo-controlled trials (excluding the Sayyah *et al.* [21] study on aripiprazole) [22] homogenized the outcome criteria from all the studies using the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) [13] scores and analyzed the outcome both as a continuous variable (Y-BOCS changes using standardized mean differences with the associated 95% CI) and as a categorical variable (responders defined as ≥35% reduction in Y-BOCS score). On both analyses, antipsychotic drugs as a group showed significant improvement compared with placebo. 28% of the patients on antipsychotics were classified as responders compared with 13% in the placebo, with a relative risk of 2.10 (N = 12; n = 394; 95% CI: 1.16–3.80). The number needed to treat (NNT) was 5.9, which is reasonably good considering the prevalence of the problem and the paucity of treatment options. Earlier meta-analyses have also reported significant benefits with antipsychotic augmentation [23–26], some reporting a better NNT of 4.5 [23,25]. Methodological variations could have contributed to these minor differences. These meta-analyses also ruled out the evidence for publication bias [23,25]. The only other study which has not been included in the meta-analyses [21] showed a positive response to aripiprazole. Hence, there is adequate evidence for the use of antipsychotic augmentation in SSRI-resistant OCD.

Table 1. Randomized placebo-controlled trials of antipsychotic augmentation in treatment nonresponders/partial responders to selective serotonin reuptake inhibitors in obsessive–compulsive disorder.

Study (year)	Antipsychotic dosage in mg mean (SD)	Patients (n)	Duration (weeks)	Duration of last SSRI trial	Mean Y-BOCS change-A (%)	Responders	Comments	Ref.
McDougle *et al.* (1994)	Haloperidol; 6.2 (3.0)	A = 17; P = 17	4	Fluvoxamine 8 weeks	26	A: 64.7% vs P: 0%‡	Haloperidol > placebo	[27]
McDougle *et al.* (2000)	Risperidone; 2.2 ± 0.7	A = 20; P = 16	6	Any SSRI 12 weeks	31.8	A: 50% vs P: 0%‡,§	Risperidone > placebo	[29]
Hollander *et al.* (2003)	Risperidone; 2.25 (0.86)	A = 10; P = 6	8	Any SSRI 12 weeks	19.04	A: 40% vs P: 0%¶	Risperidone > placebo	[38]
Erzegovesi *et al.* (2005)	Risperidone; 0.5	A = 20; P = 19	6	Fluvoxamine 12 weeks†	19.8	A: 50% vs P: 20%‡	Risperidone significantly effective only in fluoxamine refractory patients	[39]
Bystrisky *et al.* (2004)	Olanzapine; 11.2 (6.5)	A = 13; P = 13	6	Any SSRI 12 weeks	16	A: 46% vs P: 0%§	Olanzapine > placebo#	[50]
Shapira *et al.* (2004)	Olanzapine; 6.1 (2.1)	A = 22; P = 22	6	Fluoxetine (20–40 mg) 8 weeks	12.75	A: 23% vs P: 18%‡	Olanzapine = placebo	[30]
Atmaca *et al.* (2002)††	Quetiapine; 91.1 (41.1)	A = 14; P = 13	8	Any SSRI 12 weeks	26.75	A: 64.4% vs P: 0%‡	Quetiapine > placebo	[46]
Denys *et al.* (2004)	Quetiapine; 300	A = 20; P = 20	8	Any SSRI 8 weeks	31	A: 40% vs P: 20%‡	Quetiapine > placebo	[43]
Carey *et al.* (2005)	Quetiapine; 168.75 (120.82)	A = 20; P = 21	6	Any SSRI 12 weeks	17.75	A: 40% vs P: 47.6%§	Quetiapine = placebo	[31]
Fineberg *et al.* (2005)	Quetiapine; 215 (124)	A = 11; P = 10	16	Any SSRI 12 weeks	14	A: 27% vs P:10%§	Quetiapine = placebo	[44]
Kordon *et al.* (2008)	Quetiapine; 400–600	A = 20; P = 20	12	Any SSRI 12 weeks	22	A: 65% vs P: 44%‡	Quetiapine = placebo	[45]
Muscatello *et al.* (2011)	Aripiprazole; 15	A = 16; P = 14¶	16	Any SSRI 8 weeks	28.5	A: 25%‡	Aripiprazole > placebo	[54]
Sayyah *et al.* (2012)	Aripiprazole; 10	A = 18; P = 21	12	Any SSRI 12 weeks	29.5	A: 53% vs P: 17.6%§	Aripiprazole > placebo	[21]

†Responders to SSRIs included.
‡Response criteria ≥35% decrease in Y-BOCS.
§Completer analysis showed no difference, high dropout.
¶Response criteria ≥25% decrease in Y-BOCS.
#Only in SSRI nonresponders.
††Single blind study.
SD: Standard deviation; SSRI: Selective serotonin reuptake inhibitor; Y-BOCS: Yale–Brown Obsessive Compulsive Scale.

Predictors of treatment response to antipsychotics

Comorbidity with tic disorder

One of the commonly cited predictors for treatment response to antipsychotics is the presence of a comorbid tic disorder. Earlier studies with typical antipsychotics [27,28] revealed a better response to antipsychotic augmentation in people with comorbid tics. However, later studies of atypical antipsychotics like risperidone [29], olanzapine [30] and quetiapine [31] failed to reveal such an association. The meta-analysis by Bloch *et al.* [23] favored the association. The NNT increased from 5.9 in people without tic disorder to 2.3 in those with tic disorders. But the meta-analysis by Skapinakis *et al.* [24] failed to find an association between comorbid tic disorder and treatment response. However, a later subgroup analysis revealed that in people with comorbid tic disorder, a higher dosage of antipsychotics led to a better response. Hence, it appears that in people with comorbid tic disorders, an antipsychotic at a higher dosage (resulting in greater D_2 receptor blockade) may lead to a better response.

