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Treatment of Obsessive-Compulsive Disorder Resistant to Serotonin Reuptake Inhibitors – A Systematic Review

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TREATMENT OF OBSESSIVE-COMPULSIVE DISORDER RESISTANT TO SEROTONIN REUPTAKE INHIBITORS – A SYSTEMATIC REVIEW

TRATAMENTO DA PERTURBAÇÃO OBSESSIVO-COMPULSIVA RESISTENTE AOS INIBIDORES DA RECAPTAÇÃO DA SEROTONINA – UMA REVISÃO SISTEMÁTICA

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ABSTRACT

Background: Obsessive-Compulsive Disorder (OCD) is a common mental disorder and a major cause of disability worldwide. Typically, it has a chronic course, marked by recurrent intrusive thoughts (obsessions) and repetitive behaviors (compulsions). Its pharmacological first line of treatment has been well established for several years now, with the Serotonin Reuptake Inhibitors (SRIs). However, about half of the patients are resistant to this approach, representing a therapeutic challenge for clinicians. Evidence suggests that other medications can augment SRIs, enhancing its effects and achieving a bigger efficacy in these patients' treatment.

Objectives: The main goal of this work was to assess the clinical efficacy of pharmacological augmentation strategies in patients with OCD resistant to SRIs.

Methods: A systematic review was conducted searching PubMed database from the 1st of January 2000 to the 31st of December 2020 to identify randomized controlled trials comparing an active drug with placebo as an augmentation strategy in SRI-resistant OCD.

Results: Sixteen studies were selected for data extraction, including a total of 585 patients. Risperidone, aripiprazole, N-acetylcysteine, lamotrigine, riluzole, memantine and methylphenidate were efficacious for augmenting SRIs in OCD.

Conclusion: Several pharmacological augmentation options presented as potentially effective in OCD when it is resistant to Serotonin Reuptake Inhibitors, although this is still an area for further research.

Keywords: Obsessive-Compulsive Disorder, resistant, Serotonin Reuptake Inhibitors, pharmacological treatment.

RESUMO

Contexto: A Perturbação Obsessivo-Compulsiva (POC) é uma doença mental frequente e uma causa importante de incapacidade a nível mundial. Tipicamente, tem uma evolução crónica, marcada por pensamentos intrusivos recorrentes (obsessões) e comportamentos repetitivos (compulsões). O seu tratamento farmacológico de primeira linha está bem estabelecido há vários anos, com os Inibidores da Recaptação da Serotonina (SRIs). Contudo, cerca de metade dos doentes têm manifestações resistentes a esta abordagem, representando um desafio terapêutico para os médicos. A evidência sugere que outros fármacos podem ser adicionados aos SRIs, potenciando os seus efeitos e permitindo uma maior eficácia no tratamento destes doentes.

Objetivos: O principal objetivo deste trabalho foi avaliar a eficácia clínica de estratégias farmacológicas de potenciação em doentes com POC resistente aos SRIs.

Métodos: Foi feita uma revisão sistemática através da pesquisa na base de dados PubMed entre 1 de janeiro de 2000 e 31 de dezembro de 2020, para identificar estudos randomizados e controlados que comparassem um fármaco ativo com placebo como estratégia de potenciação na POC resistente aos SRIs.

Resultados: Dezasseis artigos foram selecionados para extração de dados, incluindo um total de 585 doentes. A risperidona, aripiprazol, N-acetilcisteína, lamotrigina, riluzol, memantina e metilfenidato foram eficazes na potenciação dos SRIs.

Conclusão: Várias opções farmacológicas se apresentaram como sendo possivelmente efetivas no tratamento da POC resistente aos Inibidores da Recaptação da Serotonina, embora esta ainda seja uma área para investigação adicional.

Palavras-chave: Perturbação Obsessivo-Compulsiva, resistente, Inibidores da Recaptação da Serotonina, tratamento farmacológico.

ABBREVIATIONS

CBT: Cognitive Behavioral Therapy
CGI: Clinical Global Impression
CGI-I: Clinical Global Impression – Improvement
CGI-S: Clinical Global Impression – Severity
COVID-19: Coronavirus Disease 2019
CSTC: Cortico-Striato-Thalamo-Cortical
DBS: Deep Brain Stimulation
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders – fourth edition
DSM-5: Diagnostic and Statistical Manual of Mental Disorders – fifth edition
EPA: Eicosapentaenoic Acid
ERP: Exposure and Response Prevention
ICD-10: International Classification of Diseases – tenth revision
ICD-11: International Classification of Diseases – eleventh revision
ICOCS: International College of Obsessive-Compulsive Spectrum Disorders
Imood: Immuno-moodulin
MeSH: Medical Subject Headings
MGluR5: Metabotropic Glutamate Receptor 5
MPH-ER: Methylphenidate of Extended-Release formulations
NAC: N-acetylcysteine
NMDA: N-methyl-D-aspartate
OCD: Obsessive-Compulsive Disorder
OCRN: Obsessive-Compulsive and Related Disorders Research Network
PET: Positron Emission Tomography
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SNRI(s): Serotonin-Norepinephrine Reuptake Inhibitor(s)
SRI(s): Serotonin Reuptake Inhibitor(s)
SSRI(s): Selective Serotonin Reuptake Inhibitor(s)
TMS: Transcranial Magnetic Stimulation
WHO: World Health Organization
Y-BOCS: Yale-Brown Obsessive-Compulsive Scale

