THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY
2023, VOL. 24, NO. 2, 118–134
https://doi.org/10.1080/15622975.2022.2086296

ORIGINAL INVESTIGATION

World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders – Version 3. Part II: OCD and PTSD

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ABSTRACT

Aim: This is the third version of the guideline of the World Federation of Societies of Biological Psychiatry (WFSBP) Task Force for the Pharmacological Treatment of Anxiety, Obsessive–Compulsive and Posttraumatic Stress Disorders which was published in 2002 and revised in 2008.

Method: A consensus panel of 34 international experts representing 22 countries developed recommendations based on efficacy and acceptability of the treatments. In this version, not only medications but also psychotherapies and other non-pharmacological interventions were evaluated, applying the same rigorous methods that are standard for the assessment of medication treatments.

Result: The present paper (Part II) contains recommendations based on published randomised controlled trials (RCTs) for the treatment of OCD ($n = 291$) and PTSD ($n = 234$) in children,

ARTICLE HISTORY
Received 1 March 2022
Revised 25 April 2022
Accepted 27 April 2022

KEYWORDS
Obsessive-compulsive disorder; posttraumatic stress disorder; treatment; children; guideline

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Supplemental data for this article can be accessed at https://doi.org/10.1080/15622975.2022.2086296.

adolescents, and adults. The accompanying paper (Part I) contains the recommendations for the treatment of anxiety disorders.
For OCD, first-line treatments are selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioural therapy (CBT). Internet-CBT was also superior to active controls. Several second-line medications are available, including clomipramine. For treatment-resistant cases, several options are available, including augmentation of SSRI treatment with antipsychotics and other drugs.
Other non-pharmacological treatments, including repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS) and others were also evaluated.
For PTSD, SSRIs and the SNRI venlafaxine are first-line treatments. CBT is the psychotherapy modality with the best body of evidence. For treatment-unresponsive patients, augmentation of SSRI treatment with antipsychotics may be an option.
Conclusion: OCD and PTSD can be effectively treated with CBT and medications.

Introduction

This guideline represents the third version of the guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) Task Force for the Pharmacological Treatment of Anxiety, Obsessive–Compulsive and Posttraumatic Stress Disorders, a consensus panel of international experts on anxiety disorders, OCD and PTSD (Bandelow et al. 2002). Since the second version in 2008 (Bandelow et al. 2008), many clinical studies have been published and several new treatments have emerged.

Although in the DSM-5 and ICD-11, OCD and PTSD are no longer classified as anxiety disorders, due to many similarities and overlap in phenomenology and psychobiology, it is still appropriate to prepare 'joint' guidelines for anxiety disorders, OCD and PTSD. The anxiety disorders are covered in the accompanying paper (Part I), which also contains all details on the methodology of this guideline project. A list of abbreviations is provided in Part I.

Methods

A panel of experts reviewed the available evidence from randomised controlled trials for the treatment of OCD ($n = 291$) and PTSD ($n = 234$) in adults and children. The review process is described in Part I. The main findings of all included RCTs are shown in the Supplementary Appendix, Part II (https://doi.org/10.1080/15622975.2022.2086296).

In Table 1, the definitions of OCD and PTSD are presented. Part I contains data on a prevalence rates, gender differences, age of onset, course, burden/health care utilisation, descriptions of the available medications for the treatment of OCD and PTSD, adverse effects, dose recommendations, general treatment standards and the principles of psychotherapeutic interventions for the treatment of these disorders.

The treatment recommendations for medications are based on randomised controlled trials (RCTs) comparing the drug with placebo are an established reference drug. Evidence for the efficacy of psychotherapeutic interventions is based on studies comparing psychotherapy condition with an active control condition (i.e. psychological placebo, pill placebo, treatment as usual, psychoeducation, relaxation and others). Studies with a waitlist control are listed in the tables; however, they have not been considered when determining the efficacy of a certain psychotherapy. When there was inconsistent evidence, e.g. when an almost equal number of studies were positive or negative, respectively, meta-analyses were performed, and the decision was based on a significant result in the meta-analysis. The meta-analytic procedure was taken from Bandelow et al. (2015).

Table 1. Short description of OCD and PTSD as defined by ICD-10/ICD-11 (WHO 1993; WHO 2017) and DSM-5 (APA 2013).

Obsessive–compulsive disorder (OCD)
OCD is characterised by recurrent obsessions and/or compulsions that cause impairment in terms of distress, time spent being preoccupied with obsessions or performing compulsions, or interference with functioning. Concerns involving contamination, harm, and sexual, aggressive and religious preoccupations are the most common obsessions. Compulsions include washing, checking, repeating, ordering, counting and touching.
Posttraumatic stress disorder (PTSD)
PTSD develops after exposure to a stressful event or situation of exceptionally threatening or horrific nature likely to cause pervasive distress in almost anyone such as death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence. The person who develops PTSD may have been the one who was harmed, the harm may have happened to a loved one, or the person may have witnessed a harmful event that happened to loved ones or strangers. The condition is characterised by recurrent and intrusive distressing recollections of the event, nightmares, a sense of reliving the experience with illusions, hallucinations, or dissociative flashback episodes, intense psychological or physiological distress at exposure to cues that resemble the traumatic event, avoidance of stimuli associated with the trauma, inability to recall important aspects of the trauma, loss of interest, other negative alterations in cognitions and mood, estrangement from others, sleep disturbances, irritability, difficulty concentrating, hypervigilance, and exaggerated startle response.

How to read the tables with evidence information

Superiority or inferiority was indicated as '>' or '<', and equal efficacy as '='. In some cases, the statements regarding evidence for a certain treatment may differ from the statements in the original article, for example when a statistical re-evaluation led to a different conclusion. Usually, the decision on efficacy was based on the primary efficacy measure of a study. If more than one scale was used in a trial, a primary efficacy measure was not identified and there were no corrections for multiple testing, a *post hoc* Bonferroni-Holm correction was applied. Thus, in some cases, a statement that a certain treatment was superior to a control, was changed to 'no difference' after applying the correction. When equal efficacy of two treatments was found, although the sample size was not large enough for a non-inferiority trial, the comparison was marked as 'underpowered'. Studies comparing two active treatments ('non-inferiority comparisons') with <50 evaluable patients per treatment arm were considered underpowered.

In the evidence tables, the studies were marked as 'long-term' if the study duration was >20 weeks. 'Relapse prevention trials' are studies in which patients were first randomised to an active drug or placebo; in a second step, the responders to the active drug were again randomised to the active drug or placebo to determine how many participants in each group experienced a relapse during a period of 26–52 weeks.

Aetiology

Hypotheses about the aetiology of OCD are currently based on a combination of vulnerability factors and stressful exposure, e.g. traumatic experiences during childhood or later in life. The vulnerability may be based on genetic factors associated with neurobiological adaptation of the central nervous system. According to a review of twin studies, heritability of OCD ranges from 27 to 47% in adults and from 45 to 65% in children (van Grootheest et al. 2005). Neurobiological abnormalities in patients with OCD that have been suggested, including dysfunctions of serotonin and dopamine systems and the hypothalamic-pituitary-adrenal (HPA) axis. Alterations were also found in cellular and humoral immunity and in electrophysiological and neuroimaging studies (Bandelow et al. 2016, 2017).

