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# The Treatment of Obsessive-Compulsive Disorder and the Approaches to Treatment Resistance

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## 1. Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive ideas, impulses, or urges (obsessions) along with overt or covert behaviors (compulsions) aimed at reducing the distress (DSM-IV-TR). Patients have either obsessions, compulsions, or, most commonly, both. Obsessions are defined as recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and inappropriate and cause anxiety. The obsessions are not simply excessive worries about real-life problems and the affected individual usually recognizes that these thoughts, impulses or images are excessive, unreasonable and a product of their own mind (DSM-IV-TR). In order to naturalize the obsessions, other thoughts or actions are performed (compulsions). Examples of obsessions include, among others, contamination (concern with dirt or germs, fear of blood) symmetry (concern about order, exactness), obsessions about safety and harm (fear of harm due to carelessness, fear of being responsible for terrible events) hoarding, pathological doubt (after completing a routine activity the affected individual wonders whether he or she performed it correctly or did it at all), numbers with special significance, etc.

Compulsions are repetitive behaviors (e.g. hand washing, ordering, checking) or mental acts (e.g. praying, counting, repeating words silently) that patients with OCD feel compelled to do in response to an obsession, or according to rules which must be applied rigidly (e.g. checking that a light switch is turned off by switching it on and off without any interruption). The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors are either not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly unreasonable or excessive. Examples of compulsive activities are washing hands until they are raw, repeatedly checking the locked door, arranging and rearranging items in a set order, counting, asking, repeating reassurance questions etc.

The diagnosis is made by clinical interview, with a specific and detailed focus on OCD. To diagnose the disorder according to the DSM-IV criteria, the patient must suffer from either obsessions or compulsions that cause great distress, are time-consuming (more then 1 hour

per day), or substantially interfere with normal function, and that, at some point of the disorder, are recognized as excessive or unreasonable. The Yale-Brown obsessive-compulsive scale (Y-BOCS) is regarded as the gold standard measure of obsessive-compulsive symptom severity and is used in most treatment trials (Goodman et al., 1989).

## 2. OCD treatment: First-line treatments and first-line treatments choice

The first case report indicating that the tricyclic antidepressant (TCA) clomipramine might have some benefit in patients with OCD was published more than 40 years ago (Fernandez et al., 1967), but more than 20 years passed before clomipramine was approved for the treatment of OCD (Thorén et al. 1980).

Since then, a wide number of researchers have been working in order to find effective pharmacological treatments, and despite treatment resistance still being a core issue in the therapeutic process, many goals have been achieved. Nowadays the clinician has the possibility of choosing a variety of treatment strategies that are effective in about the half of the patients (Pallanti et al. 2002). Both cognitive-behavioral therapy (CBT) and serotonin reuptake inhibitors (SRI) are considered valuable and safe first-line treatments for obsessive-compulsive disorder (Koran et al., 2007).

A broad range of factors may have an influence on the choice of the treatment strategy adopted by the clinician. Some of them are the severity of the symptoms, the characteristics of psychiatric or medical comorbidity and the relative treatment, the possibility to get a CBT, past and actual treatment and patient's preference. Given the fact that most of the trials are based on 3-4 months long observations, there are no reliable data concerning the best options for long-term therapies.

Behavioral therapy seems to be the most effective kind of psychotherapy, in particular exposure and response prevention (ERP) techniques (Abramowitz, 1998; Eddy et al., 2004; Fisher et al., 2005; Meyer, 1966). Also cognitive approaches, aiming at the identification and modification of dysfunctional beliefs and thoughts are considered appropriate strategies if coupled to the behavioral ones: in fact, only a small amount of data supports the efficacy of the cognitive techniques alone.

CBT with ERP is indicated as first-line treatment for patients without particular depressive or anxious symptoms, for those whose disorder's severity does not interfere with the therapeutic process, and in those who refuse a pharmacological treatment (Koran et al., 2007).

