

# Resistance and refractoriness in obsessive-compulsive disorder

## Resistência e refratariedade no transtorno obsessivo-compulsivo

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### Abstract

**Objective and Method:** Despite the existence of effective therapeutic alternatives for obsessive-compulsive disorder, a significant number of patients does not achieve or does not maintain remission after adequate treatment. The relief of these patients' suffering with the available treatments is a clinical challenge related to many unanswered questions. The objective of this literature review is to evaluate the current concepts of treatment resistance and refractoriness, to describe the intrinsic and extrinsic factors of obsessive-compulsive disorder's phenomenology that might influence treatment response to conventional treatment, and to present a flowchart of therapeutic alternatives for resistant or refractory obsessive-compulsive disorder patients. **Conclusion:** The literature demonstrates that intrinsic and/or extrinsic phenomenological aspects of obsessive-compulsive disorder may collaborate to the fact that, at least 30% of obsessive-compulsive disorder patients do not respond to conventional treatment. Several therapeutic or augmentation alternatives, psychopharmacological, biological or even psychotherapeutic alternatives exist, but more studies are necessary to evince the correct way to symptom remission.

**Descriptors:** Obsessive-compulsive disorder; Combined modality therapy; Biological psychiatry; Psychopharmacology; Behavior therapy

### Resumo

**Objetivo e Método:** Apesar de existirem terapêuticas eficazes para o tratamento do transtorno obsessivo-compulsivo, uma parcela significativa dos pacientes acometidos por tal condição não alcança ou não mantém a remissão dos sintomas mesmo com tratamento adequado. O alívio do sofrimento destes pacientes com os tratamentos existentes representa um desafio para o clínico, que, nestas situações, se vê, freqüentemente, sem respostas satisfatórias. O objetivo desta revisão da literatura é avaliar os conceitos e critérios de resistência e refratariedade ao tratamento, abordar os aspectos intrínsecos e extrínsecos à fenomenologia descritiva do transtorno obsessivo-compulsivo que possam influenciar a resposta aos tratamentos convencionais preconizados, e propor um fluxo de alternativas terapêuticas para casos resistentes e refratários às diversas abordagens. **Conclusão:** A literatura evidencia que tanto aspectos intrínsecos à fenomenologia do transtorno obsessivo-compulsivo, quanto aspectos extrínsecos podem colaborar para que pelo menos 30% dos pacientes não obtenham o resultado desejado. Várias alternativas de tratamento e/ou de potencialização, sejam psicofarmacológicas, biológicas ou psicoterápicas, estão disponíveis, mas vários estudos ainda são necessários para que as evidências apontem na direção mais adequada para a remissão dos sintomas.

**Descritores:** Transtorno obsessivo-compulsivo; Terapia combinada; Psiquiatria biológica; Psicofarmacologia; Terapia comportamental

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## Introduction

The obsessive-compulsive disorder (OCD) includes symptoms that represent several psychopathological domains. These symptoms involve perceptions, cognitions (obsessions), emotions, difficulties in social relationships and several motor behaviors (compulsions).<sup>1</sup> Obsessions are characterized by ideas, thoughts, drives or intrusive and inadequate images that cause great anxiety or suffering. Compulsions, in turn, are repetitive behaviors or mental acts whose objective is to prevent or reduce anxiety and suffering (instead of providing pleasure or reward, as it is the case of the impulsive behaviors). Compulsions are usually excessive or not realistically related to what they try to neutralize or avoid.<sup>1</sup> The contents of the obsessions may vary, but obsessions with contamination, doubts, and order, aggressive or horrifying impulses, and sexual images are common. In terms of compulsions, those related to washing and cleaning, checking, counting, collecting and symmetry, among others, are common.<sup>1</sup> Prevalence in the general population has revealed rates of approximately 0.3 to 3.1%.<sup>2</sup>

Although there are efficient treatments for OCD, it is estimated that about 40 to 60% of the OCD patients do not reach satisfactory relief of their symptoms with the appropriate treatment.<sup>3</sup> To make these patients get suffering relief with the existing treatments is a challenge for the clinical psychiatrist.

The objective of this review is to assess the concepts and criteria of OCD resistance and refractoriness, approaching the internal or external aspects of the descriptive OCD phenomenology that may influence the response to the approved conventional treatments, and propose a flow of therapeutic alternatives for the resistant and refractory cases.

## Resistance and refractoriness

It is difficult to define the criteria for OCD resistance or refractoriness. Some studies have defined them based only on the bad response to just one single antidepressive drug. Although conducted in a correct and appropriate manner, these studies did not assess the possibility of response to other treatments, even pharmacological or psychotherapeutic alternative treatments.<sup>4</sup>

Rauch and Jenike, in 1994, established the difference between "resistant" and "refractory" patients. They defined as "resistant" those who participate in a trial with any first-line therapy and do not have a satisfactory response, while the "refractory" patients are those who do not respond appropriately to several treatments administered in an adequate manner.<sup>5</sup>

The causes of inefficiency of an adequate treatment can be related to the fact that the etiology of OCD is multifactorial.<sup>6</sup> Therefore, a treatment can be efficient for OCD related to a specific etiologic factor, but show no effect on another etiologic factor. With the purpose of assessing this possibility, some authors tried to relate the clinical (assuming that these characteristics can be related to the etiologic factors), neurobiological and genetic characteristics to the treatment. Thus, if the clinical heterogeneity of OCD really reflects pathophysiological heterogeneity, then certain clinical characteristics can predict which treatments could be more recommended for each case.