INTRODUCTION

According to the most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, Obsessive-Compulsive Disorder (OCD) is a disabling illness, characterized by recurrent intrusive thoughts (obsessions) and repetitive behaviors (compulsions).[1]

Epidemiology and Classification

OCD affects up to 1% of the global population,[2] with a lifetime prevalence of 2.3%, although these numbers might be underestimated, since not all patients seek help. The average age of onset is 19.5 years old and some patients, particularly males, can have an early onset, before 10 years of age.[3]

In 2017, the World Health Organization (WHO) listed anxiety disorders, including OCD, as part of the top 10 causes of years lost to disability in all WHO regions; also in this report, anxiety disorders were the sixth largest contributor to non-fatal health loss on a global scale.[4] In addition, an article from 2018 revealed that anxiety disorders were the most common mental illnesses in Portugal, including OCD and specific phobia as the most prevailing conditions.[5]

In fact, in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, published in 1994, OCD was included in the anxiety disorders category, and several recent epidemiologic studies still consider it as such, even though *DSM-5* placed it in a new category in 2013, called "Obsessive-Compulsive and Related Disorders".[6] This change was due to behavioral and neurobiological differences exposed by modern technologies.[6,7]

The new category in which OCD is inserted also includes body dysmorphic disorder, hoarding disorder, trichotillomania, excoriation disorder and obsessive-compulsive and related disorders induced by substances or medications, due to another medical condition or other specified and unspecified.[1]

Diagnosis and Clinical features

According to the *DSM-5*, there are four criteria to diagnose OCD: obsessions and/or compulsions must not only be present, but also be time-consuming (more than one hour per day) or distressing, not attributable to another medical condition or substance use, and not better explained by another mental disorder.[1]

Obsessions are thoughts, urges or images that are recurrent and persistent, intrusive and unwanted, distressing and ego-dystonic.[1,8] In an attempt to suppress or neutralize such thoughts, many patients perform repetitive behaviors or mental acts, called compulsions. In fact, most individuals with OCD have both obsessions and compulsions.[1]

The most common obsessions and respective compulsions are: contamination and cleaning; symmetry and repeating, ordering and counting; fears of harm and checking; as well as aggressive, sexual or religious concerns and related acts.[1] Also common are the following: obsessions with fear of behaving unacceptably or making a mistake, excessive doubt, moral concerns, compulsions of hoarding, asking for reassurance, repeating words silently, ruminations and "neutralizing" thoughts.[2,8]

Although the usual purpose of compulsions is to prevent the obsession-related events, these acts are not realistically linked to those events, or are performed in an excessive and rigid way, allowing only a temporary relief of anxiety.[1,8] Hence, it becomes clear that, because of their nature, obsessions and compulsions consume a large amount of the patient's time and create clinically significant distress or functioning impairment, mostly at the social and occupational level. These patients can experience strong feelings of disgust, uneasiness and recurrent panic attacks, which conducts them to avoid certain people, places and trigger situations.[1]

In the 10th revision of the International Classification of Diseases (ICD-10), endorsed in 1990, there was a duration criterion of at least two consecutive weeks of symptoms for OCD diagnosis. However, in the 11th revision (ICD-11), released in 2018, this duration criterion was removed, since there was no evidence to validate it.[9] The ICD-11 workgroup suggested that OCD diagnosis should be made with caution in patients with a very short duration of illness (such as less than one month), and that other diagnoses should be excluded in case of an acute or fulminant onset of OCD.[10]

The dysfunctional beliefs observed in these patients can be associated with an enlarged sense of responsibility, threat overestimation, intolerance to uncertainty, perfectionism, and overvaluation of thoughts. According to their insight on such beliefs, patients can be divided into three groups: if they recognize that those beliefs are definitely or probably false, they have good or fair insight; instead, if they consider those beliefs as probably true, they have poor insight; finally, if they are convinced that those beliefs are true, they have an absent insight/ delusional beliefs (representing 4% or less). This is a relevant specifier since poorer insights have been associated with worse long-term outcomes.[1]

The fact that most of the patients recognize the senseless nature of their thoughts and behaviors may lead to feelings of shame and reluctance to seek help. It is fairly common that these individuals present to non-psychiatrists in the first place, for indirect symptoms or other comorbid disorders, like depression or anxiety.[8] The treatment delay can reach an average of 17 years (increasing with the age at onset), for several reasons, including unawareness of the disorder and its treatment, embarrassment or fear.[11]

Once the diagnosis of OCD has been suggested, standardized instruments are useful to define the symptom profile, estimate severity and disability, and follow treatment response.

The most widely accepted screening tool for OCD is the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), approved for both children and adults.[8] It ranges from zero to 40 points (40 being the most severe condition), calculated after the patient grades 10 items from zero to four, based on severity. Five of those items are about obsessions and five are about compulsions, assembling a score for each subscale. The items included are as follows: time spent on obsessions and on compulsions, interference and distress they cause, resistance against them and control over them.[12] Besides Y-BOCS, there is another widely used tool, applicable to all psychiatric disorders – the Clinical Global Impression (CGI) scale. It has two components: the CGI-Severity (CGI-S), which rates illness severity from one (normal) to seven (among the most extremely ill patients), and the CGI-Improvement (CGI-I), which rates change from the baseline of treatment, from one (very much improved) to seven (very much worse).[13]

It is also pertinent to specify if the patient has a current or past history of a tic disorder, which happens in up to 30% of OCD patients (mostly males with early onset). In these cases, the pattern of familial transmission, the symptoms and even the disease course can differ from the patients without such association.[1]

