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Research Article

COMPARING THE EFFECT OF SECOND-GENERATION ANTIPSYCHOTICS VERSUS SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN REFRACTORY OBSESSIVE-COMPULSIVE DISORDER: A SYSTEMATIC REVIEW OF THE PAST, PRESENT, AND FUTURE CLINICAL TRIALS

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ABSTRACT

Objective: In this concise and systematic review, the trend of using major medication modalities prescribed for refractory obsessive-compulsive disorder (OCD), including serotonin-specific reuptake inhibitors (SSRIs) and second-generation antipsychotics (SGAs) are discussed.

Methods: We systematically searched PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) systematically using Mesh terms. OCD is extremely disabling and associated with considerable depression and other serious psychiatric illnesses.

Results: Through databases, we found 78 randomized clinical trials (RCTs), which included selective SSRI compared with routine drug therapy or placebo. Out of these 78 studies, 62 studies were conducted on adult patients with OCD, comprising 7920 cases. While only 16 RCTs were performed on children and adolescents with OCD, including 1313 people. We found 24 clinical trial studies related to SGAs, of which were conducted on adult patients with OCD, including 992 cases.

Conclusion: As our data showed among the SSRIs, fluvoxamine has been particularly well studied and used in RCTs in both children and adolescents with OCD. According to the summary of our review, it will be better when therapists use SGAs in the early treatment programs of refractory OCD. Thus, considering our reviewed, it seems that the first choice of early treatment programs of refractory OCD is fluvoxamine in combination with quetiapine or aripiprazole.

Keywords: Obsessive-compulsive disorder, Refractory, Second-generation antipsychotic drugs, Selective serotonin reuptake inhibitors.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a mental health condition with an unwanted, unpleasant thought, image, or urge that repeatedly enters a person's mind. OCD affects about 2-3% of people over the course of their lifetimes [1,2]. OCD is the result of common psychological social and genetic factors interaction [3]. In the biological factors could mention the serotonin disorder in the brain, which for the treatment of this aspect, drug treatment is recommended to set serotonin in the brain.

Drug treatment is one of the most common methods of treatment of acute agitation in patients with clinical mental health disorders. Antipsychotic drugs are, therefore, used in the acute treatment, chronic psychotic disorders, and other psychiatric conditions [4,5]. First-generation antipsychotic medications (FGAs), which are also known as classical neuroleptic or traditional antipsychotics, which typically used to treat psychosis such as schizophrenia, acute mania, agitation, and other psychiatric conditions [6]. The FGAs act through blocking the dopamine (DAT) D_2neuro-receptor, which leads to the development of a subsequent series of new antipsychotics [7]. According to the potency of FGAs in binding to DAT D_2neuro-receptor, these drugs divided into two categories include low and high potency groups [8,9]. Some of the reported complications compose dyskinesia, hyperkinesia, and involuntary movements in the face and extremities [10]. Second-generation antipsychotic drugs (SGAs) that were introduced in 1989, which is also known as atypical antipsychotics are generally lower risk of extrapyramidal side effects compared with FGAs [10]. However, these drugs generally cause higher rates of weight gain and life-shortening metabolic disturbances, although side effects of any medication profile are different [11].

Selective serotonin reuptake inhibitors (SSRI), deal with neurochemical imbalance that is the key reason in mental health disorders [12,13]. People with acute mental health condition, suffer from a lack of serotonin in certain areas of the brain [14]. Serotonin is a chemical neurotransmitter that plays an important role in the mood regulation, is one of the key factors in lack of balance in mood disorders such as anxiety and depression [15]. SSRI has serotonin reuptake reduction in specific neurons, causing an increase in the brain serotonin and reduce the symptoms of mental health disorders. SSRI, in general, are safer than others but have their own side effects, which are usually sexual, metabolic, and gastrointestinal [16-18].

In patients with OCD, the response to medication should be evaluated after a time period of about 8-12-w. This time is usually more than the time period of the response to medication in patients with depression (3-4 w). Of course, the time may vary slightly, but mainly in the OCD treatment, the patient needs more time and dosage as well.

The main goal of medication is to reduce obsessive thoughts and actions so that the patient can naturally reduce activity and performance. Usually, 25-35% in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) considered as a favorable clinical response [19]. Currently, about 40% to 60% of patients show significant improvement by taking first SSRI drug, but few responses to drugs are very high [20,21].

The latest available systematic reviews on antipsychotic therapies in resistant OCD are done from 2005 to 2006 [22,23]; thus, many new relevant researches have been published, an update of the current available literature seems necessary. We aimed to systematically

evaluate the effects of SSRI compared with SGAs considering all published randomized clinical trials (RCT) studies for people with OCD.

Pharmacology

It seems that the FGAs and SGAs inhibit postsynaptic DAT D2 receptors in the brain. Several studies attest to the role of DAT D2 receptors in the antipsychotic drugs activity, including connections between these drugs and receptor and the clinical potency. Functional imaging studies show that 60-65% of DAT D2 receptors should be tackled by the effect of antipsychotic medications [24,25]. SGAs also bind to serotonin receptors that increase their affinity for connection to DAT D2 receptors, which this effect is not seen in the FGAs [26]. Largely for this reason, serotonin receptors may reduce the risk of extrapyramidal side effects of most second-generation drugs, known as atypical antipsychotics, compared to the first-generation agents, especially in case of high potency drugs [27]. SSRIs primarily inhibit serotonin transporter (SERT) and the uptake of serotonin (5-HT) in the brain. These drugs also have controversial effects on DAT and norepinephrine transporters (NET). SSRI play a role in improving depression symptoms through inhibiting the binding of the neurotransmitter, serotonin (5-HT), to SERT, which results in increased 5-HT concentration and it's binding to postsynaptic receptors.

