

Treating refractory obsessive-compulsive disorder: what to do when conventional treatment fails?

Tratando o transtorno obsessivo-compulsivo refratário:
o que fazer quando tratamentos convencionais falham?

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Abstract

Obsessive-compulsive disorder (OCD) is a chronic and impairing condition. A very small percentage of patients become asymptomatic after treatment. The purpose of this paper was to review the alternative therapies available for OCD when conventional treatment fails. Data were extracted from controlled clinical studies (evidence-based medicine) published on the MEDLINE and Science Citation Index/Web of Science databases between 1975 and 2012. Findings are discussed and suggest that clinicians dealing with refractory OCD patients should: 1) review intrinsic phenomenological aspects of OCD, which could lead to different interpretations and treatment choices; 2) review extrinsic phenomenological aspects of OCD, especially family accommodation, which may be a risk factor for non-response; 3) consider non-conventional pharmacological approaches; 4) consider non-conventional psychotherapeutic approaches; and 5) consider neurobiological approaches.

Keywords: refractoriness, resistance, obsessive-compulsive disorder, treatment response, risk factors, prognosis.

Resumo

O transtorno obsessivo-compulsivo (TOC) é uma doença crônica e incapacitante. Uma pequena porcentagem de pacientes se torna assintomática após o tratamento. O objetivo deste trabalho foi revisar as alternativas terapêuticas para o tratamento de TOC quando os tratamentos convencionais falham. Os dados foram extraídos de estudos clínicos controlados (medicina baseada em evidências) publicados nas bases de dados MEDLINE e Science Citation Index/Web of Science entre 1975 e de 2012. Os resultados são discutidos e sugerem as seguintes abordagens para profissionais que lidam com TOC refratário: 1) rever aspectos fenomenológicos intrínsecos ao TOC, o que pode levar a entendimentos diferenciados e à escolhas terapêuticas distintas; 2) rever aspectos fenomenológicos extrínsecos ao TOC, principalmente acomodação familiar, que pode ser fator de risco para a não resposta; 3) considerar abordagens farmacológicas não convencionais; 4) considerar abordagens psicoterapêuticas não convencionais; e 5) considerar abordagens neurobiológicas.

Descritores: refratariedade, resistência, transtorno obsessivo-compulsivo, resposta ao tratamento, fatores de risco, prognóstico.

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Introduction

Obsessive-compulsive disorder (OCD) is a chronic and impairing condition¹ with prevalence rates ranging from 0.3 to 3.1%.^{1,2} Despite the availability of several treatment approaches for OCD, full remission is quite rare.^{3,4} Previous studies have shown that almost 60% of the patients treated with selective serotonin reuptake inhibitors (SSRIs) experience a 25-35% decrease in symptoms according to the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), which is not enough to reach quality of life.⁵⁻⁷ Non-response is defined as a reduction of < 25% in Y-BOCS scores,⁸ whereas response is characterized as a 35-50% score reduction.⁹ Despite the modest percentage reduction in Y-BOCS scores considered to be indicative of treatment response, it is far higher than the response traditionally obtained with placebo (3 to 5%).¹⁰

OCD remission has been defined in the literature as improvement observed after an intervention, characterized by the absence of symptoms or a Y-BOCS score ≤ 16 .¹¹ Pallanti et al.¹² have proposed the term recovery to indicate an almost complete disappearance of symptoms, corresponding to a Y-BOCS value of ≤ 8 . Table 1 lists the different treatment response categories usually considered in OCD.

Table 1 – Treatment response categories in OCD (based on Pallanti et al.¹¹)

I) Recovery: Not at all ill; score ≤ 8 on Y-BOCS
II) Remission: Score ≤ 16 on Y-BOCS
III) Full response: $\geq 35\%$ reduction in Y-BOCS
IV) Partial response: 25-35% reduction in Y-BOCS
V) Non-response (resistant): < 25% reduction in Y-BOCS
VI) Relapse: Symptoms return (25% increase in Y-BOCS) after 3 months of "adequate" treatment/remission
VII) Refractory: No change (improvement or worsening) with any conventional therapy

OCD = obsessive-compulsive disorder; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Table 2 – Conventional treatment options available for OCD (based on Bandelow et al.⁶)

Pharmacological treatment
First line:
Escitalopram, 10-20 mg/day
Paroxetine, 40-60 mg/day
Sertraline, 50-200 mg/day
Fluvoxamine, 100-300 mg/day
Fluoxetine, 40-60 mg/day
Clomipramine, 75-300 mg/day
Second line:
Citalopram, 20-60 mg/day
Mirtazapine, 30-60 mg/day
Psychotherapy
Cognitive-behavioral therapy (exposure and response prevention)

OCD = obsessive-compulsive disorder.

