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OBSESSIVE-COMPULSIVE DISORDER: EMERGING TREATMENTS

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Abstract: Obsessive-compulsive disorder (OCD) is a chronic and debilitating condition, characterized by obsessions and compulsions that significantly compromise the quality of life of individuals. Despite the effectiveness of conventional treatments, such as selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT), a substantial proportion of patients show an unsatisfactory response, constituting cases of resistant OCD. This scenario has led to a search for emerging therapeutic approaches. This literature review analyzed recent publications on new pharmacological strategies, such as the use of glutamatergic modulators (N-acetylcysteine, memantine, riluzole), anti-inflammatories and drugs with new neurobiological mechanisms, as well as neuromodulation techniques and combination therapies. In the psychotherapeutic field, advances in CBT stand out, especially with a focus on inhibitory learning as the central mechanism of exposure with response prevention (EPR). The integration of innovative treatments and therapeutic personalization represent a promising advance in the management of refractory OCD, expanding the possibilities of clinical and functional response in patients.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic, often disabling neuropsychiatric condition characterized by obsessions - intrusive and unwanted thoughts, impulses or images that cause intense suffering - and compulsions, which consist of repetitive behaviors or mental acts performed as a way of relieving the anxiety associated with the obsessions or preventing feared events. With an estimated prevalence of between 2% and 3% of the global population, OCD is among the most debilitating mental disorders, negatively impacting the quality of life, occupational functionality and interpersonal relationships of affected in-

dividuals. (KAYSER, 2020; SPENCER et al., 2023) In addition, most patients have psychiatric comorbidities, which aggravate the clinical course and make therapeutic management more difficult. (SPENCER et al., 2023)

From a neurobiological point of view, although the pathophysiology of OCD has not yet been fully elucidated, there is robust evidence of functional dysfunction in the cortico-striato-thalamo-cortical (CSTC) circuits, with increased activity in specific brain regions identified through functional neuroimaging studies. (GOODMAN; STORCH; SHETH, 2021; KAYSER, 2020) This structural and functional dysfunction has been identified as a common substrate for various therapeutic modalities, both pharmacological and non-pharmacological, whose action seems to converge on modulating the CSTC circuit. (GOODMAN; STORCH; SHETH, 2021) In addition, recent genetic studies suggest that OCD has a significant hereditary basis, with heritability estimates close to 48%, with the SLC1A1 gene - responsible for glutamate transport - being one of the main candidates associated with the disorder. These findings reinforce the glutamatergic hypothesis and drive the search for treatments that act on this specific neurochemical system (GOODMAN et al., 2021).

Historically, the treatment of OCD has been based on a combination of cognitive-behavioral therapy (CBT), with an emphasis on the technique of exposure and response prevention, and the use of selective serotonin reuptake inhibitors (SSRIs), including clomipramine, as the main therapeutic interventions. (HOLM; JANSSON; NORDGAARD, 2020; KAYSER, 2020) CBT is widely considered to be the first-line psychotherapeutic treatment, with consistent empirical grounding. (SPENCER et al., 2023) However, despite the documented efficacy of SSRIs, it is estimated that around 40% to 60% of patients show a partial or unsatisfactory clinical response, even after prolonged courses with adequate doses. (GOODMAN; STORCH; SHETH, 2021; KAYSER, 2020) In addition, dose-dependent side effects, such as sexual dysfunction and gastrointestinal symptoms, can compromise adherence and limit the continued use of these drugs, especially at high doses, which are generally necessary in OCD. (KAYSER, 2020)

In cases of therapeutic resistance - the definition of which remains controversial, but often involves failure of multiple clinical trials with SSRIs at appropriate doses - alternative strategies have been considered. Among them, potentiation with atypical antipsychotics is the only additional pharmacological approach supported by substantial clinical evidence. (GOODMAN; STORCH; SHETH, 2021; KAYSER, 2020) However, the absence of new effective serotonergic agents for OCD, coupled with limited knowledge about their molecular basis, has driven the investigation of alternative neurochemical pathways, especially those related to glutamatergic neurotransmission. (GOODMAN; STORCH; SHETH, 2021)

Recently, attention has turned to emerging treatments that include glutamate modulators, non-invasive neuromodulation techniques such as transcranial magnetic stimulation (TMS), and invasive methods such as deep brain stimulation (DBS). These approaches aim to selectively modulate the neural circuits involved in the genesis of obsessive-compulsive symptoms and represent a promising front in dealing with refractory OCD (GOODMAN; STORCH; SHETH, 2021). Given this panorama, it is imperative to explore the most recent advances in the therapeutic field, with an emphasis on innovative and emerging treatments that could redefine the clinical management of OCD in the coming years.