Although PTSD aetiology is linked to traumatic experiences and other psychosocial risk factors, individuals with a certain predisposition may show more intensive reactions to trauma. Subjects who develop PTSD have an increased ratio of psychiatric disorders before the trauma, such as pre-existing affective, anxiety or substance abuse disorders (Breslau et al. 1997; Perkonigg et al. 2000; Mayou et al. 2001). Other risk factors include unstable family conditions during childhood (King et al. 1996), sexual or physical abuse (Koenen 2006; Cougle et al. 2009) and lack of social support after trauma (Olff et al. 2007). Women have been observed to have a higher risk of developing PTSD. In a large random sample of American adults, 60.7% had been exposed to traumatic events; on average 8.2% of men and 20.4% of women suffering from a comparable trauma develop PTSD (Kessler et al. 1995).

Treatment

Obsessive-compulsive disorder (OCD)

This overview is focused on the treatment of OCD and does not cover OCD-related disorders, including body dysmorphic disorder, hoarding disorder, trichotillomania, excoriation disorder, tic disorders, Gilles de la Tourette syndrome, paediatric acute-onset neuropsychiatric syndrome (PANS) and others.

The treatment of OCD is sometimes associated with lower response rates than the treatment of anxiety disorders. Sometimes, only partial remission is achieved even when all standard treatments have been tried.

In the following chapter, a systematic review of all available RCTs for the OCD is presented. The treatment recommendations for OCD are summarised in Table 2. This table contains references to tables in the Supplementary Appendix which contain all RTCs included in the review (and some open studies for deep brain stimulation and neurosurgical methods).

Medications for OCD in adults

The recommendations for medication treatment of OCD are listed in Table 2.

SSRIs (escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline) are the first-line treatments for OCD. For *citalopram*, one study showing superiority to placebo exists (LoE A/RG 1).

The *TCA clomipramine* has long been a standard treatment for OCD. It has been discussed whether clomipramine is more effective than all SSRIs (Denys 2006). A meta-analysis does not confirm this hypothesis (Skapinakis et al. 2016). Also, direct comparisons with SSRIs did not find differences in efficacy. Adverse effects may occur with clomipramine more often than with SSRIs (LoE A/RG 2).

Table 2. Summary of recommendations for the treatment of OCD. RCTs (suppl.), tables in the Supplementary Appendix containing the RCTs on which this decision was based.

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Medications				Table 1
SSRIs escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline	Escitalopram, fluvoxamine, fluoxetine, paroxetine, and sertraline are first-line treatments for OCD	A	1	
TCA clomipramine	Clomipramine is effective in OCD. Data are inconclusive whether it is more effective than SSRIs	A	2	
SSRI citalopram	Citalopram was effective in a placebo-controlled study	B	2	
SNRI venlafaxine	Venlafaxine was as effective as paroxetine in one study	B	2	
NaSSA mirtazapine	Mirtazapine was effective in one placebo-controlled study	B	2	
Serotonin precursor 5-HTP	5-hydroxytryptophane (5-HTP) was effective in one DBPC study	B	2	
COMT-inhibitor tolcapone	Tolcapone was effective in one DBPC study	B	2	
MAOI phenelzine	Phenelzine was not effective in one DBPC study and less effective than fluoxetine	B-	2-	
Herbal preparation St. John's wort	St. John's wort was not effective in one DBPC study	B-	2-	
	N-acetylcysteine as monotherapy is not effective	A-	1-	
Medications for treatment-unresponsive OCD	The following treatments have been examined in treatment-unresponsive patients. Some of these treatments are experimental			
	Clomipramine (i.v.) > clomipramine (oral)	A	2	Table 2
	Aripiprazole add-on to SSRIs > placebo add-on			
	Haloperidol add-on to SSRIs > placebo add-on			
	Risperidone add-on to SSRIs > placebo add-on			
	Memantine add-on to SSRIs > placebo add-on			
	Ondansetron alone or as add-on to SSRIs > placebo add-on			
	Granisetron add-on to SSRIs > placebo add-on			
	Celecoxib add-on to SSRIs > placebo add-on			
	Lamotrigine add-on to SSRIs > placebo add-on			
	Pindolol add-on to SSRIs > placebo add-on			
	CBT add-on to SSRI > placebo add-on	B	2	
	Methylphenidate add-on to SSRIs > placebo add-on	B	3	
	Topisetron add-on to SSRIs > placebo add-on			
	Amantadine add-on to SSRIs > placebo add-on			
	N-acetylcysteine add-on to SSRIs > placebo add-on			
	L-carnosine add-on to SSRIs > placebo add-on			
Psychotherapy				Table 3
CBT/ERP	CBT/ERP is a first-line treatment for OCD. CBT/ERP is more effective than active controls (psychological placebo, pill placebo, relaxation, and psychoeducation)	A	1	
Internet interventions based on CBT (iCBT)	iCBT was superior to active controls. Meta-analysis revealed a large effect size difference between iCBT and active controls	A	1	
EMDR	For EMDR, only one underpowered comparison with CBT is available	D	4	
Treatments for OCD unresponsive to CBT				Table 4
Fluvoxamine	Patients not responding to CBT improved with fluvoxamine	B	2	
	Patients not responding to CBT did not improve with mindfulness CBT	B-	2-	
Combination of psychotherapy and medication				Table 5
CBT/ERP vs. drug	Comparisons of CBT/ERP and medication were inconclusive. Two studies did not show a difference, one showed superiority of CBT/ERP, another one superiority of drug treatment	D	4	
Combination vs. drug alone	The combination of CBT/ERP + drug is more effective than drug treatment alone	A	1	
Combination vs. CBT/ERP alone	The combination of CBT/ERP + drug is not more effective than CBT/ERP alone	B-	2-	
Enhancing of CBT/ERP with d-cycloserine				Table 6
CBT/ERP + d-cycloserine	Enhancing of CBT/ERP with d-cycloserine is ineffective	A-	1-	
External magnetic and electric stimulation				Table 7
Repetitive transcranial magnetic stimulation (rTMS)	Approximately half of the rTMS studies do not show a difference to sham controls. However, two meta-analyses found medium effect size differences between rTMS and sham	B	2	
Deep Transcranial Magnetic Stimulation (dTMS)	dTMS was superior to sham in two studies, but it should be restricted to carefully selected treatment-refractory sufferers from OCD	A	3	
Transcranial direct current stimulation (tDCS)	tDCS was superior to sham in some but not all studies	D	4	
Invasive methods for severely ill treatment-unresponsive cases				
Modified electroconvulsive therapy (mECT)	mECT + medications was superior to medications alone, but should be restricted to carefully selected treatment-refractory sufferers from OCD	B	2*	Table 7
Deep Brain Stimulation (DBS)	In the majority of studies, DBS was superior to sham. It should be restricted to carefully selected treatment-refractory sufferers from OCD.	A	3*	Table 7 Table 8
Gamma Knife ventral capsulotomy	Ventral capsulotomy was superior to sham in one study but it should be restricted to carefully selected treatment-refractory sufferers from OCD	B	3*	Table 7
MRT-guided focussed ultrasound surgery (MRgFUS)	For MRgFUS, only case reports are available. It should be restricted to carefully selected treatment-refractory sufferers from OCD	C1	3*	Table 8
Neurosurgery with thermocoagulation (with skull opening)	Only uncontrolled studies exist. As neurosurgery with thermocoagulation may be associated with disabling adverse effects and less invasive methods are available, it cannot be recommended except in unique situations.	C1	3*	Table 8

*This recommendation grades refer only to treatment-refractory patients with OCD.
The colours indicate the recommendation levels (see Table 4, Part I): RG = 1, dark green; RG = 2, light green; RG = 3, yellow; RG = 1-, dark red; RG = 2-, light red; RG = 3-, orange.

