

# Obsessive–compulsive disorder: a critical review of therapeutic perspectives

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**Objective:** Obsessive–compulsive disorder (OCD) is a chronic disabling disease with profound implications for social functioning. Thirty per cent of all patients with OCD show insufficient improvement with state-of-the-art treatment. Conventional treatment and alternative treatment options for this population were investigated.

**Method:** A selective review of the relevant scientific literature on OCD treatment and treatment resistance was conducted.

**Results:** In addition to serotonin reuptake inhibitors (SRIs) and cognitive-behavioural therapy, alternative monotherapies, SRI augmentation strategies with a variety of drugs and electroconvulsive therapy have shown results in individual cases, but no conclusive evidence has been found in placebo-controlled trials. While studies investigating neurosurgery for refractory OCD show positive results, most of these studies have methodological shortcomings.

**Conclusion:** Novel approaches currently under investigation that have shown promising effects for treatment-resistant OCD include SRI augmentation with atypical antipsychotics and chronic deep brain stimulation, a new surgical technique. Placebo-controlled trials for both treatment options will be needed to confirm preliminary findings.

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## Introduction

Obsessive–compulsive disorder (OCD) is a chronic and severely disabling anxiety disorder with a fluctuating course. Although once thought to be relatively rare, the lifetime prevalence of OCD is, in fact, approximately 2–3% in the general population (1). OCD is characterized by recurrent, intrusive thoughts that evoke discomfort or anxiety, the so-called obsessions. Typical obsessions include fear of contamination, doubt and recurring thoughts with a connotation of violence, sexuality or religion. These obsessions are usually accompanied by repetitive ritualistic, seemingly senseless behaviours aimed at reducing this discomfort and anxiety, the so-called compulsions. Typical compulsions include washing, checking, hoarding, sorting and counting. The symptoms are recognized by the patient as irrational and ego-dystonic and cause severe impairment in the patient's psychosocial functioning. The disorder has a male predominance in childhood, but the sex ratio equalizes with age (2–5). In 50–65% of the patients

onset occurs before the age of 25, with a peak incidence around the age of 20. Over 85% of patients will have developed the illness before the age of 35 (3, 5–7). Studies have found a high degree (50–77%) of comorbidity with other axis I disorders (2, 5), the most common being major depression and other anxiety disorders. Substance abuse, eating disorders, trichotillomania and Tourette's syndrome have also been found to be comorbid disorders in OCD (2, 5, 8).

The OCD was once thought of as relatively treatment-resistant. However, with the recent development of pharmacological and behavioural therapy, the prognosis of patients suffering from this extremely disabling disorder has improved significantly. Nevertheless, despite these major therapeutic advances, about 30% of OCD patients fail to respond to conventional treatment (9).

Aims of the study

Aim of the present review was to provide an update on currently available treatment options, with a

special emphasis on the use of novel approaches in managing treatment-resistant OCD.

### Material and methods

For the literature selection in Medline (1900 to current), the following search terms were used in combination with OCD (2175 hits), behavio(u)ral therapy (122 hits), cognitive therapy (116 hits), pharmacological therapy (one hit), treatment resistant (30 hits), neurosurgery (37 hits), cingulotomy (12 hits), capsulotomy (16 hits), limbic leucotomy (six hits), subcaudate tractotomy (four hits), deep brain stimulation (DBS, 10 hits). Subsequently, bibliographies of papers selected via the first strategy were searched. Controlled studies and meta-analyses in English were included, as well as open studies specifically concerning therapy resistance or novel techniques such as DBS, leaving 122 studies to be used. Preliminary results in the form of abstracts or posters were not included.

### Results

#### Conventional treatment

The treatment options for patients suffering from OCD have significantly advanced over the last decade. Nowadays, conventional treatment can be divided into pharmacological and behavioural therapy. Many authors have suggested that a combined pharmacological and behavioural approach is better than a single approach (10, 11). Therefore, to achieve an optimal treatment response, a combined pharmacological and behavioural approach is often recommended. Treatment for OCD is usually started with either cognitive-behavioural therapy (CBT) alone, especially in mild cases, or with an SSRI combined with CBT, depending upon severity, age and other factors.

