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 7,920 cases. While only 16 RCTs were performed on children and adolescents with OCD, including 1,313 people. We found 24 clinical trial studies related to SGAs, 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.

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 neurolepitic 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) D2 receptor, which leads to the development of a subsequent series of new antipsychotics [7]. According to the potency of FGAs in binding to DAT D2 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]. SRII 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 receptor 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 compuls* or OCD) and “atypical antipsychotic” or “second-generation antipsychotic” or “second-generation antipsychotic” and ((obsess* or compuls* 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).
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 SSRIs 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].
Table 1: Summary of recent clinical trials that was found by initial search

| Design                                | Outcome                                                                 | Study arms                  | Participant*                        | Author, year, country |
|---------------------------------------|-------------------------------------------------------------------------|----------------------------|-------------------------------------|-----------------------|
| Randomized double-blind clinical trial| Y-BOCS score, patient characteristics predictive of assignment compliance | FLU BT                      | 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                                                  | PBO                        | 44 youths with OCD                  | Bussing et al. 2015, USA [29] |
| Randomized controlled trial           | CY-BOCS total score, clinical response                                  | SER CBT                    | 54 children and adolescents (age 7-17 years) with primary OCD | Skarpfedinsson et al. 2015, Norway [30] |
| Randomized, parallel assignment, single blind clinical trial | CGI-SA, CY-BOCS, CGI-SI                                                  | MT MT+CBT                  | 124 youth (aged 7 to 17 years) with primary OCD | Coneka et al. 2014, USA [31] |
| Double-blind clinical trial           | DUOCS                                                                    | FLX FLX+CBT                | 30 cases with OCD                    | Giasuddin et al. 2013, Bangladesh [32] |
| Randomized double-blind placebo-controlled trial | Y-BOCS score, efficacy, tolerability YBOCS                         | FLU PBO                    | 42 patients with OCD                  | Humble et al. 2013, Sweden [34] |
| Double-blind placebo-controlled randomized clinical trial | YBOCS                                                                    | PAR PBO                    | 36 adults with OCD                    | Jakubovský et al. 2013, Germany [35] |
| Randomized clinical trial             | TEASAP score                                                             | SER PBO                    | 56 youth (aged 7-17) with OCD         | Bussing et al. 2013, USA [36] |
| Randomized placebo-controlled clinical trial | YBOCS                                                                    | FLX CBT                    | 29 adult patients with OCD           | Hoexter et al. 2013, Brazil [37] |
| Randomized controlled trial           | YBOCS                                                                    | FLU CBT                    | 31 adult patients with OCD           | Sayyah et al. 2012, Iran [38] |
| Randomized, double-blind controlled clinical trial | YBOCS                                                                    | FLX CBT                    | 118 subjects with OCD                | van Balkom et al. 2012, Netherlands [39] |
| Randomized, single-blind clinical trial | Y-BOCS score, obsessions                                                | SER CBT                    | 46 patients with a primary OCD       | Hoexter et al. 2012, Brazil [40] |
| Randomized double-blind placebo-controlled trial | Y-BOCS score, symptoms of obsessions and compulsions YBOCS-SC           | CEL+FLU PBO+FLU            | 50 patients with OCD                  | Borges et al. 2011, Brazil [41] |
| Randomized, placebo-controlled trial | Y-BOCS score, side effects                                               | YBOCS-SC                   | 112 youth (aged 7-17) with OCD        | García et al. 2010, USA [43] |
| Randomized double-blind placebo-controlled trial | Y-BOCS score, side effects                                               | FLU S.M                    | 35 patients with OCD                  | Sayyah et al. 2010, Iran [44] |
