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Psychotherapies and digital interventions for OCD in adults: What do we know, what do we need still to explore?

David Castle[a,b,*], **Jamie Feusner**[b,c], **Judith M. Laposa**[b,d], **Peggy M.A. Richter**[b,e], **Rahat Hossain**[b], **Ana Lusicic**[a,b], **Lynne M. Drummond**[f]

[a]Centre for Addiction and Mental Health, 60 White Squirrel Way, Toronto, Ontario M6J 1H4, Canada

[b]Department of Psychiatry, University of Toronto, 250 College Street, Toronto, Ontario M5T 1R8, Canada

[c]Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario M5T 1RB, Canada

[d]Campbell Family Mental Health Research Institute, Center for Addiction and Mental Health, 100 Stokes St., Toronto, Ontario M6J 1H4, Canada

[e]Frederick W Thompson Anxiety Disorders Centre, Sunnybrook Health Sciences Centre, 2075 Bayview, Toronto, Ontario M4N 3M5, Canada

[f]Service for OCD/ BDD, South-West London and St George's NHS Trust, Glenburnie Road, London SW17 7DJ, United Kingdom

Abstract

Background: Despite significant advances in the understanding and treatment of obsessive compulsive disorder (OCD), current treatment options are limited in terms of efficacy for symptom remission. Thus, assessing the potential role of iterative or alternate psychotherapies is important. Also, the potential role of digital technologies to enhance the accessibility of these therapies, should not be underestimated. We also need to embrace the idea of a more personalized treatment choice, being cognisant of clinical, genetic and neuroimaging predictors of treatment response.

Procedures: Non-systematic review of current literature on emerging psychological and digital therapies for OCD, as well as of potential biomarkers of treatment response.

Findings: A number of 'third wave' therapies (e.g., Acceptance and Commitment Therapy, Mindfulness-Based Cognitive Therapy) have an emerging and encouraging evidence base in OCD. Other approaches entail employment of elements of other psychotherapies such as Dialectical Behaviour Therapy; or trauma-focussed therapies such as Eye Movement Desensitisation and Reprocessing, and Imagery Rescripting and Narrative Therapy. Further strategies include Danger Ideation Reduction Therapy and Habit Reversal. For these latter approaches, large-scale randomised controlled trials are largely lacking, and the precise role of these therapies in treating

[*]Corresponding author at: Centre for Addiction and Mental Health, 60 White Squirrel Way, Toronto, Ontario M6J 1H4, david.castle@camh.ca (D. Castle).

people with OCD, remains to be clarified. A concentrated 4-day program (the Bergen program) has shown promising short- and long-term results. Exercise, music, and art therapy have not been adequately tested in people with OCD, but may have an adjunctive role. Digital technologies are being actively investigated for enhancing reach and efficacy of psychological therapies for OCD. Biomarkers, including genetic and neuroimaging, are starting to point to a future with more 'personalised medicine informed' treatment strategizing for OCD.

Conclusions: There are a number of potential psychological options for the treatment of people with OCD who do not respond adequately to exposure/response prevention or cognitive behaviour therapy. Adjunctive exercise, music, and art therapy might be useful, albeit the evidence base for these is very small. Consideration should be given to different ways of delivering such interventions, including group-based, concentrated, inpatient, or with outreach, where appropriate. Digital technologies are an emerging field with a number of potential applications for aiding the treatment of OCD. Biomarkers for treatment response determination have much potential capacity and deserve further empirical testing.

Keywords

Obsessive-compulsive disorder; Treatment; Psychological interventions; Digital technologies; Biomarkers

1. Introduction

This article forms part of a Special Edition of *Comprehensive Psychiatry*, on behalf of the International College of Obsessive Compulsive Spectrum Disorders (ICOCS). The intent of this article is to address issues at the cutting edge of psychological treatment approaches for obsessive compulsive disorder (OCD) in adults. It does not serve as a comprehensive review of the field of psychological therapeutics for OCD, as that has been recently published by ICOCS [1]. It is also not a systematic review per se, nor have we embarked upon meta-analyses. Rather, we have based the topic selection on the recent ICOCS review [1], and have scoped the published recent literature for studies reporting novel psychological treatments for OCD, along with other treatment modalities. Due to space limitations, some therapies have been excluded, which we acknowledge, but have attempted to cover the main emerging psychological approaches with applicability to OCD in adults. We include papers reporting on childhood OCD only where findings are directly relevant to adults. We also provide some clinical guidance as to how these heterogeneous therapies might be deployed, and their potential place in the future for the treatment of OCD. We have integrated a discussion about the role of emerging digital technologies and their place in therapeutics. Finally, we discuss potential biomarkers of treatment response for some of these emerging paradigms. But first, we look at some current controversies regarding the 'established' psychotherapeutic approaches for OCD.

2. ERP, CBT and CT: what works, in what combinations, for whom?

There is widespread consensus that Exposure and Response Prevention (ERP) and Cognitive Behaviour Therapy (CBT) are first line treatments for OCD [2]. In clinical practice ERP and CBT are often used in conjunction with serotonin reuptake inhibitor antidepressants

(SSRIs) but are also effective alone, especially in motivated patients with milder symptoms. They are listed in international OCD treatment guidelines [3-5] and meta-analyses reveal large pre-post effects [6,7]. However, there is still some debate as to precisely which element(s) of ERP and CBT are actually required for efficacy, whether the cognitive element is truly needed, and whether cognitive approaches alone have a place in the treatment of OCD. When performing ERP, individuals with OCD purposely and repeatedly trigger their obsession, and then resist engaging in their compulsion/avoidance/safety behaviour. ERP leads to habituation of a learned anxiety response, and tests out whether the feared consequences happen or not, leading to a decrease in anxiety, reduction of compulsive behaviour, and changes in fear-based interpretations of the obsession. An exposure hierarchy is usually agreed upon, and/or exposure targeted to what the individual most needs to learn, using inhibitory learning techniques [8]. CBT for OCD includes both ERP and cognitive therapy techniques [9] that directly address the common obsession appraisal themes evident in OCD, for example, overimportance of thought, overestimated threat, intolerance of uncertainty, and inflated responsibility.

The use of cognitive therapy (CT) alone for OCD focuses on behavioural experiments, which although similar to exposures, do not focus on habituation of anxiety, and instead target the negative interpretation of the obsession held by the individual with OCD. Randomised controlled trials (RCTs) of CT have compared it to medication, waitlist, stress/anxiety management, and ERP, and found CT to be effective in decreasing OCD symptoms [10-15]. Although some hypothesize that CT may be easier to tolerate than ERP, recent research suggests comparable drop out rates in ERP and CT [16]. CT, ERP and CBT all have Level 1 evidence for the treatment of OCD. All three treatments include psychoeducation and relapse prevention, and have a large home practice component, where individuals practice the therapy skills between sessions. In practice, most clinicians who incorporate CT do so in addition to ERP strategies, as opposed to using CT alone.

Studies directly comparing whether CT augments ERP, are few. Vogel et al. [17] conducted a small controlled study ($N = 35$) of CT + ERP vs. ERP + Relaxation and found no between-group differences. However, the study was underpowered, and the authors noted that they used rather generic CT strategies, as opposed to the more recent OCD-specific cognitive models and therapy interventions. Rector et al. [18] recently reported the first adequately statistically powered RCT comparing combined ERP + CT to ERP alone. Although both interventions significantly decreased OCD symptoms and obsessive beliefs, ERP + CT was associated with greater symptom reduction, across all OCD sub-types, and also had more treatment responders. The additive effect of CT to ERP was a medium to large treatment effect [18]. This RCT awaits replication.

A related issue is whether people with different OCD symptom sets and different comorbidities, respond differentially to different psychological interventions. As stated above, ERP, CBT and CT are all highly effective. Steketee et al.'s [19] mega-analysis of RCTs and clinical studies showed large effect sizes for CBT, CT and ERP for OCD and depression symptom reduction. However, OCD symptom severity decreases were slightly smaller for ERP in comparison to treatments that incorporated CT. Furthermore, significantly fewer individuals receiving ERP (36%) achieved clinically

significant improvements on OCD symptoms vs. CT (56%); CBT was in the middle (48%). Improvements in depression were larger for CBT than ERP, with CT not being different from the other two; this suggests the addition of CT to ERP may be particularly useful for those with severe depressive symptoms. Moderator analyses revealed no effect of medication status or comorbidity, but did show that outcomes were negatively affected by baseline depression scores for ERP, but not CT or CBT. Higher education and lower severity of OCD were associated with better outcomes in the CT groups only, suggesting that the use of ERP could be especially important when treating severe OCD. Among those individuals who held responsibility/threat beliefs most tenaciously, those who received CT or CBT were more likely to improve, but this effect was not observed with ERP. Additional research with large representative samples is needed to further guide clinical decision-making regarding which of the three treatments - or which combinations – is optimal for a given patient with OCD. patient.

3. Emerging and novel applications of psychotherapy in OCD

3.1. Acceptance and commitment therapy (ACT)

Acceptance and Commitment Therapy (ACT) aims to increase psychological flexibility through six processes: values, defusion, present moment awareness, acceptance, self as context, and committed action. ACT helps individuals move toward acceptance of symptoms, coupled with commitments to living consistent with their values, creating a different relationship with the OCD symptoms [20]. Many see ACT as part of the umbrella of CBT-related therapies, as many of the ideas of ACT are incorporated in CBT [21].

Ost's [22] systematic review and meta-analysis showed that ACT was probably efficacious for OCD, whilst Bluett et al. [23] concluded that evidence is modest for ACT with OCD. Since then, further RCTs have compared ACT to various other treatments, including psychiatric medication. Rohani et al. [24] recruited 46 women with OCD who were all on optimal doses of an SSRI, and then compared ACT+SSRI to SSRI alone. Both treatments decreased OCD and depression symptoms, with ACT+SSRI showing superiority at the two month follow up. This is consistent with other studies finding larger effects for ACT than anti-depressant alone [25,26]. Twohig et al. [27] randomised 79 people with OCD to 8 weekly session of ACT or to progressive relaxation training, and reported better outcomes for ACT in the final two sessions. Further analysis of data from this RCT found that post treatment psychological flexibility levels mediated decreases in OCD severity from pre-treatment to three month follow up [28]. In another RCT by this group, ACT+ ERP vs. ACT (total $N = 58$) showed no between-group differences on outcomes, including OCD symptoms, obsessional beliefs, psychological inflexibility and depression at post-treatment and follow up. These dimensions decreased significantly in both conditions, and there were also no between-condition effects of exposure engagement, treatment acceptability, or attrition [29].

Taken together, these studies suggest that ACT can decrease OCD and related symptoms, and there is evidence for the mediating role of psychological flexibility. However, ACT has not been shown to be superior to other first line treatments for OCD, and as such may be complementary to, as opposed to a replacement for, CBT/ERP/CT for OCD. There is also

much to be explored in terms of treatment moderators. Ong et al. [30] examined moderators of treatment response to ACT+ERP vs. ERP and found that participants with fewer dysfunctional appraisals at pre-treatment had a better response with ERP. In both treatment conditions, OCD severity was related to interpretation of intrusions and psychological inflexibility. Further research is needed to determine who may optimally benefit from and/or prefer ACT techniques, how ACT works for OCD (additional mediators), as well as replication of findings by independent research groups.

3.2. Mindfulness based cognitive therapy (MCBT)

Mindfulness Based Cognitive Therapy (MBCT) is well established in the treatment of depression [31]. Over the last 15 years, MBCT has also been deployed for OCD. Mindfulness based interventions increase one's ability to pay attention purposefully in the current moment, with a non-judgemental stance. In MBCT, these interventions are used in combination with cognitive therapy elements. The treatment is typically eight sessions, and includes a volume of home practice similar to that used in CBT. Individuals with OCD tend to supress or avoid their obsessions; MBCT cultivates a non-judgemental acceptance stance toward all types of thoughts, which would be expected to create less distress in response to an obsession, and therefore decrease urges to engage in compulsions. Changes in mindfulness are often assessed with the Five Facet Mindfulness Questionnaires [32], encompassing: observing, describing, acting and awareness, non-reactivity, and non-judging. Individuals with OCD score higher than other anxiety disorder groups on acting with awareness, and describing, with the latter predicting pre-treatment OCD symptom severity [33].

Most published studies of MBCT for OCD have examined MBCT after a course of ERP/CBT, with additional decreases in self reported OCD symptoms [34]. In a qualitative study of acceptability and perceived benefit, MBCT following a course of CBT showed improvements in OCD symptoms, coping, and quality of life [35]. In a separate study, Didonna et al. [36] provided MBCT as a standalone treatment for OCD ($N = 35$), and reported significant decreases in OCD symptoms with a robust effect size (Cohen's $d = 0.72$); symptom reduction was associated with increases in acting with awareness, non-judging and non-reactivity.

In RCTs, MBCT for OCD has been shown to be superior to stress management training [37] and waitlist control for treatment augmentation for residual OCD symptoms after CBT, with large effect sizes for OCD, depression and anxiety symptoms, as well as high participant satisfaction [38]. The RCT of Kölz and colleagues [39] compared MBCT to psychoeducation, in individuals with residual OCD symptoms after completing CBT. MBCT had stronger effects on self-report OCD symptoms (but not clinician rated) at the end of treatment, but not at 6 month follow up. The same research group conducted a small RCT ($N = 38$) of MBCT vs. psychoeducation for people with residual OCD symptoms after CBT, and found no significant benefit of MBCT on negative or positive affect, acceptance of momentary emotions, or distress associated with OCD symptoms [40].

Taken together, although outcomes from RCTs have been mixed, MBCT may be a helpful secondary treatment for residual symptoms following CBT/ERP for OCD. Additional

research is needed to determine the efficacy of MBCT as a standalone treatment before CBT/ERP, as well as the efficacy of MBCT vs. CBT/ERP. In addition, there is a paucity of empirical research on the potential role of new technologies to enhance mindfulness in OCD. In one of the few such RCTs, Hawley and colleagues [41] found that technology supported (EEG-based biofeedback device) mindfulness, in comparison to a control condition, led to increased non-reactivity and decreased mind wandering, both of which were associated with OCD symptom improvement. Future research is required to determine how technological advances may bolster the effects of MBCT for OCD.

3.3. Dialectical behaviour therapy (DBT)

Distress tolerance (DT) is a transdiagnostic vulnerability factor for anxiety related disorders, including OCD, and low DT is associated with greater OCD symptom severity [42]. Dialectical Behaviour Therapy (DBT) is an empirically supported treatment for borderline personality disorder, which incorporates building DT skills, in addition to mindfulness, emotional regulation, and interpersonal effectiveness. Although DBT is used in some day treatment and inpatient OCD settings as an adjunct to ERP, we are not aware of any study examining DBT as a treatment for individuals with a primary diagnosis of OCD. However, there are theoretical reasons to believe that some components of DBT skills training may be relevant, for example, mindfulness (see Section 3.2) and DT skills [43].

