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Canadian Network for Mood and Anxiety Treatments (CANMAT) and International College of Obsessive-Compulsive Spectrum Disorders (ICOCS) 2025 international guidelines for the management of patients with obsessive-compulsive disorder

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A B S T R A C T

Background: As a joint effort by the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS), these treatment guidelines provide an up-to-date synthesis of published literature on the efficacy, safety, and tolerability of the range of interventions available for the management of obsessive-compulsive disorder (OCD) across the lifespan. The primary goal is to provide clear, easy to use recommendations for practicing clinicians.

Methods: A global group of OCD experts were divided into panels to develop specific sections based on internal group discussions and the evidence extracted from systematic literature searches. CANMAT-defined Levels of Evidence, as well as level of clinical support were used to inform Lines of Treatment and final treatment recommendations. Drafts were revised based on feedback from individuals with lived experience, expert peer review, and a defined expert consensus process.

Results: These OCD Guidelines include seven sections spanning foundations of management and diagnosis, psychological, pharmacological, and neuro-modulation treatment modalities, treatment resistance, children and adolescents, special populations and future directions. Recommendations are summarized in tables for ease of reference and caveats and limitations of the current evidence are discussed.

Conclusions: The CANMAT/ICOCS 2025 OCD International Guidelines synthesize the evidence on the efficacy, safety, and tolerability of the range of interventions available for the management of OCD. It is anticipated that these new OCD guidelines will enable psychiatrists and other clinicians to provide systematic, evidence-based care for their patients with OCD across the lifespan.

Commonly used acronyms

ACC = Anterior Cingulate Cortex
ACT = Acceptance and Commitment Therapy
ADHD = Attention Deficit Hyperactivity Disorder
ALIC = Anterior Limb of the Internal Capsule
ALS = Amyotrophic Lateral Sclerosis
APA = American Psychiatric Association
APN = Ablative Psychiatric Neurosurgery
ASD = Autism Spectrum Disorder
B4DT = Bergen 4-Day Treatment program
BDZs = Benzodiazepines
CAM = Complementary and Alternative Medicine
CBT = Cognitive Behavioural Therapy
fCBT = Family-based CBT
CI = Confidence Interval
CPD = Continuing Professional Development
CGI-I = Clinical Global Impression (Improvement) scale
CGI-S = Clinical Global Impression (Severity) scale
CIHR = Canadian Institutes for Health Research
CSTC = Cortico-Striato-Thalamo-Cortical circuit
CT = Cognitive Therapy
CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale
DA = dopamine
DAT = Dopamine transporter
DBPC = Double Blind Placebo Controlled
DBS = Deep Brain Stimulation
DBT = Dialectical Behavioural Therapy
DCS = D-cycloserine
DLPFC = Dorsolateral Prefrontal Cortex
DSM-5 = Diagnostic and Statistical Manual of Mental Disorders (5th revision)
dTMS = deep repetitive TMS
DUI = Duration of Untreated Illness
ECT = Electroconvulsive Therapy
ED = Excoriation Disorder
EEG = Electroencephalogram
EMDR = Eye Movement Desensitization and Reprocessing
EPA = Eicosapentaenoic Acid
ERP = Exposure and Response Prevention

HAM-D = Hamilton Depression rating scale
HF = High Frequency
ICBT Internet-delivered Cognitive Behavioural Therapy
ICD-10 = International Classification of Diseases, 10th Revision
ICD-11 = International Classification of Diseases, 11th Revision
IOP = Intensive Outpatient Program
IV = Intravenous
LF = Low Frequency
MAOIs = Monoamine Oxidase Inhibitors
MBCT = Mindfulness-Based Cognitive Therapy
MCT = Meta-Cognitive Therapy
MD = Mean Difference
MDD = Major Depressive Disorder
MRgFUS = Magnetic Resonance-guided Focused Ultrasound
MI = Motivational Interviewing
mPFC = Medial Prefrontal Cortex
MRR = Mortality Rate Ratio
NAC = N-Acetylcysteine
NaSSA = Noradrenergic and Specific Serotonergic Antidepressant
NE = norepinephrine
NET = norepinephrine transporter
NNH = Number Needed to Harm
NSAIDS = Non-Steroidal Anti-Inflammatory Drugs
OC = Obsessive-Compulsive
OCD = Obsessive Compulsive Disorder
OCPD = Obsessive Compulsive Personality Disorder
OCRDs = Obsessive Compulsive Related Disorders
OFC = Orbitofrontal Cortex
OR = Odds Ratio
PANDAS = Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections
PANS = Pediatric Acute-onset Neuropsychiatric Syndrome
PCC = Primary Care Clinician
PMR = Progressive Muscle Relaxation
PTSD = Post Traumatic Stress Disorder
RCT = Randomized Control Trial
RRBs = Restrictive Repetitive Behaviours
rTMS = repetitive TMS
SA = Suicide Attempts
SAE = Serious Adverse Event
SAD = Social Anxiety Disorder
SMT = Stress and Anxiety Management Therapy
SDAM = Serotonin-Dopamine Activity Modulators
SERT = serotonin transporter
SGAs = Second Generation Antipsychotics
SI = Suicidal Ideation
SMA = Supplementary Motor Area
SMD = Standard Mean Difference
SNRIs = Serotonin Noradrenaline Reuptake Inhibitors
SP = Social Phobia
SRIs = Serotonin Reuptake Inhibitors
SSRIs = Selective Serotonin Reuptake Inhibitors
TAU = Treatment as Usual
TBS = Theta Burst Stimulation
TCAs = Tricyclic Antidepressants
tDCS = Transcranial Direct Current Stimulation
TEAS = Transcutaneous Electrical Acupoint Stimulation
TMS = Transcranial Magnetic Stimulation
TR = Treatment Resistant
TS = Tourette's Syndrome
TSPO = Translocator Protein
TTM = Trichotillomania
Y-BOCS = Yale-Brown Obsessive Compulsive Scale
YMRS = Young Mania Rating Scale
5-HT = 5-hydroxytryptamine, serotonin

1. Introduction

Obsessive-Compulsive Disorder (OCD) is a disabling and relatively common psychiatric disorder, with lifetime prevalence estimates ranging from 1.3 % to 2.4 % (Bandelow and Michaelis, 2015; Fawcett et al., 2020). It is associated with significant morbidity and functional impairment, impacting quality of life. OCD is characterized by a wide range of symptom profiles which can influence the diagnostic and treatment delay (Fineberg et al., 2020). Clinical treatment guidelines are a potential tool to assist clinicians in understanding, recognizing, and treating this chronic disorder.

The primary goals of the Canadian Network for Mood and Anxiety Treatments (CANMAT) are to generate scientific evidence, synthesize, and translate evidence into clinical guidelines and task force reports, and deliver up-to-date scientific information in the form of educational activities for clinicians, patients, their families, and the public. Since its founding, CANMAT has published a series of treatment guidelines for key mental illnesses including Major Depressive Disorder and Bipolar Disorder. This is the first guideline for the management of patients with OCD developed and published by CANMAT in collaboration with the International College of Obsessive-Compulsive Spectrum Disorder (ICOCS; www.icocs.org).

The ICOCS is an organization which aims to help mental health professionals develop research in the field of obsessive-compulsive spectrum disorders. By improving professional and public awareness of these disorders, the ICOCS seeks to help improve the diagnosis, deployment of resources, and treatments for OCD and related disorders.

The scope of these guidelines is to review recent published literature on OCD across clinical populations and provide a synthesis of the evidence on the efficacy, safety, and tolerability of the range of interventions available for the management of OCD. The primary goal is to provide clear, easy to use recommendations for practicing clinicians. As with previous CANMAT guidelines, it is anticipated that the current guideline will enable psychiatrists and other clinicians, including primary care clinicians, to provide evidence-based care for their patients with OCD across the lifespan. These guidelines are not meant to substitute clinical judgment or establish definitive standards of care.

As these guidelines are a joint effort between CANMAT and ICOCS, they are developed to be used internationally. However, not all interventions included in the guidelines will be available in all countries. It is recommended that clinicians follow the directions of local regulatory bodies.

1.1. Methods

1.1.1. Guideline structure

A global group of expert OCD clinicians and researchers were identified and contacted. Expert panels, each with a team lead, were established for each section. Panel members were selected due to their expertise in the areas of OCD pharmacology, psychotherapy, and neuromodulation. Each group developed their section based on internal group discussions and the evidence extracted from systematic literature searches. Team leads divided out the sections within their members and manuscript drafts were distributed amongst section members for discussion and agreement. The editorial team then reviewed and revised each section if necessary, merging sections to reach consensus and ensure consistency and clarity. A consensus meeting of section leads was held to obtain agreement on the major recommendations in the guidelines. A draft of the guidelines was also presented at the annual ICOCS meeting. Individuals with lived OCD experience were present and their

Table 1a
CANMAT grading system: Levels of evidence (LoE).

Level	Evidence
1	Meta-analysis with narrow confidence intervals and/or 2 or more double-blinded randomized controlled trials (RCTs) with adequate sample size (n ≥ 30 per active treatment arm), including placebo-controlled (or in the case of psychotherapy studies, including an active control condition* with adequate blinding**).
2	Meta-analysis with wide confidence intervals and/or 1 double-blinded RCT with adequate sample size (n ≥ 30 per active treatment arm) with placebo or an active comparison condition*.
3	At least one double-blinded RCT with placebo or active control comparison condition (n = 10–29 per active treatment arm) or health system administrative data. In the case of psychotherapy studies, one RCT with an active control condition* (n = 10–29 per active treatment arm).
4	For both pharmacological and psychotherapy studies: RCTs with no active control condition or without placebo, open and uncontrolled trials, case series, anecdotal reports, or expert opinion.

Notes for psychological studies.

* Active control conditions include psychological placebos (talking sessions with no specific psychotherapeutic techniques being used), pill placebos, supportive therapy, relaxation techniques, psychoeducation, or treatment as usual (TAU). Waitlist and no-treatment groups are not considered active control conditions. Although waitlist conditions are meant to control for the natural progression of time and symptom severity, recent research suggests waitlist conditions are not an accurate representation of this measure (Mohr et al., 2009; Patterson et al., 2016). Moreover, a meta-analysis reported much larger effect sizes for psychological placebos when it was compared to waitlist conditions as opposed to no-treatment conditions (Furukawa et al., 2014). These findings demonstrate that waitlist control conditions cannot be equated with no-treatment conditions. Biases exist in both waitlist and no-treatment conditions. Thus, waitlist participants may be motivated to maintain their symptom severity in hopes of receiving treatment, while no-treatment participants may seek therapy and/or treatment elsewhere, viewing the research study as a lost cause in treating their illness (Furukawa et al., 2014).

** Adequate blinding: in psychotherapy studies if an active control condition is used, we can assume proper blinding of the participants. However, if inactive control conditions, such as waitlist control or no-treatment conditions are used, participants are not blinded. Under these conditions, participants' expectations may bias the outcome measures (Bandelow et al., 2022). Furthermore, assessors/raters should be blind to the participant's condition group and not be the ones providing the psychotherapy treatment. A study by Hróbjartsson et al. (2013) reported that non-blinded raters exaggerate the effect size by 68 %, leading to greater type I errors and false-positive results (Hróbjartsson et al., 2013).

Table 1b
CANMAT grading system: Lines of treatment.

Line	Level of Evidence
First	Level 1 or 2 evidence with efficacy, plus clinical support for safety/tolerability
Second	Level 3 or higher evidence with efficacy, plus clinical support for safety/tolerability
Third	Level 4 or higher evidence with efficacy, plus clinical support for safety/tolerability
Not recommended	Level 1 or Level 2 evidence with lack of efficacy, plus expert opinion
Unable to make recommendation	Level 3 or Level 4 evidence with lack of efficacy, plus expert opinion

feedback was incorporated into the guideline document. Final manuscripts were approved by all authors.

The resulting CANMAT/ICOCS 2025 OCD Guidelines includes seven sections: 1) Introduction, 2) Foundations of Management, 3) Treatments, 4) Treatment Resistant OCD, 5) Neurostimulation and Neuromodulation, 6) Children and Adolescents, 7) Other Populations, and 8) Future Directions and Knowledge Gaps (Table 1–1).

Table 1c
The CANMAT lines of treatment and corresponding symbols.

Level of Evidence	Symbol	
	Positive Level of Evidence	Negative Level of Evidence
1		
2		
3		
4		

1.1.2. Evidence review and grading of recommendations

A comprehensive systematic literature review was conducted to identify all treatment studies of OCD, including case reports, open-label, randomized controlled trials (RCTs), systematic reviews, and meta-analyses published prior to April 30, 2024. The method used to grade published evidence in previous CANMAT guidelines was utilized (Tables 1-2) (Lam et al., 2024; Yatham et al., 2018). Evidence from meta-analyses was considered the highest level and was ranked by width of confidence intervals, sample size, number of studies included, and the methodological variability within each individual study. For treatment recommendations, both the evidence base and level of clinical support were used in order to arrive at the final recommendations for lines of treatment (Table 1–3). Visual symbols were added to indicate the level of evidence and if the study intervention was positive, meaning efficacious, or negative, not showing efficacy (Table 1–3). The final recommendations were then expressed as either first, second, third line, unable to make recommendation, or not recommended, based on levels of evidence of efficacy, clinical support, and consensus ratings of safety and tolerability.

Given that evidence from meta-analyses ranks at the highest CANMAT level of evidence, we evaluated each meta-analysis cited. Firstly, the trustworthiness of each paper was evaluated using the AMSTAR 2 (A Measurement Tool to Assess systematic Reviews) checklist (Shea et al., 2017). All meta-analyses ranked in AMSTAR were then evaluated for quality using the Grades of Recommendation, Assessment, Development, and Evaluation method (Guyatt et al., 2011), using GRADEpro GDT software, where studies were assessed for the certainty of the findings (including study design, risk of bias, inconsistency, indirectness, and imprecision), effect, and importance. GRADE evaluations were used to support the line of treatment recommendations in each section. If the quality of evidence supporting a Level 1 or 2 treatment was rated as “Low” or “Very Low” the guideline authors, then looked to the individual RCTs to make the line of treatment recommendation. Additionally, in cases where a meta-analysis only included 1 or 2 RCTs for an intervention, the sample size of the treatment group from each RCT was considered when making the line of treatment recommendation. In cases where the quality of the evidence was poor and resulted in down-grading of the line of treatment, it was noted in the recommendation summary table for that treatment. Finally, the pharmacological evidence is presented using Neuroscience-based Nomenclature (NbN), see Box 1.1.

1.1.3. Feedback and consensus process

As with previous CANMAT guidelines, a formal iterative process was used to achieve consensus among the authors for the final recommendations, and author consensus was sought after each level of review, from initial drafts through to external peer reviews.

1.1.4. Funding and conflicts of interest

The guideline process and publication were funded entirely by internal CANMAT funds; no external support was sought or received. No honoraria were paid to authors, and no professional editorial assistance was used. The CANMAT is a project-driven organization governed by a

Box 1-1
Neuroscience-Based Nomenclature for Psychotropic Medication

The prevailing nomenclature for psychotropic medications is not based on mechanisms of action but instead is based primarily on indications (e.g. antipsychotics, antidepressants, anxiolytics). Given that medications are often effective across a broad range of diagnostic categories, a more scientific nomenclature has emerged: the Neuroscience-based Nomenclature (NbN). In these guidelines, we will often use newer NbN terms to better describe medications according to mechanism of action, e.g. serotonin-dopamine modulator instead of atypical antipsychotic drug as most patients with OCD do not have psychotic symptoms, and monoamine enhancer for depression instead antidepressant drug as many patients with OCD are not depressed. This prevents the use of a clinically inadequate vocabulary, avoids confusion about the goals of the treatments for patients, and helps decrease stigma. However, for the most part in these guidelines we have used the NbN nomenclature side by side with the older terminology because clinicians are still more familiar with these terms.

voluntary, unpaid Advisory Board with no permanent staff or dedicated offices. CANMAT activities involve research, knowledge translation (e.g., guidelines dissemination, national and international conferences, publications), and Continuing Professional Development (CPD). The CANMAT has a Conflict-of-Interest policy that includes disclosures by all participants, and academic institutions accredit all CPD projects. CANMAT activities are funded from various sources: academic projects from peer-review or philanthropic foundations, conferences from societies, registrations and multiple industry sponsors, and CPD from universities and industry sponsors. Research studies are independently funded by agencies such as the Canadian Institutes for Health Research (CIHR) and are administered by the academic institutions of the principal investigators. In the past five years (2019–2024), sources of CANMAT revenue (excluding CIHR and research funding) included government funding agencies (52 % of revenue), national scientific conferences (20 %), and publications (28 %); no pharmaceutical or industry funding was received. The ICOCS is a registered UK charity and as a company limited by guarantee (and not having a share capital). The ICOCS is governed by an unpaid voluntary board and activities are funded from various sources including academic societies, member registrations, charities, and industry sponsors. All scientific activities are reviewed by an independent scientific committee.

2. Foundations of management

2.1. Epidemiology

OCD is a disabling condition with significant morbidity and functional impairment that compromises quality of life. Due to its high clinical heterogeneity, there is frequent debate about the definition of OCD as well as its place within the taxonomy of psychiatric disorders. Currently, it is classified within the "Obsessive-Compulsive and Related Disorders" chapters of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (Association (APA), 2013) and the 11th Revision of the International Classification of Diseases (ICD-11) (World Health Organization, 2022).

According to the DSM-5 criteria (Association (APA), 2013) and ICD-11 requirements (World Health Organization, 2022), obsessions, compulsions, or both together characterize OCD. Obsessions are repetitive and persistent thoughts, impulses, or images that are intrusive, inappropriate, and cause significant distress. Compulsions are repetitive, ritualistic behaviours or natural acts (e.g. hand washing, counting) that individuals feel compelled to perform typically in response to an obsession; however, these behaviours are clearly excessive and not always logically connected to the event they aim to neutralize or prevent (Substance Abuse and Mental Health Services Administration, 2016). The DSM-5 stipulates that for a diagnosis of OCD, obsessions and compulsions should be time-consuming and/or cause significant distress or functional impairment. Additionally, these symptoms cannot be attributed to physical effects of substance use or explained by other medical or mental disorders.

There are a series of disorders with a similar symptom profile to OCD: however, they do not meet all the diagnostic criteria outlined by the DSM-5/ICD-11 above. These disorders are classified as Obsessive-Compulsive Related Disorders (OCRDs), a new chapter in both the DSM-5 and ICD-11. They include body dysmorphic disorder, excoriation disorder (skin picking disorder), trichotillomania (hair pulling disorder), and hoarding disorder, as well as substance/medication induced OCD, OCD due to other medical conditions, and other specified and unspecified OCRDs (Steketee, 2011). Additional OCRDs in the ICD-11 include hypochondriasis and olfactory reference disorder (World Health Organization, 2022). These conditions are also found in the DSM-5, however, under different names (somatic symptom disorder and olfactory reference syndrome, respectively), and are not categorized under OCD and its related conditions. OCRDs have frequent comorbidity with OCD, as do tic disorders, anxiety disorders, major depressive disorder, and alcohol use disorder. While tic disorders are frequently comorbid with OCD, they are classified as neurodevelopmental disorders in the DSM-5 and movement disorders in ICD-11, not as an OCRD. As these OCRDs are distinct from OCD, they are not addressed in these guidelines.

2.1.1. Prevalence

Previously considered a rare condition, OCD is now recognized as a common psychiatric disorder. The 6–12 month prevalence is estimated at 0.8 %–2.4 % globally (Bandelow and Michaelis, 2015; Fawcett et al., 2020), with lifetime prevalence (proportion of population who had OCD at some point in their life) estimates ranging between 1.3 % and 2.4 % (Bandelow and Michaelis, 2015; Fawcett et al., 2020). As with other mental disorders, reported prevalence in the general population is likely an underestimate due to help-seeking barriers resulting from lack of information, secretiveness related to specific subtypes, and stigma.

2.1.2. Demographic factors

Biological sex: While some surveys report similar prevalence rates among females and males (Canals et al., 2012; Fullana et al., 2009; Valleni-Basile et al., 1996), others found modestly higher rates in females (Fawcett et al., 2020; Osland et al., 2018; Wittchen and Jacobi, 2005). This trend was noted for adult as well as childhood/adolescent populations (Fawcett et al., 2020; Flament et al., 1988). On the other hand, most studies report an earlier onset of OCD in males compared to females (Ruscio et al., 2010; Taylor, 2011).

Heritability: OCD is considered a moderately heritable psychiatric condition, with genetic factors accounting for approximately 50 % of the variance in liability (Mataix-Cols et al., 2024; Blanco-Vieira et al., 2019). Both a comprehensive meta-analysis of family and twin studies (Blanco-Vieira et al., 2019) and a large-scale twin study using clinically diagnosed cases (Mataix-Cols et al., 2024) found negligible influence from shared environmental factors, while non-shared environments explained the remaining variance. Notably, heritability appeared stronger in early-onset OCD cases compared to adult-onset cases (Blanco-Vieira et al., 2019).

Marital status: Investigation of the interrelationship between

marital status and OCD prevalence report contradictory findings. While some found OCD to be more common among divorced and separated individuals (Karno et al., 1988), others report symptoms to be twice as prevalent in individuals who are married or widowed compared to those who are single, separated, or divorced (Bland et al., 1988). Nevertheless, all reports consistently found that among OCD sufferers, women are more likely than men to be married or in a stable relationship (Benatti et al., 2022).

Ethnicity: Several epidemiological studies that examined OCD prevalence in the Epidemiology Catchment Area (ECA) study, a survey of 5 communities in the USA, found the prevalence of OCD to be higher in "Caucasians"* compared to "non-Caucasian" ethnic groups (Karno et al., 1988; Zhang and Snowden, 1999). However, in these studies, 68.6 % and 69.5 % of the total population assessed was "Caucasian", respectively. More recent meta-analyses and survey studies have found a similar prevalence of OCD across different ethnic groups, although "non-Caucasian" individuals are less likely to receive treatment or experience remission (Williams et al., 2018). African and Asian Americans have reported greater severity of contamination obsessions compared to European Americans in some studies (Wheaton et al., 2013; Wilson and Thayer, 2020). There is a lack of evidence for other ethnicities and countries of study outside of the USA.

*The term Caucasian was included as per the terminology used by the authors of the referenced papers.

Religion: Studies report a complex interaction between religion and OCD. While the religious backgrounds of OCD patients are not different from that of the general population, there is evidence that a greater degree of religious observance may be associated with increased frequency or severity of symptoms (Steketee et al., 1991).

2.1.3. Age of onset

OCD can manifest at any age; some studies have reported a bimodal pattern, however, others report a steady increase in cases with age. One meta-analysis (Taylor, 2011) found that the age of onset followed a bimodal distribution with a peak in late childhood (age 8–12 years) and again in early adulthood (age 20–25 years) (Taylor, 2011). Of the nine studies included, 76 % of those with OCD had early-onset presentations (Taylor, 2011), a finding consistent with the clinical impression that early onset OCD is more prevalent than late onset illness. A longitudinal study of the general population in Switzerland did not observe this bimodal pattern, but rather a steady increase in cases from age 10 to 22, and few cases developing after 30 years of age (Fineberg et al., 2013). This study defined age of onset as the time obsessive-compulsive (OC) symptoms were reported with significant distress/anxiety when trying to stop, and impairment in work or social life. In a recent meta-analysis that included 20 studies of OCD, the proportion of individuals with onset of OCD/OCRDs before the age of 14, 18, or 25 was 24.6 %, 45.1 %, and 64.0 %, respectively (Solmi et al., 2022). They found a steady increase in OCD proportion up to a peak age of onset at 14.5 years. When broken down by biological sex, the peak age of onset was 10.5 years for males and 15.5 years for females, while the median age of onset was 20 and 23 years, respectively (Solmi et al., 2022). Perinatal factors such as protracted labour and edema during labour have been reported to be associated with a higher risk of childhood onset of OCD (Vasconcelos et al., 2007).

Furthermore, there is a lack of consistency in the literature of the definition of an "early" vs "late" onset of OCD. Some researchers have defined early onset as occurring prior to age 11 (de Mathis et al., 2013), intermediate onset if OC symptoms presented between ages 11–18, and late onset if OC symptoms presented after 18 years of age (de Mathis et al., 2009), while others have proposed 15 years (De Luca et al., 2011) or 18 years (Girone et al., 2024; Grover et al., 2018; Wang et al., 2012) as the cut between early and late onset.

Regardless, it is widely recognized that an earlier age of onset is associated with greater symptom severity, presence of frequent comorbidities with OCRDs and other mental illnesses (Taylor, 2011), and overall negative outcomes (Dell'Osso et al., 2013), with several studies reporting an earlier onset in males compared to females (Benatti et al., 2022; Fineberg et al., 2013; Ruscio et al., 2010; Solmi et al., 2022; Taylor, 2011). However, an observational cohort study found that youth were significantly more likely than adults to achieve partial or full OCD remission (Mancebo et al., 2014). In the youth sample, the average age of onset was 9.2 years and age of first treatment was 10.8 years, and in the adult sample, the average age of onset was at 17 and mean age of first treatment was 29 years (Mancebo et al., 2014). The authors suggested that latency to treatment and impairment in functioning predicted the course of illness and has a negative impact on likelihood of remission. Similarly, other studies have found that the mean duration of untreated illness (DUI) ranges between 2 and 3 years in children and 7 and 10 years in adults (Dell'Osso et al., 2019; Fineberg et al., 2019). Several studies have confirmed that a longer DUI (>24 months) is associated with poorer treatment response (Albert et al., 2019a; Dell'Osso et al., 2010; Poyraz et al., 2015). Additionally, the worse outcome and higher treatment resistance common in patients with an earlier age of onset appear to be related to the DUI and the number of years spent with OCD (Albert et al., 2019a; Fineberg et al., 2013, 2019). Therefore, OCD symptom severity and treatment response may be influenced by both the age of onset and the DUI (for more information see Section 2.3.5).

Studies have shown the prevalence of OCD in older adults is less than the general population (0 %–0.8 % compared to 1.3 %–2.4 %) (Canuto et al., 2018; Dell'Osso et al., 2017a). Investigations of OCD in older adult and elderly populations have been sparse; nevertheless, there is general agreement that symptom onset after age 50 is rare (Kohn et al., 1997). An investigation by the ICOCS found that older OCD patients (>65) had a significantly later age of onset, with more frequent adult onset, compared with younger patients (Dell'Osso et al., 2017a). Additionally, a later age of onset was associated with different comorbidities than an earlier age of onset (Dell'Osso et al., 2017a). Regardless, OCD is largely chronic, and the reduced prevalence in older adults may be due to loss to follow up, predominance of other medical conditions, and other factors. Thus, age of onset in OCD patients may have clinical significance and could impact the course and overall management of the illness. For more on OCD in older individuals, refer to Section 7.2.