METHODS

Types of studies

We included all double-blind, randomized controlled trials.

Types of participants

We included studies in which people with a primary diagnosis of OCD according to Diagnostic and Statistical Manual-III (DSM-III)/DSM-IV or International Classification of Diseases-10 both children and adults. We did not exclude any OCD trials in participants with a serious concomitant medical illness.

Types of interventions

SGAs and SSRIs could be given as a monotherapy or as adjunctive therapy compared with placebo or other antidepressants. There were no limits in terms of study duration.

Search methods for identification of studies

We searched PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) systematically up to 29/01/2016. The search terms used were: ((Obsess* or compul* or OCD) and "atypical antipsychotic*" or "second-generation antipsychotic*" or "second-generation antipsychotic*") and ((obsess* or compul* or OCD) and "atypical antipsychotic*" or "second-generation antipsychotic*" or "second-generation antipsychotic*" or "SSRI")). We also searched www.clinicaltrials.gov using search terms for intervention and condition, e.g., SGAs AND OCD, SSRI and OCD. No language restrictions were applied.

RESULTS

SSRI in refractory OCD

Through databases, we found 78 RCTs, which included SSRI compared with routine drug therapy or placebo (Table 1). Out of these 78 studies, 62 studies were conducted on adult patients with OCD, comprising 7920 cases. While only 16 RCTs were performed on children and adolescents with OCD, including 1313 people.

Comparing these two groups of patients revealed that fluvoxamine was most frequent drugs used in adults; hence, most frequent drugs used in children were sertraline (Fig. 1).

Of 78 studies, fluvoxamine was the most frequent drugs used in patients with refractory OCD with 26 (33.33%) frequency followed by paroxetine, sertraline, and fluoxetine (Fig. 2).

Four SSRIs have been approved for the adult OCD treatment by the FDA so far, including fluvoxamine, fluoxetine, sertraline, and paroxetine. Among these five SSRIs, only four drugs have also been approved for treatment of pediatric OCD, including clomipramine, fluoxetine, fluvoxamine, and sertraline [102]. Fluvoxamine is one of the SSRI drugs, which is primarily used to treat OCD, social anxiety disorder, major depression, management of obesity, and bulimia, schizophrenia, and panic disorder. Many researchers believe that the imbalance in neurotransmitters causes depression and other mental disorders. Fluvoxamine inhibits serotonin reuptake that causes mania and euphoria. Furthermore, fluvoxamine has also been approved by the Food and Drug Administration (FDA) for the OCD treatment. Antidepressants such as fluvoxamine may increase the risk of suicide in children and young adults even in the first few weeks of consumption. This drug was the first SSRI licensed for use in adults, as well as for children, in OCD in the United States and Japan [103]. A number of RCT studies have confirmed the efficacy of fluvoxamine in improving the symptoms of OCD, and subsequently reducing the disruption it causes in daily life as well [28,33,39,42,44,46]. Trend of using SSRI in RCTs on refractory OCD also showed a decreasing pattern for fluvoxamine and paroxetine (Fig. 3).

No SSRI has been verified to be more effective than others in patients with OCD. Nevertheless, patients may individually respond more satisfactorily to one SSRI than to another. The most effective SSRI in any given patient is difficult to predict. Therefore, considering cost, available formulations, side effect profile, and half-life may help the selection. Among different SSRIs, currently only generic forms of clomipramine, citalopram, fluoxetine, fluvoxamine, and paroxetine are available.

SGAs in refractory OCD

We searched PubMed and Cochrane Central Register of Controlled Trials (CENTRAL), which lead us to 24 clinical trial studies (Table 2). These 24 trials were conducted on adult patients with OCD, including 992 cases.

Of 24 studies, risperidone and quetiapine were the most frequent SGA drugs used in patients with refractory OCD with 8 (33.33%) frequencies in both (Fig. 4).

The trend of using SGAs in RCTs on refractory OCD also showed an increasing pattern only for aripiprazole, whereas in the case of olanzapine and quetiapine was decreasing (Fig. 5).

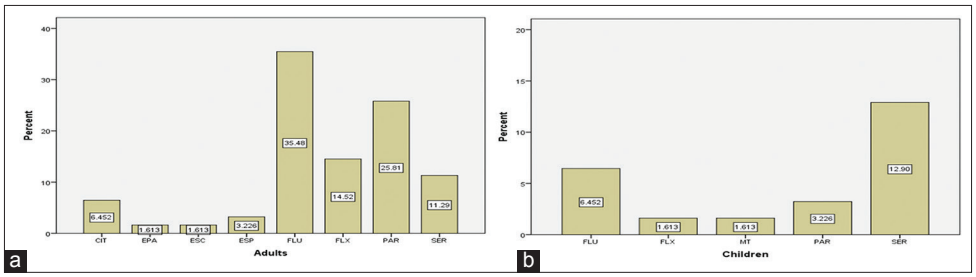

Fig. 1: Comparing the frequency of using serotonin-specific reuptake inhibitors in adult (a) versus children, (b) patients with obsessive-compulsive disorder