Increasing DT skills may allow an individual with OCD to be better able to tolerate exposure and resist urges to engage in compulsions, and some argue that DT skills should be taught to patients doing exposure therapy [44]. Conversely, these is concern that DT skills may be employed as distraction during an exposure, thereby diminishing the effectiveness of ERP. Of note, there are significant inter-relationships between DT, intolerance of uncertainty (IU) and anxiety sensitivity (AS), with some studies showing that the relationship between DT and OCD symptom severity is lost when the latter two are controlled for [42] and that those variables have stronger relationships than DT with symptom severity and impairment [45]. More research is needed, to examine the possible role of DT skills as an adjunct when treating OCD, particularly for those with severe OCD symptoms. It also remains to be determined whether increasing DT would provide superior results to focusing instead on ameliorating IU and AS, other known maintenance factors in OCD.

3.4. Metacognitive therapy (MCT)

Metacognitive therapy (MCT), as developed by Adrian Wells, targets the so-called ‘cognitive attentional syndrome’, or CAS, positing that perseverative ways of thinking (e.g., worry, rumination, avoidance) are unhelpfully adopted to ameliorate distressing thoughts and feelings, but serve to maintain symptoms of anxiety and depression [46]. The beliefs refer to the beliefs people hold about cognition itself, and these may be positive or negative. In the context of OCD, the metacognitive beliefs are about the perceived dangerousness/power of obsessive thoughts, and about the ‘need’ to perform rituals [47]. MCT identifies these metacognitive beliefs and seeks to modify them [46]. ‘Attention training’ teaches the individual how to be more flexible regarding how they attend to thoughts; and ‘detached mindfulness’ teaches how to distance emotionally from triggering thoughts [48].

MCT has an emerging evidence base, with a recent systematic review [48] encompassing 780 patients across 25 studies (15 of which were controlled trials) employing MCT for a range of 'psychological complaints' (mostly depression and anxiety). Robust effect sizes were reported for reducing anxiety, depression, and 'dysfunctional metacognitions' ((Hedges' $g = 1.57$) whilst comparison with waitlist controls also showed a large effect size (Hedges' $g = 2.06$). For those eight studies comparing MCT to CBT, a post-treatment pooled effect size of 0.69 was reported.

Only one of the studies included in the systematic review of Normann and Morena [48] was for OCD. This was an open trial of MCT in 25 OCD outpatients, which reported a large effect size for reduction in OCD symptoms (Hedges g = 0.99) [49]. A subsequent pilot RCT ($N = 37$) compared MCT to ERP in a 14 week outpatient trial [50]. Both treatments were effective in reducing OCD symptoms, with no significant difference between them apart from therapist time, which was lower for MCT than ERP.

In sum, MCT has evidence for efficacy, with large effects sizes, for depression and anxiety symptoms across a range of disorders, but to date research in OCD is sparse and mostly limited to case reports and pilot studies. There is also no clarity as yet regarding which OCD patients would be particularly amenable to MCT. Larger, fully powered studies are required, and some are already in planning. For example, Melchior et al. [51] have published a trial protocol in which 100 OCD patients will be randomised to MCT or ERP, exploring not only efficacy but also comparative efficacy.

3.5. Habit reversal therapy (HRT)

Habit Reversal Therapy (HRT) is a form of Behaviour Therapy first developed in the 1970s by Azrin and Nunn [52], targeting a variety of habit disorders and tics including nail-biting, thumb-sucking, eyelash-picking, head-jerking, shoulder-jerking, tongue-pushing and lisping. There are four main components of habit reversal, the first of which is finding means to increase the individual's awareness that they are performing the target behaviour, as many habits are performed automatically and without awareness. Awareness is achieved by recording target symptoms and other strategies. Secondly, a competing response – that is, a new response which is incompatible with the target behaviour - is devised and practiced. Thirdly, the patient is taught habit-control motivation, encompassing reminding them of the negative consequences of the target behaviour, for example using cue cards. Finally, generalisation-training is introduced, to ensure that the competing response practice can be incorporated into daily life without attracting untoward attention.

HRT has a reasonably well-established place in the treatment of certain disorders within the OCD grouping, including skin picking [53] and hairpulling [54], as well as the tics associated with OCD and Tourette Syndrome [55]. However, some researchers have made a case for HRT to be employed for core OCD symptomatology, notably for symptoms that have become 'habitual'. In the traditional learning theory of OCD, the individual experiences intrusive, abhorrent or anxiety provoking obsessive thoughts, images or impulses. In order to control this dysphoria, compulsions, which may be thoughts or acts, are engaged in, to reduce this anxiety and discomfort. However, the anxiolytic effect of the compulsions tends to be partial and short-lived [56]. Whereas the role of compulsions

as alleviating anxiety is true for many people with OCD, others, particularly those with more chronic OCD, describe their compulsions as being habitual, being performed without deliberate thought. Also, a growing number of neuropsychological studies suggest that the neurocognitive mechanisms mediating behavioural inhibition (motor inhibition, cognitive inflexibility), reversal learning, and habit formation (shift from goal-directed to habitual responding) contribute toward compulsive activity in a broad range of disorders, including OCD [57]. For these reasons, HRT might have a place in addressing some of the habitual components of OCD, but this awaits empirical testing.

3.6. Danger ideation reduction therapy (DIRT)

Danger Ideation Reduction Therapy (DIRT) is a form of therapy using Rational Emotive Behaviour Therapy (REBT), and was initially developed for OCD dominated by fears of contamination. REBT itself has been shown to have some possible therapeutic effects in OCD [58], but the benefits of including cognitive reattribution in addition to ERP for patients with OCD has been widely debated. Unlike REBT, most cognitive therapy for OCD has been based around the idea that an over-inflated sense of responsibility is the major thinking error in OCD [59]. This was challenged by Australian researchers in the 1990s, with a counter-proposal that the key cognitive element in OCD is that of an inflated estimation of danger in differing situations [60]. Further, it was argued that an idea of inflated sense of responsibility makes sense only if there is an underlying excessive estimation of danger. Based on this premise, DIRT was developed as a new treatment for OCD with contamination fears. DIRT encompasses a number of elements, including corrective information, cognitive restructuring, filmed interviews, microbiological experiments, attentional focusing, and Hoekstra's [61] probability of catastrophe estimation task. Treatment is delivered over six to ten, one hour sessions. The important feature of DIRT that differentiates it from ERP, is that it does not entail any form of exposure in real life, via imagery or on screen.

The first controlled trial of DIRT compared it to waiting list control in a total of 21 people with OCD. Whereas there was some reduction in symptoms in the DIRT group, no significant difference was found between the control and active treatment group at follow-up [60]. In a further study, five people with intractable contamination OCD who had failed to respond to ERP, were treated with DIRT and four of these showed marked clinical improvement. The authors concluded that whereas ERP remains the treatment of choice for compulsive washing/cleaning behaviour, DIRT represents a viable alternative [62].

A subsequent controlled trial compared DIRT with ERP in 22 people with washing and cleaning compulsions. Both groups improved with no significant differences between them, albeit there appeared to be a greater improvement on some measures in the DIRT group at follow-up [63]. Further case studies using DIRT with patients with profound, refractory OCD have reported good outcomes [64,65]. DIRT has also been modified for people with OCD who have checking compulsions [66].

In summary, although the evidence-base is very small, DIRT may be an option for those OCD patients with contamination fears, who fail to respond to ERP or who have poor

insight. In addition, components of the DIRT programme have been used to encourage those with chronic, refractory OCD with contamination fears to engage in ERP [67].

3.7. Eye movement desensitisation and reprocessing (EMDR)

A number of studies have reported OCD to be associated with traumatic life events, as varied as minor head injury [68] through to a five-fold increase in risk of OCD associated with childhood sexual abuse [69]. In a study of 265 people with OCD, over half (54%) reported a traumatic life event during their lifetime [70]. However, the presence of traumatic events was assessed by presenting participants with a list of such events and asking whether they had experienced any of them: this may have inflated reporting. Also, there was no comparison group. A more recent study examined 7,054 young people (11–21 years) with obsessive compulsive symptoms, and found an association with reported traumatic life events that was stronger for females than males [71]. The type of life event might impact the manifestation of OCD symptoms. For example, a recent large study suggests that whereas people who report non-traumatic major life events in the year before the onset of OCD symptoms were more likely to experience contamination fears, whilst traumatic life events were associated with hoarding problems [72].

Reports about life events preceding the onset of OCD symptoms have led some researchers to propose that all OCD is generated by traumatic life events. This assertion is difficult to substantiate, given the lack of research comparing life events in people with OCD and those in the general population. There may also be a tendency for people to attribute bad things that happen, such as developing OCD, with other stressful events in their lives (i.e., attribution bias). However, there is now a considerable volume of research linking life events and the onset of depression [73]. OCD is frequently comorbid with depression [74], hence life events may be important in the onset, severity and chronicity of OCD.

Thus, trauma-oriented therapies could play a role in treating OCD itself. One candidate is Eye Movement Desensitisation and Reprocessing (EMDR), first developed for Post-Traumatic Stress Disorder (PTSD) [75]. EMDR consists of 8 stages [76]. Firstly, a full history and assessment of the trauma is taken. Different types of eye movement stimulation are then introduced: for example, moving the eyes horizontally with noises at each side of the head. Thirdly, the patient is encouraged to describe the entire experience of the traumatic memories and the bodily sensations associated with this as well as establishing a calming scene or ‘safe place’. Next, the patient is asked to imagine the traumatic image whilst the bilateral stimulation or eye movements are deployed. The patient is then asked to imagine the ‘safe place’ image and this is also accompanied by bilateral stimulation. Following this, the patient repeats the original thought and ‘safe place’ pairing with bilateral stimulation. The therapist then explains the possible side effects that may occur before asking the patient for a re-evaluation of the memory to check whether it has been processed fully.

EMDR has been mostly used to treat people with PTSD. How EMDR compares to standard CBT for PTSD is controversial, with a meta-analysis concluding a slight benefit for EMDR but with the caveats that the number of studies was low and often of poor quality [77]. There is a paucity of research on EMDR in OCD. In a 12-week trial, Nazari et al. [78] compared EMDR with citalopram (20 mg daily) in 30 patients with OCD. Both groups

improved significantly over the course of the trial, but EMDR was associated with greater improvement than citalopram. However, 12 weeks is arguably too short a period to establish full benefit from the medication, and the daily dose is low for OCD [1]. Also, the authors did not provide details of what interventions the citalopram group received beyond the medication; the amount of therapist contact associated with EMDR may itself improve symptoms in the short-term. There was no longer term follow-up. A further RCT compared CBT with EMDR in 55 patients with OCD. Around two thirds (68%) of patients completed the treatments and 30% achieved reliable and clinically significant reduction in symptoms, but there was no significant difference in outcomes between the two treatment arms [79].

A systematic review of the use of EMDR in a variety of conditions concluded that there was less evidence for efficacy of EMDR in OCD and addictions than most other anxiety disorders and pain syndromes [80]. In sum, there is currently insufficient evidence to recommend EMDR as a standalone treatment for OCD although it may have a role as an adjunctive treatment for people with a clear history of trauma or refractory OCD.

3.8. Imagery rescripting (ImRs)

As detailed above, traumatic life events are not uncommonly reported by people with OCD. These events can be associated with intrusive, disturbing mental imagery [81]. This phenomenon opens up a novel avenue for therapeutics, namely employing imagery rescripting (ImRs). ImRs involves the recognition of past events that intrude unhelpfully on the present, and teaches people to ‘re-imagine’ the traumatic sequence into a more desired and ‘safer’ narrative [82]. A preliminary cognitive restructuring element can be added to reappraise unhelpful beliefs associated with traumatic memories [83].

ImRs has mostly been used for treating PTSD, but has also been trialed in people with OCD who have a trauma history and have not responded adequately to ERP [83]. Veale et al. [81] delivered a single ImRs session to 12 people with OCD who experienced distressing imagery and reported seven of them to have ‘clinically significant’ improvement at 3 month follow up; OCD symptom (Y-BOCS) scores reduced from a mean of 24.1 pre-treatment, to 10.7 at 3 months. Maloney et al. [82] describe a case series ($N = 13$) of 1–6 sessions of ImRs, the number of sessions dependent upon the individual achieving a target of >35% reduction in Y-BOCS scores; nearly half (46%) achieved this target with just one ImRs session.

In conclusion, ImRs appears to have applicability in people with OCD who have a trauma history and associated intrusive imagery that feeds their OCD symptomatology. It has an augmenting role rather than being a standalone psychological therapy, mostly having been deployed after ERP.

3.9. Narrative therapy

Narrative therapy entails addressing the unique narratives each person builds about illness in their lives. Attending to unhelpful narratives using different perspectives, externalizing dominant problems and removing oneself to a position of an observer, helps create ‘new mental images and meanings’ and develop ‘internal strength and responsiveness’ [84,85]. We are aware of only one published study exploring this approach in comparison to

other psychotherapies in adults with OCD. In that study, Esfahani et al. [85] used a semi-experimental design to compare time perspective therapy, ACT, narrative therapy and waitlist control in 60 OCD patients. ACT and narrative therapy were associated with significant reductions in Y-BOCS scores at end-point, relative to the other two groups. Needless to say, more research is needed to establish the potential place for narrative therapy in trying to help people with OCD.

4. Other therapies

4.1. Exercise

Physical exercise has been shown to be effective in improving symptoms in depression [86] and anxiety disorders [87]. A small body of work has examined the impact of exercise on OCD, with a few observational studies and uncontrolled trials, but only one published RCT [88]. Single arm studies found that exercise led to decreases in OCD symptoms [89-91], maintained at one and six month follow up [89,90], and also when exercise was combined with CBT [88]. Comorbid depressive symptom improvement might have played a mediating role on OCD symptom improvement [90-92]. The only RCT of exercise in OCD found that exercise was associated with a decrease in OCD symptoms, but no more so than the comparison psychoeducation condition [93]. Of note, randomization led to differences between conditions in pre-treatment severity of OCD symptoms that barely missed the statistical significance cut off, which may have influenced the results. In any event, the study was underpowered ($N = 56$) for the primary outcome.

