CRITICAL ISSUES IN THE PHARMACOLOGICAL TREATMENT OF OBSESSIVE-COMPULSIVE DISORDER

Donatella Marazziti, Francesco Mungai, Laura Vivarelli, Bernardo Dell'Osso

Summary

The developments of specific drugs to increase the availability of serotonin (5-HT) in the synaptic cleft, namely, the selective 5-HT re-uptake inhibitors (SSRIs), has provided therapeutic tools to manage obsessive-compulsive disorder (OCD) and to promote research in this area. Although SSRIs represent great clinical advancements, they are not perfect and provoke a series a side-effects which, although not as severe as those elicited by tricyclics, may still reduce the compliance to treatment and impair daily life.

Scope of this paper is to critically review pharmacological studies in OCD, with a special emphasis to long-term trials, given the evidence that this disorder require to be treated for several years.

Key words: OCD – SSRIs - Long-Term Treatments – Side-Effects

Declaration of interest: none

Donatella Marazziti, Francesco Mungai, Laura Vivarelli, Bernardo Dell'Osso
Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, University of Pisa

Corresponding Author
Donatella Marazziti, Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, University of Pisa, Via Roma, 67, 56100 Pisa, Italy. Telephone: +39 050 835412, fax: +39 050 21581, e-mail: dmarazzi@psico.med.unipi.it

Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric condition characterized by the presence either of obsessions or compulsions or both. Obsessions are defined as 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. Compulsions are defined as repetitive behaviours or mental acts which a person feels driven to perform in response to an obsession or according to rigid rules: such behaviours are aimed at preventing or reducing distress or a dreaded event and are always unrealistic or excessive (APA 1994). Although the sufferer generally recognizes that the obsessions or compulsions are products of his or her own mind, the degree of insight can vary and a subtype with poor insight has been recognized.

Once considered rare and resistant to treatments, OCD has now emerged as one the most common psychiatric conditions, with a lifetime prevalence of about 2.5 %, and as a major cause of long-term disability to patients and their families (Karno et al. 1988, Hollander and Stein 1999). However, OCD is still underdiagnosed, not only by general practitioners, but also by psychiatrists. An epidemiological study has shown that 17 years is the average time between the onset of the first symptoms and the correct diagnosis (Hollander and Weilgus-Kornwasser 1997). There are different reasons for this underdiagnosis: one of the main one is represented by the secretive nature of the disorder, so that the patients think to be "crazy" and try to hide the symptoms for the social stigma linked to psychiatric disorders. This delay in diagnosis has a profound impact on subjective sufference, as well as in terms of psychosocial disability and economic costs to society, in spite of the availability of effective drugs for its treatment.

The treatment of OCD has, in fact, changed dramatically over the last decade following the utilization of selective serotonin (5-HT) re-uptake inhibitors (SSRIs), such as fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and the evidences that OCD is unique in the response to serotonergic agents and it has been clearly demonstrated that non-serotonergic antidepressants such as desipramine have no effect (Montgomery et al. 1994, Greist et al. 1995, Piccinelli et al. 1995, Finiberg et al. 1996).

The first observations highlighting the role of 5-HT in the pharmacological response of OCD were those related to the effectiveness of clomipramine, a tricyclic antidepressant (TCA) with a prevalent inhibitory activity on 5-HT reuptake. Studies comparing clomipramine with nortriptyline, amitriptyline, imipramine, and desipramine showed that, while these TCAs are effective in depression, they are not useful on OCD symptoms (Finiberg 1996, Hohen-Saric 2000). Subsequently, the

introduction into the clinical practice of selective 5-HT reuptake inhibitors (SSRIs) hence supported the crucial role of the 5-HT system in the pathophysiology and treatment of OCD; different placebo-controlled studies, in fact, demonstrated the efficacy of fluvoxamine, fluoxetine, sertraline, paroxetine and citalopram in OCD (Zohar et al. 2000).