Although there are no sufficiently controlled trials to provide solid evidence, the experts agree on the optimal duration of the treatment, which should at least consist of 13-20 sessions (Koran et al., 2007).

The use of a SRI without CBT intervention is indicated for those patients who were already treated in the past with a drug with good results or that prefer an exclusive pharmacological treatment. However, an initial approach with a SRI may be helpful in comprehensively increasing the compliance of the patient to all the components of the treatment, as an effect of the reduction of the symptoms' severity. Therefore, the use of a SRI alone is indicated also for the patients who are not eligible for a CBT intervention because of their scarce compliance and collaboration or when psychotherapy is not available (Koran et al., 2007).

The Food and Drug Administration (FDA) have approved clomipramine, fluoxetine, fluvoxamine, paroxetine and sertraline for the treatment of obsessive-compulsive disorder. There are sufficient evidences that support the efficacy of citalopram and escitalopram, although the FDA still does not approve them.

Citalopram is the most selective serotonin reuptake inhibitor. Its efficacy and safety as first line treatment or in case of treatment-resistance for OCD has been proved in various single and double blind trials (Marazziti et al, 2001; Pallanti et al, 1999; Pidrman et al., 1997; Stengler-Wenzke et al., 2006).

Montgomery et al. (Montgomery et al., 2001) confronted in a double-blind trial the efficacy of different citalopram dosages (20, 40, 60 mg/die) and placebo; the Authors reported the effectiveness of all of the three dosages, with a slight advantage for the higher one, particularly in terms of rapidity of response.

Escitalopram is the left enantiomer of citalopram; due to the fact that the right enantiomer (that contrasts the effect of citalopram on serotonin) is not included in the drug, escitalopram has a greater re-uptake blocking efficacy.

A series of open and retrospective studies supports the potential efficacy of citalopram in OCD (Dougherty et al., 2009; Galvao-de Almeida et al., 2007; Rabinowitz et al., 2008; Shim et al., 2008). These results have been confirmed by two double-blind placebo controlled trials (Kahn et al., 2007; Stein et al., 2007). Stein et al. recruited 466 patients with a diagnose of OCD that were randomly treated with escitalopram 10 or 20 mg/die, paroxetine 40 mg/die, or placebo for 24 weeks. After 12 weeks of therapy, the mean Y-BOCS score reduction in comparison with placebo was of 3.21 points (p<0.1) for escitalopram 20 mg and 2.47 point (p<0.5) for paroxetine 40 mg. After 24 weeks there was a statistically significant difference for all the groups in comparison with placebo (p<0.5 for escitalopram 10 mg, p<0.1 for escitalopram 20 mg and paroxetine); the mean Y-BOCS score reduction was of 3.10 points for escitalopram 10 mg, 3.12 for escitalopram 20 mg and 4.24 for paroxetine 40 mg. Escitalopram was better tolerated when compared with paroxetine, as proved by the smaller number of treatment withdrawals caused by adverse effects, although this difference was not statistically significant. Moreover, escitalopram has been proved to be effective in the long-term treatment and in the prevention of the exacerbation of the obsessive-compulsive symptoms after treatment discontinuation (Fineberg et al., 2007).

With regards to the supposed superiority of Clomipramine (CMI) over SSRIs clear evidences are still lacking. Nevertheless, the experts agree on the fact that SSRIs have to be considered first-choice treatments because of their more favorable side-effects profile (Koran et al., 2007). The efficacy of the different SSRIs does not differ in a critical way from one to another, but the response may be patient-specific. The reasons of this issue are still not clear and accurate predictors of response to be used in the clinical practice are still lacking.

Important aspects to be considered when choosing a SSRI are the tolerability for the individual patient of the specific side-effects of the drug, previous treatments and relative responses to them, the presence of psychiatric or medical comorbidities (i.e. paroxetine should never be prescribed to patients suffering from diabetes or neurologic bladder, as it is the SSRI most frequently associated with weight gain and anticholinergic effects (Koran et al., 2007).