4.2. Art and music

There is little available evidence for the use of music or art therapy in the treatment of OCD. Indeed, a systematic review of complementary medicine, self-help, and lifestyle interventions for OCD and related disorders included ‘art therapy’ and ‘music therapy’ among the search terms but found no studies that met their inclusion criteria (i.e., controlled studies with measurable outcomes on an OCD scale) [94]. There are presently no published studies of art therapy for OCD except one case report as an adjunct to psychoanalysis in a patient with obsessive-compulsive neurosis [95]. This case study reported that art therapy aided the identification of defenses and a re-emergence of self-expression.

A more recent systematic review of music and OCD found three studies examining the use of music therapy as an adjunct to standard treatment for patients with OCD [96]. Two of the studies used receptive music therapy, which involved listening to classical music: one study implemented daily, 50-min sessions over a three-month period and the other used 12 sessions of listening over a span of four weeks. Both studies found significantly less severe obsessive symptoms compared to the control groups who received standard treatment only. A third study reviewed by Truong et al. [96] examined improvisational music therapy and music listening sessions as adjunctive treatments for re-socializing in a sample of 24 patients but only two of them were diagnosed with OCD (with the remainder diagnosed with mood disorders and schizophrenia).

The paucity of studies using art or music therapy interventions is regrettable, but the absence of literature in this area presents an opportunity for future investigations to inform the use of these possibly adjunctive tools.

4.3. Further strategies

Given that OCD is often associated with substantial distress and associated autonomic arousal, strategies to reduce these symptoms have been explored. Studies have assessed efficacy of Stress Anxiety Management Therapy (SAMT) [97] and Progressive Muscle Relaxation (PMR) – including via the internet [98] for OCD, finding neither as effective as ERP/CBT.

Finally, attempts to enhance engagement and outcomes for in OCD have utilized Motivational Interviewing (MI) as an adjunct to ERP [99], and Cognitive Remediation Therapy (CRT) [100] but to date outcomes have been disappointing and such approaches cannot be recommended without further positive evidence for efficacy and cost effectiveness.

5. How should psychotherapies be deployed, for OCD?

5.1. Group therapy

Individual ERP/CBT for OCD delivered on an outpatient basis is the most common mode of delivery, but other approaches have been explored. Group CBT for OCD has demonstrated positive signals for retaining efficacy while introducing some efficiency in cost. Both individual and group CBT lead to significant decreases from pre- to post-treatment on the Y-BOCS [101,102], with approximately 50% of participants experiencing a response and 30%, remission [101]. No differences were found between group and individual CBT across 12-months of follow-up [101-104] though there was a trend toward additional effectiveness in favour of individual CBT [101,103]. Treatment gains appear to be maintained at 2 years [104]. Similar to individual CBT for OCD, group therapy does not demonstrate significant differences in shorter term outcome compared to other active controls or pharmacotherapy [102]. Calculations of savings in therapist time are approximately 25–50% for group compared to individual therapy [101,102]. Advantages for patients participating in group therapy include a sense of belonging amid the experience that others have similar problems; the ability to encourage and motivate each other and to solve problems using feedback; and to have the opportunity to compare and contrast appraisals of obsessive thoughts [102]. However, patients could also experience a loss of control, individuality, privacy, and safety in group therapy [104]. Thus, group therapy has potential benefits in terms of therapist time, camaraderie and mutual learning, but some patients find the group setting confronting and should be offered 1:1 as an alternative modality.

5.2. Concentrated program delivery

The notion of a ‘concentrated’ brief ERP program has also been explored. The Bergen program (B4DT) [105] from Norway deploys concentrated ERP to outpatients, framed as the ‘Lean into The anxiety’ or LET technique, often accompanied with loop tape exposure emphasising uncertainty. Groups of 3–6 people with OCD are paired with therapists and

group and 1:1 work is performed, and individualised homework is set. A 1:1 three month follow-up allows reinforcement of the principles of ERP.

This program has encouraging short- and longer-term outcomes. Successful open-label work led the developers to deliver a ‘mass intervention’ to address long waiting times for therapy [105]. Of the 101 people on the waitlist, 90 received the intervention from therapists drawn from 22 specialised OCD teams from across the country. At post-treatment, 91.1% of patients were considered responders, and 72.2% were in remission. The lack of a control group is a shortcoming, but a subsequent RCT randomised 48 OCD patients to B4DT, self-help or waitlist control (n = 16 each arm) and found response rates (≥ 35% reduction in Y-BOCS) of 93.8%, 12.5% and 0%, respectively [106]. A long term follow-up of 77 patients showed a decrease in Y-BOCS scores from 25.9 at baseline, to 10.0 post-treatment and 9.9 at four-year follow-up, with a remission rate of 69% [106]. These long-term data are impressive, but lack of a control condition limits the conclusions that can be drawn.

Overall, this concentrated approach shows efficacy and potentially allows cost-effective use of specialist resources. It deserves further evaluation in other jurisdictions.

5.3. Home-based and outreach delivery

Access to treatment for OCD among people who are low income or marginalized is limited, and many OCD studies exclude people with psychosis. One strategy to try to address this gap is home- and community-based outreach programs such as behavioural therapy teams [107]. Featuring a mix of group and individual CBT, such programs attained large effect sizes on the Y-BOCS compared to treatment-as-usual. However, treatment gains tend to fluctuate and are not consistently maintained over time. Mancebo et al. [108] reported that 25% of participants in their program were responders; however, there was an overall low treatment completion rate (57%), reflective of the challenges of delivering ERP to people with serious mental illness. Home-based ERP has elsewhere been found to reduce total Y-BOCS from the severe range to the mild range compared to individual outpatient ERP with no statistically significant differences [109]. However, both behavioural therapy teams and home-based ERP encounter discomfort and sometimes rejection from participants, due to the fear of feeling awkward or the risk of ‘contamination’ by the therapist at home [108,109].

5.4. Inpatient programs

Individuals with OCD that is too severe to enable effective outpatient therapy or who have failed such treatments are often admitted to intensive residential or day hospital/partial hospitalization programs. Such programs deliver CBT with ERP and other therapies on a daily schedule with treatments lasting cumulatively for hours each day, often across 12 or more weeks. Intensive residential treatment programs appear particularly suited for treatment of severe OCD [110] and may help to achieve improvement in those who did not respond to outpatient therapy [111].

A systematic review and meta-analysis found that residential or inpatient intensive treatment reduced Y-BOCS scores by 10.7 points, representing a large effect size [112]. Recent studies of intensive programs published after that meta-analysis have reported largely similar mean

reductions in the Y-BOCS [106,108-110]. Response rates have ranged from 43 to 79% and remission from 26 to 58% [113,114]. Exit interviews with participants reveal four major themes related to intensive programs: (a) validation in speaking with others with experience of OCD; (b) less impact from their symptoms and re-engaging in activities; (c) intensity and necessity of ERP for recovery and the support of the team; and (d) personal and program-related challenges and satisfaction [115]. Though programs are most often 12 weeks or longer in duration, 2- and 3-week intensive programs have been assessed which report substantial improvements at discharge though also some loss of treatment gains at follow-up [116,117].

5.5. Stepped care

Stepped care approaches integrating the different delivery modalities may facilitate a targeted and personalized deployment of psychological interventions for OCD. Patients can start with a lower intensity, less expensive treatment and then transition to higher intensity options if required [118,119]. Both standard ERP and stepped care involving clinician-guided brief-CBT (with the potential to transition to standard ERP) have demonstrated no apparent differences in efficacy, response, or patient satisfaction [118]. There was a moderate effect size for cost savings when comparing stepped care to standard ERP though non-responders to the lower intensity intervention accrued further costs attributable to the illness itself [119].

5.6. D-cycloserine (DCS) as an adjunct to psychological interventions

Medications such as serotonin reuptake inhibitors are established therapies for OCD, as reviewed elsewhere [1]. They are often used in conjunction with psychological interventions; indeed, the review of Reid and colleagues of psychological treatments for OCD showed that in 70% of trials medication use was not an exclusion criterion [2]. More directly relevant to this article is the potential role of the partial NMDA-agonist, D-cycloserine (DCS) as an augmenter of ERP in particular. DCS has been evaluated to determine the potential to reduce the required number of ERP sessions, reduce treatment cost, improve treatment adherence, and improve access to care [120]. Across meta-analyses, DCS augmentation of ERP relative to placebo has consistently revealed no significant benefits in terms of efficacy, response, or remission [120,121]. However, an individual participant data meta-analysis suggested that people given DCS augmentation might experience benefit from a dose of 50 mg administered more than 60 min prior to exposure sessions [122]. It was also suggested that people with lower baseline illness severity might be more likely to benefit from this strategy [122].

Kvale et al. [123] investigated the relative efficacy of DCS in ERP non-responders or those who had relapsed with moderate to severe symptoms, using a concentrated ERP treatment delivered consecutively for four days in a combined small-group/individual format. They found no indication that DCS potentiated the treatment response at post-treatment or 12-month follow-up. The impact of antidepressants on outcomes associated with DCS augmentation in OCD has been mixed, with some studies showing no significant effect, but others finding that a significantly greater proportion of those given DCS without concurrent antidepressants achieved remission at follow-up [124]. Exploratory subgroup

analysis examining the effect of DCS according to symptom dimensions of OCD found that participants with contamination/cleaning symptoms improved more with the addition of DCS compared to those using placebo [125].

In sum, the use of DCS to enhance the efficacy of psychological interventions for OCD has a highly inconsistent evidence base but might have benefit for selected patients using very specific dosing regimes.

5.7. Conclusions

CBT for OCD can be deployed across a number of modalities taking into account various findings of efficacy, cost-effectiveness, and individual patient factors. The strongest evidence for efficacy is available for group and individual CBT for OCD with no statistically significant differences at follow-up between these two approaches. The highest response and remission rates with sustained improvement are demonstrated by B4DT, however, the lack of a control group in current evaluations limits the reliability of the evidence. For individuals who do not respond to outpatient treatments or who have severe OCD, inpatient programs such as residential or day hospital/partial hospitalization programs may produce large effect sizes though response and remission rates are variable across the existing literature. Home and community-based outreach programs can attain large treatment effect sizes for hard-to-reach individuals; however, gains are not consistently maintained over time with low treatment completion rates. Modalities such as B4DT would benefit from further evaluation using RCT methodologies to determine the comparative efficacy relative to individual and group outpatient therapy. As well, all modalities require further evaluation to determine relative cost-effectiveness. Patient preferences are also a consideration, given that group therapies may introduce a loss of privacy or individuality while home and community-based treatments may engender discomfort with seeing therapists at the patient's home. Stepped care approaches may be the ideal integration, focusing on the use of lower intensity, less expensive treatments with the possibility of stepping up from group to individual to concentrated or intensive residential/partial hospitalization programs. While still experimental, DCS augmentation of ERP may benefit a narrow selection of patients with lower baseline illness severity, contamination fears/compulsive hygiene symptoms, and those not taking antidepressants.

6. Novel digital interventions in obsessive-compulsive disorder

A major challenge currently for clinical OCD care is limited access to evidence-based psychotherapy [126]. CBT and ERP, while considered first-line treatments for OCD (see section 2.0), are not universally accessible. There is a limited supply of specialty-trained therapists, there are cost barriers for many, and it is less available in certain geographical areas.

To meet these challenges, in the past two decades there has been a rise in treatment delivered remotely [127,128]. Further, with the global COVID-19 pandemic, many mental health treatments that were once in person have converted to remote delivery to reduce infectious risk. 'Remote' treatments for OCD are those that are provided through the internet, video, or telephone. Such treatments include 'therapist-guided' real-time interactions with therapists,

typically by phone or video teletherapy, or ‘self-guided’ treatments that are typically available on the internet. Although some internet CBT includes varying degrees of (typically asynchronous) clinician guidance or support, for the purpose of this review ‘therapist-guided remote treatments’ will refer to those that include synchronous, live interactions between therapist and patient via streaming video or telephone, whereas ‘Internet CBT’ (iCBT) will refer to web-based treatments that are primarily self-guided but may include clinical support.

6.1. Therapist-guided remote treatments

Are remote treatments for OCD as effective as in-person treatments? The latter has the advantage of the live, in-person presence of a therapist to help with in-session exposures. In addition, the office space provides a confidential setting that might not be available to everyone doing remote sessions. Remote treatments, on the other hand, allow patients to be in the specific settings that most trigger their obsessional thoughts, images, or urges – for example, in the home – where context-specific exposure exercises and response prevention may be the most effective. While not everyone has a computer or smartphone to do video-based remote treatments, as of 2021, it was estimated that approximately 81% of the world’s population owns a smartphone. Also, it is challenging and inefficient logistically for therapists to do home visits or travel far to non-office settings to administer exposures and help patients practice response prevention.

Are remote treatments accepted by patients, and are they able to establish a working alliance? Patients subjectively rate remote treatments comparably to in-person treatments on satisfaction and therapeutic alliance for individual psychotherapy - although comfort levels may be lower for group therapy [129-131]. Further, evidence supports the ability to establish rapport, as well as high patient satisfaction, and for a comparable patient-rated working alliance for internet CBT for OCD [132] including text-based internet CBT [132]. A review of qualitative studies of video telemental health concluded that patient acceptance was higher if there were more barriers to accessing the clinic in-person, if they had established care initially in-person, if the technical interruptions were not pervasive, if the patient had prior expectations that the remote treatment would be effective, and if the patients’ issues addressed were generally less complex [133].

In terms of efficacy, remote ERP has been demonstrated in a meta-analysis to significantly improve OCD symptoms [128]. Individual studies of remote therapist-guided treatments, delivered in real-time by phone or video, show similar, large effect sizes to controlled studies of in-person treatment. In addition, head-to-head studies demonstrated only small differences in outcome between remote and in-person treatment [128]. Further, the effectiveness of remote ERP in a real-world clinical sample was demonstrated in a large retrospective observational study of 3552 adults with OCD [134].

6.2. Internet CBT (iCBT)

Self-guided treatments include iCBT or bibliotherapy-based CBT. These consist of structured modules, or lessons, of CBT that patients progress through, akin to an online or paper workbook. Multiple randomised controlled studies have demonstrated the efficacy of iCBT for OCD [135,136].

In general for this type of treatment, when clinician support is additionally available it may result in improved outcomes [137-139]. Specifically for OCD, a meta-analysis found small effect sizes ($g = 0.33$) for self-administered self-help, moderate effect sizes ($g = 0.68$) for predominantly self-help, and large effect sizes ($g = 0.91$) for minimal contact self-help [140]. Further, dropouts decreased as clinician contact increased. A RCT published after this meta-analysis, however, found that weekly scheduled calls providing coaching and support did not result in differences in outcomes compared with no calls (despite 73% of respondents on a user questionnaire who 'agreed' or 'strongly agreed' that they needed coaching to succeed in the treatment) [141]. Interestingly, 48% said they preferred computer-based treatment, 33% preferred traditional face-to-face therapy, and 19% had no preference. A single-blind, non-inferiority study compared unguided iCBT to guided iCBT to face-to-face in-person CBT [142]. All three groups significantly improved, with the largest symptom improvements seen with face-to-face CBT. However, non-inferiority results among the three treatments were inconclusive. Response rates for unguided iCBT (16%) were significantly lower than for face-to-face (77%), while the guided iCBT response rate (45%) was not significantly different from the other two treatments. Both unguided and guided iCBT showed substantial cost-effectiveness over face-to-face CBT.