Clomipramine was the first agent approved by the US Food and Drug Administration for the treatment of OCD: a significant reduction in OCD symptoms in non-depressed patients (mean Y-BOCS reduction between 38% and 44%) compared with placebo (mean Y-BOCS reduction between 3% and 5%) was demonstrated in ten weeks-treatment studies (CCSG, 1991).

Since OCD is a chronic and disabling condition and its symptoms are likely to recur within a few weeks after discontinuation of drugs, long-term maintenance treatment is frequently necessary and the first line treatment should be planned while considering efficacy and good tolerability profile of the compound. The main side effects associated with clomipramine are anticholinergic, 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) (CCSG 1991, Lydiard 1996). The head-to-head comparison between clomipramine and SSRIs has generally shown similar effectiveness with a better tolerability profile for the SSRIs. It has been observed that the drop-out rate for adverse effects on clomipramine (around 17%) was consistently higher than that for the SSRIs (around 9%) that are in general better tolerated, although they may provoke more frequently asthenia, insomnia and nausea. Considering the higher safety, the tolerability profile and the lower rates of premature discontinuation, SSRIs should be considered the first line treatment, with clomipramine as a second line treatment reserved for patients who do not tolerate SSRIs or have failed to respond to them.

Discussion

Clomipramine: the effectiveness of clomipramine in OCD has been documented by several open-label studies since its availability in the clinical practice in the 60's (Lopez-Ibor 1967). Since that time, its anti-obsessional activity was distinguished from the antidepressant one and a longer latency of response in OCD patients was observed. The official indication as anti-obsessional compound arrived just in the 80's after the contribution of several studies (Flament et al. 1985, Mavissakalian et al. 1985, Murphy et al. 1985). In a double-blind controlled versus placebo trial the effectiveness of clomipramine (100-300 mg/day) was assessed in 263 OCD patients (Kats et al. 1990); subsequently, responders to treatment (n=124) were entered a double-blind extension period of further 52 weeks. At the end of this period, more than one half of those patients who received clomipramine had significantly improved their symptoms. The discontinuation rate due to adverse events was 22.7% of clomipramine-treated patients versus 0% of placebo patients.

In spite of its higher rate of side effects, clomipramine has demonstrated the same potency of newer compounds, and it appeared even more effective in some meta-analysis (Song et al. 1993, Mitchell et al. 1997, Anderson 2000) or in studies which were not supported by pharmaceutical companies (DUAG 1986, DUAG 1990). Another advantage of this drug is probably the possibility of its parenteral administration, which may be particularly relevant in non-responder patients. Although no data from studies performed with multiple fixed doses are available, the suggested doses to be used in OCD patients would range between 100 and 300 mg/daily, while the minimal effective dose has been considered to be 75 mg/daily (Montgomery 1980).

SSRIs: given their similarities, the choice between one SSRI and another largely depends upon personal preference or the possibility of drug interactions. Sertraline and citalopram are relatively weak inhibitors of the haepatic cytochrome P450 enzymes which metabolize commonly prescribed drugs and may be preferred if drug interactions are likely to be a problem. Fluoxetine and paroxetine are potent inhibitors of the CYP 2D6 iso-enzyme which metabolizes TCAs, antipsychotics, antiarrhytmics and beta-blockers. Fluvoxamine inhibits both the CYP 1A2, which eliminates warfarin and TCAs, and CYP 3A4, which metabolises benzodiazepines and some antiarrhytmics.

Fluoxetine: fluoxetine was the first SSRI approved for the treatment of OCD. Long-term treatment trials (Montgomery 1993, Tollefson 1994, Romano 2001) reported fluoxetine, administered at fixed doses (40, 60, 80 mg/day), to be superior to placebo in ameliorating OCD symptoms. A statistically significant improvement from the baseline was observed at either 60 and 80 mg/day doses. A report of a study in Austrian patients confirmed the more significant effectiveness of 40 and 60 mg/day of fluoxetine (Zitterl et al. 1999).