2.1.4. Course of illness

OCD is a chronic and persistent illness with a fluctuating course. Early retrospective analyses conducted prior to the introduction of current OCD treatments noted low remission rates in clinical populations. A study of 144 inpatients reported 11 % full and 17 % partial remission over ten years, with 20 % full remission and 28 % partial remission at the 40-year follow-up (Skoog and Skoog, 1999). Probabilities have varied significantly in subsequent studies, from 25 % to 76 % for remission (Catapano et al., 2006; Eisen et al., 1999; Marcks et al., 2011; Reddy et al., 2005; Steketee et al., 1999) and 25 %–60 % for relapse (Catapano et al., 2006; Eisen et al., 1999; Marcks et al., 2011). These studies had limitations due to small sample sizes and variable treatment protocols, and highlight the need for larger investigations that include evaluations of predictor variables.

In a prospective 2-year study (Brown Longitudinal Obsessive-Compulsive Study, BLOCS) (N = 214), probabilities of full and partial remission were estimated to be 6 % and 24 %, respectively (Eisen et al., 2010). Of the 48 patients that fully or partially remitted, only one relapsed. The study found decreased likelihood of remission in patients with an earlier age of onset and older age at therapy intake. Among male subjects, a greater severity of illness was associated with poorer outcome. Patients with principal obsessions relating to over-responsibility for harm were nearly three times more likely to experience remission compared to patients with other obsessions. Obsessions relating to hoarding were associated with poor outcome, where only 1 of the 19 patients with this obsession experienced partial remission. In contrast, the number of comorbidities and treatment

variables were not associated with likelihood of remission (Eisen et al., 2010).

A 5-year extension of the BLOCS (Eisen et al., 2013) further confirmed that lower severity and shorter duration of illness were associated with increased probability of remission, as was a principal obsession of over-responsibility for harm compared to other obsessions (Eisen et al., 2013). Of the 83 (39 %) patients in the study who achieved full or partial remission, 49 (59 %) eventually relapsed. Comorbid obsessive-compulsive personality disorder and partial remission were associated with an increased likelihood of later relapse, while duration of OCD and its severity were not associated with relapse ($p = .37$ and $p = .52$, respectively) (Eisen et al., 2013). Interestingly, insight (measured using the Brown Assessment of Beliefs Scale [BABS] total score) was not associated with relapse in the BLOCS, however, a larger study reported that poor insight was independently associated with poorer course (Visser et al., 2017), and linked with increased OCD severity, chronicity, and comorbidity that in turn predict adverse outcomes (Eisen et al., 2010, 2013; Visser et al., 2017).

Other proposed factors influencing the course of illness include biological sex, stressful life events, and family illness (Goldberg et al., 2015; Rosso et al., 2012; Torresan et al., 2009). Males have reported a more severe course of OCD compared to females, including earlier onset of obsessive-compulsive (OC) symptoms and earlier impairments in functioning (Torresan et al., 2009). A subsequent study demonstrated that this relationship was partly dependent on family history of OCD, tics, Tourette's, or anxiety-related disorders (Goldberg et al., 2015). Male sex was associated with an increased probability of chronic course, but only with low levels of family OCD history, while female sex was predictive of chronicity with higher levels of family history of OCD. Exposure to stressful life events prior to OCD onset was associated with increased chronicity at low levels of family illness (Goldberg et al., 2015). For many patients, stress can trigger or intensify OCD symptoms and lead to poorer outcomes (Raposo-Lima and Morgado, 2020; Rosso et al., 2012). The very limited evidence in this area also suggests there may be some fluctuations in the course of illness due to hormonal changes (Mojgani et al., 2025).

A greater likelihood of remission has been suggested in youth compared to adults (Mancebo et al., 2014). For example, in a 3-year study of 60 youth with OCD (6–18 years of age, mean = 13.7 years), the probability of partial remission was 53 % and the probability of full remission was 27 %. Of the 24 youth who remitted, 19 (79 %) remained in remission throughout the duration of the study and 5 (21 %) relapsed. In comparison, the probabilities of partial and full remission among adults over 3 years were 34 % and 13 %, respectively. A better course of illness was predicted by early treatment and prior to significant impacts on functioning (Mancebo et al., 2014).

2.1.4.1. Burden of illness. OCD carries a high burden of illness, with significant impact on individuals, their families, and society.

Physical impact. Longitudinal research has found that when other concurrent mental health disorders are controlled for, OCD is associated with an increased physical health burden (Meier et al., 2016). From an individual perspective, there is evidence that a diagnosis of OCD is associated with increased risk of mortality. A nation-wide cohort study conducted in Denmark reported a higher mortality rate among people with OCD compared to people without OCD (Mortality rate ratio [MRR] 2.14, 95 % CI 1.65–2.40) (Meier et al., 2016). Even after adjusting the analysis for psychiatric comorbidities, OCD conferred an increased mortality risk (MRR 1.88, 95 % CI 1.26–2.67) (Meier et al., 2016). A study in India found that individuals with OCD scored lower on the physical health domain of the World Health Organization Quality of Life scale compared to healthy controls (Sahoo et al., 2017). Individuals with OCD may be more prone to certain physical complications, such as renal damage or hyperlipidemia, if their compulsions are associated with washing, hygiene, and food/fluid intake (Drummond et al., 2012). These studies suggest that those with OCD often perceive their physical health to be poor and are susceptible to physical health complications.

Comorbid conditions further increase the illness burden, as OCD presenting with comorbid conditions tends to be more severe, chronic, and have a greater negative impact on daily functioning (Hofmeijer-Sevink et al., 2013). In the Netherlands Obsessive Compulsive Disorder Association (NOCDA) study, those with a diagnosis of OCD plus two comorbid disorders had more severe and chronic OCD than those with OCD plus one comorbid disorder, indicating that the number of comorbid conditions may also influence the degree of illness burden (Hofmeijer-Sevink et al., 2013).

Those with OCD often perceive their physical health to be poor and are susceptible to physical health complications. In a meta-analysis of 14 studies, subjects with OCD reported lower perceived physical health status compared to healthy controls (Pozza et al., 2019). It is important to consider not only the physical health impacts of compulsions, but also the perceived worsened health people with OCD may face.

The adverse impact on overall physical wellbeing has been investigated in specific subtypes of OCD. It has been reported that the subgroup with obsessions of over-responsibility for harm and contamination are more likely to report impaired health-related quality of life (Schwartzman et al., 2017). Similarly, individuals who engage in compulsions such as handwashing, cleaning, and checking behaviours can often experience physical health complications such as dermatologic, dental, and other hygiene problems.

Social impact. It is evident that OCD has a major negative impact on social functioning. Compared to those with major depressive disorder (MDD), panic disorder, and schizophrenia, patients with OCD report significantly poorer social functioning (Kugler et al., 2013). Further, it has been demonstrated that the domain of social relationships is more affected in those with OCD compared to people with any other mental or physical illness (Subramaniam et al., 2013). Contamination and symmetry-related symptom subtypes have been specifically associated with dissatisfaction with social relationships (Schwartzman et al., 2017), possibly due to shame or embarrassment. These findings suggest that OCD may affect frequency and quality of time with others and reduce positive social interactions. There is also evidence to suggest social skill impairments in OCD, particularly in those with early onset OCD (da Silva et al., 2024). It has been proposed that obsessions and compulsions early in life may decrease social exposure, which can affect the acquisition of social skills (da Silva et al., 2024). Further, deficits in the social cognitive mechanisms that contribute to social functioning have also been found in adults with OCD. Specifically, impairments have been found in facial affect recognition (particularly in the recognition of disgust), theory of mind/mentalizing, and emotion regulation skills (Bora, 2022; Grisham et al., 2010; Jansen et al., 2020).

Family impact. Family accommodation is the term used to describe participation of family members in the individual's OCD-related rituals or rules in order to relieve distress (Lebowitz et al., 2016). Family accommodation can dictate family routines and act as a major source of conflict among family members, leading to high levels of expressed negative emotions (Maina et al., 2006). For example, family accommodation can include opening a "contaminated" door, handling dirty laundry, performing extensive cleaning rituals dictated by the affected OCD individual or providing frequent verbal reassurance for checking behaviours. Families of patients with OCD frequently encounter disruption of family routines, interactions, leisure plans, and finances (Vikas et al., 2011), (also see Section 6.1: *Family Accommodation*). Previous research has noted behaviours such as concealing obsessions and compulsions, fears about being a burden to their partner, celibacy due to sexual or aggressive obsessions, or fears around contamination can present barriers to the formation and maintenance of intimate relationships for those with OCD (Abbey et al., 2007). A few studies have shown OCD to be associated with problems in sexual functioning and marital distress (Aksaray et al., 2001; Emmelkamp et al., 1990; Staebler et al., 1993). The observed significant familial impact associated with

OCD has led to exploration of couple-based interventions as part of its management (Abramowitz et al., 2013b).

Occupational impact. OCD frequently has a marked impact on occupational functioning. An early study noted reduced working hours and job loss was common in those with OCD, as was employment in occupations unrelated to professional training (Yaryura-Tobias and Neziroglu, 1997). Analyzing a sample of 238 patients with OCD, Mancebo et al. (2008) reported that OCD severity was the strongest predictor of occupational disability (Mancebo et al., 2008). This suggests that although OCD commonly starts in adolescence, its disabling effect may impact individuals once they enter the workforce.

Quality of life. Individuals with OCD experience a high degree of overall disability, which is often long-term. Huppert et al. (2009) found individuals with active OCD symptoms to have significantly poorer quality of life than those in remission (Huppert et al., 2009). However, even individuals with remitted OCD had poorer quality of life compared to healthy controls. A significant proportion of patients with OCD have trouble working efficiently and effectively, and often have difficulties completing household tasks, self-care, and personal hygiene because of their symptoms (Jacoby et al., 2014; Thara et al., 1988; Vikas et al., 2011).

Cognitive functioning. OCD has been shown to negatively impact cognitive function. A meta-analysis of 115 studies found that patients with OCD performed significantly worse on tasks of attention, working memory, executive function, processing speed, visuospatial abilities, and overall memory – which had the largest effect size (d = −0.630, 95 % CI -0.751-(-0.509)) (Abramovitch et al., 2013). A multi-level meta--analysis found those with OCD perform worse on memory tasks, primarily driven by deficits in executive functioning (Persson et al., 2021). Another multi-level meta-analysis of 131 studies identified a top-down and bottom-up framework to explain the memory deficits in OCD (Harkin et al., 2023). They found that deficits in working memory, affecting maintenance and updating (how task-relevant information is focused on and updated), and in sensory memory, affecting perceptual integration, predicted overall memory and cognitive deficits (Harkin et al., 2023). More research is needed in this area to determine their impact on overall disability in OCD, and to look at these areas of deficits for future targeted interventions.

Societal impact. At the societal level, OCD carries a substantial economic burden largely due to increased healthcare utilization and loss of productivity at work. The worldwide economic burden of OCD is not well studied, with limited information on per-patient healthcare costs or comparative data with the general population. A cost-effectiveness study on the economic burden of OCD conducted through the National Health Service in the United Kingdom estimates that OCD may have a similar economic burden (estimated £5.1 billion per year) to depression (£7.5 billion per year), but with increased use of pharmacotherapeutics (Kochar et al., 2023; Skapinakis et al., 2016). Similarly, an Australian study reported that OCD accounts for a $3.4 billion annual loss when examining both direct and indirect costs (McCallum et al., 2019).

2.1.4.2. Suicide risk. Although elevated suicide risk has not been traditionally associated with OCD, recent evidence has dispelled this notion and indicates a clear link between OCD and suicidality. A meta-analysis of 61 studies from Europe, Brazil, and the USA, found that one in eight patients with OCD attempts suicide in their lifetime (pooled odds ratio [OR]: 0.135, 95 % CI 0.123–0.147), while one third has current suicidal ideation (pooled OR: 0.273, 95 % CI 0.214–0.335) and nearly half have experienced suicidal ideation in their lifetime (pooled OR: 0.473, 95 % CI 0.397–0.548) (Breet et al., 2019; Pellegrini et al., 2020). The current literature presents a broad range of rates for suicide attempts (SA) (6–52 %) and suicidal ideation (SI) (26–74 %) in populations with OCD (Albert et al., 2019b; Borges et al., 2010). A systematic review reported that OCD significantly increased the odds of lifetime SI (pooled OR: 1.9–10.3) as well as lifetime SA (pooled OR: 1.6–9.9) compared to the general population (Albert et al., 2019b). Although information on completed suicides in OCD is scarce, two prospective longitudinal cohort studies found significantly elevated risks for completed suicide in individuals with OCD compared to matched controls with an MMR of 3.02 (95 % CI 1.85–4.63) (Meier et al., 2016), and pooled OR of 9.83 (95 % CI 8.72–11.08) (Fernández de la Cruz et al., 2017). Risk factors for SA in patients with OCD include a higher severity of obsessions, lower severity of compulsions, longer duration of untreated illness (DUI), comorbid substance use disorders, higher severity of depressive symptoms, lifetime history of depressive episodes, lifetime intermittent explosive disorder, cognitive impulsivity, and a general family psychiatric history (Benatti et al., 2020; Dell'Osso et al., 2018, 2015; Nagy et al., 2020; Pellegrini et al., 2020; Salvo et al., 2020). Positive predictors of SI in OCD include higher severity of obsessions, lower education, higher rates of unemployment, lifetime alcohol use disorder, personality disorders, and a family history of completed suicides (Pellegrini et al., 2020). Interestingly, aggressive, sexual, and religious obsessions and the presence of a lifetime comorbid anxiety disorder were found to be associated with lower rates of SI in a recent meta-analysis (Pellegrini et al., 2020), contrary to previous reports that these factors were associated with increased risk of suicidality in OCD (Albert et al., 2019b; Angelakis and Gooding, 2020; Ay and Erbay, 2018; Benatti et al., 2021; Fawcett et al., 1990; Khosravani et al., 2017; Kim et al., 2016; Velloso et al., 2016). In relation to biological sex, study results are mixed, with some indicating female sex as protective (Fernández de la Cruz et al., 2017) and others as a risk factor (Breet et al., 2019).

Given the elevated risk of suicidal ideation and suicide attempts in patients with OCD, it is essential that clinicians actively screen for suicidality in their patients with OCD. While specific treatments for suicidality in OCD have not been examined in the literature, clinicians should perform a therapeutic assessment, address risk factors, and implement suicide prevention approaches as appropriate to reduce the risk (Hawton et al., 2022).

Key Points
- Lifetime prevalence of OCD is 1–2 %; OCD is moderately heritable.
- Onset is typically in childhood; earlier onset is associated with greater symptom severity.
- Course of OCD is chronic with symptom fluctuations over the lifespan.
- OCD is associated with substantial functional impairment, economic burden, and impairments in cognitive functioning.
- Suicide risk is elevated; 1 in 8 patients with OCD reports attempting suicide in their lifetime.

2.2. Diagnostic assessment

2.2.1. OCD nosology, DSM-5-TR/ICD-11 criteria

The latest edition of the Diagnostic and Statistical Manual of Mental Disorders-Text Revised (DSM-5-TR) made important changes in the classification of OCD. The previous edition (DSM-IV-TR) grouped OCD in the "Anxiety Disorders" chapter, however scientific evidence in terms of symptomatology, treatment differences, genetics, and neurobiological considerations prompted the creation of a separate group for OCD Related Disorders (Hirschtritt et al., 2017; Monzani et al., 2014; Shin and Liberzon, 2010; Stein et al., 2010; Thomsen, 2013).

2.2.1.1. Diagnostic criteria and specifiers in DSM-5-TR. As noted earlier, in the DSM-5-TR, OCD is considered the archetypical disorder of a new grouping of OCRDs. Apart from repetitive thoughts and behaviours, these conditions share neurocircuitry and neurochemical abnormalities (Milad and Rauch, 2012; Nikolaus et al., 2010), familiality and genetic risk factors (Bienvenu et al., 2012; Monzani et al., 2014), as well as overlapping approaches of assessment and treatment (Fineberg et al., 2014). Additionally, the DSM-5-TR includes two specifiers (whereas in DSM-IV-TR there was just one): the insight specifier and the new

tic-related specifier. The degree of insight is clinically relevant – it could help to reduce the risk of misdiagnosing OCD with psychotic disorder or obsessive-compulsive personality disorder and to choose the correct therapy (Simpson and Reddy, 2014). Moreover, poor or absent insight can be associated with increased OC symptom severity, hoarding symptoms, and unemployment (Jakubovski et al., 2011). Given that 30 % of individuals with OCD will have a lifetime tic disorder, which occurs more frequently in men, this suggests that these conditions share neurocircuitry to a certain degree (Vries et al., 2016). The introduction of the tic-related OCD specifier is important for a therapeutic approach, as some studies have highlighted that patients with OCD and comorbid tic disorder respond better to augmentation with antipsychotics (in particular haloperidol or aripiprazole) than people without comorbid tic disorder (Rothenberger and Roessner, 2019; Van Ameringen et al., 2014). Finally, due to the high comorbidity between OCD and tics, it has also been proposed to introduce an autonomous phenotype of illness called Obsessive-Compulsive Tic Disorder (OCTD) as many experts believe the two disorders may represent a subtype of illness (Dell'Osso et al., 2017b). In fact, obsessive-compulsive symptoms, disorder, and tics are deeply interconnected on the basis of clinical, biological, and epidemiological evidence (Dell'Osso et al., 2017b).

2.2.1.2. Diagnostic specifiers and differences in ICD-11. Focusing on the classification system proposed by the World Health Organization, the current edition of the International Classification of Disease (ICD-11), anxiety disorders and OCD were already considered separate categories and additionally included the OCRDs hypochondriasis and olfactory reference disorder.

The ICD-11 has removed the term "stereotyped", which was used in the ICD-10 to define compulsions, aiming to reduce confusion with stereotypes and stereotypic movement disorder (Simpson and Reddy, 2014). Differently from DSM-5-TR, the ICD-11 does not underline the causality direction between obsessions and compulsions (Shavitt et al., 2014). Furthermore, while in the ICD-10 obsessions were considered to be uniquely cognitive events and compulsions as just motor behaviours (Marras et al., 2016), in the ICD-11 (as well as in the DSM-5), the cognitive or motor nature of compulsions and obsessions is underlined. In fact, it has been shown that the vast majority of OCD patients have mental as well as behavioral rituals (Simpson and Reddy, 2014).

Furthermore, while in the ICD-10, obsessions and compulsions have to be present "most days for at least two weeks", the ICD-11 (as well as the DSM-5-TR) does not define a specific duration requirement. Nonetheless, obsessions and compulsions must be "time consuming" and/or cause distress or functional impairment to warrant a diagnosis. In terms of specifiers, rather than including the differentiation present in the ICD-10 between subtypes (i.e., predominantly obsessional thoughts or rumination, predominantly compulsive act, mixed obsessional thoughts and compulsions), which has been shown to have low validity in predicting treatment response and outcomes (Math et al., 2007), the ICD-11 includes two degrees of insight as specifiers: with fair to good insight and with poor to absent insight.

2.2.2. Differential diagnosis

Due to the wide variability of OCD presentation, a careful assessment

Table 2a
Differential diagnosis of OCD.

Diagnosis	Distinguishing features
Anxiety disorders	
Generalized Anxiety Disorder	Recurrent thoughts/worries about real life. No compulsive behaviours.
Specific Phobia	Fear reaction to specific objects or situations. No rituals.
Social Anxiety Disorder	Specific social worries and avoidance behaviours are limited to social interactions.
Major Depressive Disorder	Mood-congruent thoughts usually concern self-criticism. No compulsive rituals.
Major Depressive Disorder with peripartum onset	Infant correlated worries/thoughts emerge from contingent depressive mood. Onset during pregnancy or within 4 weeks of delivery.
Other Obsessive-Compulsive and Related Disorders	
Body Dysmorphic Disorder	Obsessions and compulsions are limited to physical appearance.
Trichotillomania (Hair-Pulling Disorder)	Compulsive behaviours are limited to hair pulling. No obsessions.
Hoarding Disorder	Symptoms are limited to the persistent distress in discarding items and excessive accumulation of objects.
Somatic Symptom Disorder (DSM-5) **Hypochondriasis (ICD-11)**	Obsessions and compulsions are limited to fear of having or developing serious medical illness.
Jikoshu-kyofu/Olfactory Reference Syndrome (DSM-5) **Olfactory Reference Disorder (ICD-11)**	Obsessions and compulsions are limited to concerns about body or breath odour.
Feeding and Eating Disorders	Obsessions and compulsions are limited to weight and food concerns.
Tic Disorder and Stereotypic Movement Disorder	Symptoms are typically less complex than compulsions and are not aimed at alleviating anxiety.
Psychotic Disorders	Features of schizophrenia or schizoaffective disorder (e.g., hallucinations or formal thought disorder) are present.
Other Compulsive-like Behaviours* **Substance-Related and Addictive Disorders (e.g. Gambling Disorder), Disruptive, Impulse-Control, and Conduct Disorders (e.g. Kleptomania, Pyromania), or Paraphilic Disorders**	Pleasure is usually correlated to symptomatology and avoidant behaviours are acted only for worries about deleterious consequences.
Obsessive-Compulsive Personality Disorder	Pervasive maladaptive pattern of excessive perfectionism, preoccupation with rules, order, lists, and rigid control. No intrusive thoughts, images, or urges and repetitive behaviours.
Autism Spectrum Disorder (ASD)**	Repetitive behaviours are ego-syntonic (pleasurable, comforting, self-regulating) and referred to as restricted, repetitive behaviours (RRBs) in ASD vs ego-dystonic (intrusive, unwanted, distressing) compulsions in OCD. Unlike OCD, ASD is associated with lifelong social communication deficits. Routine-oriented behaviour in ASD is conducted without a fear of harm or attempting to neutralize a feared outcome.

Adapted from Koran et al. (2007)

Key Points
- Similar to ICD-11, in DSM-5-TR OCD is now included as the archetypal disorder in a new chapter: Obsessive-Compulsive and Related Disorders (OCRDs).
- Careful assessment is required to differentiate OCD from other disorders including the Anxiety Disorders, Major Depressive Disorder, other OCRDs, Tic Disorder, psychotic disorders, other compulsive behaviours and Obsessive Compulsive Personality Disorder.

* Classified in the DSM-5 in a number of categories and disorders.
** See Section 7.3 for a more detailed description of the distinguishing features and intersections of OCD and ASD.

is necessary to differentiate its symptomatology from other conditions (Table 2–2).

2.3. Principles of management

2.3.1. Where to go for treatment

For many people with OCD, treatment is best initiated in the primary health care setting. The primary care clinician (PCC) usually has the most comprehensive overview of the patient's health status, as well as has access to the family and family history, the ability to prescribe treatments for OCD, and the knowledge regarding what may be most appropriate. In addition, the PCC will remain involved as patients progress through their treatment journey, even in cases where the treatment is provided elsewhere. It is therefore highly recommended that the PCC is actively involved at an early stage in discussions with the patient about their first-line treatment options in order to reach a collaborative decision. For more complex cases of OCD, such as those with more severe symptoms or comorbidities, those who have failed to respond to first-line treatments, or those with significant negative predictors or risks (See Section 2.3.4 below), early referral to designated mental health care services for more expert or intensive care is appropriate. For the small number of people with highly resistant or severe forms of OCD who do not respond to treatments offered in generalist mental healthcare settings, referral to more highly specialized OCD services, with experience of managing complex, severe, treatment resistant (TR) OCD, may be required. These services may offer longer and more intensive courses of Cognitive Behavioural Therapy (CBT) with Exposure and Response Prevention (ERP), including inpatient care, advanced pharmacotherapy, neurostimulation, and neurosurgical options.

2.3.2. Which type of treatment should you start with: pharmacotherapy or psychotherapy?

First-line recommendations for OCD include cognitive behavioural forms of psychotherapy (CBT) (Level 1●) and pharmacotherapy with drugs acting as serotonin reuptake inhibitors (SRIs) (Level 1●). In principle, decisions about treatment at all stages of care should be collaborative and fully involve the patient, their family, and collaborating clinician(s). The choice of initial treatment for OCD is usually based on the research-based evidence of effectiveness, treatment availability, patient preference, and individual patient factors that may render a particular treatment modality more or less suitable (for example, adherence to therapy and contraindications for the use of SRIs). Although it is important to consider patient preference when selecting a treatment modality, it should be acknowledged that some patients may avoid selecting efficacious psychological treatments which may induce distress. This is particularly the case for exposure and response prevention (ERP) strategies.

Based on current evidence, both psychological and pharmacological interventions appear equally efficacious in the short term and are first-line treatment recommendations (Level 1●) (Reid et al., 2021; Skapinakis et al., 2021). However, while serotonin reuptake inhibitors (SRIs) are efficacious at preventing relapse of OCD, the long-term efficacy of CBT has not been adequately evaluated (Fineberg et al., 2018). As few studies have adequately evaluated the adverse effects associated with psychological therapies for OCD, it is difficult to compare the relative tolerability of these two interventions.

2.3.3. Dosage; time duration until response; switching treatments

The effects of CBT and medication on OCD symptoms are often gradual, and benefits typically accrue over time. Therefore, it is important to avoid switching or discontinuing an intervention prematurely. Early adverse effects such as anxiety and distress with ERP and gastrointestinal side effects of medication usually emerge before signs of improvement. Thus, it is important to provide reassurance to continue treatment adherence and encourage family support. With satisfactory adherence, a trial of approximately 12 weeks generally provides signals of improvement indicating the effectiveness of treatment. Several controlled trials showed that patients still improve their symptoms up to 12 weeks after treatment initiation (Menchon et al., 2019). The notion that the onset of the anti-obsessive effect of SSRIs is delayed compared to their antidepressive effect has been challenged by a recent meta-analysis of double-blind placebo-controlled (DBPC) trials. The results showed that SSRIs outperform placebo by the second week of treatment – an early response of OC symptoms to SSRIs (Issari et al., 2016). In this study, 75–80 % of short-term symptom improvement occurred in the first 6 weeks, although a positive dose-response correlation was also found. The authors concluded that ongoing symptom improvement decreases with time, and that it would be reasonable for treatment to continue for an additional 4 weeks after achieving the maximum tolerated dose (Issari et al., 2016).

Often clinical response is inadequate. Options including dose optimization, switching to another first-line agent, or augmentation strategies including the addition of psychotherapy, should be considered. These are reviewed in the chapters on treatments and treatment resistant OCD (Sections 3.1 and 4.0).

