Current pharmacological and non pharmacological treatments for obsessive-compulsive disorder

Terapie farmacologiche e non del disturbo ossessivo-compulsivo

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Summary

Objectives

Although the treatment of obsessive-compulsive disorder (OCD) represents one of the most important achievements of psychopharmacology, even with the introduction of selective serotonin (5-HT) reuptake inhibitors (SSRIs) in clinical practice, about 30% of patients do not respond to standard therapeutic strategies. Herein, a comprehensive and critical review of pharmacological and other treatments commonly used in OCD is presented, with particular attention to resistance and predictors of response.

Methods

The PubMed (1980-2010) database was queried using the following key words: OCD, clomipramine, SSRIs, resistance, predictors of response, CBT, ERP, transcranial magnetic stimulation, deep brain stimulation, neurosurgery and ECT.

Results

The 5-HT system is undoubtedly central to the pharmacological treatment of OCD, as demonstrated by the clinical effectiveness of serotonergic modulation. However, as numerous studies have revealed abnormalities in other neurotransmitter systems, neuropeptides and second messengers, it can be hypothesised that the heterogeneity of pathophysiological mechanisms may underlie the different clinical presentations and responses to treatment. Moreover, the latest developments in the pharmacology of SSRIs have shown that while they share the common property of 5-HT reuptake blockade, with the exception of citalopram and escitalopram, they nonetheless interact with other receptors and systems.

Conclusions

Although the treatment of OCD represents one of the major achievements of psychopharmacology of the last decades, there are still a number of problems that must be resolved in order to integrate this data with improved management of individual patients.

Key words

Obsessive-compulsive disorder • Selective serotonin reuptake inhibitors • Resistance • Predictors of response • Cognitive behavioural therapy • ERP • Transcranial magnetic stimulation • Deep brain stimulation • Neurosurgery • Electroconvulsive treatment

Introduction

Obsessive-compulsive disorder (OCD) is characterised by the presence of obsessions and/or compulsions. The obsession is an idea or impulse characterised by persistence, recurrence and forcefulness that the patient perceives as intrusive and inappropriate, which creates discomfort and does not disappear in spite of attempts to ignore or suppress it. The compulsion is a repetitive behaviour or mental act carried out in response to the obsession according to precise rules. Many of these behaviours have the aim of reducing or neutralising the anxiety, or avoiding the feared event, which is frequently excessive or unrealistic [1]. Even if the patient recognises that the obsession and compulsion have been created by him/herself, the degree of awareness of the pathology is highly variable, and in this regard there is a diagnostic subtype that is defined with "poor insight".

Once believed to be rare and resistant to treatment, OCD is now considered one of the most common psychiatric disorders, with a lifetime incidence of 0.3% in Taiwan and 5.5% in some Western countries (mean 2.5%), and an important cause of long-term disabilities for both patients and their families [2-5]. OCD, however, is frequently underdiagnosed, not only by general practitioners, but also by psychiatrists. An epidemiological study demonstrated that the time between the appearance of symptoms and correct diagnosis is about 17 years [6]. There are many reasons why the disorder goes unrecognised: patients tend to hide their symptoms, fearing that they will appear 'crazy', and only seek specialist help when the clinical picture is complicated with anxiety and depression [7 8]. In addition, may physicians do not recognize specific symptoms, leading to a delay in correct diagnosis, which has a negative impact on subjective suffering and social/work adaptation,

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as well as costs to society; this occurs in spite of the availability of effective pharmacotherapies.

Clomipramine was the first agent approved by the FDA for treatment of OCD. In a 10-week study, clomipramine led to significant improvement of symptoms vs placebo, as shown by a reduction of 38-44% in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), which is most commonly used in OCD [9]. Clomipramine is a tricyclic antidepressant (TCA) that primarily inhibits re-uptake of serotonin (5-HT), and has shown greater efficacy in OCD compared to other TCAs with noradrenergic action such as nortriptyline, amitriptyline, imipramine and desipramine [10-16]. Subsequently, the serotoninergic hypothesis of OCD has led to a more widespread use of selective serotonin re-uptake inhibitors (SSRI), including fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram.