However, it is probable that the most common causes of lack of response to the treatment are not the inefficiency of drugs or the psychotherapeutic method. Some of these causes are: use of drugs that are not the first choice for the OCD treatment; administration of insufficient doses; or use for a short period

**Table 1 – Internal factors to the OCD phenomenology that predict response to the conventional treatments**

Internal factor
<b>Early onset</b> <sup>14,17</sup>
<b>Content of obsessive-compulsive symptoms</b>
- Hoarding <sup>18,19,21</sup>
- Sexual <sup>19,22,23</sup>
- Religious <sup>19,22,23</sup>
- Symptomatic <sup>17,24</sup>
<b>Sensorial phenomenon</b> <sup>14,25</sup>
<b>Higher severity in the symptoms onset</b> <sup>23</sup>
<b>Poor critical reasoning</b> <sup>24,27</sup>
<b>Presence of tics</b> <sup>29,30</sup>
<b>Comorbidities</b>
- Schizotypal, borderline and paranoid personality disorders <sup>30-32</sup>
- Anancastic personality disorder <sup>7</sup>

of time. In addition, some biological characteristics that may change the pharmacokinetics of the drugs used can affect their efficacy.<sup>7</sup> Regarding the psychotherapeutic strategies, the therapists' training and the patients' motivation to take part in the treatment can be crucial for the therapeutic response. Also, with respect to the developing countries, it seems that the difficulties to receive appropriate treatment may contribute to the existence of untreated patients or patients inadequately treated.

## Factors related to the resistance and refractoriness to the conventional treatment

### 1. OCD internal factors

The predictors of inadequate response to the conventional treatment that have been found in scientific studies are listed in Table 1.<sup>3,6,8-20</sup> Although some of these factors have been found in several studies as absent response factors, the causal relation between some of them and the resistance to the treatment has not been established yet.

There are factors that can possibly have an influence on the response to the treatment, but there have not been demonstrated based on scientific studies, such as chronic course of the disease, diagnosis of major depression and family history of OCD.

### 2. OCD external factors

Among the OCD external factors that can interfere with adequate treatment, we can mention family support and functioning, with their effects on the maintenance of obsessive-compulsive symptoms.<sup>13</sup> In addition, it is necessary to consider the constitutional characteristics of each individual, such as the absorption capacity and the time taken to metabolize the drug, and other factors that involve the patient's adherence to the treatment. Finally, the influence of the elevated costs associated with the therapeutic methods prescribed for OCD cannot be underestimated. All these factors are discussed in more detail next.

#### 1) OCD patients' family support and functioning

The participation of relatives in the symptoms (such as, for example, the mother that washes the door handle because her son with OCD thinks that it is contaminated; the husband that checks if the door is locked because his wife with OCD is already in bed; the mother who takes her daughter with somatic obsession to see several doctors to check if she is sick, etc.) can be called family accommodation. When the relative takes part in the symptom in a direct manner, providing the patient with the appropriate situation to perform the compulsion, he/

she is reinforcing the patient's symptom without realizing it. In an original study, Calvocoresi et al. found 61% of the families of patients with OCD showing mild or absent family accommodation.<sup>21</sup> Stেকেtte et al. reported that the high scores of family accommodation index (FAI) were associated with the worst therapeutic results of behavioral therapy.<sup>22</sup> This relation can point out to a direct reinforcement of the symptoms or the level of deterioration of family relations due to the disease, therefore, it is reasonable to expect that the FAI is higher in families with more severe, resistant or refractory patients.

Ferrão et al. observed that the FAI of the families of patients who responded to the treatment was low, while in the families of refractory patients this index was high.<sup>13</sup> The study mentioned above, however, allows for discussions on the reverse causality: on one hand, the condition of resistance/refractoriness, due to its chronicity and severity, eventually makes the patients and relatives to feel "tired", making them more "accommodated" to this condition; or, on the other hand, the family accommodation is, indeed, a factor that makes it difficult to have an adequate response to the OCD treatment.

Another factor that can be related to the family functioning aspects is the level of hostility noticed by the patient regarding how his/her relatives deal with his/her feelings. Similarly to the family accommodation, previous studies have related high rates of hostility noticed with worse therapeutic performance, especially regarding the behavioral therapy. Stেকেtee et al. carried out a longitudinal study and analyzed the levels of hostility in a heterogeneous group of 75 adult patients (mean age: 35.8 years old) with diagnosis of OCD and panic disorder with agoraphobia who underwent behavioral therapy.<sup>23</sup> After 16 weeks, they found that the perception of family hostility by the patients influenced the responses to the exposure treatment, and those patients who lived in environments with higher hostility and who reported feelings of sadness because of the high level of criticism presented higher levels of anxiety during the sessions.

## 2) Constitutional characteristics

Each individual presents his/her own characteristics regarding the absorption of psychiatric drugs. It depends on drug administration route; biological membranes capacity to diffuse drugs; bioavailability (drug portion that enters blood circulation); distribution; degree of perfusion of the target organs; interaction with plasma proteins; passage through the blood-brain barrier; metabolic efficiency; and rate of drug clearance.

In addition, other characteristics of the individual can change the psychiatric drug effect, such as genetic factors, age, weight, body composition and nutritional status, among others. Similarly, external aspects that depend on the psychiatric drugs, such as physical and chemical characteristics, pharmaceutical formulation and conditions of use (dose, acute or chronic administration and interaction with other drugs), can significantly change the intended effect of the drug that is being used. As the clinical practice demonstrates, a large portion of the patients do not use only one drug during treatment, which leads us to consider the induction or inhibition of hepatic enzymes caused by these drug interactions.