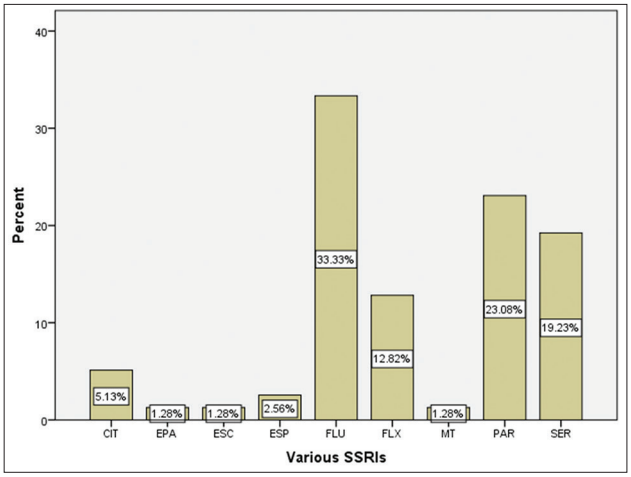

Fig. 2: Percentage of used various serotonin-specific reuptake inhibitors in clinical trials on patients with refractory obsessive-compulsive disorder. FLU: Fluvoxamine, ESC: Escitalopram, MT: Medication therapy, including citalopram (CIT), ESC, FLU, paroxetine (PAR), Clomipramine (CLO), Venlafaxine (VEN); Risperidone (RIS); Fluoxetine (FLX); Sertraline (SER)

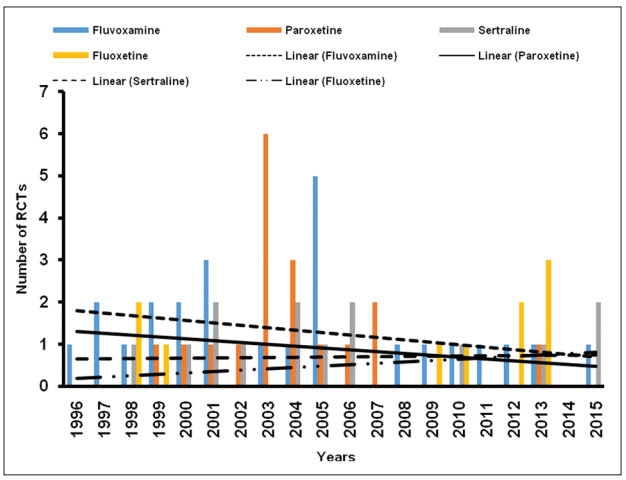

Fig. 3: Trends of the most frequent used serotonin-specific reuptake inhibitors in obsessive-compulsive disorder from 1996 to 2016

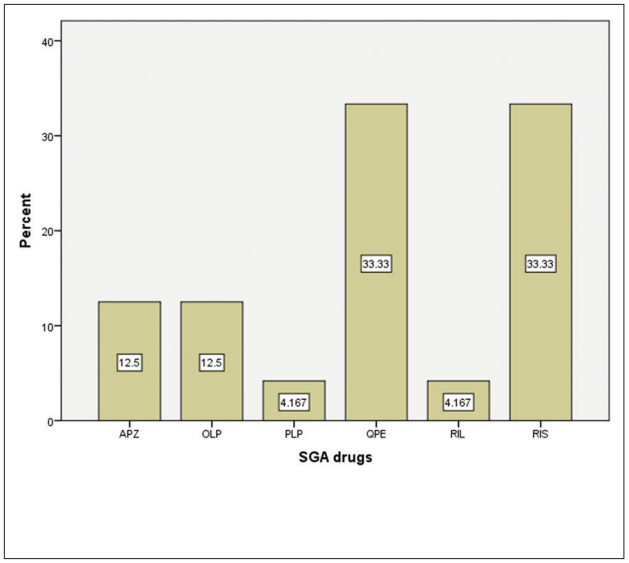

Fig. 4: Percentage of used various SGA in clinical trials on patients with refractory obsessive-compulsive disorder. PLP: Paliperidone, APZ: Aripiprazole, QPE: Quetiapine, OLP: Olanzapine, RIL: Riluzole, RIS: Risperidone

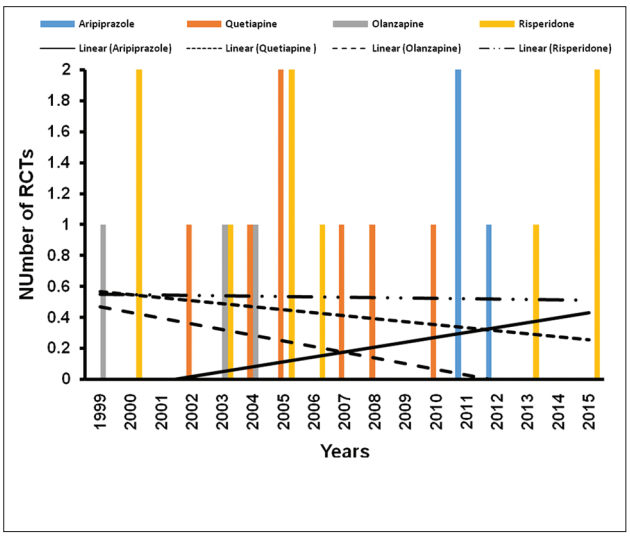

Fig. 5: Trends of the most frequent used serotonin-specific reuptake inhibitors in obsessive-compulsive disorder from 1996 to 2016

Mixed SSRI and SGAs in refractory OCD

Through our search, we included only 4 RCTs with 252 participants on SGAs plus SSRIs in refractory OCD patients (Table 3). All trials investigated the effects of adding SGAs to SSRIs with the duration of more than 6-w.