| Double-blind randomized clinical trial | YBOCS                                                                    | FLX PBO                    | 42 adult patients with OCD           | Soltani et al. 2010, Iran [45] |
| Randomized, controlled trials         | YBOCS                                                                    | FLU PAR                    | 44 adults with OCD                    | Matsunaga et al. 2009, Japan [46] |
| Randomized, double blind, fixed-doses | CY-BOCS, CGI                                                             | FLX CIT                    | 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 YBOCS, CGI-I                      | ESC PBO                    | 466 adults with OCD                   | Stein et al. 2008, South Africa [48] |
| Randomized to open label              | Y-BOCS score, efficacy, tolerability YBOCS, CGI-I                       | FLU+GBP                    | 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 |
|---------------------------------------------------------------|--------------------------|------------|-----------|--------------|-----------------------|
| A randomized, double-blind placebo-controlled trial randomized, double-blind study | Y-BOCS       | PAR        | 12 week   | 91 outpatients with OCD | Denys et al. 2007, Netherlands [50] |
| A randomized, double-blind placebo-controlled trial randomized, double-blind study | Y-BOCS       | PBO        | 12 week   | 100 patients with OCD   | Khan et al. 2007, Pakistan [51] |
| A randomized, double-blind placebo-controlled trial randomized, double-blind study | Y-BOCS       | PBO        | 24 week   | 466 adults with OCD   | Stein et al. 2007, South Africa [52] |
| A randomized, double-blind placebo-controlled trial randomized, double-blind study | Y-BOCS       | PBO        | 24 week   | 320 patients with OCD   | Fineberg et al. 2007, UK [53] |
| A randomized, double-blind placebo-controlled trial randomized, double-blind study | Y-BOCS       | PBO        | 24 week   | 117 outpatients with OCD   | Ninan et al. 2007, USA [54] |
| A randomized, double-blind placebo-controlled trial randomized, double-blind study | Y-BOCS       | PBO        | 24 week   | 40 subjects (9 and 17 years) with OCD 90 patients with OCD | Asbahr et al. 2005, Brazil [55] |
| A randomized, double-blind placebo-controlled trial randomized, double-blind study | Y-BOCS       | PBO        | 24 week   | 31 patients with OCD   | Nakao et al. 2005, Japan [56] |
| A randomized, double-blind placebo-controlled trial randomized, double-blind study | Y-BOCS       | PBO        | 24 week   | 112 patients (7-17 years) with a primary OCD | Denys et al. 2005, Netherlands [57] |
| A randomized, double-blind placebo-controlled trial randomized, double-blind study | Y-BOCS       | PBO        | 24 week   | 37 adult patients with OCD | Geller et al. 2004, USA [58] |
| A randomized, double-blind placebo-controlled trial randomized, double-blind study | Y-BOCS       | PBO        | 24 week   | 207 Children (7-11 years of age) and adolescents (12-17 years of age) with a primary OCD | Tenneij et al. 2004, USA [59] |
| A randomized, single-blind clinical trial A randomized, double-blind placebo-controlled trial randomized, double-blind placebo-controlled trial Open-label clinical trial | Y-BOCS       | PBO        | 12 week   | 49 adult patients with OCD 191 patients with a primary OCD | Pallanti et al. 2004, Italy [60] |
| A randomized, single-blind clinical trial A randomized, double-blind placebo-controlled trial randomized, double-blind placebo-controlled trial Open-label clinical trial | Y-BOCS       | PBO        | 12 week   | 49 adult patients with OCD 191 patients with a primary OCD | Kamijima et al. 2004, Japan [61] |
| A randomized, single-blind clinical trial A randomized, double-blind placebo-controlled trial randomized, double-blind placebo-controlled trial Open-label clinical trial | Y-BOCS       | PBO        | 12 week   | 49 adult patients with OCD 191 patients with a primary OCD | Fux et al. 2004, Israel [62] |
| A randomized, single-blind clinical trial A randomized, double-blind placebo-controlled trial randomized, double-blind placebo-controlled trial Open-label clinical trial | Y-BOCS       | PBO        | 12 week   | 49 adult patients with OCD 191 patients with a primary OCD | Neziroglu et al. 2004, USA [63] |
| A randomized, single-blind clinical trial A randomized, double-blind placebo-controlled trial randomized, double-blind placebo-controlled trial Open-label clinical trial | Y-BOCS       | PBO        | 12 week   | 49 adult patients with OCD 191 patients with a primary OCD | Hollander et al. 2003, USA [64] |
| A randomized, single-blind clinical trial A randomized, double-blind placebo-controlled trial randomized, double-blind placebo-controlled trial Open-label clinical trial | Y-BOCS       | PBO        | 12 week   | 49 adult patients with OCD 191 patients with a primary OCD | Hollander et al. 2003, USA [65] |
Table 1: (Continued)