## 3) Adherence to the available treatments

Adequate adherence to the treatments can be a cause of nonresponsivity. Usually even initial doses of drugs can provide undesirable effects such as dry mouth, constipation, sexual disorder, sleep alterations, etc. Since the doses given to OCD patients are generally higher,<sup>24</sup> the probability and the intensity of such effects increase. In those patients who do not respond to the usual doses, the alternative option is

the attempt to enhance the effect<sup>24</sup> through drug association, which also results in a probable increase in the side effects that can reduce the patient's adherence to the treatment.

Similarly to the psychiatric drugs, the psychotherapies for OCD (such as behavioral therapy) usually recommend greater number of sessions and longer treatment.<sup>24</sup> Therefore, it is possible to assume that the treatment of OCD patients is often more expensive if compared to the treatment of other psychiatric disorders.

Unfortunately, there are not studies presenting the average cost of the treatment of OCD patients in Brazil, either considering the costs directly (drugs or psychotherapy) or indirectly (losses and disabilities caused by the disease) related to the treatment. Since it is one of the top ten diseases with the highest rates of morbidity,<sup>25</sup> OCD can be responsible for significant financial expenses for the public health systems due to the frequent and continuous use of these resources by patients who, in addition, have an impaired work capacity. In 1990, the Epidemiological Catchment Area (ECA) estimated that the OCD patients' reduction or loss of the productive capacity cost to the United States, during that year, approximately \$5.9 billion dollars or 70.4% of the total cost that OCD caused to the government.<sup>2</sup>

## 4) Cost of conventional treatments

### i) Psychiatric drugs

The cost of some medications do not allow that a large portion of the population with OCD acquire the drugs continuously, leading the patient to look for less expensive alternatives, which sometimes are not effective.

Therefore, the national governmental agencies have policies regarding free drug supply for the population, and each Brazilian State has its own policy of drug standardization. However, the lists of standardization not always benefit OCD patients. For example, in Rio Grande do Sul there are not any anti-obsessive drug included in the standardized list of basic drugs (Resolution 226/05 of the State Health Department) or in the list of special drugs (Decree 238/2006 of the State Health Department); except for fluoxetine and sertraline, which have been included by means of an administrative process. In the State of São Paulo, the Health Department provides fluoxetine, sertraline and clomipramine as part of the Mental Health Program.

### ii) Psychotherapy

If the access to the psychiatric drugs is restricted because of the cost and the availability provided by the public services, the access to psychotherapies is a reason for even greater concern. In the case of OCD, the techniques of proven efficacy<sup>26</sup> (behavioral-cognitive psychotherapy or only behavioral psychotherapy) are limited to centers of professional training and university hospitals and services.

Attempts to socialize the psychotherapeutic techniques involve group sessions resulting in the design of treatment manuals<sup>26</sup> and distance care programs (telephone or Internet).<sup>27</sup> Although several studies are still necessary to demonstrate the efficacy of distance programs, group sessions have presented good response rates. However, there are not data available on group behavioral-cognitive therapy for OCD patients who are resistant or refractory to treatment.

### Maintenance of the therapeutic response and treatment alternatives

Despite the adherence to the treatment, relapses are common in long-term studies with OCD patients.<sup>28</sup> One of the best manners to avoid relapses is the total remission of the symptoms.<sup>28</sup> Nevertheless, only for a small number of OCD patients response to the treatment means the same as permanent remission of symptoms. Even though the clinical trials consider a response rate of about 50% of patients, depending on the criteria used, this rate can drop to only 30%.<sup>28</sup> In addition, even more strict response criteria (such as reduction of the YBOCS score to  $\geq 35\%$  and improved or much improved response in the global clinical assessment scale in an analysis including all the patients who had intention to treat) cannot assure that the patient has few symptoms when he/she meets these criteria. That is, some patients who are considered as responders in clinical trials can remain very symptomatic and may need complementary intervention. In addition, the inclusion criteria of the clinical trials are usually limited and do not include a large portion of the patients.

### Psychotherapeutic alternatives

Some techniques of behavioral therapy and cognitive therapy are part of most of the psychotherapeutic protocols that have been tested in OCD patients. The technique showing the best evidence of efficacy is exposure and response prevention (ERP), performed in individual or group therapy sessions.<sup>26,28,29</sup> However, this technique is not available to some patients with very severe symptoms because it requires exposure to high levels of anxiety and attendance of frequent therapy sessions. According to Cordioli et al., 30% of the patients refuse ERP.<sup>30</sup> In addition, there are manners to “deceive” the exposure, for example, when the patient transforms a motor behavior into a mental ritual (which is not noticed by the therapist), or when he/she does not perform the rituals in the session, but “counterbalances” later by performing more rituals. The patients' characteristics that tend to show the worst response to ERP include lower age of OCD symptoms onset,<sup>31</sup> higher initial severity,<sup>32</sup> longer disease period<sup>32</sup> and higher intensity of the overvalued ideas.<sup>14</sup> In its turn, the maintenance of the long-term response obtained with the ERP procedure is associated with fast response to the treatment,<sup>32</sup> higher intensity of the improvement<sup>3</sup> and total remission of the symptoms.<sup>28,29</sup>

Some authors suggest the cognitive techniques as an alternative treatment for the patients resistant to ERP. The central intervention of the cognitive techniques includes questioning the dysfunctional thoughts with the purpose of changing the exaggerated interpretations regarding the risks present in the OCD.<sup>33</sup> There was not a significant difference of the efficacy between the cognitive techniques and ERP in comparative studies.<sup>33</sup> Therefore, the advantage of the cognitive techniques is that they can be accepted by the patients who refuse ERP.