2.3.4. Measuring treatment response

2.3.4.1. OCD symptoms. During the diagnosis and assessment, the baseline extent and severity of the disorder should be documented using one of the validated instruments in Table 2-3. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989c) is arguably the gold-standard OCD measure. It is based on a semi structured interview and is divided into two parts (symptom checklist and severity questionnaire). Scoring is independent of type or number of obsessions or compulsions. It involves 10 items, five covering obsessions and five covering compulsions, with each item of frequency, interference, distress, resistance, and control rated on a scale from 0 to 4. The Y-BOCS is short, well validated, and found to be sensitive to measuring change. It therefore has clinical utility and may be used routinely outside the research setting to monitor clinical progress. The total score ranges from 0 to 40. People scoring $\geq$30 on the Y-BOCS are considered to be severely unwell, while those scoring $\leq$10 are considered to be in remission.

2.3.4.2. Other measures. Other validated scales that could be considered for use in OCD include the Compulsive Personality Assessment Scale (CPAS) (Fineberg et al., 2007a) or the Pathological Obsessive Compulsive Personality Scale (POPS) (Sadri et al., 2018) for evaluating traits of obsessive-compulsive personality disorder (OCPD), the presence of which is associated with poorer clinical outcomes and relapse (Eisen et al., 2006). As impaired insight and tics represent DSM-5 diagnostic specifiers, outcome measures, and possible clinical predictors of response, routine measurement of these using the Brown Assessment of

Table 2b
OCD outcome measures.

Scale	Indication	Number of Items
Observer-Rated		
Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989c)	OCD symptom presence and severity	10 item severity rating + symptom checklist (>50 items)
Self-Rated		
Yale-Brown Obsessive-Compulsive Scale Self-Report (Baer et al., 1993)	OCD symptom presence and severity	10 item severity rating + symptom checklist (6 less than Y-BOCS)
Obsessive-Compulsive Inventory-Revised (OCI-R) (Foa et al., 2002)	OCD symptom severity	18 item severity and impact rating
Florida Obsessive-Compulsive Inventory (FOCI) (Storch et al., 2007b)	OCD symptom presence and severity	20 item symptom checklist + 5 item severity rating

Beliefs Scale (BABS) (Eisen et al., 1998) or the shorter Nepean Belief Scale (Brakoulias et al., 2018) for insight, and the Yale Global Tic Scale (Leckman et al., 1989) for tics, may also be advantageous.

The cognitive assessment instrument for obsessions and compulsions (CAIOC-13), measuring OCD-related functional impairment, is a 13-item self-rated dimensional measure which includes functional anomalies such as difficulties with reading, slowness, doubts, perfectionism, and making choices, which may provide useful information for the treating clinician (Dittrich et al., 2011).

2.3.5. Impact of delayed treatment

OCD is typically characterized by a delayed diagnosis and first treatment, particularly of pharmacological nature (Albert et al., 2019a; Benatti et al., 2016; Dell'Osso et al., 2019). In epidemiologic studies, the proportion of patients with untreated OCD worldwide varies significantly. It is estimated to be between 22 % and 92 %, with 38 %–90 % of individuals not seeking treatment or advice for OCD (García-Soriano et al., 2014). Several factors are likely responsible. First, patients with OCD often manifest symptoms before adulthood, with the majority of them showing childhood or adolescent onset (Dell'Osso et al., 2016; Fineberg et al., 2019), where the responsibility of obtaining treatment would be with the parents. Additionally, the secretiveness and shame about the symptoms that frequently characterize this disorder can prevent patients from seeking help. Patients' beliefs that OC symptoms do not represent a medical condition and that their symptoms will remit spontaneously also influence treatment-seeking behaviour (Poyraz et al., 2015). Moreover, societal factors (i.e., poor access to psychiatric services with expertise in the diagnosis and management of OCD) and/or treatment related-factors (i.e., requirement of moderate-to-high doses of medications for at least 12 weeks to elicit a response) have been reported (Albert et al., 2019a).

Considering the above, research studies investigating the duration of untreated illness (DUI) in OCD, defined as the interval between the onset of the disorder and the administration of the first pharmacological treatment at standard dosages and for an adequate period of time, in adherent subjects (Dell'Osso and Altamura, 2010) showed that the mean DUI ranges between 7 and 10 years in adults, and exceeds 2–3 years in children, which represents, on average, a portion ranging between 40 and 70 % of the overall duration of illness (Dell'Osso et al., 2019; Fineberg et al., 2019). The importance of reducing the DUI becomes evident when examining treatment response patterns according to this modifiable parameter. Preliminary data indicate that response rates were lower in subjects with a DUI >24 months than those with a shorter DUI, even though, in the same study, a logistic regression analysis did not report a significant correlation, neither between response nor remission rates and the DUI expressed in months (Dell'Osso et al., 2010). A more recent investigation confirmed response rates were significantly reduced in subjects with a DUI >24 months, and regression analyses supported this parameter as a predictor of poorer response to serotonergic medications (Albert et al., 2019a). On the other hand, another study found that the DUI (as a continuous variable or using a 4-year categorical cut-off) was not statistically predictive of remission (defined by a total Y-BOCS score ≤10): however, p-values indicated a distinct trend toward significance (Poyraz et al., 2015). A long DUI (average of 153±134.69 months) was associated with the development of a greater burden in terms of associated general medical conditions (Aguglia et al., 2018), possibly determined by persistent avoidance of medical consultations associated with untreated fear of contamination, which could lead to a failure to get appropriate diagnosis and treatment (Albert et al., 2019a).

Overall, delayed OCD treatment has relevant consequences for outcomes and costs for affected individuals, their caregivers, and society as a whole (Fineberg et al., 2019). Early detection is critical, as the literature reveals that adult and child OCD patients spend more than half of their illness pharmacologically untreated, and that a longer DUI is a negative prognostic factor. Mental health professionals and policy makers should pay particular attention to the epidemiologic and clinical correlates of delayed OCD treatment, as well as to early detection and intervention programs for affected patients (Dell'Osso et al., 2019), and should provide education and early screening of young people in non-clinical settings (Brakoulias et al., 2021).

2.3.6. Maintenance therapy (How long to treat, when can treatment be discontinued, risk of relapse)

OCD is a chronic, relapsing illness, and therefore the goal of treatment must include maintaining wellness in the longer term and reducing the risk of relapse. Since relapse is common, even after remission, it is essential to discuss the role of long-term medication with patients and the high risk of relapse in cases of treatment discontinuation (Fineberg et al., 2018). Selective serotonin reuptake inhibitors (SSRIs) and clomipramine have been shown to be efficacious at reducing the risk of relapse. Therefore, the duration of the pharmacological treatment should be considered for at least 12 months, possibly indefinitely, providing acceptable tolerability (Level 4). If discontinuation is needed for any reason (e.g., patient refusal or intolerable side effects) it is best to stop medication gradually to mitigate possible withdrawal effects. In such cases, it is recommended patients are referred to a specialist mental health team. In the case of CBT, long-term studies in OCD are lacking. However, for some patients the positive effect of CBT wanes over time. There is empirical evidence from clinical practice that booster sessions of CBT may be helpful for sustaining response in the longer term, but there is no clear evidence that this prevents relapse (Andersson et al., 2014). A recent randomized controlled trial (RCT) (N = 101) examined whether SSRIs can be discontinued when treatment with CBT/ERP is added. At 24 weeks no difference was found in Y-BOCS scores between those on placebo + CBT/ERP versus SSRI + CBT/ERP, however, the placebo group had higher rates of clinical worsening, suggesting that co-administration of SSRI with CBT/ERP is advisable in the longer term, at least for those who have initially benefited from SSRI (Foa et al., 2022).

2.3.7. Chronic disease management

Residual symptoms remain in nearly one-third of patients despite prolonged, evidence-based treatment. Moreover, many patients with OCD report functional difficulties, such as managing the sleep wake cycle or executive functioning, which are thought to be closely linked to OCD-related difficulties in cognitive processing and can substantially impact many aspects of daily living. Such patients are likely to benefit from long-term care and support from multidisciplinary mental health services (Nezgovorova et al., 2022). While research into the role of alternative treatments for OCD remains at a preliminary stage, expert consensus suggests that structured occupational therapies such as activity scheduling or alternative forms of CBT including habit reversal therapy are helpful in some cases (Fineberg et al., 2020), however, for more in depth commentary on alternative treatments, refer to the treatment resistant OCD section, Section 4. In chronic OCD, it is important to maintain an invested therapeutic relationship with the patient, nevertheless if the goal of treatment is symptom improvement or improving quality of life and functionality.

PRINCIPLES OF MANAGEMENT: RECOMMENDATIONS

- ❖ Individuals with OCD should access care via a primary care clinician or another mental health care provider (Level 4)
- ❖ In the case of individuals referring themselves for various forms of treatment and are not responding well, they should consider consulting with a practitioner with experience in the treatment of OCD to determine next steps (Level 4)
- ❖ Clinicians should familiarize themselves with the clinical presentations of OCD and proactively inquire further into cases showing signs of possible OCD, especially those who have a family member with OCD (as it is highly familial), as early detection and treatment is key to reduce duration of untreated illness (Nestadt et al., 2000)
- ❖ We recommend evaluating risk of suicide in all cases presenting with OCD and identifying opportunities for suicide prevention strategies (Hawton et al., 2022)

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(*continued*)

PRINCIPLES OF MANAGEMENT: RECOMMENDATIONS
❖ We recommend reducing family accommodation (regardless of the age), and continually monitoring psychosocial functioning (Demaria et al., 2021)
❖ We recommend using an objective scale that is sensitive to change to monitor clinical outcomes e.g. Yale Brown Obsessive Compulsive Scale (Y-BOCS) or self-rated scales e.g. Obsessive Compulsive Inventory- Revised (OCI-R) or an alternative (Wootton, 2016)
o Obtaining collateral information may be helpful
❖ We recommend 12 to 14 sessions (range 5–23) of individual psychotherapy using CBT that incorporates ERP techniques as initial treatment, if not initially using pharmacotherapy (Level 3◐)
❖ If starting treatment with pharmacotherapy, we recommend at least a 12-week trial of an SSRI to evaluate improvement. We recommend titrating the dose to the maximum dosage according to licensing authorization (Level 4◔)
o In the case of a partial response, consider an extended trial
o If the response remains incomplete, consider next steps for non-response (see Section 3.1.2)
❖ In those who have responded to an SRI and are tolerating it well, we recommend continuing the treatment for at least 12 months and possibly indefinitely to prevent relapse (see Section 2.3.6) (Level 4◔)
❖ Considering the high rate of relapse of OCD and worsening of mood following discontinuation of SRIs, patients should be engaged in a relapse prevention plan (Krebs and Lewis, 2018)
o SRI withdrawal should be gradual and patients should be closely monitored for signs of relapse and suicide risk (see Section 3.1.4)
❖ In cases where comorbidity exists, this should be monitored closely as well (see Section 3.1.2) (Pallanti and Grassi, 2014)
❖ We recommend routinely monitoring treatment adherence, as patients with OCD often find engaging in treatment (psychotherapy or medication) to be challenging (Simpson et al., 2011)
❖ We do not recommend using CBT as a method to protect against relapse following SRI withdrawal (Level 3, negative◧)
❖ In cases with residual impairments including functional difficulties following a course of treatment for OCD, multidisciplinary team involvement is recommended as long as patients remain significantly impaired (Nezgovorova et al., 2022)
o Support for families including psychoeducation and help with accommodation of OCD should be offered where relevant (Albert et al., 2017)

Key Points
- OCD treatment is often initiated in primary care settings.
- Delays in diagnosis and treatment are common; early identification of OCD is crucial to avoid negative consequences of long duration of untreated illness.
- Firstline psychological and pharmacological treatments appear equally efficacious in the short term.
- Both modalities require at least 12 weeks of treatment at adequate doses to indicate a signal of efficacy.
- Pharmacological treatment should continue for at least 12 months.
- Use of a validated symptom severity scale at baseline and throughout treatment is important; the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) is considered the gold standard.

3. Treatments

3.1. Pharmacotherapy

3.1.1. Evidence

The history of OCD pharmacotherapy is relatively recent. In the early and mid-eighties, clomipramine (serotonin, norepinephrine reuptake inhibitor [SERT, NET (metabolite)]; the most selective serotonergic drug among tricyclic agents) was found to have a specific anti-obsessive effect compared to other tricyclic agents (such as nortriptyline, amitriptyline, and imipramine that have more noradrenergic effects) (Ananth et al., 1981; Grassi et al., 2020; Thoren et al., 1980; Volavka et al., 1985). From that discovery, in subsequent years, the role of the serotonergic system in OCD pathophysiology has become the center of the investigation, and serotonergic agents have been largely studied for the treatment of OCD patients, rapidly gaining the role of first-line treatments (Skapinakis et al., 2021).

From early reports of serotonergic agents for OCD, the response criteria of anti-obsessional interventions have been operationalized. Responder patients in clinical trials are usually divided into partial and full responders. Full response is defined as a 35 % or greater symptom reduction on the Y-BOCS (Goodman et al., 1989b, 1989c) and a Clinical Global Impression (Improvement) Scale score of 1 or 2 (improved or much improved) (Guy, 1976). Partial response is defined as a greater than 25 % but less than 35 % symptom reduction on the Y-BOCS. Non-response is defined as a less than 25 % symptom reduction (Pallanti et al., 2002a). Response criteria for OCD substantially differ from those of other psychiatric conditions, including anxiety and depressive disorders, in which response is usually defined as a 50 % reduction in symptoms. A 35 % symptom reduction in OCD is usually associated with a significant improvement in a patient's quality of life; furthermore, the placebo response rate in OCD patients is typically lower than in other disorders (Huneke et al., 2024; Sugarman et al., 2017). Two studies aiming to refine treatment response criteria found a 35 % reduction on the Y-BOCS to be the optimal cut off for treatment response (Lewin et al., 2011a; Simpson et al., 2006). Using signal detection analysis, a 35 % reduction on the Y-BOCS was found to have the greatest sensitivity and specificity compared to other possible cut-off scores (Lewin et al., 2011a).

3.1.1.1. Serotonin reuptake inhibitors. According to several international guidelines, serotonergic agents (serotonin reuptake inhibitors (SRIs), encompassing SSRIs and clomipramine) are widely considered as first-line treatment for the pharmacological management of OCD patients (Menchon et al., 2019). Overall, according to the most recent and comprehensive meta-analysis, SSRIs and clomipramine are significantly superior compared to placebo (Level 1●) (Skapinakis et al., 2016). Several placebo-controlled trials conducted with SRIs consistently showed positive effect on OC symptoms. Sertraline showed significant efficacy and tolerability versus placebo at different daily doses (50–200 mg) in four double-blind placebo-controlled (DBPC) trials (Level 1●) (Chouinard et al., 1990; Greist et al., 1995b; 1995a; Jenike et al., 1990a; Kronig et al., 1999; Ushijima et al., 1997). Fluvoxamine showed greater efficacy versus placebo at different daily doses (100–300 mg) in seven DBPC trials (Level 1●) (Goodman et al., 1989a, 1996; Hollander et al., 2003d; Jenike et al., 1990b; Nakatani et al., 2005; O'Connor et al., 2006; Perse et al., 1987). Paroxetine showed a significantly greater efficacy versus placebo (in a daily dose range of 20–60 mg) in four DBPC trials (Level 1●) (GlaxoSmithKline, 2008; Hollander et al., 2003a; Kamijima et al., 2004; Zohar and Judge, 1996). Fluoxetine showed greater efficacy versus placebo at different daily doses (20–60 mg) in four DBPC trials (Level 1●) (Jenike et al., 1997; Montgomery et al., 1993; Tollefson et al., 1994; Zitterl et al., 1999). One DBPC trial for citalopram (Level 2◔) and one for escitalopram (Level 2◔) showed greater efficacy versus placebo at daily dose ranges of 20–60 mg and 10–20 mg, respectively (Montgomery et al., 2001; Stein et al., 2007b). Clomipramine showed greater efficacy at daily dose range of 100–250 mg compared to placebo in seven DBPC trials (Level 1●) (DeVeaugh-Geiss et al., 1991; Foa et al., 2005; Greist et al., 1990; Jenike et al., 1989; Mavissakalian et al., 1985; Thoren et al., 1980; Zohar and Judge, 1996).

According to meta-analyses and the available studies directly comparing different SSRIs, SSRIs do not differ in terms of efficacy, with no evidence to suggest that one is better than the others (Level 1●) (Skapinakis et al., 2016). SSRIs are generally well-tolerated, although common adverse effects include headache, irritability, gastrointestinal complaints, insomnia, sexual dysfunction, weight gain, increased anxiety, drowsiness, and tremor (Katzman et al., 2014). Most adverse effects are transient and occur during the first two weeks of treatment, however, side effects such as sexual dysfunction and weight gain, may persist for the duration of treatment (Katzman et al., 2014). A good review on the management of antidepressant side effects can be found in Kelly et al. (2008).

Interestingly, clomipramine has long been considered to be superior

to SSRIs. However, results from meta-analyses and head-to-head comparisons between clomipramine and SSRIs show that its superiority is not statistically significant, and is only marginal when old trials with incomplete outcome assessments and completer analyses only are excluded (Skapinakis et al., 2016). Clomipramine showed a slightly worse tolerability compared to SSRIs in trials directly comparing them (Skapinakis et al., 2016). Common adverse effects of clomipramine include anticholinergic effects (e.g., dry mouth, constipation, blurred vision, urinary retention, orthostatic hypotension, weight gain, and sedation). Cardiac arrhythmias (QTc prolongation risk <1/10,000 and Torsade de pointes arrhythmia risk <1/10,000) (Elsayed et al., 2021), seizures (<0.1 % under regular doses) (Bloechliger et al., 2016), drug interactions, and liver toxicity in overdose are infrequent but major safety concerns (Borue et al., 2015; Katzman et al., 2014), Thus, clomipramine should be considered as a second-line medication option.

3.1.1.2. Other agents. Beyond SRIs, other agents have been investigated as first-line pharmacotherapy interventions for OCD. Venlafaxine (serotonin, norepinephrine reuptake inhibitor [SERT and NET]) has been investigated as a first-line treatment for OCD. An early, small DBPC trial was conducted on 30 patients in 1996 and showed a statistically significant superior effect at a trend level for venlafaxine versus placebo, however, no significant between-group differences were found (Level 3, negative) (Yaryura-Tobias and Neziroglu, 1996). Then, a single-blind non-inferiority trial (Level 4) showed a comparable efficacy of venlafaxine and clomipramine (at a daily dose range of 225–300 mg and 100–225 mg, respectively), while a subsequent non-inferiority double-blind randomized trial Level 2) showed a comparable efficacy of venlafaxine and paroxetine (at daily doses of 300 mg and 60 mg respectively) (Albert et al., 2002; Denys et al., 2003). However, meta-analyses showed that the mean effect of venlafaxine versus placebo compared to the mean effect of venlafaxine versus other SRIs is not statistically significant (Skapinakis et al., 2016). Also, although the adverse effects associated with SNRIs are similar to those described above for SSRIs, venlafaxine especially at higher doses, has more potential side effects compared to SSRIs, such as hypertension and gastrointestinal problems (Beaulieu et al., 2019). Venlafaxine is a second-line treatment because of these potential side effects and the lack of placebo-controlled RCTs.

3.1.2. Recommendation

According to the current evidence, the SSRIs sertraline, fluoxetine, fluvoxamine, citalopram, escitalopram, and paroxetine should be considered as the first-line pharmacological approach for OCD. Although clomipramine has been consistently reported as one of the most effective interventions for OCD, its tolerability profile compared to those of SSRIs does not allow it to be considered a first-line approach. Clinicians should achieve the maximum tolerable dose for SSRIs and the duration of the acute treatment should be at least 12 weeks in order to adequately evaluate treatment response (Level 1) (Bloch et al., 2010; Issari et al., 2016). Indeed, meta-analyses of fixed doses trials showed a dose-response relationship with higher doses associated with greater treatment efficacy and a continued treatment improvement up to 12 weeks (Bloch et al., 2010). Of note, there is some evidence to suggest that significant SSRI response can be observed at 2 weeks, and it has been suggested that early SSRI response may predict pharmacotherapy outcome (Issari et al., 2016).

As the current literature does not show differences in terms of efficacy across different SSRIs, the choice of one SSRI with respect to others should be individualized according to the patient's profile. Firstly, the choice of the SSRI should take into account the impact of its side effect profile on the specific patients. For instance, paroxetine may induce more weight gain compared to other SSRIs (Serretti and Mandelli, 2010), while both citalopram (over 40 mg) and escitalopram (in a dose-dependent trend) may cause QTc prolongation (Beach et al., 2013, 2014; Ojero-Senard et al., 2017). Evidence from large trials in MDD with comorbid cardiovascular disease, has indicated that although QTc prolongation risk is present, the impact of this is considered to be low (see footnote Table 3.3) (Lam et al., 2024). Of note, QTc prolongation risk has not been evaluated specifically in pharmacovigilance trials and monitoring of QTc intervals when treating patients with escitalopram or citalopram is recommended at this time.

If prescribing fluvoxamine, paroxetine, or fluoxetine, possible drug interactions should be considered and regularly checked due to inhibition of cytochromes CYP 1A2, 2C9, C219, and 3A4 by fluvoxamine and CYP2D6 by paroxetine and fluoxetine. Moreover, clinicians should consider and monitor the potential sexual side effects and the risk of hyponatremia (especially for older patients and patients under thiazide diuretics) (De Picker et al., 2014).

Second, the pharmacological choice should consider the comorbidity pattern of the specific patient. It is reasonable to prefer a certain agent when it is also considered a first-line treatment for the comorbid condition (e.g., choosing fluoxetine for comorbid OCD and bulimia nervosa), or when it could be effective for both comorbid conditions (e.g., choosing venlafaxine for comorbid OCD and hoarding disorder). However, this choice is still not evidence-based and remains a clinical challenge since current literature is lacking studies prospectively assessing the different effectiveness of anti-obsessive agents according to comorbidities. Therefore, in comorbid patients, when OCD is the primary diagnosis, the only current evidence-based approach is to choose the SSRI according to its side effect profile after a comprehensive discussion with the patient. For more on comorbidities and treatment response, see Section 3.1.3.

3.1.2.1. Specific OCD populations: tic-related OCD. OCD is a heterogeneous condition, and the DSM-5 introduced the tic-related specifier in order to better characterize a specific subgroup of patients with OCD in clinical and research settings (Association (APA), 2013; Dell'Osso et al., 2017b). Dopaminergic partial agonists and serotonin-dopamine activity modulators (SDAMs, most antipsychotics) (e.g. aripiprazole, risperidone, etc.) are widely considered as first-line treatment for chronic tic disorder and represent a first-line augmentation strategy to SSRIs for treatment resistant OCD patients (Grassi et al., 2020). Early reports on tic-related OCD saw a lower rate of response to SSRIs and a greater response to SDAM augmentation compared to tic-free treatment resistant patients (McDougle et al., 1993, 1994). This data led some authors to propose their use in association with SSRIs as a first-line approach in tic-related OCD patients. However, several trials did not show any effect of tics on treatment response to SSRIs and a recent longitudinal study confirmed that the presence of tics does not influence treatment outcome at 2 years follow-up (Level 4, negative) (Husted et al., 2007; Jakubovski et al., 2013; Shavitt et al., 2006; Vries et al., 2016). Moreover, recent meta-analyses suggested that SDAM augmentation response is not moderated by the presence of tics and it may be even less robust in tic-related versus tic-free OCD patients (Level 1) (Veale et al., 2014; Zhou et al., 2019b). Thus, current available evidence does not support a

Table 3a
Clinical, biological, and genetic factors modulating treatment response in OCD.

Factors Modulating Treatment Response to CBT	Factors Modulating Treatment Response to Pharmacotherapy
Comorbid severe depression	Early onset/longer DUI
Comorbid tic disorder	Hoarding symptoms
Poor insight	Previous course of inadequate SRI response
Hoarding symptoms	Poor adherence to treatment
Previous course of failed CBT	
Poor adherence to ERP homework	
Poor therapeutic alliance	
Family history of OCD	

Table 3b
Treatment of OCD comorbidity - expert recommendations.

Comorbid Condition	Treatment
Depression	SRI
Anxiety and Related Disorders	SSRI
Bipolar I	Stabilize mood first with mood stabilizers* or SDM (atypical antipsychotics) or a combination of mood stabilizers and agents for psychosis. Augment with CBT (ERP) or TMS or SSRI for persistent OC symptoms; patients augmented with SSRIs should be monitored for (hypo)manic switch.
Bipolar II/Bipolar Spectrum Disorder	Stabilize mood first with mood stabilizers* or SDM (atypical antipsychotics). Augment with CBT (ERP) or TMS or SSRI for persistent OC symptoms.
Schizophrenia	Augment antipsychotic treatment with SRI and/or aripiprazole or switch the DA blocker (antipsychotic) (other than clozapine) to aripiprazole. Consider CBT/ERP if feasible.
Attention Deficit Hyperactivity Disorder	SRI + psychostimulant
Body Dysmorphic Disorder	SRI
Hoarding Disorder	Venlafaxine or paroxetine
Eating Disorder	Treat both conditions. Fluoxetine for comorbid bulimia, olanzapine for comorbid anorexia nervosa, lisdexamfetamine for comorbid binge eating disorder.
Trichotillomania (Hair Pulling Disorder)/Excoriation Disorder (Skin Picking Disorder)	Consider memantine or NAC for SPD and TTM, or SSRI for SPD and olanzapine for TTM.

CBT – Cognitive Behavioural Therapy; NAC – N-acetylcysteine; SPD– Skin Picking Disorder; SRI – Serotonin Reuptake Inhibitor; SSRI – Selective Serotonin Reuptake Inhibitor; TTM – Trichotillomania.

* A common mood stabilizer in the treatment of BD is valproate. Valproate products (valproate/valproic acid/divalproex sodium) have been associated with significant teratogenic and neurodevelopmental risks after fetal exposure during any stage of pregnancy (Vigod et al., 2025; Yatham et al., 2018). Due to this risk, Health Canada, the FDA, and European Medicines Agency have warned that valproate products should not be used in female children, female adolescents, or women of childbearing potential unless alternative treatments are ineffective or not tolerated (European Medicines Agency, 2018; Health Canada, 2017; US Food and Drug and Drug Administration, 2016). Although some regulatory bodies have cautioned prescribing valproate to men under 55 (or 3 months before conception), two recent population-based studies (Christensen et al., 2024; Tomson et al., 2020) saw no association between male valproate use and congenital malformations or intellectual disability in offspring.

different first-line pharmacological approach for tic-related versus tic-free OCD patients. However, the impact of tics on the patient's quality of life should be considered in the initial decision-making process, and for some specific patients with disabling tics a combined approach (SSRI + SDAM agents) could be considered.(see Table 3a, 3b, 3d, 3f, 3g, 3h, 3i).