DISCUSSION

Drug treatment is one of the most common methods of treatment of patients with clinical mental health disorders such as OCD. Although using SSRI drug in trials is beneficial with a selective efficacy in OCD, up to 40% to 60% of OCD patients claim no satisfactory outcome [20,21]. As yet little is known about the efficacy and side effects of SGAs and SSRI in people suffering from OCD.

Due to the irrational and excessive nature of OCD, the treatment of refractory OCD is the major concern of psychiatrists. Unfortunately, despite advance in therapy and developing new and effective treatment modalities in the treatment of OCD, majority of patients suffering from OCD and at an increased risk of developing the disorder. One of the reasons can be the diverse nature of OCD. Considering DSM-III, DSM-III-R, and DSM-IV, OCD was classified as an anxiety disorder, whereas in ICD-10, this disorder was separated from the anxiety disorders. Recent advances in understanding illness anxiety have led to the question of whether OCD should no longer be classified as anxiety disorders in DSM-V or not [131,132].

According to the trials reviewed in this article can say that both fluvoxamine and quetiapine are the drug of choice and first-line agents in the early treatment of OCD. However, due to the growing trend of aripiprazole seems that soon this antipsychotic agent replaced the use of quetiapine in the treatment of refractory OCD. As the treatment of refractory OCD generally requires high doses of SSRIs, this higher dose increases the side effects, especially loss of sexual drive [133]. In agreement with our findings, Irons in a review studied the use of fluvoxamine in the treatment of mental health disorders, claimed that this SSRI agent is well-tolerated and does not cause sedation or

Table 1: Summary of recent clinical trials that was found by initial search

Design	Outcome	Study arms		Follow-up	Participant*	Author, year, country
		Drug	Placebo			
Randomized double-blind clinical trial	Y-BOCS score, patient characteristics predictive of assignment compliance	FLU	BT	12 week	48 patients with OCD resistant to a BT	Landsheer *et al*. 2015, Netherlands [28]
A multi-site, parallel, double-blind, randomized, placebo controlled trial	CGI-SA, CY-BOCS, CGI-SI	SER	PBO	8 week	44 youths with OCD	Bussing *et al*. 2015, USA [29]
Randomized controlled trial	CY-BOCS total score, clinical response	SER	CBT	16 week	54 children and adolescents (age 7-17 years) with primary OCD	Skarphedinsson *et al*. 2015, Norway [30]
Randomized, parallel assignment, single blind clinical trial	CGI-SA, CY-BOCS, CGI-SI	MT	MT+CBT	12 week	124 youth (aged 7 to 17 years) with a primary OCD	Conelea *et al.* 2014, USA [31]
Double-blind clinical trial	DUOCS	FLX	FLX+CBT	13 week	30 cases with OCD	Giasuddin *et al.* 2013, Bangladesh [32]
randomized double-blind placebo-controlled	Y-BOCS score, efficacy, tolerability	FLU	PBO	8 week	42 patients with OCD	Ghaleiha *et al.* 2013, Iran [33]
Double-blind placebo-controlled randomized clinical trial	YBOCS	PAR	PBO	12 week	36 adults with OCD	Humble *et al*. 2013, Sweden [34]
Randomized open trial	YBOCS	FLX	CBT	12 week	160 cases with OCD	Jakubovski *et al*. 2013, Germany [35]
Double-blind randomized controlled trial	TEASAP score	SER	PBO	4 week	56 youth (aged 7-17) with OCD	Bussing *et al.* 2013, USA [36]
Randomized clinical trial	YBOCS	FLX	CBT	12 week	29 adult patients with OCD	Hoexter *et al.* 2013, Brazil [37]
Randomized placebo-controlled clinical trial	YBOCS	FLX	PBO	8 week	31 adult patients with OCD	Sayyah *et al.* 2012, Iran [38]
Randomized controlled trial	YBOCS	FLU	CBT	12 week	118 subjects with OCD	van Balkom *et al*. 2012, Netherlands [39]
Randomized, double-blinded controlled clinical trial	YBOCS	FLX	CBT	12 week	38 adult patients with OCD	Hoexter *et al.* 2012, Brazil [40]
Randomized, single-blinded clinical trial	Y-BOCS score, obsessions	SER	CBT	12 week	46 patients with a primary OCD	Borges *et al.* 2011, Brazil [41]
randomized double-blind placebo-controlled	Y-BOCS score, symptoms of obsessions and compulsions	CEL+FLU	PBO+FLU	8 week	50 patients with OCD	Sayyah *et al.* 2011, Iran [42]
Randomized, placebo-controlled trial	YBOCS-SC	SER	PBO	12 week	112 youth (aged 7-17) with OCD	Garcia *et al*. 2010, USA [43]
randomized double-blind placebo-controlled	Y-BOCS score, side effects	FLU	S.M	8 week	35 patients with OCD	Sayyah *et al.* 2010, Iran [44]
Double-blind randomized clinical trial	YBOCS	FLX	PBO	8 week	42 adult patients with OCD	Soltani *et al.* 2010, Iran [45]
Randomized, controlled trials	YBOCS	FLU	PAR	12 week	44 adults with OCD	Matsunaga *et al.* 2009, Japan [46]
Randomized, double blind, fixed-does	CY-BOCS, CGI	FLX	CIT	6 week	29 children and adolescents (7-18 years) with OCD	Alaghband-Rad *et al.* 2009, Canada [47]
Randomized double-blind placebo-controlled	Y-BOCS score, efficacy, tolerability	ESC	PBO	12 week	466 adults with OCD	Stein *et al*. 2008, South Africa [48]
Randomized to open label	YBOCS, CGI-I	FLU+GBP	FLU	8 week	40 patients with IC-IUD	Onder *et al.* 2008, Turkey [49]