OCD is a chronic disorder, that is severely disabling, with symptoms that tend to recur within several weeks after withdraveal of pharmacotherapy, rendering long-term treatment necessary. Considering this, it is of particular importance to use an agent that has a good tolerability profile. The main adverse effects of clomipramine are for the most part related to its anticholinergic action, and in particular, xerostomia, constipation, dizziness, sedation, weight gain, increase in orthostatic heart rate and reduction in systolic blood pressure. SSRIs have an efficacy that is similar to clomipramine, and a more favourable tolerability profile, even if they are frequently associated with asthenia, insomnia, nausea, gastrointestinal distress and sexual dysfunction (reduced desire, impotence and anorgasmia). In the case of clomipramine, the frequency of discontinuations due to adverse events is substantially higher that with SSRIs (17 *vs*. 9%, respectively). All major guidelines recommend that SSRIs should be considered as first-line therapy, followed by clomipramine only in the case of intolerance or a lack of response to SSRIs.

The aim of the present review is to provide an overview of therapeutic and pharmacological/non-pharmacological strategies in OCD, with a particular attention to treatment resistance and factors that are predictive of response. A literature search in PubMed (1980-2010) was carried out using the following key words: obsessive-compulsive disorder, clomipramine, SSRI, resistance, predictors of response, cognitive-behavioural therapy, prevention of response, repeated transcranial magnetic stimulation, deep brain stimulation, neurosurgery and electroconvulsive therapy.

Pharmacological treatment

Clomipramine

The efficacy of clomipramine in the treatment of OCD is well documented by numerous studies starting from the 1960s, when the agent was introduced in clinical practice [17]. From the very beginning, differences in anti-obsessive and antidepressant activities were noted, as well as the longer time to response in OCD compared to depression, in addition to its specificity with respect to other TCAs. An approved indication as an anti-obsessive drug was obtained in the mid-1980s [18-20]. The efficacy of clomipramine was first demonstrated in a double-blind study (100-300 mg/day) in 263 patients [21]. In a second phase, patients that responded to treatment (n = 124) were followed for 52 weeks, and more than 50% of patients on clomipramine had significant improvement of symptoms. Discontinuations due to adverse events were seen in 22.7% of patients in the clomipramine arm and 0% in the placebo group. Clomipramine has an efficacy that is similar to newer agents, and in some cases even greater, as shown in many meta-analyses [22-24] and in studies that were not sponsored by pharmaceutical companies [25 26]. Moreover, clomipramine can even be administered parenterally, thus providing a valid alternative in treatment-resistant cases. In clinical practice, the most effective dose is from 100 to 300 mg/day, while the minimally effective dose is 75 mg/day [27].

SSRIs

SSRIs are a group of compounds with similar characteristics; the choice of one molecule over another is essentially based on personal decisions and eventual pharmacological interactions. Sertraline, citalopram and escitalopram are weak inhibitors of cytochrome P450 (CYP), which is responsible for the metabolism of many drugs: fluoxetine and paroxetine are potent inhibitors of CYP2D6 which metabolises TCA, antipsychotics, antiarrhythmics and beta-blockers. Fluvoxamine, in contrast, inhibits both CYP1A2 and CYP3A4, which are involved in the metabolism of warfarin, TCAs, benzodiazepines and some antiarrhythmics. In treatment of OCD, higher doses of SSRIs are generally used compared to those used for mood stabilisation, based on initial studies [28-31]. Recently, additional studies have shown that sertraline and escitalopram are more effective in OCD at doses higher than those used in depression [32 33].

Fluoxetine

Fluoxetine was the first SSRI approved for the treatment of OCD. At doses of 40, 60 and 80 mg/day, fluoxetine is superior to placebo, with good tolerability and a rate of discontinuations that is similar to placebo [28 34]. Significant improvement in symptoms is seen at doses of 60 and 80 mg/day, while an Austrian study has demonstrated that fluoxetine is effective even at a dose of 40 mg/day [35]. In the only long-term study available, no differences were seen between fluoxetine and placebo [36].