Some of the alternatives that represent a chance of higher efficacy than the conventional treatment for severe patients who are resistant or refractory to the treatment are: in-hospital treatment,<sup>34</sup> intensive home therapy (IHT)<sup>35</sup> and the inclusion of the family approach in the treatment protocols.<sup>36</sup>

The in-hospital treatment presents some limitations due to the fact that it requires a team of trained nurses and assistants, in addition to psychiatrists and therapists. Therefore, probably the most important obstacle for this type of treatment is the difficulty of being admitted to a specialized hospital ward. As mentioned above, family behavior factors seem to have an

influence on the treatment. Attempts of intervention with the purpose of decreasing the levels of family accommodation and improve the levels of expressed emotion have been tested in OCD patients and their relatives. The results of these interventions were higher than those of the conventional treatment without approaching the relatives of patients considered as refractory to several types of treatment,<sup>22</sup> and they were replicated in the treatment of children with OCD and their relatives.<sup>36</sup> A promising aspect about the approach of relatives during treatment is that the changes obtained seem to remain for long periods.<sup>22</sup> However, a standard protocol of family intervention has not been designed yet. Most of the studies included psychoeducational techniques and training in ERP techniques with patients and relatives. Before prescribing more invasive treatments for resistant and refractory patients, attempts should be made to involve the relatives who have a close relationship with the patient in the treatment.

#### 1) Enhancers of the response to behavioral therapy

An alternative method that has been tested in OCD patients and that has already been proven efficient for other anxiety disorders<sup>37</sup> is the use of the D-cycloserine agent as an enhancer of the habituation caused by ERP. Recent studies involving animals suggest that the D-cycloserine, a partial agonist of the N-methyl-D-aspartic acid (NMDA) type glutamatergic receptor, can increase the extinction learning (which is compatible with the concept of habituation in human beings).<sup>38</sup> The habituation is the process experienced during ERP that make the anxiety symptoms absent when there are neutral stimuli. The use of D-cycloserine would facilitate this learning process and, therefore, would improve the therapeutic response. However, the efficacy of this agent for OCD patients resistant or refractory to the treatment has not been sufficiently studied. A preliminary study suggested a faster response to the behavioral therapy with the use of ERP in patients who received D-cycloserine if compared to those who took placebo (Wilhems, personal communication), while another study did not find any differences between these groups of patients.<sup>38</sup>