Venlafaxine was shown to be as effective as paroxetine; placebo-controlled studies are lacking (LoE B/RG 2).

The NaSSA antidepressant *mirtazapine* was effective in one placebo-controlled study (LoE B/RG 2).

As complete remission of OCD is often not achieved with initial standard treatments, many other drugs have been tried. However, these are not routinely used in OCD treatment.

- *5-Hydroxytryptophane*, a serotonin precursor, was effective in a DBPC study (LoE B/RG 2).
- *Tolcapone* is a catechol-O-methyl-transferase (COMT) enzyme inhibitor that augments cortical dopaminergic transmission. It was effective in a DBPC study (LoE B/RG 2).
- The MAOI *phenelzine* was not effective in a DBPC study. It was less effective than fluoxetine (LoE B-/RG 2-).
- The herbal preparation *St. John's wort* was not effective in a DBPC study (LoE B-/RG 2-).

Benzodiazepines have not been studied in DBPC trials in OCD. In a double-blind crossover study which did not fulfil the criteria of this guideline, 40% of individuals not responding to clomipramine had a clinically significant response to *clonazepam* treatment (Hewlett et al. 1992).

Dosing. Dosage recommendations are overviewed in Table 3. In general, higher doses of the antidepressants are often used in OCD, as compared with other anxiety disorders or major depression. Fixed-dose comparator studies provide inconsistent evidence for a dose-response relationship with SSRIs, higher doses being associated with greater efficacy in most (Montgomery et al. 1993; Zitterl et al. 1999; Romano et al. 2001; Hollander et al. 2003; Stein et al. 2007) but not all evaluations (Tollefson et al. 1994; Greist et al. 1995; Montgomery et al. 2001). According to a meta-analysis of RCTs that compared multiple, fixed doses of SSRIs to one another and to placebo, higher doses of SSRIs were associated with improved treatment efficacy but also with a higher proportion of dropouts due to side-effects (Bloch et al. 2010). However, in these studies, only doses within the normal range were used. In non-responders, greater symptom improvement was seen with doses exceeding the normal range. In a double-blind study comparing sertraline 200 mg/day with higher doses (250–400 mg/day) in nonresponders, greater symptom improvement was seen in the high-dose group (Ninan et al. 2006). In a retrospective case-note survey it was found that higher doses of SSRIs were associated with clinical improvement (Pampaloni et al. 2010). In an open-label study, patients who did not respond to escitalopram 20 mg/day showed improvement after a dosage increase (maximum 50 mg/day) (Rabinowitz et al. 2008). In another open-label study, escitalopram 30 mg/day was more effective than 20 mg/day (Dougherty et al. 2009). In a retrospective analysis of 21 patients, higher doses of escitalopram (41.9 mg/d) were well tolerated and effective (Shim et al. 2008). However, caution should be used when considering prescribing off label dosages of citalopram (exceeding 40 mg/day) and escitalopram (exceeding 20 mg/day) because of the risk of dose-dependent QT_C prolongation, particularly when combined with other medicines that can also affect the QT_C interval or when treating patients >65 years. If a decision is made to proceed, periodic ECG monitoring is advisable.

Table 3. Dosing recommendations for medication treatment of OCD.

Treatment	Examples	Recommended daily dose for adults
SSRIs	Citalopram	20–40 mg*
	Escitalopram	10–20 mg*
	Fluoxetine	20–40 mg
	Fluvoxamine	100–300 mg
	Paroxetine	20–60 mg
	Sertraline	50–200 mg
SNRIs	Venlafaxine	75–225 mg
TCAs	Clomipramine	75–250 mg
NaSSA	Mirtazapine	30–60 mg
Atypical antipsychotics	Aripiprazole	10–30 mg
	Risperidone	0.5–6 mg

*Caution should be used when considering prescribing off label dosages of citalopram (exceeding 40 mg/day) and escitalopram (exceeding 20 mg/day) because of the risk of dose dependent QT_C prolongation, particularly when combined with other medicines that can also affect the QT_C interval or when treating patients >65 years. If a decision is made to proceed, periodic ECG monitoring is advisable.

Long-Term treatment. OCD requires long-term treatment. In long-term and relapse prevention studies, escitalopram, fluoxetine, paroxetine, sertraline, clomipramine and mirtazapine were superior to placebo (Table 1, Supplementary Appendix). These trials lasted 24–52 weeks and suggested that ongoing treatment for at least one year is necessary to prevent relapse.

Within the limits of the acute treatment phase, response to treatment with SSRIs is characteristically partial. Between 30 and 60% cases in acute phase DBPC studies reached a clinically relevant level of improvement. However, according to a DBPC study, responder rates increased to 70% by 24 weeks (Stein et al. 2007). During the open-label phase of a DBPC relapse prevention trial, 78% cases achieved clinical response status by the 16 week endpoint (Fineberg

et al. 2007). Gains may even accrue for at least two years (Rasmussen et al. 1997).

In a 7-year follow-up study after treatment with CBT in combination with either fluvoxamine or placebo in a randomised design, 29 of 30 patients still needed additional psychotherapy and/or medication. This may indicate that OCD patients usually require ongoing treatment to maintain their improvements over long periods (Rufer et al. 2005).

Taken together, these results suggest that OCD requires long-term treatment of at least one year at an effective dose-level and that continuation of SSRIs protects patients against relapse. The possibility that some patients may retain response at a lower dose must be weighed against the possibility that reinstatement of treatment after relapse may be associated with a poorer response.

As there are no RCTs studying the use of lower maintenance doses, it is recommended to use the same doses in long-term treatment as in the acute treatment phase.

Medications for treatment-resistant OCD. About 40% OCD patients treated with SSRIs fail to fully respond to initial treatment and continue to exhibit significant symptoms. Many alternative treatments, some of which have been experimental, have been tried in these treatment-resistant cases. In most of these studies, augmentation of SSRI treatment was examined (Table 2).

The definition of treatment refractoriness varied among the studies. In most studies, nonresponders were defined as unresponsive (defined as less than 25% improvement in Y-BOCS) to courses of treatment with one or two different SSRIs at a maximum tolerated dose for 8–12 weeks.

There are only a few studies that investigate the switch from one drug to another. In one double-blind study, the switch from venlafaxine to paroxetine and *vice versa* was investigated in non-responders. Overall, 42% of the patients showed improvement after the switch. 56% of the venlafaxine-nonresponders improved with paroxetine. Conversely, only 19% of the paroxetine-nonresponders showed benefits from being switched to venlafaxine (Denys et al. 2003). In a case series, switching from an SSRI to the SNRI duloxetine was successful in a number of treatment-resistant patients (Dell'osso et al. 2008).

In a study with children and adolescents with OCD who failed to respond to an SSRI, the addition of N-acetylcysteine to SSRIs was more effective than adding placebo to SSRIs.

Psychotherapies for OCD in adults

Cognitive behavioural therapy (CBT)/exposure and response prevention (ERP). In the psychotherapy of OCD, *cognitive behavioural therapy and exposure/response prevention* are usually combined. CBT/ERP therapy for OCD is more effective than waitlist, psychological placebo, pill placebo, relaxation, and psychoeducation (Table 2) (LoE A/RG 1). A limitation is that 80% of psychotherapeutic trials for OCD included patients who were taking stable doses of antidepressants (Skapinakis et al. 2016).