"Resistant patients" were defined by Rauch & Jenike¹³ as patients who participated in trials assessing first-line therapies but did not show a satisfactory response; "refractory patients" were defined as patients who did not respond appropriately to several adequately administered conventional treatments. However, the authors do not specify how many treatments should be tested before a patient can be classified as refractory. Conventional treatment options are listed in Table 2.

The purpose of this paper was to review the therapeutic alternatives available for the treatment of OCD when conventional treatment fails. Data are discussed and organized into five subheadings.

Methods

The present paper draws on evidence from controlled clinical studies, thus adhering to the principles of evidence-based medicine. Data were collected from articles published on the MEDLINE and Science Citation Index/Web of Science databases between 1975 and June 2012. A few additional trials were retrieved by hand-searching. Open studies and case reports were also reviewed with a focus on treatment suggestions for patients not responding to conventional treatments. However, the results of these articles have to be interpreted with caution, because of their strong placebo effect and possible publication bias.

Results

Intrinsic phenomenological aspects of OCD as risk factors for refractoriness

Table 3 lists intrinsic risk factors related to the phenomenology of OCD that may influence response to conventional treatment. Most of such risk factors are described in more detail below.

Table 3 – Intrinsic phenomenological risk factors for poor response to conventional treatment of OCD

Early onset
Content of obsessive-compulsive symptoms
Hoarding
Sexual
Religious
Somatic
Overvalued ideas and poor insight
Sensorial phenomena
Higher symptom severity at onset
Presence of tics
Comorbidities
Schizotypal, borderline and paranoid personality disorders
Anankastic personality disorder

Early onset

According to some studies,^{14,15} patients with early onset OCD have a poor prognosis, with a chronic course and little response to treatment with clomipramine.¹⁴ In a community treatment group, more severe initial symptoms were associated with greater improvement during treatment.¹⁶ Otherwise, studies have failed to find relationships between early onset and treatment response.¹⁷

Hoarding

Hoarders were significantly more likely than non-hoarding patients to have severe OCD symptoms, poor insight, a high prevalence of comorbid schizotypal or obsessive-compulsive personality disorders, a close association with the symmetry dimension, and a poor treatment outcome.¹⁸

Overvalued ideas and poor insight

Overvalued ideas appear to have an important role in OCD treatment outcome. Although some reports have indicated that patients with overvalued ideas improve following intensive treatment,^{19,20} other reports suggest that treatment often fails or is not very effective,^{20,21} or yet that exposure and response prevention is not as effective as drug treatment^{19,22} in these patients. In the study by Neziroglu et al.,²³ the presence of high-intensity overvalued ideas was related to a worse response to pharmacological treatment combined with behavioral psychotherapy.

Patients with impaired or poor insight also tend to respond less effectively to pharmacological and behavioral treatment.^{24,25} Eisen et al.,²⁶ however, found no correlation between the degree of insight and response to sertraline in a multicenter study.

Comorbidities

Several studies have suggested that personality disorders are associated with greater symptom severity and poorer outcomes in OCD.²⁷⁻²⁹ A cross-sectional study aimed to compare possible differences in personality traits between responder and non-responder OCD patients found positive associations, especially for low self-directedness, with poor treatment response in obsessive-compulsive patients²⁷: patients with low self-directedness were more susceptible to engaging in responses aimed at allaying the anxiety (compulsions) rather than responses with delayed but healthier consequences (preventing compulsions).²⁷

Tics

The only predictive factor of poor therapeutic response so far confirmed in OCD is the presence of comorbid tic disorders.³⁰ The early onset of tics has also been associated with a worse prognosis.³¹

Sex

Therapeutic response has not been associated with sex in several studies on predictors of pharmacological treatment response in OCD patients.³²⁻³⁵

Extrinsic phenomenological aspects of OCD as risk factors for refractoriness

Table 4 lists some external factors that may interfere with adequate treatment outcomes in OCD patients.³⁶ Figure 1 illustrates how these factors relate to one another.