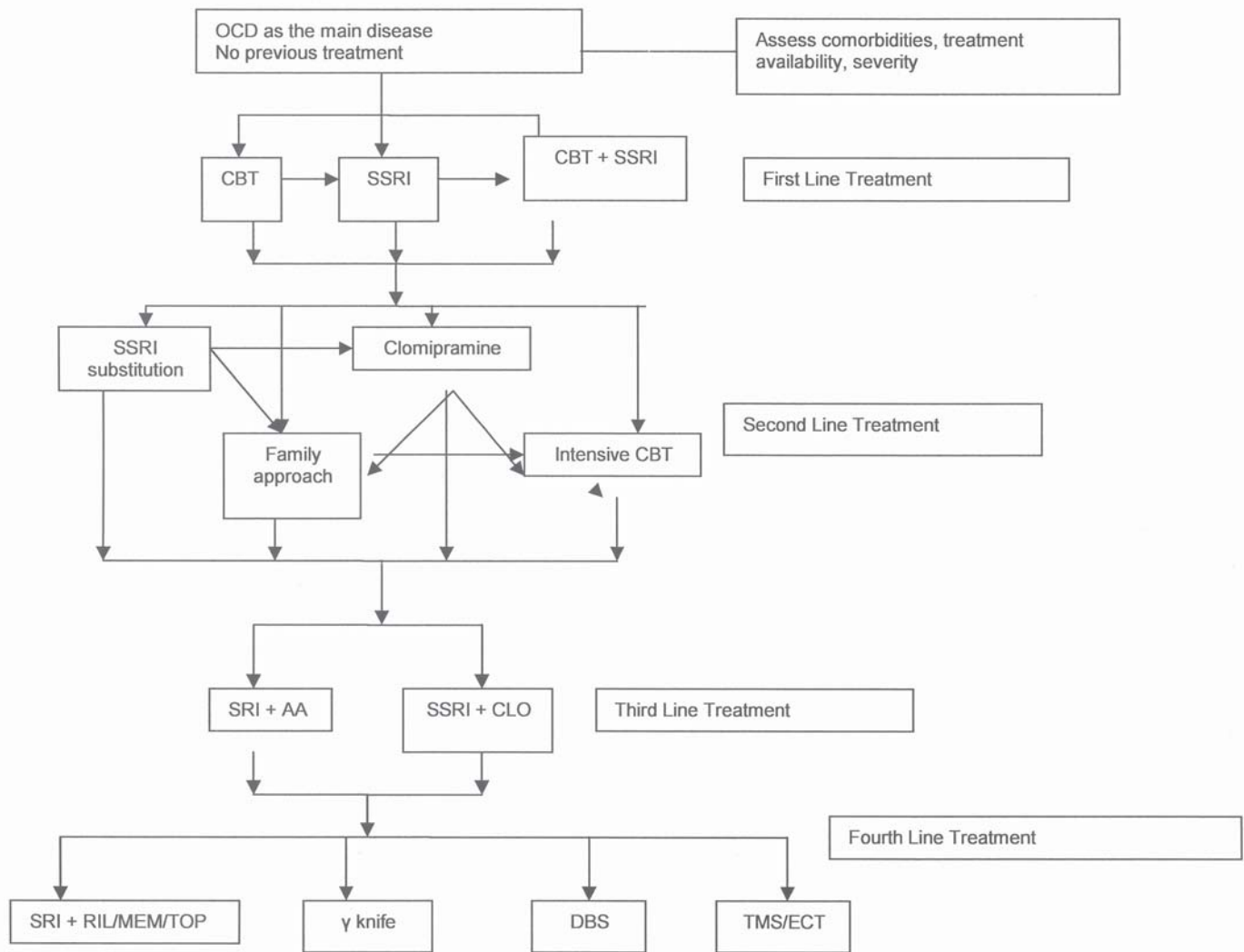
### Pharmacological interventions

#### 1. Monotherapies

Antidepressives with effect on the serotonin reuptake (clomipramine and selective serotonin reuptake inhibitors – SSRI) are the most efficient drugs for the monotherapy treatment of OCD. However, the lack of response to the treatment with one of these substances seems not to have an influence on the lack of response to all the substances of this class of drugs.<sup>39</sup> That is, if the patient does not respond to a serotonin reuptake inhibitor (for example, fluoxetine), he/she might respond to a second drug of the same class (for example, paroxetine). Therefore, as an alternative for the patients who do not respond to a first line pharmacological treatment, it is possible to substitute the drug by another one of the same class or recommend the association with a psychotherapeutic approach, as suggested in the algorithm of treatment showed below (Figure 1).

There is not consensus about which serotonin reuptake inhibitor must be the initial drug for the OCD treatment. Because they has fewer side effects, the SSRIs are preferred as opposed to clomipramine. In all direct comparisons with the adequate methodology, clomipramine did not prove to be better than the SSRIs.<sup>40-42</sup> However, it can be more efficient than the SSRIs according to some metaanalysis.<sup>40-42</sup> Therefore, an attempt using clomipramine before diagnosing the patient as refractory is considered necessary.





**Figure 1 – Algorithm of obsessive-compulsive disorder treatment proposed by the Obsessive-Compulsive Disorder Project (PROTOC) of the Institute of Psychiatry, School of Medicine, Universidade de São Paulo.**

*Legend: OCD = obsessive-compulsive disorder; SSRI = Serotonin Selective Reuptake Inhibitor; CLO = clomipramine; AA = atypical antipsychotic; RIL = riluzole; MEM = memantine; TOP = topiramate; γ knife = neurosurgery (anterior capsulotomy) using γ knife method; DBS = deep brain stimulation; TMS = transcranial magnetic stimulation; ECT = electroconvulsive therapy.*

In short, there is no evidence of superiority of one specific drug among the drugs available for use in oral monotherapy with standardized doses.

## 2. Alternatives for monotherapy

The following alternatives are available for patients who do not respond to the standard monotherapy: use of an over dosage of monotherapy; use of intravenous monotherapy; use of drug association; and use of other biological approaches.

### 1) Overdosage

Although these strategies have already been included in some algorithms of treatment of OCD patients,<sup>43</sup> these data still remain preliminary in order to assess the relationship between risks and benefits of this type of intervention whatever the drugs used. Therefore, cautious use of over dosage in patients who do not respond to the first line treatment is recommended.

### 2) Intravenous drug

There is evidence suggesting that the intravenous drugs are an efficient alternative in the treatment of OCD-resistant patients.<sup>44</sup> Although the reason is not well clarified yet, it seems that, since the drug does not have to go through the hepatic metabolism, this administration route increases the bioavailability of the active principle of these drugs in the CNS. In addition, it takes a shorter time to reach the maximum concentration in the blood and the CNS. Intravenous clomipramine has proven efficient for the treatment of patients resistant to the first line treatment.<sup>44</sup> The intravenous administration of citalopram also showed efficient results in an open study.<sup>35</sup> However, these alternatives are not available in most countries. This is the reason why the algorithm of treatment described below does not include these alternatives (Figure 1).

### 3) Drug association

As mentioned above, a hypothesis used to explain the

patient's resistance to the first line treatments is the fact that OCD, being a disease of multiple and heterogeneous etiology, must be related to the impairment of different brain circuits or different sites of these circuits in specific groups of patients.<sup>7,46</sup> Therefore, some types of this disorder could require drugs that affect other circuits besides those that are sensitive to the serotonergic drugs. Based on that, the use of drug associations that affect other neurotransmitters like, for example, the dopaminergic and the glutamatergic system, associated to the serotonin reuptake inhibitors, was tested for OCD. Another possible strategy is related to the enhancement of the serotonergic effect through the association of two serotonergic drugs. Table 2 shows a summary of the main studies that assessed drug association for resistant patients.

#### 4) Modulators of the dopaminergic system

There are several studies that demonstrate the participation of the dopaminergic system in the physiopathology of OCD. Neuroimage studies showed changes in the brain regions with a large number of dopaminergic neurons, such as the basal

ganglia, suggesting an increase in the dopaminergic transmission. These studies also demonstrated that there are drugs that increase the dopamine release or reduce its reuptake (e.g.: methylphenidate, cocaine, bromocriptine) and induce obsessive-compulsive symptoms. Moreover, some studies that assessed the dopaminergic receptors revealed a decrease in the density of the D2 receptors in the basal ganglia of OCD patients<sup>47</sup> and an increase in the density of the dopaminergic transporter in the basal ganglia of OCD patients.<sup>48</sup> Finally, serotonergic neurons produce inhibitory tonus on dopaminergic neurons in the basal ganglia, suggesting that the effect of SSRI on the improvement of the obsessive-compulsive symptoms can also affect dopaminergic mechanisms. Therefore, the combination of SSRI with neuroleptics is one of the most largely studied therapeutic strategies for the treatment of the patients who are refractory to the conventional treatments, showing the highest level of efficacy evidence. The combination of a SSRI with antipsychotics such as pimozide<sup>18</sup> and haloperidol<sup>17</sup> proved to be efficient for patients