| Design                                                                 | Outcome                                                                 | Study arms          | Follow-up | Participant*                                      | Author, year, country |
|------------------------------------------------------------------------|-------------------------------------------------------------------------|---------------------|-----------|--------------------------------------------------|-----------------------|
| Double-blind, fixed-dose, parallel trial                               | long-term efficacy, safety, and impact on relapse prevention            | PAR                 | 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                 | 12 week   | 140 patients with primary OCD                    | Denys et al. 2003, Netherlands [73] |
| A randomized, double-blind, placebo-controlled trial                  | Y-BOCS, CGI                                                           | PAR                 | 16 week   | 193 adult OCD patients                           | Hollander et al. 2003, USA [74] |
| A randomized, double-blind, placebo-controlled trial                  | Y-BOCS, CGI                                                           | FLU                 | 8 week    | 43 young OCD patients                            | Liebowitz et al. 2002, USA [76] |
| A randomized, single-blind, controlled trial                          | Y-BOCS, CGI                                                           | PAR                 | 12 week   | 73 OCD patients                                  | Albert et al. 2002, Italy [77] |
| Open-label trial                                                      | Y-BOCS                                                                | CIT                 | 12 week   | 39 OCD patients                                  | Pallanti et al. 2002, Italy [21] |
| Randomized, single-blind, placebo controlled study                    | Y-BOCS score, efficacy                                                | FLU                 | 52 week   | 130 patients with primary OCD**                  | Romano et al. 2001, USA [88] |
| A randomized, double-blind, controlled trial                          | YBOCS, CGI                                                            | SER                 | 24 week   | 150 patients were OCD                             | Bergeron et al. 2002, Canada [79] |
| A large randomized placebo-controlled trial                            | YBOCS, CGI                                                            | CIT                 | 12 week   | 71 patients were OCD                              | Stein et al. 2001, South Africa [80] |
| Open-label treatment                                                   | YBOCS, BABS                                                           | SER                 | 16 week   | 71 patients were OCD                              | Eisen et al. 2001, USA [81] |
| A double-blind, placebo-controlled                                    | CY-BOCS, CGI-S, CGI-I                                                 | SER                 | 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                 | 13 week   | 103 Children (7-17 years) with OCD               | Geller et al. 2001, USA [83] |
| A randomized, double-blind, controlled trial                          | YBOCS, BAABS                                                          | PAR                 | 12 week   | 36 patients were OCD                              | Humble et al. 2001, Sweden [84] |
| A randomized, double-blind, placebo-controlled, multicenter study     | CY-BOCS                                                               | FLU                 | 10 week   | 120 Children (7-17 years) with OCD               | Riddle et al. 2001, USA [85] |
| A randomized, double-blind, placebo-controlled study                  | Y-BOCS                                                                | FLU                 | 10 week   | 33 patients with OCD                              | Peter et al. 2000, Germany [86] |
| A randomized, double-blind, placebo-controlled trial                  | Y-BOCS, HAM-A, MADRS                                                  | PAR                 | 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, CGI-I scores                | FLU                 | 12 week   | 10 children/adolescents with OCD                 | Neziroglu et al. 2000, USA [88] |
| A randomized, double-blind, placebo-controlled, multicenter study     | CY-BOCS, HAM-A, MADRS                                                 | SER                 | 12 week   | 166 patients with OCD                             | Hoehn-Saric et al. 2000, USA [89] |
| Randomized, open-label trial                                          | Y-BOCS                                                                | CIT                 | 12 week   | Sixteen adult outpatients with OCD               | Pallanti et al. 1999, Italy [90] |
| Open-label trial                                                       | CY-BOCS, HAM, CI                                                     | PAR                 | 12 week   | 20 OCD outpatients (8 to 17 years)               | Rosenberg et al. 1999, USA [91] |
| Double-blind placebo-controlled trial                                 | YBOCS, CGI                                                            | FLX                 | 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 |
|-----------------------------------------------------------------------|----------------------------------|-------------------------------|-----------|--------------|-----------------------|
| 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, the Padua Inventory-Revised YBOCS, CGI | FLU CT | 16 week | 117 patients with primary OCD | van Balkom et al. 1998, Netherlands [94] |
| Double-blind placebo-controlled trial                                | YBOCS                            | FLX PBO                       | 12 week   | 14°C patients| Greenberg et al. 1998, USA [95] |
| Randomized, double-blind, placebo-controlled trial                   | CY-BOCS, NIMH, GOCI, 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| Mundo et al. 1997, Italy [99] |
| Multicenter, placebo-controlled, fixed-dose trial                    | Y-BOCS                           | 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 CGI IS scales         | FLU CLO                       | 8 week    | 26 individuals with OCD | Milanfranchi et al. 1997, Italy [100] |
| Double-blind controlled trial                                        | Y-BOCS and CGI IS 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, 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, HDS: Hamilton depression scale, DS: Depressive symptoms, CGI: Clinical global improvement, PIN: Pindolol, CT: Cognitive therapy, GIT: Citalopram, HRS: Hamilton rating scale, CLO: Clomipramine, BT: Behavior therapy.