Table 4 – Extrinsic phenomenological risk factors for poor response to conventional treatment of OCD

Constitutional/individual physiological features
Family support and functioning ³⁶
Compliance with available treatments (psychiatric drugs, psychotherapies)
High costs associated with OCD treatment (psychiatric drugs, psychotherapies)
Other psychosocial barriers

OCD = obsessive-compulsive disorder.

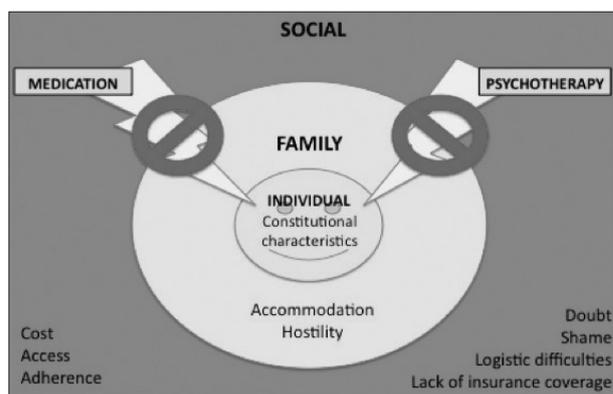


Figure 1 – External factors that may interfere with adequate treatment

Constitutional/individual physiological features

Individual characteristics such as genetic factors, age, weight, body composition, and nutritional status can modify the effects of drugs on the patient's system. Similarly, external aspects inherent to the drugs can also significantly change the intended effects, e.g., physical and chemical characteristics, pharmaceutical formulation and conditions of use (dose, acute or chronic administration and interaction with other drugs). It is particularly important to consider the induction or inhibition of hepatic enzymes resulting from drug interactions.

Family support and functioning

Family accommodation

Family accommodation is the process whereby family members of patients with OCD assist or participate in

the patients' rituals; it can be measured using the Family Accommodation Scale (FAS).^{37,38} Calvocoresi et al. reported 61% of mild or no accommodation in families of patients with OCD.³⁷ Stekette et al. reported that a high family accommodation index was associated with worse therapeutic results after behavioral therapy,³⁹ pointing to a direct relationship between symptom reinforcement and deterioration of family relations. It is therefore reasonable to expect higher family accommodation scores in families with more severe, resistant or refractory patients.

Ferrão et al. observed low family accommodation scores in the families of patients who responded to treatment vs. high scores in those of refractory patients.¹⁷ Albert et al. showed that family accommodation was common, occurring on a daily basis in most family members, with provision of reassurance (47%), participation in rituals (35%) and assisting with avoidance strategies (43%) being the most frequent practices.

Family hostility

Similarly to family accommodation, previous studies have related high rates of perceived hostility with worse therapeutic response, especially in patients receiving behavioral therapy. Stekette et al. carried out a longitudinal study and analyzed the levels of hostility in a heterogeneous group of 75 adult patients with OCD and panic disorder with agoraphobia receiving behavioral therapy.⁴⁰ After 16 weeks, perceived family hostility influenced the patients' responses to exposure treatment: those who lived in more hostile environments and who reported feelings of sadness because of perceived criticism showed higher levels of anxiety during the sessions. Other studies have also associated higher ratings of family hostility and criticism with poorer outcomes.⁴¹ In particular, Emmelkamp et al. demonstrated that paternal, but not maternal, rejection was associated with poorer outcome.⁴²

In an inpatient group, Boschen et al. found that marital status was a significant predictor of treatment outcome, with better outcomes for those who were married or lived with a partner vs. those not in a relationship. This same association was not observed in the community treatment group.¹⁶

Compliance with and cost of available treatments

Psychiatric drugs

Usually, even initial doses of psychiatric medications can cause undesirable effects such as dry mouth, constipation, sexual disorders, sleep alterations, etc. Because the doses given to OCD patients are generally high,⁴³ the probability and intensity of such effects increase. In patients who do not respond to standard

doses, one possibility is to enhance treatment effects⁴³ by combining other drugs; however, this strategy may maximize side effects and thus reduce patient compliance.