The duration of the therapy and the dosage of the chosen drug represent two features of primary importance in the treatment of OCD. In fact, in order to obtain a clinical response in OCD the usual settings fixed for depression or other anxiety disorders are not functional.

Most of the patients do not achieve particular symptomatology improvements before 4-6 weeks of treatment, but some of them don't obtain it even before 10-12 weeks from the beginning of the therapy.

Thus, 12 weeks is the minimal duration of treatment necessary to correctly estimate the efficacy of a drug and plan long-term strategies. Instead, in order to obtain the full response

6 months are necessary: consequently, the treatment of the acute phase of the disorder should be administered for at least 6 months at full dose (Zohar et al., 2007).

With regards to the dosages, these are considerably higher that the ones used for depression and other anxiety disorder and often is necessary to prescribe the maximal dose in order to obtain a good response (Koran et al., 2007). In the following table (Table 1) the dosage details of the most commonly used SRIs are illustrated.

| SRI | Starting dose (mg/day) | Usual target dose (mg/day) | Maximum dose (mg/day) |
|---|---|---|---|
| Citalopram | 20 | 40-60 | 120 |
| Escitalopram | 10 | 20 | 60 |
| Fluoxetine | 20 | 40-60 | 120 |
| Fluvoxamine | 50 | 200 | 450 |
| Paroxetine | 20 | 40-60 | 100 |
| Sertraline | 50 | 200 | 400 |
| Clomipramine | 25 | 100-250 | 300 |

Table 1. (Modified by that of Koran et al. (Work group on obsessive-compulsive disorder): Practice guideline for the treatment of patients with obsessive-compulsive disorder. 2007) (American Psychiatric Association)

In case of adequate response to the first-choice drug, the duration of the maintaining phase of the treatment should last not less than 2 years at the dose necessary to elicit the clinical response. After this period, if relapse and symptom exacerbation have not occurred, is possible to slowly reduce the dose over some months, strictly monitoring the course of the disorder, otherwise the treatment should be continued.

A careful planning of long term treatment should consider the possibility of using lower doses of that used in the acute phase of the disorder. If many authors suggest keeping the dosage always at the same level, others state that is possible to greatly reduce it after the acute phase. In this perspective, it seems sensible to consider the efficacy and the tolerability of the therapy during the previous stages of the illness as the main guidance criteria, reducing the daily dose only in patients that achieve a complete, stable and long-lasting recovery after the treatment of the acute phase or in that patients that do not well tolerate high dosages of SRIs.

Other drugs have been proposed as first-line treatment in the acute phase of OCD, even if no clear evidence about their efficacy is available.

Increasing attention has been paid to the possible role of serotonin–norepinephrine reuptake inhibitors (SNRIs) in patients with OCD. The first evidence of the effectiveness of these compounds came from the observation that clomipramine is an inhibitor of the reuptake of serotonin as well as of norepinephrine (Dell'Osso et al., 2006). Venlafaxine is a 2-phenyl-2 ethylamine derivate that is chemically unrelated to tricyclic, tetracyclic or other available antidepressant. It shows different degrees of serotonin, norepinephrine and dopamine reuptake inhibition, as a function of the dosage (at higher dosis, the action on the noradrenergic and dopamine system becomes more marked) (Dell'Osso et al., 2006). Although mostly not placebo-controlled, the majority of venlafaxine short and intermediate-

term trials suggests the efficacy of this drug in both treatment-naïve and treatment-resistant OCD patients (Dell'Osso et al., 2006). Venlafaxine was as effective as paroxetine and clomipramine, and it was generally well tolerated by patients. However, due to the absence of double-blind placebo-controlled trials, venlafaxine should not be considered a first line medication treatment for patients with OCD at this time. Perhaps venlafaxine might be considered in specific clinical situations such as OCD with comorbid attention/deficit/hyperactivity disorder (ADHD) (Dell'Osso et al., 2006).