Depression is the most frequent comorbid condition in patients with OCD, followed by specific phobia, social phobia, eating disorder, alcohol dependence, schizophrenia and panic disorder.[14]

Concerning the disease course, two major types are seen – chronic and episodic. The chronic course is typical of OCD, with phasic exacerbations and incomplete remissions. Less frequently, the symptoms may occur during an episode and then remit, with or without treatment, in an episodic course.[15]

Etiology and Pathophysiology

OCD's exact etiology remains unknown, and it is most likely multifactorial. As much as 45 to 65% of the disorder's variance can be attributable to genetic factors, showing a higher heritability in OCD when compared to most anxiety disorders.[16]

The underlying neurobiological mechanisms of OCD are not completely understood. It is thought that this disorder is associated with an anomalous function of the cortico-striato-thalamo-cortical (CSTC) circuits and the frontolimbic circuit.[17] In fact, several neurological disorders in which these circuits are affected are linked to OCD, such as traumatic brain injury, epilepsy, Sydenham's chorea and Tourette's syndrome.[18-20]

Within CSTC circuits, many neurotransmitter systems are found, particularly serotonin, dopamine and glutamate, and these might play an important role in sustaining OCD symptoms. Indeed, this disorder has been associated with alterations in levels of serotonin and its metabolites in the cerebrospinal fluid (which normalize after successful treatment), with variants in serotonergic genes and with altered serotonin transporter receptor binding in the

midbrain. Furthermore, OCD has been linked to some variants in catecholaminergic genes and alterations in specific dopaminergic receptors, such as a decrease in striatal dopamine D2 receptors. In fact, dopamine is known to have a major role in cognitive and affective processes (including reward processing) and in stereotypic behavior, as seen in tic disorders, frequently associated with OCD. Finally, alterations in glutamatergic metabolites and variants in glutamatergic genes have also been related to this disorder;[17] recent findings from a positron emission tomography (PET) study in OCD showed significant positive correlations between metabotropic glutamate receptor 5 (mGluR5) distribution volume ratio and obsessions, suggesting that OCD symptoms may be associated with glutamatergic pathology and mGluR5.[21]

Management

Currently, approved medications for OCD treatment are serotonin reuptake inhibitors (SRIs), including selective serotonin reuptake inhibitors (SSRIs) and clomipramine (non-selective SRI).[22]

SSRIs are considered the first-line pharmacotherapy, because of their higher safety and tolerability profile when compared to clomipramine (a tricyclic antidepressant that was the first agent to show efficacy in OCD). However, SSRIs need a minimum of eight weeks of sustained treatment until clinical improvement in seen.[17] In addition, they are known to cause dose-dependent side effects, including gastrointestinal discomfort, sedation and sexual dysfunction, which can be a barrier, especially because the doses required for OCD treatment are higher than the ones used for anxiety or depressive disorders.[23]

Around half of the patients will not show a complete response to SSRIs.[24] In fact, the concept of “treatment responsiveness” in OCD remains controversial, but a widely used definition is an improvement of 25-35% from baseline on the Y-BOCS score. Likewise, the concept of “treatment resistance” can vary, but it is often based on the number of failed treatment trials.[25] Several clinical predictors have been associated with a poor response, including male gender, religious and sexual obsessive thoughts, hoarding compulsions, poor insight, greater functional impairment, multiple comorbidities and a positive family history.[17]

In case of resistance, the current guidelines from the American Psychiatric Association recommend optimizing the dose of the prescribed SSRI in the first place, climbing up to 60mg/d of escitalopram, 120mg/d of fluoxetine, 450mg/d of fluvoxamine, 100mg/d of paroxetine and 400mg/d of sertraline.[22] The trials should last at least 8 to 12 weeks, with 4 to 6 weeks at the maximum tolerated dose.[22,26] If the patient remains resistant, switching to another SSRI, or to a serotonin-norepinephrine reuptake inhibitor (SNRI) or even to clomipramine might be the answer.[17,26] However, combining an SSRI with clomipramine might be dangerous, due to the risk of severe and potentially life-threatening events such as seizures, cardiac arrhythmias and

serotonergic syndrome.[17]

Cognitive behavioral therapy (CBT) is also a first line approach for OCD, and it can be used as an alternative or an adjunct to SRI treatment.[27]

When monotherapy is insufficient, augmentation with atypical antipsychotics (including risperidone, quetiapine, olanzapine or aripiprazole) tends to be the next step.[28] Unfortunately, only one third of OCD patients will respond to antipsychotic augmentation, so several other options have been studied as adjunct treatments.[29] In particular, glutamate modulators, such as N-acetylcysteine (NAC), memantine, lamotrigine, topiramate, riluzole and mavoglurant have been assessed for this purpose.[17]

When patients do not respond to pharmacological and psychological interventions, there is evidence supporting transcranial magnetic stimulation (TMS) or even deep brain stimulation (DBS).[30,31] Finally, for the most severe refractory cases, a few centers perform ablative neurosurgical procedures in specific regions of the CSTC circuit, such as the anterior cingulotomy and the gamma ventral capsulotomy. Attending to the possibility of irreversible adverse effects, including personality changes and cognitive deterioration, these surgeries should be reserved for the final lines of treatment.[32]