Comorbid schizotypal personality disorder

Not many studies have addressed this issue, perhaps due to the relative rarity of patients with schizotypal disorder. Open-label trials [28,32] have supported the notion that OCD patients with comorbid schizotypal personality disorder have greater improvement with antipsychotics. However, an RCT with risperidone [29] did not support this conclusion.

Table 2. Randomized controlled trials of antipsychotic augmentation with active comparators.

Study (year)	Method	Drugs compared	N (completers)	Duration of trial	SSRI	Results	Ref.
Li *et al.* (2005)	Double-blind, placebo-controlled, crossover study	Risperdone (1 mg/day) vs haloperidol (2 mg/day) vs placebo	16 (12)	2 weeks of each drug	Any SSRI for 12 weeks	Active drugs > placebo	[40]
Maina *et al.* (2008)	Single-blind randomized trial	Olanzapine (2.5–10 mg) vs risperidone (1–3 mg)	50	8 weeks	Any SSRI 16 weeks	Both drugs equally effective	[51]
Diniz *et al.* (2010)	Double-blind, placebo-controlled trial	Clomipramine (≤75 mg) vs quetiapine (≤200 mg) vs placebo added to fluoxetine (40–80 mg)	54	12	Fluoxetine 8 weeks	Placebo + fluoxetine and clomipramine + fluoxetine > quetiapine + fluoxetine	[69]

Neuroimaging predictors

Using functional neuroimaging by FDG-PET, Buchsbaum *et al.* evaluated predictors of response to risperidone augmentation in SSRI nonresponders [33]. They found that patients with low relative metabolic rates in the striatum and high relative metabolic rates in the anterior cingulate gyrus showed a better response to risperidone augmentation. Lower metabolic activity in the right caudate has also been found to be associated with poor response to SSRIs [34]. Fineberg *et al.* [35] suggest that this may be a probable radiological endophenotype of SSRI-resistant antipsychotic responsive OCD. However, this finding has not yet been replicated.

Other clinical variables

Carey *et al.* [36] evaluated the predictors of response for quetiapine augmentation using logistic regression analysis. In this study, fewer previously failed SSRI trials, higher overall baseline scores for obsessions and compulsions, as well as counting/ordering and arranging compulsions, were associated with better response to quetiapine.

Duration of SSRI trial

Meta-analyses [22,25] show that in studies with a duration of SSRI trial less than 10–12 weeks before augmentation, there were no significant differences between an antipsychotic drug and placebo. This could be due to the continued improvement with SSRI in the placebo group leading to lack of significant difference between the groups. These results are at odds with a recent placebo-controlled trial [37], which showed that addition of quetiapine to citalopram, even in drug-naive or drug-free patients, lead to better improvement rates.

Choice of antipsychotics

Risperidone

Risperidone [22–24,26] is the only antipsychotic that is consistently effective as an augmentation strategy when compared with placebo. Three placebo-controlled RCTs [29,38,39], one placebo-controlled crossover trial with haloperidol [40] and multiple open-label trials (e.g., [41,42]) have shown positive response to risperidone. There is no negative trial with risperidone.

Quetiapine

It has been studied in five double-blind placebo-controlled trials [31,37,43–45], one single-blind placebo-controlled trial [46] and many open-label trials [47,48]. Barring a few negative results [31,48], most of the studies have shown a positive response to quetiapine. However, meta-analysis results have been unfavorable with only one [26] out of four meta-analyses showing positive results with quetiapine.

Olanzapine

Despite positive results from open-label trials [32,49], the two placebo-controlled RCTs have shown conflicting results [30,50]. Meta-analyses of these two studies also failed to find a significant response. In an 8-week, single-blind, randomized trial comparing risperidone and olanzapine augmentation, both were equally efficacious [51]. Nevertheless, more studies are needed before commenting on the clinical utility of olanzapine in OCD.

Aripiprazole

Data from multiple case series [52,53] and two placebo-controlled RCTs [21,54] have demonstrated the efficacy of aripiprazole augmentation in treatment-resistant OCD.

Other antipsychotics

The efficacy of haloperidol as an augmenting agent in OCD has been demonstrated in a randomized placebo-controlled trial [27] and in a brief placebo-controlled crossover trial with risperidone [40]. The evidence for other antipsychotics, such as amisulpride [55] and pimozide [28], is in the form of case series.

To summarize, risperidone appears to be the drug of choice when an antipsychotic is considered for augmentation in OCD, followed by aripiprazole and haloperidol, while olanzapine and quetiapine need to be studied further. It is not clear whether this apparent difference in efficacy among antipsychotics is due to methodological variations in studies or due to a true difference. A head-to-head comparative trial between olanzapine and risperidone did not demonstrate any difference in the efficacy between the two agents [51]. Hence, further studies are necessary to clarify this issue.

Dose of antipsychotics

Two meta-analyses [22,24] demonstrated that medium to higher dosages of antipsychotics are more effective in treatment augmentation than lower doses, while low doses were not significantly more effective than placebo. Skapinakis [24] classified the dosages based on the ability to block at least 60–65% of the dopamine D_2 receptors, that is, dosages traditionally required for antipsychotic effect. This is equivalent to 2 mg of risperidone, 10 mg of olanzapine, 400 mg of quetiapine and 2 mg of haloperidol. Taking into consideration the findings of meta-analyses and the doses employed in individual studies (Table 1), it appears that moderate doses may be more effective than very low doses. At the same time, it appears that standard antipsychotic dosages (e.g., 4–6 mg of risperidone, 15–20 mg of olanzapine, 600–800 mg of quetiapine and 10–20 mg of haloperidol) may not be employed for augmentation strategy.