3.1.3. Factors modulating treatment response

In order to guide discussions about treatment at an individual level, it is useful for clinicians to have an awareness of factors that may predict a positive, or conversely, a poorer response to treatment. A few of the most investigated factors are discussed below:

3.1.3.1. Clinical Predictors of Response. For CBT, predictors of a poorer outcome include; comorbid severe depression or tic disorder, a family history of OCD, poor levels of insight, hoarding symptoms, a previous failed course of CBT and poor adherence to ERP homework tasks, as well as difficulties regulating emotional reactions and a poor working alliance with the therapist (Bloch et al., 2014; Garcia et al., 2010; Simpson et al., 2011). In the case of pharmacotherapy, predictors of poor response include; poor treatment adherence, hoarding symptoms, and a previous inadequate response with an SRI (Ackerman et al., 1998; Bloch et al., 2014; Eisen et al., 2013; McDougle et al., 1993). The issue of treatment adherence is a key factor in determining outcomes for both psychotherapy and pharmacotherapy, and in the case of CBT/ERP, acted as the key mediating factor for the other risk factors in one analysis (Simpson et al., 2011). In addition, while the presence of family accommodation has been reported as predictive of a poor response to both SRI treatment and CBT in early studies (Ferrao et al., 2006; Storch et al., 2007a), a recent meta-analysis suggested that its impact on treatment outcomes is not significant (Hermida-Barros et al., 2024). High levels of cognitive inflexibility on cognitive tasks have also been found to predict a poor outcome with CBT/ERP (D'Alcante et al., 2012; Eisen et al., 2013) but not with SRI treatment. Commonly comorbid disorders associated with high levels of cognitive inflexibility and a poor treatment response include OCPD (Cavedini et al., 1997; Eisen et al., 2013) and autism spectrum disorders (ASD) (Storch et al., 2010a), therefore specific adaptations of CBT may be helpful.

3.1.3.2. Early-onset and biological sex. OCD patients with an early age of onset seem to have a specific clinical and biological profile, tend to have a worse outcome, and tend to be more treatment resistant compared to adult-onset patients (Dell'Osso et al., 2013; Grassi et al., 2021). However, as suggested by the available long-term follow-up studies, the worse outcome and higher degree of treatment resistance of these patients seems to be related to the DUI and the number of years spent with OCD (Albert et al., 2019a; Fineberg et al., 2013, 2019). In fact, there is growing evidence that treating pediatric OCD patients with an appropriate intervention (CBT, SRIs, augmentation with serotonin-dopamine activity modulators/antipsychotic agents) results in a better outcome even compared to what can be achieved in adult patients (Fineberg et al., 2019; Melin et al., 2018). Current evidence about a possible role of biological sex in treatment response to SRIs is still inconclusive. While it is well known that male and female OCD patients have specific clinical characteristics (previously discussed in the principles of management chapter, Section 2.3), there is no clear evidence of a different impact of first-line treatments according to patients' biological sex (Mathes et al., 2019). However, other variables, such as relative safety during pregnancy and lactation, may influence treatment selection with respect to biological sex (see chapter on OCD and pregnancy and lactation, Section 7.1).

3.1.3.3. Comorbidities. OCD is associated with substantial comorbidities. A recent meta-analysis on clinical adult OCD samples found a pooled prevalence of comorbidities of 70.8 % (Sharma et al., 2021). When OCD occurs alongside other medical or mental health conditions, it tends to be more disabling, chronic, and treatment resistant, and treatment of the comorbid condition can add complexity to the treatment course (Pallanti and Grassi, 2014). Common disorders that are comorbid with OCD are depression, bipolar disorders, obsessive-compulsive related disorders (OCRD), tic disorders, anxiety disorders, posttraumatic stress disorder, ADHD, eating disorders, and psychosis/schizophrenia (Lochner et al., 2014). Autism spectrum disorders are also commonly comorbid conditions, and their assessment and management are specifically addressed in section 7.3.

Depression. Depression is a very frequent condition comorbid to OCD, with a lifetime prevalence of around 40 % in adults with OCD (Hofmeijer-Sevink et al., 2013; Ruscio et al., 2010; Sharma et al., 2021). This high association may be related to the distress and functional impairment due to OCD, but other factors, such as common genetic vulnerabilities, may also be involved. Among various classes of antidepressant medications, SRIs have been found to improve both disorders (Hoehn-Saric et al., 2000; Valerio et al., 2012). In fact, a double-blind study that compared the efficacy of sertraline and desipramine, a predominantly NET inhibitor in 166 patients diagnosed with both OCD and

Table 3c
Levels of evidence and lines of treatment for pharmacotherapy in non-treatment resistant OCD.

Intervention	Level of Evidence	Line of Treatment	Recommended Daily Dose Range
Escitalopram	1	first line	10–20 mg*
Fluoxetine	1	first line	20–80 mg
Fluvoxamine	1	first line	200–300 mg
Paroxetine	1	first line	40–60 mg
Sertraline	1	first line	100–200 mg
Citalopram	1	first line	20–40 mg**
Clomipramine	1	second line	100–250 mg***
Venlafaxine	2	third line	150–300 mg

RECOMMENDATIONS FOR FIRST-LINE PHARMACOTHERAPY

- The SSRIs sertraline, fluoxetine, fluvoxamine, citalopram, escitalopram, and paroxetine are the first line of pharmacological treatment (Level 1), without any significant difference in terms of efficacy.
- Comorbidity as well as tolerability needs to be taken into consideration when choosing an SRI.
- Duration of the acute treatment should be at least 12 weeks, using the maximally tolerated dose in order to adequately evaluate treatment response (Level 1).
- A number of factors modulate treatment response, such as clinical factors, age of onset, comorbidities, pharmacogenetics, etc.
- Due to the high risk of relapse, the duration of the pharmacological treatment should be considered indefinite in many individuals, providing acceptable tolerability (Level 4).

* Doses up to 30 and 50 mg/day have been effective in clinical trials, although doses higher than 20 mg/day have not been recommended due to the risk of QT prolongation and doses greater than 10 mg/day should be used carefully in patients older than 65 years of age. Regular electrocardiogram testing is recommended for doses higher than 20 mg.

** Doses up to 80 mg/day have been effective in clinical trials, although doses higher than 40 mg/day have not been recommended due to the risk of QT prolongation; further, doses greater than 20 mg/day should be used carefully in patients who are CYP2C19 poor metabolizers, those who may be taking concomitant CYP2C19 inhibitor drugs, or those who are older than 65 years of age. Regular electrocardiogram testing is recommended for doses higher than 40 mg. The recent CANMAT depression treatment guidelines (Lam et al., 2024) recognize that citalopram carries a risk of QTc prolongation, however, has deemed the clinical risk as low. Four large RCTs have investigated the use of citalopram to treat depression in those with coronary heart disease, with none finding a significantly increased risk of cardiac adverse events due to citalopram compared to another medication for MDD (mirtazapine) or placebo (De Jonge et al., 2007; Lespérance et al., 2007; Rollman et al., 2009; van den Brink et al., 2002). One trial (N = 284) found that citalopram was not significantly different from placebo in any blood pressure or electrocardiogram measures, including QTc intervals (Lespérance et al., 2007). Nevertheless, monitoring of QTc intervals remains highly recommended.

*** Despite some studies using daily doses up to 300 mg, doses above 250 mg significantly increase the risk of seizures and cardiac arrhythmias.

major depression, found that sertraline showed a significant greater improvement than desipramine in both OCD and depressive symptoms (Level 2) (Hoehn-Saric et al., 2000). Clomipramine has also shown to be effective in the treatment of OCD and depressive symptoms (Level 3) (Thoren et al., 1980; Volavka et al., 1985). Therefore, treatment with SRIs should be the first choice for the treatment of OCD with depression.

Anxiety and related disorders. Anxiety disorders constitute common comorbid conditions with OCD, with prevalence rates in meta-analyses of 32.7 % (Sharma et al., 2021). They tend to improve with the usual treatment of OCD (Valerio et al., 2012). Several studies have found that comorbid generalized social phobia (SP)/social anxiety disorder (SAD) is associated with a poor response to SSRIs in OCD patients. One open-label study with fluoxetine found that comorbid social phobia in OCD predicted a worse response to CBT or fluoxetine (Level 4) (Bertolin et al., 2021). Another study found a marked improvement of both SP and OCD with phenelzine, although the number of subjects was low (N = 5) and the design of the study was a retrospective case series (Level 4) (Carrasco et al., 1992). Regarding posttraumatic stress disorder (PTSD), one open study found that the rate of responders to SSRIs was not significantly different between OCD patients with versus without PTSD but, there was a significantly better response for the group of patients with OCD and PTSD when treatment response was considered as a continuous variable (Level 4). Indeed, in this study, the presence of PTSD with OCD was associated with a better response to SSRIs (Level 4) (Shavitt et al., 2010). Conversely, another study reported that patients with OCD had significantly better treatment responses than patients with comorbid PTSD when treated with self-guided ERP and group therapy with or without adjunctive pharmacotherapy (Level 4) (Gershuny et al., 2002). Case reports have documented the effectiveness of sertraline with adjunctive aripiprazole, a partial dopamine (DA) agonist, for the treatment of OCD and comorbid PTSD (Level 4) (Rossi et al., 2020). Ideally, a serotonergic agent should be chosen that will treat both the anxiety/anxiety-related disorder and OCD (Level 4).

Bipolar disorder (BD). OCD and BD commonly co-occur. Among clinical population studies on adults with a primary diagnosis of BD, the prevalence of comorbid OCD ranges from 3 % to 23.2 %, with a pooled prevalence in meta-analyses around 10 % (De Filippis et al., 2024; Ferentinos et al., 2020). The prevalence of BD in adult patients with primary OCD is around 5 %, however ranges in the literature from 0.3 to 53.3 % (De Filippis et al., 2024; Dell'Osso et al., 2020; Sharma et al., 2021). A recent ICOCS study found that OCD patients with comorbid BD showed more frequent previous hospitalizations, more complex therapeutic regimens, and a greater severity of OCD (Dell'Osso et al., 2020). Other studies showed an increased suicide risk and higher rates of substance use disorders compared to non-bipolar patients (De Filippis et al., 2024; Domingues-Castro et al., 2019). Moreover, several studies showed that BD-OCD patients exhibit a higher prevalence of episodic OCD compared to non-comorbid patients, with the majority of OCD symptoms occurring exclusively during depressive episodes or a worsening of symptoms during periods of depression or mixed states (De Filippis et al., 2024).

Most studies examining treatment for comorbid BD in OCD are cross-sectional studies or case reports, with only a few published placebo-controlled trials with small samples. Across uncontrolled and cross-sectional studies on patients with BD and comorbid OCD, most patients were treated with mood stabilizers alone or in combination with serotonin-dopamine modulators (SDM formally denoted atypical antipsychotics) and/or SRIs (Bisol and Lara, 2009; Di Salvo et al., 2021;

Table 3d
Levels of evidence and lines of treatment for psychological interventions of OCD.

Intervention	Level of Evidence	Line of Treatment
Cognitive Behavioural Therapy with Exposure and Response Prevention (CBT/ERP)	●	first line
Cognitive Therapy (CT)	●	first line
Acceptance and Commitment Therapy (ACT)	◔	second line
Eye Movement Desensitization and Reprocessing (EMDR) Therapy	◔	second line
Imagery Rescripting	◔	third line
Metacognitive Therapy (MCT)	◔	third line
Mindfulness Meditation with Electroencephalogram (EEG) Biofeedback	◔	third line
Stress and Anxiety Management Therapy (SAMT)	■	not recommended
Progressive Muscle Relaxation (PMR)	■	not recommended
Mindfulness-Based Cognitive Therapy (MBCT)	■	not recommended

Table 3e
Levels of evidence and lines of treatment for individual and group psychotherapy treatment formats.

Treatment Type	Individual Intervention		Group Intervention	
	Level of Evidence	Line of Treatment	Level of Evidence	Line of Treatment
Cognitive Behavioural Therapy with Exposure and Response Prevention (CBT/ERP)	●	first line	●	first line
Cognitive Therapy (CT)	●	first line	■	not recommended
Acceptance Commitment therapy (ACT)	◔	second line	not studied	unable to make recommendation
Bergen 4-Day Treatment (B4DT)	◔	third line	not studied	unable to make recommendation*
Metacognitive Therapy (MCT)	◔	third line	not studied	unable to make recommendation
Mindfulness-Based Cognitive Therapy (MBCT)	■	not recommended	■	not recommended

* B4DT is not delivered in a typical group format, as each participant has an individual therapist.

Kazhungil et al., 2017; Khan et al., 2019; Kim et al., 2014; Ozdemiroglu et al., 2015; Petrikis et al., 2004; Saraf et al., 2017; Shashidhara et al., 2015; Tonna et al., 2021). Lithium and valproate are the most used mood stabilizers while aripiprazole has been the most investigated SDM (atypical antipsychotic) augmentation agent. In one study, BD-OCD patients with manic, depressive, and OC symptoms had valproate augmented with risperidone (n = 31) or aripiprazole (n = 30), with both drugs significantly reducing mean Hamilton Depression Rating Scale (HAM-D) and Young Mania Rating Scale (YMRS) scores, however aripiprazole was more effective in reducing the OC symptoms (Level 2◔) (Khorshidian et al., 2023). Three small placebo-controlled trials from the same group in Iran with BD-OCD patients in a current manic episode displaying concurrent OCD symptoms (Y-BOCS ≥16), showed the groups receiving topiramate (up to 200 mg) or memantine (20 mg)

Table 3f
Levels of evidence and lines of treatment for digital psychological treatments of OCD.

Intervention	Level of Evidence	Line of Treatment
Internet-Delivered Cognitive Behavioral Therapy (ICBT)	●	first line
Metacognitive Bibliotherapy	◔	third line
Smartphone App-Delivered Cognitive Behavioral Therapy	◔	third line

Table 3g
Levels of evidence and lines of treatment for cognitive behavioural therapy with exposure and response prevention (CBT/ERP) combined with an additional OCD treatment.

CBT + Additional Intervention	Level of Evidence	Line of Treatment*
Serotonin Reuptake Inhibitors (SRI)**	●	second line
Cognitive Therapy (CT)	◔	second line
Transcutaneous Electrical Acupoint Stimulation (TEAS)	◔	third line
Music Therapy	◔	third line
Electroencephalogram (EEG) Biofeedback	◔	third line
Family Interventions (addressing accommodation)	◐	third line
Motivational Interviewing (MI)	◐	third line
Mindfulness-Based Treatment	◐	third line
Acceptance and Commitment Therapy (ACT)	◐	third line
Nabilone	◔	third line
D-cycloserine (DCS)	■	unable to make recommendation

* No recommendation is first line as efficacious monotherapies should be tried first as a more efficient strategy, see Table 3–5 for recommendations.
** When compared to SRI monotherapy, SRI + CBT is superior in efficacy, however when comparing SRI + CBT to CBT monotherapy, they are equal in efficacy.

augmentation of the combination lithium + olanzapine + clonazepam had significantly greater improvements compared to placebo (Level 3◐) (Sahraian et al., 2014, 2017). As well, those receiving augmentation of lithium + clonazepam with aripiprazole (up to 30 mg) also had greater Y-BOCS score reductions post-treatment than placebo (Level 3◐) (Sahraian et al., 2018). Another placebo-controlled trial from the same group showed significant efficacy of quetiapine augmentation (mean

Table 3h
Levels of evidence and lines of treatment for the augmentation of existing, stable OCD treatments with additional forms of treatment.

Intervention	Level of Evidence	Line of Treatment
Augmenting existing stable SSRI treatment		
Cognitive Behaviour Therapy with Exposure Response Prevention (CBT/ERP)	◔	second line
Acceptance and Commitment Therapy (ACT)	◐	third line
Cognitive Therapy (CT)	◐	third line
Stress and Anxiety Management Therapy (SAMT)	■	not recommended
Augmenting existing stable CBT/ERP treatment		
Cognitive Therapy	◧	unable to make recommendation

Table 3i
Levels of evidence and lines of treatment for complementary and alternative treatments for OCD.

Intervention	Level of Evidence	Line of Treatment
Inositol	3	third line
Milk Thistle *(Silybum marianum)*	4	third line
Borage (*Echium amoenum)*	4	third line
Valerian Root (*Valeriana officinalis)*	4	third line
Ashwagandha *(Withania Somnifera)*	4	third line
Saffron *(Crocus sativus)*	4	third line
Yoga:		
Kundalini Yoga Augmentation	4	third line
Validated OCD Yoga Intervention (Bhat et al., 2024) Augmentation	3	third line
Hatha Yoga Monotherapy	1	not recommended
Cannabis	2	unable to make recommendation
Aerobic exercise	2	unable to make recommendation
Adjunctive Glycine	2	unable to make recommendation
St. John's Wort (*Hypericum perforatum*)	1	not recommended

dose of 325 mg) of lithium + clonazepam compared to placebo in patients with euthymic BD type 1 with concurrent OCD symptoms (Level 3) (Sahraian et al., 2022). There are currently no trials of CBT or any psychotherapy in BD-OCD, yet behavioural therapy, in combination with pharmacotherapy, has been shown to be effective in limited case studies (Baer, 1993). However, some of the common features of OCD in BD patients correlate with predictors of poor response to psychotherapy, like poor insight and comorbid anxiety disorders (Kazhungil and Mohandas, 2016). As well, some patients may have severe symptoms which prevent their participation in CBT.

Drug-induced bipolar states. SRI-induced manic and/or hypomanic symptoms have been reported in BD and may pose a risk when using these agents as a monotherapy (Viktorin et al., 2015). However, a meta-analysis (McGirr et al., 2016), as well as a propensity score analysis study (Vöhringer et al., 2025) have concluded that there is no evidence that SSRIs used as augmentation of a mood stabilizer or atypical antipsychotic in acute bipolar depression (either bipolar I or II) or as maintenance adjunctive treatment in bipolar patients poses increased risk of treatment-emergent mania or hypomania compared to placebo (McGirr et al., 2016; Vöhringer et al., 2025; Yatham et al., 2023). This conclusion is further supported by a task report from the International Society for Bipolar Disorders on antidepressant use in BD (Pacchiarotti et al., 2013) and by large-scale health-registry studies (Rohde et al., 2024; Viktorin et al., 2015), which did not find an increased risk of manic/hypomanic switch when SSRIs were used as augmentation in mood stabilized BD patients.

Nevertheless, in the small but emerging OCD-BD literature, there have been reports of an increased risk of manic/hypomanic switch in this comorbid population. A clinic-based study (n = 314) found a three-times higher incidence of manic/hypomanic switch in the BD-OCD population compared to those with BD alone ($p < .001$), and high lifetime rates (up to 60 %) of manic/hypomanic switch in patients exposed to medications for MDD (unspecified) (Jeon et al., 2018). Another cross-sectional study showed that clomipramine, and to a lesser extent SSRIs, are associated with manic/hypomanic switches, especially in those patients not on treatment with mood stabilizers (Perugi et al., 2002). Moreover, a recent systematic review showed several case studies and reports of first manic/hypomanic episodes induced by serotonergic agents in OCD patients with no history of bipolarity (Bertolin et al., 2021). This study also found that most of the manic/hypomanic episodes appeared within the first 12 weeks of initiation of the medication for MDD, with fluoxetine being the most frequently reported SRI associated with emerging manic/hypomanic episodes in OCD patients (Bertolin et al., 2021). There was no significant difference in the risk of mood-switching between fluoxetine and clomipramine (Bertolin et al., 2021), however several older studies (Amerio et al., 2014; Perugi et al., 2002) have advised against the use of clomipramine in BD-OCD due to a potential increased risk of induced manic/hypomanic switch. Non-pharmacological treatments for OCD such as CBT and TMS do not appear to be associated with increased risk of mood switching. A recent meta-analysis and systematic review evaluated patients with mood disorders including BD (Miuli et al., 2021) and found no significantly increased risk of a manic or hypomanic switch between those receiving active TMS (n = 576) compared to sham (n = 487).

Treatment recommendations for BD-OCD. An important foundational goal in treating BD-OCD patients is mood stabilization, which, for some patients, may alleviate comorbid symptoms of OCD without the need for medication for MDD (Yatham et al., 2018). According to recent CANMAT bipolar treatment guidelines (Yatham et al., 2018), first-line pharmacotherapy agents for bipolar I disorder mood stabilization include mood stabilizers and atypical antipsychotics, while specifically quetiapine, lithium, and lamotrigine are preferred for bipolar II and bipolar spectrum disorder. Although there is limited evidence for the pharmacological treatment of BD-OCD comorbidity, case reports (Level 4) suggest lithium, drugs for seizure disorder (anticonvulsants), olanzapine, risperidone, quetiapine, and aripiprazole may be beneficial (Bond et al., 2012; Yatham et al., 2018). Once mood is stabilized, if there are persistent OC symptoms in patients with BD I, BD II, or bipolar spectrum disorder and OCD comorbidity, clinicians could consider adding SSRIs for the treatment of the OCD. CBT (see Section 3.2.2) or TMS (see Section 5.1.1) could be considered for mild or moderate OCD symptoms if SSRIs are used, it is important to ensure that patients are on adequate therapeutic doses of mood stabilizers to minimize the potential risk of manic/hypomanic switch. Further, patients should be advised about such risk and carefully monitored particularly in the first 8 weeks of treatment so that any treatment emerging switches can be identified early and managed as appropriate. For severe and complex patients, cooperation with a specialized service for BD should be considered. See the CANMAT bipolar guidelines for more detail on the management of patients with bipolar disorder (Yatham et al., 2018).

Schizophrenia. The presence of OCD and OC symptoms in schizophrenia is a very common clinical observation with mean prevalence rates in meta-analyses ranging from 4.5 % to 13 % for OCD, and up to 30 % for OC symptoms (Sharma et al., 2021; Swets et al., 2014). Several cases of *de novo* onset or worsening of OCD in patients with schizophrenia have been associated with the use of serotonin-dopamine activity modulators/atypical antipsychotic drugs, particularly clozapine (Grassi et al., 2014; Grover et al., 2019; Kim et al., 2020). However, some case reports observed an improvement of OC symptoms with the partial DA agonist cariprazine, clozapine, or other serotonin-dopamine activity modulators (De Berardis et al., 2020; Poyurovsky et al., 2000; Tibbo and Gendemann, 1999). Nonetheless these findings have been anecdotal or derived from the observation of patients with active psychotic symptoms (Level 4). Several clinical trials, mostly open-label, have found that adding SSRIs or clomipramine to the antipsychotic treatment in stabilized patients with schizophrenia resulted in an improvement of obsessive and psychotic symptoms, although in one study of fluvoxamine 3 out of 10 patients dropped out because of the appearance of aggressiveness or acute exacerbation of the psychosis (Level 4) (Agarwal and Agarwal, 2000; Berman et al., 1995; Poyurovsky et al., 1999, 2003; Rahman et al., 1998; Reznik and Sirota, 2000; Stryjer et al., 2013; Zohar et al., 1993). An open-label study reported that DA blockers (antipsychotics) augmentation with high-dose escitalopram (up to 40 mg/d) significantly improved the Y-BOCS scores of patients with schizophrenia and comorbid OCD (Level 4) (Rubin-Kahana et al., 2019). In another open-label study (Glick et al., 2008), the antipsychotic treatment was switched to aripiprazole in 15

patients with schizophrenia and OC symptoms, and 6 out of the 7 patients who completed the trial after 6 weeks showed a Y-BOCS reduction greater than 35 % (Level 4). An open-label study (N = 29) reported that augmentation with the SDM (antipsychotic) ziprasidone improved the Y-BOCS scores (≥25 % score reduction) of 55 % of patients with schizophrenia and OCD (Level 4) (Juven-Wetzler et al., 2014). Of note, a small open study showed some efficacy of lamotrigine as an add-on to antipsychotic treatment (Level 4) (Poyurovsky et al., 2010). The available reports on clozapine-related OC symptoms and/or OCD management showed some effectiveness of SRIs and/or aripiprazole add-on, but while reducing clozapine dose seem to be effective in some cases, it has also been related to worsening of psychotic and mood symptoms (Kim et al., 2020). Finally, only a few anecdotal reports exist on the use of CBT in this population (Kim et al., 2020; Tundo and Necci, 2016). For patients with comorbid OCD and schizophrenia, adjunctive SRIs and/or aripiprazole or switching the DA blocker (antipsychotic) (other than clozapine) to aripiprazole should be considered. Dose reduction in clozapine-treated patients is still not evidence-based and could be potentially related to worsening of psychotic and mood symptoms. CBT/ERP should be considered according to its feasibility. A multidisciplinary approach is often recommended.

ADHD. ADHD and OCD comorbidity has a prevalence in meta-analyses of 16.2 % and is more common in pediatric and early-onset adult patients compared to later onset patients (Blanco-Vieira et al., 2019; Farrell et al., 2020; Sharma et al., 2021; Walitza et al., 2008). Recognizing ADHD in patients with OCD is often a clinical challenge since patients with OCD may present ADHD-like symptoms (such as inattention) that are linked to the presence of obsessions and ADHD patients may display some OC symptoms as a coping strategy (Grassi et al., 2021). Patients with ADHD-OCD comorbidity tend to have more severe and treatment resistant OCD with an increased risk of suicide attempts (Blanco-Vieira et al., 2019). Also, patients that initially present with ADHD and then subsequently develop OCD have higher lifetime frequencies of substance abuse and dependence and greater worsening of the OCD course (de Mathis et al., 2013). Studies on ADHD in patients with OCD, which are mainly case reports or case series in children or young subjects, show an improvement of OCD following DA/NE enhancers (stimulant) administration and generally recommend treating both conditions with standard first-line treatments (Level 4) (Cabarkapa et al., 2019; Dogan-Sander and Strauss, 2021; King et al., 2017). The risk of OCD worsening or symptom induction with stimulants is not supported by evidence since, in the current literature, only a few case reports on an adolescents and a single case report on an elderly patient showed stimulant-induced OCD onset (Level 4) (Jhanda et al., 2016; Koizumi, 1985; Kotsopoulos and Spivak, 2001; Kouris, 1998; Serby, 2003; Woolley and Heyman, 2003). Notably, two controlled trials on patients with treatment resistant OCD (without ADHD comorbidity) showed OCD symptom improvement with methylphenidate(Level 3) and dextroamphetamine (unable to evaluate Level of Evidence, see footnote Tables 4–1) (Koran et al., 2009; Zheng et al., 2019). Therefore, psychostimulant treatments used as first-line agents in ADHD may be of benefit to treatment resistant OCD even in the absence of clear ADHD comorbidity (discussed further in Section 4.1.1). Additionally, the presence of ADHD could potentially interfere with the patients' adherence to CBT, thus, the pharmacological treatment of ADHD in patients with comorbid OCD should be highly considered (See Table 3b).