Several studies have demonstrated maintenance of gains at long-term follow-up between 3 and 24 months [142-144]. Further, supported computer-based CBT and guided self-help resulted in population-based cost savings over 12 months [145].

6.3. Digital therapist messaging

Some therapists, for many years and in many settings, have been using text messaging to communicate with patients. Beyond individual, ad hoc use, there are descriptions in the literature of WhatsApp groups that enable therapists and patients to have more immediate communication about challenges and progress with treatment [1]. The creation of specially tailored mobile texting platforms allows for the creation and integration of automated feedback with therapist feedback to enhance care. A small usability study reported on the feasibility and acceptability of a mobile texting app in an OCD intensive outpatient program [146]. A high proportion of patients found that the app was relevant to their recovery and effective at helping to complete treatment plans.

6.4. Technology-based tools for ERP/CBT

There has recently been an explosion in technology-based, and app-based tools in particular, for mental health, giving rise to a field of medicine called mHealth [147]. However, less than 5% have been evaluated [148,149]. While meta-analyses suggest that apps for depression and anxiety show small- to medium effect sizes [150], meta-analyses of studies of apps for OCD have yet to be published. Nevertheless, technology-based self-help tools may have individual elements that have been empirically validated such as psychoeducation and ERP [151].

6.5. App tools for exposure exercises and response prevention

There are multiple available apps for mobile devices designed to enhance ERP treatment such as facilitating exposure exercises and/or resisting compulsions. One of the major

challenges of studying the efficacy (and safety) of app-based tools is the necessity for them to be updated relatively frequently to address bugs and improve the user interface including updating the aesthetics to keep up with general trends. One, at least partial, solution to this is frequently-updated databases and reviews of mental health apps, such as those provided by the nonprofit project One Mind Psyberguide .

6.6. App tool for cognitive therapy techniques

Mobile or computer-based tools provide opportunities for enhancing not only exposure and response prevision but also cognitive therapy, whether remote or in-person. One tool helps users with OCD address maladaptive beliefs; a case report demonstrated its benefits to a patient with OCD with relapse prevention [152]. Other tools aimed at addressing OCD-related maladaptive beliefs have been tested in non-clinical populations [153,154].

6.7. Digital treatments using games

A challenge of mental health app-based tools is that use and adherence in real-world settings tends to be low, ranging from 1 to 29% for those for mood or anxiety [155]. Attempts to make app use, and treatment in general, more engaging is through ‘gamification’. One small study compared results of treatment from those who received traditional offline CBT (n = 15) to those (n = 12) who did a treatment program of education sessions, ‘quests’, and casual games [156]. There was no significant difference in OCD or depression outcomes, but the game-based treatment group showed greater improvements in anxiety and greater changes in brain connectivity in the thalamus and insula, measured with fMRI.

6.8. Virtual reality tools for OCD treatment

Virtual reality (VR) can present digital virtual environments that feel closer to being immersed in a real environment compared with viewing a 2D or 3D digital image. This is due to the scenes moving when users move their head and, in some environments, the ability to navigate freely within a 3D virtual space. VR has the potential to provide virtual environments to patients for therapy that would be difficult to produce in vivo.

To-date there have been no published clinical trials of VR-based therapy for OCD. However, there have been several case reports [157] and case series [158,159] that suggest benefits of using VR for exposures exercises in the context of ERP/CBT for OCD. In addition, proof-of-concept studies have examined the degree that VR environments can elicit emotional responses in those with OCD, in the interest of gauging the potential utility of using these methods for ERP/CBT [160-163]. Similarly, a proof-of-concept study was done to examine the utility of VR to enhance a component of Acceptance and Commitment Therapy consisting of a verbal repetition exercise [164].

One of the challenges of VR for OCD, as opposed to its use in other conditions that are more circumscribed such as fear of spiders or heights, is the almost infinite variety of different situations, within and across patients, that can trigger obsessions. This, coupled with the expense and time involved in creating VR environments, might limit the usefulness of this approach. Even with contamination fears (which may seem on the surface to be

more circumscribed than other subtypes) something that seems horribly contaminated to one person may have no effect on the next person, due to the idiosyncratic nature of OCD.

In sum, there are early indications that VR might be useful for enhancing ERP/CBT in certain situations and for certain patients, but the practicality may be limited. Controlled clinical trials demonstrating efficacy above and beyond in vivo or traditional imaginal exposures are needed.

6.9. Novel digital tools and interventions

Aside from the use of digital technologies such as live video to deliver ERP/CBT, online self-guided or therapist-assisted ERP/CBT treatment modules, or app-based ERP/CBT tools, there are numerous other opportunities for digital technologies to assist with the clinical management of OCD. The field has begun to explore and test the use of digital strategies for assessment, monitoring, interventions, and prediction, including approaches that employ machine learning [165]. This also includes passive data collection with wearables or smartphones, social media, monitoring of internet behaviour, and facilitation of symptom monitoring to aid in therapist-guided ERP/CBT [166]. This is still in relatively early phases, and, to date, most published reports do not involve randomised controlled trials.

6.10. Digital technology for monitoring of symptoms

Global position signals (GPS) could be used to help patients and therapists monitor patient behaviours which, particularly if stereotyped, might provide a digital signature associated with a compulsion. One app described in the literature provides feedback if the user has moved less than a predefined distance outdoors for a certain amount of time [167]. This case report described its use in a patient and how it assisted him to reach his clinic appointment on time after several previous failed attempts due to checking behaviours on the street.

6.11. Potential future research using passive data collection to assist with treatment

Passive data collection in combination with artificial intelligence opens up the possibilities of identifying OCD illness-specific patterns, providing digitally-assisted monitoring of behaviours or other symptoms [166]. This, for example, could enhance the ability of both patient and therapist to monitor symptoms more accurately as they are beginning to occur, or potentially even before they occur. This could potentially be fed back to the patient in real-time to quickly intervene with response prevention, or even apply behavioural techniques to prepare ahead of time mentally and physically to resist compulsions. There are several challenges inherent in these strategies. OCD symptoms are protean across patients, and within patients may not follow the same patterns in novel situations; training an algorithm might therefore result in it being too specific, or not specific enough, and thereby misreading certain situations. One could imagine a scenario in which digital feedback alerts someone in a ‘real’ dangerous situation, such as sustaining a laceration and therefore cleaning it, that they are performing a washing compulsion; the user might need to turn off the alert, yet, as is the nature of OCD, may not always know what is a ‘real’ danger situation in which to do so. In addition, such digital behavioural fingerprinting may work with those with prominent physical compulsions but less well with those with predominantly obsessional thinking and/or with mental compulsions.

6.12. Conclusions

In sum, there is strong evidence for the efficacy of remote therapist-guided CBT or ERP for OCD, with comparable results to in-person treatment. There is also strong evidence for iCBT, with generally better results associated with more clinician contact. Other types of technology-based interventions hold promise but have not yet been established in multiple, large studies.

As for many facets of clinical care, and daily life for most, technology has impacted the way that treatment is delivered, whether it be through a 'light touch' of enhancing treatment communication within traditional face-to-face psychotherapy, e.g., through SMS message, or fully computerized versions of treatment. Although there is evidence for the efficacy and acceptability of remote treatments for OCD on the whole, the field still needs to understand the degree to which patient characteristics such as socioeconomic status, location of residence, comfort with technology, and trust in the safety of their personal health information influence seeking these treatments and benefiting from them. In addition, there may be subtypes of OCD symptoms for which the treatment is more or less effective. Further, there are fewer existing studies of therapist-guided remote group CBT or ERP for OCD, which, if effective, could further improve accessibility and individual and societal cost savings. In addition, whether non-CBT/ERP remote treatments for OCD such as ACT are effective has not been established. There are many potential opportunities and underdeveloped areas for interfacing technology with standard existing treatments. The efficacy, safety, acceptability, adherence, and cost benefits are all factors that need to be evaluated, yet the traditional ways of doing so with controlled trials and peer-reviewed publications are challenged to keep pace.

7. Potential biomarkers of response to psychological therapies in OCD

As detailed in section 1.1, ERP and CBT are effective treatments for OCD, but the likelihood of achieving remission is only around 20–50% [168], leaving many individuals improved but nonetheless experiencing clinically significant symptoms. Furthermore, some individuals with OCD refuse this modality as it requires willingness to tolerate a significant degree of distress, opting instead for pharmacotherapy. Consequently, there would be considerable value in being able to identify in advance those individuals more or less likely to benefit from psychological therapy. This 'personalized medicine' approach is increasingly seen as the future of clinical care and is being used successfully in a number of areas of medicine such as oncology [169].

Numerous factors have been studied in attempts to identify predictors of treatment outcome in OCD. Worse prognosis and treatment response has been consistently associated with earlier age of onset, greater illness severity, and longer duration of illness [170]; symptom dimensions, comorbidity - notably depression - and a family history of tics have also been implicated [171]. However, most of these studies are potentially confounded by co-administration of medication; 'dosing' of psychological treatments is quite variable; and few studies incorporate a treatment-naïve or non-treatment arm. Furthermore, many studies have not used a validation or cross-validation approach, so cannot be effectively utilized to predict response for any single individual. Perhaps the greatest success to date has been

with machine learning paradigms, achieving an accuracy of 59–75% [172-174]. Biological data or biomarkers which may relate more closely to underlying neurobiological substrates arguably show greater potential for use at the individual level, primarily using genetic and neuroimaging approaches.

7.1. Genetic markers of therapy response

The term ‘therapygenetics’ has been coined to describe the relationship between genetic variation and psychological treatment outcome [175]. Initial studies focused on individual candidate genes such as the brain-derived neurotrophic factor gene (BDNF), a potential susceptibility gene for OCD [176,177]. Fullana et al. [178] reported only 36% of those carrying the BDNF Met allele (associated with decreased activity-dependent BDNF release) responded to CBT, as compared to 60% of BDNF Val homozygotes. However, similar studies in populations with anxiety/panic disorder and PTSD have had inconsistent results [179-181]. The serotonin transporter has been widely implicated in the development of OCD [182], with most genetic studies focusing on the promoter-region polymorphism (5-HTTLPR) of the gene SLC6A4, relevant to gene expression [183]. This variant has shown inconsistent results in therapy outcome in PTSD, anxiety disorders and depression [184] and a recent meta-analysis of studies of CBT for anxiety disorders (excluding OCD) was negative [185]. The Catechol-*O*-methyltransferase (COMT) gene has also been implicated in OCD risk [185]. COMT is involved in degradation of catecholamine neurotransmitters such as dopamine and norepinephrine [186]. The COMT Val158Met met/met genotype has been associated with impaired extinguishing of learned fear response and poorer response to CBT in panic disorder [187] but not in social anxiety disorder [188], and remains unstudied in OCD. The studies to-date have mostly focused on a limited set of ‘usual suspect’ candidate genes. This is likely too narrow of a scope to provide meaningful predictions of outcomes given the complexity of OCD as a psychiatric disorder and the factors involved in success in psychotherapy treatment.

There has been increasing interest in exploring epigenetic regulation in relation to treatment response. Epigenetics refers to DNA modifications that regulate genetic expression. Unlike variation in genetic coding, epigenetic status is dynamic and mutable, and may therefore better serve as a treatment response marker [189,190]. Gene methylation, the best characterized and most stable epigenetic regulatory mechanism, has shown reasonable correlation in methylation between blood and brain for genes implicated in psychiatric conditions [191,192]. Schiele et al. [185] reported that lower baseline 5HTTLPR methylation predicted impaired treatment response, consistent with reports of SLC6A4 promoter hypomethylation correlating with CBT non-response in childhood OCD and anxiety [193].

As far as we are aware, neither BDNF nor SLC6A4 methylation have been studied in connection with therapy response in OCD. MAOA (monoamine oxidase-A) has been implicated in risk of numerous psychiatric conditions - including OCD - given its importance as a mitochondrial enzyme catalyzing the breakdown of amine neurotransmitters. The neuropeptide oxytocin regulates social behaviour and impacts cognitive processes, including memory consolidation and retrieval [194], and may impede

response to exposure therapy [195]. Altered oxytocin receptor methylation has been reported in OCD [196,197], and two studies have identified elevated baseline methylation as a potential predictor of impaired CBT response [185,198].

Genome-wide approaches – which have the virtues and the drawbacks of being hypothesis-free [199] - have been inconclusive in studies of CBT response in adults and children with mood and anxiety disorders [200,201]; none have been published in OCD. One small exploratory study of genome-wide methylation in OCD [202] identified two differentially methylated genes correlating with a set of 70 co-expressed genes that were up-regulated in CBT non-responders. Further work with significantly larger samples is needed.

7.2. Neuroimaging and EEG markers

Functional neuroimaging studies utilizing FDG-PET or SPECT have reported a relationship between higher baseline resting OFC activity and therapy response [203,204] although PET did not [205]. Studies utilizing either resting state or task activation fMRI have generally not identified an association between abnormal activity and CBT response [206-209]. Norman et al. [210] demonstrated an association between better treatment response and higher pre-treatment activation in the right temporal lobe and rostral ACC during cognitive control, and with the OFC, ventromedial and lateral prefrontal, and amygdala regions during reward processing while performing an incentive flanker task.

Magnetic resonance spectroscopy (MRS) can assay the concentrations of neurochemicals such as glutamate, glutamine, or tNAA (*N*-acetylasparate and *N*-acetylaspartylglutamate), a marker of neuronal integrity. O'Neill and colleagues [211] reported a negative correlation between baseline tNAA in the right pregenual ACC and improvement in OCD symptoms.

In two morphometric studies, larger baseline size of the left OFC correlated with subsequent CBT response [212], while Hoexter et al. [213] reported a correlation between larger baseline right medial prefrontal cortex (PFC) and response to CBT. Fullana et al. [214] demonstrated decreased cortical thickness in the left rostral ACC at baseline in CBT responders; this is one of the few studies to test this as a predictive biomarker, yet it only explained 8% of inter-subject variability in response to ERP.

Diffusion tensor imaging (DTI) permits evaluation of white matter tracts and microstructure. Two studies have used this technique to study baseline white matter integrity and CBT-related changes in OCD, with negative outcomes [215,216].