#### Pharmacotherapy

Current pharmacological treatment mainly focuses on the efficacy of serotonin reuptake inhibitors (SRIs). Numerous controlled studies have shown the efficacy of clomipramine, the tricyclic antidepressant with the most preferential SRI properties, vs. placebo (12–17), as well as the efficacy of selective serotonin reuptake inhibitors (SSRIs), including fluvoxamine (16, 18, 19), fluoxetine (20–23), paroxetine (15, 24), sertraline (22, 25–28) and, recently, citalopram (8, 29, 30) vs. placebo in the treatment of OCD. Moreover, studies have shown

that agents with little affinity for serotonin receptors, such as desipramine, have little effect (31, 32). However, venlafaxine, a serotonin and noradrenaline reuptake inhibitor (SNRI), was recently shown to be effective in a single-blind (33) as well as in a large double-blind trial, (34) followed by a cross-over study in the non-responders (35). An open, retrospective study suggested that venlafaxine may even be beneficial in treatment-resistant OCD (36).

Current guidelines recommend standard pharmacological treatment consisting of three adequate trials (10–12 weeks at the maximum doses) of different serotonergic agents. The first step is to start a trial with an SSRI. If this proves ineffective, the next step is typically a trial with a different SSRI. The third step is to switch from SSRIs to clomipramine (37).

Although SSRIs are considered to be the drugs of choice in the treatment of OCD, there are no large double-blind randomized controlled studies directly comparing the relative efficacy of the different SSRIs. However, a large meta-analytic study comparing data from multi-centre placebo-controlled trials of sertraline, fluvoxamine, fluoxetine and clomipramine found equal efficacy for all three SSRIs (16). This study also found clomipramine to have a higher efficacy than the SSRIs. Nevertheless, one should bear in mind that, as clomipramine was the first agent to be studied, it was studied in populations new to SRIs. However, SSRIs were studied in populations including patients who had failed to respond to clomipramine. These populations, therefore, included patients more likely to be treatment-resistant, favouring the higher efficacy of clomipramine. However, most direct comparative studies have shown equal efficacy for clomipramine and SSRIs, but with fewer side-effects in the SSRI group (15, 38, 39). Because it is not only an inhibitor of serotonin reuptake but also a blocker of adrenergic and cholinergic receptors, clomipramine is associated with higher rates of anticholinergic and anti-adrenergic side-effects. Moreover, clomipramine could increase seizure incidence at high dosages (9). Another important drawback of clomipramine is the fact that it is cardiotoxic; therefore, caution should be taken when prescribing it for patients with cardiac problems or suicide risks. So although clomipramine might have a higher efficacy, standard treatment is to start with SSRIs because of the more favourable side-effect profile.

All SSRIs show selectivity with respect to serotonin, but they all have a different receptor profile (40). Citalopram is the most selective, and although studies have proved citalopram to be an

effective treatment for OCD orally (8, 29) as well as in infusion, (41) there have, as yet, not been any placebo-controlled double-blind studies directly comparing citalopram with the other SSRIs. One small single-blind study comparing the efficacy of fluvoxamine, paroxetine and citalopram suggested a similar efficacy for all three SSRIs (29). However, a recent study showed citalopram to be effective in patients with treatment-resistant OCD who had not responded to previous trials of clomipramine and SSRIs (40). A direct head-to-head comparison would, therefore, be of great interest (Table 1).

#### Behavioural therapy

Cognitive-behavioural techniques have been proved very effective in the treatment of anxiety disorders (42, 43). Among those, the development of exposure and response prevention (ERP) resulted in the first empirically validated treatment for OCD (44). In practice, it involves exposing the patient to anxiety provoking situations until anxiety levels decrease. At the same time the patient resists performing the rituals he normally uses to decrease the anxiety level. By blocking rituals and thereby the negative reinforcement of the ritual, extinction occurs, but this procedure may bring considerable discomfort to the patient. Approximately 25% of all patients refuse behavioural therapy (45) and the dropout rate is around 20% (46). Therefore sometimes pharmacotherapy is given in addition to ERP.

