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REVIEW

Efficacy of treatments for patients with obsessive-compulsive disorder: A systematic review

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Systematic review; obsessive-compulsive disorder; efficacy of medication.

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Abstract

Purpose: This systematic review examines the efficacy of pharmacological therapy for obsessive-compulsive disorder (OCD), addressing two major issues: which treatment is most effective in treating the patient's symptoms and which is beneficial for maintaining remission.

Data sources: Seven databases were used to acquire articles. The key words used to search for the relative topics published from 1996 to 2007 were "obsessive-compulsive disorder" and "Yale-Brown obsession-compulsion scale." Based on the inclusion and exclusion criteria, 25 studies were selected from 57 potentially relevant studies.

Conclusions: The effects of treatment with clomipramine and selective serotonin reuptake inhibitors (SSRIs: fluvoxamine, sertraline, fluoxetine, citalopram, and escitalopram) proved to be similar, except for the lower adherence rate in case of clomipramine because of its side effects. An adequate drug trial involves administering an effective daily dose for a minimum of 8 weeks. An augmentation strategy proven effective for individuals refractory to monotherapy with SSRI treatment alone is the use of atypical antipsychotics (risperidone, olanzapine, and quetiapine).

Implications for practice: Administration of fluvoxamine or sertraline to patients for an adequate duration is recommended as the first-line prescription for OCD, and augmentation therapy with risperidone, olanzapine, or quetiapine is recommended for refractory OCD.

Introduction

Obsessions are recurrent and persistent thoughts, ideas, impulses, or images that are experienced as intrusive and senseless. Individuals with obsessive-compulsive disorder (OCD) recognize that these thoughts are trivial, ridiculous, or aggressive but they cannot stop, forget, or control them. Compulsions can be defined as repetitive behaviors that are performed in a particular manner in response to an obsession to prevent discomfort and to bind or neutralize anxiety. Obsessions or compulsions cause distress, are time-consuming, and interfere with usual daily functioning (Keltner, Schwecke, & Bostrom, 2007). Nonpharmacological treatments have been tried in an attempt to control these symptoms, including cognitive behavioral treatment (CBT), psychotherapy, and group therapy. CBT has been prescribed frequently for OCD symptoms: systematic desensitization, flooding, exposure and response prevention, thought stopping, and aversive therapy. The efficacy of psychotherapy and group therapy for OCD patients has been proven in many studies. Clomipramine and selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed to treat the symptoms of OCD; however, many other drugs have been studied in an effort to find the most effective treatment. The main issue is which treatment is the most effective to treat the patient's symptom and beneficial to maintain remission.

A systematic review involves applying scientific strategies in ways that limit bias to the assembly, critical appraisal, and synthesis of all relevant studies that address a specific clinical question. Systematic reviews have developed in response to a growing need for policy makers, researchers, and educators to have access to the latest

research evidence when making decisions. The rigorous methods adopted for data collection allow the researcher to analyze and draw conclusions only from trustworthy data, thus producing new knowledge by bringing the results of many studies together. Systematic reviews can help clinicians keep abreast of the medical literature by summarizing large bodies of evidence and helping to explain the differences among studies on the same question (Harden & Thomas, 2005). This systematic review examines the efficacy of pharmacological therapy for OCD to answer the following question: which treatment is most effective in treating the patient's symptoms and maintaining remission?

Diagnosing OCD

The Yale-Brown obsessive-compulsive scale (Y-BOCS) is a widely used clinician-administered measure that assesses the severity of obsessive-compulsive symptoms over the previous week. The 10 Y-BOCS items are rated on a 5-point Likert scale based on patient reports as well as others' accounts and the clinician's observations and judgment. Obsession and compulsion severity are each rated on five items: distress, frequency, interference, resistance, and symptom control. As per the originally proposed scoring structure, the Y-BOCS provides three summary scores: the obsessions severity score (range, 0–20), the compulsions severity score (range, 0–20), and a total score, which is the sum of all items (range, 0–40). The children's version of the scale (CY-BOCS) is a clinician-rated, semistructured instrument that is a downward age extension of the adult version, the Y-BOCS (Storch et al., 2006).

