Treatment-Resistant OCD

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***Abstract*—OCD can keep difficult to treat. This paper focuses on pharmacological and psychotherapeutic approaches used in clinical practice. Medication should generally be combined with psychotherapy. In some cases, augmentation therapies with two, or rarely more, different drugs may be necessary. Positive effects can in individual cases take a long time, which needs to be discussed with the patient.**

The first step in the pharmacological treatment of OCD is to determine whether psychotherapy alone is sufficient.

If psychotherapy alone is not sufficient, an SSRI may be used, if there are no contraindication to using one. Paroxetine has traditionally been the first choice.

If the SSRI does not work or not sufficiently enough, an increase of the dose may be necessary. It can take a while to see an effect.

The switch to another SSRI can be considered after about 3 to 6 months on one SSRI.

If an SSRI alone does not work, augmentation with an atypical neuroleptic (second generation antipsychotic) in a moderate dose can be tried, as long as there are no contraindications and the patient is fully informed.

***Index Terms*—obsessive-compulsive disorder, OCD, treatment resistance, treatment**

I. Introduction

OCD in many cases responds to a combination of psychotherapy and medication. However, in about a third of the cases it does not. Up to 40% of patients who present to psychiatrists fail to respond adequately to either cognitive behavior therapy, drugs, or a combination of the two. Careful reassessment with detection and treatment of related problems may improve outcomes.

According to the NICE guidance, cognitive behavior therapy is recommended as the first line treatment for children and adolescents, because of the assumption that it has fewer risks than SSRIs. [1] However, there is some controversy around, which mode of psychotherapeutic treatment is most effective. [2] In clinical practice, the psychodynamic and the CBT treatments seem to be both effective.

Psychotherapy or pharmacotherapy can be offered first. The best psychotherapeutic approach seems to be a combination of psychodynamic and cognitive behavioral therapy. Uncertainty remains as to whether a combination of psychotherapy and drug therapy is superior to psychological or drug monotherapy.

Some studies suggest that addition of drugs increases the efficacy of cognitive behavior therapy, whereas others show no additional benefit. Psychotherapy, either alone or in combination with drug treatment, might help to prolong remission and prevent relapse on discontinuation of the drug.

II. Pharmacological Approaches

A. Selective Serotonin Reuptake Inhibitor (SSRI)

Obsessive-compulsive disorder responds specifically to drugs that inhibit the synaptic reuptake of serotonin— that is, the tricyclic antidepressant clomipramine and the more highly selective serotonin reuptake inhibitors (SSRIs). They have provided the mainstay of OCD medication management for decades.

Higher doses of SSRIs than those used for depression may be needed to effectively treat obsessive-compulsive disorder. SSRIs have largely superseded clomipramine for treating obsessive-compulsive disorder because of their lesser toxicity in overdose, more favorable side effect profile and apparently higher effectiveness. This is especially important for children, in whom cardiac toxicity may be a risk.

The therapeutic response to drug treatment in obsessive-compulsive disorder increases gradually over weeks and months. Often patients need to be told this in advance. Studies suggest that even at six months, there can still be an additional positive effect.

Patients also need to be told that side effects such as nausea and agitation often appear before the positive effect is felt. Especially in anxious patients, higher side effects in the beginning can mean better effectiveness in the long-run. Escitalopram may be better tolerated than sertraline and paroxetine, for example, while paroxetine is often the first choice among clinicians.

A trial of at least 12 weeks at the maximum tolerated dose is advisable before effectiveness is judged. Several studies have shown that people with obsessive-compulsive disorder continue to benefit from long term drug treatment and that a large number relapse if the drug is discontinued or switched to placebo under trial conditions.

Possibly, patients with greater comorbidity are at most risk of relapse. For at least some cases, therefore, treatment may need to be continued indefinitely.