Currently, it is relevant to mention that, from all the individuals with mental illness, OCD patients might be the ones that are most directly affected by the Coronavirus Disease 2019 (COVID-19) pandemic, especially those with contamination obsessions and cleaning compulsions. Some of them are expressing doubts about the rationality of the therapies they have been following, particularly the CBT with exposure and response prevention (ERP). The International College of Obsessive-Compulsive Spectrum Disorders (ICOCS) and the Obsessive-Compulsive and Related Disorders Research Network (OCRN) of the European College of Neuropsychopharmacology recommended that CBT with ERP is adapted or paused in this context. For this reason, pharmacotherapy was indicated as the first option for adults and children with contamination obsessions during the pandemic.[33]

According to the ICOCS and OCRN clinician's guide, the medication status of these patients should be reviewed as a priority. Most of them should receive an SSRI at the optimal dose, and, if not responsive, another SSRI or clomipramine should be tried. In case of SSRI resistance, a low dose of adjunctive antipsychotic should be considered.[33]

Aim

Based on the current pertinence and wide range of OCD's pharmacological treatment approaches, our work was designed to review the clinical efficacy of several augmentation strategies for adult patients that are resistant to SRIs, according to the available evidence in the literature.

METHODS

This Systematic Review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

PubMed Database was searched with the following Medical Subject Headings (MeSH) terms: "((("Obsessive-Compulsive Disorder" [Mesh]) AND "Serotonin Uptake Inhibitors" [Mesh]) AND "Treatment Outcome" [Mesh])", from the 1st of January 2000 to the 31st of December 2020. The search was restricted to English language.

The inclusion criteria were randomized controlled trials/ clinical trials that discussed pharmacological treatment possibilities and their outcomes for Obsessive-Compulsive Disorder resistant to SRIs, upon an augmentation strategy. The population chosen for this review were adults above eighteen years old. Data were collected from articles available in full-text form.

We compared the outcomes from patients who were treated with an SRI plus the augmentation substance with the ones treated with SRI plus placebo.

RESULTS

Through online database searching, we identified 353 articles. Only 29 of those were sorted out for full-text assessment and 16 were chosen for inclusion and data extraction.[34-49] Figure 1 shows the PRISMA flow diagram for the exclusion and inclusion process.

Table 1 presents the characteristics of the included articles, all randomized controlled trials. Overall, the studies involved 585 adult patients.

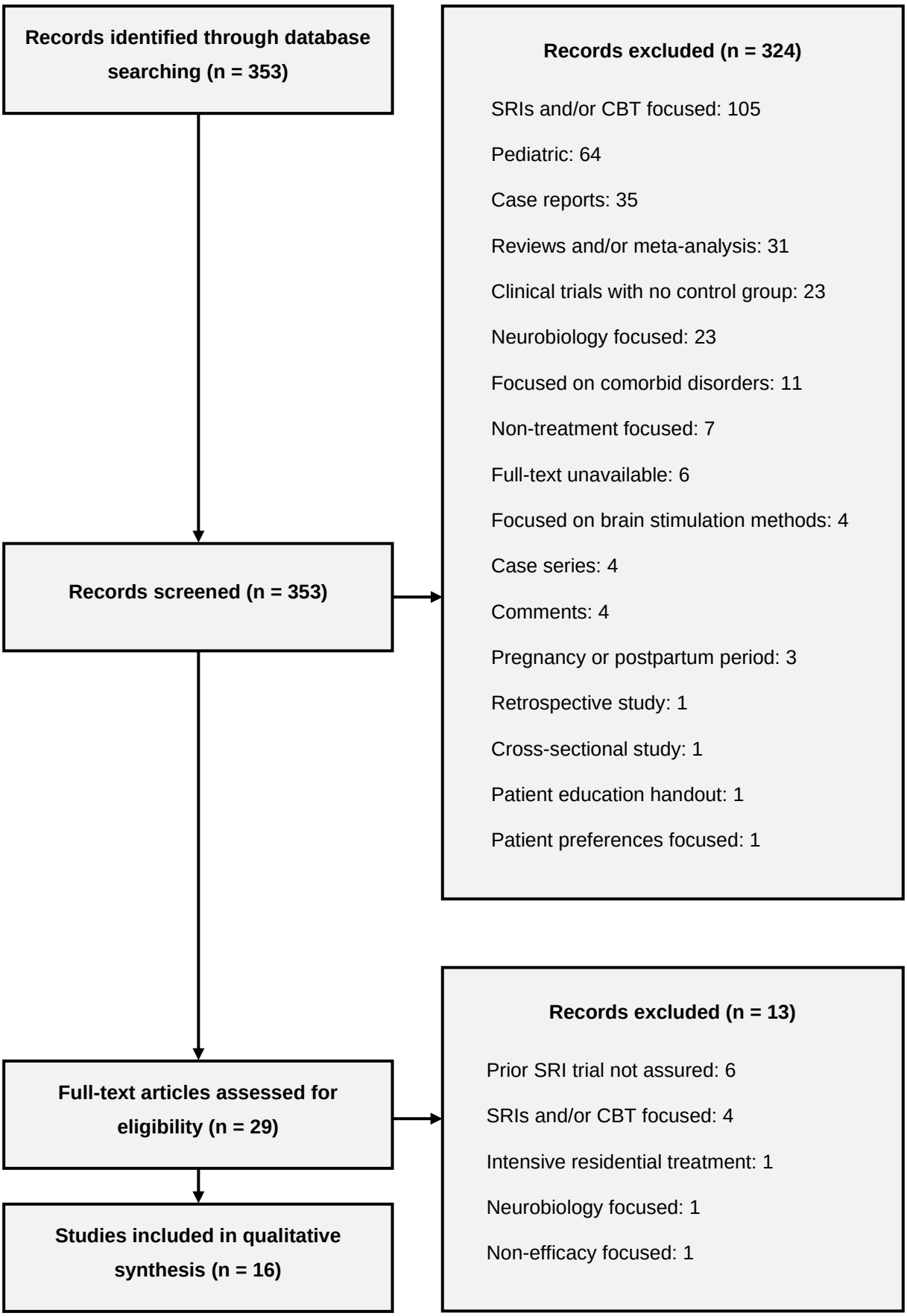

Figure 1. Flow diagram for the exclusion and inclusion process. SRI(s): Serotonin Reuptake Inhibitor(s); CBT: Cognitive Behavioral Therapy.