One placebo-controlled trial supports the efficacy of phenelzine (MAO inhibitor) (Vallejo et al., 1992). However, another one that compared phenelzine both to fluoxetine and to placebo demonstrated superiority over placebo for fluoxetine but not for phenelzine (Jenike et al., 1997).

Mirtazapine is an antidepressant that does not enhance 5-HT neurotransmission directly, but disinhibits the norepinephrine activation of 5-HT neurons and thereby increases 5-HT neurotransmission by a mechanism that does not require a time dependent desensitization of receptors (unlike SSRIs). The treatment of OCD patients has been tested in a single-blind study, which compared citalopram alone to a combination of mirtazapine and citalopram. This study indicated that the responses were faster (after four weeks) but that there was no difference between the groups after eight weeks and twelve weeks (Pallanti et al., 2004). Another open study showed the superiority of mirtazapine to placebo (Koran et al., 2005).

## 3. Approaches to treatment resistance and pharmacological strategies in resistant-OCD

Even if SSRIs have brought to a significant progress in the treatment of OCD, clinical evidence suggests that a high percentage of patients, ranging from about 40% to 60%, does not reach satisfying clinical improvement and does not "respond" properly to therapy (CMI-group, 1991; Goodman et al., 1992; Jenike and Rauch, 1994; McDougle et al., 1993; Piccinelli et al., 1995; Pigott et al., 1999; Rasmussen et al., 1993), with a strong impact on their quality of life, both in terms of disability and morbidity (Hollander et al., 1996).

We introduced operational criteria for the evaluation of the different "stages of response" in order to provide to the clinician a template to organize the best treatment strategy (Pallanti et al., 2002). The response to treatment is seen as a continuum of steps that ranges from the worse outcome, the refractoriness to all type of therapies, to the best outcomes, "remission" and "recovery".

Some terminological issues need to be clarified in order to avoid misunderstandings.

The term "resistant" should be used in case of a fail of one trial of therapy with a first choice treatment (at least 10-12 weeks with full dose of an SRI), whereas "refractory" only after at least three trials with SRI agents (one of them with Clomipramine), two augmentation trials with atypical antipsychotics, and at least 20-30 hours of cognitive-behavioral therapy.

Also the concept of "recovery" is different from that of "remission", although in OCD this last one seems to be a rare event; episodic course has been described in adults (Perugi et al., 1998; Ravizza et al., 1997) and because of this, the introduction of these two different definitions in the staging of illness seems to be rational and practical, as proposed by Frank et al. (1991) for depression.

"Recovery" should be used in case of complete absence of symptoms after treatment, corresponding to a Y-BOCS score of less than 8. Unfortunately, full recovery concerns only

the 5% of patients with an episodic course of OCD (Rasmussen and Eisen 1997). The most probable result in a case of non-episodic courses is instead "remission", that indicates a reduction of the symptoms after treatment to the lower limit, which corresponds to a Y-BOCS score of 16 or less (see Table 2).

The presence of comorbid conditions also influences the course of the response to treatment. Non-responsive patients are more likely to meet criteria for comorbid psychiatric disorders and the presence of a specific comorbid condition could be a distinguishing feature in OCD, with influence on the treatment adequacy and outcome (Pallanti & Quercioli, 2006). For example, conditions such as bipolar disorder and ADHD (attention deficit hyperactivity disorder) are common in treatment-resistant patients, but there are only few studies investigating their impact on treatment resistance (Magalhães et al., 2010; Sheppard et al., 2010).

