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Pharmacotherapy for treatment-respondent vs. refractory obsessive–compulsive disorder in children and adults: strategies, meta-analyses and clinical guidelines

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Summary

Obsessive–compulsive disorder (OCD) is a common mental health disorder that occurs at all ages, but more commonly in younger people. It affects 1–1.5% of the general population. Many pharmacological therapies have been reported to diminish OCD symptoms, as well as increase the patient's quality of life. So far, several meta-analyses have directly compared such treatment approaches in treatment-responsive and treatment-resistant OCD. This review evaluated all treatment options for OCD in both children and adolescents, and aimed to establish whether existing pharmacological therapies work similarly well, taking into account medical comorbidities such as substance use, anxiety, metabolic disorders, and finally, an overview of issues related to safety and monitoring. Our review included data from 16 meta-analyses and 8 practical guidelines focusing on OCD patients. In adults with OCD, we found that combined therapy shows favorable outcomes versus SRI alone and produced better results. In children with OCD the greatest incremental treatment gains occur early in treatment with selective serotonin reuptake inhibitors (SSRIs). Finally, in treatment-resistant OCD augmentation of SRIs can be regarded as an evidence-based measure in pharmacological therapy. The results of this review mostly support the previous reviews on the pharmacological management of OCD. However, we noted that combination/augmentation of SSRIs significantly improved symptoms in treatment-resistant OCD compared with monotherapy. From a clinical perspective, antipsychotics combination/augmentation of SSRIs should be used in comorbid psychosis, a frequent comorbidity in OCD, especially as the presence of comorbidities is highly associated with treatment resistance in OCD.

Obsessive–compulsive disorder (OCD); pharmacotherapy; selective serotonin reuptake inhibitors (SSRIs); antidepressants; treatment augmentation

INTRODUCTION

Obsessive–compulsive disorder (OCD) is a common mental health disorder that occurs at all ages, but is more common in younger people, with uncontrollable, repeated thoughts, urges or mental images (obsessions) and repetitive behaviors and feelings in response to an obsessive thought (compulsions) [1]. Although OCD

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may initially reduce anxiety in the individual, it generally affects their lifestyle. Symptoms of OCD span a mild to severe range. Some people may have obsessive thoughts, while some may be able to control obsessive thoughts and involuntary behaviors for a short time and thus mask their symptoms when at school or at work. But in more severe cases, OCD can take over so much of a person's life that they can no longer work or perform day-to-day activities, as they spend a lot of their time on an obsessive ritual. Obsessions include thoughts, images or impulses that occur repeatedly (such as hesitation and doubt about doing a job); the person thinks they are outside of their control and find them uncomfortable, disturbing and meaningless [2]. Compulsive obsessions are compulsory acts that a person performs repeatedly and in accordance with a series of rules and rituals to neutralize their obsessive thoughts, such as rechecking, washing, numbering, asking, preoccupation with symmetry and accuracy, and storing too many objects. But symptoms such as hate or anxiety about body secretions (urine, feces, saliva), fear of the possibility of terrible events happening (fire, death of a relative, wasting and excessive worship, belief in special properties of numbers like 13, chewing nails) may also be considered obsessive symptoms [2]. OCD is sometimes associated with depression, eating disorders (overeating or anorexia nervosa), substance abuse (addiction), personality disorder, attention deficit and hyperactivity disorder (ADHD) or other anxiety disorders, which probably occur because of universal dimensions of distress or negative affectivity, a common genetic predisposition and a shared neurobiology [3]. Combining these disorders with the desire to hide the problem makes it difficult to diagnose and treat it and so people with OCD do not receive treatment for many years after the onset of the symptoms.

Despite advances in effective as well as safe treatments in pediatric OCD, a considerable proportion of patients with OCD do not achieve a suitable relief for their symptoms. Further, between 25 and 30% of patients do not show a substantial response with first-line therapies for OCD [4]. Many patients with OCD judged to be considered as clinical responders in studies still have considerable remaining symptoms. Considering the best evidence-based care provided by the most skilled clinicians, more than 46% of patients with OCD do not achieve remission of their symptoms [4]. Such patients have treatment-resistant (refractory) OCD.

Some clinical reviews focused on the assessment and treatment of children with refractory OCD, which is defined as failing to achieve adequate symptom relief despite receiving an adequate course of therapy [5]. There is no agreed definition for treatment-resistant OCD, but what is emphasized is that before considering the disorder as refractory, the adequacy of self-medication should be considered. Many patients who are considered as resistant to the treatment do not in fact receive adequate treatment. Many have received cognitive therapy before, relaxation, regular depression therapy or cognitive-therapeutic treatment alone, none of which is an indicator of OCD treatment [6]. Overall, there is currently no common language between the experts for treatment resistance in OCD. What is important is that, despite having received adequate therapeutic efforts, a considerable number of these patients have only a slight reduction in their OCD symptoms or may even show no reduction in symptoms at all.