METHODOLOGY

This research is configured as a literature review with the aim of compiling and critically analyzing the most recent evidence on emerging treatments for obsessive-compulsive disorder, considering the advances presented in the specialized literature. To this end, a targeted search was carried out in the PubMed database, including studies published in the last five years. The selection was based on a combination of the descriptors: "Obsessive--Compulsive Disorder" and "Treatment", with the aim of comprehensively capturing the content pertinent to the proposed theme.

Articles were selected that dealt directly or indirectly with therapeutic approaches to obsessive-compulsive disorder, as long as they were available in full on the database consulted. Publications in any language were accepted, as long as they were accessible and understandable, and presented methodological consistency, scientific relevance and thematic appropriateness. Original studies, narrative reviews and update texts were included. Articles that were out of scope, duplicated or unavailable on the PubMed database were excluded.

RESULTS AND DISCUSSION

Selective serotonin reuptake inhibitors (SSRIs) remain the first-line pharmacological treatment for obsessive-compulsive disorder (OCD). However, clinical evidence shows that a significant proportion of patients do not respond satisfactorily to SSRI monotherapy. In these cases, a progressive therapeutic algorithm has been recommended: initially, optimization of the dose and time of exposure to the SSRI is promoted, with verification of therapeutic adherence, possibly by measuring plasma levels. If symptoms persist, substitution with another SSRI or clomipramine is indicated, and later a serotonin and noradrenaline reuptake inhibitor (SNRI) can be tried. In the absence of an adequate response, it is appropriate to add adjuvant agents, such as atypical antipsychotics or modulators of the glutamatergic system. Among the adjuvant agents studied, N-acetylcysteine (NAC) has stood out as a potential glutamatergic modulator. In five randomized clinical trials, three demonstrated that the addition of NAC to conventional pharmacotherapy resulted in a significant improvement in obsessive-compulsive symptoms, using doses between 600 mg and 3000 mg per day (KAYSER, 2020). Psychotherapeutic treatments, such as exposure with response prevention (ERP), and somatic interventions, including repetitive transcranial magnetic stimulation (rTMS) or neurosurgery, should be integrated when clinically indicated (KAYSER, 2020).

Doses higher than those usually stipulated by the pharmaceutical industry have demonstrated therapeutic efficacy, and the current clinical guidelines of the American Psychiatric Association recognize, in specific contexts, the administration of high dosage regimens, such as: up to 60 mg/day of escitalopram, 120 mg/day of fluoxetine, 450 mg/day of fluvoxamine, 100 mg/day of paroxetine and 400 mg/day of sertraline (KAYSER, 2020). In a clinical investigation involving individuals refractory to the standard dose of sertraline (200 mg/day), dose escalation up to 400 mg/day resulted in superior symptomatic improvement, without significant impairment of tolerability, when compared to maintaining the initial dose. However, it is important to note that high-dose regimens are also associated with an increase in treatment discontinuation rates, mainly due to the occurrence of adverse effects (KAYSER, 2020).

Recent studies have been exploring emerging pharmacological alternatives for patients with a limited response to traditional treatments. When the therapeutic response to an SSRI proves unsatisfactory, even after a re-

gimen with a dose and duration considered adequate, substitution with another pharmacological agent is a legitimate approach. Viable alternatives include the introduction of a second SSRI, the use of an NRTI or the prescription of clomipramine. Of these options, the available evidence offers the most support for trying a different SSRI. Randomized clinical trials involving the SNRIs venlafaxine and duloxetine indicate that both have therapeutic potential in the management of OCD symptoms, although the findings are inconsistent in terms of the magnitude of the effects observed (KAYSER, 2020).

Meta-analyses indicate that clomipramine may be more effective than selective serotonin reuptake inhibitors (SSRIs). However, recent clinical trials that have made direct comparisons between clomipramine and SSRIs cast doubt on the clinical superiority of clomipramine. In addition, clomipramine is associated with a more severe adverse effect profile, including anticholinergic, antihistaminic and anti-alpha-adrenergic reactions, as well as arrhythmogenic potential and a decreased seizure threshold. To mitigate the risk of toxicity, it is recommended to avoid doses of more than 250 mg a day, the limit set by the FDA, and to monitor total plasma levels of clomipramine and its metabolite desmethylclomipramine, keeping them below 500 ng/mL. Given these considerations, SSRIs remain the first choice therapy (KAYSER, 2020). Although several classes of antipsychotics have been evaluated, a recent meta-analysis showed that risperidone has the greatest efficacy in treatment. Another study indicated that aripiprazole also shows comparable efficacy. It is recommended to use low doses of these antipsychotics - for example, risperidone up to 3 mg/day and aripiprazole up to 15 mg/day - due to the profile of adverse effects associated with their use (KAYSER, 2020).