The majority of the proposed treatment-resistance therapeutic options are not FDA approved, but they are strongly recommended on the basis of preclinical and clinical evidences.

| Stage of response | Stage | Description |
|---|---|---|
| I | Recovery | Not at all ill; less than 8 on Y-BOCS |
| II | Remission | Less than 16 on Y-BOCS |
| III | Full Response | 35% or greater reduction of YBOCS and CGI 1 or 2 |
| IV | Partial Response | Greater than 25% but less than 35% YBOCS reduction |
| V | Non-response | Less than 25% YBOCS reduction, CGI 4 |
| VI | Relapse | Symptoms return (CGI 6 or 25% increase in Y-BOCS from remission score) after 3+ months of "adequate" treatment |
| VII | Refractory | No change or worsening with allavailable therapies |

Table 2. Stages of response

## 3.1 Switching

Switching consists in replacing a serotoninergic agent with another one, or with a molecule of another class of drugs. The successfulness of this strategy in resistant patients is suggested by a number of studies (Ackerman et al., 1998; Denys et al., 2004; Goodman et al., 1997; Hollander et al., 2002; Koran et al., 2006; Rasmussen et al., 1997), but is not possible to predict the response of the patient to another drug. As suggested by clinical experience, the response rate to a successive treatment is around 50%, but it also declines with an inverse relationship to the number of failed trials (Koran et al., 2007).

The majority of the authors suggest switching from a SSRI to clomipramine (CMI) or vice versa, while the advantages of shifting from a SSRI to another one still remain unclear (Bogetto et al., 2003; Koran et al., 2007). The only data available are that of an open-label trial showing that a non-response to a SSRI does not imply the non-response to other molecules of the same class: 18 non-responders patients to at least two SSRI trials were treated with

citalopram 40 mg/die and a response rate of 77% was obtained (Marazziti et al., 2001). In a case series, switching from SSRIs to the SNRI duloxetine was successful in a number of treatment-resistant patients (Dell'Osso, 2008). Some other trials have been performed with venlafaxine and mirtazapine. The switch from venlafaxine to paroxetine showed an improvement in 56% of the cases after the treatment, while from paroxetine to venlafaxine the rate was only 19% (Denys et al., 2004). The switch to mirtazapine is supported by one open pilot study and a double blind discontinuation trial (Koran et al., 2005).

So, considering the fact that there are no double blind studies that confirm the efficacy of switching a SSRI with another one, the rationale of this strategy derives from pharmacokinetic and side-effects issues. Citalopram and sertraline are for example poor inhibitors of the cit. P-450, which is involved in the metabolism of largely prescribed drugs, and could be therefore used in cases of complex pharmacological interactions. Instead, fluoxetine and paroxetine significantly inhibit the enzymes CYP2D6, that metabolize tricyclic antidepressants, antipsychotics, antiarrhythmic drugs and beta-blockers; fluvoxamine inhibits CYP1A2 and CYP3A4, which are implicated respectively in the elimination of warfarin and tricyclic antidepressants, benzodiazepines and antiarrhythmic drugs. Fluoxetine has a long half-life and an active metabolite that reduces the effects of abstinence, and this could result useful in patients with a low compliance (Pallanti & Koran, 2003).

### 3.2 Augmentation
### 3.2.1 SRIs
This augmentation strategy consists of the combination of two serotoninergic drugs, usually clomipramine or SSRIs, depending on which was the initial agent. Sertraline and citalopram represent first choice SSRIs augmentation molecules to clomipramine, due to the fact that they have a minor inhibitor effect on cit P-450 (Bogetto et al., 2003). The efficacy of clomipramine as augmentation agent to SSRIs is supported by a number of studies (Pallanti et al., 1999; Ravizza et al., 1996; Szegedi et al., 1996) and by a large expert-consensus (Koran et al., 2007). It's recommended to check the plasmatic concentration of clomipramine and of his metabolite desmethyl-clomipramine during an augmentation therapy and keep it below 500 ng/ml, because of cardiac and CNS toxic side effects. Fluvoxamine seems to be the SSRI that primarily has such an increasing effect (Koran et al., 2007).