Meta-analysis. As there was conclusive evidence for the efficacy of CBT from the original studies, no meta-analysis was performed by the guideline task force.

A meta-analysis found that CBT/ERP for OCD was more effective than psychological placebo conditions (Reid et al. 2021).

A significant proportion of OCD patients refuse treatment or terminate treatment programs early, because they fear high levels of revulsion, fear or even 'magical' consequences when not performing their rituals. Moreover, even among those who do complete treatment, a substantial proportion of patients do not respond.

Internet psychotherapeutic interventions based on CBT (iCBT) for OCD. Comparisons of *iCBT* vs. waitlist were mostly positive. Four of five comparisons with active controls found a significant difference (Table 2).
Meta-analysis. Our meta-analysis of studies with active controls showed a large significant difference between iCBT and active controls (Cohen's $d = 0.82$; CI 0.46–1.18; $p < .0001$) (Figure 1; Supplementary Appendix) (LoE A/RG 1).

Another meta-analysis found that iCBT was more effective than inactive controls, but did not differ from active controls (Hoppen et al. 2021).

EMDR. For EMDR, only one underpowered comparison with CBT is available (LoE D/RG 4).

Psychotherapies/medications for treatment-unresponsive OCD. Only few studies have been conducted with OCD patients who did not respond to CBT (Table 2). One study showed that patients not responding to CBT improved when fluvoxamine was added (LoE B/RG 2). In another study, patients with incomplete response to CBT who were switched to mindfulness CBT or psychological placebo did not show further improvement when compared to the control group (LoE B-/RG 2-).

Long-term treatment. Most psychotherapy trials have a relatively short duration (e.g. 8–24 weeks). There is a lack of studies comparing the efficacy of shorter and longer treatments (e.g. 12 weeks vs. 24 weeks). Therefore, evidence-based recommendations for long-lasting treatments (e.g. for one year or more) cannot be given.

Comparisons of psychotherapy and pharmacotherapy and their combination

The results of studies comparing drugs (clomipramine or SSRIs) with CBT or ERP are not easy to interpret (Table 2). Two studies did not show a difference, one showed superiority of CBT/ERP, another one superiority of drug treatment (LoE D/RG 4).

The combination of CBT/ERP + drug is more effective than drug treatment alone (LoE A/RG 1), while the combination was not more effective than CBT/ERP alone (LoE B-/RG 2-).

According to a meta-analysis, the combination of psychotherapeutic and psychopharmacological interventions was more effective than are psychotherapeutic interventions alone, at least in severe OCD (Skapinakis et al. 2016).

Enhancing CBT/exposure with D-cycloserine. Some studies have evaluated the potential of D-cycloserine for enhancing the effects of exposure or CBT for OCD (Table 2). Only one study found an effect of the combination when compared to CBT and placebo, one found a deterioration, and the remaining ones found no difference.

Meta-analysis. A meta-analysis of these studies did not find any overall effect (Cohen's $d = 0.05$; CI −0.47–0.56; $p = .86$, N. S.) (Figure 2; Supplementary Appendix) (LoE A-/RG 1-).

Neurostimulation methods and neurosurgery

As there are many patients with OCD who do not respond to standard treatments, several neurostimulation methods have been tried (Table 4).

Non-invasive methods use external magnetic (e.g. rTMS) or external electric modulation (e.g. tDCS).

Some invasive methods are used as *ultima ratio* in severe treatment-resistant cases of OCD (Table 2).

Clinical consensus is that there is a very limited role for ECT in the treatment of OCD, except for symptomatic treatment of OCD comorbidities, including depression or catatonia, rather than targeting the core OCD pathology. A systematic review failed to find evidence supporting the use of ECT in OCD, as the literature was restricted to case reports and series (Fontenelle et al. 2015). According to a systematic review on OCD-related disorders (not pure OCD), single case reports or case series of ECT in treatment-unresponsive patients showed at least some response in 70% of the reports (Dos Santos-Ribeiro et al. 2018). There is only one newer study that supports the use of modified electroconvulsive therapy (mECT) in OCD.

Table 4. Neurostimulation methods and neurosurgery.

Method	Description
External magnetic modulation	
Repetitive transcranial magnetic stimulation (rTMS)	An electromagnetic coil is placed against the forehead and delivers a magnetic pulse that stimulates nerve cells in certain regions of the brain
Deep transcranial magnetic stimulation (dTMS)	dTMS is a special form of rTMS that uses special combinations of coils ('H coils') that are capable of reaching 4 cm beneath the surface of the skull
Theta burst stimulation (TBS)	In contrast to rTMS, the magnetic pulses are applied in a certain pattern, called bursts, which allows using a lower stimulation intensity and a shorter time of stimulation
External electric modulation	
Modified electroconvulsive therapy (mECT)	mECT is still based on the induction of a brief seizure in a controlled setting, while the motor signs of the seizure are absent
Transcranial direct current stimulation (tDCS)	To stimulate brain cells, a constant low electric current is delivered via electrodes on the head without inducing a seizure
Internal electric modulation	
Deep brain stimulation (DBS)	A coiled wire (lead) with four electrodes is placed in certain regions of the brain. The lead is connected with a battery-powered pulse generator which is placed subcutaneously below the clavicle via an insulated wire that runs below the skin
Stereotactic leasioning without opening the skull	
Radiosurgery (e.g. Gamma Knife)	Radiation is used to inactivate defined targets in the brain, without the need for a surgical incision
MRT-guided focussed ultrasound surgery (MRgFUS)	High-power ultrasound waves are applied across the skull to induce a peak temperature in the target region between 51 and 56°C to precisely ablate a target in the brain
Stereotactic surgery with skull-opening	
Ablative neurosurgery with thermocoagulation	Lesions are made by thermocoagulation with a leucotome inserted into a burr hole in the skull. Common methods include cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy

Neurosurgery should be used exclusively for severely ill and treatment refractory cases.

After the first broadly destructive frontal lobotomies in 1935, which occasionally had dramatic adverse effects, stereotactic thermocoagulation was used since 1949 to create lesions in the internal capsule. Newer methods do not require opening of the skull, but they are still associated with lesions of brain tissue. In 1953, radiosurgical capsulotomy was developed which does not require open surgery. The Gamma Knife, which uses radioactive isotopes of cobalt was developed in 1967 (Miguel et al. 2019). This method has permitted the design of blinded, controlled studies. Other non-cranium-opening ablative neurosurgery methods use ultrasound thermocoagulation guided by magnetic resonance tomography.

Since 1999, the availability of reversible and adjustable deep brain stimulation (DBS) has led to a decrease in the use of ablative neurosurgical procedures. It requires skull opening but does not cause lesions in the brain.

Repetitive transcranial magnetic stimulation (rTMS). Many controlled studies showed efficacy of repetitive transcranial magnetic stimulation (rTMS); however, also many negative reports exist (Table 2).

In a 2018 meta-analysis of 18 studies (Rehn et al. 2018) and a more recent one (Perera et al. 2021), which included 21 studies, moderate effect size difference between rTMS and sham were found (Hedges' g of 0.79 and 0.64, respectively) (LoE B/RG 2).

The US-American FDA has approved rTMS for the adjunctive treatment in adults with OCD.

Transcranial direct current stimulation (tDCS). tDCS has shown potential efficacy, at least in the short term, in a small number of small, sham-controlled RCTs of treatment-resistant OCD. However, there was marked inconsistency in the stimulation protocols, the use of concurrent treatments and the outcomes, suggesting that replication studies are needed to determine the optimal stimulation protocol and the typical effect size with confidence (LoE D/RG 4).