The high cost of some medications restricts access to treatment and motivates the patient to look for less expensive alternatives, which sometimes are not effective.

Psychotherapy

Similarly to psychiatric drugs, psychotherapies available for OCD (e.g., behavioral therapy) usually require a greater number of sessions and a longer treatment course.⁴³ It is therefore possible to assume that OCD treatment will often be more expensive when compared with other psychiatric disorders. Unfortunately, there are no studies on the average cost of OCD treatment in Brazil, considering either direct or indirect costs (drugs or psychotherapy vs. OCD-related loss and disability). However, OCD is among the top 10 conditions with the highest rates of morbidity,⁴⁴ so it probably accounts for significant costs to the public health system, both due to the frequent and continuous use of health care facilities and the patients' impaired work capacity. In 1990, the Epidemiological Catchment Area (ECA) program estimated that OCD-related reduction or loss of productive capacity cost to the United States, during that year, approximately \$5.9 billion dollars, or 70.4% of the total cost of OCD to the government.²

If access to psychiatric drugs is already restricted because of their high cost and low availability at public health care services, access to psychotherapies provides grounds for even greater concerns. In the case of OCD, techniques with proven efficacy⁴⁵ (cognitive-behavioral psychotherapy or only behavioral psychotherapy) are offered only at professional training centers or university hospitals/services. Attempts to extend the reach of these techniques involve group sessions focusing on the writing of treatment manuals⁴⁵ and distance treatment programs (via telephone or internet).⁴⁶ The efficacy of distance programs still has to be demonstrated, whereas group sessions have reported good response rates⁴⁵. However, there are no data available on group cognitive-behavioral therapy offered to resistant or refractory OCD patients.

Other psychosocial barriers

According to our review, most patients with OCD were not in contact with a mental health professional, and apparently very few were receiving appropriate treatment, namely, SSRIs and cognitive-behavioral therapy. On an internet survey, the majority of patients who sought psychotherapeutic treatment received "talk

therapy.⁴⁷ In another study, only 5% of OCD patients were receiving cognitive-behavioral therapy, 2% were taking SSRIs, and 10% were taking tricyclic antidepressants.⁴⁸ Logistic difficulties, lack of insurance coverage, shame, and disbelief in treatment effectiveness were the barriers to treatment most commonly endorsed.⁴⁷

Pharmacological approaches to refractory OCD

The alternative therapies available to patients not responding to conventional treatment include higher doses of standard therapy, intravenous monotherapy, drug combination/augmentation, and other biological interventions, e.g., the use of fatty acids.

Higher doses of standard therapy

This strategy appears in some algorithms for the treatment of refractory OCD, however it should be considered with caution, carefully balancing the risks and benefits involved.³⁶ Success with doses greater than those recommended in the summary of product characteristics has been shown in some treatment-refractory patients, e.g., sertraline at 250 to 400 mg daily.⁴⁹ Obsessive but not compulsive symptoms also responded faster to high-dose sertraline (200 mg daily). Finally, higher doses of SSRIs were well tolerated and produced similar rates of adverse effects when compared with standard doses, although the severity of such adverse effects may have been higher. Pampaloni et al. described that refractory patients on high-dose treatment showed significant intragroup improvements, although the Y-BOCS scores of the high-dose group remained significantly higher than those of control patients treated for the same period. No differences were found between cases and controls regarding adverse effects, although sample size was small and the findings limited by the retrospective study design.⁵⁰

Intravenous monotherapy: clomipramine and citalopram

There is limited evidence⁵¹ suggesting benefits of the use of intravenous clomipramine in reducing OCD symptoms as assessed by Y-BOCS.⁵² Some anecdotal cases suggest that pulse intravenous clomipramine may produce a decrease of obsessive-compulsive symptoms in patients who did not respond to or did not tolerate clomipramine taken orally.⁵³ However, use of this therapy is limited because of the close medical supervision and cardiac monitoring required during administration.⁵⁴ Citalopram has also demonstrated efficacy in open trials in patients resistant to conventional treatment.⁵⁵ Nevertheless, such intravenous alternatives are not available in most countries.