Table 1. Characteristics of the included studies.

Study (year, country)	Total of patients	Treatment (number of patients)	Number of dropouts (reason)	Doses	Duration	Results
McDougle *et. al* (2000, USA)[34]	36	SRI + **risperidone** (20)	2 (1 for adverse event and 1 for non-compliance)	**SRI:** maximum tolerated dose. **Risperidone:** 1-6 mg/d, as tolerated.	6 weeks (following at least 12 weeks of SRI treatment)	50% of the patients on risperidone and 0% on placebo were responders (χ^2=8.0, P<.005). Risperidone was superior to placebo in reducing OCD (P<.001), depressive (P<.001), and anxiety (P=.003) symptoms. Other than mild sedation, risperidone was well tolerated.
		SRI + placebo (16)	1 (non-compliance)			
Hollander *et. al* (2003, USA and Italy)[35]	16	SRI + **risperidone** (10)	1 (unsatisfactory clinical response)	**SRI:** maximum tolerated dose. **Risperidone:** 0.5-3 mg/d, as tolerated.	8 weeks (following at least 12 weeks of SRI treatment), with a 3 month follow up of the responders	40% of the patients on risperidone and 0% on placebo were responders with both a CGI-I score of 1 or 2 and a Y-BOCS decrease ≥25%. The results did not achieve statistical significance (Fisher exact test, p=.115) due to small sample size. Risperidone was generally well tolerated. Follow-up of the 4 responders showed maintenance of clinical improvement and no additional side-effects.
		SRI + placebo (6)	2 (unsatisfactory clinical response)			
Atmaca *et. al* (2002, Turkey)[36]	27	SRI + **quetiapine** (14)	None	**SRI:** fluoxetine 40 mg/d, fluvoxamine 200 mg/d or clomipramine 150 mg/d. **Quetiapine:** 50-200 mg/d, depending on clinical response.	8 weeks (following 12 weeks of SRI treatment)	64.4% of the patients on quetiapine showed a significant response (≥60% improvement on the Y-BOCS) and 7.1% showed a partial response (≥30% improvement on the Y-BOCS), whereas 0% improved in the placebo group. There was a statistically significant difference between the groups (χ^2, P<.0001). Other than nausea, mild sedation and dizziness, quetiapine was well tolerated.
		SRI + placebo (13)	None			
Carey *et. al* (2005, South Africa and Canada)[37]	42	SRI + **quetiapine** (21)	3 (2 for adverse events and 1 for late exclusion)	**SRI:** maximum tolerated dose. **Quetiapine:** 25-300 mg/d, depending on clinical response.	6 weeks (following at least 12 weeks of SRI treatment)	There was significant Y-BOCS improvement in both groups (quetiapine, p<.0001; placebo, p=.001). 40% of quetiapine and 47.6% of placebo treated subjects were responders, so quetiapine did not demonstrate a significant benefit over placebo (F=.19; p=.636). It was generally well tolerated.
		SRI + placebo (21)	None			

Kordon *et. al* (2008, Germany)[38]	40	SRI + **quetiapine** (20)	6 (4 for adverse events and 2 discontinued prematurely)	**SRI:** maximum tolerated dose. **Quetiapine:** 400-600 mg/d, depending on clinical response.	12 weeks (following at least 12 weeks of SRI treatment)	33.3% of the patients under quetiapine and 15% under placebo were responders (Fisher exact test, P=.26), with a ≥35% decrease on the Y-BOCS. However, no statistically significant differences were found between the treatment groups. Quetiapine was generally well tolerated.
		SRI + placebo (20)	3 (2 for adverse events and 1 discontinued prematurely)			
Shapira *et. al* (2004, USA)[39]	44	Fluoxetine + **olanzapine** (22)	5 (3 were lost to follow-up and 2 for adverse events)	**Fluoxetine:** 40mg/d, except one subject, who took 20mg/d. **Olanzapine:** 5–10 mg/d, as tolerated.	6 weeks (following 8 weeks of SRI treatment)	Both groups improved significantly [F(3,113) = 11.64, p<.0001]; however, the treatment x time interaction was not significant for olanzapine versus placebo. 23% of the patients under olanzapine and 18% under placebo showed a ≥35% improvement on the Y-BOCS; 41% in both groups showed a ≥25% improvement on the Y-BOCS. Overall, olanzapine was well tolerated.
		Fluoxetine + placebo (22)	2 (adverse events)			
Muscatello *et. al* (2011, Italy)[40]	40	SRI + **aripiprazole** (20)	4 (2 for non-compliance and 2 refused to participate)	**SRI:** maximum tolerated dose. **Aripiprazole:** 15 mg/d.	16 weeks (following at least 12 weeks of SRI treatment)	CGI-S scores at baseline were higher in the aripiprazole than in the placebo group (χ^2=9.602, P=.008). At the end of the study, a significant improvement was seen in the aripiprazole group (χ^2=17.419, P=.002). 68.7% of those patients were responders: 43.7% partial responders (25%-34% reduction on Y-BOCS) and 25% full responders (≥35% reduction on Y-BOCS). Aripiprazole was generally well tolerated.
		SRI + placebo (20)	6 (2 for concurrent illness and 4 for non-compliance)			
Sayyah *et. al* (2012, Iran)[41]	39	SRI + **aripiprazole** (18)	3 (refused to continue)	**SRI:** maximum tolerated dose. **Aripiprazole:** 10 mg/d.	12 weeks (following at least 12 weeks of SRI treatment)	There was a significant difference between the two groups at the end point (Mann–Whitney U test; P=.0001). Y-BOCS scores decreased a mean of 29.5% in the aripiprazole group. 53% of those patients and 17.6% of the ones in the placebo group had a ≥25% reduction in total of Y-BOCS scores. Aripiprazole was generally well tolerated.
		SRI + placebo (21)	4 (2 for non-compliance and 2 refused to continue)			