Various meta-analyses have been conducted to assess the relative efficacy of ERP, pharmacotherapy or a combination of both treatments. Van Balkom et al. (47) found in their meta-analysis behavioural therapy to be more effective than SRIs. In addition, the combination of behavioural therapy and SRIs was found superior to SRIs only. No difference could be demonstrated between the combination of SRIs with behavioural therapy

and behaviour therapy only. These results were found on self-ratings, whereas on assessor-ratings, no differences were found between the treatments. In another meta-analysis, Kobak et al. (48) found no significant differences between ERP, SRIs and combined ERP/SRI treatment, when methodological differences were controlled for. Such meta-analysis has been the subject of criticism as both poorly and well-designed studies are sometimes included in one meta-analysis. Moreover, published studies can be biased towards positive findings.

Studies which have directly compared ERP, pharmacotherapy and a combination of the two are scarce. A study of Hohagen et al. (49) tested the additive effect of combination treatment, consisting of behavioural therapy plus fluvoxamine, against behavioural therapy plus placebo. Both treatment groups showed a highly significant reduction in OCD symptoms as measured by Yale-Brown OCS total score. No significant differences were found between groups concerning compulsions. However, in the group receiving fluvoxamine and behavioural therapy, obsessions were significantly more reduced than in the other group. A study of Hembree et al. (50) investigated the long-term outcome of patients who selected ERP alone, serotonergic drugs alone, or ERP with concomitant antidepressant medication. Their most important findings were as follows. First, serotonergic medications seem to produce long-term benefits equivalent to those of ERP as long as patients stay on the medication. Secondly, patients treated with medication alone tended to have more severe symptoms at follow-up if they were no longer taking medications. In addition, the ERP-plus-medication group had the lowest OCD severity ratings, although not significantly lower than the ERP group. There is also some evidence that combination therapy is superior to behavioural therapy or pharmacotherapy alone in case of comorbid depression (49, 51).

It is difficult to give an overall conclusion on the basis of these studies. However, it could be concluded that the combination of ERP and SRIs is very effective in reducing OCD symptoms, especially when the obsessions play a more prominent role or when patients refuse to participate in an exposure procedure. However, behavioural therapy given by itself has proved very effective as well. Some caveats, which may have influenced the results and which make it difficult to compare the results of the different studies, have to be considered. For instance, ERP is not a homogeneous concept. Abramowitz (52) examined the differences in effectiveness of various types of

Table 1. Pharmacological monotherapy for OCD: double blind, controlled studies

	Dose range (mg)	Effective	Reference
SSRIs			
Fluoxetine	20–80	+	20–23, 38
Fluvoxamine	100–300	+	18, 19, 39
Sertraline	50–200	+	22, 25, 26, 28
Citalopram	20–60	+	8
Paroxetine	20–60	+	15, 24, 34, 35
SNRI			
Venlafaxine	300	+	34, 35
TCA			
Clomipramine	100–300	+(+)	12–15, 38, 39

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant.

ERP. He found that therapist-controlled exposures are significantly more effective than are self-controlled exposures. He also found that behavioural therapies that use total response prevention produce better outcomes than do those that use partial response prevention. In addition, the clinical picture of a particular patient may influence the effectiveness of a therapy and to affect the results more in favour of this therapy. If a patient predominantly suffers from obsessions, the addition of pharmacotherapy may improve treatment outcome, whereas with patients with mainly compulsions, pharmacotherapy adds less to their improvement. Thirdly, some therapists may have also engaged in cognitive therapies during the exposures, which may have affected outcome (53). In addition, (cognitive) behavioural studies share a common shortcoming, namely the absence of a proper placebo condition.

A number of cognitive theorists have proposed that OCD can be treated cognitively. Cognitive therapy can be used to facilitate compliance with ERP and may be of value for patients with mainly obsessions. Although OCD is characterized by several forms of cognitive dysfunction, a relatively small number of studies have addressed the issue of cognitive treatment with obsessive compulsives. In a study of Emmelkamp et al. (54) the effects of rational emotive therapy (RET) were compared with those of self-controlled ERP. On the obsessive-compulsive targets, RET was equally effective as ERP. In another study by Emmelkamp and Beens (55) no difference was also found between RET and ERP. They also addressed the issue whether a combined package would be superior to ERP alone. It was found that the combined treatment was no more effective than ERP alone. Conclusions from these studies must be drawn with caution. The studies had small sample sizes and used early cognitive treatment that may not have addressed the appraisals that are now thought to be relevant to OCD. Van Oppen et al. (56) examined the effects of a version of cognitive therapy based on the model of Salkovskis (57) against those of ERP on obsessive-compulsive targets and on associated psychopathology. The central ideas within the model of Salkovskis are based on general cognitive theory for anxiety disorders with the addition of addressing two potentially biased reasoning styles: overestimation of danger and inflated perception of responsibility. Behavioural experiments were also included. Findings were as follows: the effect sizes on the obsessive-compulsive measures were larger in the cognitive therapy than in the exposure condition. However, cognitive therapy without the beha-