OCD with comorbid Obsessive-Compulsive and Related Disorders (OCRDs) and comorbid eating disorders

Despite the high rates of comorbidity with OCD of 17.5 % (Sharma et al., 2021), there have not been treatment studies examining OCD comorbid with OCRDs such as body dysmorphic disorder, hoarding disorder, trichotillomania or excoriation disorders, or eating disorders. The following recommendations for comorbid treatment are based upon expert opinion as there are currently no studies examining the treatment of the comorbid condition with OCD (Level 4). Given the lack of data on treating the conditions together, we have reported the evidence for treating the comorbid condition alone.

Body Dysmorphic Disorder (BDD): The treatment of co-occurring BDD and OCD should be based on available controlled trials on BDD, which suggest using high doses of SRIs, similar to OCD (Castle et al., 2021). The SRIs with proven efficacy in DBPC trials for BDD are fluoxetine, escitalopram, and clomipramine, but other SRIs such as fluvoxamine and citalopram showed efficacy in open trials (Castle et al., 2021; Hollander et al., 1999; Phillips et al., 1998, 2002, 2016; Phillips and Najjar, 2003). There are currently no studies examining OCD with BDD comorbidity.

Hoarding Disorder (HD): While several trials with patients with OCD showed the presence of hoarding symptoms as a predictor of non-response to SSRIs (see Clinical Predictors of Response above), pharmacological data on patients with a DSM-5 diagnosis of HD are limited to small open trials. An early open trial of paroxetine for patients with primary HD showed a good response but a poor tolerability, while a more recent open trial on venlafaxine (225 mg/d) showed 70 % treatment response and a good tolerability after 12 weeks (Saxena and Sumner, 2014). Additionally, two ADHD medications (methylphenidate and atomoxetine) showed encouraging positive effects on HD in two small open trials (Grassi et al., 2016; Rodriguez et al., 2013a).

Trichotillomania (TTM) (Hair Pulling Disorder) and Excoriation Disorder (Skin Picking Disorder - SPD): At present, there are no first-line medications approved for the treatment of TTM or SPD and evidence-based treatments for these disorders as comorbidities with OCD are limited. Concerning TTM, while some open trials with SSRIs (escitalopram, citalopram, and fluoxetine) showed some effectiveness, the two available controlled trials with fluoxetine showed a lack of efficacy (Christenson et al., 1991; Gadde et al., 2007; Stein et al., 1997; Streichenwein and Thornby, 1995; Winchel et al., 1992). On the other hand, in an early trial, clomipramine showed greater effects on TTM symptoms than desipramine, and in another trial showed greater symptom reduction than placebo, but without statistical significance (Ninan et al., 2000; Swedo et al., 1989a). Interestingly, olanzapine and memantine, two agents that showed some efficacy as augmentation strategies in treatment resistant OCD, showed their efficacy in monotherapy controlled trials for TTM (Grant et al., 2023; van Ameringen et al., 2010). There is also some evidence of the efficacy of N-acetylcysteine (NAC) in TTM from one controlled trial (Grant et al., 2009).

Concerning SPD, fluoxetine showed significant efficacy in two small controlled trials (Bloch et al., 2001; Simeon et al., 1997), and fluvoxamine and escitalopram showed efficacy in open trials (Arnold et al., 1999; Keuthen et al., 2007), while a controlled trial of citalopram did not show superiority versus placebo (Arbabi et al., 2008). Memantine and N-acetylcysteine (NAC) showed efficacy in adults with SPD in controlled trials (Grant et al., 2023, 2016). Thus, while SSRIs could be reasonably considered as a first choice for the treatment of comorbid OCD and excoriation disorder, their use for treating both comorbid trichotillomania and OCD is not recommended. For this latter population, augmentation strategies such as memantine or olanzapine to SSRIs, or the use of NAC, should be considered.

Eating disorders. Eating disorders and OCD also share a high comorbidity. The lifetime prevalence of OCD in eating disorders has recently been estimated at almost 14 % (with studies ranging from 10 to 60 % in clinical samples) (Drakes et al., 2021; Godart et al., 2002), while the prevalence of anorexia or bulimia nervosa among patients with OCD is 3.8 % and 2.8 % respectively (Sharma et al., 2021). One study (Olatunji et al., 2010) examined the improvement of 508 females among patients with eating disorders, half of whom had comorbid OCD, and found that the improvement of one condition mediated the improvement of the other, and that the reduction of eating disorder symptoms fully mediated improvements in OCD symptoms. Another study found that treatment of both conditions with psychological approaches and pharmacological treatment was an effective strategy (Simpson et al., 2013b). According to a recent meta-analysis, the medications that showed some benefits for both eating disorders and for OC symptoms

Table 4a
Levels of Evidence and Lines of Treatment for Adjunctive, Combined, or Monotherapy Treatments in Treatment Resistant OCD (Line of Treatment refers to Treatment Resistant OCD).

Treatment Resistant OCD		
Medication	Level of Evidence	Line of Treatment
DOPAMINERGIC AGENTS		
DA Modulators (Antipsychotics)		
Adjunctive Risperidone		first line
Adjunctive Aripiprazole		first line
Adjunctive Haloperidol		first line
Adjunctive Olanzapine		unable to make recommendation**
Adjunctive Quetiapine		unable to make recommendation**
Adjunctive Paliperidone		unable to make recommendation
DA/NE enhancers (Psychostimulants)		
Adjunctive Methylphenidate		third line
Adjunctive d-Amphetamine***	unable to evaluate	unable to make recommendation
Adjunctive Caffeine		third line
GLUTAMATERGIC AGENTS		
Glutamate Release Modulators		
Adjunctive Lamotrigine		second line
Adjunctive Topiramate		third line
Adjunctive Pregabalin		third line
Adjunctive Troriluzole		not recommended
Clonazepam Monotherapy		unable to make recommendation
Adjunctive Riluzole		unable to make recommendation
Adjunctive Minocycline		unable to make recommendation
NMDA Receptor Antagonists		
Adjunctive Memantine		second line
IV Ketamine Monotherapy		third line
Adjunctive IV Ketamine		unable to make recommendation
Adjunctive Intranasal Ketamine		unable to make recommendation
NMDA Receptor Modulators		
Adjunctive N-acetylcysteine (NAC)		unable to make recommendation
SEROTONERGIC AGENTS		
Selective Serotonin Reuptake Inhibitors		
High Dose SSRI Monotherapy		second line
Adjunctive IV Citalopram		third line
Tricyclic SERT Inhibitor (Tricyclic Antidepressant)		
IV Clomipramine		third line
Adjunctive Clomipramine		third line
Combined Clomipramine with SSRI		third line
Adjunctive IV Clomipramine		unable to make recommendation
Other Antidepressants		
Duloxetine Monotherapy		third line
Mirtazapine Monotherapy		third line
Venlafaxine Monotherapy		unable to make recommendation
5-HT$_3$ Antagonists		
Adjunctive Ondansetron		third line*
Adjunctive Granisetron		third line
5-HT$_{1A}$ Antagonist		
Adjunctive Pindolol		unable to make recommendation**
Other Serotonergic Agents		
Inositol Monotherapy		third line
Psilocybin Monotherapy		unable to make recommendation
Adjunctive Psilocybin		unable to make recommendation
Adjunctive Inositol		unable to make recommendation
Adjunctive Buspirone		unable to make recommendation
OPIOIDS		
Opioid Receptor Agonists		
Adjunctive Morphine		third line
Tramadol Monotherapy		third line
Adjunctive Buprenorphine		unable to make recommendation
Opioid Receptor Antagonists		
Adjunctive Naltrexone		unable to make recommendation
OTHER AGENTS		
Cannabinoids		
Adjunctive Dronabinol		third line
Statins		

(*continued on next page*)

Table 4a (*continued*)

Treatment Resistant OCD		
Medication	Level of Evidence	Line of Treatment
Adjunctive Atorvastatin		third line
Nonsteroidal Anti-inflammatory Drugs		
Adjunctive Celecoxib		third line
Mood Stabilizers		
Adjunctive Lithium		unable to make recommendation
Adjunctive Eicosapentaenoic acid (EPA)		unable to make recommendation
PSYCHOTHERAPY		
Adjunctive CBT/ERP		first line
PHYSICAL THERAPIES		
Adjunctive Aerobic Exercise		unable to make recommendation

Key Points
- Inadequate response to first-line OCD treatments is common.
- The literature lacks a standardized definition of what constitutes treatment resistance and treatment refractoriness in OCD.
- A broad range of augmenting agents have been examined in treatment-resistant OCD.
- The strongest evidence supports the adjunctive use of atypical anti-psychotics or CBT.

SSRI – Selective Serotonin Reuptake Inhibitor; CBT/ERP - Cognitive Behavioural Therapy with Exposure and Response Prevention.
***In the Koran et al., study (2009), both the caffeine and D-amphetamine augmented group did have a significant response by week 1, however there was no analysis in the study comparing the groups to each other. The authors stated they expected the caffeine to not have any therapeutic benefit, seemingly intending it as an active control group. Authors may have misjudged the lack of effect of caffeine as there were 7 responders in the caffeine group and 6 in the D-amphetamine group after week 1. As mentioned in their paper, caffeine is known to have some effect on dopamine and serotonin pathways, which could have contributed to a higher response rate than expected. Given that both groups improved significantly from baseline but there is no statistical comparison between the caffeine control group and the D-amphetamine intervention, we are unable to assign a level of evidence to this study. It appears that both D-amphetamine and caffeine were positive.
[*] Line of treatment **downgraded** due to poor quality (GRADE) and/or poor trustworthiness (AMSTAR) of meta-analyses.
[**] Line of treatment **upgraded** due to poor quality (GRADE) and/or poor trustworthiness (AMSTAR) of meta-analyses.

(assessed by the Y-BOCS or Yale-Brown-Cornell Eating Disorder Scale) were fluoxetine for bulimia nervosa plus OC symptoms and lisdexamfetamine for binge eating disorder plus OC symptoms (Fornaro et al., 2023). In patients with OCD and comorbid eating disorder, simultaneous treatment of both conditions seems the preferable strategy and fluoxetine should be preferred to other SSRIs in patients with OCD and comorbid bulimia nervosa.

3.1.3.4. Symptom dimensions. Data from the first DBPC trials of SRIs (clomipramine, fluvoxamine, fluoxetine, sertraline, and paroxetine) identified the presence of hoarding obsessions and compulsions as a predictor of non-response to treatment (Mataix-Cols et al., 1999). Subsequent data from DBPC trials on citalopram and escitalopram showed that hoarding and symmetry symptoms were associated with a poorer response to treatment (Stein et al., 2007a, 2008). It is important to note that these studies were published before the recognition of hoarding disorder as a separate condition by DSM-5 in 2013. Therefore, these results should be interpreted with caution, and they could be biased by the presence of OCD patients with comorbid hoarding disorders or hoarding disorder patients diagnosed as OCD with hoarding symptoms. On the other hand, randomized controlled trials of clomipramine, fluvoxamine and fluoxetine showed an increased rate of SRI response by patients with harm-related obsessions (Landeros-Weisenberger et al., 2010). Results of subsequent studies have been mixed, and long-term longitudinal studies did not find any association between specific symptom dimensions and long-term outcome (Level 4, negative) (Bloch et al., 2013). In summary, symptom dimensions are still not evidence-based predictors of response to first-line treatment in OCD.

Studies on the impact of the degree of insight on SRIs response are still inconclusive. While early studies suggested a poorer response to SRIs of OCD patients with poor insight (Level 4) (Catapano et al., 2001; Erzegovesi et al., 2001), more recent case-control and longitudinal studies did not support poor insight as a moderator of response (Level 4, negative) (Eisen et al., 2001; Kim et al., 2011). Data on longitudinal trials seem to show a co-improvement of OC symptoms and insight with SSRI treatment (Eisen et al., 2001).

3.1.3.5. Pharmacogenetics. Pharmacogenetics (a way of taking into account one's genetic information, which will influence drug metabolism, transport, and mechanism of action) may significantly contribute to a better prediction of drug response and side effect tolerability for each OCD patient. Several studies have tried to address this issue, but results are still inconclusive, and the available studies do not have enough power to draw conclusions. While the data on the dopaminergic system have been inconclusive and those on the glutamatergic system are still preliminary, the most consistent evidence is related to the serotonergic system. In fact, the genetic status of CYP2D6 and the polymorphism of the serotonergic genes HTR2A and HTR1B appear to modify SSRI response in OCD patients. However, these data are preliminary since they are based on small samples and are lacking proper replication studies (Zai et al., 2014). Thus, pharmacogenetic testing is still not recommended in routine clinical practice (more discussion is reported in the Future Directions and Knowledge Gaps Section 8).

3.1.4. Long-term pharmacological treatment

Several studies investigated the long-term efficacy of SRIs and their relapse-prevention effectiveness in adult OCD patients. One-year efficacy of SRIs has been reported by a DBPC on sertraline (Level 2) and on clomipramine (Level 2) (Greist et al., 1995b; Katz et al., 1990). Six months efficacy of SRIs has been reported by two DBPC studies on paroxetine (Level 1) (Hollander et al., 2003a; Stein et al., 2007b), two DBPC on escitalopram (Level 1) (Fineberg et al., 2007b; Stein et al., 2007b) and one DBPC study on fluoxetine (Level 2) (Tollefson et al., 1994). SRIs showed their superiority over placebo in relapse prevention across several studies. Sertraline, paroxetine, and escitalopram showed their superiority over placebo in DBPC studies (Level 1) (Fineberg et al., 2007b; Hollander et al., 2003a; Koran et al., 2002), while a DBPC trial on fluoxetine showed its superiority over placebo in relapse prevention only for the 60 mg dose (Level 2) (Romano et al., 2001). Clomipramine showed its superiority over placebo in relapse prevention in two DBPC studies (Level 3) (Flament et al., 1985; Pato et al., 1988; Yaryura-Tobias et al., 1976). Of note, fluvoxamine and citalopram long-term relapse prevention efficacy has not been investigated with randomized controlled trials. DBPC relapse prevention studies have

Table 4b
Levels of evidence and lines of treatment for transcranial magnetic stimulation (TMS) subtypes.

Treatment	Administration		Level of Evidence	Line of Treatment	Population
rTMS	**LF**	**HF**			
Adjunctive rTMS at bilateral pre-SMA	+	not studied	1●	first line	TR-OCD*
Adjunctive rTMS at bilateral DLPFC	not studied	+	1●	first line	TR-OCD*
Adjunctive rTMS at right DLPFC	+**	+	1●	first line	TR-OCD*
Adjunctive rTMS at left DLPFC	–	+/–	3■	unable to make recommendation[a]	TR-OCD
Adjunctive rTMS at left or right OFC	–	not studied	3■	unable to make recommendation[a]	TR-OCD
Monotherapy rTMS at bilateral pre-SMA	–	not studied	3▯	unable to make recommendation	unspecified
Monotherapy rTMS at left DLPFC	not studied	–	3▯	unable to make recommendation	Non TR-OCD
dTMS	**LF**	**HF**			
Adjunctive dTMS at ACC and mPFC	–	+	2◔	second line	TR-OCD
TBS* **					
Adjunctive cTBS at (bilateral) SMA – Condensed Protocol	+		3◐	third line	Non TR-OCD
Adjunctive cTBS at (bilateral) SMA – Extended Protocol	–		3▯	unable to make recommendation	TR-OCD
Adjunctive cTBS at left or right OFC – Condensed Protocol	–		3▯	unable to make recommendation	TR-OCD
Adjunctive iTBS at left DLPFC – Extended Protocol	+		4◔	third line	TR-OCD
Accelerated TBS at frontal-striatal circuit	+		4◔	third line	TR-OCD

rTMS - repetitive Transcranial Magnetic Stimulation; dTMS - deep Transcranial Magnetic Stimulation; TBS - Theta Burst Stimulation; cTBS - continuous Theta Burst Stimulation; iTBS - intermittent Theta Burst Stimulation; PFC - Prefrontal Cortex; DLPFC - Dorsolateral Prefrontal Cortex; OFC - Orbitofrontal Cortex; SMA - Supplementary Motor Area; mPFC - medial Prefrontal Cortex; ACC - Anterior Cingulate Cortex; TR-OCD - Treatment resistant OCD.
+ and - indicates whether significant efficacy was observed (for rTMS and dTMS significance is indicated for both LF or HF stimulation) compared to sham stimulation (i.e. + is significant, - is non-significant).
* Majority of patients included in the analysis had some degree of treatment resistance.
** In the case of adjunctive rTMS at right DLPFC, LF stimulation is considered more efficacious.
*** TBS involves 3 pulses delivered at 50 Hz (i.e., 20 ms between each stimulus), repeated every 200 ms (i.e., at 5 Hz) typically for a total of 600 pulses per session. Condensed protocols compress the course of treatment (conventionally 4–6 weeks; extended protocol) to a much shorter duration through the administration of multiple TBS sessions per day.
[a] Line of treatment **downgabaminergicgraded** due to poor quality (GRADE) and/or poor trustworthiness (AMSTAR) of meta-analyses.

demonstrated that switching from SRIs to placebo has generally high OCD relapse rates, ranging from 31.9 % for fluoxetine to 94.4 % for clomipramine (67 % for sertraline, 59 % for paroxetine, 52 % for escitalopram) (Fineberg et al., 2007b; Hollander et al., 2003a; Koran et al., 2002; Pato et al., 1988; Romano et al., 2001).

Considering SRIs as a group, there is evidence of long-term efficacy up to one year (Level 1●) and of relapse prevention (Level 1●). Due to the high risk of relapse, the duration of the pharmacological treatment should be considered at least 12 months, possibly indefinitely, providing acceptable tolerability (Level 4◔). Before reducing or discontinuing SRIs, several factors should be cautiously considered. The long-term tolerability of SRIs, the co-occurrence of depressive symptoms and/or current or previous suicidal ideation or attempts, the illness duration, and the severity of OCD are all factors to be weighted before discontinuing or reducing SRIs.

Key Points
- SSRIs are supported by the strongest evidence as first-line pharmacotherapy for OCD.
- Although effective, the SRI clomipramine is considered a second-line agent due to its tolerability profile.
- Choice of specific agent should be individualized to a patient's profile, including comorbidity patterns.

3.2. Psychotherapy

In this section, we briefly describe the primary psychotherapeutic strategies and review their evidence-base, focusing on RCTs when available. We also review the evidence for efficacy of different modes and formats for treatment delivery as well as combination and adjunctive treatments to augment psychotherapy for OCD. This section draws specifically from the literature on adults with OCD; readers should refer to the later section for tailored treatment recommendations for children with OCD (Section 6).

3.2.1. *Primary psychotherapeutic treatments*

The modality of psychotherapy with the strongest evidence of efficacy for treating OCD is cognitive behavioural therapy (CBT) (Öst et al., 2022; Reid et al., 2021; Skapinakis et al., 2021). CBT is a broad category that, for OCD, includes the subtype exposure and response prevention (ERP), which emphasizes behavioural strategies to diminish OCD-driven distress (Foa et al., 2012). Cognitive therapy (CT), which emphasizes cognitive strategies but also typically includes some behavioural strategies (Wilhelm and Steketee, 2006), also has strong evidence (Cottraux et al., 2001; Jones and Menzies, 1998; McLean et al., 2001; van Balkom et al., 1998; van Oppen et al., 1995; Whittal et al., 2005, 2010; Wilhelm et al., 2009). Additionally, other psychotherapeutic treatments have been examined for OCD, as described below, which have less evidence but have shown some therapeutic benefit.

3.2.1.1. Cognitive behavioural therapy (CBT). The principal evidence-based psychotherapeutic treatment for OCD is CBT. There are commonalities across evidence-based CBT protocols for OCD, which all include therapeutic components such as psychoeducation, hierarchy development, homework assignments, and relapse prevention. However, there are some notable distinctions between protocols. While most CBT protocols for OCD emphasize the behavioural technique of ERP, other CBT protocols emphasize cognitive therapy and behavioural experiments.

3.2.1.2. Exposure and response prevention (ERP). The first step of ERP, as with most evidence-based CBT protocols, is psychoeducation. This includes education about the multifactorial etiology of OCD, the psychological mechanisms that maintain OCD symptoms, and the treatment approach of how ERP strategies will affect these mechanisms. Following psychoeducation, a treatment plan is created, based on a hierarchy of stimuli/situations in which OCD symptoms are present and that focuses therapeutic strategies on the less distressing stimuli/situations first

before progressing onto more challenging ones. During ERP, patients practice encountering stimuli/situations that elicit OCD distress (i.e., an exposure). At the same time, they work on refraining from engaging in compulsive behaviours, safety behaviours, and/or avoidance to alleviate this distress (i.e., response prevention). Over successive exposure trials and across ERP sessions, patients learn that the initial behavioural response (e.g., compulsion, safety behaviour, avoidance behaviour) is not needed for distress to abate. Exposures can take on several forms including *imaginal* exposures (e.g., visualization of the distressing stimuli/situation), *in vivo* exposures (e.g., intentionally interacting with distressing stimuli/situations), and *in virtuo* exposures (e.g., encountering distress stimuli/situations in a virtual reality environment).

To date, ERP has been evaluated in several RCTs that have compared it to other psychological treatments (e.g., stress management training, progressive relaxation training, cognitive therapy, acceptance, and commitment therapy) and/or pharmacotherapies. Evidence from RCTs (Anderson and Rees, 2007; Andersson et al., 2012; Fals-Stewart et al., 1993; Fineberg et al., 2005; Foa et al., 2005; Freeston et al., 1997; Greist et al., 2002; Kyrios et al., 2018; Lindsay et al., 1997; Mahoney et al., 2014; McLean et al., 2001; Nakatani et al., 2005; Simpson et al., 2008b; van Oppen et al., 1995; Vogel et al., 2014; Volpato Cordioli et al., 2003) and meta-analyses (Carpenter et al., 2018; Hofmann and Smits, 2008; Olatunji et al., 2013; Öst et al., 2022; Reid et al., 2021; Skapinakis et al., 2021) suggest that ERP is an efficacious and effective treatment for OCD and produces superior reductions in OCD severity relative to comparison treatments (Level 1●). Evidence from these RCTs suggests that multiple approaches (e.g., daily therapy, weekly therapy, twice weekly therapy) and modalities (e.g., individual, group, telehealth, internet CBT) can be used to deliver ERP in research and clinical practice. While treatment duration is influenced by the delivery approach (i.e. a course of intensive daily therapy is often shorter than a course of weekly therapy), most ERP protocols in clinical trials include between 12 and 14 sessions (but can range between 5 and 23 sessions). While some clinicians have expressed concern that this treatment approach may lead to patient dropout (McGuire et al., 2018), evidence suggests there is low attrition in clinical trials of ERP for OCD—no different than active comparators (Johnco et al., 2020; Ong et al., 2016). However, there still remains some question about the precise underlying mechanisms of change in ERP (i.e., emotion processing theory versus inhibitory learning theory) that influences how exposures are implemented in clinical practice (Arch and Abramowitz, 2015; McGuire and Storch, 2019). While additional research is essential to elucidate the precise mechanisms and clarify optimal exposure implementation, there is overwhelming evidence that ERP is beneficial for individuals with OCD either alone or in combination with SRI pharmacotherapy. It is important to note that 75 % (n = 27) of studies of ERP for OCD included in a recent meta-analysis of ERP did not exclude concurrent medications, while 25 % (n = 9) did (Reid et al., 2021); thus, a large percentage of the empirically-demonstrated efficacy of ERP to date has been combined ERP and medication. Of note, 11 out of the 27 studies included in this meta-analysis were for child and adolescent OCD, with no subgroup analysis for adult OCD.

(Henceforth, we will refer to ERP, sometimes called CBT with ERP, as "CBT/ERP.")

3.2.1.3. Cognitive therapy (CT). Cognitive conceptual models suggest that cognitive appraisals of intrusive thoughts (and not necessarily the intrusive thought itself) is a key problem underlying OCD. Several problematic appraisals, or misappraisals, have been found to be associated with obsessive thoughts. These include but are not limited to; overestimation of threat, inflated sense of responsibility, perfectionism, intolerance to uncertainty, doubt, and thought action fusion. In order to counteract the misappraisals of intrusive thoughts, an individual with OCD learns to implement cognitive strategies to challenge and restructure maladaptive cognitions, accurately appraise threat, retrain attention away from threat misappraisals, and conduct behavioural experiments to test out the perceived consequences about the accuracy of the maladaptive/misappraised thoughts and behaviours. While behavioural experiments may seem similar to exposures, the focus of the two therapeutic activities is markedly different; for exposures as part of ERP, the goal is habituation/fear inhibition while in CT the goal is testing perceived consequences of threat misappraisals.

To date, CT has been evaluated in several RCTs that have compared it to other psychological treatments (e.g., stress/anxiety management training, ERP), SRI medications, and/or waitlist conditions. Evidence from RCTs using active controls (Cottraux et al., 2001; McLean et al., 2001; van Balkom et al., 1998; van Oppen et al., 1995; Whittal et al., 2005, 2010) suggest that CT is efficacious for the treatment of OCD (Level 1●). Multiple modalities - individual and group - have been used to deliver CT in research and clinical practice. While the duration of treatment is influenced by delivery modality (i.e., individual versus group), most protocols last around 16 sessions (but can range between 2 and 22), which vary in length between 60 min (individual) and 2.5 h (group). While there is evidence that CT alone can reduce OCD severity (Level 1●), many clinicians implement these therapeutic strategies alongside ERP in clinical practice.

3.2.1.4. Other psychological interventions. Other psychological treatment interventions have been examined in OCD but are, as of yet, associated with negative outcomes and poor-quality methodology. Based in cognitive and behavioural models, action-oriented acceptance and commitment therapy (ACT), attempts to improve psychological flexibility and has been examined in 1 RCT (n = 41) compared to progressive muscle relaxation (PMR) therapy (n = 38) in adults with OCD (Level 2◔) (Twohig et al., 2010). Although improvement was observed in both treatment groups in the eight-session treatment, ACT produced greater reductions in OCD severity and more patients experienced a clinically meaningful improvement in the ACT group relative to the PMR therapy group. This initial evidence suggests that ACT could be further explored as a treatment for OCD (Level 2◔).