Duration of antipsychotic treatment

Conflicting evidence exists on the minimum duration of antipsychotic treatment for treatment response. The meta-analysis by Skapinakis *et al.* [24] suggested that studies with treatment duration of at least 8 weeks showed a statistically significant result, while this was not evident in the group of studies with lesser duration. Bloch *et al.* [23] demonstrated in their analysis that treatment of more than 4 weeks may not confer an additional advantage. Individual studies tracking the improvement over time [29,46] have found that the treatment response was apparent from 3 and 6 weeks onwards. Considering these findings, it would be advisable to continue antipsychotics for at least 6–8 weeks to assess their efficacy.

One retrospective chart review revealed that discontinuation of effective augmentation with antipsychotics leads to increased chance of relapse [56]. Hence, it may be advisable to continue antipsychotics over a long-term period once they have shown improvement. Open-label trials of long-term use of antipsychotics in OCD have shown that they are generally well tolerated [57], while they may be effective in the long term for at least a subset of patients [58].

Tolerability of antipsychotic treatment

As expected, many trials reported adverse effects; restlessness with haloperidol and aripiprazole, weight gain with olanzapine, drowsiness, headache, dryness of the mouth and weight gain with quetiapine, sedation and dry mouth with risperidone. Meta-analysis revealed that discontinuation rates were not significantly different for the antipsychotic group compared with placebo, but stratification revealed that quetiapine had higher dropouts compared with placebo [22]. The decreased tolerability of quetiapine, coupled with its doubtful efficacy precludes the use of this agent as a first-line augmentation strategy.

Mechanism of action

Atypical antipsychotics have a curious relationship with OC symptoms. While they are effective as an augmentation strategy in OCD, they have also been shown to induce *de novo* OC symptoms in people with psychosis [59,60]. The action of atypical antipsychotic agents on both 5HT and dopamine D_2 receptors have been used to explain this relationship [59]. Atypical antipsychotics block 5HT receptors at low doses and the D_2 blockade increases as the dose increases [24]. 5HT blockade at low doses may precipitate OC symptoms and dopamine blockade at higher doses may explain their improvement of OC symptoms at higher doses. This is supported by the meta-analytic findings described above. Some clinical evidence also supports this dose–response relationship [61]. But there is conflicting evidence that suggests that OC symptoms induced by clozapine can be decreased by dose reduction [60]. Furthermore, in augmentation trials, usually, a lower dose of antipsychotic is used; for example, 1–2 mg of risperidone. On the other hand, OC symptoms manifest when antipsychotics are used in optimum doses in schizophrenia. Hence, the dose–response relationship is not clear. There is also a possibility that differential blockade and activation of $5HT_{2A}$ and non-$5HT_{2A}$ receptors may play a role in their mediation of antiobsessional activity of SSRIs [62]. Second generation antipsychotics, such as risperidone and olanzapine, and to an extent quetiapine, are potent antagonists of $5HT_{2A}$ receptors, and also mirtazapine, which may have some antiobsessional property. There is also a suggestion that antiobsessional activity may be related to D_2-blocking properties and this view is supported by the fact that risperidone and haloperidol are more effective than other antipsychotics.

Enhancing serotonergic neurotransmission

Consequent to the serotonin hypothesis, other drugs acting on the serotonin system have been tried as augmenting agents to boost the serotonergic action of SSRIs.

Ondansetron

Ondansetron is a serotonin antagonist for the $5HT_3$ receptor, used as an antiemetic agent. It has also been used as an anticraving agent for substance use disorders. Ondansetron was useful in a double-blinded RCT of ondansetron augmentation (4 mg/day) to low-dose fluoxetine (20 mg/day [63]). Askari *et al.* [64] conducted a two-center, randomized, double-blind, placebo-controlled, parallel-group study on the efficacy of granisetron (1 mg twice daily), another $5HT_3$ antagonist, as an augmenting strategy and found it to be efficacious and well tolerated.

Mirtazapine

Mirtazapine is an antidepressant with specific noradrenergic and serotonergic receptor antagonistic properties. It enhances serotonin neurotransmission indirectly. There is preliminary evidence of its use as an anti-obsessional agent as a monotherapy [65]. Pallanti *et al.* [66] tested the augmenting efficacy of mirtazapine (at 15–30 mg/day) for citalopram in a single-blind RCT. They found that mirtazapine was associated with earlier onset of response and reduced adverse effects. However, the final outcome did not differ between mirtazapine and placebo.

Clomipramine

Another interesting strategy is the addition of clomipramine as an augmenting strategy to SSRIs in treatment-resistant patients.

It is commonly used with citalopram, perhaps because of the decreased pharmacokinetic interaction potential of citalopram. An open-label trial demonstrated a significant improvement with the combination of citalopram (40 mg/day) and clomipramine (150 mg/day) to citalopram alone [67]. Another uncontrolled study demonstrated the augmentation efficacy of citalopram to clomipramine in 20 treatment-resistant patients [68]. The benefit of clomipramine–fluoxetine combination has been demonstrated in two-case series and an RCT, in which this combination was superior to fluoxetine–quetiapine combination [69]. Such combinations, when used, should be monitored for adverse effects, particularly cardiac events, EEG changes, myoclonus and seizures.

Buspirone

Buspirone is a $5HT_{1A}$ partial agonist used in the treatment of generalized anxiety disorder. Buspirone augmentation of SSRIs has not been found to be useful [70].

