REVIEW ARTICLE

Current Treatment Strategies of Obsessive-Compulsive Disorder

Donatella Marazziti, Federico Mucci, Liliana Dell'Osso
Department of Clinical and Experimental Medicine, Section of Psychiatry, University of Pisa

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ABSTRACT
In the last decades, the treatment of obsessive-compulsive disorder (OCD) has dramatically improved with the introduction into the clinical practice of the selective serotonin reuptake inhibitors (SSRIs). However, a large part of patients do not respond to first-line drugs and different augmentation strategies have been proposed. More recently, some non-pharmacological techniques have been proposed, but the evidence of effectiveness is just preliminary. In this paper, the most recent works on pharmacological and alternative treatments of OCD will be reviewed.

Donatella Marazziti

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a relatively common psychiatric condition characterized by the presence either of obsessions or compulsions, or both and that is becoming one of the most severe causes of long-term disability to patients and their families.[1,2] The definition of obsessions is "recurrent and persistent thoughts, impulses or images which are experienced in an intrusive and inappropriate way, at some time during the disorder, which cause marked anxiety and distress and which persist despite all attempts to try to ignore, suppress or neutralize them", while compulsions are "repetitive behaviors or mental acts which a person feels driven to perform in response to an obsession or according to rigid rules: such behaviors are aimed at preventing or reducing distress or a dreaded event, and are always unrealistic or excessive".[1] OCD presents different levels of insight but, even if a poor-insight subtype has been described, the patients are usually aware that the obsessions or compulsions originate from their mind. OCD has been considered in the past years as a rare and treatment-resistant disorder, nevertheless current literature reports a mean lifetime prevalence of 2.5%, ranging between 0.3% in Taiwan and 5.5% in some Western countries.[1,2] Despite those data, OCD remains still underdiagnosed and, in particular, the gap between the onset of the first symptoms and the correct diagnosis might take several years. The main reason of underdiagnosis seems to be connected to the social

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Corresponding Author:
Dr. Donatella Marazziti, Dipartimento di Medicina Clinica e Sperimentale, Section of Psychiatry, University of Pisa, Via Roma, 67, I-56100 Pisa, Italy.
Telephone: +39 050 2219768, Fax: +39 050 2219787, E-mail: dmarazzi@psico.med.unipi.it

stigma related to psychiatric disorders: in OCD symptoms are perceived as disturbing, intrusive and unrealistic and patients try to hide them, fearing to be classified as "crazy".[1-3] Usually, psychiatric counseling is sought because of the concomitant presence of anxiety or depression.[2,3] The failure in the assessment for OCD symptoms is another important reason of underdiagnoses. Taken together, those data reveal how the delay in diagnosis relates to a remarkable impact on subjective sufferance, on psychosocial disability and on economic burden, nonetheless the existence of effective pharmacological treatment strategies. The first drug approved for the treatment of OCD by the US Food and Drug Administration was clomipramine: ten weeks-treatment studies demonstrated a significant reduction of specific symptoms in non-depressed OCD patients. The mean Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score reduction was ranging between 38% and 44%, compared with a mean Y-BOCS reduction between 3% and 5% in the placebo group.[4] Clomipramine is a tricyclic antidepressant (TCA) possessing a prevalent inhibitory activity on the serotonin (5-HT) reuptake and, compared to other non-predominantly serotonergic antidepressants (such as nortriptyline, amitriptyline, imipramine, and desipramine), clomipramine showed to be effective in OCD while the aforementioned TCAs demonstrated to be useful in depression but not in OCD. Therefore, amongst the numerous neurotransmitters potentially involved in the development of OCD, 5-HT may be strictly related to its pathophysiology and to its pharmacological response.[5,6] Subsequently, the successful introduction of selective 5-HT re-uptake inhibitors (SSRIs), such as fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram supported the hypothesis that OCD is unique in the response to serotonergic agents. Due to its chronic and disabling condition and since its symptoms possess an elevated relapse rate within a few weeks after discontinuation of drugs, OCD usually requires a long-term maintenance treatment. For this reason, the first line treatment plan should be discussed parallel to an adequate analysis of the compound efficacy and tolerability profile. Clomipramine possesses mainly anticholinergic side-effects, such as dry mouth, constipation, postural dizziness, somnolence, weight gain, and cardiovascular adverse effects (increase in standing heart rate, decrease in standing systolic blood pressure).[4] On the other hand SSRIs have less anticholinergic effect, even though they are likely related to asthenia, insomnia, nausea gastro-intestinal distress and sexual problems (decreased libido, impotence and anorgasmia).[7] Compared to clomipramine, SSRIs appear to have similar effectiveness and better tolerability profile, therefore they should be considered the first line treatment because of the higher safety, the side-effect profile and the lower rates of premature discontinuation and clomipramine should be considered as a second line, reserved to patients that did failed to respond to SSRIs or do not tolerate them.[7,8] The aim of this paper is to review and discuss the pharmacological and non- therapeutic strategies adopted in the management of OCD.