Serotonin-norepinephrine reuptake inhibitors (SNRI)

Several case reports have suggested that venlafaxine and duloxetine may be beneficial when used as anti-obsessive agents. However, there are no randomized clinical trials (RCTs) confirming this finding.⁵⁶⁻⁵⁹

Psilocybin

Psilocybin is the main psychoactive component found in mushrooms of the genus *Psilocybe*, more commonly known as “magic mushrooms.” Psilocybin acts as an agonist of 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C}. Moreno et al. conducted a small proof-of-concept study (Phase I) with nine refractory OCD patients who showed improvement of symptoms.⁶⁰ Unfortunately, this study has not been replicated.

Combining drugs to enhance the efficacy of SSRIs

Due to the multifactorial, heterogeneous etiology of OCD, a common strategy has been to combine other drugs with SSRIs so as to activate other neurotransmitters (such as glutamate and dopamine). The combined use of two SSRIs has also been reported.³⁶

The drugs most frequently combined with SSRIs are described below.

Trazodone

Trazodone is an atypical antidepressant with potent antagonist action on 5-HT₂/1C receptors. Some case reports have described a significant and rapid improvement in symptoms after the introduction of trazodone associated with an SSRI. However, two clinical trials failed to confirm this finding.^{61,62} Despite the growing positive evidence in the literature, adequate RCTs are still needed to better define the role of trazodone in the treatment of OCD.⁵²

SNRIs

The association between citalopram and reboxetine produced a favorable response in one case report.⁵⁹ However, no RCT has so far tested this combination.

Antipsychotics

A recent meta-analysis conducted by Bloch et al.⁶³ concluded that adjuvant treatment with antipsychotics may be useful in cases of refractory OCD patients. The benefits were most evident with the use of risperidone.⁶⁴⁻⁶⁶ Haloperidol and pimozide were effective adjuvants in patients with comorbidities such as tics or trichotillomania,⁶⁷ and open-label trials have described a relative effectiveness of olanzapine in combination to SSRIs⁶³⁻⁶⁸. This result was confirmed in two RCTs,⁶⁸ suggesting a promising role of these drugs in patients

refractory to monotherapy with SSRIs.⁶⁵ Other studies, however, have shown conflicting results on the real benefit of olanzapine.⁶⁶

Placebo-controlled RCTs have also shown significant improvement in Y-BOCS scores in refractory patients receiving quetiapine.^{69,70} In the largest of these trials (n = 66), quetiapine proved to be significantly superior to placebo, but was associated with a higher rate of treatment discontinuation due to adverse effects. A meta-analysis has also suggested that quetiapine may be effective in combination with SSRIs.⁷¹ However, two open clinical trials showed no efficacy of quetiapine as an adjunctive therapy, and a double-blind, placebo-controlled study showed that quetiapine as an adjunctive therapy was not more effective than placebo.⁷² Finally, one study showed reduction in Y-BOCS scores and improvement of obsessive-compulsive symptoms with the combined use of amisulpride and an SSRI.⁶⁷

Ziprasidone is an atypical antipsychotic and a potent 5-HT_{1A} receptor agonist, inhibiting the reuptake of serotonin and norepinephrine, which could make this drug more effective than other antipsychotics as an adjuvant treatment in refractory OCD. However, the only comparative study so far conducted has suggested it to be less effective than quetiapine in this population.⁷³

Benzodiazepines

One study compared the use of clonazepam versus placebo in patients treated with clomipramine or fluoxetine and suggested no benefits of this association.⁷² Otherwise, many reports suggest the efficacy of this benzodiazepine when used both alone and as an adjuvant. Negative results have also been reported.⁶⁵ There are case reports showing benefits with alprazolam augmentation, but the existing data are not enough to recommend the regular use of this drug in the treatment of refractory OCD.⁷⁴