Modified electroconvulsive therapy (ECT). There is only one RCT that showed that modified electroconvulsive therapy (mECT) was more effective than drugs alone in treatment-unresponsive patients with OCD. Although ECT is an 'invasive' method, the side effect profile is moderate. It should be tried before more invasive methods like DBS or neurosurgery are considered (LoE B/RG 2).

Deep brain stimulation (DBS). The majority of studies showed that DBS was superior to sham procedures (LoE A/RG 3).

Also, according to a meta-analysis, DBS differed significantly from those of sham procedures (Martinho et al. 2020). A meta-analysis showed that DBS is as effective as ablative surgery (Hageman et al. 2021). According to the World Society for Stereotactic and Functional Neurosurgery (WSSFN), DBS represents an emerging, but not yet established therapy (Wu et al. 2021) (see also comment by (van Wingen et al. 2022). It should only be used in patients with chronic (more than 5 years), severe and treatment-resistant OCD. Along with informed consent, an independent review by a multidisciplinary team is mandatory.

Neurosurgery. Many open studies and case reports investigating 'traditional' *neurosurgery* which requires skull opening have been published (Table 8, Supplementary Appendix). Side effects may vary according to the surgical technique. For some patients these may be particularly serious (including headache, weight-gain/loss, nausea/vomiting, urinary disturbances, insomnia, apathy, hypomania, transitory hallucinations, epileptic seizure, behaviour disorders, reduced intellectual, emotional, memory and cognitive functions, and death by suicide). In a follow-up of 5 patients after neurosurgery, all patients failed to maintain initial improvements after surgery and relapsed. In addition, they became depressed with suicidal ideation or attempts (Yaryura-Tobias et al. 2000). In a long-term follow-up of 25 consecutive OCD capsulotomies, only two patients achieved remission, while severe side effects were observed in a substantial number of patients (Rück 2006). As some newer less invasive methods for treating treatment-resistant OCD are available, 'traditional' neurosurgery should be restricted to unique cases (LoE C1/RG 3).

There is only one controlled study showing that *Gamma Knife radiosurgery* (anterior capsulotomy) for OCD ventral capsulotomy was superior to sham (LoE B/RG 3).

Magnetic resonance-guided focused ultrasound capsulotomy (MRgFUS) was shown to be effective in patients with OCD in open studies (Table 8, Supplementary Appendix). No serious adverse events were reported (LoE C1/RG 3).

A meta-analysis comparing open and controlled studies with ablative neurosurgery and DBS found equal efficacy (Hageman et al. 2021). The rate of adverse events was similar. Impulsivity as a side effect was more frequent with DBS.

Table 5. Summary of recommendations for the treatment of OCD in children/adolescents. RCTs (suppl.), tables in the Supplementary Appendix containing the RCTs on which this decision was based.

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Medications				Table 9
SSRIs (fluvoxamine, fluoxetine, sertraline)	Fluvoxamine, fluoxetine, and sertraline are first-line drug treatment for OCD	A	1	
TCA clomipramine	Clomipramine is effective for treating OCD in children/adolescents	A	2	
SSRI paroxetine	Evidence for the efficacy of paroxetine is inconsistent	D	4	
SSRI citalopram	Evidence for the efficacy of citalopram is insufficient	D	4	
Psychotherapy				Table 10
Cognitive behavioural therapy (CBT)	CBT for OCD in children/adolescents is more effective than waitlist and pill placebo and as effective as sertraline	A	1	
Internet interventions based on CBT (iCBT)	iCBT was superior to waitlist in one study, less effective than personal CBT in one, and as effective as personal CBT in an underpowered study. It can be used as add-on to standard treatments or to bridge the waiting period for face-to-face CBT	C1	3	
Combination of psychotherapy and medication				Table 11
CBT/ERP vs. drug	CBT/ERP is as effective as drug treatment	B	2	
Combination vs. drug alone	The combination of CBT/ERP + drug is more effective than drug treatment alone	A	1	
Combination vs. drug alone	The combination of CBT/ERP + drug was more effective than CBT alone in an adequately powered study; two studies showing no difference between CBT alone and the combination were underpowered	B	2	
Enhancing CBT with d-cycloserine	Enhancing CBT with d-cycloserine was not more effective than placebo + CBT	A-	1-	Table12

The colours indicate the recommendation levels (see Table 4, Part I): RG = 1, dark green; RG = 2, light green; RG = 3, yellow; RG = 1-, dark red; RG = 2-, light red; RG = 3-, orange.

OCD in children and adolescents

The treatment recommendations for OCD in children/adolescents are summarised in Table 5.

Medications for children and adolescents with OCD

Similar to the treatment of adults, the efficacy of the SSRIs *fluvoxamine, fluoxetine and sertraline* was confirmed in studies with children and adolescents suffering from OCD (Table 5) (LoE A/RG 1). Regarding doses of the SSRIs, it has been suggested that maintenance treatment should be on a medium to high dose (Romano et al. 2001).

The efficacy of the TCA *clomipramine* was confirmed in studies with children and adolescents suffering from OCD (LoE A/RG 2).

For *paroxetine*, one DBPC trial showed superiority over placebo. However, in a relapse prevention study, it did not differ from placebo (LoE D/RG 4).

For *citalopram*, only one underpowered comparison with fluoxetine is available (LoE D/RG 4).

Regarding an increased risk of suicidal ideation and behaviour associated with antidepressant treatment of young people aged less than 25 years, see section 'Treating Children and Adolescents' (Part I).

Psychotherapies for children and adolescents with OCD

CBT strategies involving exposure and response prevention (ERP) are considered most effective and are often combined with family education in children and adolescents with OCD (Table 5). CBT/ERP was more effective than waitlist, pill placebo and as effective as sertraline. In a comparison of CBT alone, sertraline alone, combined CBT and sertraline, or pill placebo, all active groups were superior to placebo.

Meta-analysis. A meta-analysis of studies with active controls showed a large significant difference between CBT and active controls (Cohen's d = 1.1 (0.60–1.60); $p<.0001$) (LoE A/RG 1) (Figure 3, Supplementary Appendix).

For *internet-based CBT*, the evidence was inconclusive, as it was less effective than face-to-face CBT in one study. Another comparison showing no difference to face-to-face CBT was underpowered (LoE C1/RG 3). It can be used as add-on to standard treatments or to bridge the waiting period for fac-to-face CBT.

Combination of psychotherapy and medication for OCD in children and adolescents

Based on a few studies comparing CBT, drug treatment and their combination, a tentative conclusion can be drawn that CBT/ERP may be as effective as drug treatment (LoE B/RG 2) and that a combination of both may be more effective than drug treatment alone (LoE A/RG 1) but not more effective than CBT alone (LoE A-/RG 1-).

A meta-analysis found that CBT was as effective as SSRIs (Uhre et al. 2020).

Enhancing CBT/exposure with D-cycloserine in children and adolescents with OCD. Two studies have evaluated the potential of D-cycloserine to enhance the effects of exposure or CBT for OCD, both with a negative result (LoE A-/RG 1-).

Posttraumatic stress disorder (PTSD)

The treatment recommendations for PTSD are summarised in Table 6. Dosing recommendations are listed in Table 7.