The aim of this review was to assess pharmacotherapy strategies available for the conventional treatment of OCD and when treatment fails, as well as study the trends, meta-analyses and clinical guidelines in both children and adults with OCD.

DIAGNOSIS

OCD diagnosis presents diagnostic challenges due to the similarity and overlapping of symptoms with those of personality, anxiety, depression, schizophrenia or other mental health disorders [7]. Moreover, it is possible to have OCD comorbid with another mental health disorder [8]. Usually an OCD diagnosis is made by clinical interview based on DSM-IV diagnostic criteria for OCD, which include the existence of obsessions and compulsions. Adolescence, impulses, reversible mental retardation, disruptive and maladaptive disturbances leading to anxiety or discomfort could all be misdiagnosed as OCD [9]. Patients with OCD take approximately 10

years to be diagnosed correctly; thus, if it is diagnosed correctly at an early stage, OCD can be treated well and efficiently [10].

PREVALENCE

Epidemiological studies have shown the prevalence of OCD ranging from 1 to 3%, ranking it the 4th most often occurring psychiatric disorder. Usually about 10% of patients are referred to neurologists, psychiatrists and psychologists. According to the World Health Organization (WHO), OCD is the fourth substance-related and major depressive disorder. Among adolescents, boys suffer from this disorder more often than girls, and the prevalence rate is the same among adults [11-13]. Onset is on average at the age of 20; in men it happens a bit earlier and in women it is at about 22.

TREATMENT APPROACHES

- *Conventional treatment for OCD*

Similar to adults with OCD, as well as children and adults with major depression, the highest incremental treatment gains in pediatric patients with OCD happen early in SSRI treatment [14]. Former studies have revealed that nearly 60% of the patients with OCD treated with SSRIs showed a 25–35% reduction in symptoms according to the Yale–Brown Obsessive Compulsive Scale (Y-BOCS), which is not enough to reach an acceptable level of quality of life [15,16]. A decline of <25% in a Y-BOCS score is seen as non-response to treatment [17], while response to therapy is defined as a 3550% Y-BOCS score decrease [18]. Even with a modest reduction in Y-BOCS scores, a response to therapy of more than 3 to 5% reduction of symptoms is usually attained with placebo [19]. The term recovery has been proposed to describe a nearly complete OCD remission or a widespread absence of symptoms, as well as a Y-BOCS score of ≤ 8 [20]. It was also proposed that treatment-resistant OCD occurs in patients who had been exposed to first-line therapies but did not achieve a satisfactory response to treatment; in this paper, refractory OCD is defined as OCD in a patient who did not respond suitably to several conventionally effective treatments [6]. A flow diagram of conventional treatment options usually considered in OCD is presented below (Figure 1).

- *Treatment approaches for treatment-resistant (refractory) OCD*

Treatment-resistant OCD, defined as OCD in patients who are treated with a sufficient course of SRI therapy (clomipramine or SSRI) but who do not respond or display an unsatisfactory response; it accounts for 40–50% of all cases of OCD [21,22]. When treatment resistance is present, a logical next strategy is augmentation with a pharmacological agent such as an antipsychotic; however, even augmentation with a pharmacological agent created a substantial response in only one-third of patients [23]. Studies revealed a more effective response in patients with a history of maximal SSRI monotherapy for more than 12 weeks. Further treatment approaches comprise continuing with the selected SSRI for 3 to 6 months, dose titration to the maximum tolerated dose, switching medications or augmenting treatment with another first-line agent. Switching to further treatment approaches is recommended when patients still do not respond to treatment. In one study, authors reported that the ethanol-like experience suggests that μ-agonists and glutamate antagonists might be an option during the exacerbation of symptoms; however, these treatments warrant further validation [24]. Despite significant advances in OCD diagnosis and treatment strategies, some patients either do not respond at all or show little response to treatment [25]. Some patients with OCD get slightly better, but they remain with symptoms that are associated with no improvement in performance and quality of life. OCD can also be difficult to treat with an exposure and response prevention therapy [26]. Pharmacological management of treatment-resistant OCD is summarized in Figure 2. The meta-analyses revealed the effectiveness of a combination treatment with antipsychotics and SRIs, as well as the possible consideration of risperidone as an agent of first choice, which should be preferred to quetiapine and olanzapine, especially in patients who do not respond to conventional pharmacotherapies.