Fluoxetine was in general well tolerated and the rate of relapse was numerically lower, as compared with patients who received placebo.

Fluvoxamine: it was the first SSRI to be investigated in OCD. Positive results were reported in a series of relatively small studies carried out in the 80's: a modest albeit significant advantage compared with placebo was seen after two weeks' treatment in a comparison study which included 42 patients, with an increasingly significant later effectiveness (Goodman et al. 1989). A multicentre placebo-controlled study including 160 patients and which lasted 10 weeks, reported a significant advantage for fluvoxamine compared with placebo (Goodman et al. 1996).

The efficacy of long-term fluvoxamine treatment in OCD has been reported in double-blind trials (Cottraux 1990, Mallya 1992, Hollander 2003) where fluvoxamine (50-300 mg/day) was associated with a statistically significant reduction in OCD severity and was found to be safe and well tolerated. The most common adverse events were sedation, tiredness and anorgasmia (Mallya 1992). However, in several cases, a discontinuation of fluvoxamine was associated with recurrence of OCD symptoms within a few days (Mallya 1992). In a double-blind, multicenter comparison study

with clomipramine, fluvoxamine showed to be as effective as clomipramine with a better tolerability profile (Mundo 2001).

Sertraline: the effectiveness of sertraline at the doses of 50-200 mg/day was firstly demonstrated in a small flexible–dose study carried out in 81 patients which lasted 8 weeks (Chouinard et al. 1990). A 12 week-long study on 167 patient showed a significant advantage of sertraline, as compared with placebo (Kronig et al. 1999). In the first double-blind, multicenter study (Jenike 1990), the superiority of sertraline versus placebo in ameliorating OCD symptoms was reported, followed by other long-term studies. Differences related to the effectiveness do not seem to be associated with increasing doses regimen, except for the onset of side effects which, however, seem to decrease during prolonged treatment (Rasmussen 1997). Other studies showed that long-term administration was not associated with the occurrence of significant abnormalities in laboratory tests, vital signs, or electrocardiogram (Greist 1995). It has been reported that a rapidly escalating dose regimen was associated with an earlier improvement of symptoms (Bogetto et al. 2002). Sertraline was also found to be superior to placebo in preventing discontinuations due to relapse or insufficient response and in maintaining clinical improvement (Koran 2002). In a comparison study aiming at assessing the efficacy of sertraline (50-200 mg/day) versus fluoxetine (20-80 mg/day), a similar and significant improvement with both the compounds was observed, however, the response to sertraline was more rapid: in fact, a higher percentage of patients in remission within the first 24 weeks was observed amongst the sertraline group (Bergeron 2002).

Paroxetine: a few data are available for the treatment of OCD patients with paroxetine. Preliminary reports from a large, placebo-controlled comparison of three doses of paroxetine (20, 40 and 60 mg/day) have shown the significant effectiveness of the two higher doses after 12 weeks (Wheadon et al. 1993). An important large placebo-controlled multicentre study, including 399 patients treated for 12 weeks demonstrated a significant superiority over placebo (Zohar and Judge 1996). Hollander et al. (2003) evaluated the acute and long-term effectiveness, safety, and impact on relapse prevention of paroxetine: this drug given at 40 mg/day and 60 mg/day (but not 20 mg/day) resulted effective in treating acute OCD, while long-term administration showed to be effective and safe, to decrease the rate of relapse, and to lengthen the time of relapse.

Citalopram: a case report was the first suggesting the potential effectiveness of citalopram in the treatment of OCD (White 1986), followed by open treatment studies: in one of these, the effectiveness of citalopram (40 mg/day) was evaluated in refractory OCD patients along a period of 4 months, and a significant reduction of symptoms with no relevant side-effects was reported in a high percentage of them (Marazziti et al. 2001). The effectiveness of citalopram has been confirmed in a recent 12-week placebo-controlled study where all tested doses of citalopram (20 mg, 40 mg and 60 mg/day) were shown to be better than placebo (Montgomery et al. 2001).