Pharmacological Treatments

Clomipramine

Clomipramine has been available in the clinical practice since the 60's and numerous open-label studies have reported its effectiveness, especially highlighting its anti-obsessional activity and distinguishing it from the antidepressant one and, by the mid 80's, clomipramine gained the official indication as anti-obsessional compound.[4] A considerable number of studies and meta-analyses demonstrated its superiority versus placebo and showed that clomipramine has the same effectiveness of newer compounds, if not even more, despite an higher rate of side effects (which in turn is related to a significant ratio of discontinuation).[8] Finally, clomipramine may be administrated through parenteral injection, which could be of notable importance in non-responding patients.

SSRIs

SSRIs are fairly similar each other and a particular choice amongst those agents mostly depends on possible drug interactions: in fact, many commonly prescribed drugs are metabolized throughout the cytochrome P450 (CYP) enzymes and, therefore, if there is the suspect of any eventual unsafe drug interactions, it should be preferred the use of SSRIs with a weak inhibiting action on CYP, for example sertraline, citalopram and escitalopram. CYP 2D6 iso-enzyme, which is responsible of TCAs, antipsychotics, antiarrhythmics and beta-blockers metabolism, is powerfully inhibited by fluoxetine and paroxetine. On the other hand, fluvoxamine inhibits either the CYP 1A2, that metabolizes warfarin and TCAs, either the CYP3A4 which eliminates some antiarrhythmics and benzodiazepines. Current literature is consistent on OCD requiring higher doses of SSRIs in comparison to depressive and anxiety disorders.[8,9]

Fluoxetine

The first SSRI agent approved for the treatment of OCD was fluoxetine. Several short-term treatment trials reported fluoxetine to be superior to placebo in the improvement of OCD symptoms when administrated at fixed doses of 40, 60 or 80 mg/day.[9-11] Another long-term trial reported no difference between fluoxetine and placebo, although the study was underpowered.[9,10]

Fluvoxamine

Fluvoxamine was the first SSRI to be investigated in OCD, obtaining encouraging results from several relatively small studies carried out since the 80's. Goodman et al. compared fluvoxamine to placebo and reported a modest but significant improvement within two weeks and an

increasingly significant effectiveness later.[12] These results were confirmed either from a subsequent multicentre placebo-controlled study that highlighted a significant advantage for fluvoxamine compared with placebo, either from other authors.[8,12] In comparison with clomipramine, fluovaximine showed the same effectiveness of the aforementioned TCA agent, with a better tolerability profile.[12,13] Some double-blind trials have reported the long-term effectiveness of fluvoxamine treatment (50-300 mg/day) in OCD. In particular, the administration of fluvoxamine was statistically significant associated to the reduction of symptoms with a relatively modest rate of side effects (the most common were sedation, tiredness and anorgasmia) and, in several cases, its discontinuation was found to be related to the relapse of OCD symptoms within a few days.[12,13]

Sertraline

An eight-weeks small flexible-dose study carried out in 81 patients demonstrated for the first time the effectiveness of sertraline (50-200 mg/day) in OCD.[14] The superiority of sertraline to placebo was firstly reported in a 12-weeks study carried out in 167 patients, in a double-blind multicenter study, and was subsequently confirmed by other long term-studies.[15] In comparison to placebo, sertraline was found to be superior either in maintaining global improvement of symptoms either in preventing discontinuations due to insufficient response or relapse. The increase of sertraline doses does not seem to be associated to any difference of the effectiveness, while adverse effects seem to decrease within the course of prolonged treatments. In particular, abnormalities in laboratory tests, vital signs or electrocardiogram were not associated to long-term administration of the drug and, of note, an earlier improvement of symptoms was reported when dose regimen was rapidly escalated.[15,16] Bergeron et al. performed a comparison study of sertraline (50-200 mg/day) versus fluoxetine (20-80 mg/day) in which both compounds showed a similar and significant improvement of OCD symptoms but the response to sertraline was more rapid, with a higher remission rate within the first 24 weeks of treatment.[17]