Functional connectivity analyses have had heterogeneous findings. Fullana et al. [178], using resting state fMRI) found that decreased basolateral amygdala-ventromedial PFC connectivity at baseline predicted better outcomes, consistent with a study by Gottlich et al. [217]. Others have reported response to be associated with increased connectivity between the left DLPFC and right OFC at baseline [218]. Kwak et al. [219] utilized support vector machine analyses in 107 OCD patients treated with both pharmacotherapy and CBT, to identify a less responsive subgroup with impaired baseline resting-state functional connectivity within the default mode network, as well as with other brain regions. Reggente et al. [174] used a machine learning multivariate approach to explore the predictive value

of pre-treatment resting state MRI, showing that FC within the default mode network and visual network predicted post-treatment OCD severity, explaining up to 67% of the variance. Moreover, the two networks were able to correctly classify responders with up to 70% accuracy. The results demonstrated specificity in that these networks did not predict anxiety or depression changes, pre-treatment OCD severity, nor changes with the passage of time in a no-treatment arm.

The use of electroencephalogram (EEG) to further understanding of OCD has been relatively neglected. EEG permits good temporal resolution of brain electrical activity albeit with limited spatial resolution. Given its low cost and ready availability, it merits further consideration for exploration for treatment response biomarkers [220]. Krause et al. [221] utilized Low-Resolution Brain Electromagnetic Tomography (LORETA), which permits inference of electrophysiological activity regionally within the brain, and found lower beta 1, beta 3 and alpha 2 activity in the ACC of responders at baseline. Dorhmann et al. [222] found that responders to CBT, SSRIs or combined treatment spent less time at the highest level of CNS arousal at baseline. A third predictive study [223] reported that higher beta band EEG complexity was able to discriminate between CBT responders and non-responders with 89.7% accuracy.

7.3. Conclusions

In summary, there have been multiple studies examining clinical and neurobiological predictor of response to psychological therapy (mostly CBT) in OCD. A limitation of many studies has been the focus solely on pathological candidate brain regions or genetic markers. While such strategies can facilitate ‘back translation’ to understand how the pathology relates to treatment outcome, it provides a limited set of potential predictive features and does not necessarily capture neural (or behavioural or clinical) features that could portend success with CBT, thus presenting a likely ceiling on overall accuracy. In sum, while high variability appears to preclude use of imaging biomarkers for robust prediction of response at the individual level at present, improved technology as well as combinatorial approaches, using a variety of clinical and imaging and/or genetic biomarkers may in coming years be accurate enough for clinical use.

8. Conclusions

There are a number of people with OCD who do not respond adequately to exposure/response prevention or cognitive behaviour therapy. A wide range of alternative or augmenting psychotherapies have been developed and are building various levels of evidence. In addition, adjunctive exercise, music, and art therapy might be useful, albeit the evidence base for these is very small. Consideration should be given to different ways of delivering psychological therapies, including group-based, concentrated, inpatient, or with outreach, where appropriate. Digital technologies are part of an emerging field with a number of potential applications for aiding the treatment of OCD. Biomarkers for treatment response determination have potential capacity and deserve further empirical testing.

References

[1]. Fineberg NA, Hollander E, Pallanti S, Walitza S, Grünblatt E, Dell'Osso BM, et al. Clinical advances in obsessive-compulsive disorder: a position statement by the international college of obsessive-compulsive spectrum disorders. Int Clin Psychopharmacol 2020;35:173. [PubMed: 32433254]

[2]. Reid JE, Laws KR, Drummond L, Vismara M, Grancini B, Mpavaenda D, et al. Cognitive behavioural therapy with exposure and response prevention in the treatment of obsessive-compulsive disorder: a systematic review and meta-analysis of randomised controlled trials. Compr Psychiatry 2021:106:152223. [PubMed: 33618297]

[3]. American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. Am J Psychiatry 2007;164(7 Suppl):5–53.

[4]. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry 2014;14:83. [PubMed: 24645731]

[5]. NICE. Obsessive-compulsive disorder and body dysmorphic disorder: Treatment. In: Nice guideline (CG31); 2005. Retrieved from, https://www.nice.org.uk/guidance/cg31.

[6]. McKay D, Sookman D, Neziroglu F, Wilhelm S, Stein DJ, Kyrios M, et al. Efficacy of cognitive-behavioral therapy for obsessive–compulsive disorder. Psychiatry Res 2015;225:236–46. [PubMed: 25613661]

[7]. Olatunji BO, Davis ML, Powers MB, Smits JAJ. Cognitive-behavioral therapy for obsessive-compulsive disorder: a meta-analysis of treatment outcome and moderators. J Psychiatr Res 2013;47:33–41. [PubMed: 22999486]

[8]. Arch JJ, Abramowitz JS. Exposure therapy for obsessive–compulsive disorder: an optimizing inhibitory learning approach. J OCRD 2015;7:174–82.

[9]. Wilhelm S, Steketee GS. Cognitive therapy for obsessive compulsive disorder: a guide for professionals. Oakland, CA: New Harbinger Publications; 2006.

[10]. Anholt GE, Kempe P, de Haan E, van Oppen P, Cath DC, Smit JH, et al. Cognitive versus behavior therapy: processes of change in the treatment of obsessive-compulsive disorder. Psychother Psychosom 2007;77:38–42. [PubMed: 18087206]

[11]. Cottraux J, Note I, Yao SN, Lafont S, Note B, Mollard E, et al. A randomized controlled trial of cognitive therapy versus intensive behavior therapy in obsessive compulsive disorder. Psychother Psychosom 2001;70:288–97. [PubMed: 11598428]

[12]. McLean PD, Whittal ML, Thordarson DS, Taylor S, Söchting I, Koch WJ, et al. Cognitive versus behavior therapy in the group treatment of obsessive-compulsive disorder. J Consult Clin Psychol 2001;69:205–14. [PubMed: 11393598]

[13]. van Balkom Anton JLM, de Haan E, van Oppen P, Spinhoven P, Hoogduin KAL, van Dyck R. Cognitive and behavioral therapies alone versus in combination with fluvoxamine in the treatment of obsessive compulsive disorder. J Nerv Ment Dis 1998;186:492–9. [PubMed: 9717867]

[14]. Van Oppen P, de Haan E, Van Balkom AJLM, Spinhoven P, Hoogduin K, Van Dyck R. Cognitive therapy and exposure in the treatment of obsessive compulsive disorder. Behav Res Ther 1995;33:379–90. [PubMed: 7755525]

[15]. Wilhelm S, Steketee G, Fama JM, Buhlmann U, Teachman BA, Golan E. Modular cognitive therapy for obsessive-compulsive disorder: a wait-list controlled trial. J Cogn Psychother 2009;23:294–305. [PubMed: 21072138]

[16]. Ong CW, Clyde JW, Bluett EJ, Levin ME, Twohig MP. Dropout rates in exposure with response prevention for obsessive-compulsive disorder: what do the data really say? J Anxiety Disord 2016;05(40):8–17.

[17]. Vogel PA, Stiles TC, Götestam KG. Adding cognitive therapy elements to exposure therapy for obsessive compulsive disorder: a controlled study. Beh Cogn Psychotherapy 2004;32:275–90.

[18]. Rector NA, Richter MA, Katz D, Leybman M. Does the addition of cognitive therapy to exposure and response prevention for obsessive compulsive disorder enhance clinical efficacy? A

randomized controlled trial in a community setting. Br J Clin Psychol 2019;58:1–18. [PubMed: 29984550]

[19]. Steketee G, Siev J, Yovel I, Lit K, Wilhelm S. Predictors and moderators of cognitive and behavioral therapy outcomes for OCD: a patient-level mega-analysis of eight sites. Behav Ther 2019;50:165–76. [PubMed: 30661557]

[20]. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. Behav Res Ther 2006;44:1–25. [PubMed: 16300724]

[21]. Grayson J. ACT vs. ERP for OCD: is it war or marriage? The behavior therapist36; 2013. p. 84–9.

[22]. Öst L. The efficacy of acceptance and commitment therapy: an updated systematic review and meta-analysis. Behav Res Ther 2014;61:105–21. [PubMed: 25193001]

[23]. Bluett EJ, Homan KJ, Morrison KL, Levin ME, Twohig MP. Acceptance and commitment therapy for anxiety and OCD spectrum disorders: an empirical review. J Anxiety Disord 2014;28:612–24. [PubMed: 25041735]

[24]. Rohani F, Rasouli-Azad M, Twohig MP, Ghoreishi FS, Lee EB, Akbari H. Preliminary test of group acceptance and commitment therapy on obsessive-compulsive disorder for patients on optimal dose of selective serotonin reuptake inhibitors. J OCRD 2018;16:8–13.

[25]. Baghooli H, Dolatshahi B, Mohammadkhani P, Moshtagh N, Naziri G. Effectiveness of acceptance and commitment therapy in reduction of severity symptoms of patients with obsessive-compulsive disorder. Adv Environ Biol 2014:2519–25.

[26]. Vakili Y, Gharaee B, Habibi M. Acceptance and commitment therapy, selective serotonin reuptake inhibitors and their combination in the improvement of obsessive-compulsive symptoms and experiential avoidance in patients with obsessive-compulsive disorder. Iran J Psychiatry Behav Sci 2015:9.

[27]. Twohig MP, Hayes SC, Plumb JC, Pruitt LD, Collins AB, Hazlett-Stevens H, et al. A randomized clinical trial of acceptance and commitment therapy versus progressive relaxation training for obsessive-compulsive disorder. J Consult Clin Psychol 2010;78:705. [PubMed: 20873905]

[28]. Twohig MP, Vilardaga JCP, Levin ME, Hayes SC. Changes in psychological flexibility during acceptance and commitment therapy for obsessive compulsive disorder. J Contextual Behav Sci 2015;4:196–202.

[29]. Twohig MP, Abramowitz JS, Smith BM, Fabricant LE, Jacoby RJ, Morrison KL, et al. Adding acceptance and commitment therapy to exposure and response prevention for obsessive-compulsive disorder: a randomized controlled trial. Behav Res Ther 2018;108:1–9. [PubMed: 29966992]

[30]. Ong CW, Blakey SM, Smith BM, Morrison KL, Bluett EJ, Abramowitz JS, et al. Moderators and processes of change in traditional exposure and response prevention (ERP) versus acceptance and commitment therapy-informed ERP for obsessive-compulsive disorder. J OCRD 2020;24:100499.

[31]. Goldberg SB, Tucker RP, Greene PA, Davidson RJ, Kearney DJ, Simpson TL. Mindfulness-based cognitive therapy for the treatment of current depressive symptoms: a meta-analysis. Cogn Beh Ther 2019;ll(48):445–62.

[32]. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Five facet mindfulness questionnaire. Assessment. 2006;13:27–45. [PubMed: 16443717]

[33]. Hawley LL, Rogojanski J, Vorstenbosch V, Quilty LC, Laposa JM, Rector NA. The structure, correlates, and treatment related changes of mindfulness facets across the anxiety disorders and obsessive compulsive disorder. J Anxiety Disord 2017;49:65–75. [PubMed: 28432894]

[34]. Hertenstein E, Rose N, Voderholzer U, Heidenreich T, Nissen C, Thiel N, et al. Mindfulness-based cognitive therapy in obsessive-compulsive disorder – a qualitative study on patients' experiences. BMC Psychiatry 2012;12:10. [PubMed: 22333556]

[35]. Sguazzin CMG, Key BL, Rowa K, Bieling PJ, McCabe RE. Mindfulness-based cognitive therapy for residual symptoms in obsessive-compulsive disorder: a qualitative analysis. Mindfulness 2017;8:190–203.

[36]. Didonna F, Lanfredi M, Xodo E, Ferrari C, Rossi R, Pedrini L. Mindfulness-based cognitive therapy for obsessive-compulsive disorder: a pilot study. J Psychiatr Pract 2019;25:156–70. [PubMed: 30849066]

[37]. Mathur S, Sharma MP, Balachander S, Kandavel T, Reddy YCJ. A randomized controlled trial of mindfulness-based cognitive therapy vs stress management training for obsessive-compulsive disorder. J Affect Disord 2021;282:58–68. [PubMed: 33401124]

[38]. Key BL, Rowa K, Bieling P, McCabe R, Pawluk EJ. Mindfulness-based cognitive therapy as an augmentation treatment for obsessive–compulsive disorder. Clin Psychol Psychother 2017;24:1109–20. [PubMed: 28194835]

[39]. Külz AK, Landmann S, Cludius B, Rose N, Heidenreich T, Jelinek L, et al. Mindfulness-based cognitive therapy (MBCT) in patients with obsessive–compulsive disorder (OCD) and residual symptoms after cognitive behavioral therapy (CBT): a randomized controlled trial. Eur Arch Psychiatry Clin Neurosci 2019;269:223–33. [PubMed: 30446822]

[40]. Landmann S, Cludius B, Tuschen-Caffier B, Moritz S, Külz AK. Changes in the daily life experience of patients with obsessive-compulsive disorder following mindfulness-based cognitive therapy: looking beyond symptom reduction using ecological momentary assessment. Psychiatry Res 2020;286:112842. [PubMed: 32065984]

[41]. Hawley LL, Rector NA, DaSilva A, Laposa JM, Richter MA. Technology supported mindfulness for obsessive compulsive disorder: self-reported mindfulness and EEG correlates of mind wandering. Behav Res Ther 2021;136:11.

[42]. Laposa JM, Collimore KC, Hawley LL, Rector NA. Distress tolerance in OCD and anxiety disorders, and its relationship with anxiety sensitivity and intolerance of uncertainty. J Anxiety Disord 2015;33:8–14. [PubMed: 25956557]

[43]. Choudhary V, Sinha VK. Transdiagnostic applications of dialectical behaviour therapy's distress tolerance skills in psychological management of OCD. Asian J Psychiatr 2018;38:1–2. [PubMed: 30359843]

[44]. Kichuk SA, Austad CS. Toward increased tolerability of exposure treatment for obsessive-compulsive disorder. Behav Ther 2010;33:111–6.

[45]. Michel NM, Rowa K, Young L, McCabe RE. Emotional distress tolerance across anxiety disorders. J Anxiety Disord 2016;40:94–103. [PubMed: 27161839]

[46]. Wells A. Metacognitive therapy for anxiety and depression. New York, NY: Guildford Press; 2022.

[47]. Papageorgiou C, Carlile K, Thorgaard S, et al. Group cognitive-behaviour therapy of group metacognitive therapy for OCD? Benchmarking of comparative effectiveness in a routine clinical service. Front Psychol 2018;9:2551. [PubMed: 30618972]

[48]. Normann N, Morina N. The efficacy of metacognitive therapy: a systematic review and meta-analysis. Front Psychol 2018;9:2211. [PubMed: 30487770]

[49]. Van der Heiden C, van Rossen K, Dekker A, et al. Metacognitive therapy for obsessive-compulsive disorder: a pilot study. J OCRD 2016;9:24–9.