Citalopram, such as clomipramine, may be administered intravenously and this constitutes a potential tool for resistant patients: in fact, a recent study performed in a group of OCD patients unresponsive to orally administered SRI's showed that intravenous citalopram (40 to 80 mg/day) rapidly effective and safe (Pallanti 2002).

Refractory OCD: despite the effectiveness of SRI's, nearly 40% of OCD patients experience poor or no improvement with these treatments; furthermore, a few patients experience full symptoms remission (McDougle 1993). It has been reported that, notwithstanding a significant improvement in functioning, interferring symptoms usually persist (Goodman 1989). Several therapeutical strategies have been proposed, including the use of standard pharmacologic agents in higher dosages or administered via an alternative route, combination drug treatment, and the use of novel compounds.

The neurobiological basis of these augmentation strategies consist in enhancing the 5-HT function, or in adding a dopamine receptors antagonist, such as some typical or atypical antipsychotics, to ongoing SRI drugs, however, most of these modalities have not been confirmed at the bedside or by means of rigorous studies. No controlled studies of augmentation with tryptophan have been published and the available data suggest this approach not to be useful (Mattes 1986). Two placebo-controlled trials of lithium augmentation and three placebo controlled trials of buspirone augmentation of SSRIs found these strategies to be no more effective than placebo. A small open-abel case series has reported encouraging results with the co-administration of clomipramine and fluoxetine in adolescent OCD (Simeon 1990); the beneficial effects of this combination have also been reported in three adult cases of severe OCD (Browne 1993). The data relative to the augmentation strategies with typical and atypical neuroleptic drugs are more convincing. In a double-blind comparison with placebo, haloperidol (mean dose: 6.2 mg/day) was significantly more effective when added to ongoing treatment in adult OCD patients not responding to fluvoxamine alone (McDougle 1994). The atypical neuroleptic drugs, which modulate both the dopamine and 5-HT function and may be associated with lower incidence of extrapyramidal side effects, have been the focus of a growing interest. Risperidone, added to an SRI in patients who failed to respond to monotherapy, showed to be effective in an open trial (Saxena 1996), followed by two double-blind placebo controlled studies, even in presence of tic disorder or schizotypal personality disorder (McDougle 2000, Hollander 2003). Data relative to the use of olanzapine in refractory OCD are still controversial. In two open-label trials olanzapine was shown to be effective when administered as augmentation of paroxetine (D'Amico 2003) and fluvoxamine (Bogetto et al. 2000), whereas a recent double-blind, placebo-controlled trial indicated no additional advantage of adding olanzapine in fluoxetine-refractory OCD patients (Shapira 2004). The effectiveness of the augmentation strategy with quetiapine is still to be clarified. In a single-blind placebo-controlled study, this drug showed a significant improvement (Atmaca 2002), and encouraging data derive also from an open-label study (Denys 2002) and

a retrospective evaluation (Mohr 2002). However, a recent open-label trial assessing the effectiveness of quetiapine (150 mg/day) in addition to ongoing SRI treatment, suggests that low doses of this drug may not be effective in resistant OCD patients (Sevincok 2003).

Following a series of case reports (Marazziti et al. 2003), a recent randomised double-blind comparison study of venlafaxine in OCD patients showed that this drug was as effective as paroxetine in improving OCD symptoms (Denys 2003).