Paroxetine

The first preliminary reports about this SSRI compound dates back to the early '90s, when a large placebo-controlled compared the administration of paroxetine at different doses (20, 40 and 60 mg/day), demonstrating a significant effectiveness at 40 and 60 mg/day after 12 weeks of treatment.[18,19] The acute and long-term effectiveness, safety and impact on relapse prevention was evaluated by Hollander et al. in 2003. In particular, the administration of paroxetine at 40 mg/day and 60 mg/day resulted to be effective in the treatment of acute OCD. Moreover, they found that its long-term administration was associated to a decrease of the relapse rate and to a lengthen of the relapse time.[20]

Citalopram

The first evidence of a potential effectiveness of citalopram in the treatment of OCD dates back to the mid '80s. Marazziti et al. investigated the effectiveness of citalopram (40 mg/day) in an open-label trial which evaluated refractory OCD patients for 4 months and reported a significant reduction of symptoms without any relevant adverse effects in an elevated percentage of subjects.[21] Another placebo controlled study confirmed that the administration of citalopram at three different doses (20 mg, 40 mg and 60 mg) was superior than placebo, within a period of 12 weeks [30]. Intravenous citalopram (40 to 80 mg/day) was found to be safe and rapidly effective in a group of resistant OCD patients that were unresponsive to oral SSRIs [59].

Escitalopram

Escitalopram was compared to placebo and paroxetine in a three-arm study and it was reported to be either superior to placebo either to possess earlier onset, higher response and remission rates, improved function and better tolerability than paroxetine.[22] Another open label study randomized a group of escitalopram-responder OCD patients to escitalopram or to placebo to assess the relapse: subjects who received escitalopram had a significantly lower relapse rate. Finally, a 16-week prospective study reported that escitalopram resulted to be quite effective and well toleated.[11]

Other drugs

Venlafaxine was proved to be as effective as paroxetine for the improvement of OCD symptoms in resistant patients in a randomised double blind comparison study and in a series of case reports.[23] Mirtazapine was shown to be superior to placebo and to fasten the response.[24] Although some studies about phenelzine, inositol, d-cycloserine, riluzeole and morphine showed some evidence effectiveness, they were carried out in small samples or were not controlled or replicated, therefore those compounds should be considered mere suggestions.[25-29]

Non-pharmacological Treatments

Psychological treatments

The most effective psychological intervention in OCD is considered to be the so-called "exposure and response prevention" (ERP), which consists in encouraging patients to expose themselves to those situations that usually elicit obsessions but they are not allowed to perform compulsions in response. Response prevention, distraction and thought stopping are commonly employed to reduce and/or to interrupt rumination and rituals, whereas systematic desensitization, paradoxical intention,

flooding and satiation are the most used in vivo or in imagination exposure techniques. The effectiveness of ERP in OCD patients has been proved in several studies,[30] two of them reporting very high response rates (up to 85.8%) [146-147]. The beneficial effects of ERP were confirmed by (at least) two meta-analyses. The first took in account 24 trials and ERP to be related large pre- to post-therapy effect size (1.2), with outcomes stable over a 18 weeks follow-up (1.1). A further meta-analysis reported an effect size of 0.99 for ERP, similar to that found for SRIs (0.87) or for combination treatment (ERP plus SRIs) (1.07). These results suggest a similar effectiveness for the three therapeutic strategies. Studies on cognitive therapy (CT) for OCD led to less clear results and, in some cases, controversial.[31,32] The various cognitive models proposed for OCD suggest that the anxiety deriving from the erroneous appraisal of intrusive thoughts that are given an overestimated importance would develop and maintain OCD symptoms.[33] Also, the tendency to overestimate intrusive thoughts and impulses would be involved in the origin of the excessive sense of responsibility, that is a characterizing trait of OCD patients. CT was found to possess a higher efficacy than ERP in a controlled comparing study carried out on 71 patients,[32] although at a not statistical significant level. In particular, subjects who were exposed to CT had 57% of complete remission and 75% of significant improvement. In addition, some studies report a possible adjunctive benefit when cognitive and behavioral techniques are combined, especially in subjects who failed to respond to ERP alone.[34] The combination of ERP with cognitive behavioral technique (CBT) was found to be more successful than ERP alone in a comparative study,[34] and to appear particularly helpful in managing ruminations.Unfortunately, the results of studies comparing the effectiveness of psychological (ERB and/or CBT) and SRIs treatments are inconclusive.[35] In fact, when psychological and pharmacological treatments were combined, they appeared to possess a similar efficacy with broadly equivalent effect size.[36] Foa et al. compared ERP with clomipramine, the combination of this compound with the abovementioned psychological technique and placebo.[35] They found that the combination of clomipramine and ERP led to a 58% reduction of Y-BOCS, that was significantly higher than the results observed with placebo (11%) or clomipramine alone (31%). Interestingly, ERP alone had an Y-BOCS reduction percentage of 55%. In other words, the response of compulsions to SRIs was poorer than to ERP. If these results are combined to the fact that SRIs seem to be effective only in a half of OCD subjects, it becomes evident that CBT is possibly the best available treatment for OCD, in both the short-term and in the long term. CBT, in fact, is recommended as the first line treatment for most cases of OCD by the American Psychiatric Association's guidelines.