Benzodiazepines

Clonazepam, a benzodiazepine with putative serotonergic properties, has been found to be ineffective as an augmenting agent in an RCT [71]. The use of clonazepam as a monotherapy has yielded conflicting results in two RCTs [72,73].

β-blockers

Pindolol, a β-adrenergic blocker with putative antagonistic action at presynaptic $5HT_{1A}$ receptor has shown efficacy (at a dose of 2.5 mg three-times daily) as an augmenting agent to paroxetine in a 6-week, double-blind, placebo-controlled trial in OCD patients (n = 23) resistant to treatment with at least two SSRIs [74], but not in another RCT [75].

Trazodone

Trazodone has antagonist action at $5HT_{2/1C}$ receptors, along with serotonin reuptake inhibiting action. It was not found to be effective as a monotherapy for OCD in a small placebo-controlled trial (n = 21) [76].

Glutamatergic drugs

Several lines of evidence, including genetic studies, magnetic resonance spectroscopy studies, CSF analysis and animal studies, point to a glutamatergic dysfunction in OCD [77]. Glutamate is the major excitatory neurotransmitter in the adult brain. It has two major types of receptors; ionotropic (including the AMPA, kainate and NMDA receptors) and metabotropic receptors. Currently available drugs in the market either act on ionotropic receptors (especially the NMDA receptors) or modulate glutamate neurotransmission through other mechanisms. These drugs, which are currently used in many CNS disorders like dementia, epilepsy, amyotropic lateral sclerosis, and so on, have also been tested for their efficacy in OCD.

Riluzole

Riluzole is a glutamate modulator used in the treatment of amyotrophic lateral sclerosis. It is hypothesized to modulate glutamate transmission by various mechanisms, including inhibition of voltage-gated sodium channels in excitatory neurons and potentiation of the extrasynaptic reuptake of glutamate in glial cells [77]. Riluzole is one of the earliest glutamate modulators tried in refractory OCD. In these trials, riluzole given at 50 mg twice daily was effective in at least 50% of the patients with refractory OCD [78,79]. It was well tolerated, but the few cases of pancreatitis in children on riluzole raises concern about its use.

Memantine

Memantine is an NMDA antagonist used in the treatment of Alzheimer's disease. Its use in OCD has been demonstrated in open-label trials [80,81]. A recent RCT found significant improvement in the memantine group compared with controls [82]. It was tried at a dose of 10 mg twice daily and was generally well tolerated.

Anticonvulsants

Lamotrigine is an anticonvulsant that blocks sodium channels and consequently glutamate neurotransmission. In a recent placebo-controlled RCT of 40 patients with SSRI-resistant OCD, lamotrigine addition at 100 mg/day was associated with significant improvement [83].

In a placebo-controlled randomized trial [84], SSRI augmentation with topiramate (mean dosage: 180.15 mg/day) in treatment nonresponders resulted in a mean decrease of 32.0% in Y-BOCS score, compared with a 2.4% decrease for those receiving placebo. In another placebo-controlled RCT [85], in 36 OCD patients, topiramate (mean dosage: 177.8 ± 134.2 mg/day) resulted in significant improvement in compulsions, but not in obsessions. In this study, topiramate was not well tolerated – 28% (5/18) of the subjects discontinued the drug for adverse effects and 39% (7/18) required a dose reduction.

Pregabalin is an antiepileptic that binds to the $\alpha_2\delta$ subunit of the voltage-dependent calcium channel in the CNS and decreases neurotransmission in excitatory neurotransmitters like glutamate. Its efficacy as an augmenting agent (at 150–675 mg/day) has been explored in uncontrolled open-label trials [86,87]. Gabapentin, with a similar mechanism of action as pregabalin, hastened the response to fluoxetine, but not the efficacy [88].

Ketamine

Ketamine, an NMDA antagonist with demonstrated acute antidepressant effects, was not found to be useful in an open-label trial involving ten patients with treatment refractory OCD; there was a transient decrease in OCD symptoms, unlike depressive symptoms which had a more significant improvement [89].

Glycine

In contrast to other glutamatergic drugs, glycine acts as a coagonist at the NMDA receptor site and hence increases glutamate transmission. In a double-blind RCT, patients on glycine at 60 mg/day showed nonsignificant improvement in OCD symptoms, but it was associated with poor tolerability due to unpleasant taste and nausea [90].

Sarcosine

Sarcosine is a glycine transporter inhibitor and increases glycine action at the receptor [91]. In an open-label trial, sarcosine reported significant improvement in OCD symptoms with acceptable tolerability.

Other drugs

Stimulants

Psychostimulants increase catecholamine neurotransmission. In a double-blind RCT of dextroamphetamine (30 mg/day) and caffeine (300 mg/day) in partial responders/nonresponders to SSRIs/serotonin–norepinephrine reuptake inhibitors (n = 24), around 50% of the patients showed improvement within the first week of treatment, and the scores improved over the study period [92]. The finding suggests that psychostimulant augmentation can cause a rapid improvement in OCD, but it needs replication before further use.

Mood stabilizers

Despite initial promise, later controlled trials failed to establish the efficacy of lithium as an augmenting agent [93]. There is no evidence to support the use of other mood stabilizers such as valproate and carabamazepine.

Inositol

Inositol, an isomer of glucose and a precursor in the phosphatidylinositol cycle, was effective as a monotherapy (18 mg/day) in a small, double-blind crossover trial [94], but its use as an augmenting agent is not supported by recent trials [95].