Fluvoxamine

Fluvoxamine was the first SSRI that was studied in OCD. In an initial investigation in a cohort of 42 patients, significant improvement in symptoms was seen starting from the second week of treatment, which further improved with continuing therapy [37]. A successive placebo-controlled multicentre trial in 160 patients followed for 10 weeks confirmed the superiority of fluvoxamine over placebo [38]. A comparative trial between fluvoxamine and clomipramine showed that these agents have similar efficiacies [39-41]. The long-term outcomes of fluvoxamine, in terms of reduction in severity of symptoms, safety and tolerability have been confirmed in several double-blind trials [42-44] at doses from 50 to 300 mg/day. The most common adverse events observed with fluvoxamine are sedation, asthenia and anorgasmia [43]. In many cases, recurrence of symptoms is seen within a few days of suspension of treatment [43]. An extended-release formulation is available that has similar efficacy, rapid action (within 2 weeks) and greater compliance as it is a single daily dose of 100 mg/day [44-46] taken in the evening.

Sertraline

The first investigation on sertraline in OCD was an observational study in 81 patients followed for 8 weeks: significant efficacy was seen at doses from 50 to 200 mg/day [47]. Later studies showed the superiority of sertraline over placebo [48 49]. Response to the drug did not appear to be correlated with the strategy of initial titration, while adverse events, and in particular diarrhoea, nausea and headache, appeared to be transient; there were no significant alterations on laboratory values, vital signs or ECG [48 50 51]. A rapid increase in dose was associated with more rapid improvement in symptoms [52]. Sertraline was superior to placebo even in preventing discontinuation of treatment due to partial response or recurrence of symptoms, and in maintaining clinical benefits [53]. In addition, it had the same efficacy as fluoxetine, with a faster response time [54].

Paroxetine

The results of a placebo-controlled trial investigating three difference doses (20, 40 and 60 mg/day) showed a significant effect of the two highest doses after 12 weeks of treatment [55], and superiority over placebo, as shown in a large multicentre study [56]. There are limited data with regards to long-term outcomes. Hollander et al. [31] reported on the efficacy of paroxetine in both the short- and long-term at doses of 40-60 mg/day, as well as on safety and ability to prevent recurrence: paroxetine was efficacious in the short-term, and at 2 years appeared to be safe and reduce the risk of recurrence.

Citalopram

Initially, a single case report suggested that citalopram may have anti-obsessive activity [57]. A subsequent study in 18 patients with treatment-resistant OCD administered citalopram (40 mg/day) showed a good response in 80% of cases with few adverse events [58]. These data were confirmed in a further placebo-controlled trial [30]. Citalopram in a valuable agent as it can also be administered intravenously (40-80 mg/day), and this formulation is particularly effective in patients that do not respond to oral treatments [59].

Escitalopram

Escitalopram is the most recent SSRI to be introduced in clinical practice. As shown in a study in 466 patients with OCD, it is superior to placebo and compared to paroxetine had a faster response time, higher remission rates and good tolerability [60]. The risk of recurrence is significantly lower than placebo [61]. Moreover, in a 16-week prospective study escitalopram was found to be well tolerated [33].

Other drugs

Venlafaxine and duloxetine belong to the group of 5-HT-noradrenaline reuptake inhibitors (SNRI). There are few studies with these drugs in OCD, even if promising results have been reported. As an example, venlafaxine has been shown to have an en efficacy similar to paroxetine, especially in management of treatment-resistant OCD [62 63].

Mirtazapine is a tetracyclic antidepressant with a mechanism of action that specifically acts on di the noradrenergic and serotoninergic systems (NaSSA). The drug acts by blocking both the auto-and central α_2-adrenergic heteroreceptors as well as the 5-HT_2 and 5-HT_3 serotoninergic receptors. It has an efficacy that is significantly greater than placebo [64] and a more rapid response time [65].