vioural experiments was as effective as ERP. McLean et al. (58) found a mild to moderate superiority of ERP compared with CBT in size of treatment effect. However, the treatments were delivered in group format. This may have favoured the outcome of ERP, as cognitive treatment may lend itself better to individual treatment, because of the complexity of cognitive appraisals. Another important critical point of this study is that approximately half of the patients were already stabilized on psychotropic medications. Because there were relatively more of these patients in the ERP condition, caution in the interpretation of the results is warranted. A direct comparison of cognitive therapy and behavioural therapy alone vs. a sequential combination with fluvoxamine has been made by Van Balkom et al. (59). The sequential combination of fluvoxamine with cognitive therapy or ERP was found not to be superior to either cognitive therapy or ERP alone. This was confirmed by a study of O'Connor et al. (60). CBT alone, CBT with medication and CBT following medication gave statistically equivalent benefits. Therefore, from the preliminary studies there is evidence for the efficacy of CBT for OCD. CBT can produce significant reductions in obsessive and compulsive symptoms (61). Because of the scarcity of well-controlled studies, we cannot draw firm conclusions about the differential effect of CBT over behavioural treatments alone. Clark puts forward that in choosing a certain kind of treatment, one has to consider the severity of symptoms and also the subtype of OCD one is dealing with (61).

The question has been raised as to the statistically significant improvement in OCD symptoms after treatment is also clinically significant (52). Even with treatments that have large effect sizes, it is possible for treated patients to still display OCD symptoms beyond a 'normal' level. To address the issues meta-analytic procedures have been employed to compare symptoms in treated OCD patients with samples from the general population. Abramowitz found that the average patient was functioning, at post-test, at a level more similar to the general population (52). However, they did remain more symptomatic than members of the general population.

In conclusion, many studies have demonstrated the effectiveness of ERP and cognitive techniques, alone or in combination, for OCD. However, it is not expected that treatment will result in complete alleviation of the symptoms. A combination of pharmacotherapy and behavioural therapy has not been shown to be superior to behavioural therapy alone in pure OCD without overt compulsions.

However, in the case of patients with predominantly obsessional ruminations or additional depression, a combined approach does seem to enhance treatment outcome. Moreover, adding behavioural therapy to pharmacological therapy will most likely reduce the degree of relapse after discontinuation. Further, developing a real placebo condition for behavioural therapy would be of great value.

#### Alternative treatment options for refractory OCD

The introduction of SRIs and behavioural therapy has significantly improved the prognosis of patients suffering from OCD. Unfortunately, although pharmacotherapy and/or behavioural therapy seem to benefit a large group of patients, 30% of all patients do not respond adequately to these therapies and are considered treatment-resistant (9). According to the guidelines of the expert consensus group on the treatment of OCD, patients are considered treatment-resistant when they have failed adequate trials of SRIs and behavioural therapy. The criteria for 'adequate' is usually taken to be a minimum of three trials of pharmacotherapy, consisting of two different SSRIs and clomipramine, for at least 10–12 weeks at the maximum doses and behavioural therapy consisting of at least 20 h of exposure with response prevention (37).

One should bear in mind that OCD is one of the most disabling psychiatric disorders. The degree and extent of suffering experienced by OCD patients should not be underestimated. Patients do not only suffer from their symptoms, but OCD also has a profound influence on their psychosocial functioning. A study on the quality of life showed that, compared with the general population, social functioning and instrumental role functioning are impaired in OCD patients and that the more severe the OCD, the greater the impairment in social functioning (62). So although a large group of patients seems to benefit from conventional treatment, other non-conventional treatment options must be considered for those who do not.