Repetitive transcranial magnetic stimulation (rTMS)

rTMS is a not invasive and sufficiently tolerated technique for which, however, only few and controversial data are available. In addition, data are hardy comparable because they included different brain areas, or used different stimulatory parameters.[37] It is speculated that its utilization will increase in the future years, especially in resistant cases.

Deep brain stimulation (DBS)

DBS is an invasive technique, usually performed in both anterior limbs of the internal capsules. Nevertheless only scant data are available for OCD, DBS is considered effective in severe cases.[38,39] Of note, the results emerging from data on DBS applied to the ventral caudate nucleus and to the right nucleus accumbens seems encouraging.[40]

Neurosurgery

Bilateral anterior capsulotomy, cingulotomy, leucotomy and subcaudate tractotomy are the neurosurgery techniques reserved to severe, and otherwise untreatable, OCD patients. In fact, neurosurgery is involved in several and potentially grievous adverse effects including suicidal behaviors.[41-43]

Electroconvulsive therapy (ECT)

Although some authors reported a certain level of effectiveness in some patients, most of studies carried out about ECT were uncontrolled.[44,45]

Future Perspectives

Even though one third of the patients do not respond to the common medications used, such as SSRIs or clomipramine, the psychopharmacological management of OCD patients is considered one of the most successful achievements of the last decades. In other words, these compounds are unable to treat the basic disorder because of the limited knowledge of the causal mechanisms. Nevertheless our possibilities of intervention are confined to the pathophysiological levels, these drugs remain successfully effective on symptoms (or dimensions). The role of 5-HT in OCD is indeed of crucial importance as proven either by the continuously growing bulk of new data implicating 5-HT in the patophysiology of this disorder, either by the current pharmacotherapy OCD (for which 5-HT system is central). Although such a convergence of data has not been found in any other psychiatric disorder, 5-HT is far from representing the only neurotransmitter involved and, in fact, several studies suggest disturbances at the level of other neurotransmitters, in particular dopamine and norepinephrine, of neuropeptides (e.g., oxytocin, and of other mechanisms, such as infections and disorders of the immune system, or second messengers.[46,47] With the exception of citalopram and escitalopram, SSRIs seem to interact with other receptors and systems in a more heterogeneous way than previously hypothesized, besides

commonly sharing the representative feature of 5-HT reuptake blockade. Of note, sertraline and citalopram appear to be still quite successful in OCD patients resistant to other SSRIs.[16,21] It might be assumed that such an heterogeneity of clinical features could be underlying to as many different biological mechanisms, but only a sharper definition of these mechanisms would lead to a more focused therapeutic tailoring. Obviously, further controlled studies are urgently needed. Augmentation strategies in OCD are for the largest part affected to the limitation of the 5-HT paradigm, based on poor clinical observation, not completely convincing and in need of further, more accurate, investigations.[28,47] Therefore, the current challenge is represented by the development of new, alternative and unrelated to 5-HT system therapeutic strategies. At the present time, amongst the possible pharmacological compounds, only haloperidol, pimozide and risperidone seem to posses available and convincing data for the treatment of some OCD patients, whereas the evidences are poorer for other antipsychotics, in particular for those of second generation. The clinical use of lithium salts, tryptophan or buspirone in resistant OCD is not supported by any controlled study. Results of psychological interventions, such as CBT and ERP, are indeed encouraging but further studies are still required to give additional details about their effectiveness, especially when combined with pharmacological treatments. On the other hand, given their intriguing potentialities and safety, rTMS and DBS would deserve supplemental controlled studies, possibly performed with standardized and/or comparative methods. The nature and level of adverse effects, especially within the course of long time treatments, are of crucial importance regarding to patient's compliance and to the odds of a successful outcome. Whereas in the short-term use SSRIs appear to be better tolerated than clomipramine, in the long-term those compounds are related to the development of invalidating adverse effects, amongst which we mention sexual dysfunctions. As a final note, it shall be remarked how the treatment of OCD represents one of the most successful achievements of psychiatry in the last decades, nonetheless several issues requires still to be solved.

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