In addition, even if from a non-controlled trial that have not been reproduced, encouraging data have been reported for phenelzine, a monoamine oxidase (MAO) inhibitor [66], inositol, a modulator of second messenger systems [67], glutamate modulators such as cycloserine, a glutamatergic agonist [68], riluzole, an antiglutamatergic agent [69 70] and morphine [71].

Preliminary data have also been published for topiramate, an antiepileptic with glutamatergic properties. Recent neuroimaging data have shown that there are high levels of glutamate in children affected with OCD. Treatment with an SSRI leads to a reduction in symptoms, and is also accompanied by a reduction of the levels of glutamate in the caudate nucleus. In a study in 16 patients with resistant OCD and treated with an SSRI and topiramate for 14 weeks, about 70% of cases showed an improvement in symptoms as judged by the Global Impression-Sever-

ity (CGI-S) and Global Impression-Improvement (CGI-I) scales [82].

Treatment-resistant OCD

Even if serotoninergic agents are effective in pharmacotherapy of OCD, about 40% to 60% of patients show partial or no response, and only a relatively small percentage achieve the complete remission [72]. Moreover, persistent symptoms often remain [37]. For these reasons, several different therapeutic strategies have been proposed that include the use of standard drugs at high doses, alternative routes of administration, polypharmacy or the use of new agents [73-75]. These approaches are based on the direct or indirect functionality of the serotoninergic system, through association of SSRIs or clomipramine and tryptophan, lithium or buspirone. At present, there are no data available that indicate that tryptophan has any efficacy [76]. The results on combined therapy with either lithium or buspirone are also disappointing. Data are also available on resistant OCD treated with co-administration of clomipramine and fluoxetine in adolescents and adults [77 78], and with clomipramine and citalopram [79]. It has also been reported that patients administered paroxetine, but not fluvoxamine, have a better response when associated with pindolol, a beta-blocker that acts on presynaptic 5-HT_{1A} receptors [80 81]. Another potential strategy is the association of an SSRI or clomipramine with typical and atypical antipsychotics. In fact, it has been hypothesised that in addition to the serotoninergic system, the dopaminergic system also plays an important role in OCD. This possibility is supported by numerous studies suggesting that there are both anatomic and functional interactions between the two types of neurons. Indeed, 5-HT inhibits the release of dopamine by acting on 5-HT_{2A} receptors. Haloperidol, for example, in association with fluvoxamine, has been reported to be more effective compared to monotherapy with fluvoxamine [83]. More recently, atypical neuroleptic agents have been proposed as they act on both the dopaminergic system and 5-HT_{2A} receptors, and since they have fewer extrapyramidal effects. Initial studies evaluated risperidone which was shown to be effective in combination with an SSRI [84], in patients with or without tic disorders or schizotypal personality [85 86]. In contrast, the results with olanzapine are more controversial: in association with paroxetine or fluvoxamine is appears to be efficacious [87 88], but not when associated with fluoxetine [89]. During long-term treatment, olanzapine has an efficacy similar to risperidone, and may be useful for short- and long-term treatment in patients with OCD and comorbid bipolar disorder [90 91]. To date, there are still unclear results when combined with quetiapine, even if some studies have reported that it is more effective than placebo [92-95]. At any rate, relatively high doses appear necessary (> 150 mg/day) [96]. Preliminary results are also available for aripiprazole in association with serotoninergic agents at doses from 5 to 20 mg/day, which showed a significant improvement of symptoms after 12 weeks of treatment [97]. In conclusion, the administration of serotoninergic antipsychotics is a potential treatment strategy in resistant OCD, as demonstrated by several meta-analyses [98 99].