**Table 2 – Summary of the literature on the increased effectiveness of Serotonin Selective Reuptake Inhibitors (case reports and open studies were excluded)**

Typical antipsychotics	Design	n	Results
Haloperidol+SRI	Controlled, double-blind <sup>63</sup>	34	Association with haloperidol is more efficient than with placebo
Haloperidol+SRI	Controlled, double-blind, cross-over with risperidone <sup>64</sup>	17	Risperidone and haloperidol are associated with the improvement of obsessions, and risperidone was more efficient than haloperidol in the improvement of depressive symptoms
Atypical antipsychotics	Design	n	Results
Risperidone + SRI	Double-blind, randomized <sup>65</sup>	36	Association was more efficient than placebo
Risperidone + SRI	Double-blind, controlled with placebo	16	Association was more efficient than placebo
Risperidone + SRI	Double-blind, controlled, cross-over with haloperidol <sup>67</sup>		Risperidone and haloperidol are associated with the improvement of obsessions, and risperidone was more efficient than haloperidol in the improvement of depressive symptoms
Risperidone + SRI	Double-blind, randomized <sup>68</sup>	15	Low metabolism in striatum and high metabolism in anterior cingulate regions (measured by PET) were related to a better response
Risperidone + SRI	Metaanalysis <sup>69,70</sup>		Risperidone was better than placebo when it was associated with SRI for the OCD treatment
Quetiapine + SRI	Controlled, single-blind study <sup>71</sup>	27	64% of responders, higher than placebo
Quetiapine + SRI	Controlled, double-blind study <sup>72</sup>	40	40% of responders, higher than placebo
Quetiapine + SRI	Controlled, double-blind study <sup>73</sup>	41	40% of responders, no difference regarding the placebo group
Quetiapine + SRI	Controlled, double-blind study <sup>74</sup>	21	14% of responders, tending to be higher than the placebo, but with no statistical significance
Quetiapine + SRI	Metaanalysis <sup>70</sup>		Further studies are needed to determine the efficacy of quetiapine associated with SRI
Olanzapine + SRI	Controlled, double-blind study <sup>75</sup>	44	41% of responders, similar to placebo
Olanzapine + SRI	Controlled, double-blind study <sup>76</sup>	26	46% of responders, higher than placebo
Olanzapine + SRI	Open study, with longitudinal follow-up <sup>77</sup>	26	65% of responders with response maintenance in the next months
Olanzapine + SRI	Metaanalysis <sup>70</sup>		Further studies are needed to determine the efficacy of olanzapine associated with RI
Enhanced serotonergic responsivity	Design	n	Results
Pindolol+paroxetine	Controlled with placebo, randomized, double-blind study <sup>78</sup>	14	Pindolol better than placebo
Pindolol+fluvoxamine	Controlled, double-blind study <sup>79</sup>	15	No difference regarding placebo
Clonazepam+sertraline	Controlled, randomized, double-blind study <sup>80</sup>	37	It was not better than monotherapy
Buspirone+clomipramine	Controlled, double-blind study <sup>81</sup>	14	Association was not better than monotherapy
Lithium+fluvoxamine	Controlled, double-blind study <sup>82</sup>	30	Association with buspirone was not better than placebo
Lithium+fluvoxamine	Controlled, double-blind study <sup>83</sup>	16	Association with buspirone was not better than placebo
Inositol+SSRI	Controlled, double-blind study <sup>84</sup>	13	Association with inositol was not better than placebo
Other agents	Design	n	Results
Morphine+SRI	Controlled, double-blind study <sup>85</sup>	23	7 improved with morphine 4 improved with lorazepam 1 improved with placebo Significant difference between morphine and placebo, but not between morphine and lorazepam or lorazepam and placebo
Desipramine+SSRI	Controlled, double-blind study <sup>86</sup>	30	Desipramine was not more efficient than placebo

*N = sample size; SRI = Serotonin Selective Reuptake; SSRI = Serotonin Selective Reuptake Inhibitors. The superscribed numbers are references of the study; superscribed numbers with the letter "T" before them are references of this table.*

with OCD associated with nervous tics. Among the atypical antipsychotics, risperidone is the drug with the best level of efficacy evidence,<sup>49</sup> but olanzapine<sup>50</sup> can also be beneficial for OCD patients, regardless the presence of tics.

Before using more invasive treatments, the association of SSRIs with antipsychotics, such as the one described in the algorithm (Figure 1), should be tried.

#### 5) Serotonergic enhancement

Several agents have been used to stimulate the enhancement of the serotonergic effect of SSRI on OCD patients. Lithium, clonazepam and inositol have been studied and showed poor efficacy (Table 2). The association of SSRI with clomipramine is the only association of serotonergic enhancement that seems to be promising.<sup>51</sup> The probable mechanisms that could explain the better efficacy of the association between clomipramine and SSRI have pharmacokinetic origin (the most well-known) and pharmacodynamic origin (the least known). Based on the knowledge about the pharmacokinetics, it is possible to state that high doses of fluoxetine, paroxetine and sertraline reduce the isoenzymes' activity (enzymatic inhibition) of the system in the cytochrome P450 (e.g.: CYP 2D6), causing the inhibition of the clomipramine metabolization and, as a result, increasing the concentration of nonmetabolized clomipramine that reaches the CNS. On the other hand, based on our knowledge on pharmacodynamics, one can suppose that because of the association there is an enhancement of the serotonergic activity by other means besides the reuptake inhibition and the activity in secondary neurotransmitters (noradrenaline, dopamine).