Conclusions

Although the treatment of OCD patients represents one of the greatest psychopharmacological achievements at the end of the old millennium, it should be noted that one third of the patients do not respond to the common medications used, such as SSRIs or clomipramine, as it is almost the rule for other psychiatric disorders. This means that these drugs are effective on symptoms (or dimensions), but cannot treat really the basic disorders. Obviously this gap is related to the meager knowledge of the causal mechanisms, so that our possibilities of intervention remain limited to the pathophysiological levels, but, in spite of this, are quite successful. However, if with no doubt the 5-HT system is central to the pharmacological treatment of OCD and the current bulk of evidences implicating 5-HT in the pathophysiology of OCD is increasing at a level and with a convergence not found in any other psychiatric disorder, it is unlikely that 5-HT represents the whole story. Different studies sugggest abnormalities in other neurotransmitters, such as dopamine and norepinephrine, in neuropeptides in particular oxytocin, and in other mechanisms, such as infections and disorders of the immune system (Swedo et al. 1997), or second messengers (Marazziti et al. 2003) that need to be elucidated. It can be hypothesized that the heterogeneity in pathophysiological mechanisms might underlie the different clinical pictures. Obviously, a better definition of these mechanisms would lead to more focused therapeutic tailoring, beyond the 5-HT paradigm. Moreover, latest developments in the pharmacology of SSRIs have shown that, although sharing the common property of 5-HT reuptake blockade, apart citalopram and escitalopram, they do interact with other receptors and system and are more heterogenous than previously assumed. A few observations have, in fact, proposed that sertraline and citalopram may be still quite effective in OCD patients resistant to other SSRIs (Marazziti et al. 2001, Bogetto et al. 2002). In any case, further controlled studies are needed to elucidate the possible different clinical responses or specificity on target symptoms of the SSRIs.

The limitations of the 5-HT paradigm in the pharmacological treatment of OCD is evident also in the augmentation strategies that are mainly centered on this neurotransmitter: most of the currently proposed strategies are actually based upon a few clinical observations which are not convincing and need to be tested more throughly (Mc Dougle 1997). No controlled clinical studies support the use of buspirone, lithium salts or tryptophan in resistant OCD. Alternative strategies, not related to the serotonin system must be developed: the only convincing data available nowadays are those related to haloperidol, pimozide and risperidone.

OCD requires treatment for a long time and current guidelines suggest that two months is the minimum time to evaluate the clinical response: for this reason short-term clinical trials, albeit controlled, must be interpreted with cautions. In addition, with long treatments, the nature and level of side effects are important to get the patient's compliance and, therefore, to to the likehood of a successful outcome. If SSRIs, in the short-term use, are better tolerated than clomipramine, they produce invalidating effects in long-term utilization, such as those involving sexual functions: this coupled to the results of some meta-analyses suggesting that clomipramine may be more effective not only in resistant patients raise the issue a throughougly re-evaluation of their effectiveness in OCD.

In conclusions, although the treatment of OCD patients represents one of the greatest success of psychiatry in this last decade and was not achieved through serendipity, as it occurred for other psychiatric disorders, several problems need to be resolved as yet, in particular the integration of different piece of information and findings that would lead to a proper management of the disorder.

References

American Psychiatric Association Committee on Nomenclature and Statistics (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition. Washington, DC, American Psychiatric Press.

Anderson IM (2000). Selective serotonin reuptake inhibitors versus tryciclcic antidepressants: a meta-analysis of efficacy and tolerability. *J Affect Disord* 58(1), 19-36.

Atmaca M, Kuloglu M, Tezcan E, Gecici O (2002). Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. *Int Clin Psychopharmacol* 17(3), 115-9.

Bergeron R, Ravindran AV, Chaput Y, et al (2002). Sertraline and fluoxetine treatment of obsessive-compulsive disorder: results of a double-blind, 6-months study. *J Clin Psychopharmacol* 22, 148-154.

Bogetto F, Albert U, Maina G (2002). Sertraline treatment of obsessive-compulsive disorder: efficacy and tolerability of a rapid titration regimen. *Eur Neuropsychopharmacol* 12(3), 181-6.

