

Management of treatment-resistant obsessive-compulsive disorder: An update on therapeutic strategies

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Abstract

Background: Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by recurrent, persistent thoughts and/or repetitive compulsive behaviors that cause anxiety or distress, are time-consuming, and cause significant socio-occupational dysfunction. Although OCD can be alleviated with pharmacological and behavioral treatments, up to 40-60% of patients do not have a satisfactory outcome. This paper aims to review the operational definitions and management of treatment-resistant OCD. **Materials and Methods:** A computerized search on Pubmed carried from 1980 to April 2006 led to the summarization of the results. **Results:** There are several strategies to manage treatment-resistant OCD. To start with, it is necessary to define it and differentiate it from other comorbid psychiatric disorders. Adequate trials of selective serotonin reuptake inhibitors (SSRIs), including clomipramine, at the maximum recommended dosages for at least 12 weeks needs to be tried, along with cognitive behavioral therapy (CBT), before trying out other modalities of treatment, which include ECT, rTMS, and neurosurgery. **Conclusion:** OCD has various clinical and therapeutic implications as it has a chronic course. Unless diagnosed and treated in an effective manner, it carries the risk of becoming resistant to treatment. This paper attempts to present an algorithm of management that can be followed in treatment-resistant OCD. It also emphasizes the need to maximize the effect of each course of treatment before moving on to the next step of management.

Keywords

Obsessive-compulsive disorder, obsessive-compulsive disorder, treatment-resistant obsessive-compulsive disorder

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Introduction

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by recurrent persistent thoughts (obsessions) and/or repetitive compulsory behaviors (compulsions) that cause anxiety or distress, are time-consuming, and cause significant socio-occupational dysfunction.^[1] OCD is unique among the anxiety disorders in that it appears to be much more dominated by cognitive and related complex behavioral symptomatology, with autonomic dysregulation playing little role. The neurotransmitter system of interest in both the etiology and pharmacological treatment of OCD is the serotonergic system.^[2] It has been suggested that the brain dopaminergic system also plays an important role in the genesis of OCD.^[3]

OCD can now be alleviated with modern pharmacological and behavioral treatments. Controlled trials with SSRIs demonstrate a selective efficacy in OCD in only about 40-60% of patients,^[4-11] with about 30% of patients failing to respond to conventional treatment.^[11] With a lifetime prevalence of 2-3% in the general population, this leads to significant disability and morbidity.^[12] This paper aims

to review the operational definitions and management of treatment-resistant OCD, the prevalence of which has been estimated to be around 30%.^[11]

Methodology

We carried out a computerized search on Pubmed/MEDLINE for all articles in English published from 1980 to April 2006; we used combinations of the following words: OCD, obsessive-compulsive disorder, treatment, resistance, management, behavioral therapy, cognitive therapy, pharmacological therapy, neurosurgery, cingulotomy, capsulotomy, limbic leucotomy, subcaudate tractotomy, deep brain stimulation, ECT, rTMS, and vagal nerve stimulation. Subsequently, we searched the bibliographies of the papers selected via the first strategy. Full-text articles were retrieved with the help of institutional online access and by writing personally to the authors. Assessment of this literature led to the identification of pertinent articles, which were then weighted according to a rating scheme based on levels of evidence.^[13] This was as follows:

Level Ia: Evidence obtained from meta-analysis of randomized controlled trials

Level Ib: Evidence obtained from at least one randomized controlled trial

Level IIa: Evidence obtained from at least one well-designed controlled study without randomization

Level IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study

Level III: Evidence obtained from well-designed, nonexperimental descriptive studies, such as comparative studies, correlation studies, and case studies

Level IV: Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

These levels were further divided into grades, which were:

Grade A (evidence levels Ia and Ib): Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency, addressing the specific recommendation.

Grade B (evidence levels IIa, IIb, and III): Requires availability of well-conducted clinical studies, but no randomized clinical trials, on the topic of recommendation.

Grade C (evidence level IV): Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. It indicates the absence of directly applicable clinical studies of good quality.

