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Optimizing first line treatments for adults with OCD

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ABSTRACT

OCD is characterized by obsessions (recurrent, intrusive, unwanted thoughts, images or impulses and compulsions (repetitive behaviors or mental acts that the individual feels compelled to perform), which can manifest together or separately (Fineberg et al., 2020). NICE guidelines suggest that low intensity psychological treatments (including ERP) is the first line treatment for OCD, and that a "stepped care" treatment approach for OCD reserves combination treatment for adults with OCD with severe functional impairment, and for adults without an adequate response to: 1) treatment with an SSRI alone (12 weeks duration) or 2) CBT (including ERP) alone (NICE, 2005). Existing US treatment guidelines (APA guidelines) suggest that there are three first-line treatments for OCD (SSRI, CBT, SSRI+CBT) and recommends combined treatment for patients with an unsatisfactory response to monotherapy or for patients with severe OCD. Although, systematic review and meta-analysis of studies published in 1993–2014 suggest that combination treatment was not significantly better than CBT plus placebo (Ost et al., 2015), based on data from a recent systematic and meta-analysis which searched the two controlled trials registers maintained by the Cochrane Collaboration Common Mental Disorders group, the combination treatment approach is likely to be more effective than psychotherapeutic interventions alone, at least in severe obsessive-compulsive disorder (Skapinakis et al., 2016a). Based on data from Optimal treatment for OCD study conducted by Fineberg et al., (2018) combined treatment appeared to be the most effective especially when compared to CBT monotherapy, but SSRI monotherapy was found as the most cost effective. In this review we summarize available treatment recommendations.

1. Considerations for using the combined therapy for the treatment of OCD

OCD is characterized by obsessions (recurrent, intrusive, unwanted thoughts, images or impulses) and compulsions (repetitive behaviors or mental acts that the individual feels compelled to perform), which can manifest together or separately [1].

According to *the National Institute for Health and Care Excellence (NICE) CG31 guidelines* for the treatment of OCD in adults, a "stepped care" approach for treatment of different patient groups is recommended and therefore patients with mild functional impairment should be directed towards low-intensity CBT/ERP (Cognitive behavioral therapy/ Exposure and response prevention, <10 h of therapist input for patient) [2]. If ineffective, more intensive cycles of SSRI (serotonin-reuptake inhibitor) or CBT (more than 10 h) are considered comparably effective [2]. Adults with OCD with moderate functional impairment should have the opportunity to choose between an intensive SSRI or CBT cycle [2]. If functional impairment is severe, combined treatment with a SSRI and CBT/ERP is recommended [2]. Overall, NICE guidelines recommend combination treatment for adults with OCD with severe functional impairment and for adults without an adequate response to treatment with an SSRI alone (within 12 weeks) or CBT (including ERP) alone (more than 10 therapist hours per patient) [2]. NICE guidelines also suggest that patients with OCD starting treatment with SSRIs should be informed about the delay in onset of therapeutic response (up to 12 weeks). Further challenges include the time course of treatment, the possible side effects and the need to take the medication as prescribed, which might be challenging and might result in a switch to a different SSRI or clomipramine and/or use of antipsychotic medication augmentation treatment approach, in case of not adequate response to

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the initial 12 weeks of the combined treatment. NICE guidelines specify that more research has to be conducted as to effect of treatment for combination versus single-strand treatments and involve a follow-up of 1, 2 and 5 years [2].

Per American Psychiatric Association (APA) guidelines, an SSRI alone may also be considered in patients who have severe OCD or are not otherwise able to cooperate with the demands of CBT [3]. A short duration of SSRI therapy could induce a bias due to slower response to treatment in some patients [7].Therefore, APA guidelines recommend a period of at least 8–12 weeks of SSRI treatment (with at least 4–6 weeks at the maximum tolerable dose) before considering a change in drug strategy. A SSRI alone may also be necessary if CBT is not accessible or available [3]. Combined SSRI and CBT treatment can be provided when the patient has a co-occurring disorder, which is SSRI responsive or has a partial response to monotherapy [3]. Per APA guidelines, recommendation to start with CBT, an SSRI, or combined treatment will depend on: nature and severity of the patient's symptoms, nature of any co-occurring psychiatric and medical conditions and their treatments, the availability of CBT, the patient's past treatment history, current medications, and preferences [3]. These guidelines also emphasize that because treatment studies have been of 3–4 months' duration, only limited data is available to guide long term treatment decisions. APA guidelines further clarify, that combined treatment can be superior to monotherapy in some patients suffering from OCD (for example, with co-occurring depression or other disorders, which are responsive to SSRI treatment), but that it is not necessary for all patients suffering from OCD [3]. APA guidelines further state that more studies are needed to determine optimal methods to achieve the fastest onset of therapeutic action, the greatest degree of response, and the least likelihood of relapse during active treatment and following treatment discontinuation.