Bogetto F, Bellino S, Vaschetto P, Ziero S (2000). Olanzapine augmentation of fluvoxamine-refractory obsessive-compulsive disorder (OCD): a 12-week open trial. *Psychiatry Res* 96(2), 91-8.

Browne M, Horn E, Jones TT (1993). The benefits of Clomipramine-fluoxetine combination in obsessive-compulsive disorder. *Can J Psychiatry* 38, 242-3.

Chouinard G, Goodman W, Greist J, Jenike M, Rasmussen S, White K, Hackett E, Gaffney M, Bick PA (1990). Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive disorder. *Psychopharmacol Bull* 26(3), 279-84.

Clomipramine Collaborative Study Group (1991). Clomipramine in the treatment of patients with obsessive-compulsive disorder. *Arch Gen Psychiatry* 48, 730-738.

Cottraux J, Mollard E, Bouvard M, et al (1990). A controlled study of fluvoxamine and exposure in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 4, 517-30.

D'Amico G, Cedro C, Muscatello MR, Pandolfo G, Di Rosa AE, Zoccali R, La Torre D, D'Arrigo C, Spina E (2003). Olanzapine augmentation of paroxetine-refractory obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 27(4), 619-23.

Danish University Antidepressant Group (DUAG) (1986). Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. *Psychopharmacol* 90, 131-138.

Danish University Antidepressant Group (DUAG) (1990). Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *J Affect Disord* 18, 289-299.

Denys D, van der Wee N, van Megen H, Westenberg H (2003). A double-blind comparison of venlafaxine and paroxetine in obsessive-compulsive disorder. *J Clin Psychopharmacol* 23(6), 568-575.

Finiberg N (1996). Refining treatment approaches in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 11(suppl.5), 13-22.

Flament MF, Rapoport JL, Berg CJ et al (1985). Clomipramine treatment of childhood obsessive-compulsive disorder: a double blind controlled study. *Arch Gen Psychiatry* 42, 977-983.

Goodman WK, Price LH, Rasmussen SA et al (1989). The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) part I development, use and reliability. *Arch Gen Psychiatry* 46, 1006-11.

Goodman WK, Price LH, Rasmussen SA et al (1989). The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) part II validity. *Arch Gen Psychiatry* 46, 1012-16.

Goodman WK, Price LH, Rasmussen SA, Heninger GR, Charney DS (1989). Fluvoxamine as an antiobsessional agent. *Psychopharmacol Bull* 25(1), 31-5.

Greist JH, Jefferson JV, Kobak KA, Katzelnick DJ, Serlin RC (1995). Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. A meta-analysis. *Arch Gen Psychiatry* 52, 53-60.

Hoehn-Saric R, Ninan P, Black DW, et al (2000). Multicenter double blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. *Arch Gen Psychiatry* 57, 76-82.

Hollander E, Allen A, Steiner M, Wheadon DE, Oakes R, Burnham DB (2003). Acute and long-term treatment and prevention of relapse of obsessive-compulsive disorder with paroxetine. *J Clin Psychiatry* 64(9), 1113-21.

Hollander E, Koran LM, Goodman WK, Greist JH, Ninan PT, Yang H, Li D, Barbato LM (2003). A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. *J Clin Psychiatry* 64(6), 640-7.

Hollander E, Rossi NB, Sood E, Pallanti S (2003). Risperidone augmentation in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Int J Neuropsychopharmacol* 6(4), 397-401.

Hollander E, Stein D (1999). *Obsessive-compulsive disorder.* Oxford Press.

Hollander E, Weilgus-Kornwasser J (1997). Counting the cost-the psychosocial and economic burden of OCD. *Focus on OCD* 5, 3-5.

Jenike MA, Baer L, Summergrad P, Minichiello WE, Holland A, Seymour R (1990). Sertraline in obsessive-compulsive disorder: a double-blind comparison with placebo. *Am J Psychiatry* 147(7), 923-8.