Crino, Slade, and Andrews (2005) reported that compared to individuals without OCD, those with OCD were significantly more likely to have met the criteria for at least one affective, anxiety, substance use, or personality disorder, with 79.7% of those with OCD having another disorder. OCD subjects were also significantly more likely to have two, three, or more other disorders than those without a diagnosis of OCD, with 46% of OCD individuals meeting the criteria for three or more disorders in the 12 months before the interview. Among the individual disorders, comorbidity with major depression was the highest at 54%. Although a general association between OCD and any other anxiety disorder was observed, the presence of OCD was significantly associated only with the presence of panic disorder and posttraumatic stress disorder (Fontenelle & Hasler, 2008).

Early pharmacologic therapy for OCD

Clomipramine and SSRIs are prescribed as the first choice to treat the symptoms of OCD. The first evidence of the responsiveness of medication for obsessive-compulsive symptoms was reported 30 years ago by Fernandez-Cordoba and Lopez-Ibor Alino (1967). Their case study documented the successful treatment of the obsessions of a depressed patient using clomipramine (Cartwright & Hollander, 1998). Later researchers compared the efficacy of clomipramine, placebo, and the following SSRIs: fluoxetine, sertraline, fluvoxamine, citalopram, and escitalopram (Bergeron et al., 2002; Fineberg, Tonnoir, Lemming, & Stein, 2007; Hollander et al., 2003; Koran, Hackett, Rubin, Wolkow, & Robinson, 2002; March et al., 2004). A group of studies was conducted to investigate the efficacy of augmentation with atypical antipsychotics on SSRIs for patients with refractory OCD. The results demonstrated that augmentation therapies were effective in patients who did not respond to monotherapy (Atmaca, Kuloglu, Tezcan, & Gecici, 2002; Bogetto, Bellino, Vaschetto, & Ziero, 2000; Carey et al., 2005; de Geus, Denys, & Westenberg, 2007; Denys, de Geus, van Megen, & Westenberg, 2003; Denys, Fineberg, Carey, & Stein, 2007; Denys et al., 2004; Marazziti et al., 2005; McDougle, Epperson, Pelton, Wasylink, & Price, 2000). This article examines the efficacy of clomipramine, SSRIs, and augmentation with atypical antipsychotics for OCD by means of systematic review.

Methods

The following seven databases were used to find articles: EBSCO EJS, Korean studies Information Service System, ProQuest Academic Research Library, PsycINFO, PubMed, ScienceDirect, and Wiley InterScience. Relevant topics were searched using the keywords "obsessive-compulsive disorder" and "Y-BOCS (Yale-Brown Obsession-Compulsion Scale)" in studies published from 1996 to 2007. The study inclusion criteria were treatment effectiveness from clinical trials with clomipramine, SSRIs, or atypical antipsychotics. The exclusion criteria included research from secondary data sources, unclear research procedures, or the inclusion of subjects with comorbid disorders. The Jadad scale was used to rate the quality of clinical trials. The Jadad scale is comprised of the following five questions: (1) Is the study randomized? (2) Is the study double blinded? (3) Is there a description of withdrawals? (4) Is the randomization adequately described? (5) Is the blindness adequately described? Each question demands a yes or no response. A total of five points can be awarded, and higher scores indicate superior quality (Jadad et al., 1996).

Results

Fifty-seven potentially relevant studies were included by searching for keywords from the databases. Abstracts of

these studies were carefully reviewed to determine whether or not to include them based on the inclusion and exclusion criteria. Finally, 25 studies were included for this review. The Jadad scores ranged from 1 to 5 (Table 1).