- *Combination therapy: old procedure, new path*

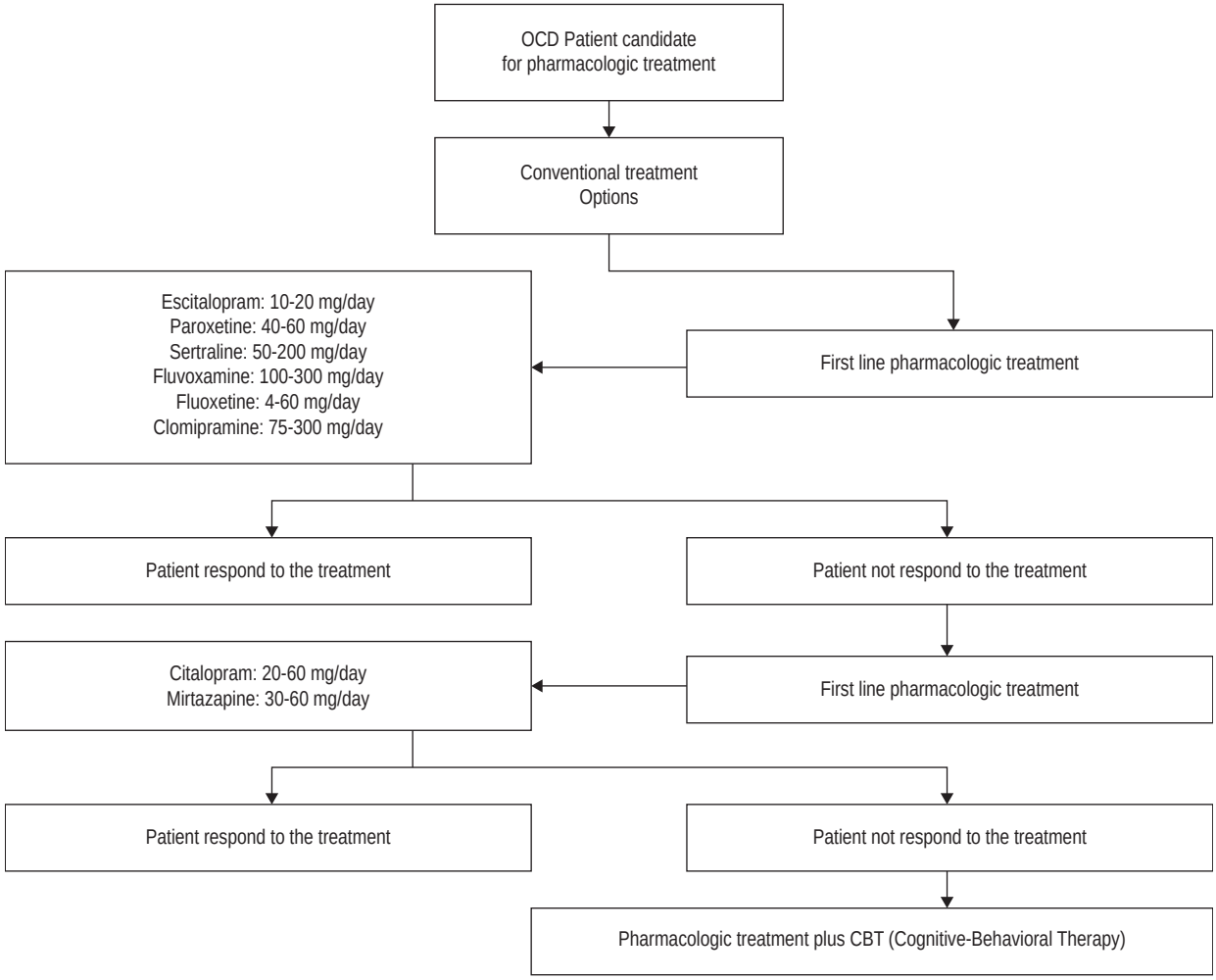

Figure 1. Conventional treatment options usually considered in Obsessive-Compulsive Disorder (OCD)