[50]. Glombiewski JA, Hansmeier J, Haberkamp A, et al. Metacognitive therapy versus exposure and response prevention for obsessive-compulsive disorder – a pilot randomized trial. J OCRD 2021;30:100650.

[51]. Melchior K, Franken I, Deen M, van der Heiden C. Metacognitive therapy versus exposure and response prevention for obsessive-compulsive disorder: study protocol for a randomised controlled trial. Trials 2019;20:1–11. [PubMed: 30606236]

[52]. Azrin NH, Nunn RG. Habit-reversal: a method of eliminating nervous habits and tics. Behav Res Ther 1973;11:619–28. [PubMed: 4777653]

[53]. Lochner C, Roos A, Stein DJ. Excoriation (skin-picking) disorder: a systematic review of treatment options. Neuropsychiatr Dis Treat 2017;13:1867–72. [PubMed: 28761349]

[54]. Grant J. Trichotillomania (hair pulling disorder). Indian J Psychiatry 2019;61(Suppl. 1):S136–9. [PubMed: 30745687]

[55]. Liu S, Li Y, Cui Y. Review of habit reversal training for tic disorders. Pediatr Investig 2020;4:127–32.

[56]. Marks IM. Fears, phobia and rituals. New York: Oxford University Press; 1987.

[57]. Fineberg NA, Potenza MN, Chamberlain SR, Berlin HA, Menzies L, Bechara A, et al. Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. Neuropsychopharmacol 2010;35:591.

[58]. Dryden W, David D. Rational emotive behavior therapy: current status. J Cogn Psychother 2008;22:195–209.

[59]. Salkovskis PM. Obsessional-compulsive problems: a cognitive-behavioural analysis. Behav Res Ther 1985;23:571–83. [PubMed: 4051930]

[60]. Jones MK, Menzies RG. Danger ideation reduction therapy (DIRT): preliminary findings with three obsessive-compulsive washers. Behav Res Ther 1997;35:955–60. [PubMed: 9401136]

[61]. Hoekstra R. Treatment of obsessive–compulsive disorder with rational emotive therapy. In: Paper presented at the first world congress of cognitive therapy. Oxford: 28 June–2 July 1989; 2022.

[62]. Krochmalik A, Jones MK, Menzies RG. Danger ideation reduction therapy (DIRT) for treatment-resistant compulsive washing. Behav Res Ther 2001;39:897–912. [PubMed: 11480831]

[63]. Krochmalik A, Jones MK, Menzies RG, Kirkby K. The superiority of danger ideation reduction therapy (DIRT) over exposure and response prevention (ERP) in treating compulsive washing. Behav Chang 2004;21:251–68.

[64]. Govender S, Drummond LM, Menzies RA. Danger ideation reduction therapy for the treatment of severe, chronic and resistant obsessive-compulsive disorder. Behav Cogn Psychother 2006;34:1–4.

[65]. Drummond LM, Kolb PJ. Obsessive compulsive contamination fears and anorexia nervosa; the application of the new psychoeducational treatment of danger ideation reduction therapy (DIRT). Behav Chang 2008;25:44–9.

[66]. Vaccaro LD, Jones MK, Menzies RG, Wootton BM. Danger ideation reduction therapy for obsessive–compulsive checking: preliminary findings. Cogn Behav Ther 2010;39:293–301. [PubMed: 21104477]

[67]. Dissanayake A, Drummond LM. Pilot study examining the potential use of the psychoeducation component of danger ideation reduction therapy (DIRT) as an adjunct to treatment for contamination fears in patients with profound refractory obsessive compulsive disorder. Eur Neuropsychopharmacol 2017;27:612.

[68]. Drummond LM, Gravestock S. Delayed emergence of obsessive-compulsive disorder following head injury: case report and review of its theoretical implications. Br J Psychiatry 1988;153:839–42. [PubMed: 3256390]

[69]. Saunders BE, Villeponteaux LA, Lipovsky JA, Kilpatrick DG, Veronen LJ. Child sexual assault as a risk factor for mental disorders among women. J Interpers Violence 1992;7:189–204.

[70]. Cromer KR, Schmidt NB, Murphy DL. An investigation of traumatic life events and obsessive-compulsive disorder. Behav Res Ther 2007;45:1683–91. [PubMed: 17067548]

[71]. Barzilay R, Patrick A, Calkins ME, Moore TM, Gur RC, Gur RE. Association between early-life trauma and obsessive compulsive symptoms in community youth. Depress Anxiety 2019;36:586–95. [PubMed: 31066996]

[72]. Murayama K, Nakao T, Ohno A, Tsuruta S, Tomiyama H, Hasuzawa S, et al. Impacts of stressful life events and traumatic experiences on onset of obsessive-compulsive disorder. Front. Psychiatry 2020:1361.

[73]. Penner-Goeke S, Binder E. Epigenetics and depression. Dialogues Clin Neurosci 2019;21:397–405. [PubMed: 31949407]

[74]. LaSalle VH, Cromer KR, Nelson KN, Kazuba D, Justement L, Murphy DL. Diagnostic interview assessed neuropsychiatric disorder comorbidity in 334 individuals with obsessive–compulsive disorder. Depress Anxiety 2004;19:163–73. [PubMed: 15129418]

[75]. Shapiro F Eye movement desensitization: a new treatment for post-traumatic stress disorder. J Beh Ther Exper Psychiatry 1989;20:211–7.

[76]. Navarro PN, Landin-Romero R, Guardiola-Wanden-Berghe R, Moreno-Alcázar A, Valiente-Gómez A, Lupo W, et al. 25 years of eye movement desensitization and reprocessing (EMDR): the EMDR therapy protocol, hypotheses of its mechanism of action and a systematic review of its efficacy in the treatment of post-traumatic stress disorder. Revista de Psiquiatría y Salud Mental 2018;11:101–14. [PubMed: 26877093]

[77]. Chen L, Zhang G, Hu M, Liang XJ. Eye movement desensitization and reprocessing versus cognitive-behavioral therapy for adult posttraumatic stress disorder: systematic review and meta-analysis. J Nerv Ment Dis 2015;203:443–51. [PubMed: 25974059]

[78]. Narizi H, Momeni N, Jariani M, Tarrahi MJ. Comparison of eye movement desensitization and reprocessing with citalopram in treatment of obsessive–compulsive disorder. Int J Psychiatr Clin Prac 2011;15:270–4.

[79]. Marsden Z, Lovell K, Blore D, Ali S, Delgadillo J. A randomized controlled trial comparing EMDR and CBT for obsessive–compulsive disorder. Clin Psychol Psychother 2018;25:10–8. [PubMed: 28836318]

[80]. Scelles C, Bulnes LC. EMDR as treatment option for conditions other than PTSD: a systematic review. Front Psychol 2021;12:644369. [PubMed: 34616328]

[81]. Veale D, Page N, Woodward E, Salkovskis P. Imagery rescripting for obsessive compulsive disorder: a single case experimental design in 12 cases. J Behav Ther Exper Psychiatry 2015;49:230–6. [PubMed: 25805628]

[82]. Maloney G, Koh G, Roberts S, Pittenger C. Imagery rescripting as an adjunct clinical intervention for obsessive compulsive disorder. J Anxiety Disord 2019;66:102110. [PubMed: 31357037]

[83]. Strachan LP, Hyett MP, McEvoy PM. Imagery rescripting for anxiety disorders and obsessive-compulsive disorder: recent advances and future directions. Curr Psychiatry Rep 2020;22:1–8. [PubMed: 31912372]

[84]. Martín-Vázquez MJ. Cognitive-behavior and narrative therapy in obsessive-compulsive disorder. Obsessive-compulsive disorder: the old and the new problems. 2014. p. 119.

[85]. Esfahani MH, Kjbaf MB, Abedi MR. Evaluation and comparison of the effects of time perspective therapy, acceptance and commitment therapy and narrative therapy on severity of symptoms of obsessive-compulsive disorder. J Ind Acad Appl Psychol 2015;41:148.

[86]. Morres ID, Hatzigeorgiadis A, Stathi A, Comoutos N, Arpin-Cribbie C, Krommidas C, et al. Aerobic exercise for adult patients with major depressive disorder in mental health services: a systematic review and meta-analysis. Depress Anxiety 2019;36:39–53. [PubMed: 30334597]

[87]. Asmundson GJG, Fetzner MG, DeBoer LB, Powers MB, Otto MW, Smits JA. Let's get physical: a contemporary review of the anxiolytic effects of exercise for anxiety and its disorders. Depress Anxiety 2013;30:362–73. [PubMed: 23300122]

[88]. Freedman DE, Richter MA. A narrative review of exercise and obsessive-compulsive disorder. Gen Hosp Psychiatry 2021;71:1–10. [PubMed: 33887525]

[89]. Brown RA, Abrantes AM, Strong DR, Mancebo MC, Menard J, Rasmussen SA, et al. A pilot study of moderate-intensity aerobic exercise for obsessive compulsive disorder. J Nerv Ment Dis 2007;195:514–20. [PubMed: 17568300]

[90]. Lancer R, Motta R, Lancer D. The effect of aerobic exercise on obsessive-compulsive disorder, anxiety, and depression: a preliminary investigation. Beh Ther 2007;30:57–62.

[91]. Rector NA, Richter MA, Lerman B, Regev R. A pilot test of the additive benefits of physical exercise to CBT for OCD. Cogn Beh Ther 2015;44:328–40.

[92]. Abrantes AM, Farris SG, Brown RA, Greenberg BD, Strong DR, McLaughlin NC, et al. Acute effects of aerobic exercise on negative affect and obsessions and compulsions in individuals with obsessive-compulsive disorder. J Affect Disord 2019;245:991–7. [PubMed: 30699885]

[93]. Abrantes AM, Brown RA, Strong DR, McLaughlin N, Garnaat SL, Mancebo M, et al. A pilot randomized controlled trial of aerobic exercise as an adjunct to OCD treatment. Gen Hosp Psychiatry 2018;49:51–5.

[94]. Sarris J, Camfield D, Berk M. Complementary medicine, self-help, and lifestyle interventions for obsessive compulsive disorder (OCD) and the OCD spectrum: a systematic review. J Affect Disord 2012;138:213–21. [PubMed: 21620478]

[95]. Wittels B. The treatment of the obsessional artist, in psychoanalysis and in art therapy. Art Psychother 1976;3:103–9.

[96]. Truong TP, Applewhite B, Heiderscheit A, Himmerich H. A systematic review of scientific studies and case reports on music and obsessive-compulsive disorder. Int J Environ Res Public Health 2021;18:11799. [PubMed: 34831558]

[97]. Simpson HB, Zuckoff A, Page JR, Franklin ME, Foa EB. Adding motivational interviewing to exposure and ritual prevention for obsessive-compulsive disorder: an open pilot trial. Cogn Behav Ther 2008;37:38–49. [PubMed: 18365797]

[98]. Kyrios M, Ahern C, Fassnacht DB, Nedeljkovic M, Moulding R, Meyer D. Therapist-assisted internet-based cognitive behavioral therapy versus progressive relaxation in obsessive-compulsive disorder: randomized controlled trial. J Med Internet Res 2018;20:e242. [PubMed: 30089607]

[99]. Simpson HB, Zuckoff AM, Maher MJ, Page JR, Franklin ME, Foa EB, et al. Challenges using motivational interviewing as an adjunct to exposure therapy for obsessive-compulsive disorder. Behav Res Ther 2010;10:941–8.

[100]. Van Passel B, Danner UN, Dingemans AE, Aarts E, Sternheim LC, Becker ES, et al. Cognitive remediation therapy does not enhance treatment effect in obsessive-compulsive disorder and anorexia nervosa: a randomised controlled trial. Psychother Psychosom 2020;89:228–41. [PubMed: 32074624]

[101]. Jónsson H, Hougaard E, Bennedsen BE. Randomized comparative study of group versus individual cognitive behavioural therapy for obsessive compulsive disorder. Acta Psychiatr Scand 2010;123:387–97. [PubMed: 20946200]

[102]. Schwartze D, Barkowski S, Burlingame GM, Strauss B, Rosendahl J. Efficacy of group psychotherapy for obsessive-compulsive disorder: a meta-analysis of randomized controlled trials. J OCRD 2016;10:49–61.

[103]. Pozza A, Dèttore D. Drop-out and efficacy of group versus individual cognitive behavioural therapy: what works best for obsessive-compulsive disorder? A systematic review and meta-analysis of direct comparisons. Psychiatry Res 2017;258:24–36. [PubMed: 28982038]

[104]. Whittal ML, Robichaud M, Thordarson DS, McLean PD. Group and individual treatment of obsessive-compulsive disorder using cognitive therapy and exposure plus response prevention: a 2-year follow-up of two randomized trials. J Consult Clin Psychol 2008;76:1003–14. [PubMed: 19045968]

[105]. Kvale G, Hansen B, Bjorgvinsson T, Bortveit T, Hagen K, Haseth S, et al. Successfully treating 90 patients with obsessive compulsive disorder in eight days: the Bergen 4-day treatment. BMC Psychiatry 2018;18:323. [PubMed: 30286745]

[106]. Launes G, Hagen K, Sunde T, Ost L-G, Klovning I, Laukvik IL, et al. A randomised controlled trial of concentrated ERP, self help and waiting list for obsessive-compulsive disorder. Front Psychol 2019;10:2500. [PubMed: 31803089]

[107]. Hansen B, Kvale G, Hagen K, Havnen A, Ost L-V. The Bergen 4-day treatment for OCD: four years follow-up of concentrated ERP in a clinical mental health setting. Cogn Beh Ther 2019;48:89–105.

[108]. Mancebo MC, Yip AG, Boisseau CL, Rasmussen SA, Zlotnick C. Behavioral therapy teams for obsessive-compulsive disorder: lessons learned from a pilot randomized trial in a community mental health center. Beh Ther 2021;52:1296–309.

[109]. Rowa K, Antony MM, Summerfeldt LJ, Purdon C, Young L, Swinson RP. Office-based vs. home-based behavioral treatment for obsessive-compulsive disorder: a preliminary study. Beh Res Ther 2007;45:1883–92.