Opioid system

The opioid system has been reported to be involved in the pathology of OCD. A placebo-controlled, double-blind trial for 2 weeks demonstrated the efficacy of once-weekly morphine, an opioid agonist, as an augmenting agent [96]. The opioid antagonist naltrexone, which has been used in many impulse control disorders, has not been found to be effective in OCD as an augmenting agent. Rather, it appears to increase dysphoria in people with OCD [97].

Cognitive-behavior therapy

Behavior therapy (BT) in the form of exposure and response prevention (ERP) is a first-line intervention for OCD. Cognitive interventions, usually in combination with ERP are also used commonly. Many RCTs have failed to find an advantage of combining SSRIs and CBT *ab initio* over either treatment alone [98]. However, recent multicenter RCTs have supported this approach in adults [99] and children [100].

There have been many uncontrolled trials that have demonstrated the efficacy of CBT in people with partial/poor response to one or more SSRIs [101]. It has also been seen that this effect persisted up to 1 year post-treatment in well-characterized SSRI nonresponders [102]. These encouraging results have been confirmed by RCTs. Tolin *et al.* [103] conducted an RCT to study the effect of either self-directed or therapist-directed CBT in 41 patients who have responded inadequately to at least one SSRI. Both treatment arms showed improvement, but the therapist-directed treatment was superior. Simpson *et al.* compared ERP with stress management in an RCT in 108 patients with inadequate response to SSRIs, and found ERP to be superior, with a NNT of 2 [104]. A total of 74% of patients on ERP were found to be responders, compared with 22% of those on stress management training. Furthermore, 33% of patients on ERP had minimal symptoms (≤12 Y-BOCS score) after treatment compared with 4% in the other group. CBT has also been found to be superior to medications alone in pediatric patients who have experienced partial response to a previous SSRI trial, as demonstrated in the Pediatric OCD Treatment Study II (POTS II) RCT [105]. In this study, the patients were randomized into three augmentation groups, namely medication management alone, medication management plus instruction in CBT or medication management plus CBT. The CBT group performed better than the other two groups with an NNT of 3. Treatment guidelines recommend addition of behavioral therapy/CBT to people who have not responded to SSRIs [201]. Considering the available evidence and the demonstrated efficacy of both the treatments individually, this seems to be a rational recommendation.

Repetitive transcranial magnetic stimulation

Despite initial encouraging results from uncontrolled studies, randomized controlled studies have shown that repetitive transcranial magnetic stimulation (rTMS) applied to the right or left dorsolateral prefrontal cortex does not decrease obsessive compulsive symptoms significantly compared with placebo [106]. The efficacy of low frequency rTMS applied over supplementary motor area (SMA) has been demonstrated in an RCT [107]. In another RCT involving sequential administration of low frequency rTMS over right dorsolateral prefrontal cortex and bilateral SMA, there was no significant post-treatment difference between the active group and the sham treatment group [108]. From the available evidence, there is no convincing evidence to support the use of rTMS in OCD [109].

Neurosurgery

Neurosurgical procedures include either ablative procedures or deep brain stimulation. With progressive improvements in precision and safety of neurosurgical techniques, they are currently being studied more as a treatment option in treatment-resistant psychiatric disorders [110]. Patients are carefully selected for surgical interventions, but only when they prove to be refractory to traditional pharmacotherapy and CBT.

The common ablative procedures practiced include anterior cingulotomy, capsulotomy, subcaudate tractotomy and limbic leucotomy [111]. There are no controlled or comparative studies on ablative surgeries for OCD. The use of γ-knife for surgery, especially for ventral capsulotomy (γ-ventral capsulotomy), has made surgery more precise and less invasive. The outcome is usually observed after 6 months to 2 years postsurgery. Review of the uncontrolled studies suggests that at least 50–60% of the patients show a response to surgery [112]. A recent review [113]

suggests that capsulotomy may be a more effective procedure for OCD. There may be some rare serious adverse effects including intracerebral hemorrhage, infection, postoperative convulsions and so on which are more commonly seen with open surgeries. γ-knife surgeries may lead to edema. Long lasting personality alterations and cognitive disturbances have been reported but are not frequent complications.

In deep brain stimulation, electrodes are inserted in specific regions in brain and electrical stimulation in these areas is provided through implanted neurostimulators. The mechanism of action of DBS is still not clear; it is hypothesized that it suppresses pathological network activity, while allowing normal information transmission to occur [114] in the underlying brain region. The advantage with this procedure is that it is reversible and can be studied using placebo controls by sham stimulation. The disadvantage is that it is more expensive, needs battery change intermittently and is invasive compared with γ-knife surgery. In OCD, electrodes are commonly implanted in the ventral capsule/ventral striatum, which includes the nucleus accumbens. The other brain regions, such as inferior thalamic peduncle and subthalamic nucleus, have also been tried. A few double-blind crossover studies have been conducted. A review of the 90 patients for whom DBS has been reported in the international literature showed that around 50% improvement occurs in OCD, depressive and anxiety symptoms [115]. Adverse effects are rare and include surgical complications like intracranial hemorrhage, electrode breakage and so on, and stimulation-induced adverse effects like hypomania, agitation, anxiety and so on.

Table 3 provides a summary of all RCTs of augmenting strategies other than antipsychotic drugs in the treatment of OCD.