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

| Design                                                                 | Outcome                          | Study arms                     | Follow-up | Participant* | Author, year, country |
|-----------------------------------------------------------------------|----------------------------------|-------------------------------|-----------|--------------|-----------------------|
| 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 34 patients (aged 24-67 years) with OCD | Simpson et al. 2013, USA [106] |
| Double-blind, placebo-controlled, pilot trial                        | YBOCS, CGIIS                      | PLP PBO                       | 8 week    | 39 adult patients with OCD | Storch et al. 2013, USA [107] |
| Double-blind, randomized, placebo clinical trial                     | YBOCS                             | APZ PBO                       | 12 week   | 201 patients (20-70 years) 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-blind clinical trial                              | YBOCS                             | APZ RIS                       | 12 week   | 90 patients (18-65 years) with OCD | Sevi 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...)
Outcome

OLP evaluated the efficacy of antipsychotic agents in 44 adults with OCD. PBO 30 adult patients with OCD. 40 patients with a primary OCD. 10 week 16 adult OCD patients. PBO+FLU PBO 12 week 16 outpatients with OCD. Shapira PBO PBO PBO RIS YBOCS PBO 54 patients with a primary OCD. 12 week PBO PBO PBO Denys YBOCS QPE 8 week 21 adult OCD patients. 8 week Open-label, add-on trial YBOCS, CGI QPE PBO 12 week 21 adult OCD patients. Open-label trial YBOCS QPE PBO 8 week 10°CD patients. A single-blind, placebo-controlled study YBOCS, CGI QPE PBO 8 week 27 patients were refractory OCD. 12 week Open-label trial YBOCS QPE PBO 12 week 20 refractory OCD outpatients. A randomized, double-blind, placebo-controlled study YBOCS RIS PBO 12 week 36 refractory OCD outpatients. 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: Rutinose, PBO: Placebo, RIS: Risperidone, BABIS: Brown assessment of beliefs, CGI: Clinical global impression, PPL: Paliperidone, CGIIS: Clinical global impression improvement and severity, SMTC: Stress management training condition, APE: Aripiprazole, QPE: Quetiapine, HDS: Hamilton depression scale, OLP: Olanzapine

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

| Design | Outcome | Study arms | Follow-up | Participant* | Author, year, country |
|--------|---------|------------|-----------|--------------|-----------------------|
| Randomized, placebo-controlled, clinical trial | Y-BOCS | QPE+QPE | 10 week | 46 adult patients with OCD | Valkink et al. 2012, Netherlands [117] |
| Randomized, double-blind controlled clinical trial | Y-BOCS | QPE+FLX, CIT+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] |
| Double-blind, placebo-controlled | YBOCS | OLP+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, FLX: Fluoxetine, 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 claims, we showed there sufficient evidence in the literature on
risperidone, as well as quetiapine and olanzapine. The difference 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 be used cautiously as an antipsychotic agent in non-responders to SRIs. In other reviews, Arrangunt 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 SRIs first-line treatment for many mental health disorders such as OCD. As our data showed among the SRIs, 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 SRIs 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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