However, the efficacy of this association has only been demonstrated in open studies and case reports (Table 2). Therefore, the performance of controlled studies remains necessary. In addition, caution should be used to prescribe the use of clomipramine associated with drugs that can change its serum level, since it can cause an increase in its cardiotoxicity potential, higher chances of inducing a serotonergic syndrome and reduction in the convulsive threshold. Consequently, the increases in the clomipramine doses should be continuously monitored by the following factors: clomipramine plasma levels; electrocardiogram (QT interval) – especially for patients older than 40 years or with previous history of heart diseases –; and symptoms of the serotonergic syndrome (fatigue, restlessness, mental confusion, sweating, etc.).

#### 6) Modulators of the glutamatergic system

The glutamatergic system was included in the pathophysiology of the OCD since Rosenberg et al. found an increase in the glutamate concentration in the caudate nucleus of children with OCD and normal glutamate levels after treatment with paroxetine.<sup>52</sup> Increased glutamate levels in OCD patients were also described by Chackabarty et al.<sup>53</sup> There are few data on the efficacy of the use of agents that affect the glutamatergic system of OCD patients (Table 2), however, the preliminary results seem to be promising.

#### Approaches based on brain circuits

The broader knowledge about the participation of specific brain circuits in OCD brings several consequences to the development or refinement of the treatments based on the anatomy. Different neuroimage studies suggest functional alterations (mainly increase in the metabolic activity) in different brain areas of OCD patients; more evidently in the orbitofrontal region, anterior cingulate, caudate nucleus and thalamus.<sup>54</sup> Neuroanatomic studies suggest that these regions comprise a

neural cortical-striatal-thalamic-cortical circuit, which might be hyperactive in OCD patients. The principle of the use of procedures based on the neurocircuits in OCD is that of dividing in a selective manner the brain areas that interconnect this circuit. Among several tools that are based in the neuroanatomy, we can mention transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) e deep brain stimulation (DBS), in addition to the well-known neurosurgical techniques.<sup>55,56</sup>

#### 1. Transcranial magnetic stimulation (TMS)

According to the 2003 Cochrane Database Systematic Reviews, three clinical trials have been included in a review on TMS in OCD, and two of them included data that were adequate for the analysis, but did not allow the performance of a metaanalysis. In this review, there was no difference between TMS and placebo. However, recent open studies, with some technical innovations [e.g.: stimulation in the supplementary motor area],<sup>57</sup> have described promising results. Although critical variables such as stimulation sites, length of treatment and stimulation parameters still remain controversial, the noninvasive characteristic and the good tolerability were some of the reasons for including the TMS in algorithms of treatment of resistant OCD before performing more invasive procedures.<sup>43</sup>

#### 2. Deep brain stimulation (DBS)

Neurosurgical teams in the United States and Europe have studied the DBS of the anterior ventral region of the internal capsule and adjacent ventral striatum (VC/VS) for severe and highly resistant cases of OCD. Four groups have contributed in a more consistent manner with the smaller studies in the last eight years. The first group involved was that from Leuven/Antwerp, followed by the group of the Butler Hospital/Brown Medical School from Cleveland,<sup>58</sup> and, more recently, by the University of Florida. These groups used comparable selection criteria and surgical targets. The surgical targets changed from one center to the other, but the selection criteria were the same. The long-term results of these studies reveal clinically significant decreases in the symptoms and functional improvement in approximately two thirds of the refractory patients. Neuroimage exams with Positron Emission Tomography (PET) in samples of these patients suggest that the activity of the subgenual cingulate region before the surgery is directly related to the improvement of OCD after long and deep brain stimulation.<sup>59</sup> This finding is intriguing because it implies increased activity in this region, which has been related to mood regulation as a potential marker of the response to the treatment for OCD with DBS. Clinically, DBS has been generally well tolerated and the adverse effects are transitory. The results have been better for the patients who received the implants more recently, which suggests that there is a "learning curve" inside and between the specialized centers, showing improvement and refining of the site of implantation. In the beginning, the anterior capsulotomy involved anterior-posterior lesions. With the purpose of improving the results, more posterior lesion sites were investigated and revealed that these more posterior neural circuits could be relevant for the therapeutic improvement.<sup>60</sup> It resulted in the current surgical target, that is, in the joining of the anterior capsule with the anterior commissure and the posterior ventral striatum. These data (Greenberg et al., personal communication: submitted for publication, being reviewed, June 2007) evidence that this procedure can be a therapeutic promise and that it can be successfully implemented by specialized interdisciplinary teams.