With regards to the efficacy of SSRI augmentation during clomipramine treatment, research has focused on sertraline and fluoxetine. In an open trial a 20-40 mg dose of fluoxetine was effective in clomipramine-resistant patients (Simeon et al., 1990) and sertraline augmentation was more effective when compared to the dosage increase of the first choice treatment (Ravizza et al., 1996).

Besides SSRIs, a number of studies have been performed in the last years to investigate the usefulness of other serotoninergic drugs, but the results are not clear and need further investigations before being considered as standard treatments.

### 3.2.2 Dopaminergic agents
The dopaminergic system has a central role in the pathophysiology of OCD, as supported by pre-clinical and clinical evidences. Experimental studies in animals, using dopaminergic drugs (amphetamine, bromocriptine, apomorphine and L-dopa), have provided evidence for the dopamine involvement in compulsive behaviors such as grooming and repetitive checking behaviors, which are commonly considered animal models of OCD (Denys et al

2004; Pitman 1989; Tizabi 2002). Several evidences of dopamine dysregulation in OCD have also been found in humans. An indirect strong evidence of the role of dopamine in OCD is provided by some neurological diseases associated with dopaminergic dysfunction such as Tourette's syndrome, Sydenham's chorea and Parkinson disease, which often show obsessive-compulsive symptoms in their clinical presentation (Lochner et al., 2005; Pauls et al., 1986, 1995); in addition, Tourette's Syndrome and OCD are supposed to share common neurobiological underpinnings and genetic factors, due to the fact that they are described as comorbid, mainly in the childhood-onset forms (Perani et al. 2008). Moreover, the increase in synaptic dopamine levels due to the effect of drugs such as cocaine and amphetamines have been reported to exacerbate or induce as well as to improve OCD symptoms (Westemberg et al. 2007). Also neuroimaging studies provide interesting data about the dopamine involvement in OCD. Recently Perani et al. (Perani et al. 2008) conducted a positron emission tomography (PET) study in drug-naïve OCD patients, measuring both serotonin (5HT2A) and dopamine (D2) receptors distribution in vivo. The observed reduction of D2 receptors binding potential suggests a dopaminergic dysfunction, in particular in the ventral portion of striatum.

### 3.2.2.1 Antipsychotics

The effectiveness of antipsychotics augmentation in OCD treatment-resistant patients has been tested in many studies. Evidences of the efficacy of haloperidol and risperidone are provided by some randomized double-blind placebo-controlled studies; nevertheless, data regarding the effectiveness of quetiapine and olanzapine are still open to question. The effect of antipsychotics augmentation on OCD symptoms is relative quick, and patients are unlike to improve if they have not responded after one month of intervention (Bloch et al. 2006). The reason of the greater haloperidol and risperidone effectiveness is probably that they have a greater D2-dopamine receptor affinity. Preliminary available data highlight interesting perspectives regarding the use of new agents such as aripiprazole, although they do not provide yet sufficient basis for their wide use in OCD. The identification of predictors of antipsychotics response would represent a relevant progress in the treatment of resistant patients but unfortunately at the moment there is no reliable evidence regarding this issue. However, several data show that the subgroup of OCD patients with comorbid tics have particularly beneficial response to this intervention (especially to haloperidol) as well as those with poor insight (Hollander et al. 2003) and co-occurring schizotypal personality disorder (Bogetto et al. 2000; McDougle et al., 1990).

Until recently, mainly short-term response data were produced with regards to antipsychotics augmentation. Matsunaga et al. (2009) conducted the only available trial concerning the effectiveness and safety of long-term atypical antipsychotics augmentation. SRI-resistant patients responded to augmentation with atypical antipsychotics but showed a significantly higher rate of body mass index, as well as a significantly higher level of fasting blood sugar or elevated levels of triglycerides and total cholesterol, when compared to SRI-responders. These data are consistent with previous findings from short-term clinical trials and emphasize the importance to assess the metabolic and nutritional aspects in the management of OCD treatment-resistant patients.