Good Practice Points (GPP): Recommended best practices based on the clinical experience of the guideline development group.

We then evaluated the articles in a nonquantitative manner, collated them, and conceptualized an algorithm of management after summarization of the results.

Defining treatment-resistant OCD

There have been several attempts to define and stage treatment-resistant OCD.^[14-17] An estimated 5% of OCD cases have an episodic course.^[18] Therefore, including 'recovery' and 'remission' in the staging terminology seems reasonable. Adequate stages of response have been defined by Pallanti^[19] as follows [Table 1]. Adequacy, resistance, and refractoriness of treatment have been defined by Guy^[20] (1) Adequacy of trial: when the patient has been given first-line pharmacotherapy, including at least 3 SSRIs, at the maximum recommended dosages for a trial duration of at least 12 weeks,^[21,22] then the trial is said to have been adequate. The treatment must have included the use of clomipramine and/or behavior therapy, including exposure and response prevention (ERP) with a minimum of 20 h of actual ERP. Treatment resistance is defined as failure to respond to the above adequate trial. (2) Drug resistance is defined as failure to respond to one SSRI (less than 25% reduction on the Yale Brown Obsessive-Compulsive Scale (Y-BOCS)); when

Table 1: Stages of response in obsessive-compulsive disorder

Definition	Criteria
Stage I Recovery/not at all ill	Less than 8 on Yale-Brown Obsessive Compulsive Scale (Y-BOCS)
Stage II Remission	Less than 16 on Y-BOCS
Stage III Full response	35% or greater reduction of Y-BOCS and CGI 1 or 2
Stage IV Partial response	Greater than 25% but less than 35% Y-BOCS reduction
Stage V Nonresponse	Less than 25% Y-BOCS reduction, CGI 4
Stage VI Relapse	Symptoms return (CGI 6 or 25% increase in Y-BOCS from remission score) after 3+ months
Stage VII Refractory	No change, or worsening, with all available therapies

there is failure to respond to two SSRIs, the patient is said to be refractory to treatment. However, this definition of treatment resistance has been criticized because it is not absolute; most treatment-resistant cases are actually cases of 'relative resistance' to drugs and may not have had adequate psychological treatment or complied with CBT. A clearer definition would therefore involve dividing resistance into drug resistance and treatment resistance, as follows: (a) Drug resistance: when a patient has shown less than 25% reduction on the Y-BOCS to at least 2 SSRIs, and (b) Treatment resistance: when a patient has failed to show response to the above plus 20 h of full compliance with ERP.

Methodological considerations: Diagnosis, comorbidity, and risk factors

It is important to consider a number of issues that may be responsible for refractoriness to first-line treatment.

Diagnosis

Treatment refractoriness is likely if the patient's symptoms have been misdiagnosed as OCD. The following disorders are difficult to differentiate from OCD: Major depression (depressive ruminations).^[23] Bipolar disorder (racing of thoughts).^[24] Other anxiety disorders, including posttraumatic stress disorder,^[25] generalized anxiety disorder,^[24] panic disorder,^[26] simple phobia, and social phobia.^[23] Psychotic disorders (intrusive thoughts and delusions).^[27,28] Organic mental disorders (intrusive thoughts and stereotypes). Habit disorders. Impulse control disorders.^[29] Eating disorders.^[30] Obsessive-compulsive personality disorders.^[31] Schizotypal (obsessive ruminations and magical thinking).^[32] Borderline personality disorder (ritualized self-injury).^[32] Other disorders possibly related to OCD are Tourette's disorder, trichotillomania, and body dysmorphic disorder.^[29]

Presence of comorbid disorders

An important issue in determining nonresponse to treatment is the presence of comorbid conditions; these disorders include the following: Affective disorder—depressive or bipolar disorder^[24] Other anxiety disorders^[23] Organic mental disorder such as seizure disorder Substance abuse disorder^[29] Personality disorder^[29]

Inadequate first-line anti-obsessional treatment

First-line pharmacotherapy includes trial with at least three SSRIs at an adequate dose for 12 weeks, and behavior therapy includes actual ERP for a minimum period of 20 h. Inadequate number of trials, inadequate duration of the trial, or inadequate dosage used for treatment are often responsible for treatment refractoriness. Inadequate assessment during psychiatric interview and failure to assess suitability for CBT.