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B. Switching SSRIs

Some evidence exists to support various drug strategies in resistant cases, including increasing the dose of the SSRI to the maximum tolerated dose and switching to an alternative, as response may be idiosyncratic. It is not really understood why one SSRI does not work, while the other does.

SSRIs and clomipramine have been combined. However, this works on similar pathways and could also increase the risk for the rare, but potentially fatal serotonin syndrome.

Often, paroxetine is used as first-line SSRI, and there are a number of studies that demonstrate the effectiveness of paroxetine in OCD. Even though biologically all SSRIs have a very similar mechanism, switching the antidepressant can help. Why this can lead to better outcomes in the individual patient is not well understood.

C. Atypical Antipsychotics as Augmentation

As many as half of obsessive-compulsive disorder (OCD) patients treated with an adequate trial of SSRIs fail to fully respond to treatment and continue to exhibit significant symptoms. Many studies have assessed the effectiveness of antipsychotic augmentation in SRI-refractory OCD. [4] Combined dopamine/serotonergic agents such as atypical antipsychotics are still the main OCD-augmenting strategies proven effective via randomized controlled trials.

Evidence from children and adults shows that adding first generation and second generation antipsychotics to SSRIs can increase the effectiveness of the SSRI, particularly if there are comorbid tics. Mostly, second generation antipsychotics are used in lower doses, such as 5-10 mg olanzapine. A combination of risperidone and SSRI has shown to decrease the scores on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) by at least 25%. [3]

In a systematic review on the efficacy of antipsychotic augmentation in treatment-refractory OCD, double-blind, randomized control trials involving the adult population up to and including 2000 were evaluated. The meta-analysis of these studies demonstrated a significant absolute risk difference (ARD) in favor of antipsychotic augmentation of 0.22 (95% confidence interval (CI): 0.13, 0.31). The subgroup of OCD patients with comorbid tics have a particularly beneficial response to this intervention, ARD=0.43 (95% CI: 0.19, 0.68). There was also evidence suggesting OCD patients should be treated with at least 3 months of maximal-tolerated therapy of a serotonin reuptake inhibitor (SRI) before initiating antipsychotic augmentation owing to the high rate of treatment response to continued SRI monotherapy (25.6%). Antipsychotic augmentation in SRI-refractory OCD is indicated in patients who have been treated for at least 3 months of maximal-tolerated therapy of an SRI. Unfortunately, only one-third of treatment-refractory OCD patients showed a meaningful treatment response to antipsychotic augmentation. Patients with comorbid tics are likely to have a differential benefit to antipsychotic augmentation. [4] At the time of the study, there was only sufficient evidence in the published literature for the efficacy of haloperidol and risperidone.

Olanzapine

Since olanzapine and risperidone have similar serotonergic and dopaminergic receptor binding profiles, another study tested the hypothesis that olanzapine augmentation would be beneficial in treatment-unresponsive OCD. For this 8-week trial, 10 adult OCD patients were recruited unresponsive to fluoxetine of at least 60 mg/day for at least 10 weeks, which was continued throughout the trial. Subjects had OCD for at least one year, a Y-BOCS score of at least 18, and no organic, psychotic, or other primary Axis I disorder. Two weeks after olanzapine, 2.5 mg/day, was added, and in the absence of responder status (Y-BOCS score decrease at least 25%) and limiting side effects, the dose was increased to 5 mg/day, and after 2 more weeks, to 10 mg/day for 4 weeks. The subjects had failed a mean of 3.3 SRI trials and had a mean baseline Y-BOCS score of 29.0 +/- 4.9 (1 SD). Nine patients completed the trial. The subjects' mean endpoint Y-BOCS score was 24.4 +/- 8.0 (a 16% decrease). The 3 responders' Y-BOCS scores dropped 68%, 30%, and 29%, but only 1 patient was rated "much improved." He maintained this improvement during a 6-month follow-up period taking olanzapine, 5 mg/day. Improvement in OCD was independent of improvement in mood symptoms. Six patients (60%) experienced significant weight gain. Double-blind, placebo-controlled trials were also warranted in this case, along with trials comparing risperidone and olanzapine augmentation. [5]