### 3.2.2.2 Dextroamphetamine and caffeine

A single 30 mg dose of dextroamphetamine (d-amphetamine) was superior to placebo in immediately relieving OC symptoms in two small double blind placebo-controlled studies

conducted before the introduction of SSRI for OCD treatment (Insel et al., 1983; Joffe et al., 1991). Methylphenidate monotherapy was effective in two cases of comorbid attention-deficit/hyperactivity disorder (ADHD) and OCD (van der Feltz-Cornelis, 1999). Nevertheless, in another open-label study, methylphenidate (40 mg) had no significant effect on OCD symptoms (Joffe et al., 1987).

Recently Koran et al. (2009) conducted a 5-week, double-blinded, caffeine controlled study of d-amphetamine augmentation in treatment-resistant OCD. Caffeine appeared to be slightly more effective, in both terms of number of responders (33% for d-amphetamine and 50% for caffeine) and degree of response (mean Y-BOCS score decrease was 48% for d-amphetamine and 55% for caffeine). The OC symptoms improvement associated with both drugs was maintained or increased over all the duration of the study. A possible explanation for the mechanism of this therapeutic effect could be that the increased release of dopamine induced by both drugs may increase D1 receptor stimulation in the prefrontal cortex; this enhancement is associated with improved attention regulation and working memory in patients with ADHD (Arnsten, 2006) that could lead to fewer obsessive intrusions, increased ability to shift attention away from them, and thus, decreased urges to perform compulsions (Koran et al., 2009).

### 3.2.3 Opioids

A remarkable number of studies (both preclinical and clinical) suggest the involvement of the opioid system in the pathophysiology of OCD (Amiaz et al., 2008; Koran et al., 2005b; McDougle et al., 1999; Roy et al., 1994; Urraca et al., 2004, Warneke et al., 1997). At the moment the results of the clinical trials concerning the use of opioid drugs as augmentation strategy in treatment-resistant OCD are controversial and there is no sufficient evidence supporting its use. Morphine, lorazepam and placebo were compared in a double blind study (Koran et al., 2005b) but only one patient had a sufficient response to morphine. Shapira and colleagues provided a report of the efficacy of the opioid agonist tramadol (26% reduction of the Y-BOCS score after 2 weeks of treatment) (Shapira et al., 1997). The opioid antagonist naltrexone did not improve OCD symptomatology and caused a worsening of anxiety and depressive symptoms in a double blind trial (Amiaz et al., 2008).

### 3.3 Infusion therapy

Infusion therapy is widely considered as a valid therapeutic strategy for treatment-resistant cases; clomipramine and citalopram are the drugs currently available for this kind of treatment.

The absorption of an intravenous administered drug is rapid, constant, and complete and is not affected by gastrointestinal variables, simultaneous administration of other drugs and first pass metabolism. Moreover, from a clinical point of view infusion therapy may improve treatment compliance, reinforce the therapeutic alliance and reduce the frequency of adverse events.

A greater efficacy of clomipramine i.v. versus placebo was reported in a double-blind placebo controlled study on 54 non-responders patients (in a previous 8 weeks-long trial with clomipramine per os) (Fallon et al., 1998). This could be explained considering the fact that the metabolite desmethyl-clomipramine has a weaker serotoninergic effect than clomipramine and intravenous administration may therefore increase the plasmatic clomipramine/desmethyl-clomipramine ratio and enhance the therapeutic effect.

Koran et al. (1998) compared clomipramine gradual increase administration and "pulse loading" administration. The results suggest a faster response with pulse loading administration. "Pulse loading" strategy consists in the application 150 mg i.v. at the first day, 200 mg i.v. at the second day, no administration for four consecutive days and then oral administration.

At the present time citalopram is the only SSRI available for infusion therapy. Our group administered for three weeks intravenous citalopram (followed by oral administration for other 9 weeks) to treatment-resistant OCD patients that were non-responders in at least two adequate trials with SSRI but not citalopram: 59% of the patients showed a reduction of at least 25% of the initial Y-BOCS score after the first 3 weeks of therapy, and improved more at the end of the 12 weeks (Pallanti et al., 2002b).