In an eye movement desensitization and reprocessing (EMDR) Therapy framework, OCD is proposed to be the manifestation of unresolved trauma and/or stressful life events (Marsden et al., 2018). Modest positive results have been found for EMDR in OCD in a case series (Level 4◕) (Marr, 2012) and one RCT (N = 90) when compared to 20 mg/day of citalopram (Level 2◔) (Nazari et al., 2011). Another RCT (N = 55) found no differences between EMDR and CBT on the primary outcome, reductions in OCD severity, however a clinically, but not statistically, significant improvement was in favor of CBT (Level 3◑) (Marsden et al., 2018). Although there may be some modest benefit from EMDR therapy for OCD, given the high attrition in both EMDR trials (30–38 %) extensive interpretation of these findings is limited (Level 2◔).

As a treatment for OCD, mindfulness-based cognitive therapy (MBCT) aims at developing a patient's ability to deliberately draw their attention in the here and now moment and engage in non-judgmental ways to internal experiences such as intrusive thoughts and feelings. The effectiveness of MBCT for the treatment of OCD has been examined in recent systematic reviews and meta-analyses (Baskaya et al., 2021; Chien et al., 2022). One of these meta-analyses found that mindfulness-based interventions demonstrated superiority to active control groups on self-rated scales (OCI-R: SMD -0.51, 95 % CI -0.94-(-0.07)), but not on clinician rated scales (Y-BOCS: SMD -0.29, 95 % CI -0.57-0.00) (Chien et al., 2022). The observations of these results did not support significant improvement in OCD symptoms in the experimental groups compared to the control groups (Level 1, negative■).

An RCT (N = 71) that administered a technology-based mindfulness intervention with electroencephalogram (EEG) biofeedback to OCD patients found increased "non-reactivity", decreased "mind-wandering", and reduced OCD symptoms in the experimental group compared to the waitlist control group (F = 1.94) (Level 4◕) (Hawley et al., 2021).

Imagery rescripting, a technique developed for symptoms arising from traumatic events (Morina et al., 2017), has demonstrated positive outcomes in two small (N = 12 to 13) controlled, but not randomized studies in adults with OCD. Improvements were maintained at 3 months in both studies (Level 4) (Maloney et al., 2019; Veale et al., 2015).

Positive results have been found for meta-cognitive therapy (MCT) for OCD, where beliefs about the meaning and consequences of intrusive thoughts and feelings, as well as beliefs about the necessity of performing rituals and/or potential consequences of failing to do so, are explored (Fisher and Wells, 2008). A pilot study (N = 25) and a small open-label study (N = 8) (Level 4) (Rees and van Koesveld, 2008; van der Heiden et al., 2016), both demonstrated efficacy. However, MCT was found to show no significant differences compared to CBT in a small non-randomized pre-post-test quasi-experimental study (N = 29) and no significant improvement in a case series (N = 6) (Level 4) (Akrami et al., 2010; Andouz et al., 2012).

To date, three RCTs (N = 18 to 111) have evaluated the efficacy of stress and anxiety management therapy (SAMT) in adults with OCD. SAMT was found to be superior to waitlist but inferior to ERP and CT (Lindsay et al., 1997; Simpson et al., 2008a; Whittal et al., 2010), indicating limited evidence for SAMT in the reduction of OCD symptoms (Level 2, negative).

Progressive muscle relaxation (PMR) therapy has been examined in 5 RCTs compared to either CBT, ERP, or ACT (Fals-Stewart et al., 1993; Fineberg et al., 2005; Greist et al., 2002; Kyrios et al., 2018; Twohig et al., 2010). Although some benefit was found for PMR in the reduction of OCD symptoms, this was not significant when compared to other psychological interventions (Fals-Stewart et al., 1993; Fineberg et al., 2005; Greist et al., 2002; Kyrios et al., 2018; Twohig et al., 2010). While PMR therapy was delivered across multiple modalities (e.g., individual, group, self-help, internet) in adequate sample sizes (N = 41 to 218), the number of sessions ranged between 8 and 24 and the delivery of internet PMR had an elevated attrition rate (≈30 %) (Kyrios et al., 2018). Taken together, the evidence suggests only minimal benefit of PMR therapy for reducing OCD severity (Level 1, negative).

While psychodynamic and psychoanalytic treatments may help patients with OCD to identify and address interpersonal relationship conflicts (Chlebowski and Gregory, 2009; Gabbard, 2001) there is insufficient evidence to recommend these therapies for the treatment of OCD. Case reports have described the utility of psychoanalytic treatment for patients with OCD (Leib, 2001; McGehee, 2005); however, there are no controlled studies that have evaluated its efficacy (de Maat et al., 2013; Katzman et al., 2014; NICE, 2005). There is also insufficient evidence to recommend transactional analysis, hypnosis, or marital or couple therapy for patients with OCD (Cawley, 1974). Low intensity forms of psychological therapy have previously been recommended for consideration in cases of mild functional impairment or if this is in line with patient preference (NICE, 2005).

3.2.2. CBT treatment formats

As described above, CBT with ERP (CBT/ERP) is currently the first-line psychotherapy treatment for OCD (Koran et al., 2007; NICE, 2005). The administration/delivery of CBT/ERP can be therapist-assisted or the patient can direct their own. If the patient presents with some of the most common complicating comorbidities of OCD such as depression (Abramowitz et al., 2005; Reddy et al., 2017), ideally the administration of CBT/ERP should be therapist-assisted as it has been shown to be associated with improved depression symptoms compared to self-directed CBT/ERP (Rosa-Alcázar et al., 2008). The adequate number of sessions likely to yield symptom improvement should also be considered. As such, an RCT reporting 17 sessions of individual CBT/ERP offered to adult patients who had started the treatment with at least moderate severity OCD was associated with symptom improvement (Simpson et al., 2013a). In the United Kingdom, the OCD treatment guidelines recommend that an adult with OCD with moderate functional impairment should be offered more than 10 therapist hours of ERP (NICE, 2005), whilst a US treatment guideline recommends a minimum of 13 sessions (Koran et al., 2007). Further, therapist-assisted treatment can be provided in outpatient or inpatient settings (Reddy et al., 2017).

Three meta-analyses conclude that remote approaches are just as beneficial as face-to-face CBT/ERP in improving OCD symptoms (Dèttore et al., 2015; Salazar de Pablo et al., 2023; Wootton, 2016). However, Salazar de Pablo et al. (2023) also reported that face-to-face CBT/ERP was more effective than remote CBT in reducing symptoms in patients with more severe OCD at baseline (β = 0.092, p = .036). Thus, it may be that patient-level factors such as symptom presentation can influence these outcomes.

3.2.2.1. Face to face individual and group formats. CBT/ERP delivered face-to-face in either an individual or in a group setting can be effective (Fals-Stewart et al., 1993). However, individual level interventions appear more effective than group formats (Cabedo et al., 2010). A meta-analysis of 12 studies reported that group psychotherapy was superior to a waitlist control group (g = 0.97, 95 % CI 0.57–1.37; p < .001), and not significantly different from individual psychotherapy (g = -0.23, 95 % CI -0.62-0.15; p = .232) in treating OCD (Level 1) (Schwartze et al., 2016). In an individual/group hybrid format, CBT/ERP can also be delivered in a "concentrated" manner over four consecutive days and appears to improve OCD symptoms. A number of RCTs (Kvale et al., 2018; Tjelle et al., 2024) and non-RCTs (Hansen et al., 2018; Launes et al., 2019) examined the effects of concentrated CBT/ERP in OCD patients using the Bergen 4-day treatment (B4DT) program. The studies show B4DT has promising efficacy, with significant symptom reduction and high remission rates. The delivery of B4DT in a group setting involves the assignment of one therapist per participant, ensuring individualized treatment, however, deviates from the norm of collective therapy delivery seen in traditional group settings. Typically, group psychotherapy treatments, such as CT, involve a single or two therapists treating multiple patients collectively, which contrasts with the 1:1 therapist-to-patient ratio observed in B4DT group settings. The majority of completed studies provide Level 4 () evidence due to the lack of double blinding, small sample sizes, and uncontrolled designs. Further supporting evidence is needed to recommend the use of this approach in clinical settings.

One large RCT (N = 77) comparing group CT to group CBT/ERP reported significantly greater reduction in Y-BOCS scores at endpoint and 2-year follow-up in the group CBT/ERP compared to group CT conditions (Level 2, negative) (Whittal et al., 2008). The effectiveness of MBCT for the treatment of OCD has been examined across three RCTs that span individual (Mathur et al., 2021) and group treatment formats (Kulz et al., 2016; Zhang et al., 2021). When delivered in an individual format, MBCT produced greater reductions in OCD severity when compared to SAMT (Level 3) (Mathur et al., 2021), however, a recent network meta-analysis of acceptable quality did not find individual MBCT to be superior (Level 1, negative) (Chien et al., 2022). Meanwhile, when delivered in a group format, MBCT did not produce greater reductions in clinician-rated OCD severity when compared to either a psychoeducation group (Kulz et al., 2016; Zhang et al., 2021) or SSRIs (Level 1, negative) (Zhang et al., 2021). A meta-analysis of 11 studies reported that there was no significant difference in the efficacy of mindfulness-based interventions delivered in a group setting (d = 0.186, 95 % CI 0.026–0.346) or individually (d = 0.580, 95 % CI 0.457–0.704) for treating OCD (F = 2.90, p = .123, reported as an indirect comparison of individual and group conditions through ANOVA) (Riquelme-Marín et al., 2022). Although this meta-analysis mainly assessed studies investigating the efficacy of MBCT, other types of mindfulness-based interventions were also included in their analyses, as well as child and adolescent OCD studies, with no sub-analysis of adult OCD studies.

3.2.3. Digital interventions

Despite its proven efficacy, psychotherapy is not always accessible to patients with OCD looking for treatment. Barriers include a lack of adequately trained therapists, shame and stigma when disclosing symptoms, costs, and logistical barriers such as travel time to the clinic (Marques et al., 2010; Shapiro et al., 2003). Digital interventions for OCD have been developed to overcome some of these barriers. With the evidence surrounding digital interventions growing in the last 10 years, many have started implementing digital treatments in regular healthcare (Andersson et al., 2019).

3.2.3.1. Internet-delivered CBT. Internet-delivered cognitive behavior therapy (ICBT), typically hosted on a web platform, has been developed as a full standalone treatment for OCD since 2011 (Andersson et al., 2011). Treatment materials such as psychoeducation and worksheets are available on the platform, with content divided into modules or chapters that are unlocked as the patient progresses through treatment (Andersson et al., 2011; Mahoney et al., 2014; Wootton et al., 2013). Therapist support is typically delivered via scheduled telephone calls 1–2 times per week or through unscheduled messages on the platform (with therapists responding within 24 h on weekdays). As in established face-to-face protocols (Foa et al., 2012), the emphasis is on CBT/ERP and treatment lasts 8–10 weeks (Andersson et al., 2012; Mahoney et al., 2014; Wootton et al., 2013). Thus, the difference compared to face-to-face CBT/ERP is in mode of delivery rather than content.

Evidence for the efficacy of ICBT comes from several RCTs (Andersson et al., 2012; Mahoney et al., 2014; Schröder et al., 2020; Wootton et al., 2013) and meta-analyses (Dèttore et al., 2015; Polak and Tanzer, 2024; Salazar de Pablo et al., 2023; Wootton, 2016). In the first RCT of ICBT for OCD, 101 participants received either ICBT or online supportive therapy, where ICBT was superior with a large between-group effect size on the Y-BOCS post-treatment (d = 1.12, 95 % CI 0.69–1.53) (Level 2◔) (Andersson et al., 2012). Another RCT (N = 121) allocated individuals to unguided ICBT or a treatment as usual control (TAU), with the ICBT group showing a significantly greater reduction in OCD symptoms and a medium effect size (η_p^2 = .06) (Level 4◔) (Schröder et al., 2020). Similarly, there was a large between-group effect size on the dimensional Y-BOCS when comparing ICBT to TAU (e.g., continued medication using antidepressants) in a RCT with 86 participants (d = 0.78, 95 % CI 0.29–1.26) (Level 4◔) (Mahoney et al., 2014). Another RCT (N = 56) compared ICBT and bibliotherapy to a waitlist control and found large between-group effect sizes on the Y-BOCS of both active conditions compared to waitlist at post-treatment (ICBT d = 1.57, 95 % CI 0.74–2.32; bibliotherapy d = 1.40, 95 % CI 0.65–2.09), however, there was no significant difference between ICBT and bibliotherapy group (Level 2◔) (Wootton et al., 2013). Follow-up studies have found sustained effects up to 24 months after ICBT for OCD (Andersson et al., 2014; Wootton et al., 2015). Several meta-analyses have compared ICBT and other digital interventions to various other active and inactive controls, showing a positive effect and moderate effect size for ICBT against TAU or supportive therapy, and non-inferiority compared to active treatment controls. However, the conclusions drawn from these meta-analyses are limited as the meta-analyses have pooled the effects of ICBT from studies in adults, children and adolescents, studies comparing ICBT to active controls, and studies comparing to waitlist. These analyses lack a sub-group analysis of adult OCD studies and/or of studies comparing ICBT to an active control (Dèttore et al., 2015; Salazar de Pablo et al., 2023; Wootton, 2016). A more recent meta-analysis that included a specific examination of studies of ICBT that compared guided self-help to active control treatments in adults (N = 9) found greater improvements in ICBT but with a small effect size (g = 0.38, 95 % CI 0.014–0.742; p = .042) (Level 1●) (Polak and Tanzer, 2024).

The specific effects, and comparisons of digitally delivered (purely) self-guided ICBT and therapist-assisted self-guided ICBT has been examined in several studies. A meta-analysis (N = 10 studies) found that digitally delivered CBT with low personal contact intensity significantly reduced OCD symptoms compared to active (PMR, in person/video CBT, relaxation) and waitlist control groups (Level 1●) (Hoppen et al., 2021). A meta-analysis covering multiple types of self-guided psychotherapy for OCD found that while both self-guided and therapist-assisted self-guided therapy were beneficial in reducing OCD severity, the therapist-assisted treatment was associated with a large effect size (g = 0.91) compared to purely self-guided treatment, which had a small effect size (g = 0.33) (Level 1●) (Pearcy et al., 2016). However, a meta-analysis that included a specific examination of studies that directly compared self-guided ICBT to therapist-assisted self-guided ICBT found no significant difference, although there were only three studies included in this sub-analysis, limiting the ability to make firm conclusions (Level 1●) (Polak and Tanzer, 2024). The overall evidence suggests that more therapist involvement is associated with greater symptomatic improvement (Level 1●).

When evaluating ICBT compared to traditional in-person CBT, a meta-analysis of 22 studies (N = 1796) found no significant difference in the efficacy of remotely delivered CBT (including ICBT, computerized CBT, telephone delivered CBT, and app-based CBT) compared to in-person CBT/ERP (g = −0.104, 95 % CI -0.391-0.184; p = .479) when evaluating adult and pediatric OCD RCTs (Level 1●) (Salazar de Pablo et al., 2023). However, higher baseline OCD severity was associated with better response for in-person CBT/ERP than ICBT (β = 0.092, p = .036). On the contrary, a study comparing self-guided ICBT, therapist assisted self-guided ICBT, and in-person CBT failed to demonstrate non-inferiority for both ICBT groups compared with in-person CBT, indicating that although all three treatment groups showed improvement in OCD symptoms, in-person CBT was superior to either ICBT group (Level 2, negative■) (Lundström et al., 2022). The evidence indicates that ICBT and in person CBT are both efficacious first-line psychotherapeutic options, but that in person CBT may be more effective for those with higher baseline symptom severity (Level 1●).

The ICBT literature has substantial heterogeneity as, although studies to date have included mostly self-referred participants, they have included participants with any severity of OCD, ongoing antidepressant medication, and common comorbidities such as depression and anxiety disorders (Andersson et al., 2012; Mahoney et al., 2014; Wootton et al., 2013). Further, the role of the therapist varies, with some ICBT treatments incorporating telephone calls while others have built-in messaging systems, and other protocols do not involve a therapist at all. ICBT for OCD has been implemented in routine care in several countries, where it has been found to be safe and efficacious with medium effect sizes when the treatment is delivered with or without therapist support (Internetpsykiatri, 2022; Luu et al., 2020; Wootton et al., 2021). The treatments reviewed above required substantially less therapist time per patient (7–129 min in total) compared to face-to-face therapy, but the optimal type and intensity of therapist support in ICBT is not known (Pearcy et al., 2016; Polak and Tanzer, 2024). Overall, ICBT is recommended as a first-line treatment for OCD (Level 1●).

3.2.3.2. Metacognitive bibliotherapy. A self-guided metacognitive treatment for OCD has been developed and evaluated as a bibliotherapy, where patients receive the treatment manual in PDF-format and are instructed to work with the content for six weeks. The manual includes traditional cognitive and behavioral techniques (e.g., self-guided ERP), but also "third wave" techniques from metacognitive therapy (e.g., correcting dysfunctional beliefs such as perfectionism) and acceptance and commitment therapy (Moritz et al., 2018).

Metacognitive bibliotherapy has been compared to psychoeducation in an RCT (N = 128) (Level 2◔). While both groups improved in their symptom severity, the improvement was greater in the metacognitive group with a small effect size on the Y-BOCS at post-treatment ($\eta^2_{partial}$ = 0.04), however there was no difference between the groups at follow-up

($n^2_{partial} = 0$) (Level 2) (Hauschildt et al., 2016). In one RCT (N = 70), the metacognitive self-help manual myMCT was compared to a waitlist condition and there was a large between-group effect size on the Y-BOCS at post-treatment ($n^2_{partial} = 0.307$) (Level 4) (Moritz et al., 2018). In another study by the same group, participants with OCD and/or depression were randomized to metacognitive bibliotherapy or waitlist (N = 80) (Moritz et al., 2020). There was no difference between groups on the Y-BOCS at post-treatment ($n^2_{partial} = 0$), however, only one third of the sample fulfilled diagnostic criteria for OCD (Level 4, negative). The treatment has also been evaluated in Arabic-speaking countries in a RCT where it was compared to a waitlist control (N = 160) (Moritz et al., 2019). There was no significant improvement compared to waitlist; however, the sample was again predominantly represented by patients with depression, less than half of the participants fulfilled diagnostic criteria for OCD, and only 37 % of the treatment group completed the study (Level 4, negative) (Moritz et al., 2019).

The use of mixed samples and waitlist controls in these studies limits the conclusions that can be drawn about the efficacy of metacognitive bibliotherapy as a treatment for OCD. While endpoint data suggests metacognitive bibliotherapy is a promising approach to target OCD symptoms, further research is required on the lasting effects of this intervention (Level 2).

3.2.3.3. Use of apps. Treatment delivered via smartphone apps is promising as it can be accessed in daily life and strategies can be deployed as symptoms occur. In contrast to ICBT treatments, which are typically developed as full standalone alternatives to face-to-face CBT, some apps focus on skills training, such as mindfulness (Mohr et al., 2017) while others are developed for use alongside other therapeutic interventions (Lindgreen et al., 2018). There are also apps that have been developed as full standalone treatments with a suite of therapeutic strategies adapted to the smartphone format, and such apps for OCD are reviewed below.

To date, two apps have been evaluated in the treatment of OCD. In one open trial, a smartphone app designed to promote ERP exercises was integrated into treatment after 3–5 face-to-face sessions, with 14 of 33 participants (42 %) responding to treatment (Level 4) (Gershkovich et al., 2021). An open trial (N = 21) of self-guided use of a smartphone app using ERP found a small reduction in symptoms on the self-rated Y-BOCS from pre-treatment (21.3) to post-treatment (17.9) (Level 4) (Boisseau et al., 2017). Thus, it is clear that more evidence of efficacy is needed, particularly RCTs comparing app-based treatments to active controls. A meta-analysis that included 66 studies of RCTs on app-based interventions for mental health (but no studies on OCD) found small effect sizes compared to control groups (e.g., depressive symptoms g = 0.28, 95 % CI 0.21–0.36) (Linardon et al., 2019). Another meta-analysis of 32 RCTs of app-based interventions for anxiety and depression found significant, small effect sizes for anxiety (g = 0.31, 95 % CI 0.22–0.39) and depression (g = 0.35, 95 % CI 0.26–0.44) (Seegan et al., 2023). As few trials have evaluated app-delivered treatment for OCD, it is recommended as a third-line treatment with level 4 evidence ().

As more and more mental health apps become available, several issues need to be addressed before they can be recommended in the treatment of OCD. First, claims of effectiveness in mental health apps are rarely supported by high-quality, direct evidence (Larsen et al., 2016, 2019). Second, many mental health apps collect sensitive data about their users, and improved data safety is needed (Huckvale et al., 2015, 2019). Third, user engagement is often low. For example, in one of the open trials mentioned above, only 7 % of participants reported using the OCD app multiple times per day (Boisseau et al., 2017). Additional challenges include the "digital divide" whereby patients may have low digital literacy, inability to access/purchase a computer or mobile phone, and/or lack internet access (Lam et al., 2023). To address these challenges, multiple initiatives are now underway such as websites that provide information about available apps (Neary and Schueller, 2018), establishing standards for smartphone apps and digital mental health (Torous et al., 2019), and app development that involves patients in all stages of design and testing (Wilhelm et al., 2020). A good discussion on factors to consider when evaluating the efficacy and safety of digital health interventions, including apps, can be found in the recent the CANMAT depression guidelines (Lam et al., 2023).

3.2.4. Combination treatments to psychotherapy

Although CBT is efficacious for the majority of individuals, approximately 30–40 % do not respond adequately (Öst et al., 2015, 2016). In such situations, combination strategies (where treatments are started approximately simultaneously) would be useful to provide additive or synergistic effects to CBT or otherwise address factors that may influence CBT outcomes.

3.2.4.1. Motivational interviewing (MI). The primary goals of CBT/ERP are to confront distressing situations (exposures) and refrain from engaging in behavioural responses (response prevention). However, sometimes patients may have difficulty tolerating this treatment approach, which can lead to poor adherence and/or treatment discontinuation. While multiple reasons may underlie poor adherence and/or treatment discontinuation of ERP, one possibility is that patients are "ambivalent" or caught between mutually exclusive courses of actions (Simpson et al., 2010). They want to reduce time spent with obsessions and compulsions, however, may not want or are unable to adhere to the ERP procedures designed to achieve their goal. Motivational interviewing (MI) is a client-centered, goal-oriented treatment to enhance motivation to change by helping individuals explore and resolve ambivalence. Thus, the addition of MI could theoretically help patients with OCD who are receiving ERP optimally adhere to therapeutic strategies and achieve better outcomes. The combination of MI with ERP has been explored in case series (Level 4) (Simpson et al., 2008b) and one RCT in OCD (Simpson et al., 2010). In the RCT, 30 adults with OCD were randomly assigned to receive 18 individual hour-long sessions of either ERP (n = 15) or ERP + MI (n = 15). Both groups exhibited significant reductions in OCD severity, and there were no significant differences between groups in OCD severity or patient adherence to ERP (Level 3) (Simpson et al., 2010). While the limited evidence shows benefit of the combined ERP and MI therapy strategy, there is no apparent benefit of this combination therapy over ERP monotherapy (Level 3).

3.2.4.2. Family interventions. Family member and partner accommodation behaviours are often present in OCD and incorporated into an individual's treatment hierarchy and exposures in ERP. The incorporation of parental/caregiver accommodation is common practice in the treatment of childhood OCD (Storch et al., 2018) but has gained increasing awareness and evaluation in adults with OCD. One approach has been to evaluate whether a couple-based treatment approach could be used to enhance ERP for individuals with OCD (Abramowitz et al., 2013b). In a small open-label trial, 21 adults and their partners received 16-h long sessions of a specialized program that emphasized three main therapeutic components: (1) partner-assisted ERP, (2) techniques targeting the reduction of partner accommodation of OCD symptoms, and (3) techniques targeting non-OCD-related relationship stressors (Abramowitz et al., 2013a). After treatment, substantial improvements in OCD severity and relationship functioning were observed for participants (Level 4). An RCT examined the effect of ERP in combination with brief family intervention (n = 9) compared to ERP alone (n = 9), finding that patient's whose families received the intervention had significantly lower Y-BOCS scores and reduced accommodation scores (as per the Family Accommodation scale) compared to families who did not receive any intervention (Level 3) (Thompson-Hollands et al., 2015).

3.2.4.3. Acceptance and commitment therapy (ACT). Given the

complementary goals of ERP and ACT (i.e., distress reduction and valued living), there is a rationale for presenting the two together to enhance outcomes, as each therapeutic approach has distinct treatment targets (i.e., habituation/extinction and psychological flexibility). One RCT (N = 58) compared the benefit of combining ACT and ERP relative to ERP alone (Twohig et al., 2018). In this RCT, participants received 16 individual twice-weekly sessions of either ERP (n = 28) or ACT + ERP (n = 30), with both treatment groups exhibiting significant reductions in OCD severity. No group differences were observed in OCD outcomes, processes of change, or acceptability, suggesting no observed benefit from the addition of ACT to ERP, although both treatment groups did improve OCD symptoms significantly from pre-to post-treatment (Level 3◐).

3.2.4.4. Cognitive therapy (CT). While some CBT approaches use integrated cognitive techniques with ERP (see CBT above), there has only been one randomized controlled study that evaluated the benefit of combining CT and ERP versus ERP alone. The study (N = 127) found that the combined treatment demonstrated greater OCD symptom reduction, with a medium effect size of d = 0.61, compared to ERP alone (Level 2◔) (Rector et al., 2019). Overall, CT combination therapy with ERP has level 2 evidence based on one RCT.

3.2.4.5. Transcutaneous electrical acupoint stimulation (TEAS). TEAS is a form of peripheral nerve stimulation that was developed as a non-invasive alternative to acupuncture (Han et al., 1994), and may modulate brain activity (Zhang et al., 2012). A large, randomized, double-blind controlled study (N = 360) compared 1) TEAS combined with CBT and clomipramine, 2) TEAS combined with CBT and placebo, and 3) sham (simulated) TEAS combined with CBT and clomipramine (Feng et al., 2016). Both active TEAS groups showed significantly larger OCD symptom response and remission compared with the sham + CBT + clomipramine group, suggesting the potential benefit of this combination treatment (Level 2◔).

3.2.4.6. Music therapy. One small RCT (N = 30) examined the combination of music therapy and a standard treatment for OCD (pharmacotherapy and CBT) (Shiranibidabadi and Mehryar, 2017). Addition of music therapy demonstrated significantly greater OCD symptom reduction than standard treatment alone (Level 4◕). A subsequent RCT (N = 36) found adding music therapy to regular pharmacological treatment significantly lowered obsession and compulsions compared to only pharmacological treatment (Level 4◕) (Abdulah et al., 2019). Limitations of music therapy as a combination treatment includes the small sample size and no blinding conditions of the available studies (Level 4◕).

