EXPERT OPINION

Emerging drugs to treat obsessive–compulsive disorder

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Introduction: Obsessive–compulsive disorder (OCD) is a chronic and disabling neuropsychiatric disorder with a lifetime prevalence of approximately 1 – 2% and a rate of treatment resistance of 40%. Other disorders have been related to OCD and have been grouped together in a separate DSM-5 chapter, hypothesizing the existence of an 'OC spectrum', showing a paradigm shift in the conceptualization of the disorder.

Areas covered: A review of the most important and recent neurobiological findings that sustain the hypothesis of a more sophisticated model of the disorder is provided, together with a brief overview of the most relevant pharmacological animal models of OCD and its first-line treatments. Current research goals, new compounds tested and the rationale behind the development of these new pharmacologic agents are then explained and reviewed.

Expert opinion: In the past years, no effective novel compounds have emerged for the treatment of OCD, even if many efforts has been made in the study of its neurobiological underpinnings. Relevant changes in the conceptualization of the disorder, suggested by interesting new neurobiological evidences, may result helpful in the development of new treatments.

Keywords: anxiety, medication, obsessive–compulsive disorder, OCD, treatment

Expert Opin. Emerging Drugs [Early Online]

1. Background

1.1 Introduction

Obsessive–compulsive disorder (OCD) is a neuropsychiatric disorder affecting approximately 1 – 2% of the population in their lifetime and is the fourth psychiatric disorder for frequency [1].

A number of other disorders such as body dysmorphic disorder, hoarding disorder, trichotillomania, excoriation disorder and several other less studied debilitating conditions (e.g., obsessional jealousy, body-focused repetitive behavior) are related to OCD and characterized by the presence of obsessions (repetitive intrusive thoughts entering into the stream of consciousness that are difficult to suppress) and/or compulsions (repetitive mental or physical rituals undertaken according to rigid rules or in response to obsessions) [2]. All these diagnostic categories share phenomenological characteristics and do frequently overlap with OCD. Therefore, it has been argued that they may be part of an 'OC spectrum'.

With the introduction of DSM-5, these conditions are not listed anymore under 'anxiety disorders' and have now a new dedicated chapter.

This is due to the increasing research evidence that suggests a close relationship between these disorders and more complex neurobiological underpinnings, broadening the focus of attention from amygdalar hyperactivity-driven anxiety to dysfunctional cortical–striatal circuitries involved in cognitive/behavioral inflexibility and reward mechanisms.

Individuals with OCD can present disparate, non-overlapping symptom patterns, indicating that it is not a homogeneous diagnostic entity. This heterogeneity

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complicates the interpretation of findings from natural history, genetic and neuroimaging studies, and results of clinical trials.

First-line treatments include selective serotonin reuptake inhibitors (SSRI) and cognitive-behavioral therapy (CBT). In case of treatment resistance, augmentation strategies with antipsychotics may provide some benefit. It is now evident that only 60% of the patients respond and research for new treatments beyond current guidelines are mandatory.

New treatment should involve more sophisticated models of the disorder considering the emerging concept of the involvement of different circuitries for different subtypes, according to the RDoC approach [3].

1.2 Shifting the focus of attention from anxiety to addiction, from prefrontal cortex–amygdala to reward circuitries?

From a clinical, psychopathological and phenomenological point of view, although anxiety symptoms are a core feature of OCD, current literature shows growing evidences of a reward dysfunction in OCD, mainly in resistant patients [4]. On the other hand, reward dysfunction represents a key feature of addiction progression. These data support the hypothesis that addiction and OCD share some common neurobiological dysfunctions and corroborate the idea that OCD may start as an anxiety disorder and successively become a behavioral addiction through the same stages of other substance dependences. A common link between all substance abuses and addictive behaviors is their rewarding effect. Compulsion is a suffering-reducing activity that might step on the border of rewarding experience due to its capacity to reduce anxiety and distress generated by obsessions. In this perspective, compulsion could be potentially addictive. From this perspective, it is possible to conceptualize the course of OCD as a slow progression to a sort of behavioral addiction.