Medications for PTSD in adults

Medications for PTSD are listed in Table 6. The *SSRIs fluoxetine, paroxetine, and sertraline* and the *SNRI venlafaxine* can be considered first-line treatments for PTSD (LoE A/RG 1).

The *TCAs amitriptyline and imipramine* are second-line options because, in comparison to the SSRIs, they are associated with a higher incidence of side effects, risk of overdose, and poor compliance rates (LoE A/RG 2).

Also, the *MAOI phenelzine* should only be used as second-line option due to its side effects and possible interactions (LoE A/RG 2).

Mirtazapine was effective in one DBPC study (LoE B/RG 2).

The *antipsychotic risperidone* should only be used as a third-line option, due to possible side effects such as extrapyramidal symptoms or akathisia, even when the doses used in PTSD are lower than in the treatment of schizophrenia (LoE A/RG 3).

The *antipsychotic quetiapine* should only be used as a third-line option, due to possible side effects such as metabolic syndrome (LoE B/RG 3).

The *anticonvulsant lamotrigine* has been associated with skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. These risks can be minimised by up-titrating the drug with once weekly increases. It should only be used in otherwise treatment-unresponsive cases (LoE B/RG 3).

The cyclopyrrolone hypnotic ('Z-substance') *eszopiclone* was effective in a DBPC study (LoE B/RG 3).

The effects of α_1 blocker *prazosin* on nightmares in PTSD patients were shown in some studies, most of which were positive. Data on improvement of global PTSD symptoms are lacking (LoE A/RG 2 for nightmares).

Infusion of the NMDA receptor antagonist *ketamine* was superior to midazolam infusion in one DBPC study (LoE B/RG 3).

Long-term treatment. PTSD is often a chronic disorder and requires long-term treatment. Long-term efficacy was demonstrated for the SSRIs fluoxetine and sertraline and the SNRI venlafaxine. These trials lasted 24 to 52 weeks and suggested that ongoing treatment for at least one year is necessary to prevent relapse.

As there are no RCTs studying the use of lower maintenance doses, it is recommended to use the same doses in long-term treatment as in the acute treatment phase.

Treatment-resistant posttraumatic stress disorder. Some studies have investigated treatment-resistant PTSD. The definition of treatment refractoriness varied among the studies. In most studies, nonresponders were defined as unresponsive (e.g. defined as less than 70% improvement in CAPS) to courses of treatment with one or two different SSRIs at a maximum tolerated dose for 8–12 weeks.

Olanzapine as monotherapy or as add-on to SSRIs may be tried (LoE A/RG 3). Efficacy of augmentation with risperidone was shown in two studies, while a third study did not demonstrate an effect (LoE B/RG 3). Treatment with antipsychotics maybe associated with metabolic syndrome (olanzapine) or extrapyramidal side effects/akathisia (risperidone) and other adverse effects.

Prevention of PTSD. Prophylactic treatments have been suggested for preventing the emergence of posttraumatic symptoms in people who have been exposed to major trauma.

Of medications used for prevention of PTSD immediately after trauma, most failed, including benzodiazepines, escitalopram, propranolol, gabapentin, and oxytocin administered intranasally. Only *hydrocortisone infusion* was shown to be effective in 3 studies (LoE A/RG 2). However, a Cochrane analysis of medications for secondary prevention of PTSD came to the conclusion that the evidence does not support the use of any medicines for the prevention of PTSD in people exposed to a traumatic event, regardless of whether or not they have psychological symptoms (Bertolini et al. 2022).

Psychotherapy for PTSD

Cognitive behavioural therapy. The majority of RCTs of CBT in PTSD used only waitlists as comparisons (Table 6). Moreover, in a substantial number of studies, CBT was not even superior to waitlist. Also, many comparisons with active control groups revealed no difference.

Table 6. Summary of recommendations for the treatment of PTSD. RCTs (suppl.), tables in the Supplementary Appendix containing the RCTs on which this decision was based.

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Medications				Table 13
SSRIs (fluoxetine, paroxetine, sertraline)	Fluoxetine, paroxetine, and sertraline are first-line treatments for PTSD	A	1	
SNRI venlafaxine	Venlafaxine is a first-line treatment for PTSD	A	1	
TCA amitriptyline	Amitriptyline is effective in PTSD. It is associated with more side effects than SSRIs/SNRIs	A	2	
TCA imipramine	Imipramine was effective in DBPC studies; however, it was less effective than phenelzine in one study and as effective as phenelzine in an underpowered study	B	2	
Irreversible MAOI phenelzine	Phenelzine was effective in DBPC studies; it was more effective than imipramine in one study and as effective as imipramine in an underpowered study	A	2	
NaSSA mirtazapine	Mirtazapine was effective in one DBPC study	B	2	
Antipsychotic risperidone	Risperidone is effective in PTSD according to DBPC studies. Due to increased adverse effects, it should only be used when standard treatments have failed or have not been tolerated	A	3	
Antipsychotic quetiapine	Quetiapine was effective in one DBPC study. Due to a higher rate of adverse effects, it should only be used when standard treatments have failed or have not been tolerated	B	3	
Anticonvulsant lamotrigine	Lamotrigine was effective in PTSD according to a placebo-controlled study. Due to its adverse effects, it should only be used when standard treatments have failed or have not been tolerated	B	3	
Benzodiazepine analogue eszopiclone	Eszopiclone was effective in PTSD according to a DBPC study.	B	3	
α_{2A} blocker prazosin	Prazosin was effective in treating nightmares in PTSD	A	2*	
NMDA receptor antagonist ketamine	Ketamine infusion was superior to midazolam infusion	B	3	
Medications for treatment-unresponsive patients				Table 14
Olanzapine	Olanzapine was effective in treatment-unresponsive patients with PTSD according to a DBPC study. Due to increased adverse effects, it should only be used when standard treatments have failed or have not been tolerated	B	3**	
Olanzapine add-on to SSRIs	Olanzapine add-on to SSRIs was effective in treatment-unresponsive patients with PTSD according to a DBPC study. Due to increased adverse effects, it should only be used when standard treatments have failed or have not been tolerated	B	3**	
Risperidone add-on to SSRIs	Risperidone add-on to SSRIs was effective in treatment-unresponsive patients with PTSD according to a DBPC study. Due to increased adverse effects, it should only be used when standard treatments have failed or have not been tolerated	B	3**	
Medications for secondary prevention of PTSD				Table 15
Hydrocortisone	Hydrocortisone was effective in placebo-controlled studies	A	2	
Benzodiazepines	The prophylactic administration of benzodiazepines was not effective in preventing PTSD	A-	1-	
Escitalopram	The prophylactic administration of escitalopram was not effective in preventing PTSD	A-	1-	
Propranolol	The prophylactic administration of propranolol was not effective in preventing PTSD	A-	1-	
Gabapentin	The prophylactic administration of gabapentin was not effective in preventing PTSD	B-	2-	
Oxytocin intranasal	The prophylactic administration of intranasal oxytocin was not effective in preventing PTSD	B-	2-	
Psychotherapy				Table 16
Cognitive behavioural therapy (CBT)/ Narrative Exposure Therapy (NET)	Evidence for the superiority of CBT and NET for PTSD to active controls is inconsistent, with many studies showing no difference. The meta-analysis of CBT/NET vs. active controls results showed a medium effect size. However, effect sizes may have been overestimated, as indication for publication bias was found.	A	1	
Dialectical behavioural therapy (DBT)	DBT was more effective than CBT in one study	B	2	
Internet interventions based on CBT (iCBT)	iCBT was superior to waitlist in some, but not all studies, and not superior to active controls (psychological placebo, TAU)	A-	1-	
Virtual reality exposure (VRE)	VRE was more effective than waitlist and as effective as imaginal exposure	B	2	
EMDR	EMDR was superior to waitlist in some, but not all studies. It was superior to psychological placebo and pill placebo, but not superior to psychological placebo or TAU. Comparisons with CBT are inconclusive	A-	1-	
'Debriefing'	Immediate psychotherapy after trauma (debriefing) is not effective and may worsen symptomatology	A-	1-	
Combination of psychotherapy and medication				Table 17
CBT vs. drug	CBT was as effective as drug treatment in one study	B	2	
Combination vs. CBT alone	There is inconsistent evidence whether the combination of CBT + medication is more effective than CBT alone	D	3	
Combination vs. drug alone	There is inconsistent evidence whether the combination of CBT + medication is more effective than medication alone	D	3	
Enhancing exposure/virtual reality exposure				Table 18
D-cycloserine + exposure	Using D-cycloserine for enhancing exposure therapy is not effective	B-	2-	
Neurostimulation				
Repetitive transcranial magnetic stimulation (rTMS)	rTMS was effective in one sham-controlled study	B	2	