3.2.4.7. Electroencephalogram (EEG) biofeedback. One RCT (N = 79) compared the addition of EEG biofeedback to CBT and medication treatment (sertraline) vs. CBT and medication treatment. There was no sham or other placebo control for the EEG, however. The addition of EEG biofeedback resulted in significantly greater improvement in OCD symptoms, emerging at week 6 (Level 4◕) (Deng et al., 2014).

3.2.4.8. Mindfulness-based treatment. One small (N = 37) randomized controlled pilot study compared the combination of mindfulness strategies with group ERP versus group ERP alone (Strauss et al., 2018). The combined treatment did not result in clinically important differences from ERP alone (Level 3◐). While the evidence points to the efficacy of the combination group, there appears to be no added benefit of combining mindfulness with group ERP in comparison to group ERP monotherapy.

3.2.4.9. Combination and adjunctive pharmacological strategies

3.2.4.9.1. D-cycloserine. N-methyl-D-aspartate (NMDA) receptors for the neurotransmitter glutamate are involved in extinction of fear (Davis, 2002). D-cycloserine (DCS) is an NMDA receptor partial agonist which, in animals and humans, has been demonstrated to enhance fear extinction (Davis, 2002; Davis et al., 2006; Norberg et al., 2008). Based on the premise that habituation in ERP is a result of fear extinction (Myers and Davis, 2007), multiple controlled studies have tested if DCS enhances the effect of ERP in those with OCD. Multiple meta-analyses of these RCTs have examined the evidence for DCS in enhancing exposure-based CBT for OCD (Gu et al., 2017; Mataix-Cols et al., 2017; McGuire et al., 2017; Xia et al., 2015). While one meta-analysis reports that the combination of DCS and CBT can result in small, significant effects over placebo + CBT when controlling for antidepressant use at endpoint but not follow-up (Mataix-Cols et al., 2017), others demonstrate there is no evidence of significant effects at endpoint (Gu et al., 2017; McGuire et al., 2017; Xia et al., 2015). These meta-analyses are limited by the small number of included studies (N = 6–8), small sample sizes, and the combination of adult and pediatric OCD studies with no sub-group analysis (Mataix-Cols et al., 2017; McGuire et al., 2017). Although an initially promising translational strategy for patients with anxiety or fear-based symptoms (Davis et al., 2006), on aggregate, the RCTs and meta-analyses on DCS combined with CBT have demonstrated little or no benefits for OCD (Level 1, negative■).

3.2.4.9.2. Nabilone. Nabilone is a synthetic THC agonist. In a study of 11 previously unmedicated patients, some received nabilone only, while some had a combination of nabilone and CBT/ERP. In the nabilone only group, the average decrease in Y-BOCS after 4 weeks was 2.5, while the average decrease in Y-BOCS in the combination treatment group was 11.2 (Level 4◕) (Kayser et al., 2020b).

3.2.4.10. Combining SRIs and psychotherapy. Serotonin reuptake inhibitors (SRIs) are recommended as first-line pharmacotherapy treatments (APA, 2007; Koran et al., 2007; NICE, 2005). A 2014 meta-analysis (N = 13 studies) reported that the combination of SRI + CBT/ERP significantly improves OCD symptoms compared to just SRI treatment alone (Level 1●), although no difference was noted between SRI + CBT/ERP and CBT/ERP alone (Level 1●) (Romanelli et al., 2014). This conclusion by the meta-analysis was made based on very few adult OCD studies, however, aligns with the conclusion of various other RCTs and meta-analyses.

In a network meta-analysis (N = 48 studies) excluding wait-list controlled trials, ERP and clomipramine combination therapy was superior to drug placebo (MD -11.68, 95 % CI -16.73-(-6.65)) and SSRIs alone (MD -8.01, 95 % CI -13.18-(-2.95)), as per the mean reduction in Y-BOCS scores (Level 1●) (Skapinakis et al., 2021). Notably, these estimates were only based on the one trial conducted by Foa et al. (2005) and the validity of this network meta-analysis' estimates have been questioned (Ming, 2016; Skapinakis et al., 2021).

A second meta-analysis reported no significant difference between treatment with CBT + SRI or CBT alone (Level 1●) (Guzick et al., 2018). However, of the four included studies in this meta-analysis (Guzick et al., 2018), two were of children and adolescents (Pediatric OCD Treatment Study (POTS) Pediatric OCD Treatment Study Team, 2004; Storch et al., 2013) and one of the (adult) studies included a wait-list comparison arm, which tends to overestimate effect sizes for active interventions (Furukawa et al., 2014; Watts et al., 2015). Of the two adult RCTs, one was an augmentation rather than combination study. The remaining study was a double-blind RCT (N = 122) of adults with OCD that compared the effects of ERP (n = 29), clomipramine (n = 36), combined ERP and clomipramine (n = 31), and pill placebo (n = 26) (Foa et al., 2005). At week 12, all three active treatment groups were superior to placebo, as per the Y-BOCS. ERP monotherapy was not significantly different from ERP and clomipramine combination therapy (Level 2◔); however, both treatments were superior to clomipramine monotherapy (Level 2◔) (Foa et al., 2005).

A pilot study (N = 44, n = 23 completers) conducted in the UK was

an RCT to compare the use of sertraline alone, in combination with CBT/ERP, and with CBT/ERP alone. This study excluded patients who had failed to respond to one trial of CBT/ERP performed by an accredited professional or two trials of SRI drugs at maximum approved dosage, thus, it excluded many patients who would be classified as resistant in other studies. Overall, combination treatment was more effective than either monotherapy in reducing OCD symptom severity as measured by the Y-BOCS, although sertraline as a monotherapy appeared more cost effective (Level 3◐) (Fineberg et al., 2018).

In summary, multiple meta-analyses demonstrated the efficacy of combination treatment over SRI treatment alone, while the meta-analyses did not support the efficacy of combined treatment over CBT alone. One study published after the meta-analyses (Fineberg et al., 2018) supports the efficacy of combined treatments over SRI treatment or CBT/ERP treatment alone, however several RCTs (Cottraux et al., 1990; De Haan et al., 1997; Foa et al., 2005) showed no benefit of combining SSRIs and CBT compared to CBT alone (Level 1●). Therefore, the overall evidence for combination SRI and CBT/ERP supports designation as Level 1, with combination therapy being better than SRI alone (Level 1●), but the same as CBT alone (Level 1●). The recommendation is to preferentially use combination treatment (CBT and SRI) over SRI monotherapy, however CBT monotherapy over the combination treatment.

It is important to note here that although there are few studies measuring the effect of combination psychotherapy and pharmacotherapy, around 80 % of published CBT studies allow participants to continue their OCD medication if they remain on a stable dose (Nezgovorova et al., 2022). This makes analysis of the efficacy of CBT complicated as these studies can be viewed as possible combination studies, but because the pharmacotherapy treatments were not controlled, no conclusions about the combining of CBT and SRIs can be made from these studies. In addition, the efficacy of SRI augmentation of CBT for adults with inadequate response to CBT has not been empirically studied, despite its common occurrence in clinical practice.

3.2.5. Augmentation of OCD treatments with psychotherapy

Adjunctive treatments add an additional form of treatment to augment an already initiated CBT/ERP, psychotherapy, or SRI treatment. In one large RCT participants were randomly assigned to 17 h-long sessions of SAMT (n = 55) or ERP (n = 56), with all participants already taking a stable-dose SRI medication for at least 12 weeks (Simpson et al., 2008a). While some reduction in OCD severity was observed in the SAMT + SRI group, although not significant (Level 2, negative▪), the ERP + SRI group had significantly greater improvements in comparison (d = 1.31, 95 % CI 0.86–1.75). 74 % of participants in the ERP + SRI group attained response while only 22 % attained response in the SAMT + SRI group (Level 2◔) (Simpson et al., 2008a). When examining the augmentation of fluvoxamine with psychotherapies, one RCT randomized participants to one of five treatment groups; 1) Cognitive therapy for weeks 1–16 (n = 25), 2) ERP for weeks 1–16 (n = 22), 3) Fluvoxamine for weeks 1–16, with CT from weeks 9–16 (n = 24), 4) Fluvoxamine for weeks 1–16 with ERP from weeks 9–16 (n = 28), or 5) Waiting list control (n = 18). At post treatment, all four of the active treatment groups had improved OCD symptoms compared to baseline and the waitlist control, with no significant differences between the groups (Level 3◐) (van Balkom et al., 1998). This study suggests there was no added benefit of augmenting fluvoxamine with either CT or ERP psychotherapy, however all groups did improve OCD symptoms, as per Y-BOCS scores. The design of this study has limitations as there lacks a drug-only 16-week treatment, making it unclear if the drug treatment alone would have done as well as the individual psychotherapies, and if the drug augmented with psychotherapy would have had a similar effect. Which treatment was better than another is unclear and unable to be concluded without a drug-only condition.

Two studies have examined the benefits of augmenting SSRI treatment with ACT. A randomized study (n = 48) had individuals continue their SSRI monotherapy (stable for 4 weeks, although minimal duration of treatment was not specified) or augment it with the addition of ACT (Rohani et al., 2018). The augmented treatment group had greater reductions in symptoms at follow-up (Level 3◐). Another RCT (N = 40) comparing the augmentation of 12 weeks of stable SSRI treatment with ACT, ERP, or nothing found both ACT + SSRI and ERP + SSRI conditions reduced OCD symptoms compared to just SSRI treatment and were not significantly different from each other (Level 3◐) (Zeeshan et al., 2022). Overall, the augmentation of SSRI therapy with psychotherapy (ERP, ACT, CT) has shown efficacy in RCTs compared to controls (Simpson et al., 2008a) or SSRI monotherapy (Level 2◔) (Rohani et al., 2018; Zemestani et al., 2022).

One small study (N = 35) found no added benefit of adding CT after 6 weeks of ERP, as there was no significant difference in OCD improvement compared to the group receiving relaxation training after 6 weeks of ERP, although there was a lower attrition rate in the ERP + CT group (Level 3, negative▪) (Vogel et al., 2004). There is, however, a significant lack of studies investigating the augmentation of CBT/ERP with other forms of psychotherapy, which limits the recommendations given for this type of adjunctive treatment. No studies have examined the augmentation of psychotherapy with SRI treatment.

3.2.6. Switch treatments

If patients do not respond to an adequate trial of psychotherapy or pharmacological interventions, clinicians may choose to switch treatment. For example, if a psychosocial intervention did not lead to any improvements in OCD symptoms, it may be beneficial to switch the patient to a pharmacological treatment. Patients may not want combination treatments or augmentation for a variety of reasons and therefore switching treatments may be the best course of action. One RCT (N = 48) in patients not responding to a 12-week ERP program compared switching patients to fluvoxamine compared to CT. The authors found switching to fluvoxamine significantly reduced OCD symptoms compared to CT (Level 3◐) (van Balkom et al., 2012).

3.2.7. Synthesis of evidence and clinical recommendations for psychotherapy treatment for OCD

3.2.7.1. Synthesis of evidence for psychotherapy treatment. Meta-analyses have clearly demonstrated the effectiveness of CBT for the treatment of OCD, with large effect sizes (Level 1●) (Öst et al., 2022; Reid et al., 2021; Skapinakis et al., 2021). Multiple studies demonstrate efficacy for the subtype of CBT that primarily emphasizes behavioural techniques (ERP), yet there is also evidence for the efficacy of psychotherapy that emphasizes cognitive techniques (CT). Both CT and ERP, as researched and in real world clinical practice, typically integrate both cognitive and behavioural techniques to some degree. While these forms of CBT have a significant amount of research to validate their rank as a first-line treatment, recent meta-analyses (Reid et al., 2021; Uhre et al., 2020) have drawn attention to methodological shortcomings in much of the existing trial data relating to psychotherapy as well as the lack of research on the long-term efficacy of CBT and its ability to prevent relapse.

The level of evidence for treatment efficacy for primary psychotherapeutic modalities – based on the number of controlled trials, the study sample sizes, and the consistency of results – drops off considerably after CBT/ERP. To date, there is some evidence for the efficacy of acceptance commitment therapy and eye movement desensitization reprocessing. Less evidence exists for imagery rescripting, mindfulness meditation with EEG biofeedback, and metacognitive cognitive therapy, while stress anxiety management therapy, progressive muscle relaxation, and mindfulness based cognitive therapy do not appear to be effective.

Several means for delivering CBT have been studied in controlled

trials. These include individual, group, online self-guided, and remote therapy. Among the in-person treatments, there is a high level of evidence for individual CBT and group CBT. While individual CT shows promise, group CT and both individual and group MBCT were not found to be effective in treating OCD. In addition, CBT can be delivered in less intense formats such as once weekly or more intense formats including several times weekly in intensive outpatient, partial hospitalization, or residential treatment settings. Both intensive (more frequent) and less intensive treatments have been studied, with some indication that intensive treatments may be more effective (Bystritsky et al., 1996; Calvocoressi et al., 1993). When examining digital interventions, research shows internet-delivered CBT to be highly effective. There is also some evidence for metacognitive bibliotherapy and smartphone app-delivered CBT treatments. These findings suggest that within remote treatments, therapist-guided treatments are likely more effective than self-guided treatments.

Combination treatments to CBT/ERP for OCD remain relatively understudied. CT and TEAS show the highest level of evidence, followed by motivational interviewing, mindfulness, and ACT. Some evidence also exists for family interventions, EEG biofeedback, and music therapy, although further research on these topics is required. The evidence for the efficacy of combining psychotherapy and pharmacological treatments shows mixed results, as there is strong evidence of combination therapy being better than SRI monotherapy, but equally as effective as CBT/ERP monotherapy. Although the addition of SRIs to CBT is a common clinical practice, there is limited empirical evidence. One challenge for studies attempting to demonstrate efficacy of combination treatments to CBT/ERP is that CBT/ERP alone routinely results in large effect sizes itself, which could present a "ceiling effect" (Guzick et al., 2018).

There is also some, however limited, evidence of augmentation treatments, with efficacy shown for augmenting SSRI treatment with CBT/ERP, CT, and ACT, while augmenting with SAMT seems to not be effective. There is one study examining the augmentation of CBT/ERP with CT, revealing little to no effect.

3.2.7.2. Recommended first-line psychotherapy options. Based on the existing studies and level of evidence, CBT is very clearly the first-line psychotherapy treatment for OCD. The first clinical choices that treatment providers and people with OCD will need to make typically involve the format and delivery method of CBT, since not all options are available in every situation (O'Neill and Feusner, 2015). The most evidence exists for individual in-person CBT, in particular techniques that emphasize behavioural strategies (i.e., ERP). If in-person individual CBT is not available, group format or remotely-delivered CBT (one-on-one by video or phone) or therapist-assisted self-guided CBT would be the next recommendations. If neither in-person nor remote therapist-involved psychotherapy is available, the next recommendation would be remote self-guided CBT. However, if patients do not respond to remote self-guided CBT, the clinician managing the patient should recommend therapist-delivered CBT, either face-to-face or remotely delivered. If there is no managing clinician, this recommendation should be built into the remote CBT platform. This communicates to patients that a next level of care may be effective even if the self-guided CBT was not. This is to avoid prematurely ending psychotherapeutic treatments when the OCD symptoms remain inadequately or ineffectively treated. Also, regarding remote self-guided delivery, patients with severe OCD symptoms should be offered therapist-assisted as opposed to unassisted treatment; however, long-term follow-up effects of these treatment approaches are still to be studied (Pearcy et al., 2016).

RECOMMENDATIONS FOR PSYCHOTHERAPY

- ❖ CBT, in the form of exposure and response prevention (ERP), or cognitive therapy (CT), are the first-line psychotherapy treatments for OCD (Level 1●).

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(*continued*)

RECOMMENDATIONS FOR PSYCHOTHERAPY

- ❖ The current evidence supports that both ERP and CT should be delivered individually and in person (preferentially) or remotely (Level 1●). There is evidence that ERP, but not CT, could be effective in group format (Level 1 ●).
- ❖ There is evidence that internet-delivered CBT/ERP is effective (Level 1●), with therapist-guided treatments likely being more effective (Level 1 ●), however, in-person CBT is recommended for those with higher OCD symptom severity (Level 2 ◔).
- ❖ A standard initial course of ERP is between 12 and 14 sessions to achieve treatment response (can range between 5 and 23 sessions) (Level 4◕).
- ❖ For individuals with a partial or inadequate response to ERP, augmenting ERP with SSRI (Level 4◕)*, or alternatively, switching to an SSRI (Level 3 ◐), are recommended.

*Recommendation is expert consensus (Level 4◕) and is based on the CBT/ERP + SSRI combination literature which is Level 1 (●).

Key Points

- Cognitive Behavioural Therapy (CBT) in the form of Exposure and Response Prevention (ERP), as well as Cognitive Therapy (CT) is supported by the strongest evidence as first-line psychotherapy for OCD.
- Limited evidence supports the use of Acceptance and Commitment Therapy (ACT) and Eye Movement Desensitization and Reprocessing (EMDR).
- In person, individual ERP and CT or group-format ERP is supported by the strongest evidence.
- The results for combining psychotherapy and pharmacotherapy are mixed.

3.2.7.3. What if the first-line psychotherapy treatment (CBT or CT) fails or is only partially effective?. CBT for OCD can be challenging for patients as exposure exercises and resisting compulsions are, by nature, distressing. This can affect not only patients' ability to complete treatment (dropout rates in clinical settings may range from 31 to 65 %) (Garfield, 1994; Mancebo et al., 2011) but also their willingness to initiate treatment. Since psychotherapy's effectiveness can depend in part on individual therapists' skills and on the therapeutic "fit" between patient and therapist, a different therapist may be needed if a patient does not respond well to treatment with the first. Therefore, the first recommendation is to try another therapist and/or increase the "dose" of CBT/ERP to more frequent sessions (Level 4◕). Since up to half of those with OCD may not respond adequately to CBT (Öst et al., 2015, 2016; Simpson et al., 2006) adjunctive treatments may also be warranted (see Tables 3–8).

Only one study has investigated the population resistant to CBT. If patients are comfortable and/or able to switch from a psychosocial intervention to a pharmacological treatment, one study has found fluvoxamine to be effective in treating OCD in CBT/ERP non-responders (Level 3◐) (van Balkom et al., 2012). If partially or not responsive to CBT, SRIs can be added. If the patient is already on an SRI, please refer to the recommendations for treatment resistance (Section 4). In the case of inability to initiate or adhere to CBT, or if there is a poor response to CBT in different settings and with different therapists, the evidence from studies in non-treatment-resistant populations would suggest a trial of ACT or EMDR as second-line treatments. Alternatively, third-line treatments include imagery rescripting, mindfulness meditation with EEG biofeedback, and metacognitive therapy. TEAS may prove to be a viable adjunctive recommendation (Level 4◕), however this recommendation is based on the level of evidence (Level 2◔) for TEAS

combination therapy, which comes from a single trial, and TEAS itself may not be widely available.

For poor or no response to less intensive treatments, settings in which treatment can be delivered more intensely and with more frequent sessions, such as intensive outpatient, partial hospitalization, and residential treatment settings, may be necessary.

3.2.7.4. Inpatient treatments. Intensive OCD treatment delivered in inpatient or residential settings using psychotherapeutic treatments have also been examined in the literature, primarily in the form of case reports. Nonetheless, one meta-analysis combined studies where CBT, BT, or ERP was used alone or in combination with SSRIs, with the Y-BOCS as a primary outcome (N = 2306) (Veale et al., 2016). The average duration of the program was 10.4 weeks. Despite significant heterogeneity, a robust overall effect size of g = 1.87 (95 % CI 1.63–2.10) was reported for change in Y-BOCS from admission to discharge, with a mean Y-BOCS decrease of 10.7 points. The only consistent positive predictor of treatment outcome was being married or cohabitating, whereas hoarding symptoms or alcohol misuse comorbidity were the only consistent predictors of poorer outcome, however the authors concluded that patients with severe or treatment refractory OCD can make significant improvements with intensive residential or inpatient therapy (Level 1 ●) (Veale et al., 2016). Although effective, inpatient treatment is typically considered for the most severe patients with OCD.

3.3. Complementary and alternative therapy

Given the limitations of first-line treatments for OCD, there is growing interest in investigating the use of complementary and alternative medicine (CAM) therapies for the treatment of OCD. In clinical practice, CAM therapies are usually grouped into nutraceuticals, herbal medicines, and physical therapies.

3.3.1. Nutraceuticals

The benefit of nutraceuticals has been evaluated in several studies with mostly modest numbers of subjects. Further information and evidence regarding the use of nutraceuticals such as N-acetylcysteine (NAC) to treat OCD can be found in Section 4.1.2 and 4.2., the treatment resistant and immunotherapy chapters of these guidelines.

There is preliminary evidence for the benefit of glycine, an NMDA agonist that modulates glutamatergic neurotransmission. A double-blind trial of 24 subjects found the use of 60g adjunctive glycine per day reported no significant difference in Y-BOCS scores compared to the placebo group, although glycine was found to significantly reduce Y-BOCS obsessions scores (sub-scale of Y-BOCS) compared to placebo (Greenberg et al., 2009) (Level 4, negative◨). Additionally, the study had a poor participant retention rate (10 individuals dropped out), and glycine was used as an augmenting agent for first-line pharmacotherapy, thus glycine's potential benefit as a monotherapy remains to be proven. Recent case reports suggest the benefit of high-dose glycine (0.8 g/kg/day) in the treatment of OCD (Level 4◔), although significant dose related adverse effects such as nausea and dizziness pose a practical limitation (Cleveland et al., 2009).

A 12-week open-label study (N = 14) examining inositol monotherapy (18 g/day) reported significant improvements in Y-BOCS and CGI-S scores compared to baseline, with 8/14 participants reporting ≥50 % drop in Y-BOCS scores (Level 4◔) (Carey et al., 2004). For more evidence on inositol, see the serotonergic agent section under the treatment resistant chapter of these guidelines (Section 4.1.3).

3.3.2. Herbal medicines/phytotherapies

The benefits of several herbal medicines/phytotherapies have been reported for other psychiatric illnesses including depression and anxiety and are discussed below.

In the only RCT examining smoked cannabis in OCD, each participant consumed half a cigarette, containing 800 mg of cannabis with either high THC:low CBD or low THC:high CBD, or placebo. There were no significant differences in symptom improvement in either THC/CBD combination relative to placebo (Level 3, negative◨) (Kayser et al., 2020a).

St John's Wort (*Hypericum perforatum*) is purported to have antidepressant and anxiolytic properties but its role in monoaminergic transmission is indicative of a potential therapeutic benefit for OCD as well. Results from a large double-blind RCT (N = 60) did not report any differences in OCD symptoms between treatment and placebo groups (Level 2, negative◨) (Kobak et al., 2005). An open-label trial (N = 13) in moderate-to-severe OCD found statistically significant evidence for St. John's Wort improving OCD symptoms (Taylor and Kobak, 2000), although further research on this population is required (Level 4◔).

Milk thistle (*Silybum marianum*) is an herbal medicine used commonly for hepatic conditions and has been proposed as an anxiolytic agent. A case study in a patient with moderate OCD reported significant improvements in OCD symptoms after 8 weeks of using 150–300 mg BID, with a Y-BOCS score of 12 at endpoint (Level 4◔) (Grant and Odlaug, 2015). An eight-week double-blind RCT comparing fluoxetine to milk thistle monotherapy in moderate-to-severe OCD found both interventions significantly reduced participant Y-BOCS scores. The reduction was 12.5 in patients who received fluoxetine and 11 in the milk thistle group, a non-significant difference (Level 3◑) (Sayyah et al., 2010).

The plant borage (*Echium amoenum*) has been evaluated previously for benefit in depression. A 6-week RCT evaluated 44 patients with OCD who were randomly assigned to receive either borage extract monotherapy or placebo. There was a significant effect of time ($p < .01$) and of treatment ($p = .035$), indicating an improvement in OCD and anxiety symptoms in all patients, particularly in those receiving treatment. At weeks 4 and 6, patients treated with borage had lower Y-BOCS scores compared to the placebo group ($p < .01$) (Level 3◑) (Sayyah et al., 2009).

There is preliminary evidence for the benefit of Valerian root (*Valeriana officinalis*) with an 8-week pilot double-blind randomized trial (N = 31) reporting significant improvements in OCD symptoms compared to placebo ($p = .001$), a benefit possibly attributed to its GABAergic and serotonergic effects (Level 3◑) (Pakseresht et al., 2011).

A double-blind placebo-controlled trial (N = 30) reported that ashwagandha (*Withania somnifera)* as adjunctive to SSRI therapy was superior to adjunctive placebo in OCD patients. The mean reduction in Y-BOCS score was 8 in the adjunctive ashwagandha group and 2 in the placebo group ($p < .001$) (Level 3◑) (Jahanbakhsh et al., 2016).

A double-blind RCT (N = 46) found that saffron (*Crocus sativus*) monotherapy was just as effective as fluvoxamine at reducing the Y-BOCS scores of patients with mild-to-moderate OCD (Level 3◑) (Esalatmanesh et al., 2017). Similarly, a double-blind RCT (N = 50) found that crocin monotherapy, the active constituent of saffron, was just as effective as fluoxetine at decreasing the Y-BOCS scores of patients with mild-to-moderate OCD (Level 3◑) (Kazemi et al., 2021).

While these findings are promising, it is important to note that many of these studies had small sample sizes, were single-blind, and participants were often allowed to continue their previous treatments (including psychotherapy and/or pharmacotherapy). Larger and more controlled trials that evaluate the benefit of herbal remedies, as well as elucidate drug interactions and tolerability are needed.

3.3.3. Physical therapies

Physical therapies, including various forms of exercise and yoga, have been found to benefit patients with OCD. A recent systematic review examining the effect of exercise on OCD found a significant association between exercise and improvements in OCD symptom severity (g = 1.33, 95 % CI 1.06–1.60), although a moderate to large risk of bias was reported for all studies (Level 1●) (Bottoms et al., 2022). Of these 8

studies (4 RCTs, 4 open-label studies) included in the review, 4 examined yoga while 4 investigated different forms of aerobic exercise (Bottoms et al., 2022). It is important to note that 3 of the studies used a co-intervention of CBT, which if not properly controlled for, could act as an extraneous variable. An RCT compared the addition of exercise (N = 28) to the addition of health education (N = 28) for participants already on a stable OCD treatment, which could have been medication or CBT, therefore evaluating exercise as an augmentation strategy. The study found no difference between the exercise and health education groups, however there was no differentiation between those who were already being treated with CBT versus pharmacotherapy (Level 3, negative) (Abrantes et al., 2017). In a secondary analysis of the data, the authors report a significantly greater reduction in compulsions and anxiety, as well as an improvement in mood, in the exercise group compared to controls (Abrantes et al., 2019). In an earlier report by Abrantes et al. (2009), OCD subjects (N = 15) performed aerobic exercise weekly for 12 weeks, adjunctive to other treatments, such as pharmacotherapy and/or psychotherapy. They reported moderate benefit in obsessions and compulsions, and improvement in mood following the first week of the intervention. These trends were observed at week 12, though were nonsignificant (Level 4, negative) (Abrantes et al., 2009). Other open-label studies found significant improvements in OCD symptoms compared to baseline (Level 4) (Brown et al., 2007; Rector et al., 2015).