(Contd...)

Table 1: ***(Continued)***

Design	Outcome	Study arms		Follow-up	Participant*	Author, year, country
		Drug	Placebo			
A randomized, double-blind trial	YBOCS	PAR	VEN	12 week	91 outpatients with OCD	Denys *et al*. 2007, Netherlands [50]
A double blind placebo control trial.	YBOCS	ESP	PBO	12 week	100 patients with OCD	Khan *et al*. 2007, Pakistan [51]
randomized, placebo-controlled, paroxetine-referenced, fixed-dose, study	Y-BOCS score, Efficacy, tolerability, NIMH-OCS, CGI-S, CGII scores	PAR	PBO	24 week	466 adults with OCD	Stein *et al.* 2007, South Africa [52]
A randomized, double-blind, placebo-controlled trial	Y-BOCS	ESP	PBO	24 week	320 patients with OCD	Fineberg *et al*. 2007, UK [53]
A randomized clinical trial	Y-BOCS, CGI	SER	CBT	12 week	46 outpatients with an OCD	Sousa *et al*. 2006, Brazil [54]
A randomized, double-blind, controlled	Y-BOCS, CGI	SER	PBO	16 week	66 adult subjects with OCD	Ninan *et al.* 2006, USA [55]
A randomized, double-blind controlled trial	Y-BOCS, CGI	PAR	VEN	12 week	42 outpatients with OCD	Denys *et al*. 2006, Netherlands [56]
A randomized, controlled trials	Y-BOCS, CGI	FLU	CBT	12 week	122 outpatients with primary OCD	van Oppen *et al*. 2005, Netherlands [57]
A randomized, double-blind placebo-controlled trial	Y-BOCS, CGI	FLU	PBO	12 week	117 outpatients with OCD	Hollander *et al.* 2005, USA [58]
A randomized, controlled trial	Y-BOCS	SER	CBT	12 week	40 subjects (9 and 17 years) with OCD	Asbahr *et al*. 2005, Brazil [59]
A randomized, double-blind controlled trial	Y-BOCS	PAR	VEN	24 week	96 patients with OCD	Tenneij *et al*. 2005, Netherlands [60]
A randomized, placebo controlled trial	Y-BOCS, CGI	FLU	PBO	12 week	31 outpatients with OCD	Nakatani *et al*. 2005, Japan [61]
randomized, double-blind study	Y-BOCS score, efficacy	FLU	PBO	84 week	30 adults with OCD	Rufer *et al.* 2005, Germany [62]
Randomized, double-blind study	Y-BOCS score	FLU	BT	12 week	10 patients with primary OCD	Nakao *et al*. 2005, Japan
Randomized, double-blind study	Y-BOCS score	PAR	VEN	12 week	150 patients with primary OCD	Denys *et al*. 2004, Netherlands
A double-blind, randomized, placebo, parallel controlled	CGI, HAMA, Y-BOCS, BAI	SER	PBO	12 week	37 adult patients with OCD	Crockett *et al.* 2004, USA
A double-blind, randomized, placebo, parallel controlled	CY-BOCS	SER	CBT	12 week	112 patients (7-17 years) with a primary OCD	POTS, 2004 [63]
A randomized, multicenter, double-blind, placebo-controlled trial	CY-BOCS	PAR	PBO	10 week	207 Children (7-11 years of age) and adolescents (12-17 years of age)	Geller *et al.* 2004, USA [64]
A randomized, single-blind clinical trial	Y-BOCS, CGI, HDS	CIT	PBO	12 week	49 adult patients with OCD	Pallanti *et al.* 2004, Italy [65]
A randomized, double-blind, placebo-controlled trial	Y-BOCS	PAR	PBO	12 week	191 patients with a primary OCD	Kamijima *et al*. 2004, Japan [66]
A randomized, placebo-controlled trial	Y-BOCS, HAM	EPA	EPA+PBO	12 week	49 adult patients with OCD	Fux et al. 2004, Israel [67]
Open-label clinical trial	Y-BOCS, OVIS	FLU	PBO	10 week	34 outpatients with OCD	Neziroglu *et al.* 2004, USA [68]
Randomized, double-blind, parallel study of fixed doses	Y-BOCS	PAR	PBO	12 week	348 outpatients with OCD	Hollander *et al.* 2003, USA [69]
Flexibly dosed open-label	Y-BOCS	PAR	PBO	24 week	2263 outpatients with OCD	Hollander *et al.* 2003, USA [70]

(Contd...)