Improper compliance

Due to the slow response to anti-obsessional drugs, improper compliance is often seen. Behavior therapy is often improperly or inadequately practiced in home settings. Presence of psychological resistance and overvalued ideas seriously undermines the effectiveness of CBT and affects compliance. Failure to give due credit to the patient, and enrolling him in treatment without explaining treatment rationale, are also predictors of poor compliance.

Psychosocial issues

OCD patients also get active secondary gains from their families in the form of support for avoidance of work and care from family members, which reinforces their symptomatology and promotes resistance to treatment.

Treatment Strategies for Resistant OCD Patients

A practical approach should include:

1. Early screening for the illness should be undertaken by primary care physicians to identify juvenile-onset OCD or adolescent OCD.
2. Considering a differential diagnosis, if required.
3. Maximizing the effectiveness of the first trials of either pharmacotherapy or behavior therapy or both combined.
4. Conducting a systematic search for, and identifying, comorbidities.
5. Addressing the psychosocial issues.
6. Better utilization of the available nondrug treatments (multimodal CBT, intensive individual and/or group therapy.)

There are mainly three general modes of intervention: pharmacological, behavioral and experimental.

Pharmacological intervention

The initial approach should be an adequate trial of SSRIs, failing which other strategies should be tried, such as augmentation strategies, combination strategies, the use of alternative agents as monotherapies, or a trial of alternative routes of administration.

First-line pharmacotherapy

Adequate trials for at least 12 weeks at the maximum recommended dosages^[21,22] of one of the following: clomipramine at an average dose of 200-250 mg/day,^[33-39] fluoxetine at dosages of 20-60 mg/day,^[37,42-46] fluvoxamine at dosages of 100-300 mg/day,^[47,48] sertraline at a dosage of upto 200 mg/day,^[44,49-51] paroxetine^[36,52-54] and citalopram^[29,55,56] can be tried in combination with clomipramine (83% chance of improvement^[58,59] as compared to SSRIs). There is limited evidence to suggest a role for citalopram in refractory OCD, although intravenous citalopram at a starting dose of 20 mg, and 60-80 mg mean dose, has been tried successfully in refractory cases.^[57]

Partial response to SSRIs

Since 40-60% of patients do not respond adequately to SSRI treatment alone, clear strategies are required for treating those with a partial response; these are augmentation strategies, combination strategies, and using SSRIs in tandem with behavior therapy.

Augmentation strategy

Different pharmacological agents have been suggested for use, depending on the type of comorbid clinical symptoms present. Augmentation can be tried with any of the following:

1. *Clonazepam*^[60,61] Proposed action: Up-regulation of 5-HT₁ and 5-HT₂ receptors in the frontal cortex, in addition to its benzodiazepine effect. Dose range: 0.5-5 mg/day Indication: Comorbid anxiety and insomnia. Limitations: Side effects may be a limiting factor and include depression, irritability, and intoxication.
2. *Buspirone*^[62-64] Proposed action: Partial 5-HT_{1A} receptor agonism Dose range: 10-90 mg/day; Indication: Comorbid anxiety; Limitations: Irritability and forgetfulness;
3. *Lithium*^[65-67] Proposed action: Enhancement of 5-HT transmission; Dose range: Sufficient to maintain the serum Lithium at 0.4-1.0 mEq/l Indication: Comorbid mood disorder Limitations: Toxicity weighs against its use in concomitant mood disorder;
4. *Atypical antipsychotics*^[68-72] Proposed action: Antagonism of both D₂ and 5-HT₂ receptors. McDougale has hypothesized that patients with SSRI-refractory OCD have additional abnormalities in dopamine function that require augmentation with dopamine-blocking agents. Dose range: As for psychosis (risperidone 2-6

mg/day and olanzapine 5-20 mg/day), but response tends to occur at lower doses. A 4-week therapeutic trial at the maximum tolerated dose is considered sufficient. Clozapine has not been investigated as an augmentation agent.^[73] However, given the relative toxicity of this agent, its use in OCD cannot be justified at present. Recently quetiapine^[74] has been tried in a single placebo-controlled trial which was limited by a small sample size. Indications: Comorbid tics, delusional disorder, obsession bordering on delusion; Limitations: Sedation, weight gain, and extrapyramidal side effects