An inclusive systematic review and meta-analysis of all existing studies on psychotherapeutic and psychopharmacological treatments recommended a combination therapy, as it may be the most effective approach in OCD treatment [27]. In an open-label case series, patients with OCD were successfully treated with combination of clomipramine plus an SSRI, but some adverse effects appeared in most patients, including cardiovascular, tachycardia, manic switch, insomnia and in some cases headaches [28]. Thus, recommendations for combination therapy are to control electrocardiograms (ECG), drug blood concentrations and vital signs because SSRIs could raise the blood levels of clomipramine, whereas clomipramine may also possibly increase SSRI absorption. In this context, in a randomized trial of a new combined approach, patients with OCD who had responded to a 3-month drug therapy with venlafaxine or paroxetine received additional cognitive behavior therapy (CBT), and reported that this approach is useful; CBT was recommended to be added immediately after drug response was achieved [29]. In a case report, a patient with OCD who received combination therapy with escitalopram and fluvoxamine experienced a remarkable improvement, especially in social functioning [30]. Furthermore, combination therapy is more recommended for treatment-resistant OCD [31]. Another study reported a patient with treatment-resistant OCD who benefited from a combination therapy of buspirone and sertraline [32]. Despite this fact, combination therapy with two SSRIs is not recommended due to the risk of drug interactions. From a clinical perspective, antipsychotics combination/augmentation of SSRIs should be used if there is comorbid psychosis, as comorbidity is highly associated with treatment resistance in OCD [33].