*Only for treating nightmares in PTSD.
**Only for treatment-unresponsive patients.
The colours indicate the recommendation levels (see Table 4, Part I): RG = 1, dark green; RG = 2, light green; RG = 3, yellow; RG = 1-, dark red; RG = 2-, light red; RG = 3-, orange.

Table 7. Dosing recommendations for medication treatment of PTSD.

Treatment	Examples	Recommended daily dose for adults
SSRIs	Fluoxetine	20–40 mg
	Paroxetine	20–60 mg
	Sertraline	50–200 mg
SNRIs	Venlafaxine	75–225 mg
TCAs	Amitriptyline	75–150 mg
	Imipramine	75–250 mg
Benzodiazepines	Alprazolam	1.5–8 mg
	Bromazepam	1.5–6 mg
	Clonazepam	1–4 mg
	Diazepam	5–20 mg
	Lorazepam	2–8 mg
NaSSA	Mirtazapine	30–60 mg
MAOI	Phenelzine	45–90 mg
Atypical antipsychotics	Quetiapine	50–300 mg
Anticonvulsant	Lamotrigine	25–500 mg
α_1-Antagonist	Prazosin	1–10 mg

Narrative exposure therapy (NET) is a trauma-focussed short-term psychotherapy that was developed for the treatment of PTSD resulting from war and torture. As NET is similar to CBT, the results for both psychotherapies were combined in this review.

Meta-analysis. A meta-analysis of studies comparing CBT and NET with active controls showed a significant difference between CBT and active controls (medium effect size; Cohen's $d = 0.64$; CI 0.46–0.83; $p < .0001$). However, a strong indication for publication bias was found (Kendall's τ: $p = .0002$), indicating that the currently available evidence from RCTs may overestimate the effect of CBT. After adjustment with Duval & Tweedie's trim and fill method, only a small effect size of 0.35 (0.14–0.58) would remain (Figures 4 and 4 b, Supplementary Appendix) (LoE A/RG 1).

Dialectical behaviour therapy (DBT). Dialectical behaviour therapy (DBT) which is a form of psychotherapy for borderline personality disorder derived from CBT, was more effective than CBT in one study in PTSD (LoE B/RG 2). However, PTSD patients in this study also had to fulfil criteria of borderline personality disorder. Thus, the results cannot be generalised to average patients with PTSD.

Internet psychotherapeutic interventions based on CBT (iCBT). Some studies have shown superiority of *iCBT* to waitlist. However, two studies comparing these interventions with waitlist or inactive controls were negative, and two comparisons with active controls also failed. Thus, iCBT for PTSD cannot be recommended for PTSD (LoE A-/RG 1-).

Virtual reality exposure therapy. *Virtual reality exposure therapy* was more effective than waitlist and as effective as imaginal exposure in an adequately powered study. One study showing it is as effective as exposure was underpowered (LoE B/RG 2).

Eye movement desensitization and reprocessing therapy (EMDR). The evidence for *EMDR* is not sufficient to recommend this form of psychotherapy. Many comparisons have been performed with waitlist controls, of which one was negative. Comparisons with active controls did not show a difference. The only studies comparing EMDR with or without eye movements did not find a difference (Boudewyns and Hyer 1996; Devilly et al. 1998). In both of these studies, neither EMDR nor EMDR without eye movements were superior to controls.

Comparisons with CBT showed mixed results. Some showed less efficacy for EMDR, some showed superiority, and most comparisons showing equal efficacy were underpowered.

In contrast to our findings, other meta-analyses and guidelines came to the conclusion that there is a strong recommendation for EMDR (Courtois et al. 2017; Bisson et al. 2019; Lewis et al. 2020), but these analyses did not differentiate between active and inactive control groups.

Early treatment. Although up to 61% of individuals will be subjected to potentially traumatic events in their lives, only a small proportion will develop PTSD (Kessler et al. 1995). The proportion of affected persons varies between 15 and 50%, depending on the kind of trauma and their vulnerabilities to PTSD. When using prophylactic treatments, up to 100% of trauma victims would receive treatment, although many of them may not have the propensity for developing PTSD.

In order to prevent the development of PTSD, 'critical incident stress debriefing', a therapeutic conversation with an individual who has just experienced a traumatic event, was attempted. Debriefing means that all victims of trauma are included in a study with the intention to prevent PTSD. However, the available studies showed that debriefing did not differ from inactive controls or even showed a worsening when compared to 'no treatment' (LoE A-/RG 1-).

Also, a meta-analysis of debriefing showed that it did not improve natural recovery from trauma-related disorders (van Emmerik et al. 2002). A possible explanation is that healthy individuals often overcome their symptoms following a trauma ('time heals'), but when they are confronted repeatedly with the trauma in psychotherapy sessions, this may hinder the natural healing process.

In meta-analysis of early interventions for individuals exposed to a trauma who were not pre-screened for traumatic stress symptoms, there were no clinically important differences between any intervention and TAU. For individuals reporting traumatic stress symptoms, benefits for CBT and EMDR were found. Differences were greatest for those already diagnosed with acute stress disorder and PTSD (Roberts et al. 2019). Altogether, it is advisable to start early treatment only in those individuals exposed to significant trauma who show clinical signs of trauma- and stressor-related disorders.

Long-term treatment. Most psychotherapy trials have a relatively short duration (e.g. 8–24 weeks). There is a lack of studies comparing the efficacy of shorter and longer treatments (e.g. 12 weeks vs. 24 weeks). Therefore, evidence-based recommendations for long-lasting treatments (e.g. for one year or more) cannot be given.

Comparisons of psychotherapy and pharmacotherapy for PTSD and their combination

There have been very few direct comparisons of the efficacy of psychological and pharmacological treatments (Table 6). Only one study directly compared CBT and paroxetine and found no difference (LoE B/RG 2). Evidence for combining both treatment modalities is inconsistent. One study demonstrated that the combination of CBT and drug is more effective than CBT alone, while one study did not find gains from adding paroxetine to CBT (LoE D/RG 3). One study showed that the combination of CBT and drug is more effective than medication alone, while one study did not find gains from adding CBT to paroxetine (LoE D/RG 3).