Table 1: ***(Continued)***

Design	Outcome	Study arms		Follow-up	Participant*	Author, year, country
		Drug	Placebo			
Double-blind, fixed-dose, parallel trial	long-term efficacy, safety, and impact on relapse prevention	PAR	PBO	24 week	3105 outpatients with OCD	Hollander *et al.* 2003, USA [71]
A randomized, double-blind, placebo-controlled trial	Y-BOCS, HAM	PAR	VEN	12 week	150 patients with primary OCD	Denys *et al*. 2003, Netherlands [72]
Randomized, double-blind study	Y-BOCS score, efficacy	PAR	VEN	12 week	140 patients with primary OCD	Denys *et al*. 2003, Netherlands [73]
A randomized, double-blind, placebo-controlled trial	Y-BOCS, CGI	PAR	PBO	16 week	193 adult OCD patients	Geller *et al*. 2003, USA [74]
A randomized, double-blind, placebo-controlled trial	Y-BOCS, CGI	FLU	PBO	12 week	253 adult OCD patients	Hollander *et al.* 2003, USA [75]
A randomized, double-blind, placebo-controlled trial	CY-BOCS, CGI	FLU	PBO	8 week	43 young OCD patients	Liebowitz *et al*. 2002, USA [76]
A randomized, single-blind, controlled trial	CY-BOCS, CGI	PAR	VEN	12 week	73°CD patients	Albert *et al*. 2002, Italy [77]
Open-label trial	Y-BOCS	CIT	PBO	12 week	39°CD patients	Pallanti *et al*. 2002, Italy [21]
Randomized, single-blind, placebo controlled study	Y-BOCS score, efficacy	FLU	PBO	52 week	130 patients with primary OCD**	Romano *et al*. 2001, USA [78]
A randomized, double-blind, controlled trial	YBOCS, CGI	SER	FLU	24 week	150 patients were OCD	Bergeron *et al*. 2002, Canada [79]
A large randomized placebo-controlled trial	YBOCS, CGI	CIT	PBO	12 week	71 patients were OCD	Stein *et al*. 2001, South Africa [80]
Open-label treatment	YBOCS, BABS	SER	PBO	16 week	71 patients were OCD	Eisen et al. 2001, USA [81]
A double-blind, placebo-controlled	CY-BOCS, CGI-S, CGI-I	SER	PBO	12 week	132 Children (6-12 years; n=72) and adolescents (13-18 years; n=65) with OCD	Cook *et al.* 2001, USA [82]
A randomized, double-blind, controlled trial	CY-BOCS	FLU	PBO	13 week	103 Children (7-17 years) with OCD	Geller *et al*. 2001, USA [83]
A randomized, double-blind trial	YBOCS, BABS	PAR	PBO	12 week	36 patients were OCD	Humble *et al*. 2001, Sweden [84]
A randomized, double-blind, placebo-controlled, multicenter study	CY-BOCS	FLU	PBO	10 week	120 Children (7-17 years) with OCD	Riddle *et al*. 2001, USA [85]
Double-blind, placebo-controlled study	Y-BOCS	FLU	PBO	10 week	33 patients with OCD	Peter *et al.* 2000, Germany [86]
A double-blind, placebo-controlled trial	Y-BOCS, HAM-A, MADRS	PAR	PBO	6 week	14 treatment-resistant OCD patients	Dannon *et al*. 2000, Israel [87]
Randomized, double-blind study	Children's Y-BOCS score, NIMH-OCS, CGI-S, CGII scores	FLU	BT	12 week	10 children/adolescents with OCD	Neziroglu *et al*. 2000, USA [88]
A randomized, double-blind, placebo-controlled, multicenter study	Y-BOCS, HAM-A, MADRS	SER	DPM	12 week	166 patients with OCD	Hoehn-Saric *et al*. 2000, USA [89]
Randomized, open-label trial	Y-BOCS	CIT	CIT+CLO	12 week	Sixteen adult outpatients with OCD	Pallanti *et al*. 1999, Italy [90]
Open-label trial	CY-BOCS, HAM, CGI	PAR	PBO	12 week	20°CD outpatients (8 to 17 years)	Rosenberg *et al*. 1999, USA [91]
Double-blind placebo-controlled trial	YBOCS, CGI	FLX	PBO	8 week	53 patients with OCD	Zitterl *et al.* 1999, Austria [92]

(Contd...)

Table 1: ***(Continued)***

Design	Outcome	Study arms		Follow-up	Participant*	Author, year, country
		Drug	Placebo			
Double-blind placebo-controlled trial	YBOCS, CGI	FLU	PBO	10 week	50°C patients	Mundo *et al*. 1999, Italy [93]
Randomized, placebo-controlled study	Anxiety Discomfort Scale, Y-BOCS score, and the Padua Inventory-Revised	FLU	CT	16 week	117 patients with primary OCD	van Balkom *et al*. 1998, Netherlands [94]
Double-blind placebo-controlled trial	YBOCS, CGI	FLX	PBO	12 week	14°C patients	Greenberg *et al.* 1998, USA [95]
Randomized, double-blind, placebo-controlled trial	CY-BOCS, NIMH GOCS, CGI	SER	PBO	12 week	107 children (6 to 12 years) and 80 adolescents (13 to 17 years) with OCD	March *et al.* 1998, USA [96]
Randomized, double-blind, placebo-controlled trial	YBOCS	FLU	PBO	8 week	60°C patients	Hohagen *et al*. 1998, Germany [97]
Multicenter, placebo-controlled, fixed-dose trial	YBOCS	FLX	PBO	10 week	35 patients with primary OCD	Ackerman *et al.* 1998, USA [98]
Randomized, single-blind, placebo controlled study	Y-BOCS, NIMH-OC scale, the CGIIS Scale, and the HRS for depression	FLU	CIT	10 week	30 patients with primary OCD	Mundo *et al*. 1997, Italy [99]
Double-blind controlled trial	Y-BOCS and CGIIS scales	FLU	CLO	8 week	26 individuals with OCD	Milanfranchi *et al*. 1997, Italy [100]
Double-blind controlled trial	Y-BOCS and CGIIS scales	FLU	CLO	8 week	55 individuals with OCD	López-Ibor *et al*. 1996, Spain [101]