Expert commentary

Due to limited efficacy of SSRIs, augmentation strategies have become a part of standard practice in treatment of OCD. There is little evidence at present to recommend the use of augmentation strategies *ab initio*. Strategies in patients who do not respond to an initial trial with an SSRI include switching to another SSRI, use of suprathreshold doses of SSRIs and use of augmenting drugs. Among these, there is satisfactory evidence for switching SSRIs and use of augmentation strategies. Augmentation is generally recommended for those who show partial response to treatment with a SSRI or those with poor response to multiple SSRIs. Switching to a different SSRI is recommended if there is no response to the initial trial with a SSRI. If response to two SSRIs is unsatisfactory, a trial with clomipramine is recommended [9]. Augmentation strategies include pharmacological agents, psychotherapy and other somatic treatments. Antipsychotics are the most studied pharmacological augmenting agents. They are especially useful in people with comorbid tic disorder and perhaps schizotypal disorder. There seems to be variation in the efficacy between individual antipsychotics. Risperidone, aripiprazole and haloperidol have been found to be effective, while quetiapine and olanzapine have not been found to be effective consistently. Risperidone may currently be recommended as the antipsychotic of choice for augmentation in OCD, due to its consistent demonstration of efficacy. Aripiprazole and haloperidol are the next options. There is no evidence whether patients failing to respond to one antipsychotic may respond to another one. Antipsychotics should be used at moderate doses (e.g., 2 mg of risperidone) and may take 4–8 weeks for action.

After antipsychotics, other options are $5HT_3$ anatagonists, glutamatergic drugs and topiramate. However, more evidence is required to recommend their routine use as augmenting agents. Lamotrigine needs to be studied further, while ketamine has not been shown to be effective. There is preliminary evidence for drugs like pregabalin, mirtazapine, dextroamphetamine and morphine. The long-term safety and dependence potential of the dextroamphetamine and morphine preclude their regular use. Further studies on their efficacy and their long-term safety are warranted. Clomipramine augmentation may be a promising strategy, especially in people who do not tolerate high doses of a single drug, but this needs further study. Popular strategies, such as the addition of buspirone, lithium and clonazepam, have not withstood testing in well controlled trials. In essence, the best pharmacological augmenting agents are atypical antipsychotics, risperidone in particular.

CBT is one of the most effective treatments in OCD when used as a monotherapy. Its efficacy as an augmentation strategy has been demonstrated in partial responders [104,105] and to an extent in nonresponders [102]. Most guidelines recommend addition of CBT if response to SSRIs is not satisfactory. CBT should be tried early on instead of a series of pharmacological augmentation trials with questionable evidence.

At this point of time, rTMS cannot be recommended as a useful augmenting strategy. Neurosurgical interventions like DBS and ablative procedures should be employed judiciously in severely ill patients who are refractory to standard treatment options including intensive CBT. To conclude, among the pharmacological options, atypical antipsychotics have the best evidence as augmenting agents in OCD (Figure 1).

Five-year view

SSRIs and CBT have improved the outcome in people suffering from OCD. Despite this, a considerable proportion of patients do not show adequate response to treatment. Although antipsychotics have been found to be useful, they benefit only about a third of the patients. Also, the choice of antipsychotic drug, much like the choice of SSRI, remains somewhat unclear. It has to be established whether there is a real difference between the efficacies of various antipsychotics. Therefore, there is a need to compare the efficacy of different antipsychotics in head-to-head trials in OCD. The ceiling effect achieved by serotonin and dopamine-based therapies has shifted the focus toward other neurotransmitters. Glutamatergic system is an exciting frontier of approach at the moment. There have been some encouraging results from NMDA antagonists. We need larger controlled trials to verify their efficacy as augmenting agents. Drugs acting on other glutamate receptors, such as the metabotropic receptors, are currently being patented and tested [116]. Augmentation with mirtazapine should be evaluated carefully in controlled trials. Agents targeting

Table 3. Randomized controlled trials on the augmentation efficacy of other interventions in obsessive–compulsive disorder.

Study (year)	Intervention arms	Duration	Study population	Results	Ref.
Soltani *et al.* (2010)	Ondansetron (4 mg) vs placebo + fluoxetine	8 weeks	42 drug-free OCD patients	Ondansetron > placebo	[63]
Aksari *et al.* (2012)	Granisetron (1 mg b.i.d.) vs placebo + fluoxamine	8 weeks	42 OCD patients with Y-BOCS >21	Granisetron (100% response) > placebo (35%)	[64]
Pallanti *et al.* (2004)	Mirtazapine (15–30 mg) vs placebo + citalopram†	2 weeks	49 OCD patients	Earlier response to mirtazapine group, but no difference in final outcome	[66]
Grady *et al.* (1993)	Buspirone (60 mg/day) vs placebo + fluoxetine‡	4 weeks each arm	14 OCD patients on stable dose of fluoxetine for 10 weeks	Buspirone = placebo	[70]
Crocket *et al.* (2004)	Clonazepam vs placebo + sertraline	12 weeks	37 OCD patients	Clonazepam = placebo	[71]
Dannon *et al.* (2000)	Pindolol (2.5 mg/day) vs placebo + paroxetine	6 weeks	14 patients resistant to 2 SSRIs	Pindolol > placebo	[74]
Mundo *et al.* (1998)	Pindolol vs placebo + fluoxamine	12 weeks	15 OCD patients	Pindolol = placebo	[75]
Ghaleiha *et al.* (2012)	Memantine (20 mg/day) vs placebo + fluoxamine	8 weeks	42 OCD patients	Memantine > placebo	[82]
Bruno *et al.* (2012)	Lamotrigine (100 mg/day) vs placebo + SSRI	16 weeks	33 treatment-resistant OCD patients	Lamotrigine > placebo	[83]
Mowla *et al.* (2011)	Topiramate (100–200 mg/day) vs placebo + SSRI	12 weeks	49 treatment-resistant OCD patients	Topiramate > placebo	[84]
Berlin *et al.* (2011)	Topiramate (50-400 mg/day) vs placebo + SSRI	12 weeks	36 OCD patients on SSRIs	Topiramate > placebo more adverse effects	[85]
Greenberg *et al.* (2009)	Glycine (60 mg/day) vs placebo + SSRI	12 weeks	14 OCD patients on stabilized treatment	Glycine nonsignificant improvement – poor tolerability	[90]
Koran *et al.* (2009)	D-amphetamine 30 mg/day vs caffeine 300 mg/day + SSRI/SNRI	5 weeks	24 OCD patients with adequate trial of SSRI/SNRI	Both effective; response rate; D-amphetamine: 50%; caffeine: 58%	[92]
Koran *et al.* (2005)	Weekly oral morphine vs lorazepam vs placebo + SSRI‡	2 weeks each arm	23 OCD patients with at least 2 failed SSRI trials	Morphine > placebo	[96]
Tolin *et al.* (2007)	Self administered ERP vs therapist administered ERP§	Therapist group: 7.5 weeks; self-group: 6 weeks	41 patients on adequate medication trial	Therapist administered ERP > self-administered ERP	[103]
Simpson *et al.* (2008)	ERP vs stress management training + SSRI	17 twice-weekly sessions	108 OCD patients on SSRI trial	ERP > stress management	[104]
Franklin *et al.* (2011)	Medication management alone vs medication management plus instruction in CBT vs medication management plus CBT	12 weeks	124 OCD patients (7–17 years) on SSRI trial	CBT was more effective	[105]
Mantovani *et al.* (2010)	Low frequency rTMS over SMA/sham rTMS + SSRI	4 weeks double blind	21 medication-resistant patients	Active rTMS group > sham rTMS	[107]