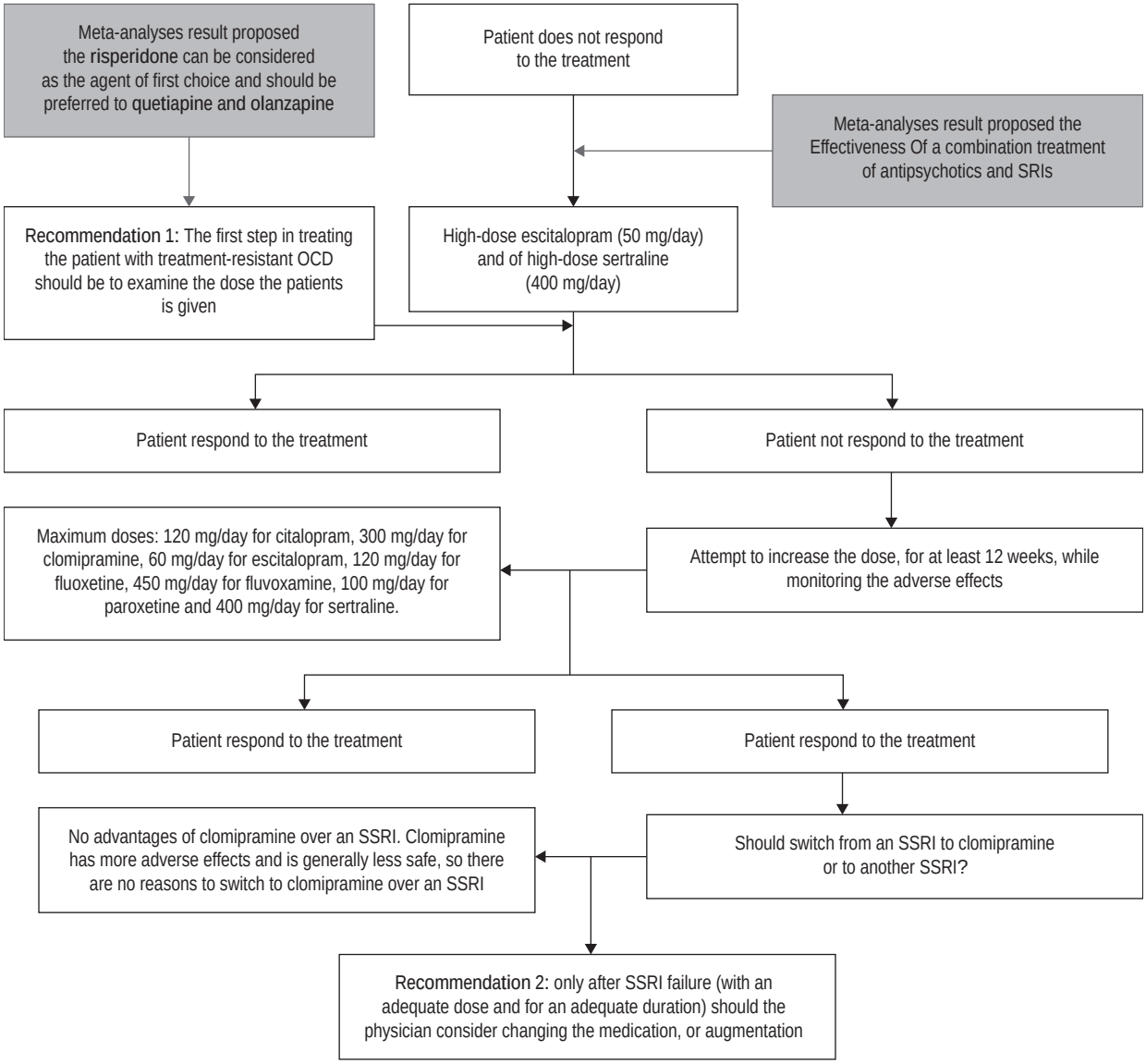

Fig. 2. Pharmacological management of treatment-resistant OCD

- *Further treatment options*

Although current pharmacotherapy strategies may be useful, as they increase the effectiveness of treatment, pharmacotherapy may not be applicable to all patients. Therefore, other therapeutic interventions are needed to target poor prognosis and resistance to therapies. New interventions should target the limitations of current therapeutic interventions. Given the importance of the route of drug administration in OCD, intravenous route (IV) could be superior to oral administration. A 3-week open-label trial of intravenous citalopram for OCD patients unresponsive to at least two orally administered SSRIs indicated a response rate of 59% [34]. In a double-blind controlled trial of IV compared with orally administered clomipramine over a 12-week treatment, pulse-loaded IV did not induce a greater Y-BOCS score reduction in treatment-resistant OCD [35]. Another open-label trial was performed to assess the efficacy of IV administered clomipramine in treatment-resistant OCD, and reported that IV route could be beneficial for patients with severe OCD that is unresponsive to several therapies, including orally administered clomipramine [36]. Other non-pharmacological treatment options are currently under evaluation, including deep brain stimulation (DBS). DBS is a neurosurgical procedure involving modulation of the brain circuits that are thought to be

implicated in OCD. This non-pharmacological treatment is a conventional approach for severe, treatment-resistant neurological disorders such as Parkinson's disease, dystonia and essential tremor [37], as well as being currently evaluated for a number of psychiatric disorders [38]. Baldermann et al., in a meta-analysis of 57 studies evaluated the efficacy of DBS for Tourette syndrome using the pooled Yale Global Tic Severity Scale (YGTSS) as the primary outcome. Even with small patient numbers (156 cases), they concluded that DBS can be considered as a valid option for medically intractable patients with Tourette syndrome [39]. Alonso et al. studied the existence of clinical predictors of response to DBS in OCD alongside its efficacy and tolerability in a meta-analysis of 31 studies involving 116 subjects. They confirmed that DBS is a valid alternative to lesion surgery for patients with severe, treatment-resistant OCD [40].

EVIDENCE

At the time of our study, 16 meta-analyses were available on the effectiveness of pharmacotherapy for patients with OCD (Table 1); 4 have examined the efficacy in treatment-resistant OCD. In 2011, Dold et al. conducted a meta-analysis of 11 double-blind, randomized, placebo-controlled trials with a total of 356 subjects on the efficacy of a combination therapy of SRIs and antipsychotics in treatment-resistant OCD. They showed significant differences regarding the antipsychotic dosage and SRI treatment duration before the augmentation [41]. They updated this systematic review in 2013 [42] and again in 2015 [43], and concluded that risperidone can be considered as the agent of first choice and more trials including higher antipsychotic doses are required to improve pharmacological treatment for treatment-resistant OCD; and that antipsychotic augmentation of SRIs can be regarded as an evidence-based measure in these cases. Recently, Soleimani et al. published a protocol for a systematic review and meta-analysis of all randomized clinical trials evaluating lithium, anticonvulsive or antipsychotic medication for patients with treatment-resistant OCD, but no results have been reported so far [44]. The remaining 14 meta-analyses included patients with treatment-respondent OCD. Of these 14 studies, 6 were about double-blind, randomized, placebo-controlled trials on pediatric patients with OCD that showed superiority of SRIs for the treatment of OCD with a moderate effect size and a non-significant risk of suicidality, as well as that combined therapy was no more effective irrespective of the initial severity of the samples [14, 45-49]. All meta-analyses found that high doses of SSRIs were more effective as first-line therapy for patients with OCD; however, combined therapy was more effective than monotherapy. Though the treatment effect of pharmacotherapy has been estimated by various statistical measures, all meta-analyses reported a significant improvement with SSRIs, as well as SSRIs in combination with other treatment approaches.