*The diagnosis of OCD based on DSM-IV-TR and a Y-BOCS score of≥21, **The diagnosis of OCD based on DSM-IV-TR and a Y-BOCS score of≤19. Y-BOCS: Yale-brown obsessive compulsive scale, MEM: Memantine, FLX: Fluoxetine, CIT, Including citalopram, ESC: Escitalopram, FLU: Fluvoxamine, PAR: Paroxetine, CLO: Clomipramine, VEN: Venlafaxine, ESC: Escitalopram, SER: Sertraline, BUP: Bupropion, GSA: Gambling severity assessmen, CGIIS: Clinical global impression improvement and severity, GA: Global assessment, ADHDR: Attention-deficit/hyperactivity disorder rating, SD: Sheehan disability, rTMS: Transcranial magnetic stimulation, RIS: Risperidone, VEN: Venlafaxine, HDS: Hamilton depression scale, DS: Depressive symptoms, CGI: Clinical global improvement, PIN: Pindolol, CT: Cognitive therapy, CIT: Citalopram, HRS: Hamilton rating scale, CLO: Clomipramine, BT: Behavior therapy

Table 2: Summary of recent clinical trials that was found by initial

Design	Outcome	Study arms		Follow-up	Participant*	Author, year, country
		Drug	Placebo			
A pilot randomized, placebo-controlled trial	Y-BOCS score obsessions	RIL	PBO	12 week	38 patients with OCD	Pittenger *et al.* 2015, USA [104]
A randomized, placebo-controlled trial	Y-BOCS social adjustment scale-SR, quality of life, HDS, BABS	RIS	PBO	8 week	100 patients with at least moderate OCD severity	Foa *et al*. 2015, USA [105]
Randomized clinical trial	YBOCS	RIS	PBO	12 week	36 adults (aged 18-70 years) with OCD	Simpson *et al*. 2013, USA [106]
Double-blind, placebo-controlled, pilot trial	YBOCS, CGIIS	PLP	PBO	8 week	34 patients (aged 24-67 years) with OCD	Storch *et al.* 2013, USA [107]
Double-blind, randomized, placebo clinical trial	YBOCS	APZ	PBO	12 week	39 adult patients with OCD	Sayyah *et al*. 2012, Iran [108]
Double-blind, randomized, placebo-controlled trial	YBOCS	APZ	PBO	16 week	201 patients (20-70 years) with OCD	Muscatello *et al*. 2011, Italy [109]
Randomized, single-blinded clinical trial	YBOCS	APZ	RIS	12 week	90 patients (18-65 years) with OCD	Selvi *et al*. 2011, Turkey [110]
Randomized, open-label trials	YBOCS, CGI	QPE	CLO	12 week	21 adults with OCD	Diniz *et al.* 2010, Brazil [111]
Randomized, double-blind, placebo-controlled trial	YBOCS	QPE	PBO	12 week	40 patients with primary OCD	Kordon *et al*. 2008, Germany [112]

(Contd...)

Table 2: (*Continued*)

Design	Outcome	Study arms		Follow-up	Participant*	Author, year, country
		Drug	Placebo			
A randomized, double-blind, placebo-controlled trial	Y-BOCS	QPE	PBO	8 Week	40 therapy-resistant OCD patients	de Geus *et al*. 2007, Netherlands [113]
A double-blind, parallel group design	Y-BOCS, CGI	RIS	PBO	8 week	15 adult subjects with OCD	Buchsbaum *et a*l. 2006, USA [114]
Double-blind, placebo-controlled study	Y-BOCS score	RIS	PBO	12 week	45 adults with OCD	Erzegovesi *et al*. 2005, Italy [115]
Double-blind, placebo-controlled, crossover study	Y-BOCS	RIS	PBO	12 week	16 outpatients with OCD	Li *et al.* 2005, USA [116]
Open-label trial	Y-BOCS	QPE	PBO	8 week	30 adult patients with OCD	Bogan *et al*. 2005, USA [117]
A double-blind, randomized, parallel-group, flexible-dose, placebo-controlled study	Y-BOCS, CGI	QPE	PBO	12 week	41 adult patients with OCD	Carey *et al*. 2005, South Africa [118]
A randomized, double-blind, placebo-controlled trial	Y-BOCS, CGI	QPE	PBO	8 week	40 patients with a primary OCD	Denys *et al*. 2004, Netherlands [119]
A double-blind, placebo-controlled trial	Y-BOCS	OLP	PBO	6 week	26 patients (18 and 65 years) with OCD	Bystritsky *et al*. 2004, USA [120]
A randomized, double-blind, placebo-controlled trial	Y-BOCS, CGI	RIS	PBO	12 week	16 adult treatment-resistant OCD patients	Hollander *et al.* 2003, USA [69]
Open-label, add-on trial	Y-BOCS, CGI	OLP	PBO	12 week	21 adult OCD patients	D'Amico *et al*. 2003, Italy [121]
Open-label trial	YBOCS	QPE	PBO	8 week	10°CD patients	Denys *et al*. 2002, Netherlands [122]
A single-blind, placebo-controlled study	YBOCS, CGI	QPE	PBO	8 week	27 patients were refractory OCD	Atmaca *et al.* 2002, Turkey [123]
Open-label trial	Y-BOCS	RIS	PBO	10 week	20 refractory OCD outpatients	Pfanner *et al*. 2000, Italy [124]
A randomized, double-blind, placebo-controlled study	Y-BOCS	RIS	PBO	12 week	36 refractory OCD outpatients	McDougle *et al.* 2000, USA [125]
Open-label trial	CY-BOCS CGI	OLP	PBO	8 week	10 patients with OCD	Weiss *et al.* 1999, USA [126]