Several studies showed that distinct OCD symptom dimensions have distinct neurobiological underpinnings and that the neural correlates of OCD seem to change during the course of illness [5-7]. In this view, it may also be possible to hypothesize a clinical staging of OCD consisting of three main stages. During the first stage ('endophenotype stage'), the patient would present only subthreshold symptoms, but would show endophenotypical abnormalities such as motor disinhibition and cognitive inflexibility. In the next one, the 'alarm stage,' there would be the onset of OCD and the anxiety dimension would be prominent. The third and last step would then be the 'reward dysfunction' stage, when the patient would become addicted to his compulsions [8].This clinical staging model and the conceptualization of OCD as a behavioral addiction have never been tested thoroughly in OCD patients. However, it represents an interesting conceptual frame that deserves further research. Similarly, from a neurobiological research perspective, there has been an important paradigm shift in the investigation of the pathophysiology of OCD. In the last decades, a large number of neuroimaging studies have highlighted the pivotal roles played by the amygdala and the prefrontal cortex (PFC), in particular the circuitries involving the medial PFC, in the mechanisms that regulate emotional responses such as fear or anxiety. Moreover, it has been shown that scarce structural and functional connectivity between these two structures provides less accurate emotion regulation and higher levels of pathological anxiety [9].

However, it is not the only network that has been postulated to be involved in the pathogenesis of OCD and related disorders. Dysfunctional frontal–striatal circuitry [10] may cause impairments in response inhibition and attentional set shifting, leading to cognitive and behavioral inflexibility, a distinct feature of the OC spectrum [11]. Furthermore, considering the rewarding anxiety relieving effect of compulsions it has been proved that impaired reward processes are also involved, allowing to conceptualize OCD as a behavioral addiction [4].

Reward process is associated with ventral striatal orbitofrontal circuitry, and neuroimaging studies provide consistent evidence that altered metabolism in this area is frequent in patients with OCD [12].

Impairments in the corticostriatal–thalamocortical circuits have been highlighted by neuroimaging studies [12,13] Volumetric abnormalities of the basal ganglia volumes, [14,15], orbitofrontal cortex (OFC), anterior cingulate gyrus, and temporal-limbic structures have been identified using MRI [16,17], whereas functional studies with positron emission tomography (PET) and single photon emission computed tomography (SPECT) suggest abnormal metabolic activity in the OFC, anterior cingulate gyrus, caudate nucleus and thalamus [12,18]. The researches of Tobler *et al.* [19] have highlighted that prefrontal regions are used to evaluation of rewards, in particular to correlate the expected value and risk.

In the already mentioned functional imaging study by Figee *et al.* [4] both reward anticipation and receipt were examined in a group of OCD patients. This group presented a significant reduction of activity in the bilateral nucleus accumbens (NAcc). Reward outcome was linked to the involvement of several areas of the brain reward network, such as the NAcc and the OFC. Patients with OCD may be less able to make advantageous choices due to altered NAcc activation. These data confirm the suggested role for these areas and the NAcc in the pathogenesis of OCD and support the theory that this disease may be defined, at least during some stages of its course, as a disorder of reward processing and behavioral addiction.

Reward processes and the understanding of its neural mechanisms in OCD could therefore represent important issues to be explored in future research, in order to develop more effective pharmacological treatments.

1.3 Overview of obsessive–compulsive disorder animal models

The animal modeling of diseases is one of the most useful strategy for advancing the understanding of the etiology and

the neurobiological underpinnings of psychiatric diseases and consequently for the development of new pharmacological treatments. Animal models can be classified in natural ethological models and laboratory-based behavioural, genetic and pharmacological models.

The focus of attention of early animal models of OC spectrum conditions was on fear/anxiety mechanism (or presumed anxiety for animals) and its relative conditioning mechanisms. Models like the seminal one of Solomon *et al.* [20] based on conditioning, contributed, for example, to the development of exposure and response prevention (ERP) therapy protocols [21], that are nowadays one of the first-line psychological treatment for OCD.