Berlin *et. al* (2011, USA)[42]	36	SRI + **topiramate** (18)	5 (adverse events)	**SRI:** maximum tolerated dose. **Topiramate:** 50–400 mg/d, as tolerated.	12 weeks (following at least 12 weeks of SRI treatment)	There was a significant treatment effect on the Y-BOCS compulsions subscale (t=2.60, P=.014), but not the obsessions subscale (t=.002, P=.99) or the total score (t=1.64, P=.11). Topiramate was not well tolerated in this study: 28% of subjects discontinued the drug for adverse events (compared to 0% taking placebo), and 39% required a dose reduction for this reason (versus 17% taking placebo).
		SRI + placebo (18)	4 (2 for lack of efficacy, 1 for subject choice and 1 for protocol violation)			
Afshar *et. al* (2012, Iran)[43]	48	SRI + **N-acetylcysteine** (24)	5 (3 for adverse events and 2 refused to participate)	**SRI:** maximum tolerated dose. **NAC:** 600-2400 mg/d, depending on clinical response and tolerance.	12 weeks (following at least 12 weeks of SRI treatment)	The Y-BOCS score reduction in the NAC group was significantly different from that of the placebo group (P=.003). 52.6% of the patients in the NAC group were full responders, which was significantly higher than 15% of the patients in the placebo group (P=.013). NAC was well tolerated.
		SRI + placebo (24)	4 (refused to participate)			
Bruno *et. al* (2012, Italy)[44]	40	SRI + **lamotrigine** (20)	3 (2 for non-compliance and 1 for adverse event)	**SRI:** maximum tolerated dose. **Lamotrigine:** 100 mg/d.	16 weeks (following at least 12 weeks of SRI treatment)	Lamotrigine was significantly more efficacious than placebo, with a mean 32.6% reduction in Y-BOCS total score, while no significant changes occurred in the placebo group. There was also a significant improvement on the CGI-S (χ^2=20.065, p<.0001). 85% of the patients on lamotrigine were responders: 50% partial responders (25%-34% reduction on Y-BOCS) and 35% full responders (≥35% reduction on Y-BOCS). Lamotrigine was generally well tolerated.
		SRI + placebo (20)	4 (2 for non-compliance and 2 for lack of efficacy)			
Pittenger *et. al* (2015, USA)[45]	40	SRI + **riluzole** (20: 14 outpatients and 6 inpatients)	1 (for protocol violation)	**SRI:** maximum tolerated dose. **Riluzole:** 50 mg twice daily.	12 weeks (following at least 8 weeks of SRI treatment)	26% of the patients under riluzole and 11% under placebo were partial responders (≥25% improvement on Y-BOCS). This difference did not reach significance in the overall sample (χ^2=1.39, p=.24) but it did in the outpatient subsample (χ2=4.36, p=.037). Riluzole was well tolerated.
		SRI + placebo (20: 15 outpatients and 5 inpatients)	2 (1 for protocol violation and 1 for problems in transportation)			