Augmenting and reducing response times

To improve the latent response times to SSRI in patients with OCD, generally about 8 to 12 weeks, several therapeutic strategies have been used. As one example, in a single blind study in 32 patients with OCD lasting 12 weeks, the efficacy and tolerability were assessed during two different titrations of sertraline: one was rapid, with a dose of 150 mg/day achieved at day 5, while the other was slow with the same dose being reached after 2 weeks. At 4 and 6 weeks, more rapid improvement was seen in the first group, although there were no differences at later times [52]. In a double-blind, randomised trial in treatment-resistant patients with OCD, pulse-loaded clomipramine was administered by vein or mouth at a dose of 150 mg/day on day 1 and 200 mg/day on day 2, and patients were switched to oral clomipramine on day 6. It was observed that pulse loading itself seemed to induce more rapid and greater improvement than expected in treatment-resistant OCD, independently of the route of administration [100]. As already mentioned, the co-administration of mirtazapine and citalopram, compared to monotherapy with citalopram, led to a more rapid response with fewer adverse events, in particular nausea, but with greater sedation [65].

Predictors of response

At present the response to treatment in OCD cannot be predicted, and the choice of pharmacotherapy is purely empirical; greater knowledge of factors that can predict response would be of obvious utility, just as it would be useful to define homogenous patient groups that could be used to develop more targeted therapies. The available data are controversial due to the low number of patients analysed, heterogeneous clinical characteristics of patients and different definitions of response to therapy; for these reasons, it is difficult to compare the results of different studies [101 102]. Response to therapy is defined as a reduction by at least 25% in the YBOCS score, with a mean reduction of symptoms between 23% and 43%. However, several interesting characteristics have emerged, such as gender, age of onset, family history of OCD, types of obsessions and/or compulsions, duration and course of disease and the presence/absence of insight, although additional confirmation is still needed.

Gender

Several studies have reported that female patients may have a better response to treatment than males, suggesting that female gender may be a positive prognostic factor to SSRIs [103-105]. Other authors have suggested that female patients may respond better to clomipramine [102].

Age of onset and family history

A late age of onset of disease is a factor that can predict positive response to therapy, while an early age of onset and male gender are considered negative prognostic factors [106-112]. Moreover, early age of onset correlates with positive family history for OCD [113], suggesting a potential relationship between the latter and response to treatment.

Subtypes of obsession/compulsion

Additional knowledge about the possible correlations between patterns of symptoms/dimensions and response to treatment could be valuable for choosing more tailored therapies by choosing the most adequate drug for any particular patient profile, which would also reduce the number of treatment failures. Several classification patterns have been proposed based on the presence/absence of specific symptoms, although with controversial results; thus at present, such an approach has no clinical utility [114 115]. The presence of compulsions and magical thinking may be correlated with poorer prognosis compared to the pure obsessive forms [116], and, on the other hand, the prevalence of obsessions with respect to rituals would seem to predict a good response to therapy [117].

Another methodology has been to identify correlated symptoms and group them into dimensions; in an initial report, three dimensions were identified in OCD: aggression/sexuality/religiosity, contamination/cleaning and symmetry/hoarding; only the latter was correlated with the comorbid presence of Tourette syndrome and chronic tic disorder, and thus potentially responsive to neuroleptic therapy [119].

Other authors have proposed the use of five symptom categories: symmetry/ordering, hoarding, contamination/cleaning, aggressive/checking and sexual/religious obsessions [115]. The presence of sexual/religious obsessions may be correlated with poor prognosis [120], especially if treated with an SSRI in association with cognitive-behavioural therapy (CBT) [115 121]. The category of symmetry/ordering does not seem to be correlated with response to therapy, while hoarding may be associated with a poor response to SSRI [115]. Contamination obsessions may be a potential negative prognostic factor, while aggressive and sexual/religious obsessions may be positive factors [117]. Symmetry/ordering and somatic obsessions may respond better to MAO inhibitors [22], and severe symmetry obsessions associated with rituals may respond to cingulotomy [123]. Patients with control and cleaning rituals may benefit from behavioural treatment, but only rarely are patients with ordering compulsion, hoarding rituals and obsessive slowness enrolled in trials using CBT [124]. Several studies have suggested that patients with cleaning rituals benefit from behavioural treatment [125] and worsen with SSRIs [110 126]. Somatic obsessions are generally more frequent in non-responders [106 127]. Lastly, hoarding and compulsions appear to be negative prognostic factors [106 118 121 128].