†Single blinded.
‡Double-blind crossover trial.
§Open-label trial.
b.i.d.: Twice daily; CBT: Cognitive-behavior therapy; ERP: Exposure and response prevention; OCD: Obsessive–compulsive disorder; rTMS: Repetitive transcranial magnetic stimulation; SMA: Supplementary Motor Area; SSRI: Selective serotonin reuptake inhibitor; Y-BOCS: Yale–Brown Obsessive Compulsive Scale.

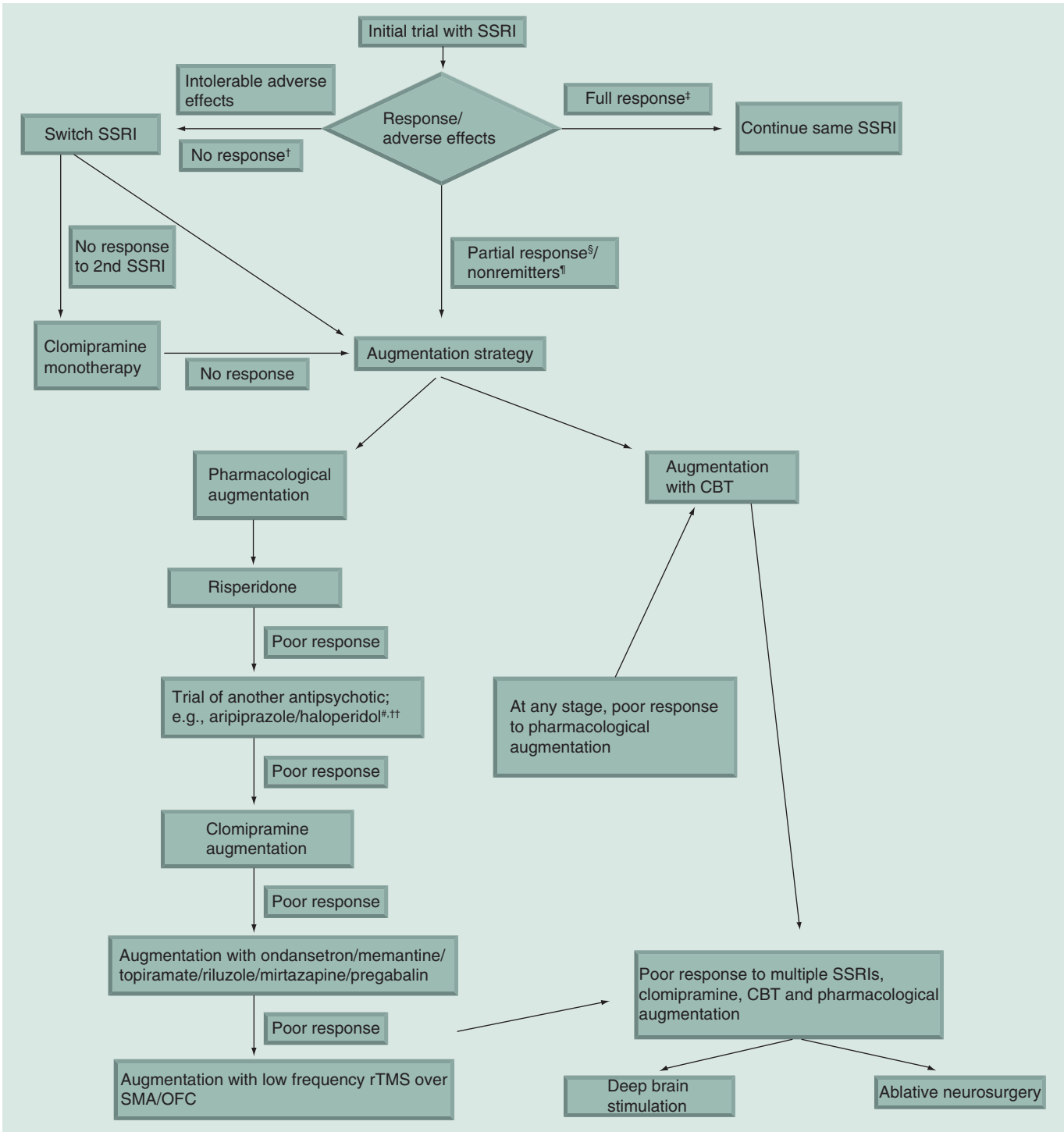

Figure 1. Evidence-based treatment flowchart for obsessive–compulsive disorder.
†Less than 25% reduction in the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) total score and Clinical Global Impression (CGI)-I of 4 suggests nonresponse to treatment
‡35% reduction in the Y-BOCS score or CGI-I of 1 or 2 suggest full response to treatment.
§Partial response defined as 25–35% reduction in Y-BOCS score despite adequate treatment duration with SSRI.
¶Have not achieved remission of symptoms (<16 on Y-BOCS) despite adequate treatment with SSRI.
#Haloperidol may be especially useful in patients with comorbid tic disorder.
††Olanzapine and quetiapine augmentation are options before proceeding to clomipramine augmentation.
CBT: Cognitive-behavior therapy; OFC: Orbitofrontal cortex; rTMS: Repetitive transcranial magnetic stimulation; SMA: Supplementary motor area; SSRI: Selective serotonin reuptake inhibitor.

$5HT_{1D}$ and $5HT_{2A/2C}$ receptors, which are currently implicated in the pathogenesis of OCD, have to be studied [117].

Abnormalities in neurotrophic factors, especially a decrease in brain-derived neurotrophic factor, have been demonstrated in people with OCD [118]. Subcutaneous infusion of brain-derived neurotrophic factor has shown antidepressant-like response in preclinical studies [119]. It may be a long way before such applications are tried in clinical populations.

Novel psychotherapies such as metacognitive therapy, acceptance and commitment therapy need further study. The authors now have few studies that have examined the role of CBT in partial responders to SSRIs. Importantly, the role of CBT in SSRI nonresponsive patients needs to be examined in well-designed controlled studies. In addition, relative merits of augmentation of SSRIs with CBT and atypical antipsychotics need to be determined, since it is unclear as to what is the next best option after an initial poor response to SSRIs. The efficacy of rTMS in SMA and OFPFC has to be replicated. The brain regions implicated in OCD lie deep in the brain (e.g., anterior cingulated cortex, orbitofrontal cortex). Hence the newly invented deep coils (e.g., H-coils), which have a penetration of around 5–6 cm, have to be tested in OCD. DBS and ablative surgery have to be studied more extensively, particularly for their long-term safety and benefits.

Key issues

- Augmentation strategies should be used in people who show partial response or poor response to selective serotonin reuptake inhibitors (SSRIs).
- Antipsychotic augmentation and cognitive-behavior therapy augmentation have the best evidence for efficacy.