5. *Typical antipsychotics* (i.e., pimozide and haloperidol) have also been successfully used in augmentation strategies for patients with OCD and comorbid tic disorder or trichotillomania.^[75-77] However, their effectiveness in treatment-resistant OCD has not been documented so far. Any strategy to augment SSRIs with typical antipsychotics should take into consideration the increased risk associated with neuroleptic treatment, especially the risk of inducing extrapyramidal symptoms and tardive dyskinesia.
6. *Fenfluramine*^[12,78] Proposed action: Increases 5-HT neurotransmission across the synaptic cleft Limitations: Fenfluramine is not approved for use by FDA, considering its cardiac side effects and the risk of pulmonary hypertension;
7. *L-Tryptophan*^[19] Proposed action: Enhancement of 5-HT activity by increasing the availability of its amino acid precursor L-tryptophan. Dose range: 3-9 g/day Limitation: May produce serotonin syndrome when combined with other SSRIs. There is also association with eosinophilic myalgic syndrome.
8. *Others*: Other agents that have been found to be relatively efficacious as augmentation agents include [Table 2]:

Combination treatment^[86]

1. *Clomipramine with an SSRI* Proposed action: Enhanced inhibition of 5-HT reuptake; Dose range: Lower doses of clomipramine (75-150 mg) than when used alone, due to interaction with SSRIs; Limitation: May produce serotonin syndrome, hence dose has to be increased gradually with careful monitoring of signs.
2. *Clomipramine with MAOI*^[87] Proposed action: Enhances synaptic 5-HT neurotransmission Dose range: Clomipramine has to be given at a low dose and increments should be gradual, otherwise the serotonin syndrome can result.

Alternative monotherapy

A few case studies have reported that monotherapy with clobazam, phenelzine, and buspirone can be effective as maintenance therapy in patients who do not respond well to augmentation or combination therapy.

Behavioral interventions

Cognitive behavior therapy may be tried alone or in combination with pharmacotherapy. The combination of ERP with pharmacotherapy has been found to be more effective than either one alone.^[88,89] In general, ERP has been found to have better long-term efficacy as compared to pharmacotherapy.^[90] It has also been observed that general pure obsessions are more resistant to behavioral treatment, whereas pure compulsions are most responsive [Table 3].

Traditional psychotherapy is not an effective treatment for OCD but may be helpful for patients with obsessive compulsive personality disorder.^[93] *Behavior therapy* for OCD includes assessment and use of either imaginal exposure or ERP. An efficacy similar to treatment with SSRIs has been reported. ERP especially helped to maintain compliance and reduce the severity of OCD.^[94,95] *Cognitive therapy* is initiated with assessment of the belief domains in OCD, which includes responsibility, threat estimation, perfectionism, over-importance of thoughts, control over thoughts, and tolerance of ambiguity; after this, cognitive therapies are employed such as Beck's cognitive therapy and rational emotive therapy. In combination with ERP, cognitive therapy has been reported to have 84% success rates.^[96]

Experimental interventions

Monotherapy

One RCT has suggested MAOIs as monotherapy,^[87] whereas one open trial and two case reports have suggested venlafaxine monotherapy^[82,83] as having anti-obsessional activity in treatment-refractory OCD; however, with these drugs, the risk of hypertensive crisis or serotonin syndrome has to be kept in mind.