Opioids

A randomized double-blind study administered oral morphine (once weekly) and lorazepam to 23 patients with refractory OCD, 17 of whom were receiving other medications at the time of the study (SSRIs, benzodiazepines, antipsychotics, gabapentin, clomipramine, bupropion, topiramate, and trazodone). The result was a rapid but transient improvement of symptoms in some patients, confirming previous findings of case reports and open studies that suggested a role of *mu* receptors in the treatment of refractory OCD.⁷⁵

Glutamate-modulating drugs

Memantine is an uncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors that has

yielded conflicting results in refractory OCD.^{76,77} Riluzole is an anti-glutamatergic drug used for neuroprotection in patients with amyotrophic lateral sclerosis. An open study used this drug as an adjuvant to SSRI in 13 OCD patients for 8 weeks. Seven (59%) of the 13 patients showed a $\geq 35\%$ reduction in Y-BOCS scores, and five (39%) were considered responders. Despite the small sample size and absence of a control group, this preliminary study is the first to suggest the involvement of glutamatergic dysfunction in the pathophysiology of OCD.⁷⁸

Other drugs

The drugs listed below have shown no evidence of efficacy in treating refractory OCD, but have been used in isolated case reports. Although these drugs may be considered as options in particular cases, extreme caution is recommended in their use.

- Carbamazepine, oxcarbazepine, divalproate, lamotrigine, topiramate: a double-blind study has suggested that topiramate may be useful for compulsions, but not for obsessions, when associated with an SSRI.⁷⁹
- Inositol,⁸⁰ pindolol: these drugs seem to benefit partial responders,⁶⁵ but more studies are required to test their use.
- Lithium: the only RCT so far conducted failed to show significant results when compared with placebo as an augmenting agent.⁶⁵
- Thyroid hormone, clonidine, ondansetron (an antiemetic that blocks 5-HT₄ and 5-HT₃ receptors): when prescribed in combination with SSRIs, these drugs showed positive effects on obsessive-compulsive symptoms after 2 weeks of treatment.⁸¹

Psychotherapeutic approaches to refractory OCD

There are limited reports on the use of cognitive-behavioral techniques, such as exposure and response prevention and cognitive therapy, in patients with severe or refractory OCD, especially because of the increased anxiety associated with exposure during treatment sessions.⁴⁷ In fact, about 30% of the patients refuse this type of therapy.⁸² In addition, many patients do not adhere to the exercises or abandon treatment, especially those with pure or overvalued obsessions.⁸³ Another limitation of these techniques is that some patients may resist performing rituals during the session, but will either compensate for them later, at home, or perform them mentally, not to be noted by the therapist.⁴⁷

Some authors have suggested cognitive techniques as an alternative treatment for patients resistant to exposure and response prevention. The following

strategies are frequently used : discussion of automatic and intrusive thoughts, fear, and dysfunctional schemas; modification of unrealistic interpretations⁸⁴; and discussion of magical thinking and thought-action fusion. Explaining the purpose of rituals and Socratic questioning are also important^{83,85} and may benefit patients with obsessive thoughts even in the absence of compulsive behavior.⁸⁴ Analysis of patients' beliefs and rules can motivate them for treatment. This method used as the only therapy still lacks confirmatory studies,⁸⁶ and the evidence suggesting that dysfunctional beliefs of OCD sufferers are different from those present in other disorders is still inconclusive.⁸²

Alternative psychotherapeutic treatments have been studied in patients refractory to conventional cognitive-behavioral therapy. Family-based therapies, for example, have been studied in children, with good results.⁸⁷

Some authors have advocated the advantages of involving both patients and family groups in therapy sessions. One study evaluated a cognitive-behavioral therapy group comprised of family members and patients who had started conventional individual treatment. The families discussed the impact of symptoms on family planning and coping strategies, while the patients performed behavioral tasks in the group.⁸⁸

Recently, studies have emphasized the importance of psychoeducational techniques for family support groups. Sessions should provide information regarding diagnosis, evaluation, OCD theories, behavioral techniques, medications, and relapse prevention.³⁸

Thorncroft et al.⁸⁹ described the results obtained in a group of patients treated with behavioral therapy, exposure and response prevention, self-control strategies, and social skills training. The family component was to reduce parental involvement in rituals, training them to monitor patients and encourage them to expose themselves, however without criticizing them. Family approaches have been shown to be superior to conventional treatments not using this approach. Strategies should include information on biological, psychological, and social strategies for dealing with OCD behaviors³⁸ in order to reduce family accommodation and improve expressed emotions.⁹⁰