A trial of 49 previously untreated OCD patients revealed that the addition of mirtazapine to citalopram accelerated the initial response to treatment, without significantly impacting its overall efficacy. Other preliminary studies have shown potential beneficial effects of stimulants such as d-amphetamine and even caffeine, although the findings still lack robust replication. Several glutamatergic modulators have been explored as potential adjuvants, including memantine, riluzole, topiramate, lamotrigine and d-cycloserine. Memantine, for example, has shown efficacy in double-blind clinical trials, surpassing placebo in response rates when added to SSRIs. Riluzole, on the other hand, although safe, has shown mixed results in controlled studies, despite positive responses in open studies (GOODMAN et al., 2021; KAYSER, 2020). At the same time, agents with anti-inflammatory properties have also aroused interest, considering the hypothesized correlation between OCD and inflammatory mechanisms. Clinical trials associating fluvoxamine with substances such as celecoxib and minocycline have shown promising results, despite methodological limitations that make it difficult to generalize the data (KAYSER, 2020).

In light of previous evidence indicating the possible benefit of the association between fluoxetine and buspirone - a 5-HT1A receptor agonist - in the treatment of resistant OCD, it is considered that new drugs with serotonergic action and activity on the same receptor, such as vortioxetine and vilazodone, may be therapeutically useful in this context, at least on a theoretical level (KAYSER, 2020). Small open studies also corroborate the association between increasing the dose of SSRIs with the use of memantine (in two trials) and intravenously administered ketamine (in one trial). To date, the effects of intranasal ketamine on OCD symptoms have been described exclusively in case reports (KAYSER, 2020).

Several compounds are currently being investigated in clinical trials, according to the ClinicalTrials.gov database. Among the agents being evaluated are tolcapone, troriluzole (BHV-4157), rapastinel, specific probiotics (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175), psilocybin, rituximab, nitrous oxide, ketamine, vitamin C, d- cycloserine, nabilone, cannabis and ondansetron. These drugs represent distinct therapeutic classes and explore new neurobiological mechanisms, with the potential to significantly expand the therapeutic options available for individuals with refractory OCD. (KAYSER, 2020) Another compound under development is troriluzole (BHV-4157), a prodrug of riluzole, which offers greater bioavailability and potentially lower liver toxicity. It is currently undergoing clinical trials as an adjunct to the treatment of resistant OCD, representing a promising innovation in glutamatergic modulation (GOODMAN et al., 2021).

The management of OCD under the non--drug neuropsychological approach is based on the reformulation or modification of negative automatic thoughts - in other words, interpretations - associated with intrusive obsessive content, as well as targeted intervention on dysfunctional core beliefs and cognitive biases. In the strand of CBT with a cognitive emphasis applied to OCD, therapeutic exercises prioritize questioning these underlying beliefs, rather than directly confronting the rationality of the obsessive thoughts themselves, since such a strategy can be counterproductive. This is due to the risk of fostering compulsive self--confidence or encouraging the suppression of thoughts, which can worsen the clinical condition (SPENCER et al., 2023). Both compulsive behaviors and avoidance strategies significantly limit adaptive behavioral repertoires, playing a central role in the functional impairment observed in individuals with OCD (SPENCER et al., 2023).

Cognitive-Behavioral Therapy, especially the EPR protocol, is a widely validated, cost-effective intervention based on empirical evidence for the management of OCD, with significant potential for alleviating symptoms and promoting the quality of life of affected individuals (SPENCER et al., 2023).

CBT, especially when associated with exposure and response prevention (ERP), is a first-line therapeutic approach and can serve as an alternative to SSRIs. In addition, CBT can act as a complement to monotherapy with SSRIs in cases of resistant OCD, showing greater efficacy in a recent study when compared to the addition of risperidone as a therapeutic enhancer (KAYSER, 2020).

From a psychotherapeutic point of view, cognitive-behavioral therapy (CBT), especially the exposure with response prevention (ERP) component, remains a central intervention in the management of OCD. The basic cognitive model proposes that the disorder is maintained by distorted interpretations of intrusive thoughts, such as thought-action fusion and intolerance of uncertainty. Thus, it is not the occurrence of intrusive thoughts that defines the disorder, but the way they are interpreted - with intense emotional salience and the attribution of dysfunctional meaning. CBT for OCD therefore focuses on restructuring these negative automatic thoughts and maladaptive core beliefs, promoting greater cognitive flexibility and reducing the functional impact of obsessions. (SPENCER et al., 2023) Recent evidence has reshaped the understanding of the effectiveness of exposure with response prevention. The inhibitory learning model proposes that the therapeutic key lies in the creation of new associations that compete with the original fears, rather than in simple emotional habituation. Strategies such as violation of expectations and exposure in multiple contexts thus become essential for strengthening these new inhibitory networks (SPENCER et al., 2023).