- Among antipsychotics, risperidone has the best evidence followed by aripiprazole and haloperidol. When used, antipsychotics should be used in their minimum antipsychotic doses.
- Cognitive-behavior therapy should be tried early on in the course of illness instead of a series of pharmacological augmentation trials with questionable evidence.
- Clomipramine augmentation may be tried, especially in people not tolerating higher doses of other SSRIs.
- $5HT_3$ antagonists like ondansetron are promising in their efficacy as well as in decreasing gastrointestinal side effects of SSRIs.
- Glutamatergic antagonists have a sound theoretical rationale, but need to be tested rigorously.
- Traditionally recommended augmenting agents like lithium, buspirone and clonazepam are not effective. Clonazepam may help in the reduction of anxiety.
- Other strategies such as mirtazapine/pregabalin/stimulants augmentation may be tried when patients fail with the above mentioned agents.
- Repetitive transcranial magnetic stimulation over supplementary motor area and orbitofrontal cortex show some evidence, but it needs replication.
- Ablative neurosurgery or deep brain stimulation may be tried in carefully selected treatment refractory patients.

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. Your patient is an 11-year-old boy with obsessive-compulsive disorder (OCD) treated with multiple selective serotonin reuptake inhibitors (SSRIs), but with poor response. Based on the review by Drs. Sundar and Reddy, which of the following statements about use of antipsychotics as augmentation strategies is most likely correct?

- ☐ **A** There is little evidence to support antipsychotic augmentation
- ☐ **B** Haloperidol is the antipsychotic with the best evidence supporting its use in augmentation
- ☐ **C** Higher doses of antipsychotics are more effective as augmentation in OCD
- ☐ **D** There is evidence to support the use of risperidone and aripiprazole

2. Based on the review by Drs. Sundar and Reddy, which of the following statements about use of other pharmacotherapy as augmentation strategies for the patient described in question 1 is most likely correct?

- ☐ **A** Lithium, buspirone, clonazepam, and other traditionally recommended augmenting agents have been proven effective
- ☐ **B** Clomipramine augmentation may be useful in patients not tolerating higher doses of other SSRIs
- ☐ **C** Several large, randomized controlled trials have proven the efficacy of glutamatergic antagonists
- ☐ **D** There is no evidence supporting the use of ondansetron, memantine, or riluzole

3. Based on the review by Drs. Sundar and Reddy, which of the following statements about use of nonpharmacological therapies as augmentation strategies in patients with OCD would most likely be correct?

- ☐ **A** Cognitive behavioral therapy (CBT) should be used only as a last resort
- ☐ **B** Repetitive transcranial magnetic stimulation should be used over temporal regions
- ☐ **C** There is no role for ablative neurosurgery
- ☐ **D** Deep brain stimulation (DBS) may be tried in carefully selected treatment-refractory patients