Other approaches for refractory patients include in-hospital treatment⁹¹ and intensive cognitive-behavioral therapy.⁸⁹ In-hospital treatment has some limitations because it requires trained nurses, nursing assistants, psychiatrists, and therapists. In addition, the number of specialized hospitals is low.⁹¹ Intensive cognitive-behavioral treatment is conducted for a shorter period, with more frequent and longer-lasting sessions. Studies including adults and children have demonstrated efficacy of this treatment.⁸⁹ Conversely, no clinical effects on

obsessive-compulsive and depressive symptoms were observed after brief dynamic therapy in OCD patients with comorbid depression.⁹²

D-cycloserine augmentation of habituation and exposure therapy has been tested in patients with OCD⁴⁷ and proved effective for other anxiety disorders.⁹³ The potential effectiveness of D-cycloserine is based on the theory that NMDA plays a primary role in neural processes, associations, and in the extinction of learned fear – all principles of exposure therapy.^{94,95} Habituation is the spontaneous disappearance of fear or discomfort reactions as the individual repeatedly comes into contact with objects or situations that provoke such reactions but are not actually dangerous.⁸² The use of D-cycloserine would facilitate this learning process and thus improve therapeutic response.⁴⁷ The efficacy of this agent in patients with resistant or refractory OCD has been little studied. Two studies have suggested a faster response to behavioral therapy with exposure and response prevention in patients receiving D-cycloserine when compared to a placebo group.^{96,97} Other studies, however, found no differences between these groups in either adults⁹³ or children.⁹⁵

Neurobiological approaches

The principle underlying the use of neurobiological procedures in OCD is the selective division of brain areas that interconnect the hyperactive cortical-striatal-thalamic-cortical circuit. Among several neuroanatomical methods currently available, repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (TDCS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS) deserve special mention, in addition to the well-known neurosurgical techniques.^{98,99}

Electroconvulsive therapy (ECT)

There are only case reports describing the use of ECT in OCD patients. A recent review of 32 cases of refractory OCD patients reported that most subjects showed considerable improvement in obsessive-compulsive symptoms and remained improved up to 1 year after therapy. Treatment response remained significant even after controlling for depressive symptoms, pointing to the need for further investigation regarding the use of ECT in OCD.¹⁰⁰

Repetitive transcranial magnetic stimulation (rTMS)

Since 1997, a total of 110 OCD patients have been treated with rTMS in published trials.¹⁰¹ Greenberg et al.¹⁰² found that a single session of high-frequency rTMS to the right lateral prefrontal cortex significantly decreased

compulsive urges. Conversely, a double-blind study using right prefrontal low-frequency rTMS failed to find significant effects.¹⁰³ An open study involving refractory OCD patients assigned to right or left dorsolateral prefrontal cortex stimulation with high-frequency rTMS found clinically significant and sustained improvement in a third of the patients.¹⁰⁴ In another recent study, neither low- nor high-frequency rTMS to the left dorsolateral prefrontal cortex produced significant effects when compared with placebo.^{104,105}

A recent neuroimaging study suggested that premotor areas such as the supplementary motor area are hyperactive in OCD, and that this hyperactivity may result in deficient inhibitory control.¹⁰⁶ The most recent randomized sham-controlled double-blind study of rTMS in OCD assigned 21 medication-resistant OCD patients to 4 weeks of active or sham rTMS bilaterally to the supplementary motor area.¹⁰⁷ The response rate among completers was 67% (6/9) for active and 22% (2/9) for sham rTMS. At 4 weeks, patients receiving active rTMS showed on average a 25% reduction in Y-BOCS scores, compared with a 12% reduction in those receiving sham. These results support further investigation into the potential therapeutic applications of rTMS in this disabling condition.