Duration and course of disease

In OCD with either a short-term or long-term duration, poor response to pharmacotherapy has been reported, while those with an intermediate duration appear to have a better prognosis [129 130].

Insight

Reduced insight appears to correlate with response to treatment [106 131 132], although inconsistent data have been reported [133 134].

Adverse events

Several studies have suggested that there is a positive association between therapeutic response and adverse effects related to pharmacotherapy. In general, the state of initial activation, and not sedation, is considered a positive prognostic factor. Some of the adverse effects of clomipramine (insomnia, erectile dysfunction, jittery behaviour) can indicate the sensitivity of a patients to the serotoninergic action of the drug [9 135]. Moreover, the early appearance of adverse effects, such as irritability and sexual dysfunction, and in particular a decrease in sexual desire following administration of fluoxetine or erectile dysfunction with clomipramine, is associated with a good response to the drug [136].

Previous treatment

Three factors have been found to be positive predictors of response to treatment: absence of previous treatment, presence of mild obsessive/compulsive symptoms and moderate depression [117]. In fact, many studies have demonstrated that patients who had previously undergone psychopharmacological therapy have a reduced probability of responding to SSRIs [11 105 108 110]. Even if the association of previous treatment and unfavourable course of disease is well documented, it is difficult to establish a direct cause or mechanism: psychological mechanisms may be taken into consideration such as a negative attitude of the patient towards new pharmacological treatment, poor compliance and neurobiological mechanisms such as desensitisation of the serotonergic system [137].

Tests for pharmacological stimulus

Clomipramine can be administered intravenously at low doses (25 mg); this type of approach can be useful to evaluate the pattern of response compared to oral administration [138]. In a recent study, 25 mg of clomipramine was administered intravenously: subjects who showed worsening of symptoms after 2 hours did not improve after 2 weeks of oral clomipramine therapy [138]. Following administration of IV clomipramine, alterations in the production of growth hormone (GH) have been noted: according to some authors, this characteristic can distinguish responders from non-responders after 8 weeks of treatment with oral clomipramine [139]. In patients that did not respond to SSRIs, Hollander et al. [140] were the first to describe a weak response of prolactin and worsening of symptoms after stimulation with meta-chlorophenylpiperazine (m-CCP), a partial 5-HT agonist with high affinity for 5-HT_{2C} receptors and lesser affinity for 5-HT_{1A} and 5-HT_{1D} receptors. Patients previously treated with sumatriptan, an agonist for 5-HT_{1D} receptors, showed an exacerbation of symptoms in the first 2 weeks of treatment, and seemed to have a better response to paroxetine [141].

Non-pharmacological treatments

Psychotherapy in OCD

The technique of exposure and response prevention (ERP) is considered to be the most effective psychological treatment for OCD. Patients are exposed to situations that normally provoke the obsession, but are obliged to not act out the compulsive ritual in response to the stimulus. The most widely used exposure techniques, either in vivo or through imagination, are systematic desensitisation, paradoxical intention and satiation/habituation, while the most commonly used preventive techniques to interrupt the ritual are thought stopping and aversion. Numerous studies have demonstrated the efficacy of ERP in OCD [142-145]: 70-80% of patients show considerable improvement [146], while in another investigation the response rate was 85.8% [147]. Meta-analyses have indicated the wide size effect for ERP. One such analysis evaluated 24 studies on ERP and reported a notable effect both pre- and post-therapy (1.2), with a stable course during 18 weeks of follow-up (1.1) [148]. Another meta-analysis [149] reported a size effect for ERP of 0.99, similar to that observed for SSRIs or combined treatment (ERP with SSRI) (1.07), while the efficacy for all three treatments assessed was similar. The advantages of CBT in the treatment of OCD have not been verified. In fact, several studies have reported that CBT is less efficacious than ERP [150 151], while others have reported encouraging results [148 152]. A number of cognitive models of OCD have been proposed: as symptoms of OCD develop, anxiety derived from an erroneous evaluation of intrusive thoughts predominates, to which excessive importance has been attributed; moreover, the exaggerated sense of responsibility that characterises patients with OCD seems to highlight their tendency to overestimate intrusive thoughts and impulses [153-156]. The first controlled study that examined the relation between ERP and CBT, in 71 patients, reported a high efficacy of CBT with 57% of complete remissions and 75% showing significant improvement, even if not statistically significant [152]. In a more recent study, patients treated with both ERP and CBT had significantly more improvement compared to the control group, while during 3-month follow-up a large proportion of patients with ERP satisfied criteria for cure [151].