For these relatively treatment-resistant patients, second-line pharmacological treatment, including alternative monotherapies and SRI augmentation strategy, electroconvulsive therapy (ECT) or even neurosurgery has been suggested (10, 63–65).

#### SRI augmentation

To date, most augmentation strategies have focused on enhancing the efficacy of the SRIs by administering a variety of other drugs. Anecdo-

tally, some case histories have shown these augmentation strategies to be very beneficial. Other drugs studied include fenfluramine, lithium, tryptophan, buspirone, trazodone, clonazepam and antipsychotics; sometimes different SRIs were combined. Although all of these drugs have appeared to be effective in open studies, there are only a few placebo-controlled trials that corroborate these results (10, 64, 66). Controlled studies with lithium, buspirone and thyroid hormone augmentation to SRI treatment do not support routine use of these strategies in the management of patients with refractory OCD (67–69).

Antipsychotics (i.e. pimozide and haloperidol) have been successfully used as augmentation strategy for patients with a comorbid tic disorder or trichotillomania (70–72). In a double-blind placebo-controlled study (70), haloperidol was given to OCD patients unresponsive to fluvoxamine treatment. The study showed that the additional administration of haloperidol to ongoing fluvoxamine treatment in patients with a comorbid tic disorder appeared to be significantly more effective than placebo in reducing the severity of OCS. However, in patients without a comorbid tic disorder, haloperidol addition appeared to be of little benefit (70). While the additional administration of antipsychotics to ongoing SRI treatment may prove beneficial for some OCD patients, the risks associated with chronic neuroleptic treatment, especially tardive dyskinesia, should not be ignored. The recently developed atypical neuroleptics (i.e. clozapine, olanzapine and risperidone) cause fewer severe extrapyramidal side-effects; because of this favourable side-effect profile, they have been of special interest. A number of open trials and case histories have reported the relative efficacy of risperidone addition to ongoing SRI treatment for patients with SRI-resistant OCD (73–78). Two recent placebo-controlled double-blind studies (79, 80) showed that the additional administration of risperidone to ongoing SRI treatment appeared to be significantly more effective than placebo in reducing the severity of OCD and symptoms of depression and anxiety. One study also found risperidone addition, in contrast with haloperidol addition, to be effective in patients with, as well as without, comorbid tic disorder (79). Because its serotonergic and dopaminergic receptor-binding profile is similar to that of risperidone, olanzapine has also been proposed as an augmentation (81). Some open trials have described the relative efficacy of additional olanzapine administration to ongoing SRI treatment (81–83). These results have recently been confirmed in two double-blind placebo-controlled trials (84, 85).

Three open, uncontrolled studies (86–88) and one single-blind placebo-controlled study (89) all suggest the novel antipsychotic quetiapine to be effective as augmentation to SRI therapy. Recently, these results were confirmed in a double-blind, controlled study (90). Further controlled trials are recommended to compare the relative efficacy between the atypical antipsychotics.

Inositol, a metabolic precursor in the phosphatidyl-inositol cycle, appeared, in a double-blind placebo-controlled crossover trial, to be effective as treatment for OCD (91). On the basis of these beneficial results, the addition of inositol to ongoing SRI treatment was investigated in a small open trial (92). Unfortunately, inositol addition appeared not to be effective in the majority of patients (Table 2).

Alternative monotherapies

Alternative monotherapy should be considered when patients have failed to respond to both conventional treatment and augmentation strategies. Open cases and placebo-controlled double-blind studies have suggested that monoamine oxidase inhibitors and clonazepam could be effective as anti-obsessional monotherapies (63, 80).

Although clozapine augmentation in patients suffering from treatment-resistant OCD has insufficiently been documented, there have been studies of clozapine monotherapy in OCD patients. In an open trial, clozapine failed to appear effective as an anti-obsessional monotherapy (93).

Venlafaxine, an SNRI, acts in a manner similar to that of clomipramine but with a more favourable side-effect profile (94, 95). Consequently, it has been postulated as an effective treatment for patients suffering from OCD. Several case reports have suggested that venlafaxine could be a beneficial anti-obsessional monotherapy (94–97), but there have been no placebo-controlled double-blind studies to corroborate these findings. However, there has reportedly been a small

placebo-controlled trial in which 30 patients were treated with 225 mg/day venlafaxine ( $n = 16$ ) or placebo ( $n = 14$ ) for 8 weeks (98). In this study, venlafaxine did not appear to be more effective than placebo. Both the dosage of venlafaxine and the duration of the trial were probably insufficient. An adequate trial should last at least 12 weeks, and it has been pointed out that venlafaxine, as treatment for OCD, should be given in a higher dosage (300–375 mg/day) in order to enable comparison with agents with established efficacy (96).