Table 1. Summary of the data obtained in previous meta-analyses on OCD treatment

Study ID	Target study design	Comparison groups		No. of paper included	Patient group	Number of cases	Estimated value	Final finding
		Intervention	Control					
Dold et al., 2011[33]	DB-RPCT	SRI plus anti-psychotic	SRI plus placebo	11 studies	TR-OCD	356 patients	RR (95%CI) : (1.36-3.43) PMC-Y-BOCS SMD(95%CI): 0.69 (0.38 – 1.00)	Effectiveness a combination treatment of antipsychotics and SRIs
Dold et al., 2013[34]	DB-RPCT	SRI plus anti-psychotic	SRI plus placebo	12 studies	TR-OCD	394 patients	RR (95%CI) : 2.10 (1.16-3.80) PMC-Y-BOCS SMD(95%CI): 0.54 (0.15–0.93)	risperidone can be considered as the agent of first choice and should be preferred to quetiapine and olanzapine

Sánchez-Meca et al., 2014[35]	DB-RPCT	PT CBT CMB	Placebo wait-list relaxation training	18 studies	P-OCD	1223 patients	d+ (95%CI) PT: 0.74 (0.36-1.13) CBT: 1.74 (1.33-2.14) CMB: 1.71 (1.0 – 2.42)	Clomipramine was more efficacious than SSRIs, but its adverse effects were more severe.
Romanelli et al., 2014[36]	HTH-RCT	PT CBT CMB	Placebo	13 studies	C-A-OCD	959 patients	PMC-Y-BOCS PT, SMD(95%CI): 0.22 (-0.02 – 0.47) CBT, SMD(95%CI): 0.37 (0.10 – 0.64)	BT is more effective than SRIs, overall, but not selective SRIs. The combination of behavioral therapy plus an SRI is more effective than an SRI alone.
Ducasse et al., 2014 [37]	DB-RPCT	SRI plus anti-psychotic	SRI plus placebo	13 studies	OCD	431 patients	————	risperidone proved its effectiveness; aripiprazole, haloperidol, and amisulpride showed good preliminary data
Skarphedinsson et al., 2015[38]	DB-RPCT	SI-CBT	Placebo	13 studies	P-OCD	757 patients	PMC-Y-BOCS SMD(95%CI): -0.2 (-2.32 – 1.9)	The effects of SI-CBT and active treatments were not significantly different
Strawn et al., 2015[39]	DB-RPCT	SSRIs SSNRIs	Placebo	9 studies	P-OCD	1,673 patients	d+ (95%CI) 0.64 (0.34 – 0.96)	Superiority to placebo for the treatment of pediatric anxiety disorders with a moderate effect size and a non-significant risk of suicidality
Ivarsson et al., 2015[40]	DB-RPCT	SSRIs	Placebo CBT	14 studies	C-A-OCD	1136 patients	PMC-Y-BOCS SMD(95%CI): -3.5 (-4.6 – -2.3)	CBT has the superior efficacy. CMB versus CBT shows that SRI treatment adds little to concomitant CBT, while CMB shows favorable outcome versus SRI alone

Dold et al., 2015[41]	DB-RPCT	SRI plus anti-psychotic	SRI plus placebo	14 studies	TR-OCD	491 patients	Hg; SMD(95%CI): -0.64 (-4.6 – -2.3) MH; RR (95%CI) : 1.98 (1.34-2.92)	Antipsychotic augmentation of SRIs can be regarded as an evidence-based measure in TR-OCD
McGuire et al., 2015[42]	DB-RPCT	PT CBT CMB	Placebo	20 studies	P-OCD	1296 patients	PT, RR(95%CI): 0.50 0.37 – 0.63) CBT, RR(95%CI): 1.21 (0.83 – 0.1.59)	The treatment effects for CBT and SRIs across three important outcome metrics, and provide evidence for moderators of CBT across trials.
Brakoulias et al., 2015[43]	ALL*	PT	——	7 studies	OCD	92 patients	ER (95%CI): 0.58 (0.37–0.76)	study encourages us to consider the use of SRIs in patients with hoarding disorder
Issari et al., 2016[44]	DB-RPCT	PT	Placebo	17 studies	OCD	3276 patients	SMD (95%CI): -0.91 (-0.54 – -1.28)	the greatest incremental treatment gains in OCD are seen early on in SSRI treatment
Skapinakis et al., 2016[45]	DB-RPCT	PT CBT CMB	Placebo	86 studies	OCD	1083 patients	SMD (95%CI): -3.49 (-5.12 – -1. 81)	In adults, psychological interventions, clomipramine, SSRIs or combinations of these are all effective, whereas in children and adolescents, psychological interventions, either as monotherapy or combined with specific SSRIs, were more likely to be effective.
Öst et al., 2016[46]	DB-RPCT	PT CBT CMB	Placebo	42 studies	P-OCD	1991 patients	g-value(95%CI) PT: 0.48 (0.26-0.70) CBT: 0.53 (0.25-0.80) CMB: 0.80 (0.48 – 1.11)	CMB was not more effective than CBT alone irrespective of initial severity of the samples. RCTs have a number of methodological problems