More recent models are related to hypothesized impairments in 'top–down' cortical control of fronto-striatal neural circuits, or alternatively from overactivity within striatal 'habit' circuitry [22], resulting then in disrupted executive functions such response inhibition and cognitive flexibility. Drug-induced behavioural alterations that resemble human OC symptoms such as perseveration, indecision and compulsive checking are at the core of pharmacological animal models that manipulate the neurotransmitter systems, which are primarily involved in the pathophysiology of OCD, mostly dopaminergic and serotonergic systems. For example, perseveration induced by serotonergic agents, such as the 5-HT1A agonist 8-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide (8-OHDPAT), has been suggested to model compulsive behaviour in OCD [23]. Furthermore, in another important model developed by [24] compulsive behavior was induced by chronic treatment of rats with the D2/D3 agonist quinpirole, reducing behavioral flexibility. Both models have tested the effects of drugs known to be effective in OCD. Acute treatment with a serotonin 1b receptor (5-HT1bR) agonist seems to induce OCD-like behaviors that tend to ameliorate after a chronic treatment with fluoxetine or clomipramine [25,26], a model that is in line with the chronological course of OCD and the relative response to pharmacological treatment in humans. 5-HT1bR (expressed in the OFC) pathway, may represent therefore a potential pharmacological target for new OCD treatments.

For a more extensive review, see Fineberg *et al.* [27] and for glutamatergic animal models of OCD, see Section 6.1.

2. Medical need

2.1 Early diagnosis and intervention

OCD remains a poorly recognized and undertreated condition despite > 20 years of research. The average duration of untreated illness has been estimated to be around 17 years [28]. Delayed recognition and treatment of OCD could have a relevant impact on illness progression, considered under the light of the result of a recent study showing that short duration of illness is correlated to high rates of remission after treatment [29].

Moreover, obsessive–compulsive symptoms have been described and associated with post-streptococcal disorders, both in children and adults, and are mediated by antistreptococcal antibodies that cross-react with neuronal proteins in structures of the human brain, such as the basal ganglia. A recent cross-sectional study found that positivity for anti-basal ganglia antibodies (ABGA) was observed more requently in OCD patients than in healthy controls, suggesting that central nervous system autoimmunity may play a role in the pathogenesis of the disorder [30]. However, more research is needed to understand if exposure to streptococcal infection in a subgroup of patients may represent a risk factor for the development of OCD, providing the opportunity for early detection and development of new kinds of pharmacological treatment. In the last years, the conceptualization of autoimmune-induced OCD syndromes has been revised, extending its definition from streptococcal-induced OCD symptoms and syndromes (PANDAS) to a more comprehensive construct named pediatric acute-onset neuropsychiatric syndromes (PANS) [31].

2.2 The dimensional approach

OCD is clearly a heterogeneous disorder from a clinical and neurobiological point of view. Several studies showed that different symptom dimensions are related to different functional and structural neuroimaging patterns, gene associations and clinical outcomes. Also gender seems to play a role in the expression of different OCD phenotypes. A relatively recent study shows, for example, that female patients have a significant higher rate of cleaning/washing symptoms and a significant lower rate of sexual/religious symptoms [32]. All these data must guide the future research in order to achieve more and more individualized treatments.

2.3 Clinical staging

Clinical staging is a routinely approach used in general medicine for chronic disorders such as diabetes, arthritis and cancers, describing the links between biomarkers, clinical phenotypes and disease extension, and promoting a personalized or stratified medicine approach to treatment planning [33] Clinical staging involves a detailed description of where an individual exists on a continuum of disorder progression that goes from an at-risk stage to an end-stage of the disease. The approach is popular due to its clinical utility and is increasingly being applied in psychiatry. The concept offers an informed approach to research and the active promotion of indicated prevention and early intervention strategies. The concept of clinical staging has been recently applied to schizophrenia and bipolar disorder in order to achieve early recognition and interventions for these chronic and disabling disorders. OCD is still lacking of a clinical staging model, despite a growing knowledge about the putative progressive shift from frontoamygdalar dysfunction to NAcc dysfunction during the course of illness.

3. Existing treatments

3.1 First-line treatments

There is a general consensus about how to treat OCD. Both CBT and serotonin reuptake inhibitors (SRIs) are considered first-line options.