The types of medication included tricyclic antidepressants (clomipramine), SSRIs (fluvoxamine, sertraline, fluoxetine, citalopram, and escitalopram), atypical antipsychotics (risperidone, quetiapine, olanzapine, and amisulpiride), and benzodiazepines (clonazepam). Daily maximum dose and duration of administration of each medication were as follows: clomipramine, 150–300 mg, 10–16 weeks; fluvoxamine, 300 mg, 10–12 weeks; sertraline, 100–200 mg, 8–16 weeks; fluoxetine, 80 mg, 16–24 weeks; citalopram, 60 mg, 52 weeks; and escitalopram, 20 mg, 40 weeks. The daily

Table 1 Study characteristics

No.	Author	Year	Jadad score	n	Intervention		Y-BOCS effect size[a]
					Duration (week)	Contents (maximum dose [mg/day])	
1	Atmaca et al.	2002	3	27	8	SSRI + quetiapine (150)	−10.7
						SSRI + placebo	−2.4
2	Bergeron et al.	2002	3	150	24	Fluoxetine (80)	−16.4
						Sertraline (200)	−15.7
3	Bisserbe et al.	1997	4	168	16	Sertraline (200)	−14.3
						Clomipramine (200)	−11.7
4	Bogetto et al.	2000	2	23	12	Fluvoxamine (300) + olanzapine (5)	−7.9
5	Carey et al.	2005	4	41	6	SSRI + quetiapine (300)	−7.1
						SSRI + placebo	−7.2
6	Crockett et al.	2007	3	37	12	Sertraline (100) + clonazepam (4.0)	−5.7
						Sertraline (100) + placebo	−7.9
7	D'Amico et al.	2003	1	21	12	Paroxetine (60) + olanzapine (10)	−7.0
8	de Geus et al.	2007	4	36	8	SSRI + quetiapine (300)	−8.7
						SSRI + placebo	−1.8
9	Denys et al.	2007	2	102	16	SSRI + quetiapine (450)	−6.8
						SSRI + placebo	−3.9
10	Denys et al.	2003	3	40	8	SSRI + quetiapine (300)	−9.0
						SSRI + placebo	−1.8
11	Erzegovesi et al.	2005	4	45	12	Fluvoxamine + risperidone (0.5)	−8.7
						Fluvoxamine + placebo	−3.9
12	Fineberg et al.	2007	3	468	14 + 6	Escitalopram (20) + escitalopram (20)	−15.7
						Escitalopram (20) + placebo	−11.6
13	Fineberg et al.	2005	3	21	16	SSRI + quetiapine (400)	−3.4
						SSRI + placebo	−1.4
14	Hollander et al.	2003	2	253	12	Fluvoxamine (300)	−8.5
						Placebo	−5.6
15	Koran et al.	2002	5	620	52 + 28	Sertraline (200) + sertraline (200)	−16.5
						Sertraline (200) + placebo	−15.8
16	Koran et al.	1996	5	79	10	Fluvoxamine (300)	−7.7
						Clomipramine (250)	−7.3
17	Liebowitz et al.	2002	3	43	16	Fluoxetine (80)	−9.7
						Placebo	−4.1
18	López-Ibor et al.	1996	4	55	8	Clomipramine (150)	−8.9
						Fluoxetine (40)	−7.5
9	Marazziti et al.	2005	1	26	52	SSRI + olanzapine (10)	−11.3
20	March et al.	1998	3	187	12	Sertraline (200)	−8.0
						Placebo	−4.2
21	McDougle et al.	2000	3	36	6	SSRI + risperidone (6)	−8.7
						SSRI + placebo	−2.6
22	Metin et al.	2003	2	20	12	SSRI + amisulpiride (600)	−14.2
23	Mundo et al.	2001	3	227	10	Fluvoxamine (300)	−12.3
						Clomipramine (300)	−12.0
24	Stengler-Wenzke et al.	2006	1	10	52	Citalopram (60)	−18.2
25	Thomsen	2006	1	17	12	SSRI + risperidone (2)	−9.0

Note. SSRI = selective serotonin reuptake inhibitor.
[a]Pre-post test difference mean of Y-BOCS.

maximum dose and duration of administration of each augmentation with atypical antipsychotics for SSRIs were as follows: risperidone, 0.5–6 mg, 6–12 weeks; quetiapine, 150–450 mg, 8–16 weeks; olanzapine, 5–10 mg, 12–52 weeks; amisulpiride, 600 mg, 12 weeks; and clonazepam, 4 mg, 12 weeks.