Aripiprazole

In a 2009 open-label, flexible-dose trial of aripiprazole addition to SRIs, patients with treatment-resistant OCD were monitored for 12 weeks. Aripiprazole was started at 5 mg/day and increased up to a maximum of 20 mg/day. Twelve patients fulfilled entry criteria; nine patients took at least one dose of study medication and eight of them completed the study he most common adverse event reported was inner unrest reported by four (44.4%) patients. The study supported the notion that adding aripiprazole to SRIs could be a valid strategy for treatment-resistant OCD patients, but asked for further double-blind studies. [6]

Quetiapine

The effectiveness of quetiapine was demonstrated in a 2005 randomized controlled treatment study. [8] However, more studies are warranted here as well.

D. Glutamatergic NMDA Receptor Antagonists

Evidence from genetic, behavioral, and neuroimaging studies have indicated glutamatergic alteration in OCD. In pediatric OCD patients, the glutamate caudate concentration was abnormally increased, but it decreased after paroxetine treatment.

Memantine

Memantine has shown to improve memory by improving the glutamatergic homeostasis in laboratory conditions. Despite increasing evidence for a pathogenic role of glutamate in OCD,

the first controlled trial of glutamatergic augmenting agents has been reported in 2010.

In the 2010 study of 22 cases of memantine augmentation, the mean (SD) Yale-Brown Obsessive Compulsive Scale score decreases were 7.2 (6.4) among the cases and 4.6 (5.9) among the matched controls, reflecting mean clinical improvement among the cases (27.0% decrease) but not the controls (16.5% decrease). Mean (SD) depression severity score decreases were 5.8 (9.5) among the cases and 4.7 (9.9) among the controls. Initial intrusive obsessions were significantly more severe among marked responders compared with limited response or nonresponse cases (4.4 vs 2.9; t = 2.15; P = 0.048). The study thus provided preliminary supportive evidence for the effectiveness of memantine as a glutamatergic augmenting agent in severe OCD. [12] Future randomized double-blind placebo-controlled trials are warranted.

Topiramate

A 2011 double-blind, placebo-controlled trial of topiramate augmentation for treatment-resistant OCD suggested that topiramate may be beneficial for compulsions, but not obsessions. Modifications in glutamatergic function may be responsible, at least in part, for the improved response in compulsions seen with topiramate. [13]

III. Other Biological Approaches

There are several approaches that are not used routinely, but which can help in some cases.

A. Deep Brain Stimulation of the Nucleus Accumbens

Deep Brain Stimulation (DBS) of the unilateral right nucleus accumbens showed positive results in patients with treatment-resistant OCD. [6] Five out of ten patients reached at least a partial response after the first year. The mean Y-BOCS scores decreased significantly from 32.2 (±4.0) at baseline to 25.4 (±6.7) after 12 months ($p = 0.012$). Five out of ten patients showed a decrease of more than 25%, indicating at least a partial response. One patient showed a decrease in Y-BOCS severity greater than 35%. Similarly, depression, global functioning and quality of life improved within one year. In contrast, anxiety, global symptom severity and cognitive function showed no significant changes. In general, DBS was reported to be well-tolerated.

IV. Psychotherapy

On the available evidence, for children, adolescents, and adults, psychological and drug treatments seem to be equally effective. According to the NICE guidance, cognitive behavior therapy is recommended as the first line treatment for children and adolescents, because of the assumption that it has fewer risks than SSRIs. For adults, cognitive behavior therapy or pharmacotherapy can be offered first. [1]

Uncertainty remains as to whether the two forms of treatment combined are superior to psychological or drug monotherapy. Several studies in adults have looked at this, and some suggest that addition of drugs increases the efficacy of cognitive behavior therapy, whereas others show no additional benefit. Cognitive behavior therapy, either alone or in combination with drug treatment, might help to prolong remission and prevent relapse on discontinuation of the drug, but this remains to be tested in long term studies.