Indian Psychiatry Society Practice guidelines for OCD recommend all three (SSRI, CBT, and their combination) as first-line therapies in all types of patients although CBT + SSRI is preferred over monotherapies for severe OCD [8]. In the Indian context however, SSRIs are first-line treatments preferred over CBT because of feasibility, affordability, and limited number of trained therapists. CBT may be considered if SSRIs alone are not beneficial [8].

The question remains open whether combination treatment is better for treatment response or remission. Another challenge is the fact that not everyone has access to adequate combination treatment services, which include care provided by multidisciplinary teams with specific expertise in OCD and some aspects of add-on therapy such as combining antidepressants or conducting antipsychotic augmentation should not be applied in primary care setting [2]. It is important also to highlight that not every patient has access to CBT or ERP therapy, which imposes limitations on CBT alone or combined treatment approach.

It is important to highlight that ERP therapy could have some practical limitations for patients as to locating a suitably trained psychologist and covering treatment associated costs [9,10]. We also would like to highlight that despite body of literature supporting the efficacy of ERP therapy, research has shown that therapists believe that clients could drop out or decompensate during difficult exposure tasks [11]. Overall, current findings indicate that ERP therapy may have treatment dropout rates similar to other treatments for OCD [11].

In a recent meta-analysis conducted by Reid and al., researchers looked at duration of CBT trials in minutes of therapy time under randomized controlled conditions and found a lot of variation between duration of treatment. It can be derived from this meta-analysis, that an average duration of ERP treatment in minutes is 1121 mins ($n = 26$), which is equal to approximately to 18.7 h of therapy [12]. Comprehensive meta-analyses, such as that recently conducted by Skapinakis et al. [5,13], conclude that most CBT studies are of short duration, and thus results of treatment longer than 16 weeks are not known.

Based on data from Optimal treatment for OCD study conducted by Fineberg et al. [6], conducted in 49 adults with OCD receiving treatment for 52 weeks, combined treatment was found to be the most clinically effective option, especially over CBT (d = 0.39) but the advantages over SSRI monotherapy were not sustained beyond 16 weeks and it is SSRI monotherapy that appeared to be the most cost-effective. Therefore, larger definitive studies are warranted [6].

Systematic review and meta-analysis of studies published in 1993–2014 by Ost and al. suggested that CBT alone was not inferior to CBT combined with pharmacological treatment (−0.25), and that combination of CBT and medication was not significantly better than CBT plus placebo (0.25) . However, the authors pointed out that "the RCTs have a number of methodological problems" and made recommendations for improving the methodological rigor in future studies. In a recent published a meta-analysis [12] of CBT trials which included thirty-six studies, involving 2020 patients, CBT was not found to be superior to other active psychological treatments (g = −0.05: 95% CI −0.27) or adequate doses of pharmacotherapy (g = 0.32: 95% CI −0.00 to 0.64). This analysis also looked at researcher allegiance and demonstrated that efficacy was strongly linked to researcher allegiance. This could indicate that CBT is more efficacious in centers with special expertise in CBT however, more studies are needed to gain clarity about this [12].

A growing body of literature supports symptom improvement following combined OCD treatment with selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral approaches [5,7,14]. Based on data from a recent systematic and meta-analysis by Skapinakis et al. including data from 54 clinical trials data from the two controlled trials registers maintained by the Cochrane Collaboration Common Mental Disorders group, the combination treatment approach is likely to be more effective than psychotherapeutic interventions alone, at least in severe obsessive-compulsive disorder [5]. Skapinakis and al. concluded that most psychotherapeutic trials can be considered variants of combination trials (since most patients were taking stable doses of antidepressant medications), and that a combination of SSRIs or clomipramine with psychotherapy is likely to offer more benefit to patients with severe illness than is monotherapy, but more research and cost-effectiveness analysis data are warranted [5,13]. This finding and the fact that many CBT trials include wait list rather than an active control indicates pressing need for more rigorously controlled 'pure' CBT trials. It is important to highlight that among patients who use theoretically appropriate treatment, 40–60% of patients suffering from OCD still exhibit residual symptoms and this justifies a need for new innovative pharmacological treatments, using augmentation strategies and applying new physical treatment techniques [15,16].