The effects of each treatment in this study were compared using Y-BOCS or CY-BOCS. Pre-post test differences of clomipramine and SSRIs from each paired total mean score were as follows: clomipramine, −7.3 to −12.0; fluvoxamine, −3.9 to −12.3; sertraline, −7.9 to −16.5; fluoxetine, −9.7 to −16.4; citalopram, −18.2; and escitalopram, −11.6 to −15.7 (Table 2). Pre-post test differences of augmentation therapy with atypical antipsychotics or clonazepam for SSRIs for refractory OCD were as follows: quetiapine, −6.8 to −10.7; olanzapine, −11.3; risperidone, −8.7 to −9.0; amisulpiride, −14.2; and clonazepam, −5.7 (Table 3).

Discussion

Clomipramine is a tricyclic antidepressant that was first recognized as an effective treatment for depression. Originally, the efficacy of clomipramine in OCD was debated because depression is frequently present in OCD patients, leading some researchers to propose that clomipramine was effective only in treating depressive symptoms. It is now clearly recognized, however, that clomipramine has unique anti-OCD effects independent of its antidepressant effects by its potent serotonin reuptake inhibition (Stahl, 1996). In this review, clomipramine administration of 150–300 mg/day for 8–16 weeks caused a decrease of 12.0–7.3 points of the Y-BOCS mean score; this is in accordance with the consensus among clinicians regarding the considerable efficacy of clomipramine (Stengler-Wenzke et al., 2006).

Prescription of SSRIs for patients with OCD is based on the serotonin hypothesis of OCD, which states that OCD is linked to 5-HT dysfunction. Fluvoxamine, sertraline, fluoxetine, and paroxetine are approved by the Food and Drug Administration (FDA) for the treatment of OCD. In this review, administration of each SSRI caused a decrease of the Y-BOCS mean score. Administration of 300 mg/day fluvoxamine for 10–12 weeks decreased the Y-BOCS mean score from 12.3 to 3.9; 100–200 mg/day sertraline for 12–80 weeks, from 16.5 to 7.9; 40–80 mg/day fluoxetine for 8–24 weeks, from 16.4 to 7.5. These findings support that two-thirds of OCD patients respond to treatment with SSRIs (Stengler-Wenzke et al., 2006).

The efficacy of clomipramine compared to SSRIs was reviewed (pre-post test difference mean of Y-BOCS): sertraline (−14.3) was more efficacious than clomipramine (−11.7); fluvoxamine (−7.7, −12.3) was as efficacious as clomipramine (−7.3, −12.0); and fluoxetine (−7.5) was less efficacious than clomipramine (−8.9) (Bisserbe, Lane, & Flament, 1997; Koran et al., 1996; López-Ibor et al., 1996; Mundo, Rouillon, Figuera, & Stigler, 2001). Mundo et al. reported that compared with fluvoxamine-treated

Table 2 Monotherapy of TCA or SSRI for OCD

Medication		Y-BOCS effect size[a]	Maximum dose (mg/day)	Duration (week)	Author	Year
TCA	Clomipramine	−12.0	300	10	Mundo et al	2001
		−11.7	200	16	Bisserbe et al.	1997
		−8.9	150	8	López-Ibor et al.	1996
		−7.3	250	10	Koran et al.	1996
SSRI	Fluvoxamine	−12.3	300	10	Mundo et al.	2001
		−8.5	300	12	Hollander et al.	2003
		−7.7	300	10	Koran et al.	1996
		−3.9	300	12	Erzegovesi et al.	2005
	Sertraline	−16.5	200	80	Koran et al.	2002
		−15.8	200	52	Koran et al.	2002
		−15.7	200	24	Bergeron et al.	2002
		−14.3	200	16	Bisserbe et al.	1997
		−8.0	200	12	March et al.[a]	1998
		−7.9	100	12	Crockett et al.	2007
	Fluoxetine	−16.4	80	24	Bergeron et al.	2002
		−9.7	80	16	Liebowitz et al.[a]	2002
		−7.5	40	8	López-Ibor et al.	1996
	Citalopram	−18.2	60	52	Stengler-Wenzke et al.	2006
	Escitalopram	−15.7	20	20	Fineberg et al.	2007
		−11.6	20	14	Fineberg et al.	2007