Placebo-controlled trials and meta-analyses support the efficacy in adulthood OCD of all available SSRIs (fluvoxamine, fluoxetine, sertraline, paroxetine, citalopram and escitalopram) and of clomipramine [34,35]. Even if clomipramine seems to be more effective than SSRIs in relieving OC symptoms [36], SSRIs tend to be considered the first choice because of their higher tolerability and safety in the long-term. The anti-obsessional efficacy is correlated to the SRIs doses, as suggested by Bloch's and colleagues meta-analysis [37], with better response to higher SRIs doses, for a minimum of 12 weeks. An open issue of the serotonergic treatments for OCD is represented by the relevance of plasmatic levels of the pharmacological agent. Two recent studies highlighted the relevance of assessing SRIs plasmatic levels in order to achieve a better response [38,39]. However, monitoring SRIs plasma levels is not a regular practice in many psychiatric clinics.

Increasing attention has been paid to the possible role of serotonin–norepinephrine reuptake inhibitors (SNRIs) in patients with OCD. Venlafaxine shows different degrees of serotonin, norepinephrine and dopamine inhibition, the action on the noradrenergic and dopamine system becoming more marked at higher doses. Despite the fact that in some clinical trials venlafaxine has been shown to be effective, controlled trials showed that venlafaxine seems to be less effective than other SRIs [40]. Thus, it should not be considered a first-line medication at this time. Instead, it could be considered in specific clinical situations such as OCD with comorbid attention/deficit/hyperactivity disorder (ADHD) [41].

Mirtazapine does not enhance 5-HT neurotransmission directly, but disinhibits the norepinephrine activation of 5-HT neurons, and thereby increasing its neurotransmission. The efficacy of mirtazapine in the treatment of OCD patients has been tested in a single-blind study, which compared citalopram to a combination of mirtazapine and citalopram. The results indicated that the responses were faster (after 4 weeks) but that there was no difference between the groups after 8 and 12 weeks [42]. Continuation therapy at the effective dose is recommended in order to avoid relapses [37]. Recent guidelines suggest that anti-obsessional treatments must be continued for at least 1 – 2 years after clinical response [43]. However, there is no consensus on the optimal duration and the doses of maintenance treatment because of the lack of systematic long-term follow-up studies.

Another important issue concerns the titration regimen. Some study suggested that a more rapid titration could result in a faster onset of the response [44-46]. However, further controlled studies must address this issue.

CBT is a specific and effective first-line treatment for OCD, and it is of great value because its protocols are highly flexible and adjustable to new reconceptualization of the disorder derived from neurobiological research advances. However, several studies showed that the cognitive part of the CBT (consisting of the procedures of cognitive challenging of intrusive thoughts) is not essential for a good response to treatment. In fact, CBT and ERP (representing the 'pure' behavioral part of the CBT) seem to be equally effective [47].

The choice between CBT and SRIs as first step treatment depends on patient's and clinician's choice. Some predictors of non-response to CBT, such as severe OC symptoms, major depressive disorder (MDD) comorbidity, poor insight, hoarding and sexual/religious subtypes of obsessions and compulsions allow the clinician to prefer pharmacotherapy [47,48]. However, CBT is generally preferred for adolescents, due to the suicide risks linked to SSRIs use in this population.

While the available pharmacological treatment required several years to be developed and validated, psychological intervention updating might require a shorter length of time. Therefore, in the last years several psychological approaches (such as Acceptance and Commitment Therapy, Motivational Interviewing, Eye Movement Desensitization, etc.) have been tested for the treatment of OCD. However, further research is needed to elucidate which psychological treatments are most effective for the different OCD presentations [49]. Finally, a promising and cost-effective approach may be represented by internet-based CBT. In a recent controlled trial, internet-CBT showed efficacy in OCD patients [50].

3.2 Approaches to treatment resistance

Treatment resistance is a frequent situation in OCD, occurring in 40 – 60% of patients, which may occur at different stages during all the course of illness, having a strong impact on the long-term prognosis of the disease [51]. Treatment response is actually represented by a symptom reduction of 35% (or more) of the initial Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) total score [51-53]. With regard to other psychiatric disorders, patients with this slight grade of clinical improvement might be still considered non-responders. Considering these issues, even if in the last years some important progresses have been made, many questions still remain open and represent a notable limit for an optimal intervention. First, the treatment for non-responders is largely not evidence-based; second, the research on predictors of response has not provided clear treatment recommendations for resistant patients, even if some elements (early onset, poor insight, hoarding symptom dimension) have been individuated [54]. Moreover, the presence of comorbid conditions also influences the course of the response to treatment. Non-responsive patients are more likely to meet criteria for comorbid psychiatric disorders and the presence of a specific comorbid condition could be a distinguishing feature in OCD, with influence on the treatment adequacy and outcome [42].