Novel strategies

Intravenous clomipramine has been used effectively in several cases of treatment-refractory OCD.^[40,41] One regimen involving 14 clomipramine infusions of upto 250 mg each has shown promising preliminary results. Currently, this strategy must be considered experimental and it is available only at a few institutions in western countries. When all other pharmacological and behavioral strategies have failed, intravenous clomipramine may be tried prior to considering neurosurgical intervention. Researchers have found that the ratio of clomipramine to its metabolites desmethylclomipramine is increased with parenteral treatment, through reduction by first-pass hepatic metabolism. A recent study^[97] has evaluated glutamate-modulating drugs like riluzole in the management of treatment-resistant OCD.

Electroconvulsive therapy

ECT has a role in cases of treatment-refractory OCD

Table 2: Other augmenting agents

	Action/ dose	Side effects
i. Clonazepam ^[60,61]	Up-regulation of 5-HT ₁ and 5-HT ₂ receptor in the frontal cortex. Dosage of 0.5-5 mg/day.	Depression, irritability, and intoxication.
ii. Buspirone ^[62-64]	Partial 5-HT _{1A} receptor agonism at dosage of 10-90 mg/day	Irritability and forgetfulness
iii. Lithium ^[65-67]	Enhancement of 5-HT transmission	Neurotoxicity
iv. Fenfluramine ^[12,78]	Increases 5-HT neurotransmission across the synaptic cleft. pulmonary hypertension	Not approved for use by FDA, considering its cardiac side effects and risk of
v. Trazodone ^[19]	50-100 mg/day	Sedation, priapism
vi. Inositol ^[79]	Only a few case trials reported	
vii. Pindolo ^[19]		
viii. Phenelzine ^[80]	OCD with associated panic	Hypertensive crisis (or cheese reaction)
ix. Desipramine ^[81]		
x. Galapentin ^[112]		
xi. Venlafaxine ^[82,83]	(1 open trial and 2 reported case studies have found venlafaxine to have anti-obsessional activity in treatment-resistant OCD)	Hypertension (at higher doses)
xii. Sumatriptan ^[84]	100 mg/day (5-HT _{1D} agonist)	
xiii. Clonidine ^[85]	Trials only in comorbid tics or Tourette's syndrome at dose of 0.2-0.5 mg/day in three divided doses.	Postural hypotension, dry mouth, irritability, and headache.

Table 3: Cognitive behavioral therapy in obsessive-compulsive disorder

	Pure obsession	Compulsion
Psychological intervention techniques ^[91,92]	Thought stopping Rubber-band technique Habituation training Distraction techniques Paradoxical intervention	ERP (prevention of the compulsive undoing behavior)

ERP - Exposure and response prevention

complicated by severe comorbid depression, suicidal ideations, and severe socio-occupational incapacitation, but it is not believed to be consistently effective for primary treatment-refractory OCD.^[98-101]

Repetitive transcranial magnetic stimulation (rTMS)

this is effective for comorbid depression but ineffective for primary treatment of refractory OCD.^[102-105]

Psychosurgery

Psychosurgery has become an intervention of last resort. One should ensure that there has been total adequacy of trials of pharmacological and, especially, psychological treatments (as defined above) prior to stereotactic surgery. It is important to balance the risk of nonintervention (physical, psychological, and social complications, including suicide) against those of surgery (frontal lobe dysfunction and psychological complications, including personality alteration, substance abuse, and suicide). There are defined criteria to select patients.^[106] such as Symptoms fulfill diagnostic criteria for OCD; Illness has lasted for more than 5 years Patient is 18-61 years old; OCD has caused substantial suffering and

had a considerable impact on psychosocial functioning. The following treatments have failed or not been well tolerated: adequate trials of all SSRIs (minimum of 3 SSRIs) and a MAOI, augmentation of at least one SSRI with two other agents (e.g., lithium, clonazepam, or buspirone, 1 month each); and in patients with comorbid tics, a low-dose antipsychotic. At least 20 h of behavior therapy using ERP; Symptomatic improvement lower than 25% in the Y-BOCS; Patient who has poor prognosis without surgery; Patient who has given informed consent and agreed to preoperative evaluation and postoperative rehabilitation