2. Evidence-based recommendations for the treatment of OCD

Following recommendations are available for:

1) *Childhood and adolescence.* The American Academy of Child and Adolescent Psychiatry practice parameter (2012) suggests that OCD in youth oftentimes has psychopathological comorbidities [17]. Assessment and management of specific comorbidities, including tic disorders, anxiety and depressive disorders, disruptive disorders, eating disorders, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and schizophrenia are pivotal for an effective treatment approach [1]. The Pediatric OCD Treatment Study (POTS I, 2004) conducted in 112 patients aged 7 through 17 years old at the 3 academic centers in the US for a duration of 12 weeks studied the efficacy of combined therapy relative to CBT alone, and concluded that combined treatment was superior to CBT and sertraline alone (Cohen's d = 1.40 vs. 0.97 and 0.67) [18]. Findings from the POTS II study, conducted in 124 patients aged 7 through 17 years old at 3 academic centers in the US highlighted superiority of medication management plus CBT with experienced providers compared to medication management alone or augmentation of medication management with the addition of instructions in

CBT by the psychiatrist [19]. Practice guidelines also suggest that CBT is the first line treatment for mild to moderate cases of OCD in children and recommend the combination (CBT and SSRI) treatment for patients with moderate to severe OCD [17,20].

2) *Adulthood* and the *elderly*. In treating OCD in adults, the same approaches as described above apply. Some current evidence continues to recommend the use of selective serotonin reuptake inhibitors as the first-line pharmacologic interventions for OCD [15]. Based on a recent meta-analysis (including 25 RCTs of CBT and 9 RCTs of SSRI), response rates of CBT (70%) and combination therapy (66%) were significantly higher than SSRI (49%) [21]. To this date, most of CBT trials reported in the literature are combination trials [12] rather than monotherapy. Further work is needed to determine which patients preferentially benefit from combination therapy.

Practice guidelines, systematic reviews and meta-analytic studies [5,13] and original research [6,18,22,23] all describe important existing evidence gaps on achieving optimal sequential treatment outcomes for individuals with Obsessive-Compulsive Disorder (OCD). These evidence gaps include 1) which acute monotherapy (CBT or SSRI) is best for both response and remission? [3,24,25]; 2) which treatment is best during long-term treatment [6,23,26]; 3) what is the best next sequential treatment for initial treatment non-remitters? [13,20]; 4) what is the best ranked overall sequence of treatments? [3,5,13,27]; and 5) which patients do best with which treatments-understanding the heterogeneity effects of family history of OCD [22] and cognitive flexibility on treatment outcome, while controlling for the impact of prior treatment [5,6,13,23].

Comprehensive reviews and meta-analyses, such as that recently conducted by Skapinakis et al. [5,13], concluded the following substantial methodological shortcomings of the existing clinical trials database of studies investigating SSRI and CBT in adults with OCD: **1)** most (80%) of the CBT trials allowed adult OCD subjects to continue stable doses of antidepressants for 3 months before inclusion, thus generalization of results in patients suffering from OCD not taking SSRI's is difficult and most studies of CBT should actually be considered as studies of variants of combination treatment; **2)** Most CBT studies were of short duration, and thus results of treatment longer than 16 weeks are not known; **3)** Generalization of trial results for subgroups of patients with specific symptoms or comorbidity (hoarding, poor insight, tic, greater OCD severity, comorbid attention deficit hyperactivity disorder (ADHD)) should be made with caution; **4)** Too few trials have adequately compared CBT with SSRI on frequency and severity of adverse events using standardised instruments, and on measures of quality of life [21,30]; **5)** There is inconsistency in the reporting of treatment response (clinically meaningful reduction in symptoms) and remission (no longer meets syndromal criteria and no more than minimal symptoms) rates in existing OCD trials [31].

3. Conclusions

In this review we summarized available treatment recommendations for the first line treatment for individuals with OCD. Future directions for their optimization could include identifying patients early on in the course of their illness to initiate the treatment and use digital medicine and pharmacogenomic tools to profile patients. More research is warranted to answer a question whether a combination treatment is best from the start.

Declaration of Competing Interest

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Dr. Fineberg has received research funding from COST Action CA16207 and NIHR. She also has a leadership role as Chair, ECNP Review Board. Secretary, International college of obsessive compulsive spectrum disorders; as a Board member, Orchard advancing research in OCD; as a Chair, World Psychiatric Association scientific section for OCD and anxiety; as a Clinical lead, National OCD treatment service; and as an Expert adviser to the MHRA. She received support to attend meetings from British Association for Psychopharmacology, European College for Neuropsychopharmacology (ECNP), Royal College of Psychiatrists, International College for Neuropsychopharmacology, European COST Action, World Psychiatric Association, International Forum for Mood and Anxiety disorders and American College for Neuropsychopharmacology. Dr. Fineberg has contributed to writing of NICE OCD guidelines.

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