Two main different strategies may be considered when first-line treatments fail, such as switching or augmenting. Switching consists in replacing a serotoninergic agent with another one, or with a molecule of another class of drugs. From a clinical point of view, the rate of success is about 50% [43], but it seems to decline with a clear inverse relationship to the number of treatment failed. Augmentation consists instead in combining two agents, not necessarily of the same class. Several options has been tested, involving mainly the concomitant use of clomipramine and SSRIs, SSRIs and dopaminergic agents, SSRIs and antipsychotics and SSRIs plus opioid agents, with controversial results [43]. Indeed, while guidelines based on expert opinion exist, in current literature only a few evidence-based options for treatment-resistant patients can be traced (**Table 1**). The most evidence-based option is the augmentation strategy with antipsychotics (e.g., haloperidol and risperidone). However, only a third of resistant patients respond to this treatment [55]. Another option is the combination of CBT and pharmacotherapy, which may be superior to pharmacological or non-pharmacological therapy alone, although literature evidences are still inconsistent [56]. After that a third option, mostly based on guidelines and again with limited evidences of efficacy, is to combine SRIs or increase the SRIs doses at supratherapeutic doses [56].

In the recent years, there has been some interest in testing several agents mainly used in the treatment of addiction, such as ondansetron and naltrexone. While ondansetron has showed efficacy in treatment-resistant OCD in a single-blind, in a double-blind trial and more recently in a discontinuation study [57-59], naltrexone failed to show any efficacy in a double-blind cross-over study [60].

A promising approach is the infusive therapy strategy. A few controlled studies indicate that infusion therapy can be considered as a valid therapeutic strategy for treatment-resistant cases [44,45,61-64]. Two molecules are currently available for this kind of treatment in OCD, clomipramine and citalopram. Moreover, current literature suggests that the titration regimen, in particular a rapid titration could be relevant also for intravenous treatments. An example of a rapid titration is the pulse-loading treatment. This regimen consists in a rapid titration of the pharmacological agent in the first days of treatment. A few studies suggested that this kind of titration with intravenous clomipramine could results in a greater and faster response than with a standard titration in OCD-resistant patients [44,62]. Recently, a small case series showed a good efficacy and tolerability of high doses (up to 80 mg) of citalopram in a pulse-loading regimen for treatment-resistant OCD patients [65]. Furthermore, patients treated with intravenous treatments (both citalopram and clomipramine) seem to have a stable response over time [63,65]. For infusion therapy with ketamine, see in Section 6.2.

3.3 Neuromodulation techniques

In the last years the neuromodulation techniques have gained increasing attention for the treatment of resistant psychiatric disorders. In the field of OCD, two techniques have been largely investigated: repetitive transcranic magnetic stimulation (rTMS) and deep brain stimulation (DBS).

DBS has showed to be a promising tool in the treatment of refractory OCD patients. The existing data show that the NAcc and the anterior limb of the internal capsule are the most promising targets for this treatment. However, further studies are needed in order to better clarify the long-term efficacy and safety of this procedure, and to better characterize the ideal patients who might have a good response to DBS.

A recent meta-analysis shows that active rTMS seems to be efficacious for treating OCD. Moreover, low-frequency rTMS and protocols targeting the OFC or the supplementary motor area seem to be the most promising. Nevertheless, future RCTs on rTMS for OCD should include larger sample sizes and be more homogeneous in terms of demographic/clinical variables as well as stimulation parameters and brain targets [66].

The development of new types of stimulation coils (e.g., H-coils) may provide better performance, both in terms of focality and depth of stimulation, allowing to reach other important structures such as the anterior cingulate and result helpful in the treatment of the disorder.

4. Market review

OCD and OCD-related spectrums conditions are relative frequent conditions in the general population, with an estimated lifetime prevalence of approximately 2% [1], even if the estimates have varied consistently across the surveys, due probably to methodological issues regarding the use of appropriate diagnostic tools and intrinsic diverse characteristics of the population [67].