The neurosurgical procedures involve the use of radio-frequency waves to destroy a small amount of brain tissue, which disrupts a specific circuit in the brain that has been implicated in OCD. This area is the corticostriatal circuit and it is comprised of the orbitofrontal cortex, the caudate nucleus, the pallidum, the thalamus, and the anterior cingulate cortex. The procedures include cingulotomy^[107-109] subcaudate tractotomy^[110] capsulotomy^[111] limbic leucotomy (cingulotomy plus subcaudate tractotomy)^[110]

The relative disadvantages include poor executive function due to frontal lobe dysfunction, personality change, depression, suicide, and increase in substance abuse.^[106,110,112] Gamma knife capsulotomy is the most common technique used, with over 60% of patients reporting a 'very meaningful improvement in their OCD.'^[113] Although any of these procedures may be used in intractable OCD, all studies have been limited by small sample sizes and moderate effect size, and the

relative efficacy of the procedures has been reported to be between 50 and 67%.^[114]

Vagal nerve stimulation^[111] (VNS)

VNS has been tried but the results have been mixed, although VNS has been used with over 11,000 epilepsy patients in 24 countries since 1988 and has already been approved for treating people with treatment-resistant depression and bipolar disorder in Canada and Europe.

Deep brain stimulation (DBS)

DBS using electrodes placed in the internal capsule is another experimental technique.^[115] This procedure involves surgically implanting two electrical stimulators, one on each side of the brain, in areas that are involved in OCD symptoms. These two stimulators are then connected to pacemaker-like devices. The devices can be adjusted to deliver the amount of electrical stimulation necessary to help control an individual's symptoms. Researchers at Brown University's Butler Hospital have been evaluating this technique since February 2001 and are cautiously optimistic about the benefits of this treatment for those with previously untreatable disease; such patients have improved by 25-50%.^[116]

Rehabilitation in OCD

The rehabilitation of OCD patients places more emphasis on work and leisure than on other areas of adjustment such as personal and family relationships.^[117] However, there is a lot of overlap in the methods used for rehabilitation of OCD and for obsessive-compulsive personality disorder. The main objective in the rehabilitation of OCD patients is the removal of the compulsive rituals, which leaves the patient with considerable free time that needs to be filled up with recreational and other social activities. Efforts are also made to help the patient find alternative interests. The removal of an obsessional approach to the upbringing of children may similarly reveal a deficit in the more normal, flexible skills of family interaction, which the patient may need to acquire. Specific help may also be needed in overcoming the strained relationships that may have built up in the family as a result of the patient's obsessional symptoms.^[118]

Conclusion

Effective management of OCD requires a methodical approach by both clinicians and sufferers. Explicit recording of the response to each intervention is essential to avoid treatment being unnecessarily repeated or prematurely aborted. Certain subcategories of OCD require alternative strategies but, currently, we have no way of identifying which patient with a standard presentation will prove refractory to first-line treatments.

Summary of recommended course of therapy

- 1st Adequate trial of SSRI or CMI or Cognitive behavior therapy (ERP)
- 2nd Adequate trial of SSRIs plus Cognitive behavior therapy (ERP)
- 3rd Trial of 2 SSRIs plus CBT
- 4th Trial of at least 3 SSRIs plus CBT
- 5th Trial of at least 3 SSRIs (including CMI) plus CBT
- 6th Trial of at least 3 SSRIs, including CMI augmentation plus CBT
- 7th Trial of at least 3 SSRIs + CMI augmentation + CBT + psychoeducation + other medications (BZDs, mood stabilizers, antipsychotics, or psychostimulants)
- 8th At least 3 SRIs (including intravenous CMI) + CBT + psychoeducation
- 9th At least 3 SRIs (including CMI) + CBT + psychoeducation and other classes of antidepressant agents (NSRI, MAOI)
- 10th All the above treatments plus any other experimental technique (ECT, rTMS, or vagal nerve stimulation)
- 11th All above treatments and neurosurgery

Early identification of refractory OCD patients and fast-tracking them to more pharmacological and/or psychological options will be definitely helpful for refractory patients.^[119]

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