A. Psychodynamic Psychotherapy

More recent psychodynamic theories of OCD, such as the object–relational model, focus on the role of ambivalent mental representations or cognitive–affective schemas of self and others. This notion of mental representations or schemas links psychodynamic formulations to cognitive–behavioral approaches of OCD.

An alternative is to use short-term psychodynamic therapy. These tend to be more direct and action orientated and therefore reduce the OCD patients' tendency to 'think too much'.

Moreover, there is increasing overlap between psychodynamic and cognitive–behavioral models concerning the core dynamics involved in OCD. Exposure to feared situations or thoughts, and the prevention of rituals, whether physical or mental, may be necessary to maximize the treatment response also in psychodynamic treatment.

Psychodynamic psychotherapy for OCD has shown to be effective in several studies.

B. CBT

In the behavioral component of CBT, he patient generates a hierarchy of feared situations and then practices facing the fear (exposure), while monitoring the anxiety and experiencing that it lessens without the need to carry out a ritual (response prevention). Engaging the person by helping them to design a graded program of exposure and response prevention, and working collaboratively on easiest challenges first, is essential. Careful education about mechanisms of anxiety, understanding that repeated exposure leads to reduced anxiety, as well as reduction in obsessions, is important for success. The cognitive model of obsessive-compulsive disorder emphasizes remedying faulty reasoning that may have developed with the disorder. Cognitive approaches encourage patients to re-evaluate overvalued beliefs about risk or personal responsibility, to regain a more realistic perspective, and to carry out "behavioral experiments" to test the validity of their

beliefs. Whether the addition of cognitive techniques significantly improves the efficacy of exposure and response prevention is as yet unclear.

NICE reviewed 17 trials in adults and concluded that cognitive behavior therapy was an efficacious treatment for obsessive-compulsive disorder. [1] In both adults and children, the specific psychological technique most strongly associated with good outcome in studies of cognitive behavior therapy is exposure and response prevention, which has response rates of up to 85% in patients who complete the therapy. [10]

One study examined 49 in-patients with obsessive-compulsive disorder who were treated over three years. The patients had failed to respond to previous treatment. Treatment consisted of in-patient exposure, occasionally combined with other interventions individually tailored to the patient's specific difficulties. This resulted in significant clinical improvements and an average 40% reduction in rituals in 31 (63.3%) of these chronic patients. These gains were maintained at an average 19-month follow-up. Checking rituals were more likely to be associated with good outcome. Women had a later onset of the disorder and a slight tendency to better prognosis. No other predictors of outcome were found. [10]

V. Conclusion

There are several approaches that can be used in treating OCD. Many studies have shown that a combination of medication and psychotherapy is the best route.

The first step in the pharmacological treatment of OCD is to determine whether psychotherapy alone is sufficient.

If psychotherapy alone is not sufficient, an SSRI may be used, if there are no contraindication to using one. Paroxetine has traditionally been the first choice.

If the SSRI does not work or not sufficiently enough, an increase of the dose may be necessary. It can take a while to see an effect.

The switch to another SSRI can be considered after about 3 to 6 months on one SSRI. There is little scientific rational why this works, but in many cases trying out two or three SSRIs may be necessary.

If an SSRI alone does not work, augmentation with an atypical neuroleptic (second generation antipsychotic) in a moderate dose can be tried, if there are no contraindications and the patient is fully informed. Olanzapine, risperidone and quetiapine have shown their effectiveness in individual cases. However, the potential side effects are generally greater than with using an SSRI alone. Also, a possible QT prolongation, weight gain and blood glucose changes (especially olanzapine), symptoms of a serotonin syndrome (especially olanzapine and risperidone) and other parameters should be monitored.

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