Data from the National Comorbidity Survey Replication (NCS-R) show that 90% of the patients with a lifetime diagnosis of OCD meet criteria for another DSM-IV disorder, most frequently other anxiety disorders or mood disorders. With regard of impairment, > 65% of showed severe role impairment in the last 12 months, resulting in an average of 45.7 days out of role [1]. However, in order to better estimate the public health consequences of OCD, more evidence is needed regarding the impact of the illness on functioning.

Anxiety disorders account for approximately one-third of US mental health expenditures, with an annual estimated cost of $42.3 billion in 1990: for the same year OCD costs were estimated at only $2.1 billion annually [68].

More recently the results of a large-scale retrospective study aimed at comparing the health care burden of patients with OCD versus depression show that during the 2 years following the diagnosis the total health costs of an adult-onset OCD patient were similar to that of an adult-onset depressed patient. However, a significant difference was found regarding the use and costs of psychotropic medications, with OCD patients showing much higher use and costs of treatment. This may be related to the fact that usually OCD requires

Table 1. Evidence-based treatment algorithm for translational obsessive–compulsive disorder studies.

Stages	Treatment options
Stage 1	SSRI (fluvoxamine, fluoxetine, sertraline, paroxetine, citalopram and escitalopram) at optimal dose (12 weeks), OR CBT (16 individual sessions), incorporating exposure and response prevention (ERP)*
Stage 2	SSRI + CBT (12 weeks)
Stage 3	SSRI + antipsychotic risperidone (0.5 – 2 mg), quetiapine (≤ 300 mg), olanzapine (≤ 15 mg), aripiprazole (≤ 20 mg), amisulpride (200 – 400 mg), haloperidol (0.5 – 2 mg), listed in decreasing preference; reserved for patients with documented failure to respond to a therapeutic trial of at least one SSRI and at least moderate impairment (12 weeks), OR high-dose SSRI (12 weeks)
Stage 4	As per Stage 3 or clinician's choice (including clomipramine, novel compounds)

Response criteria: *Full response*: > 35% improvement in baseline Y-BOCS scores. *Partial response*: ≥ 25% improvement in baseline Y-BOCS scores. *Non-response*: < 25% improvement in baseline Y-BOCS scores.

In case of full response, the patient maintains the SSRI or SSRI + antipsychotic at the effective dose for at least 1 year, or CBT follow-up for 1 year. In case of partial or non-response, the patient moves to the next treatment stage.

*For adolescents, CBT is usually used first line.

CBT: Cognitive behavioral therapy; SSRI: Selective serotonin reuptake inhibitor; Y-BOCS: Yale–Brown Obsessive–Compulsive Scale.

Taken and modified from Koran *et al.* 2007 [43].

higher doses and longer duration of SSRIs treatments compared to that needed in depression, and to the higher rates of treatment resistance [68].

Considering these facts, and the evidence regarding the chronic course of the disorder, the significantly heightened risk for suicide [69] and decreased quality of life [70] more research in the field is needed in order, on the one hand, to find pharmacological treatments more effective than SSRIs, and on the other to reduce the burden of disease, both for the patients and for the mental health system.

5. Current research goals

The main goal of the ongoing research is the identification of new neurobiological targets, both in terms of neurocircuitries and neurotransmission mechanisms. Therefore, the growing knowledge of the neurobiology of OCD has shifted the neurobiological model from the anxiety/serotonin model to a reward/dopamine–glutamate model, largely based on neuroimaging findings on reward dysfunction and glutamate dysfunction [4]. Thus, a large body of research is trying to develop and tests pharmacological agents that exert their effects on the glutamate system and on reward circuitries.

6. Scientific rational

6.1 Glutamate dysfunction

In the last 10 years, several research groups have focused their attention on glutamate dysfunction in OCD. The results of these researches highlight the role of the excitatory neurotransmitter glutamate in the pathophysiology of OCD, suggesting the existence of a hyperglutamatergic state. A neuroimaging study used proton magnetic resonance spectroscopy to compare drug-naïve pediatric OCD patients with healthy controls and found significantly higher caudate nucleus concentrations of GLX (glutamate plus glutamine) in the OCD group [71]. Furthermore, the enhanced glutamate activity normalized after paroxetine treatment [71-73]. Other neuroimaging studies showed similar results [74,75] and glutamate concentration in the cerebrospinal fluid was found to be significantly higher in OCD drug-naïve patients versus healthy controls [76,77].