Behavioral models complement this view by elucidating the negative reinforcement mechanisms that perpetuate compulsions and avoidance. According to the emotional processing theory, EPR works by allowing the patient to expose themselves to obsessive stimuli without resorting to the usual neutralizing behaviours, favouring the extinction of the association between obsessions and anxiety. This process results not only in emotional habituation, but also in the disconfirmation of catastrophic beliefs, promoting corrective learning. ERP can be appropriately adjusted to include comorbid conditions without compromising its therapeutic efficacy. Furthermore, evidence indicates that several of these comorbidities tend to show significant clinical improvement after successful completion of the protocol (SPENCER et al., 2023).

These behavioral findings are corroborated by neuroimaging studies, which show functional changes in brain circuits after CBT, especially in the connectivity between the orbitofrontal cortex, the caudate nucleus and the thalamus. These changes are associated with a reduction in symptoms, suggesting that behavioral interventions can effectively remodel neural activity in the circuits implicated in OCD (GOODMAN et al., 2021). However, more recent studies on extinction learning have proposed the inhibitory learning model, which suggests that the effectiveness of exposure does not depend exclusively on habituation, but on the creation of a new inhibitory association that competes with the original fear network. This approach involves optimizing violations of expectation, generalizing exposure contexts and developing greater tolerance to uncertainty and emotional discomfort (SPENCER et al., 2023).

In this context, it is clear that both pharmacological and psychotherapeutic treatments are constantly evolving, seeking more effective, rapid and acceptable approaches for patients. Although SSRIs remain the mainstay of pharmacological treatment, the integration of new strategies, such as glutamatergic modulation, the use of anti-inflammatory compounds and the introduction of innovative agents in clinical trials, represents a promising advance in tackling therapeutic resistance. At the same time, advances in the understanding of the mechanisms underlying EPR contribute to the personalization and improvement of CBT, with a focus on strengthening inhibitory learning. This convergence between emerging pharmacotherapy and the evolution of cognitive-behavioral psychotherapy offers an optimistic outlook for the management of OCD in the coming years (KAYSER, 2020; SPENCER et al., 2023).

Another relevant aspect in the treatment of refractory OCD is the personalization of psychotherapeutic approaches, with emphasis on advances in Cognitive-Behavioral Therapy (CBT), especially the Exposure and Response Prevention (ERP) model. Traditionally understood as a process of emotional habituation, EPR has recently been reinterpreted in the light of the inhibitory learning model, which emphasizes the strengthening of new safe associations and the deliberate violation of expectations as central therapeutic mechanisms. Strategies such as varying contexts, increasing tolerance to uncertainty and reducing cognitive avoidance are key to maximizing the effectiveness of CBT. In addition, studies indicate that EPR not only reduces obsessive-compulsive symptoms, but also improves comorbid conditions that are often present, such as depression and anxiety, reinforcing its applicability in complex clinical scenarios (SPENCER et al., 2023). At the same time, from a pharmacological point of view, current evidence points to the importance of appropriate titration of SSRIs, which may exceed conventional dosage limits in specific cases. Potentiation with atypical antipsy-

chotics, such as risperidone or aripiprazole, and the use of glutamatergic modulators such as memantine, riluzole and N-acetylcysteine (NAC), have shown benefits in subgroups of patients with a partial response. This convergence between refined psychotherapeutic interventions and alternative pharmacological strategies represents a significant advance in the management of resistant OCD, offering a broader and more individualized therapeutic range (KAYSER, 2020; SPENCER et al., 2023).

CONCLUSION

The management of Obsessive-Compulsive Disorder has evolved significantly in recent decades, especially in the face of the challenges posed by cases refractory to conventional treatments. Although SSRIs and cognitive--behavioral therapy continue to be mainstays in the treatment of OCD, their limitations in terms of efficacy and adherence on the part of patients highlight the need for more individualized and effective therapeutic alternatives. In this context, emerging treatments - such as modulation of the glutamatergic system, brain neuromodulation and the new pharmacological agents currently under investigation - offer new clinical perspectives. At the same time, advances in the understanding of psychotherapeutic mechanisms, especially EPR from the perspective of inhibitory learning, enable more effective interventions adapted to the complexity of the disorder. The convergence of innovative pharmacotherapy and refined psychotherapy represents a promising and integrated approach, capable of transforming care for patients with OCD, especially in cases that are difficult to manage. Thus, the future of OCD treatment is moving towards increasingly personalized medicine, based on robust evidence and centered on the specific needs of each individual.

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