Two placebo-controlled trials and one open trial suggest that rapid pulse loading of intravenous clomipramine produces a large and rapid decrease in OCS in clients who do not respond to, or who have an intolerance for, oral therapy. With intravenous clomipramine treatment, patients who are refractory to treatment and those who have had no prior exposure to effective treatments clinically improve more than patients with oral clomipramine treatment (99–102). An open trial with intravenous citalopram also suggests a more rapid and effective treatment for treatment-resistant OCD (103).

It has been suggested that the lack of improvement in SRI-refractory OCD patients reflects a neurobiological heterogeneity. Perhaps alterations in 5-hydroxytryptamine neurotransmission in these patients are different from those in responders, or their OCD symptoms may result from deficiencies in other neurotransmitter systems (66). Future pharmaceutical trials should therefore be grounded in knowledge of subtype of OCD and, as far as possible, in an understanding of its neurobiology.

Electroconvulsive therapy

Literature on ECT often does not mention ECT as a treatment modality for OCD (104). However, a few case studies and retrospective studies have been published that report the beneficial use of ECT in OCD (63, 104–106). No controlled studies are available. The APA task force on ECT stated that, unless severe depression is prominent, ECT is not an effective treatment option for patients suffering from OCD (107).

Neurosurgery

It has been estimated that even with all the currently available pharmacological and behavioural treatment options, a minority of OCD patients continue to have severe incapacitating symptoms and are extremely disabled. For these patients neurosurgery has proved to be an option (108).

Table 2. Pharmacological augmentation strategies for OCD: double blind, controlled studies

	Dose range (mg)	Effective	Reference
Haloperidol (+fluvoxamine)	5–10	+*	70
Risperidone (+various SRIs)	1–3	+	79, 80
Olanzapine (+various SRIs)	5–20	+	84, 85
Quetiapine (+various SRIs)	300	+	90
Bupirone (+fluoxetine)	60	–	69
Lithium (+fluvoxamine)	600–1200	–	68
Thyroid hormone (+clomipramine)	25 µg	–	67

\*Only significant improvement in patients with comorbid tic disorder.

The surgical procedures most often used for treating treatment-resistant OCD are capsulotomy, cingulotomy, limbic leucotomy and subcaudate tractotomy. Most of the studies report no adverse effects on personality and cognitive functioning, and somatic side-effects are reported to be rare and easily treatable (109, 110). Nevertheless, one must bear in mind that adverse effects do occur. General risks associated with intracranial surgery include vascular events, confusional states and postoperative epilepsy. Neurosurgery specific for OCD further carries the risk of personality changes or neuropsychological deficits (111). Unfortunately, however, most studies do not include systematic evaluation of personality or cognitive functioning using well-validated psychometric instruments. These surgical procedures are carried out in many countries around the world, and it is conceivable that a considerable proportion of side-effects is never reported in the scientific literature. Underestimation is, therefore, likely. These and other considerations have led to debate on the status of neurosurgery for mental disorders, as is illustrated by a recent example (112).

The relative efficacy of the procedures has been reported to be between 50 and 67% (110). However, many of the studies appear to have several methodological shortcomings, such as a short duration of follow-up, rater bias, the use of outcome measures with poorly proven validity and reliability and the fact that most of them are retrospective. Furthermore, some of the early studies do not take into account the possibility of the existence of an Axis II obsessive–compulsive personality disorder (OCPD). When interviewing someone relying just on diagnostic criteria, one should be aware of the distinction between OCPD and OCD. Moreover, many of the current pharmacological and behavioural treatment options were not available at that time. Patients who today would not be considered treatment-resistant could have been included, thus favouring the efficacy of neurosurgery. A prospective long-term follow-up study ( $n = 18$ ) tried to avoid most of these methodological shortcomings and only included OCD patients who were considered treatment-resistant by today's standards (113). The study indicated that between 25 and 30% of treatment-resistant OCD patients still improved significantly after cingulotomy. This percentage of improvement is consistent with a recent long-term follow-up study ( $n = 44$ , including the 18 patients from the previous study) that reported that 32% were significantly improved after cingulotomy (114). Similar percentages are reported in another recent study involving cingulotomy (115). However, it has

to be mentioned that for the definition of therapy resistance this study required only 15 sessions of behavioural therapy (in addition to three failed trials with different SRIs).