The therapeutic action of a neurosurgical lesion of a part of the anterior limb of the internal capsule also supports the hypothesis of a hyperglutamatergic activity in OCD. The selective damage of this area interrupts the projections of the OFC to the caudate nucleus; due to the fact that the efferent axons of the OFC are glutamatergic neurons, it is thus likely that the neurochemical effect of capsulotomies is to interrupt the increased glutamatergic transmission between the OFC and the caudate nucleus [78].

Genetic studies also highlight the possible implication of glutamate in the pathophysiology of OCD. In particular, a family study found an association between the *N*-methyl-D-aspartate (NMDA) glutamate receptor subunit GRIN2B (glutamate receptor, ionotropic, *N*-methyl-D-aspartate 2B) and OCD [79]. Moreover, a recent study found an association between OCD and a locus on chromosome 9p24 that codes for the amino acid transporter SLC1A1 (solute carrier family 1, member 1) that is considered to play an important role in extinguishing the action of glutamate and in maintaining the extracellular glutamate concentrations within the reference range [80,81].

Finally, research in animal models also supports an OCD–glutamate association. Welch *et al.* conducted a genetic study on SAPAP3 mutant mice [82]; SAPAP3 (SAP90/PSD95-associated protein 3) is a postsynaptic scaffolding protein in excitatory (glutamatergic) synapses, which is highly expressed in the striatum. In this study, the authors showed that mice with genetic deletion of SAPAP3 exhibit increased anxiety and compulsive grooming behavior leading to facial hair loss and skin lesions; both behaviors were alleviated by a 6-day fluoxetine treatment [83].

Given the hypothesis of glutamatergic hyperactivity, several studies investigated the clinical efficacy of glutamate receptors antagonists in the treatment of OCD patients.

Table 2. New agents in testing for the treatment of OCD.

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Bitopertin [95]	Hoffmann-La Roche	n.a.	OCD (in combination with SSRIs)	Phase II	Glycine transporter type 1 inhibitor
RG1068 [96]	n.a.	n.a.	OCD (both in combination or not with SSRIs)	Phase II	Subcutaneous synthetic human secretin

OCD: Obsessive–compulsive disorder.

6.2 Glutamate agents for OCD

Memantine is a noncompetitive NMDA receptor antagonist that has been approved by the Food and Drug Administration for the treatment of Alzheimer's disease. Case series [83-85] systematic studies [86-88] and two controlled trials [89,90] showed that memantine may be effective in treatment-resistant OCD. Furthermore, in an open-label trial comparing the efficacy of memantine in the treatment of OCD versus generalized anxiety disorder, memantine was preferentially useful in treating OCD symptoms [86].

Riluzole is a potent anti-glutamatergic agent that reduces glutamatergic neurotransmission in several ways, such as inhibiting glutamate release, inactivating voltage-dependent sodium channels in cortical neurons, and blocking of GABA reuptake [91]. In an open-label trial of riluzole (50 mg b.i.d.) in treatment-resistant patients, 54% of them resulted to be full responders (> 35% reduction in Y-BOCS scores) and 39% to be responders [91]. In a more recent open-label study of six pediatric OCD-resistant patients, four subjects responded to riluzole treatment [92].

N-acetylcysteine (NAC), an amino acid derivative that attenuates glutamatergic neurotransmission, was effective as fluvoxamine augmentation in a case report of a treatment-resistant patient and more recently in a double-blinded controlled study on treatment-resistant OCD patients [93].

Recently, a few trials investigated the potential anti-obsessive effects of ketamine (a noncompetitive antagonist of the NMDA receptor). A recent randomized controlled cross-over trial on 15 OCD drug-free patients, showed that ketamine infusion has a rapid anti-obsessional effect that can persist for at least 1 week [94].

7. Competitive environment

We systematically searched the database (in June 2013) on the website ClinicalTrials.gov using the search term 'obsessive compulsive disorder', 'OCD' and excluding studies focused mainly on other comorbid conditions. The search resulted in a total of 124 recorded studies.