Karno M, Golding JM, Sorenson SB, Burnam MA (1988). The epidemiology of obsessive-compulsive disorder in five US communities. *Arch Gen Psychiatry* 45(12), 1094-9.

Katz RJ, De Veaugh-Geiss J, Landau P (1990). Clomipramine in obsessive-compulsive disorder. *Biol Psychiatry* 28, 401-414.

Koran LM, Hackett E, Rubin A, Wolkow R, Robinson D (2002). Efficacy of sertraline in the long-term treatment of obsessive-compulsive disorder. *Am J Psychiatry* 159, 88-95.

Kronig MH, Apter J, Asnis G, Bystritsky A et al (1999). Placebo-coontrolled, multi-centre study of sertraline study for obsessive-compulsive disorder. *J Clin Psychopharmacol* 19, 172-176.

Lopez-Ibor JJ, Fernandez-Cordobe E (1967). La monclomipramina en-enfermos resistentes a otros tratamiantos. *Acta Luso-Espan Neurol Psiquiatria* 26, 119-147.

Lydiard RB, Brawman-Mintzer O, Ballenger JC (1996). Recent developments in the psychopharmacology of anxiety disorders. *J Consult Clin Psychol* 64, 660-668.

Mallya GK, White K, Waternaux C et al (1992). Short and long-term treatment of obsessive-compulsive disorder with fluvoxamine *Ann Clin Psychiatry* 4, 77-80.

Marazziti D, Dell'Osso L, Gemignani A et al (2001). Citalopram in refractory obsessive-compulsive disorder: an open study. *Int Clin Psychopharmacol* 16, 215-219.

Marazziti D (2003). Venlafaxine treatment of obsessive-compulsive disorder: case reports. *CNS Spectr* 8(6), 421-2.

Mattes J (1986). A pilot study of combined trazodone and tryptophan in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 1, 170-3.

Mavissakalian M, Turner SM, Michelson L, Jacob R (1985). Tryciclcic antidepressant in obsessive-compulsive disorder. Antiobsessional or antidepressant agents? *Am J Psychiatry* 42, 301-306.

McDougle CJ, Epperson CN, Pelton GH et al (2000). A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor refractory obsessive-compulsive disorder. *Arch Gen Psychiatry* 57, 794-801.

McDougle CJ, Goodman WK, Lechman JF, et al (1993). The psychopharmacology of obsessive-compulsive disorder: implications for treatment and pathogenesis. *Psychiatr Clin North Am* 16, 749-66.

McDougle CJ, Goodman WK, Leckman JF, et al (1994). Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder: a double-blind, placebo-controlled study in patients with and without tics. *Arch Gen Psychiatry* 51, 302-8.

McDougle CJ (1997). Update on pharmacologic management of OCD: agents and augmentation. *J Clin Psychiatry* 58(12), 11-17.

Mitchell J, Greenberg J, Finch K et al (1997). Effectiveness and economic impact of antidepressant medication: a review. *Am J Manag Care* 3(2), 323-330.

Mohr N, Vythiligum B, Emsley RA, Stein DJ (2002). Quetiapine augmentation of serotonin reuptake inhibitors in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 17(1), 37-40.

Montgomery SA (1994). Pharmacological treatment of obsessive-compulsive disorder. In: Hollander E, Zohar J, Marazziti D, Oliver B (eds): *Current insights in obsessive-compulsive disorder*. Chichester, Wiley & Sons, pp 215-226.

Montgomery SA, Kasper S, Stein D, et al (2001). Citalopram 20mg, 40mg and 60mg are all effective and well tolerated compared with placebo in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 16(2), 75-86.

Montgomery SA, Mc Auley R, Montgomery DB, et al (1980). Plasma concentration of clomipramine and desmethylclomipramine and clinical response in depressed patients. *Postgrad Med J* 56(suppl 1), 130-133.