[110]. Brennan BP, Lee C, Elias JA, Crosby JM, Mathes BM, Andre M-C, et al. Intensive residential treatment for severe obsessive-compulsive disorder: characterizing treatment course and predictors of response. J Psychiatr Res 2014;56:98–105. [PubMed: 24909787]

[111]. Balachander S, Bajaj A, Hazari N, Kumar A, Anand N, Manjula M, et al. Long-term outcomes of intensive inpatient care for severe, resistant obsessive-compulsive disorder. Can J Psychiatry 2020;65:779–89. [PubMed: 32452212]

[112]. Veale D, Naismith I, Miles S, Gledhill LJ, Stewart G, Hodsoll J. Outcomes for residential or inpatient intensive treatment of obsessive–compulsive disorder: a systematic review and meta-analysis. J OCRD 2016;8:38–49.

[113]. Herzog P, Osen B, Stierle C, Middendorf T, Voderholzer U, Koch S, et al. Determining prognostic variables of treatment outcome in obsessive–compulsive disorder: effectiveness and

its predictors in routine clinical care. Eur Arch Psychiatry Clin Neurosci 2021;272:313–26. [PubMed: 34218306]

[114]. Nanjundaswamy MH, Arumugham SS, Narayanaswamy JC, Reddy YCJ. A prospective study of intensive in-patient treatment for obsessive-compulsive disorder. Psychiatry Res 2020;291:113303. [PubMed: 32763556]

[115]. Taube-Schiff M, Rector NA, Larkin P, Mehak A, Richter MA. Effectiveness of intensive treatment services for obsessive compulsive disorder: outcomes from the first Canadian residential treatment program. Int J Psychiatry Clin Pract 2019;24:59–67. [PubMed: 31670999]

[116]. Grøtte T, Hansen B, Haseth S, Vogel PA, Guzey IC, Solem S. Three-week inpatient treatment of obsessive-compulsive disorder: a 6-month follow-up study. Front Psychol 2018:9.

[117]. Veale D, Naismith I, Miles S, Childs G, Ball J, Muccio F, et al. Outcome of intensive cognitive behaviour therapy in a residential setting for people with severe obsessive compulsive disorder: a large open case series. Behav Cogn Psychother 2015;44:331–46. [PubMed: 26122913]

[118]. Diefenbach GJ, Tolin DF. The cost of illness associated with stepped care for obsessive-compulsive disorder. J OCRD 2013;2:144–8.

[119]. Tolin DF, Diefenbach GJ, Gilliam CM. Stepped care versus standard cognitive-behavioral therapy for obsessive-compulsive disorder: a preliminary study of efficacy and costs. Depress Anxiety 2011;28:314–23. [PubMed: 21381157]

[120]. Yu X, Xia J, Du Y, Han J, Liu G. D-cycloserine augmentation i n behavioral therapy for obsessive-compulsive disorder: a meta-analysis. Drug Des Dev Ther 2015;9:2101.

[121]. McGuire JF, Wu MS, Piacentini J, McCracken JT, Storch EA. A meta-analysis of d-cycloserine in exposure-based treatment: moderators of treatment efficacy, response, and diagnostic remission. J Clin Psychiatry 2017;78:196–206. [PubMed: 27314661]

[122]. Rosenfield D, Smits JAJ, Hofmann SG, Mataix-Cols D, de la Cruz LF, Andersson E, et al. Changes in dosing and dose timing of d-cycloserine explain its apparent declining efficacy for augmenting exposure therapy for anxiety-related disorders: an individual participant-data meta-analysis. J Anxiety Disord 2019;68:102149. [PubMed: 31698111]

[123]. Kvale G, Hansen B, Hagen K, Abramowitz JS, Børtveit T, Craske MG, et al. Effect of D-cycloserine on the effect of concentrated exposure and response prevention in difficult-to-treat obsessive-compulsive disorder. JAMA Netw Open 2020;3:8.

[124]. Andersson E, Hedman E, Enander J, Radu Djurfeldt D, Ljótsson B, Cervenka S, et al. D-Cycloserine vs placebo as adjunct to cognitive behavioral therapy for obsessive-compulsive disorder and interaction with antidepressants. JAMA Psychiat 2015;72:659.

[125]. de Leeuw AS, van Megen HJGM, Kahn RS, Westenberg HGM. D-cycloserine addition to exposure sessions in the treatment of patients with obsessive-compulsive disorder. Eur Psychiatry 2016;40:38–44. [PubMed: 27837671]

[126]. O'Neill J, Feusner J. Cognitive-behavioral therapy for obsessive–compulsive disorder: access to treatment, prediction of long-term outcome with neuroimaging [internet]. Psychol Res Behav Manag 2015:211.

[127]. Van Ameringen M, Turna J, Khalesi Z, Pullia K, Patterson B. There is an app for that! The current state of mobile applications (apps) for DSM-5 obsessive-compulsive disorder, posttraumatic stress disorder, anxiety and mood disorders. Depress Anxiety 2017;34:526–39. [PubMed: 28569409]

[128]. Wootton BM. Remote cognitive–behavior therapy for obsessive–compulsive symptoms: a meta-analysis. Clin Psychol Rev 2016;43:103–13. [PubMed: 26494179]

[129]. Sucala M, Schnur JB, Constantino MJ, Miller SJ, Brackman EH, Montgomery GH. The therapeutic relationship in e-therapy for mental health: a systematic review. J Med Internet Res 2012;14:e110. [PubMed: 22858538]

[130]. Jenkins-Guarnieri MA, Pruitt LD, Luxton DD, Johnson K. Patient perceptions of telemental health: systematic review of direct comparisons to in-person psychotherapeutic treatments. Telemed J E Health 2015;21:652–60. [PubMed: 25885491]

[131]. Vogel PA, Launes G, Moen EM, Solem S, Hansen B, Håland AT, et al. Videoconference- and cell phone-based cognitive-behavioral therapy of obsessive-compulsive disorder: a case series. J Anxiety Disord 2012;26:158–64. [PubMed: 22119331]

[132]. Herbst N, Franzen G, Voderholzer U, Thiel N, Knaevelsrud C, Hertenstein E, et al. Working alliance in internet-based cognitive-behavioral therapy for obsessive-compulsive disorder. Psychother Psychosom 2016;85:117–8. [PubMed: 26807976]

[133]. Moeller AM, Christensen LF, Hansen JP, Andersen PT. Patients' acceptance of video consultations in the mental health services: a systematic review and synthesis of qualitative research. Digit Health 2022;8. 20552076221075148. [PubMed: 35154803]

[134]. Feusner J, Farrell N, Kreyling J, McGrath P, Rhode A, Faneuff T, et al. Online video teletherapy treatment of obsessive-compulsive disorder using exposure and response prevention: clinical outcomes from a retrospective longitudinal observational study. J Med Internet Res 2022;24:e36431. [PubMed: 35587365]

[135]. Andersson E, Enander J, Andrén P, Hedman E, Ljótsson B, Hursti T, et al. Internet-based cognitive behaviour therapy for obsessive–compulsive disorder: a randomized controlled trial. Psychol Med 2012;42:2193–203. [PubMed: 22348650]

[136]. Greist JH, Marks IM, Baer L, Kobak KA, Wenzel KW, Hirsch MJ, et al. Behavior therapy for obsessive-compulsive disorder guided by a computer or by a clinician compared with relaxation as a control. J Clin Psychiatry 2002;63:138–45. [PubMed: 11874215]

[137]. Lovell K, Cox D, Haddock G, Jones C, Raines D, Garvey R, et al. Telephone administered cognitive behaviour therapy for treatment of obsessive compulsive disorder: randomised controlled non inferiority trial. BMJ 2006:333:883. [PubMed: 16935946]

[138]. Johansson R, Andersson G. Internet-based psychological treatments for depression. Expert Rev Neurother 2012;12:861–9. [PubMed: 22853793]

[139]. Pearcy CP, Anderson RA, Egan SJ, Rees CS. A systematic review and meta-analysis of self-help therapeutic interventions for obsessive-compulsive disorder: is therapeutic contact key to overall improvement? J Behav Ther Exp Psychiatry 2016;51:74–83. [PubMed: 26794856]

[140]. Spek V, Cuijpers P, Nyklícek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med 2007;37:319–28. [PubMed: 17112400]

[141]. Kobak KA, Greist R, Jacobi DM, Levy-Mack H, Greist JH. Computer-assisted cognitive behavior therapy for obsessive-compulsive disorder: a randomized trial on the impact of lay vs. professional coaching. Ann Gen Psychiatry 2015;14:10. [PubMed: 25722737]

[142]. Lundström L, Flygare O, Andersson E, et al. Effect of internet-based vs face-to-face cognitive behavioral therapy for adults with obsessive-compulsive disorder: a randomized clinical trial. JAMA Netw Open 2022;5:e221967. [PubMed: 35285923]

[143]. Stefanopoulou E, Lewis D, Taylor M, Broscombe J, Larkin J. Digitally delivered psychological interventions for anxiety disorders: a comprehensive review. Psychiatry Q 2019;90:197–215.

[144]. Wootton BM, Karin E, Titov N, Dear BF. Self-guided internet–delivered cognitive behavior therapy (ICBT) for obsessive-compulsive symptoms: a randomized controlled trial. J Anxiety Disord 2019;66:102111. [PubMed: 31301476]

[145]. Lenhard F, Ssegonja R, Andersson E, Feldman I, Rück C, Mataix-Cols D, et al. Cost-effectiveness of therapist-guided internet-delivered cognitive behaviour therapy for paediatric obsessive-compulsive disorder: results from a randomised controlled trial. BMJ Open 2017;7:e015246.

[146]. Lovell K, Bower P, Gellatly J, Byford S, Bee P, McMillan D, et al. Clinical effectiveness, cost-effectiveness and acceptability of low-intensity interventions in the management of obsessive–compulsive disorder: the Obsessive–Compulsive Treatment Efficacy randomised controlled Trial (OCTET). Health Technol Assess 2017;21:1–132.

[147]. Arevian AC, O'Hora J, Rosser J, Mango JD, Miklowitz DJ, Wells KB. Patient and provider cocreation of mobile texting apps to support behavioral health: usability study. JMIR Mhealth Uhealth 2020;8:e12655. [PubMed: 32723714]

[148]. Becker S, Miron-Shatz T, Schumacher N, Krocza J, Diamantidis C, Albrecht U-V. MHealth 2.0: experiences, possibilities, and perspectives. JMIR Mhealth Uhealth 2014;2:e24. [PubMed: 25099752]

[149]. Lecomte T, Potvin S, Corbière M, Guay S, Samson C, Cloutier B, et al. Mobile apps for mental health issues: meta-review of meta-analyses. JMIR Mhealth Uhealth 2020;8:e17458. [PubMed: 32348289]

[150]. Wu A, Scult MA, Barnes ED, Betancourt JA, Falk A, Gunning FM. Smartphone apps for depression and anxiety: a systematic review and meta-analysis of techniques to increase engagement. NPJ Digit Med 2021;4:20. [PubMed: 33574573]

[151]. Lee EB, Hoepfl C, Werner C, McIngvale E. A review of tech-based self-help treatment programs for obsessive-compulsive disorder. J Obsessive Compuls Relat Disord 2019;23:100473.

[152]. Pascual-Vera B, Roncero M, Doron G, Belloch A. Assisting relapse prevention in OCD using a novel mobile app-based intervention: a case report. Bull Menninger Clin 2018;82:390–406. [PubMed: 30589573]

[153]. Roncero M, Belloch A, Doron G. Can brief, daily training using a mobile app help change maladaptive beliefs? Crossover randomized controlled trial. JMIR Mhealth Uhealth 2019;7:e11443. [PubMed: 30758294]

[154]. Roncero M, Belloch A, Doron G. A novel approach to challenging OCD related beliefs using a mobile-app: an exploratory study. J Behav Ther Exp Psychiatry 2018;59:157–60. [PubMed: 29425951]

[155]. Fleming T, Bavin L, Lucassen M, Stasiak K, Hopkins S, Merry S. Beyond the trial: systematic review of real-world uptake and engagement with digital self-help interventions for depression, low mood, or anxiety [Internet]. 2020. 10.26686/wgtn.12331259.v4. Available from.

[156]. Hwang H, Bae S, Hong JS, Han DH. Comparing effectiveness between a mobile app program and traditional cognitive behavior therapy in obsessive-compulsive disorder: evaluation study. JMIR Ment Health 2021;8:e23778. [PubMed: 33464208]

[157]. Dua D, Jagota G, Grover S. Management of obsessive-compulsive disorder with virtual reality-based exposure. Ind Psychiatry J 2021:179–81. [PubMed: 34483545]

[158]. Miegel F, Bücker L, Kühn S, Mostajeran F, Moritz S, Baumeister A, et al. Exposure and response prevention in virtual reality for patients with contamination-related obsessive-compulsive disorder: a case series. Psychiatry Q 2022. 10.1007/s11126-022-09992-5.

[159]. Laforest M, Bouchard S, Bossé J, Mesly O. Effectiveness of in virtuo exposure and response prevention treatment using cognitive-behavioral therapy for obsessive-compulsive disorder: a study based on a single-case study protocol. Front Psych 2016;13(7):99.

[160]. Cullen AJ, Dowling NL, Segrave R, Carter A, Yücel M. Exposure therapy in a virtual environment: validation in obsessive compulsive disorder. J Anxiety Disord 2021;80:102404. [PubMed: 33894550]

[161]. van Bennekom MJ, de Koning PP, Gevonden MJ, Kasanmoentalib MS, Denys D. A virtual reality game to assess OCD symptoms. Front Psych 2021;22:550165.

[162]. van Bennekom MJ, Kasanmoentalib MS, de Koning PP, Denys D. A virtual reality game to assess obsessive-compulsive disorder. Cyberpsychol Behav Soc Netw 2017;20:718–22. [PubMed: 29125791]

[163]. Kim K, Kim CH, Cha KR, Park J, Han K, Kim YK, et al. Anxiety provocation and measurement using virtual reality in patients with obsessive-compulsive disorder. Cyberpsychol Behav 2008;11:637–41. [PubMed: 18991527]

[164]. Watson C, Burley MC, Purdon C. Verbal repetition in the reappraisal of contamination-related thoughts. Behav Cogn Psychother 2010;38:337–53. [PubMed: 20380778]

[165]. Ferreri F, Bourla A, Peretti C-S, Segawa T, Jaafari N, Mouchabac S. How new technologies can improve prediction, assessment, and intervention in obsessive-compulsive disorder (e-OCD): review. JMIR Ment Health 2019;6:e11643. [PubMed: 31821153]

[166]. Vats T, Fineberg NA, Hollander E. The future of obsessive-compulsive spectrum disorders: a research perspective. Curr Top Behav Neurosci 2021;49:461–77. [PubMed: 33550566]

[167]. Olbrich H, Stengler K, Olbrich S. Smartphone based geo-feedback in obsessive compulsive disorder as facilitatory intervention: a case report. J OCRD 2016;8:75–8.