Enhancing exposure/virtual reality exposure with D-cycloserine or MDMA for PTSD. Four studies examined the effects of adding D-cycloserine to exposure therapy or virtual reality exposure. Two did not show additional gains, one demonstrated an effect, and another one even showed a deterioration. Altogether, the combination cannot be recommended (LoE B-/RG 2-).

Five controlled studies found efficacy of the psychoactive agent MDMA ('Ecstasy') as an augmentor of psychotherapy in PTSD. However, the adverse effects of the recreational drug MDMA in overdose can potentially be life-threatening, with symptoms including hypertension, faintness, loss of consciousness, seizures and hyperthermia. As MDMA is not a drug that is produced under control of regulatory administrations, its use cannot be recommended.

Neurostimulation methods

Repetitive transcranial magnetic stimulation (rTMS). Repetitive transcranial magnetic stimulation was effective in one controlled study (Cohen et al. 2004) (LoE B/RG 2).

Deep brain stimulation (DBS). There are no controlled studies with DBS for PTSD. DBS was effective in a patient with treatment-unresponsive PTSD (Langevin et al. 2016).

PTSD in children and adolescents

Treatment recommendations for PTSD in children and adolescents are summarised in Table 8.

Medications for PTSD in children and adolescents

Only two placebo-controlled studies with sertraline were performed on children and adolescents with PTSD (Table 8). One did not show superiority to

Table 8. Summary of recommendations for the treatment of PTSD in children and adolescents. RCTs (suppl.), tables in the Supplementary Appendix containing the RCTs on which this decision was based.

Treatment	Recommendation	LoE	RG	RCTs (suppl.)
Medications				Table 19
SSRI sertraline	Evidence for sertraline is inconclusive, with one study showing superiority over placebo and another one showing no difference to placebo	D	4	
Psychotherapy				Table 20
CBT	Evidence for CBT for PTSD in children and adolescents is mixed. Some studies show superiority to waitlist, but several studies do not show a difference to waitlist or no intervention. Four studies show superiority to active controls. The meta-analysis of studies with active controls showed a significant difference between CBT and active controls (medium effect size)	A	1	
EMDR	Evidence for EMDR is inconclusive. Two studies showed a difference to waitlist, two studies did not. Comparisons with active controls are lacking. Two studies showing equal efficacy of EMDR and CBT were underpowered	D	4	
Enhancing exposure with D-cycloserine				Table 21
D-cycloserine + exposure	Enhancing exposure with d-cycloserine was not effective	B-	2-	

placebo, while the other one showed that the addition of sertraline to CBT was more effective than placebo plus CBT (LoE D/RG 4).

Psychotherapies for PTSD in children and adolescents

While many studies with *CBT* found superiority to waitlist, 6 comparisons with waitlist or 'no intervention' did not show a difference (Table 8). However, 4 comparisons with active controls were positive.

Meta-analysis. A meta-analysis of studies with active controls showed a significant difference between CBT and active controls (medium effect size; Cohen's $d = 0.73$; CI 0.58–0.99; $p < .0001$) (Figure 5; Supplementary Appendix) (LoE A/RG 1).

The evidence for treating PTSD in children and adolescents with EMDR is inconsistent. In two of four studies, it was not even superior to waitlist. Comparisons with active controls are lacking. Two studies showing equal efficacy of EMDR and CBT were underpowered (LoE D/RG 4).

Enhancing exposure/virtual reality exposure with D-cycloserine for PTSD in children and adolescents

One study found no difference between D-cycloserine- and placebo-augmentation in children with PTSD (LoE B-/RG 2-).

Conclusions

This comprehensive review of available RCTs for OCD and PTSD has demonstrated that many treatments with a good body of evidence exist that can help to improve the quality of life of the sufferers from these disorders.

However, there is still room for improvement. Many patients treated with an optimal psychotherapy or medication trial will not experience full response to treatment. In particular, there are many patients with OCD that do not respond to all standard treatments and augmenting strategies. The high number of experimental treatment methods that have been studied in these sometimes desperate cases is a reflection of the shortcomings of existing treatments.

In patients not responding to first, second, or third-line treatments, invasive methods have been used. Traditional neurosurgery, which requires skull opening and destruction of brain tissue with thermocoagulation, has been almost completely abandoned. However, other invasive methods like deep brain stimulation (DBS) or radiation/ultrasound surgery are still used in carefully selected, severely ill and treatment-unresponsive patients. Although the adverse effects of these treatments are often moderate, replacing these invasive methods by highly effective medications is an important goal for future clinical research.

Although PTSD is a chronic and disabling disorder, the condition often improves with time distance from the trauma. However, many patients with PTSD still have symptoms after adequate psychotherapy and medication trials. For these patients, many treatments have been tried, some of which have an experimental character. Future research should address the unmet needs in the pharmacotherapy of PTSD.

OCD and PTSD can be effectively treated with CBT. In contrast to other guidelines, decisions on recommendations for psychotherapy were only based on RCTs that compared a treatment with an active control group (e.g. psychological placebo). Comparisons with waitlists were not taken into account, as their scientific value is very limited, and there is no convincing reason why lower standards should be applied in psychotherapy research than in medication trials. Of all controlled psychotherapy trials in OCD evaluated in this guideline, 51% were comparisons with active control groups, while the percentage for PTSD was only 34%.

In the meta-analyses, CBT was shown to be more effective than active controls in adults and children/adolescents with OCD and PTSD. However, for both disorders, a large number of the original studies did not show superiority to a psychological placebo are other active controls. Moreover, tests for publication biases suggested that the effect sizes obtained for PTSD in the meta-analysis may have been overestimated.

Cognitive behavioural interventions delivered via Internet and virtual/augmented reality exposure therapy may be future options for the treatment of OCD and PTSD. At present, it is advisable to use this treatment modalities only as add-on to standard treatments.

EMDR, a method with an unexplored mechanism of action, is often promoted as treatment for PTSD. However, there is no evidence that the gains achieved with this treatment go beyond attention effects.

Future trials with psychotherapy should fulfil certain quality standards, including use of a 'psychological placebo' instead of waitlist as a control condition, adequate sample sizes, adequate blinding, intent-to-treat analysis, and inclusion of medication-free patients.

The Task Force members hope that this guideline will be useful to improve the care of patients and to help clinicians and service commissioners in providing and planning high quality care. This international

initiative has shown that guidelines do not have to be different in various countries in the world. The discussion among the international experts was far from controversial. Altogether, the Task Force members showed a high degree of agreement even in controversial issues. Ideally, in the future, the treatment of anxiety disorders, OCD and PTSD in the whole world will be based on internationally accepted standards, following the principles of evidence-based medicine.

Acknowledgement

B. Bandelow, C. Allgulander, D. Baldwin, K. Domschke, E. Erikson, V. Masdrakis, N. Fineberg, S. Pallanti, and J. Zohar are members of the Anxiety Disorders Network (ADRN) of the European College of Neuropsychopharmacology (ECNP).

Statement of interest

The authors have worked to ensure that all information, including concerning drug dosages, schedules, routes of administration and licencing in this guideline is accurate and consistent with general psychiatric and medical standards at the time of publication. However, due to changing government regulations, continuing research, and changing information concerning drug therapy and reactions, the reader is urged to check the local prescribing information for each drug for any change in indications and dosage, or for added precautions. Moreover, specific situations may require a specific therapeutic response not included in this guideline. For these reasons and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of physicians directly involved in their care or the care of a member of their family. The authors and publisher disclaim any responsibility for any consequences which may follow from the use of information presented in this guideline. No potential conflict of interest was reported by the author(s).

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