Varigonda et al., 2016[47]	DB-RPCT	PT	Placebo	9 studies	P-OCD	801 patients	SMD(95%CI): 2.25 (1.79 – 2.72)	greatest incremental treatment gains in pediatric OCD occur early in SSRI treatment
Locher et al., 2017[48]	DB-RPCT	PT	Placebo	8 studies	C-A-OCD	807 patients	RR (95%CI) : 3.59 (1.89-6.84) g-value(95%CI) 0.39 (0.25-0.54)	SSRIs and SNRIs are more effective than placebo
Soleimani et al., 2017[49]	DB-RPCT	PT	Placebo	——-	TR-OCD	——-	——-	Only is a protocol

Selective serotonin reuptake inhibitors (SSRIs); Selective serotonin-norepinephrine reuptake inhibitors (SSNRIs); Treatment-resistant obsessive-compulsive disorder (TR-OCD); Relative risk (RR); Double-blind, randomized, placebo-controlled trials (DB-RPCT); pooled mean change in the Yale-Brown obsessive compulsive scale (PMC-Y-BOCS); Pharmacological therapy (PT); Combined therapy (CMB); Pediatric-OCD (P-OCD): d+, mean effect size; head-to-head-RCTs (HTH-RCT); Children-Adult-OCD (C-A-OCD); standard individual cognitive behavior therapy (SI-CBT); Hedges's g (Hg); Mantel-Haenszel risk ratios (MH); *, randomized controlled trial (RCT), open-label trial (OLT) or case series (CS); ER, Event Rate showing responded to pharmacotherapy; SMD, weighted mean difference on the Y-BOCS of SSRI treatment compared to placebo

PUBLISHED GUIDELINES

To date, only five guidelines for the management of OCD have been published (Table 2) [50-54]. The most recent clinical practice guidelines on the pharmacotherapy of patients with OCD have been published by the British Association for Psychopharmacology. These guidelines address various features of facility provision, pharmacological methods for individuals with OCD from different age groups. While the evidence base is quickly growing, a number of major gaps and forthcoming revisions of these guidelines will integrate new scientific evidence as it develops. These guideline offer a number of recommendations to address these gaps in evidence-based practice. Moreover, as well as introducing new pharmacotherapies for individuals with OCD, the influence of many psychiatric and medical comorbidities, such as substance use, anxiety, metabolic disorders, and finally, an overview of issues related to safety and monitoring, will be addressed by these guidelines.

Table 2. Published guidelines on treatment strategies in OCD

Study ID	Organization	Basis of the guideline	Recommendation
Baldwin et al., 2014[53]	British Association for Psychopharmacology	based on available evidence, were constructed after extensive feedback from participants	Despite the availability of many evidence-based pharmacological and psychological treatments, a substantial proportion of patients will not respond fully to initial treatments, provided in primary medical care. The criteria for referral to secondary care mental health services should be sufficiently flexible to ensure that patients with disabling and treatment-resistant anxiety disorders can have equitable access to mental health specialists.

Katzman et al., 2014[54]	Anxiety Disorders Association of Canada	Developed by Canadian experts in anxiety and related disorders through a consensus process.	Optimal management requires a good understanding of the efficacy and side effect profiles of pharmacological and psychological treatments. Many factors should be considered when treating patients with an anxiety/related disorder and comorbid chronic pain, cardiovascular disease, diabetes and metabolic syndrome
Bandelow et al. 2008[55]	World Federation of Societies of Biological Psychiatry	A consensus panel of 30 international experts, are now based on 510 published randomized, placebo – or comparator-controlled clinical studies (RCTs) and 130 open studies and case reports.	In treatment-resistant cases, benzodiazepines may be used when the patient does not have a history of substance abuse disorders. Potential treatment options for patients unresponsive to standard treatments are described in this overview.
Koran et al. 2007[56]	American Psychiatric Association	This practice guideline was developed under the auspices of the Steering Committee on Practice Guidelines.	To make the advances in treatments for OCD available to more individuals with the disorder, health services research on OCD and its treatment is needed.
NICE, 2005[57]	NICE/Royal College of Psychiatrists/ British Psychological Society	The guideline recommendations have been developed by a multidisciplinary team of healthcare professionals, people with OCD, carer and guideline methodologists after careful consideration of the best available evidence.	Assist clinicians, people with these disorders and their carers by identifying the merits of particular treatment approaches where the evidence from research and clinical experience exists.