[168]. Springer KS, Levy HC, Tolin DF. Remission in CBT for adult anxiety disorders: a meta-analysis. Clin Psychol Rev 2018;61:1–8. [PubMed: 29576326]

[169]. Ozomaro U, Wahlestedt C, Nemeroff CB. Personalized medicine in psychiatry: problems and promises. BMC Med 2013;11:132. [PubMed: 23680237]

[170]. Sharma E, Math SB. Course and outcome of obsessive-compulsive disorder. Indian J Psychiatry 2019;61(Suppl. 1):S43–50. [PubMed: 30745676]

[171]. Jakubovski E, Diniz JB, Valerio C, Fossaluza V, Belotto-Silva C, Gorenstein C, et al. Clinical predictors of long-term outcome in obsessive-compulsive disorder. Depress Anxiety 2013;30:763–72. [PubMed: 23109056]

[172]. Askland KD, Garnaat S, Sibrava NJ, Boisseau CL, Strong D, Mancebo M, et al. Prediction of remission in obsessive compulsive disorder using a novel machine learning strategy. Int J Methods Psychiatr Res 2015;24:156–69. [PubMed: 25994109]

[173]. Hilbert K, Jacobi T, Kunas SL, Elsner B, Reuter B, Lueken U, et al. Identifying CBT non-response among OCD outpatients: a machine-learning approach. Psychother Res 2021;31:52–62. [PubMed: 33175642]

[174]. Reggente N, Moody TD, Morfini F, Sheen C, Rissman J, O'Neill J, et al. Multivariate resting-state functional connectivity predicts response to cognitive behavioral therapy in obsessive-compulsive disorder. Proc Natl Acad Sci U S A 2018;115:2222–7. [PubMed: 29440404]

[175]. Eley TC, Hudson JL, Creswell C, Tropeano M, Lester KJ, Cooper P, et al. Therapygenetics: the 5HTTLPR and response to psychological therapy. Mol Psychiatry 2012;17:236–7. [PubMed: 22024766]

[176]. Taylor S Molecular genetics of obsessive–compulsive disorder: a comprehensive meta-analysis of genetic association studies. Mol Psychiatry 2013;18:799–805. [PubMed: 22665263]

[177]. Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, et al. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. Science 2010;327:863–6. [PubMed: 20075215]

[178]. Fullana MA, Zhu X, Alonso P, Cardoner N, Real E, López-Solà C, et al. Basolateral amygdala-ventromedial prefrontal cortex connectivity predicts cognitive behavioural therapy outcome in adults with obsessive-compulsive disorder. J Psychiatry Neurosci 2017;42:378–85. [PubMed: 28632120]

[179]. Lester KJ, Hudson JL, Tropeano M, Creswell C, Collier DA, Farmer A, et al. Neurotrophic gene polymorphisms and response to psychological therapy. Transl Psychiatry 2012;2:e108. [PubMed: 22832952]

[180]. Felmingham KL, Dobson-Stone C, Schofield PR, Quirk GJ, Bryant RA. The brain-derived neurotrophic factor Val66Met polymorphism predicts response to exposure therapy in posttraumatic stress disorder. Biol Psychiatry 2013;73:1059–63. [PubMed: 23312562]

[181]. Santacana M, Arias B, Mitjans M, Bonillo A, Montoro M, Rosado S, et al. Predicting response trajectories during cognitive-behavioural therapy for panic disorder: no association with the BDNF gene or childhood maltreatment. PLoS One 2016;11:e0158224. [PubMed: 27355213]

[182]. Billett EA, Richter MA, King N, Heils A, Lesch KP, Kennedy JL. Obsessive compulsive disorder, response to serotonin reuptake inhibitors and the serotonin transporter gene. Mol Psychiatry 1997;2:403–6. [PubMed: 9322235]

[183]. Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Taubman J, Greenberg BD, et al. Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. Am J Hum Genet 2006;78:815–26. [PubMed: 16642437]

[184]. Lester KJ, Eley TC. Therapygenetics: using genetic markers to predict response to psychological treatment for mood and anxiety disorders. Biol Mood Anxiety Disord 2013;3:4. [PubMed: 23388219]

[185]. Schiele MA, Thiel C, Weidner M, Endres D, Zaudig M, Berberich G, et al. Serotonin transporter gene promoter hypomethylation in obsessive-compulsive disorder - predictor of impaired response to exposure treatment? J Psychiatr Res 2021;132:18–22. [PubMed: 33035761]

[186]. Kumar P, Rai V. Catechol-O-methyltransferase gene Val158Met polymorphism and obsessive compulsive disorder susceptibility: a meta-analysis. Metab Brain Dis 2020;35:241–51. [PubMed: 31879835]

[187]. Witte AV, Flöel A. Effects of COMT polymorphisms on brain function and behavior in health and disease. Brain Res Bull 2012;88:418–28. [PubMed: 22138198]

[188]. Lonsdorf TB, Rück C, Bergström J, Andersson G, Ohman A, Lindefors N, et al. The COMTval158met polymorphism is associated with symptom relief during exposure-based cognitive-behavioral treatment in panic disorder. BMC Psychiatry 2010;10:99. [PubMed: 21110842]

[189]. Andersson E, Rück C, Lavebratt C, Hedman E, Schalling M, Lindefors N, et al. Genetic polymorphisms in monoamine systems and outcome of cognitive behavior therapy for social anxiety disorder. PLoS One 2013;8:e79015. [PubMed: 24260145]

[190]. Zhou J, Li M, Wang X, He Y, Xia Y, Sweeney JA, et al. Drug response-related DNA methylation changes in schizophrenia, bipolar disorder, and major depressive disorder. Front Neurosci 2021;15:674273. [PubMed: 34054421]

[191]. Davies MN, Volta M, Pidsley R, Lunnon K, Dixit A, Lovestone S, et al. Functional annotation of the human brain methylome identifies tissue-specific epigenetic variation across brain and blood. Genome Biol 2012;13:R43. [PubMed: 22703893]

[192]. Basu M, Wang K, Ruppin E, Hannenhalli S. Predicting tissue-specific gene expression from whole blood transcriptome. Sci Adv 2021;7:eabd6991. [PubMed: 33811070]

[193]. Roberts S, Lester KJ, Hudson JL, Rapee RM, Creswell C, Cooper PJ, et al. Serotonin transporter methylation and response to cognitive behaviour therapy in children with anxiety disorders. Transl Psychiatry 2014;4:e444. [PubMed: 25226553]

[194]. Bohus B, Kovács GL, de Wied D. Oxytocin, vasopressin and memory: opposite effects on consolidation and retrieval processes. Brain Res 1978;157:414–7. [PubMed: 719533]

[195]. Acheson DT, Feifel D, Kamenski M, Mckinney R, Risbrough VB. Intranasal oxytocin administration prior to exposure therapy for arachnophobia impedes treatment response. Depress Anxiety 2015;32:400–7. [PubMed: 25826649]

[196]. Cappi C, Diniz JB, Requena GL, Lourenço T, Lisboa BC, Batistuzzo MC, et al. Epigenetic evidence for involvement of the oxytocin receptor gene in obsessive-compulsive disorder. BMC Neurosci 2016;17:79. [PubMed: 27903255]

[197]. CI Park, Kim HW, Jeon S, Kang JI, Kim SJ. Reduced DNA methylation of the oxytocin receptor gene is associated with obsessive-compulsive disorder. Clin Epigenetics 2020;12:101. [PubMed: 32631409]

[198]. Bey K, Campos-Martin R, Klawohn J, Reuter B, Grützmann R, Riesel A, et al. Hypermethylation of the oxytocin receptor gene (OXTR) in obsessive-compulsive disorder: further evidence for a biomarker of disease and treatment response. Epigenetics 2021;16:1–11. [PubMed: 32602773]

[199]. Kitsios GD, Zintzaras E. Genome-wide association studies: hypothesis-“free” or “engaged”? Transl Res 2009;154:161–4. [PubMed: 19766959]

[200]. Coleman J, Lester K, Keers R, Roberts S, Curtis C, Arendt K, et al. Genome-wide association study of response to cognitive–behavioural therapy in children with anxiety disorders. Br J Psychiatry 2016;209:236–43. [PubMed: 26989097]

[201]. Rayner C, Coleman JR, Purves KL, Hodsoll J, Goldsmith K, Alpers GW, et al. A genome-wide association meta-analysis of prognostic outcomes following cognitive behavioural therapy in individuals with anxiety and depressive disorders. Transl Psychiatry 2019;9:1–3. [PubMed: 30664621]

[202]. Rodriguez N, Martinez-Pinteño A, Blázquez A, Ortiz AE, Moreno E, Gassó P, et al. Integrative DNA methylation and gene expression analysis of cognitive behavioral therapy response in children and adolescents with obsessive-compulsive disorder; a pilot study. Pharmgenom Pers Med 2021;14:757–66.

[203]. Brody AL, Saxena S, Schwartz JM, Stoessel PW, Maidment K, Phelps ME, et al. FDG-PET predictors of response to behavioral therapy and pharmacotherapy in obsessive compulsive disorder. Psychiatry Res Neuroimaging 1998;84:1–6.

[204]. Yamanishi T, Nakaaki S, Omori IM, Hashimoto N, Shinagawa Y, Hongo J, et al. Changes after behavior therapy among responsive and nonresponsive patients with obsessive-compulsive disorder. Psychiatry Res Neuroimaging 2009;172:242–50.

[205]. Apostolova I, Block S, Buchert R, Osen B, Conradi M, Tabrizian S, et al. Effects of behavioral therapy or pharmacotherapy on brain glucose metabolism in subjects with obsessive-compulsive disorder as assessed by brain FDG PET. Psychiatry Res 2010;184:105–16. [PubMed: 20947317]

[206]. Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, et al. Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: a functional magnetic resonance imaging study. Biol Psychiatry 2005;57:901–10. [PubMed: 15820711]

[207]. Freyer T, Klöppel S, Tüscher O, Kordon A, Zurowski B, Kuelz AK, et al. Frontostriatal activation in patients with obsessive-compulsive disorder before and after cognitive behavioral therapy. Psychol Med 2011;41:207–16. [PubMed: 20236568]

[208]. Nabeyama M, Nakagawa A, Yoshiura T, Nakao T, Nakatani E, Togao O, et al. Functional MRI study of brain activation alterations in patients with obsessive-compulsive disorder after symptom improvement. Psychiatry Res 2008;163:236–47. [PubMed: 18667293]

[209]. Olatunji BO, Ferreira-Garcia R, Caseras X, Fullana MA, Wooderson S, Speckens A, et al. Predicting response to cognitive behavioral therapy in contamination-based obsessive–compulsive disorder from functional magnetic resonance imaging. Psychol Med 2014;44:2125–37. [PubMed: 24229474]

[210]. Norman LJ, Mannella KA, Yang H, Angstadt M, Abelson JL, Himle JA, et al. Treatment-specific associations between brain activation and symptom reduction in OCD following CBT: a randomized fMRI trial. Am J Psychiatry 2021;178:39–47. [PubMed: 32854533]

[211]. O'Neill J, Gorbis E, Feusner JD, Yip JC, Chang S, Maidment KM, et al. Effects of intensive cognitive-behavioral therapy on cingulate neurochemistry in obsessive-compulsive disorder. J Psychiatr Res 2013;47:494–504. [PubMed: 23290560]

[212]. Atmaca M, Yildirim H, Yilmaz S, Caglar N, Mermi O, Korkmaz S, et al. Orbitofrontal cortex and thalamus volumes in the patients with obsessive-compulsive disorder before and after cognitive behavioral therapy. Int J Psychiatry Med 2018;53:243–55. [PubMed: 26740455]

[213]. Hoexter MQ, Dougherty DD, Shavitt RG, D'Alcante CC, Duran FL, Lopes AC, et al. Differential prefrontal gray matter correlates of treatment response to fluoxetine or cognitive-behavioral therapy in obsessive-compulsive disorder. Eur Neuropsychopharmacol 2013;23:569–80. [PubMed: 22841131]

[214]. Fullana MA, Cardoner N, Alonso P, Subirà M, López-Solà C, Pujol J, et al. Brain regions related to fear extinction in obsessive-compulsive disorder and its relation to exposure therapy outcome: a morphometric study. Psychol Med 2014;44:845–56. [PubMed: 23773479]

[215]. Zhong Z, Yang X, Cao R, Li P, Li Z, Lv L, et al. Abnormalities of white matter microstructure in unmedicated patients with obsessive-compulsive disorder: changes after cognitive behavioral therapy. Brain Behav 2019;9:e01201. [PubMed: 30623612]

[216]. Brecke V, Thorsen AL, Ousdal OT, Vriend C, Alnæs D, Hagen K, et al. Diffusion tensor imaging before and 3 months after concentrated exposure response prevention in obsessive-compulsive disorder. Front Psych 2021;12:674020.

[217]. Göttlich M, Krämer UM, Kordon A, Hohagen F, Zurowski B. Resting-state connectivity of the amygdala predicts response to cognitive behavioral therapy in obsessive compulsive disorder. Biol Psychol 2015;111:100–19. [PubMed: 26388257]

[218]. Li P, Yang X, Greenshaw AJ, Li S, Luo J, Han H, et al. The effects of cognitive behavioral therapy on resting-state functional brain network in drug-naive patients with obsessive-compulsive disorder. Brain Behav 2018;8:e00963. [PubMed: 29761016]

[219]. Kwak S, Kim M, Kim T, Kwak Y, Oh S, Lho SK, et al. Defining data-driven subgroups of obsessive–compulsive disorder with different treatment responses based on resting-state functional connectivity. Transl Psychiatry 2020;10. 1–1.4. [PubMed: 32066695]

[220]. Zaboski BA, Stern EF, Skosnik PD, Pittenger C. Electroencephalographic correlates and predictors of treatment outcome in OCD: a brief narrative review. Front Psych 2021;12:703398.

[221]. Krause D, Folkerts M, Karch S, Keeser D, Chrobok AI, Zaudig M, et al. Prediction of treatment outcome in patients with obsessive-compulsive disorder with low-resolution brain electromagnetic tomography: a prospective EEG study. Front Psychol 2016;22:1993.

[222]. Dohrmann AL, Stengler K, Jahn I, Olbrich S. EEG-arousal regulation as predictor of treatment response in patients suffering from obsessive compulsive disorder. Clin Neurophysiol 2017;128:1906–14. [PubMed: 28826021]

[223]. Altuğlu TB, Metin B, Tülay EE, Tan O, Sayar GH, Taş C, et al. Prediction of treatment resistance in obsessive compulsive disorder patients based on EEG complexity as a biomarker. Clin Neurophysiol 2020:131:716–24. [PubMed: 32000072]