Note. SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
[a]Pre-post test difference mean of Y-BOCS.

Table 3 Augmentation therapy with atypical antipsychotics or benzotropine on SSRI for refractive OCD

SSRI + medication	Y-BOCS effect size[a]	Maximum dose (mg/day)	Duration (week)	Author	Year
Olanzapine	−11.3	10	52	Marazziti et al.	2005
	−7.9	5	12	Bogetto et al.	2000
	−7.0	10	12	D'Amico et al.	2003
Quetiapine	−10.7	150	8	Atmaca et al.	2002
	−9.0	300	8	Denys et al.	2003
	−8.7	300	8	de Geus et al.	2007
	−7.1	300	6	Carey et al.	2005
	−6.8	450	16	Denys et al.	2007
	−3.4	400	16	Fineberg et al.	2005
Risperidone	−9.0	2	12	Thomsen	2006
	−8.7	0.5	12	Erzegovesi et al.	2005
	−8.7	6	6	McDougle et al.	2000
Amisulpiride[b]	−14.2	600	12	Metin et al.	2003
Clonazepam	−5.7	4	12	Crockett et al.	2007

Note. SSRI= selective serotonin reuptake inhibitor.
[a]Pre-post test difference mean of Y-BOCS.;
[b]Not approved by FDA.

patients, those treated with clomipramine had more anticholinergic side effects (dry mouth, constipation, and tremor) and premature withdrawals because of adverse events (18 versus 9). The results indicate that SSRIs are as effective as clomipramine in OCD treatment but have a better tolerability profile. Compared to clomipramine, SSRIs have a more favorable side-effect profile and are preferable as the first-line treatment of OCD.

Although citalopram and escitalopram have not been approved by the FDA for OCD treatment, they proved to be effective in patients with OCD in some studies (Fineberg et al., 2007; Stengler-Wenzke et al., 2006). The Y-BOCS score of patients who took 60 mg/day of citalopram for 52 weeks decreased by 18.2 points from the previous Y-BOCS score. Fineberg et al. assessed the efficacy of escitalopram with regard to duration of medication. The obsessive-compulsive symptoms of patients who took 10–20 mg/day escitalopram for 40 weeks improved to a greater degree as measured by Y-BOCS (−15.7) compared to those with escitalopram administration for 16 weeks (−11.6). Therefore, escitalopram is effective for long-term treatment and relapse prevention in OCD.

Black box warnings for SSRIs state that there is an increased risk of suicidality in children, adolescents, and young adults with major depressive or other psychiatric disorders during the first month of treatment, and that all patients should be observed for clinical worsening, suicidality, or unusual behavior changes. The use of medications with black box warnings requires considerable care, and documentation of assessment and follow-up are critical. Paroxetine, citalopram, and escitalopram have not been approved by the FDA for pediatric OCD treatment (Stahl, 2006).