Many authors have pointed out that another important drawback of these types of surgery is the inability to perform sham operations (e.g. the absence of control groups) due to ethical objections (65, 109, 110, 116). However, the introduction of the gamma knife reduced these ethical objections, making sham operations possible (65). To date, however, no placebo-controlled double-blind studies demonstrating the efficacy and safety of neurosurgery by means of the gamma knife in OCD have been published.

Chronic DBS, a new surgical technique, is currently successfully used to treat patients with Parkinson's disease. It is hypothesized that DBS simulates the effects of a lesion through electrical stimulation by an implanted electrode connected to a pacemaker (117). The main advantage of DBS over the previously described surgical techniques (lesioning) is the fact that there is no need to make a destructive brain lesion. The procedure is completely reversible, making placebo-controlled studies possible with this type of surgery (at least in theory), as the electrodes can easily be switched on or off. Moreover, side-effects caused by the stimulation can be controlled by reducing, altering or stopping the stimulation; as the stimulation is adaptable, stimulation parameters can be adjusted to achieve maximal efficacy (117, 118). However, some risk of surgical complications in the form of infection or bleeding will always be present in this kind of procedure as well.

A study of the effects of DBS of the subthalamic nucleus in patients suffering from Parkinson's disease showed improvement in obsessive–compulsive traits similar to those observed after pallidotomy (119). At the same time, a recent pilot study showed that DBS in the anterior limb of the internal capsule appears to have a beneficial effect in OCD (120). Long-term follow-up in three of these cases including careful psychopathological, neuropsychological and personality assessment revealed that initial improvement persisted in two patients. The third patient had not experienced any improvement following DBS. The patient elected to undergo bilateral capsulotomy, following removal of the electrodes (121). In another, mainly methodological, report on DBS some pilot data are mentioned on three patients, suggesting that the nucleus accumbens should perhaps also be considered as target in DBS for OCD (122).

These preliminary results suggest that DBS could prove to be a useful treatment for treatment-

resistant OCD. Furthermore, because of its reversibility and adjustability, DBS could prove to be a far safer and more effective surgical procedure for treating OCD. Therefore, placebo-controlled double-blind studies demonstrating the efficacy and safety and comparing the efficacy between DBS and lesion surgery, as well as between different targets, are recommended. Finally, DBS, in combination with the currently available functional imaging techniques (positron emission tomography, functional magnetic resonance imaging), provides an excellent opportunity to study the pathophysiological mechanisms involved in OCD, eventually leading to a better understanding and treatment of this disabling disorder.

### Discussion

As most of the discussion is interwoven with the presentation of the search results, we will suffice here with some general points. OCD is a common, chronic and severely disabling anxiety disorder. Numerous controlled studies have proved the efficacy of SRIs and ERP in the treatment of this disease. However, 30% of patients treated according to the current protocols are considered treatment-resistant and have severe disabling symptoms with great impairment in social functioning. Alternative monotherapies, SRI augmentation strategies with a variety of drugs and ECT have shown results in individual cases, but no conclusive evidence has been found in placebo-controlled trials. Studies investigating neurosurgery for refractory OCD have shown positive results; however, most of these studies have methodological shortcomings. Novel approaches currently under investigation that have shown promising effects in a limited number of controlled studies for treatment-resistant OCD include SRI augmentation with atypical neuroleptics, intravenous clomipramine and chronic DBS, a new surgical technique. Placebo-controlled trials for these treatment options will be needed to confirm preliminary findings.

In conclusion, novel approaches currently under investigation show promising effects for treatment-resistant OCD. These include SRI augmentation with atypical antipsychotics but also chronic DBS, a new surgical technique. However, placebo-controlled trials for both treatment options will be needed to confirm preliminary findings.

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