*The diagnosis of OCD based on DSM-IV-TR and a Y-BOCS score of≥21, All patients were treated with 1 of the 2 following selective serotonin reuptake inhibitors: Fluvoxamine or sertraline. Y-BOCS: Yale-brown obsessive compulsive scale, RIL: Riluzole, PBO: Placebo, RIS: Risperidone, BABS: Brown assessment of beliefs, CGI: Clinical global improvement, PLP: Paliperidone, CGIIS: Clinical global impression improvement and severity, SMTC: Stress management training condition, APZ: Aripiprazole, QPE: Quetiapine, HDS: Hamilton depression scale, OLP: Olanzapine

Table 3: Summary of recent clinical trials that was found by initial search

Design	Outcome	Study arms		Follow-up	Participant*	Author, year, country
		Drug	Placebo			
Randomized, placebo-controlled, clinical trial	YBOCS	CIT+QPE	PBO	10 week	46 adult patients with OCD	Vulink *et al.* 2012, Netherlands [127]
Randomized, double-blinded controlled clinical trial	YBOCS	QPE+FLX, CIT+FLX	PBO+FLX	12 week	54 patients with a primary OCD	Diniz *et al.* 2011, Brazil [128]
Randomized, controlled trial	YBOCS	EX/RP	SMT	12 week	108 patients with OCD	Simpson *et al*. 2008, USA [129]
Adouble-blind,placebo-controlled	YBOCS	OLP+FLU	PBO+FLU	6 week	44 adults with OCD	Shapira *et al.* 2004, USA [130]

*The diagnosis of OCD based on DSM-IV-TR and a Y-BOCS score of≥21. Y-BOCS: Yale-brown obsessive compulsive scale, FLU: Fluvoxamine, CIT: Citalopram, QPE: Quetiapine, FLX: Fluoxetine, SMT: Stress management training, PBO: Placebo, EX/RP: Exposure/ritual prevention therapy

cognitive impairment. He also reported that this drug is associated with a low risk of sexual dysfunction, suicidality, and withdrawal reactions; thus, it is a safe SSRI agent even in overdose and has no considerable impact on cardiovascular system and body weight [103]. In a systematic review, Bloch *et al*. evaluated the efficacy of antipsychotic agents in treatment-refractory OCD on nine studies involving 278 participants. They claimed that there is sufficient evidence in the literature about the efficacy of haloperidol and risperidone, whereas evidence of the efficacy of quetiapine and olanzapine is unconvincing [22]. Contrary to their clime, we showed there sufficient evidence in the literature on

risperidone, as well as quetiapine and olanzapine. The difference is may be due to the difference in the date limitation in the search strategy. Recently, Veale *et al*. in a systematic review and meta-analysis on 14 RCTs including risperidone, quetiapine, olanzapine, and aripiprazole [134]. They concluded that a low dose of risperidone and aripiprazole can use cautiously as an antipsychotic agent in nonresponders to SSRIs. In other reviews, Arumugham and Reddy reported that antipsychotic agents, especially risperidone and aripiprazole have shown the best evidence in refractory patients with OCD [135].

CONCLUSION AND PERSPECTIVES

As our trends show, fluvoxamine was the most frequent SSRI used in patients with refractory OCD followed by paroxetine, sertraline, and fluoxetine. Hence, risperidone and quetiapine were the most frequent SGA drugs used in patients with refractory OCD. According to the summary of our review, it seems that the first choice of early treatment programs of refractory OCD will be fluvoxamine in combination with quetiapine or aripiprazole. Recently, the treatment of patients with OCD has improved dramatically. OCD is extremely disabling and associated with considerable depression and other serious psychiatric illnesses. Therefore, this disease represents an important area of medical need. The well-known disadvantages of the traditional antipsychotics have resulted in becoming the SSRIs first-line treatment for many mental health disorders such as OCD. As our data showed among the SSRIs, fluvoxamine has been particularly well studied and used in RCTs in both children and adolescents with OCD. According to the summary of our review, it will be better when therapists use SGAs in the early treatment programs of refractory OCD. Thus, considering our reviewed, it seems that the first choice of early treatment programs of refractory OCD is fluvoxamine in combination with quetiapine or aripiprazole.

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