Need for augmentation therapy

In most cases, OCD responds slowly to pharmacotherapy, with improvements taking weeks and months to develop. In 30%–40% of OCD cases, residual symptoms are observed. Even after switching to a second SSRI, approximately 30% of the cases do not respond (March et al., 1998). Improvement following adequate OCD drug treatment is frequently partial whereupon augmentation strategies may become necessary (Cartwright & Hollander, 1998). In this review, augmentation with atypical antipsychotics in patients using SSRIs with refractory OCD was effective, and the Y-BOCS mean scores were decreased as follows: SSRI + risperidone (0.5–6 mg/day) for 6–12 weeks reduced the Y-BOCS scores from 9.0 to 8.7; SSRI + olanzapine (5–10 mg/day) for 12–52 weeks, 11.3 to 7.0; and SSRI + quetiapine (150–450 mg/day) for 6–16 weeks, 10.7 to 3.4. Amisulpiride is not approved by the FDA for use in the United States, but it is prescribed in Europe, Australia, and Korea to treat psychosis and schizophrenia (Lecrubier et al., 2001). Metine et al. (2003) reported that patients with refractory OCD improved their obsessive-compulsive symptoms by augmentation with amisulpiride (600 mg/day) with SSRI for 12 weeks, which decreased the Y-BOCS score by 14.2 points.

Because benzodiazepine drugs can potentiate serotonergic drugs, they are prescribed to reduce obsessive-compulsive symptoms. Stein et al. (1992) compared clomipramine, alprazolam, and placebo in their study and reported the lack of efficacy of alprazolam. Within the benzodiazepine family, clonazepam is considered to have unique effects on the serotonin system by enhancing serotonergic neurotransmission. Pigott et al. (1992)

conducted a controlled comparison of adjunctive clonazepam versus placebo in clomipramine- or fluoxetine-treated OCD patients, which revealed that clonazepam was more effective than placebo. The efficacy of clonazepam compared to placebo augmentation to sertraline was reviewed, and clonazepam augmentation did not cause any significant change in the Y-BOCS (Crockett et al., 2007). Thus, these results suggested an inconsistent benefit of clonazepam augmentation in OCD treatment.

Resources and referrals

Pharmacotherapy is an important component of treatment for OCD patients; however, it is important to include psychosocial components of therapy for best outcomes. For interested clinicians and patients, many helpful resources are available. The Obsessive-Compulsive Foundation (http://www.ocfoundation.org) is an international not-for-profit organization founded in 1986 by a group of individuals with OCD. It offers workshops and educational materials about OCD. The referral list of mental health professionals for OCD and support groups can be located on the website by using zip codes. The obsessive-compulsive disorder online course #987 (http://www.nursece.com/onlinecourses/987.html) is a very readable, comprehensive overview of diagnosis, treatment, and nurses' roles in helping patients with the disorder. The website of the National Library of Medicine (NLM) MedlinePlus offers a wealth of information regarding overview, latest news, treatment, self-help groups, and research (http://www.nlm.nih.gov/melineplus/obsessivecompulsivedisorder.html) on OCD. One can download "When Unwanted Thoughts Take Over: Obsessive-Compulsive Disorder" published by the National Institute of Mental Health (NIMH), which is an easy-to-read booklet on OCD that explains what it is, when it starts, how long it lasts, and how to get help (http://www.nimh.nih.gov/health/publications/when-unwanted-thoughts-take-over-obsessive-compulsive-disorder/summary.shtml).

Conclusion

Onset of improvement with pharmacotherapy in OCD is often delayed by many weeks compared to treatment response in depressive disorders. An adequate drug trial consists of administering an effective daily dose for at least 8 weeks. Clinicians must be aware of the variety of treatment options, including both pharmacological and psychological regimens, and be able to provide support to patients who suffer from this disorder. For those clinicians who prescribe medications for OCD, it is important to make sure the drug choice is the best for the condition, is prescribed at sufficient dosage, and is continued long enough to allow a treatment response. Careful monitoring of patients on drug therapy is essential to uncover early warning signs of suicidality and other adverse reactions. Based on the findings of this systematic review, clinicians now have many effective drug treatment options from which to select therapies.

In this systematic review, treatment effects using clomipramine, sertraline, fluoxetine, and fluvoxamine were demonstrated to be similar; however, the lower adherence rate of clomipramine because of its side effects must be considered. The efficacy of citalopram and escitalopram was higher than that of FDA-approved SSRIs. Augmentation of SSRIs with risperidone, olanzapine, and quetiapine offers a number of options for OCD patients who are refractory to monotherapy with SSRIs.

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