### 3. Surgical treatment

Currently, there are six techniques available for the surgical treatment of OCD. These techniques are divided according to the specific site of lesion:<sup>55</sup> 1) Anterior capsulotomy: lesions in the anterior arm of the internal capsule. Lesions in this region can be directly performed by means of stereotactic neurosurgery through deep encephalic stimulation (DES) or, indirectly, by means of radiosurgery (Gamma Knife). An improved technique, with smaller lesions, has been performed currently (Lopes, personal communication); 2) Anterior cingulotomy: Stereotactic neurosurgical lesions performed directly in the anterior cingulate of the region; 3) Subcaudate tractotomy: Stereotactic neurosurgery in the ventral striatopallidal complex (*substantia innominata*); 4) Limbic leucotomy: combined lesions in the cingulate region and in the *substantia innominata*; 5) DES of *nucleus accumbens*: neurosurgical stimulation of the nucleus accumbens shell, proximal to the anterior arm of the internal capsule; 6) Lateral central thalamotomy associated with the anteromedial pallidotomy: lesions in the posterior portion of the lateral central nucleus of the thalamus and in the anterior and medial paralimbic globus pallidus.<sup>55</sup>

Many studies regarding the techniques mentioned above have been published in the last few decades. Most of them are prospective follow-ups of one or more cohorts of patients who underwent surgery.<sup>55</sup> Only one randomized clinical trial of neurosurgery has been carried out, and it compared the capsulotomy to the cingulotomy, but with a small number of patients.<sup>61</sup> On the other hand, in DES studies of the internal capsule, we found randomized clinical trials, but they involved small samples. Currently, the first randomized clinical, double-blind and placebo controlled trial on Gamma Knife radiosurgery using the anterior capsulotomy (improved technique) is being carried out (Lopes, personal communication). In the last few years, the most frequently used techniques have been the anterior capsulotomy and anterior cingulotomy.

Generally speaking, the prevalence of postsurgical global improvement with capsulotomy, cingulotomy, subcaudate tractotomy, limbic leucotomy and thalamotomy/pallidotomy have ranged from 56 to 100%, 27 to 57%, 33 to 67% and 61 to 69% and 62.5%, respectively.<sup>55</sup> The radiosurgery has the advantage of not requiring cranial opening and the zero risk of hemorrhages and infections. Its efficacy ranges between 37.5 and 70% of the patients.<sup>62</sup>

DES consists of the implantation of electrodes by means of a stereotactic neurosurgery either in the internal capsule region or in the accumbens shell. These electrodes are connected to a neurostimulator that is able to electrically stimulate the regions of the implant. Its advantage is to allow the implantation reversibility, although the low neurosurgical risks cannot be avoided (hemorrhages, infections). Regarding its efficacy, three out of four patients<sup>62</sup> or four out of eight patients<sup>58</sup> improved with the procedure, in placebo-controlled, randomized clinical trials.

The adverse events and complications associated with the surgical treatments of OCD vary according to the surgical technique (lesion site) and type. Generally speaking, however, the most prevalent adverse effects are isolated cases of seizures, delirium immediately after the surgery, hypomania and, rarely, hemorrhages and neuroinfection.<sup>55</sup> In the radiosurgery, the most frequent side effects are headache episodes. Neuropsychological alterations are rare and, when they occur, their manifestation is mainly by means of apathy symptoms,

mental slowness, irritability, aggressiveness and behavioral lack of inhibition. These complications, however, are more common with the old techniques (limbic leucotomy and subcaudate tractotomy, especially).

It is important to highlight that these surgical procedures are only recommended in the cases of proven refractoriness to multiple pharmacological treatments and behavioral therapy, with extremely severe symptoms and reserved prognosis. Recently, we have published a manuscript presenting guidelines for the use of neurosurgery in psychiatry. These guidelines were adopted by the Technical Chamber of the Regional Medical Council of São Paulo. We suggest that all patients should follow the recommendations previously published regarding the surgical indication.<sup>56</sup> Among these recommendations, we highlight the fact that all patients must sign a written informed consent about the possible benefits and risks of the surgery. The surgical indications also must be analyzed and ratified by an independent committee of experts, who are not related to the team that selects the patients and performs the surgical procedure. There must also be a commitment to a long-term follow-up.

With these premises, we began, in collaboration with researchers from the Brown University, the first double-blind, randomized study of neurosurgery in psychiatry some years ago. In this study, we used the radiosurgery technique that represents an improvement of the anterior capsulotomy using gamma rays. This technique was developed at the Brown University and is called ventral-capsular and ventral-strial gamma ray capsulotomy, and it uses small lesions, presenting the best profile of adverse events. The objective of this study was to determine if the ventral-capsular and ventral-strial gamma ray capsulotomy in OCD is efficient regarding the decrease in the obsessive-compulsive symptoms and the global clinical improvement, as well as to define the profile of adverse events, neuropsychological and personality alterations caused by the procedure. We selected 24 patients with refractory OCD. These patients underwent this surgical technique in Brazil, and five of them participated in a pilot initial study. The other nine patients took part in the double-blind, randomized clinical trial, in which one group underwent the real radiosurgery (active group), while the other group received false radiosurgery (placebo group). Before the procedure, all of them underwent a thorough clinical and psychiatric assessment, besides a comprehensive set of instruments to define psychiatric diagnosis, OCD severity and evolution, global clinical improvement, depressive/anxiety symptoms and neuropsychological/personality alterations. The individuals were periodically assessed and followed during at least one year. Regarding the pilot study, two out of five patients (40%) responded to the treatment after one year of follow-up, or three out of five (60%) responded to the treatment in up to three years of follow-up. In the active group, one out of four patients (25%) responded to the treatment in up to one year of follow-up, or three out of four (75%) in the period between 12 and 24 months of follow-up. In the placebo group, none of the five patients responded to the false radiosurgery. The most severe adverse effect was the triggering of a short maniac episode in only one patient of the total sample. Neuropsychological or personality undesired alterations were not seen in this study. In short, this study, with preliminary findings (the final sample must include 24 patients in each group), suggests that the ventral-capsular and ventral-strial capsulotomy is relatively efficient with many adverse events.



Although the studies suggest promising results with different surgical techniques, only placebo-controlled, double-blind, randomized clinical trials including an adequate number of patients will be able to confirm the efficacy of these procedures.

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