Of these, 42 studies are listed under psychological/behavioral interventions for OCD, focused mainly on CBT, both with and without a pharmacological association. Twenty trials investigated physical treatments, mainly DBS and rTMS. The rest of the studies (62) are pharmacological trials. Of these only a very few (2) involve new agents, more precisely an NMDA receptor potentiator (still recruiting, last update April 2013) [95] and a synthetic human secretin (**Table 2**) [96]. For both of them no results are published.

8. Conclusions

OCD and its related spectrum conditions are relatively frequent, chronic and disabling disorders, causing moderate to severe dysfunction for the patient and high costs for the mental health system. At the moment there are no totally effective medications and research for new compounds is quite limited. The development of novel therapeutics should be based on new neurobiological targets taking into account the more sophisticated models and conceptualizations of the disease, in order to ameliorate the many aspects of the disease that still need to be addressed.

9. Expert opinion

Despite in the past 20 years, several efforts have been made to achieve effective pharmacological treatments for OCD, treatment resistance is still a frequent condition and the treatment for non-responders is largely not evidence-based. The research of new treatments for OCD is moving forward at a slow pace and in the last years there has been no new really effective treatment on the market, even if many efforts has been made in the study of the neurobiological underpinnings of OCD.

This state of the art is probably largely due to the failure of a categorical approach to OCD. In fact, investigating new compounds in clinical trials assuming that OCD patients are a homogenous group, despite the evidences of OCD's heterogeneity both in terms of genetic and neurobiology, has not been a successful strategy. What we know today about OCD is that several neurocircuitries (cortico-striatal loop, reward system, amygdala, insula) and neurotransmitters (serotonin, glutamate, dopamine) are involved in its pathophysiology and that different clusters of symptoms are related to different neurobiological underpinnings.

Therefore, the principal goal in this research field is to achieve a broader conceptualization of the disorder, both in terms of neurobiological etiology and phenomenological

appraisal, which are mutually interlinked. However, how to reach this goal still remains an open question.

In our opinion, two different but complementary approaches that are widely used in the rest of medicine could result helpful: the sub-classification of the syndrome and the clinical staging.

Several neuroimaging and clinical studies suggest that distinct symptom dimensions in OCD are linked to different neurocircuitries and follow different long-term course trajectories [97]. This approach has determined the classification of hoarding disorder as a separate disorder in the DSM-5 [2]. The sub-classification of OCD based on symptom dimensions could be helpful in designing clinical trials and developing pharmacological treatments with specific neurobiological targets (e.g., drugs targeting insular circuitries in patients with prominent disgust dimension symptoms or drugs targeting the dorsal parts of the striatum for patients with prominent ordering/symmetry symptoms). Another possible approach would be to sub-classify OCD patients according to their pattern of comorbidity. In this perspective, Nestadt *et al.* proposed an OCD sub-classification based on comorbidity [98]. The authors proposed a three classes solution characterized by: i) an OCD simplex class, in which MDD is the most frequent additional disorder; ii) an OCD associated with Tic disorders class, in which tics are prominent and affective syndromes are considerably rarer and iii) an OCD associated with panic disorder (PD) class, in which affective syndromes are highly presented [87]. This approach has partially been incorporated in the DSM-5 with the TIC-related specifier (DSM 5). However, this classification does not address the issue of the co-occurrence of obsessive–compulsive personality disorder and OCD. In fact, a recent study showed that the two disorders seem to have different reward system functioning as supported by the different ability of OCD and OCPD patients in delaying reward [99]. The treatment implications of this new insight must be taken into account in future studies.

The second strategy that in our opinion could result helpful is clinical staging (see Sections 1.2 and 2.3). As already mentioned, in the last years neuroimaging studies shifted the focus of attention from an anxiety model based on serotonergic dysfunction to a more sophisticated one involving reward circuitries [8], which may be interpreted as a kind addiction progression. Although anxiety symptoms are a core feature of OCD, current literature shows growing evidences of a reward dysfunction in OCD, mainly in resistant patients. These data support the hypothesis that addiction and OCD share some common neurobiological dysfunctions and corroborate the idea that OCD starts as an anxiety disorder and becomes a behavioral addiction through the same stages of substance abuse disorders.

Thus, pharmacological research should take into account these new insights and make a great effort in projecting pharmacological trials of individualized treatments based on a broader spectrum of neurobiological targets and on more articulated clinical dimensions, in order to achieve better results for the treatment of this highly disabling condition.

Declaration of interest

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