## 4. Physical therapies

### 4.1 Deep brain stimulation (DBS)

Another option to the neurosurgical interventions performed as last resource in treatment-resistant patients with extremely disabling symptoms is represented by deep brain stimulation. In deep brain stimulation (DBS) procedures, stimulation electrodes are implanted into specific brain regions and continuous electrical high frequency stimulation is delivered from a pulse generator. DBS is externally programmable and reversible, in that the stimulator can be turned on or off and controlled at the discretion of the clinician. The targets that have shown to provide the best results are both the anterior limbs of the internal capsule. The stimulation of this area seems to disrupt the activity in the loop fibers that connect the cortex with the thalamus and therefore interrupt the pathological circuit of this area (Shah et al., 2008). DBS in this site was successful in several case series (Abelson et al., 2005; Anderson and Hamed, 2003; Gabriels et al., 2003; Nuttin et al., 1999, 2003, 2008). In an open study, DBS was still effective after three years from the implantation (Greenberg et al., 2006). A multicenter randomized sham-controlled crossover study based on the stimulation of the subthalamic nucleus on 16 patients with severe OCD showed interesting results (Mallet et al., 2008). After 10 months of active stimulation 10 patients had a significant improvement of the symptoms and 4 recovered (Y-BOCS of 6 or less). However, the good results of this study are limited by the onset of some major adverse events (including a brain hemorrhage) and several minor adverse events.

### 4.2 Repetitive transcranial magnetic stimulation (rTMS)

There is no clear evidence regarding the use of rTMS in the treatment of OCD due to the fact that the design of the few studies performed differs in many important aspects such as site stimulation, parameters, and treatment duration. In double-blind sham-controlled studies, rTMS was ineffective both over the left dorsolateral prefrontal cortex was ineffective (Prasko et al. 2006; Sachdev et al. 2007) and over the right prefrontal rTMS (Alonso et al., 2001). Finally, interesting results were provided by two recent studies concerning the stimulation of the orbitofrontal cortex (Ruffini et al., 2009) and of the supplementary motor area (Mantovani et al., 2010) that showed a significant reduction of Y-BOCS score when compared to sham stimulation.

### 4.3 Electroconvulsive therapy (Ect)

Experts agree on the fact that ECT has a very limited role in OCD treatment, as there is no relevant evidence of benefits regarding the control of core symptoms of OCD (Bandelow et al., 2008) even if some case reports suggest the efficacy of it (Fukuchi et al., 2003; Strassnig et al., 2004;). Anyway, it may represent a useful tool for the treatment of OCD comorbidities such as depression, catatonia, etc. (Casey & Davis, 1994; Hanisch et al., 2009).

## 5. Conclusions and future perspectives

In conclusion, the range of therapeutic options for treatment-resistant patients is wide, and a number of them seem to have a quite good efficacy. Current research on animal and human models suggests that the discovery of more precise and distinctive neurofunctional targets is possible and that may successfully lead to a patient-tailored treatment algorithm. Identifying the different groups of patients and basing the treatment on reliable and easily detectable neurodysfunctional targets is one of the most desirable and exciting goals that in the next future may be achieved, in order to offer a highly specific treatment for each single patient.

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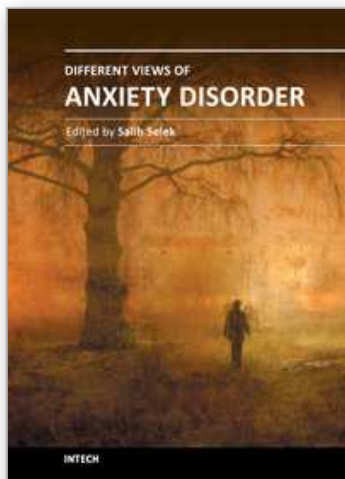
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