The association between cognitive and behavioral techniques is especially advantageous in patients who did not respond to ERP alone [157-159]. A recent study compared the efficacy of ERP alone or in combination with CBT; at the end of treatment and during follow-up, a high percentage of patients treated with CBT improved (67% and 76%, respectively), compared to ERP alone (59% and 58%, respectively) [159]. In association, cognitive and behavioral techniques appear to be particularly useful in therapy for obsessions that show a lesser response to ERP alone [157].

The results of studies comparing the efficacy of psychotherapy (ERP or CBT) and pharmacotherapy with SSRI is are relatively consistent [160 161]. In fact, numerous meta-analyses have reported a large size effect after treatment and during follow-up for both therapeutic strategies, but such results are achieved only when the treatments are combined [149 162 163]. A study comparing ERP in association with clomipramine or placebo produced interesting results [160]. ERP plus clomipramine led to a reduction in the Y-BOCS score of 58%, which was significantly less than either placebo (11%), clomipramine alone (31%), or ERP alone (55%). Compulsions seem to respond well to ERP, but not to SSRIs [164]; given that SSRIs are effective only in 50% of patients with OCD, CBT may be the best treatment available for OCD considering both short- and long-term effects. Indeed, the guidelines for treatment of OCD by the American Psychiatric Association recommend CBT as first-line therapy in the majority of cases.

Repetitive transcranial magnetic stimulation

The limited data on the efficacy of repetitive transcranial magnetic stimulation (RTMS) in OCD are controversial and difficult to compare since different brain areas or stimulation parameters have been used. Several double-blind studies with RTMS have not shown any improvement in symptoms either after stimulation of the left dor-

TABLE I.
OCD treatment algorithm [187]. *Algoritmo della terapia del DOC* [187].

Diagnosis of OCD

SSRI

Fluoxetine up to 80 mg/day, fluvoxamine up to 300 mg/day, sertraline up to 200 mg/day, paroxetine up to 60 mg/day, citalopram up to 80 mg/day, escitalopram up to 40 mg/day, for at least 24 weeks

If ineffective

Substitute with a different SSRI at an adequate dose for at least 24 weeks

If ineffective

Substitute with a different SSRI at an adequate dose for at least 24 weeks

If ineffective

Substitute with oral clomipramine (up to 300 mg/day) for at least 24 weeks

If ineffective

Add an SSRI to clomipramine

If ineffective

Administer two SSRIs or an SSRI + venlafaxine

If ineffective

IV clomipramine or citalopram

If ineffective

a)	if resistant to at least 2 SSRIs or panic occurs	add a MAO inhibitor
b)	if tic present or schizotypal or schizoid personality disorders	add a neuroleptic (haloperidol, pimozide or risperidone)
c)	marked anxiety	add buspirone or venlafaxine
d)	depression/bipolar disorder	add lithium, carbamazepine, valproate, gabapentin or topiramate
e)	no specific symptoms	add lithium, carbamazepine, valproate, gabapentin or venlafaxine
f)	risk of suicide	consider ECT

If ineffective

consider CBT, TMS or cingulotomy

solateral prefrontal cortex [165 166], or after repeated applications to the right prefrontal cortex [167]. However, since RTMS is a non-invasive technique that is well tolerated, it is possible that it may find more widespread use in the future, especially in treatment resistant cases.