Rutrick *et. al* (2017, USA, South Africa, India, Switzerland, Bulgaria and Canada)[46]	50	SRI + **mavoglurant** (26)	6 (3 for adverse events, 2 for unknown reason and 1 for protocol violation)	**SRI:** maximum tolerated dose. **Mavoglurant:** 200 mg twice daily (4-week up-titration period, followed by 12 weeks of fixed dose and 3 weeks of down-titration).	17 weeks (following at least 12 weeks of SRI treatment)	There was no significant difference in least squares (LS) mean change from baseline at week 17 in Y-BOCS score for mavoglurant compared with placebo groups [-6.9 (1.75) vs. -8.0 (1.78), respectively; LS mean difference 1.1; 95% CI - 3.9, 6.2; p=.671]. The incidence of adverse events was higher in the mavoglurant compared with the placebo group (80.8% vs. 70.8%, respectively).
		SRI + placebo (24)	7 (3 for unknown reason, 2 for administrative issues and 2 for protocol violation)			
Modarresi *et. al* (2018, Iran)[47]	32	SRI + **memantine** (16)	1 (unknown, but not for adverse event)	**SRI:** maximum tolerated dose. **Memantine:** 20 mg/d.	12 weeks (following at least 12 weeks of SRI treatment)	A reduction of 40.9% (p<.001) in the mean Y-BOCS total score in the memantine group resulted in 73.3% of patients achieving treatment response (≥35% reduction on Y-BOCS), while no improvement was observed in the placebo group. Memantine was well tolerated.
		SRI + placebo (16)	1 (unknown, but not for adverse event)			
Fux *et. al* (2004, Israel)[48]	11	SRI + **EPA** (11: 6 in the first 6 weeks and 5 in the last)	None	**SRI:** maximum tolerated dose. **EPA:** 2 g/d.	12 weeks (following at least 8 weeks of SRI treatment)	There were no effects of order of treatment. Time had a main effect on Y-BOCS scores; mean scores declined to 18.5 (±4) by week 6 on EPA and to 17.6 (±6) by week 6 on placebo (F=10.0, df=2, 18, P=.001). There was no effect of drug (F=.1, df=1, 9, not significant) and no interaction between drug and time (F=.1, df= 2, 18, not significant). No clinically relevant side effects were reported.
		SRI + placebo (11: 5 in the first 6 weeks and 6 in the last)	None			
Zheng *et. al* (2019, China)[49]	44	Fluvoxamine + **extended-release methylphenidate** (22)	2 (1 for interference by symptoms and 1 for problems in transportation)	**Fluvoxamine:** 250 mg/d. **MPH-ER:** 36 mg/d.	8 weeks (following at least 8 weeks of fluvoxamine treatment)	Cumulative response rates were higher in the MPH-ER vs placebo group (59% vs 5%; P<.001). 36.4% of the patients under MPH-ER and 4.6% under placebo were partial responders (25%-34% reduction on Y-BOCS), which reached statistical significance (χ^2=5.03, P=.025). 22.7% of the patients on MPH-ER versus 0% on placebo were full responders (≥35% reduction on Y-BOCS). MPH-ER was well tolerated.
		Fluvoxamine + placebo (22)	1 (for protocol violation)			

CGI: Clinical Global Impression (scale); CGI-I: CGI – Improvement; CGI-S: CGI – Severity; EPA: eicosapentaenoic acid; MPH-ER: extended-release methylphenidate; NAC: N-acetylcysteine; SRI: Serotonin Reuptake Inhibitor; Y-BOCS: Yale–Brown Obsessive–Compulsive Scale.

DISCUSSION

Our work intended to assess the clinical efficacy of pharmacological augmentation strategies in patients with OCD resistant to Serotonin Reuptake Inhibitors, considering the available evidence in the literature.

The selected studies involved atypical antipsychotics (risperidone, quetiapine, olanzapine and aripiprazole), glutamate modulators (topiramate, N-acetylcysteine, lamotrigine, riluzole, mavoglurant and memantine) and other substances, namely eicosapentaenoic acid (EPA) and methylphenidate of extended-release formulations (MPH-ER).

The studies are difficult to compare due to their methodological differences. It is not possible to add the results of different studies, even those related to the same substance, given the variability of the doses tested, the trials' duration and the scales for outcome reporting. In addition, some trials used a specific SRI for all patients, like fluoxetine or fluvoxamine, while most of them maintained the SRI that the patient was previously taking, considering SRIs as a group. Moreover, the criteria for SRI resistance slightly diverged, but were generally based on symptom persistence, defined by the Y-BOCS score (maintained above 16 to 18, or less than 25-35% improvement), by the CGI score (no better than "minimally improved" on CGI-I or at least moderate severity on CGI-S) and by a consensus of the authors that the patient's condition was unimproved, after at least 8 to 12 weeks of consistent SRI treatment, at maximum tolerated dose.

The articles in which a prior SRI trial was not assured were excluded because that made the resistance postulation unclear. The article where the patients were under intensive residential treatment was excluded as well, due to difficulties in comparing data and extrapolating conclusions.

According to McDougle *et. al* [34] and Hollander *et. al* [35], risperidone augmentation was efficacious and well tolerated, although the second study's results did not achieve statistical significance due to small sample size. Risperidone is a potent antagonist of the serotonin 5-HT2A and dopamine D2 receptors,[34] with lower affinity for α1 and α2 adrenergic and for histamine H1 receptors.[36]

As stated by Atmaca *et. al* [36], quetiapine augmentation seemed efficacious, but Carey *et. al* [37] and Kordon *et. al* [38] did not corroborate such assumption, even though the doses used were higher. Quetiapine has a high affinity for α1 adrenergic and histamine H1 receptors, lower affinity for α2 adrenergic and dopamine D1 receptors and no muscarinic M1 activity; like risperidone and olanzapine, it has greater affinity for 5-HT2 receptors than for D2 receptors.[36]

Shapira *et. al* [39] revealed no additional advantage on augmenting fluoxetine with olanzapine. This atypical antipsychotic has high affinity for α1 adrenergic, histamine H1 and

dopamine D1 receptors, as well as muscarinic M1 activity.[36]

Muscatello *et. al* [40] and Sayyah *et. al* [41] showed that aripiprazole augmentation was efficacious and well tolerated. Aripiprazole is a partial dopaminergic agonist, acting on both postsynaptic and presynaptic D2 receptors, and also a partial agonist at 5-HT1A and antagonist at 5-HT2A serotonergic receptors.[41]

A meta-regression analysis showed that the drugs with greater affinity to dopamine receptors (D2 and D3) correlated positively with clinical efficacy in OCD.[50] This might explain why risperidone and aripiprazole showed better efficacy compared to others with relatively lesser dopamine receptor binding, such as olanzapine and quetiapine.[51]