Deep brain stimulation (DBS)

The first experiment describing the use of DBS in OCD was carried out in Stockholm in 1998 at the Karolinska Hospital. Based on published trials and case studies, it is estimated that more than 100 individuals have received experimental DBS treatment for OCD.¹⁰⁸ DBS is a neurosurgical treatment involving the implantation of electrodes that send electrical impulses to specific brain locations, selected according to the type of symptoms to be addressed.¹⁰⁸

Several techniques and brain targets are described in the literature for DBS. The choice of the anterior limb of internal capsule (ALIC) as a brain target was based on previous experience with anterior capsulotomy for refractory OCD. This neurosurgical procedure had shown positive results in approximately 50% of participants.^{109,110}

Some structures adjacent to the internal capsule have also been targeted for DBS, including the ventral striatum, comprised of a ventral caudate nucleus and a nucleus accumbens and thought to be associated with reward and motivation mechanisms. Combined with the ventral capsule, this area is referred to as the ventral capsule/ventral striatum region. This brain target was chosen based on positive results previously obtained following gamma knife capsulotomy at the ventral region of the ALIC for refractory OCD.¹¹¹ The subthalamic nucleus and the inferior thalamic peduncle have also

been described as possible targets.¹⁰⁸

Notwithstanding, the mechanism of action of DBS in OCD remains unclear. Functional imaging studies of DBS applied to ALIC¹¹² and the subthalamic nucleus¹¹³ have shown normal activity of the orbitofrontal cortex (OFC), suggesting a final common cortical-striatal pathway. Conversely, current data suggest no decline or improvement of cognitive function caused by DBS¹⁰⁸. Serious procedure-related events are rare, and side effects can be reversed by cessation or adjustment of stimulation parameters. In sum, DBS is a promising and apparently safe therapy for patients with treatment-refractory OCD, but further investigation is still needed.

Neurosurgical treatments

The rates of global improvement after different neurosurgical techniques are quite variable: capsulotomy, 56 to 100%; cingulotomy, 27 to 57%; subcaudate tractotomy, 33 to 67%; limbic leucotomy, 61 to 69%; and thalamotomy/pallidotomy, 62.5%.³⁶ Radiosurgery has the advantages of not requiring cranial opening and having a zero risk of hemorrhage and infection, with efficacy rates ranging from 37.5 and 70%.^{110,111}

The adverse events and complications associated with neurosurgical treatments of OCD vary according to surgical technique (lesion site). The most prevalent adverse effects are isolated cases of seizures, delirium immediately after surgery, hypomania, and, rarely, hemorrhage and neuroinfection.¹¹¹ In radiosurgery, the most frequent side effects are headache episodes. Neuropsychological alterations are rare; when present, they usually manifest as apathy, mental slowness, irritability, aggressiveness, and lack of behavioral inhibition. These complications, however, are more common with the old techniques (especially limbic leucotomy and subcaudate tractotomy).¹¹¹

Vagus nerve stimulation (VNS)

Vagus nerve stimulation (VNS) is an effective anticonvulsant technique and has shown antidepressant effects in chronic treatment-resistant depression.¹¹⁴ Out of seven adult outpatients with treatment-resistant OCD who received stimulation, three (43%) were acute responders based on Y-BOCS scores, and there was some improvement in Y-BOCS scores over time.¹¹⁴ Further studies are warranted to assess the role of VNS in refractory OCD.

Conclusion

There have been significant advances in the pharmacotherapy of OCD over the last decades, but

further work remains to be done. Extensive evidence exists to support the efficacy of clomipramine and SSRIs in the treatment of OCD. Antipsychotic augmentation is recommended, but is effective and well tolerated only in some patients. Cognitive-behavioral therapy is another key development, but access to well-trained practitioners remains a problem in many countries. Finally, there have been significant advances in uncovering the neurobiology of OCD, and ongoing work may ultimately translate into novel approaches, e.g., deep brain stimulation or magnetic transcranial stimulation for the treatment of OCD. This review suggest that clinicians dealing with refractory OCD patients should: 1) review intrinsic phenomenological aspects of OCD, which could lead to different interpretations and thus to the selection of different therapeutic approaches; 2) review extrinsic phenomenological aspects of OCD, especially family accommodation, which may be a risk factor for non-response; 3) consider non-conventional pharmacological approaches; 4) consider non-conventional psychotherapeutic approaches; and 5) consider neurobiological approaches.

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