Montgomery SA, McIntyre A, Osterheider M, Sarteschi P, Zitterl W, Zohar J, Birckett M (1993). Wood AJ and the Lilly Europen OCD Study Group. A double-blind placebo-controlled of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder. *Eur Neuropsychopharmacol* 3, 143-152.

Mundo E, Rouillon F, Figuera ML, Stigler M (2001). Fluvoxamine in obsessive-compulsive disorder: similar efficacy but superior tolerability in comparison with clomipramine. *Hum Psychopharmacol* 16(6), 461-468.

Murphy DL, Siever LJ, Insel TR (1985). Therapeutic response to tryciclic antidepressants and related drugs in non affective disorder patient population. *Prog Neuro-Psychopharmacol Biol Psychiatry* 9, 3-13.

Pallanti S, Quercioli L, Koran LM (2002). Citalopram intravenous infusion in resistant obsessive-compulsive disorder: an open trial. *J Clin Psychiatry* 63(9), 796-801.

Piccinelli M, Pini S, Bellantuono C, Wilkinson G (1995). Efficacy of drug treatment in obsessive-compulsive disorder. A meta-analytic review. *Br J Psychiatry* 166(4), 424-43.

Rasmussen SA, Baer L, Shera D (1997). Previous treatment and efficacy of sertraline for OCD: combined analysis of 4 multicenter trials. Annual meeting of the American Psychiatric Association San Diego CA. May, 17-22.

Romano S, Goodman W, Tamura R, Gonzales J (2001). Long-term treatment of obsessive-compulsive disorder after an acute response: a comparison of fluoxetine versus placebo. *J Clin Psychopharmacol* 21, 46-52.

Saxena S, Wang D, Bystritsky A, et al (1996). Rieperidone augmentation of SRI treatment for refractory obsessive-compulsive disorder. *J Clin Psychiatry* 57, 303-6.

Sevincok L, Topuz A (2003). Lack of efficacy of low doses of quetiapine addition in refractory obsessive-compulsive disorder. *J Clin Psychopharmacol* 23(5), 448-450.

Shapira NA, Ward HE, Mandoki M, Murphy TK, Young MCK, Blier P, Goodman WK (2004). A double-blind, placebo-controlled trial of oloanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. *Biological Psychiatry* 55(5), 553-555.

Simeon JC, Thatte S, Wiggins D (1990). Treatment of adolescent obsessive-compulsive disorder with a clomipramine-fluoxetine combination. *Psychopharm Bull* 26, 285-90.

Song F, Freemantle N, Sheldon TA et al (1993). Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *Br Med J* 306(6879), 683-687.

Swedo SE, Leonard HL, Mittleman BB, Allen AJ, Rapoport JL, Dow SP, Kanter ME, Chapman F, Zabriskie J (1997). Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever. *Am J Psychiatry* 154(11), 1630-1.

Tollefson GD, Rampey AH, Pottvin JH et al (1994). A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* 51, 559-567.

Weadon D, Bushnell WD, Steiner M (1993). A fixed dose comparison of 20, 40,or 60mg of paroxetine to placebo in the treatment of obsessive-compulsive disorder. Presented at the American College of Neuropsychopharmecology Annual Meeting, Puerto Rico, Dec.

White K, Keck PE Jr, Lipinski J (1986). Serotonin-uptake inhibitors in obsessive-compulsive disorder: a case report. *Compr Psychiatry* 27(3), 211-4.

Zitterl W, Meszaros K, Hornik K, Twaroch T et al (1999) Efficacy of fluoxetine in Austrian patients with obsessive-compulsive disorder. *Wien Clin Wochenschr* 111, 439-442.

Zohar J, Judge R (1996). Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. *Br J Psychiatry* 169, 468-474.

Zohar J, Chopra M, Sasson Y, Amiaz R, Amital D (2000). Obsessive compulsive disorder: serotonin and beyond. *World J Biol Psychiatry* 1(2), 92-100.