The side effects of atypical antipsychotics include mild sedation, weight gain, type II diabetes mellitus, hyperlipidemia, orthostatic hypotension, QT interval prolongation, myocarditis, cataract, sexual disfunction and also extrapyramidal symptoms (although less than with conventional antipsychotics).[52,53] The different adverse effects specific to each antipsychotic medication must be considered while prescribing, in order to improve the patients' quality of life and functional outcome.[53]

In the context of glutamate modulators, Berlin *et. al* [42] suggested that topiramate augmentation may be beneficial for compulsions, but not for obsessions; nevertheless, it was not well tolerated. Topiramate is an antiepileptic that interacts with voltage-gated calcium channels and thereby modulates glutamate levels; its side effects include paresthesia, cognitive issues, micturition frequency, urolithiasis and weight loss.[54]

Afshar *et. al* [43], Bruno *et. al* [44], Pittenger *et. al* [45] and Modarresi *et. al* [47] displayed that N-acetylcysteine, lamotrigine, riluzole and memantine, respectively, showed efficacy and safety as augmentation options. NAC is a modified form of the amino acid cysteine that can modulate extrasynaptic glutamate levels through its interaction with the glial cystine-glutamate antiporter; its adverse effects are mostly gastrointestinal mild symptoms. Lamotrigine is an antiepileptic and mood stabilizer that reduces glutamate outflow through inhibition of certain presynaptic voltage-gated sodium channels; its adverse events comprise sedation, fatigue and headache. Riluzole appears to have a net glutamate-lowering effect, by reducing glutamate release from axon terminals and by potentiating glutamate uptake by the transporters on glial cells; its adverse effects consist of diarrhea, reversible transaminases elevation, hepatotoxicity and pancreatitis. Memantine is an uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor; its side effects consist of dizziness, fatigue, headache and arterial hypertension.[54]

Rutrick *et. al* [46] found no significant benefit in augmenting SRIs with mavoglurant, even though it is a potent, subtype-selective, non-competitive antagonist of the metabotropic glutamate receptor 5 (mGluR5), which has been linked to obsessions. Mavoglurant's adverse events include insomnia and anxiety.[46]

Fux *et. al* [48] concluded that eicosapentaenoic acid was not efficacious in augmenting SRIs. EPA is a component of the omega-3 polyunsaturated fatty acids, which have proven to be beneficial in major affective disorders. EPA's side effects are mainly gastrointestinal.[48]

Lastly, Zheng *et. al* [49] verified that MPH-ER augmentation demonstrated efficacy and safety. Methylphenidate is a dopamine reuptake inhibitor that blocks the presynaptic dopamine transporter, with a minor influence on the noradrenaline transporter; its adverse events include insomnia, headache, abdominal pain, anorexia and palpitations.[49,55]

Aside from the medications included in the selected studies, there are other pharmacological augmentation strategies being tested, such as ketamine, mirtazapine, celecoxib, minocycline, tolcapone, rapastinel, D-amphetamine, probiotics, psilocybin, rituximab, nitrous oxide, vitamin C, D-cycloserine, nabilone and ondansetron.[29]

New perspectives and therapeutic targets are being studied. Zhang *et. al* (2020)[56] reported an improvement of both anxiety and OCD via the histamine presynaptic H3 heteroreceptor on glutamatergic afferent terminals from the prelimbic prefrontal cortex to the nucleus accumbens core. On another note, Piras *et. al* (2020)[57] found that patients suffering from OCD present high levels of the protein Immuno-moodulin (Imood) in their peripheral blood mononuclear cells, suggesting the possibility of a new form of treatment – through antibodies, instead of the classical chemical drugs, foreseeing a reduced chance of side effects. Distinctively, Norman *et. al* (2020)[58] studied whether brain activity was associated with treatment response to CBT and their findings suggest a path for personalizing the choice of therapy, not by performing brain imaging on every patient, but by using everyday tests that measure features that might predict better success with one therapy or the other.

Evidently, this review presents some limitations. The selected articles are not an accurate representation of all the existing literature in this topic, in part because the research was conducted in only one database, but also because some articles did not have a full text available. Moreover, considering the exclusion criteria, other sources of data would inevitably have been omitted, creating a selection bias. In addition, it is relevant to point out that some studies had a small sample size, which made it difficult to take definitive conclusions from them. Yet, despite possible risk of bias and other limitations in each trial, these studies contain valuable data.

Since standard criteria for the pharmacological treatment of resistant OCD remain unavailable, this is still an area for further research. Other studies, especially randomized controlled trials, should be conducted for higher evidence level. Future studies should include more detailed reporting of outcomes and their relationship with other variables (e.g. comorbidities), preferably using larger samples to detect other effects and draw more reliable conclusions.

CONCLUSION

In this paper, several pharmacological augmentation options seemed to be potentially effective on SRI-resistant OCD, such as risperidone, aripiprazole, N-acetylcysteine, lamotrigine, riluzole, memantine and methylphenidate. For higher levels of resistance, non-pharmacological strategies like transcranial magnetic stimulation, deep brain stimulation and ablative neurosurgical procedures are options for taking into consideration.

Despite the wide range of treatment possibilities displayed for resistant OCD, this review reinforces the need for further research on this topic. New perspectives and therapeutic targets are being considered, particularly through neurocircuits regulation, immunomodulation and personalized medicine strategies that can hopefully lead to a more effective and safe therapy in the future, bringing these patients better quality of life.

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