Deep brain stimulation

Deep brain stimulation (DBS) is an invasive technique, even if it does not involve neurosurgery, that consists in the positioning of electrodes in specific brain regions that are then stimulated with a low intensity electric current. It

is most often used for treatment-resistant cases of Parkinson's disease, dystonia and cluster headaches, although DBS has recently been used in OCD. In this case, DBS carried out by stimulating the caudal portion of the nucleus accumbens with a 4 volt current. While there is only limited data to date, the results have nonetheless been encouraging [168 170-172].

Neurosurgery

The neurosurgical techniques used in OCD have utilised bilateral anterior capsulotomy [174], cingulectomy [175 176], lobotomy [177] and subcaudate tractotomy [178]. Neurosurgery should be limited to patients with very severe OCD that does not respond to other treatments, considering that surgical intervention is associated with severe adverse effects, including severe depressive episodes with suicidal ideation and attempts [173].

Electroconvulsive therapy

Electroconvulsive therapy (ECT) appears to be effective in some patients with treatment resistance, especially if comorbid depression is present, but the majority of published studies were non-controlled [179 181].

Conclusions

While treatment of OCD is one of the greatest successes of psychopharmacology of the last decade, about one-third of patients do not improve with first-line therapeutic intervention (SSRI or clomipramine) (Table I). This means that these drugs are effective on only some symptoms (or dimensions). This is mainly related to incomplete knowledge on the physiopathological mechanisms and aetiology of OCD. The possibilities for intervention, therefore, are still limited. The serotoninergic system plays a fundamental role in the physiopathology of OCD and is a main pharmacological target, although undoubtedly it is not the only neurotransmitter involved as demonstrated by the wealth of data showing alterations in the noradrenergic and dopaminergic systems, neuropeptides such as oxytocin, in addition to the possible role of the immune system [182 183] and second messengers [184]. It can be hypothesised that the heterogeneous mixture of physiopathological mechanisms is also responsible for the heterogeneity of clinical manifestations, and perhaps, to response to treatment.

The latest discoveries on the pharmacology of SSRIs have shown that these agents, even if they have the same property of inhibiting reuptake of 5-HT, also interact with other receptors and neurotransmitter systems (Fig. 1). Sertraline and citalopram appear to be relatively effective in treating OCD that is resistant to other SSRIs [52 58], but additional studies are needed to explain the different clinical responses and the specificity of SSRIs on target symptoms.

The limits of a serotoninergic model in pharmacotherapy of OCD are also evident when considering augmentation strategies based on occasional observational studies and/or those that cannot be reproduced [79 185]. Non-controlled clinical studies have proposed the use of buspirone, lithium and tryptophan, all with negative results. Considering this, new alternative strategies are needed that are not correlated with the serotoninergic system. The only convincing data available to date are relative to haloperidol, pimozide, risperidone and some psychological techniques, in particular CBT and ERP, while limited information is available on the use of second-generation antipsychotics. RTMS and DBS have the same limits, even if the former warrants further double-blind studies.

Similarly, the potential efficacy of recently proposed high doses of other SSRIs need further study in treatment-resistant OCD (e.g. 120 mg/day citalopram, 60 mg/day escitalopram, 120 mg/day fluoxetine, 450 mg/day fluvoxamine, 100 mg/day paroxetine, 400 mg/day sertraline) [186].

OCD requires long-term pharmacological treatment, and current guidelines recommend at least 2 months of treatment before response can be evaluated. As a consequence, the results from short periods of treatment must be interpreted with caution. In patients that continue drugs for an adequate period to time, it is important to evaluate the type and severity of adverse events in order to improve compliance and therapeutic outcomes. SSRIs, when administered for brief periods, are better tolerated compared to long-term administration of clomipramine, but can be associated with invalidating adverse effects such as sexual dysfunction, and for this reason some investigators have begun to propose the use of clomipramine in treatment resistant cases [187].

In conclusion, while treatment of OCD has made enormous advances in recent years, many problems still must be overcome, and in particular, the most recent scientific discoveries must be integrated with clinical practice with the aim of more personalised management.

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