PHARMACOLOGICAL THERAPY OF TREATMENT-RESISTANT OCD

Although CBT is considered first-line treatment for patients with OCD, pharmacological therapy is often used when poor response, greater severity, or difficulty with taking part in CBT is present. Medical experts dealing with treatment-resistant with OCD should take into account all phenomenological risk factors [55], which could lead to different interpretations and treatment choices, and be responsible poor response to conventional treatment (Figure 3). These phenomenological aspects of OCD are considered risk factors for poor response to treatment and can be divided into two categories, intrinsic and extrinsic aspects. Intrinsic aspects related to OCD that may lead to poor response to conventional treatment are listed in Figure 2. Some evidence shows that OCD patients with early onset OCD have a poor prognosis, and consequently poor response to conventional treatments [56, 57].

The alternative treatment approaches (non-conventional pharmacological approaches) to treatment-resistant OCD include greater doses of standard drugs used in conventional therapy considered with caution, intravenous monotherapy with clomipramine and citalopram, combined/augmented pharmacotherapy, and other biological interventions, such as fatty acids.

LIMITATIONS

Numerous clinical and methodological limitations possibly restraining the findings of meta-analyses, including no examination of some available drugs in double-blind studies; consequently, the efficacy of such drugs in treatment-resistant OCD patient remains unknown. A further limitation arises from the differences in the included meta-analyses in terms of their samples, therapeutic modalities, trials' duration, comorbidities, and the administered pharmacologic agents' doses.

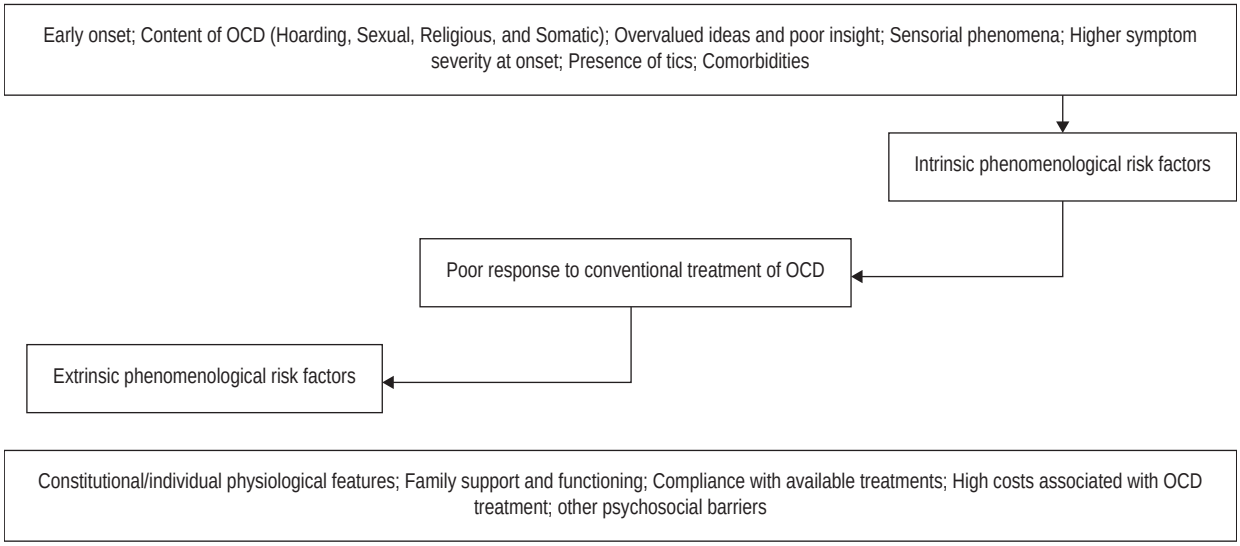

Fig. 3 Intrinsic and extrinsic phenomenological risk factor for poor response to conventional treatment of OCD.

CONCLUSIONS

SSRIs have been largely studied in both pediatric and adolescent patients with OCD reporting widely positive results. Based on the results of meta-analyses and practical guidelines for treatment-resistant OCD patients, SSRIs combined with antipsychotic drugs could be considered as evidence-based treatment choice in treatment-resistant OCD. Moreover, we are presently aware of a meta-analysis of head-to-head trials that directly compare antipsychotic and SSRI drugs in treatment-resistant OCD. Despite the aforementioned limitations, the methodological quality of the included meta-analyses was acceptable, and we could confirm that combination/augmentation of SSRIs significantly improved symptoms in treatment-resistant OCD patients compared with monotherapy. From a clinical perspective, antipsychotics combination/augmentation of SSRIs should be particularly beneficial if there are comorbidities such as psychosis.

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