Yoga, a mind and body intervention, has been evaluated in various formats in several open-label and case series studies as well as four RCTs for the treatment of OCD. In an early study (N=21), adjunctive kundalini yoga (KY), (including components of breathing, chants, and poses), was compared to a relaxation response meditation (RR) (including combination of mindfulness meditation and relaxation). A greater reduction in Y-BOCS scores in the KY group was found compared to the RR group (9.43 versus 2.86 Y-BOCS score reduction) after 3 months. (Shannahoff-Khalsa et al., 1999), (Level 4). Similarly, a more recent RCT (N = 52) compared KY to RR where some, but not all patients were also taking a stable dose of first-line OCD treatment. The authors reported significant Y-BOCS percent improvement (rated by blinded raters) at a 4.5 month endpoint in the LOCF sample (n = 48) (KY:26.90%, SD +27.63% vs. RR: 8.21%, SD +13.14%; p = .004), (Shannahoff-Khalsa et al., 2019) (Level 3). Another RCT in OCD which compared exercise-based hatha yoga monotherapy (n = 40) compared to a control group (n=20) who watched TV. Following treatment of two sessions per week for 10 weeks, no significant difference in the Y-BOCS was found between the groups (p = .35), (Level 2, negative) (Ranjbar, 2013). Bhat and colleagues developed and validated a manualized adjunctive yoga intervention for OCD (Bhat et al., 2016; Bhat et al., 2021). In a recent report, 4 weeks of adjunctive yoga (n = 25) demonstrated significant decreases in Y-BOCS scores compared to a waitlist control (n = 25), (p < 0.001), (Bhat et al., 2024) (Level 3). The current evidence indicates that the use of some yoga-based interventions may offer some benefit in OCD, however, conclusions are limited by significant heterogeneity in study designs and duration and types of yoga modalities.

Overall, the research on physical therapies for OCD appears hopeful, but studies are quite limited in size and scope, particularly for physical exercise (Brierley et al., 2021) and warrant continued investigation with larger and more diverse populations.

RECOMMENDATIONS FOR COMPLEMENTARY AND ALTERNATIVE TREATMENTS

- There is a lack of clear and strong evidence for complementary and alternative treatments for OCD
- The nutraceutical adjunctive glycine (Level 4, negative) is unable to be recommended, and there is limited evidence of the efficacy of the nutraceutical inositol (Level 4)

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RECOMMENDATIONS FOR COMPLEMENTARY AND ALTERNATIVE TREATMENTS

- Physical therapies like aerobic exercise (Level 3, negative) are also unable to be recommended, while yoga monotherapy is not recommended (Level 2, negative), augmentation with either Kundalini Yoga (Level 3), or a validated OCD-specific Yoga (Bhat et al., 2024) (Level 4) may have some benefit.
- There does seem to be some mild benefit of some phytotherapies such as milk thistle, borage, valerian root, ashwagandha, and saffron (Level 3), however St. John's Wort is not recommended (Level 2, negative).

4. Treatment resistant OCD

Pharmacological interventions for treatment resistant OCD

Approximately 40–60 % of OCD patients remain unresponsive to first- or second-line pharmacotherapies, either used alone or in combination, and they are considered treatment resistant (Pallanti and Quercioli, 2006). OCD treatment resistance is typically defined as one or two failed trials of adequately dosed SSRIs that have lasted at least 8–12 weeks (Pallanti and Quercioli, 2006; Pittenger et al., 2005). A failed SSRI trial is usually defined as failing to achieve a Y-BOCS total score ≤16, a score reduction greater than 25 % on the Y-BOCS, and/or a Clinical Global Improvement Scale rating of "much improved" or "very much improved" (Pallanti and Quercioli, 2006; Pittenger et al., 2005). Situations where a patient cannot tolerate a first-line treatment would not be considered a failed trial. While the terms treatment "resistant" and "refractory" are often used synonymously in the literature, they represent different constructs (Kayser, 2020). Treatment refractory refers to the highest level of treatment resistance, where patients do not respond to all available treatments, including three or more SRIs, as well as SSRI augmentation with clomipramine and/or cognitive behavioural therapy (Fineberg et al., 2015). Nevertheless, there are also many studies often considered to be part of the treatment resistant OCD literature which have examined next step OCD treatments in populations described as having moderate to severe OCD (usually defined by Y-BOCS score). We examined these studies in depth and discovered that many describing themselves as "augmentation trials" were actually using combination strategies where both the SSRI and the "augmenter" were started at the same time. Furthermore, these studies did not include a definition of treatment resistance; many of them used populations who were naïve to SRIs, and others examined "next-step" monotherapies in populations who may or may not have been treatment resistant. Although the results from this group of studies may provide useful information, the focus of this section will be limited to studies conducted in treatment resistant populations. This differentiates these guidelines from previous evidence-based treatment guidelines for OCD, where the evidence has not specifically focused on samples of treatment resistant OCD patients (Katzman et al., 2014). This section aims to summarize the current pharmacological literature for treatment resistant OCD, including augmentation or switch therapy and novel pharmacotherapies. Studies (including meta-analyses) were included if they specified that participants had to have failed at least one adequate trial of first-line treatment (SRI or CBT) for OCD.

4.1. Moderate to severe OCD

As with the treatment resistant literature, research into augmentative pharmacological treatments for moderate-to-severe OCD encompasses a broad range of agents. Among psychostimulants, augmentation with D-amphetamine (DA, NE transporter [DAT, NET], releaser has demonstrated superiority over adjunctive methylphenidate (also a DA/NET inhibitor and a DA/NE releaser) in small RCTs (Level 3) (Insel

et al., 1983; Joffe et al., 1991). Anti-Parkinsonian drugs such as tolcapone (Level 3◐) (Grant et al., 2021) and amantadine (Level 2◔) (Naderi et al., 2019) when used for augmentation also show promise, with tolcapone improving symptoms in the short term but requiring stringent monitoring due to hepatotoxicity. Gabapentin (a voltage-gated calcium channel blocker) (Level 2, negative▬) (Farnia et al., 2018; Önder et al., 2008) and clonazepam (GABA-A receptor positive allosteric modulator, benzodiazepine site) (Level 3, negative◧) (Crockett et al., 2004; Hollander et al., 2003c) failed to show consistent efficacy as adjunctive treatments, while riluzole demonstrated potential as an augmentation agent (Level 3◐) (Emamzadehfard et al., 2016), despite mixed outcomes in related compounds like troriluzole (Level 2, negative▬) (Aguiar et al., 2021). NMDA receptor-targeted therapies reveal some efficacy with adjunctive memantine (glutamate receptor antagonist) (Level 2◔) (Modarresi et al., 2019) while adjunctive D-cycloserine (Level 1, negative■) (Andersson et al., 2015; Bürkner et al., 2017) is largely ineffective. Adjunctive IV ketamine (glutamate NMDA antagonist) shows short-term benefits that require further investigation (Level 3◐) (Rodriguez et al., 2013b). Adjunctive N-acetylcysteine (NAC) has also demonstrated mixed results in moderate-to-severe OCD, with multiple RCTs finding significant differences between NAC and placebo, while others report no differences between groups (Level 2, negative▬) (Costa et al., 2017; Ghanizadeh et al., 2017; Paydary et al., 2016; Sarris et al., 2015, 2022). Glutamatergic agents such as minocycline (Level 2◔) (Esalatmanesh et al., 2016) and L-carnosine (Level 3◐) (Arabzadeh et al., 2017) have emerged as promising adjuncts, showing significant symptom reduction in RCTs. Among serotonergic treatments, mirtazapine (norepinephrine, serotonin receptor antagonist [NE alpha$_2$, 5-HT2, 5-HT3]) (Level 3, negative◧) (Pallanti et al., 2004), trazodone (Level 3◐) (Pigott et al., 1992b), 5-hydroxytryptophan (Level 3◐) (Yousefzadeh et al., 2020), pindolol (Level 2, negative▬) (Sassano-Higgins and Pato, 2015), buspirone (serotonin receptor partial agonist [5-HT1A]) (Level 3, negative ◧) (Grady et al., 1993) and tramadol (Level 4◔) (Goldsmith et al., 1999) augmentation yields mixed results. Limited evidence supports adjunctive cannabinoids, with no clear advantage over placebo (Level 3, negative◧) (Kayser et al., 2020a, 2020b). Augmentation with monoamine oxidase inhibitors like phenelzine (serotonin, norepinephrine, dopamine enzyme inhibitor [MAO-A and -B])(Level 3, negative◧) (Jenike et al., 1997) exhibit limited utility, while augmentation with the non-steroidal anti-inflammatory celecoxib has Level 3 evidence in moderate-to-severe OCD (Level 3◐) (Sayyah et al., 2011). Combination treatment with SRIs and 5HT3 antagonists have generally been positive for tropisetron (Level 2◔) (Shalbafan et al., 2019), and granisetron (Level 3◐) (Askari et al., 2012) with mixed Level 3 results for ondansetron (Sepehrmanesh et al., 2019; Soltani et al., 2010◐) (Heidari et al., 2014◧).

4.2. Treatment resistant OCD

Augmentation strategies

Augmentation refers to the addition of another agent to an already stable treatment, typically with a different mode of action. A broad range of agents have been examined in TR-OCD. The bulk of these have been used adjunctively and Tables 4–1 describes the level of evidence associated with each agent. Lines of treatment noted in this section are referring to an individual that has been deemed treatment resistant.

Duration of augmentation treatment

Across treatment resistant studies and meta-analyses, the treatment duration of individual augmentation studies has ranged from 2 to 20 weeks. Two recent network meta-analyses examining various augmentation agents in OCD did not find duration to be a significant moderator of treatment outcome (Maiti et al., 2023; Zhou et al., 2019a). Two meta-analyses of serotonin-dopamine modulator (SDM; antipsychotic) augmentation did not find that a duration of greater than 4 weeks conferred additional benefit (Bloch et al., 2006; Veale et al., 2014; Zhou et al., 2019b), however, one meta-analysis found that individuals treated for greater than 8 weeks had significantly better outcomes (Skapinakis et al., 2007). We would recommend that an augmentation trial should continue for at least 8 weeks (Level 1●).

4.2.1. Dopaminergic agents

The results from neuroimaging and genetic studies suggest that dysregulation of dopamine signaling in the prefrontal cortex and basal ganglia contributes to OCD pathophysiology (Koo et al., 2010; Perani et al., 2008; Sesia et al., 2013). Since diminished serotonergic signaling can contribute to enhanced dopaminergic signaling, dopaminergic agents including DA blockers (antipsychotics) and enhancers (psychostimulants, anti-parkinsonian agents) have been studied as augmentation treatments for treatment resistant OCD (Koo et al., 2010). Supporting this, Strom et al. (2025) identified significant enrichment of OCD genetic risk in D_1-and D_2-expressing medium spiny neurons within the striatum, reinforcing the relevance of dopaminergic pathways in OCD and providing genetic evidence for targeting these circuits in pharmacological interventions (Strom et al., 2025).

4.2.1.1. DA blockers (Antipsychotics). Dopamine (D2/D3) receptor agonists (antipsychotics), many of which also modulate serotonin (classified as serotonin-dopamine activity modulators, SDMs), have been the most studied augmentation agents for treatment resistant OCD (TR-OCD) and appear to be effective for one-third of OCD patients who are resistant to SRIs (Grassi et al., 2020). Several meta-analyses have investigated the utility of augmentation with these medications for psychosis for TR-OCD patients and revealed effect sizes ranging from 0.22 to 0.64 (Bloch et al., 2006; Dold et al., 2013; Ninan et al., 2006). Most recently, a network meta-analysis in patients with TR-OCD (N = 1216) found that these agents as a class were significantly superior to placebo in reducing patients' total Y-BOCS scores (MD -4.09, 95 % CI -6.22-(-1.93)) (Level 1●) (Zhou et al., 2019b).

Although, as a class, DA blocker (antipsychotic) augmentation has level 1 evidence, the strength of the evidence for recommending one antipsychotic agent over another is lower, primarily due to very small sample sizes of the individual studies (Supplementary Table 1). Many of the meta-analyses examining individual agents were associated with low AMSTAR (trustworthiness) and/or GRADE (quality) ratings. Despite having level 1 evidence, some lines of treatment associated with individual drugs were down-graded in our recommendations. The incidents where this occurred have been clearly described in the text.

Nevertheless, for augmentation with the second- and third-generation antipsychotics (SGAs), risperidone (DA, 5-HT, NE receptor antagonist [D_2, 5-HT_2, NE alpha-$_2$]) and aripiprazole (DA, 5-HT receptor partial agonist [D_2, 5-HT_{1A}] receptor antagonist [5-HT_{2A}]) are associated with the strongest evidence in TR-OCD (Level 1●) and would be a first-line treatment. Although meta-analytic results for adjunctive olanzapine (DA, 5-HT receptor antagonist [D_2, 5-HT_2]) and quetiapine (DA, 5-HT, NE receptor antagonist [D_2, 5-HT_2, alpha$_{1/2}$] and NET inhibitor (its metabolite) were negative (Level 1, negative■), the GRADE was considered low to very low with serious risks of biases found, including a small number of RCTs included per agent, therefore a conclusive recommendation on these agents could not be made (see Supplementary Table 1) (Bloch et al., 2006; Skapinakis et al., 2021; Veale et al., 2014; Zhou et al., 2019b). Furthermore, in the Zhou et al., 2019b meta-analysis, when baseline YBOCS severity was controlled, both quetiapine and olanzapine became positive (Level 1 ●), indicating a need for larger, better controlled studies in these areas and why a recommendation based upon the current evidence could not be made. It is suggested that clinicians evaluate the use of these agents on a case-by-case basis, considering their tolerability profiles before use. Meta-analytic analysis of the evidence for paliperidone (DA, 5-HT, NE receptor antagonist [D_2, 5-HT_2, NE alpha$_2$]) augmentation is negative

(Level 2, negative), with only one small paliperidone RCT, and so this treatment is unable to be recommended due to a lack of clear, strong evidence (Zhou et al., 2019a, 2019b). Similarly, although evidence from meta-analyses suggests that adjunctive haloperidol (a selective D_2 receptor antagonist), is more effective than placebo at improving Y-BOCS scores (Level 2) (Zhou et al., 2019a, 2019b) only one study (N = 17) was included, limiting the strength of this evidence. Since the mechanism of action of haloperidol is similar to that of the other DA blockers (antipsychotic agents) and it is widely available in low- and middle-income countries, we recommend it as a first line treatment for TR-OCD. Tolerability is an important issue to consider when prescribing these agents. Unlike previous, smaller meta-analyses, a large network meta-analysis found significantly higher rates of drop-outs due to adverse events that were associated with augmentation drugs for psychosis versus placebo, namely for quetiapine and paliperidone (Zhou et al., 2019b). In the one study of haloperidol (McDougle et al., 1994), it was well tolerated, and in a meta-analysis of 32 medications for the treatment of schizophrenia, the tolerability profile of haloperidol was similar to that of other antipsychotics (Huhn et al., 2019). Due to antagonism of hypothalamic $histamine_1$ receptors in the brain, metabolic adverse effects are commonly reported with treatment using SDM (second-generation antipsychotics) (Spina and De Leon, 2014). A meta-analysis reported that weight gain is associated with olanzapine, risperidone, and quetiapine (Stogios et al., 2022). Olanzapine has been associated with the greatest potential for weight gain among the SDMs with a significant dose-response relationship (Stogios et al., 2022). Hyperglycemia and/or hyperlipidemia can occur secondary to weight gain with olanzapine or quetiapine treatment (Spina and De Leon, 2014).

4.2.1.2. Psychostimulants. Psychostimulants, which increase levels of NE and DA, are commonly used to treat attention deficit hyperactivity disorder (ADHD) (Volkow et al., 2005). In a double-blind, caffeine--controlled, 1-week study in TR-OCD patients (N = 24), SRI augmentation with D-amphetamine resulted in improvement of OCD symptoms from baseline, as did the control group receiving caffeine + SRI, although the two groups were not compared to each other (unable to evaluate Level of Evidence - please see footnote on Tables 4–1) (Koran et al., 2009). Similarly, an RCT (n = 62) of TR-OCD patients found a significant (although modest) improvement in YBOCS after 8 weeks of SSRI augmentation with caffeine versus placebo (Level 3) (Shams et al., 2019). Another placebo-controlled trial (N = 44) found that combined fluvoxamine and methylphenidate improved OCD symptoms compared to fluvoxamine alone in TR-OCD patients (Level 3) (Zheng et al., 2019). Although these agents appear to be well tolerated, larger and longer-term studies are needed to better assess their efficacy, abuse potential, and side effects in the longer term.

4.2.2. Glutamatergic agents

Glutamate has long been implicated in the pathophysiology of OCD based on evidence from neuroimaging, cerebrospinal fluid, and candidate gene studies which have demonstrated glutamatergic signaling dysfunction, particularly in the cortico-striato-thalamo-cortical circuitry (Bhattacharyya et al., 2009; Chakrabarty et al., 2005; Rosenberg and Keshavan, 1998; Saxena et al., 2001; Wu et al., 2012). Both glutamate agonists and antagonists have been examined in TR-OCD and revealed effect sizes (SMD) of −1.16 to −3.81 (Level 1) (Hadi et al., 2021; Laoutidis et al., 2016). Glutamatergic agents used in OCD include glutamate release modulators, NMDA receptor antagonists, NMDA receptor agonists, and NMDA receptor modulators. A more recent meta-analysis also showed that monotherapy of glutamatergic agents were superior to placebo in those with refractory OCD (MD -1.19, 95 % CI -1.86-(-0.52)), although this analysis does include one pediatric study and one with glutamatergic agents as an augmentation to SSRIs (Level 1) (Coelho et al., 2025). In the network meta-analysis by Zhou et al. (2019a), glutamatergic agents were superior to placebo (MD -5.22, 95 % CI -7.53-(-2.84)) and there was no significant difference between the effect sizes of glutamatergic agents compared to medications for psychosis (Level 1) (Zhou et al., 2019a).

4.2.2.1. Glutamate release modulators. Lamotrigine (glutamate voltage-gated sodium channel blocker) blocks axonal voltage-gated sodium channels, leading to decreases in both glutamate release and calcium influx (Bhattacharyya et al., 2009; Chakrabarty et al., 2005) and enhanced release of 5-HT, (Shim et al., 2013). There are two positive DBPC trials of lamotrigine where significant improvements in obsessions and compulsions were noted (Bruno et al., 2012; Khalkhali et al., 2016). Positive results were supported by one meta-analysis of TR-OCD (MD = −5.66, 95 % CI -10.59-(-0.66)) (Level 1) (Zhou et al., 2019a), but was not significant in another recent network meta-analysis (Suhas et al., 2023), which included the same two RCTs. The latter was associated with low AMSTAR and GRADE ratings, and so the authors concluded that the level of evidence for lamotrigine augmentation would be level 1 () based on the high AMSTAR and GRADE ratings for the lamotrigine analysis of the Zhou et al. meta-analysis. Lamotrigine appears to be well-tolerated. Common side effects include headache, fatigue, sedation, and benign skin rash, with only one study reporting dropouts due to adverse effects (mild skin rash) (Khalkhali et al., 2016). In rare instances, lamotrigine can trigger the development of Stevens-Johnson Syndrome, characterized by flu-like symptoms followed by a blistering rash, mucocutaneous epidermal necrolysis, and detachment of the epidermis (Edinoff et al., 2021). This agent should be used with care with a gradual titration and is therefore recommended as a second line treatment.

Similarly, topiramate (GABA, glutamate facilitation of GABA transmission, receptor antagonist on AMPA and KA) is an anti-glutamatergic agent, which has demonstrated action in multiple areas including the blockade of voltage-gated sodium channels, action on AMPA/Kainate receptors, and indirect action on NMDA receptors (Mowla et al., 2010). A meta-analysis in TR-OCD found that topiramate augmentation resulted in significantly greater improvement in Y-BOCS scores relative to placebo (MD -6.05, 95 % CI -10.90-(-1.20)) (Level 2) (Zhou et al., 2019a). This meta-analysis included two negative and one positive DBPC trials, leading to wide confidence intervals due to the variability of the evidence (Afshar et al., 2014; Berlin et al., 2011; Mowla et al., 2010). Unfortunately, topiramate is often associated with intolerable side effects including paresthesia, weight loss, memory/word-finding difficulties, influenza-like symptoms, and fatigue (Afshar et al., 2014; Berlin et al., 2011; Mowla et al., 2010; Rubio et al., 2006; Van Ameringen et al., 2006). In the clinical trials of topiramate in TR-OCD, there were significantly greater discontinuations due to adverse effects relative to placebo (OR: 3.67, 95 % CI 1.01–13.34) (Zhou et al., 2019a).

Pregabalin (voltage-gated calcium channel blocker), an anticonvulsant medication, has been approved to treat epilepsy and neuropathic pain by the Food and Drug Administration (FDA), however, it also has anxiolytic effects and has been found effective in treating anxiety disorders (Baldwin et al., 2013; Blommel and Blommel, 2007). Similar to lamotrigine, pregabalin also decreases the release of glutamate by inhibiting voltage-gated sodium and calcium channels (Mico and Prieto, 2012). In TR-OCD, a RCT found that augmentative pregabalin (mean dose = 185.9 mg/d) resulted in significant decreases in Y-BOCS scores after 12 weeks, with a 57 % response rate (≥35 % Y-BOCS reduction) in patients treated with pregabalin versus 7 % in patients treated with placebo (Level 3) (Mowla and Ghaedsharaf, 2020).

Benzodiazepines (GABA-PAM BDZs) are usually not helpful in controlling obsession-related anxiety symptoms and clonazepam as a monotherapy did not show any difference compared to placebo in a DBPC trial (N = 27) for the treatment of OCD in a population including both treatment resistant and treatment naïve participants (Level 3, negative) (Hollander et al., 2003c).

Riluzole, a drug used to treat amyotrophic lateral sclerosis, inhibits

glutamate release and stimulates glial reuptake of glutamate (Pittenger et al., 2008). Contrary to results from open-label trials in TR-OCD patients (Coric et al., 2005; P. J. Grant et al., 2007; Pittenger et al., 2008), a small RCT in TR-OCD found no significant difference between 12 weeks of riluzole augmentation and placebo (Level 3, negative) (Pittenger et al., 2015). Most studies suggest that riluzole is well tolerated.

Troriluzole is a novel glutamate-modulating agent and has been examined as an adjuvant in one large RCT (N = 244) in TR-OCD (Aguiar et al., 2021). Although significant separation from placebo was found at week 8, a significant difference was not found at endpoint (week 12) (Level 2, negative) (Aguiar et al., 2021).

Minocycline is an antibiotic treatment commonly used to treat chronic acne that has strong antioxidant and anti-inflammatory properties, as well as glutamate-modulating effects (Emadi-Kouchak et al., 2016; Khodaie-Ardakani et al., 2014). In TR-OCD, a small open-label study of adjunctive minocycline treatment was negative (Level 4, negative) (Rodriguez et al., 2010).

4.2.2.2. NMDA receptor Antagonists. Memantine is a specific, non-competitive NMDA receptor antagonist that is currently approved for the treatment of Alzheimer's disease by the FDA. Several studies have demonstrated its ability to both decrease excess cortico-striatal glutamate transmission (Bormann, 1989; Mobius, 2003; Reisberg et al., 2003) and increase intracortical inhibition (Greenberg et al., 2000), which may improve obsessions and compulsions (Haghighi et al., 2013; Rosenberg et al., 2001, 2004; Yucel et al., 2008). Memantine augmentation for TR-OCD has been evaluated by a meta-analysis with wide confidence intervals (Zhou et al., 2019a) and in two RCTs with small samples sizes in the treatment arms (Level 2) (Haghighi et al., 2013; Modarresi et al., 2018). One study suggested that a memantine dose of 20 mg/d resulted in larger Y-BOCS score reduction (WMD 13.15, 95 % CI 8.96–17.35; p = .002) than a memantine dose <20 mg/d (WMD 9.05, 95 %CI 3.29–14.81, p < .001) (Modarresi et al., 2018). Memantine appears well-tolerated, as the reported adverse effects were all mild and transient, and is second line for treatment resistant OCD.

Ketamine is another non-competitive NMDA antagonist, however, it has a shorter half-life and higher affinity than memantine (Johnson and Kotermanski, 2006). In TR-OCD, a single intravenous dose of low-dose IV ketamine monotherapy had a robust and rapid (within hours) benefit in a case report (Level 4) (Rodriguez et al., 2011) but a chart review found negative results for 11/14 patients (Level 4, negative) (Sharma et al., 2020). In an open-label trial in TR-OCD adults with multiple comorbidities (N = 10) they reported minimal improvement with IV ketamine (Level 4, negative) (Bloch et al., 2012). Three randomized controlled trials have reported on racemic ketamine's rapid effect on OCD symptom reduction, two using IV ketamine (one with saline control; the other with active/midazolam control) and one using intramuscular (IM) administration (with fentanyl control) (Level 3) (Beaglehole et al., 2025; Rodriguez et al., 2013b). Although the literature remains small, the largest and best-controlled studies suggest benefit from ketamine in at least some individuals with OCD. The evidence for intranasal ketamine is restricted to case reports (Level 4) (Adams et al., 2017; Rodriguez et al., 2017), as is the evidence for esketamine, the S-enantiomer of ketamine (Level 4) (Alves-Pereira et al., 2024; Kaltenboeck et al., 2023; Matteo et al., 2021). Caution is warranted, as there is a lack of long-term safety data and ketamine is a potential drug of abuse, requiring screening for history of substance abuse and side effect monitoring (Sanacora et al., 2017). In clinical situations that prioritize rapid response to treatment (e.g. significant suicidal ideation and severe symptoms in patients for whom other first-, second-, and third-line treatments have been unsuccessful), ketamine may be considered although clinicians need to be aware that the data for efficacy are limited and the effects are transient.

4.2.2.3. NMDA receptor Agonists. D-cycloserine modulates glutamatergic signaling by acting as a partial agonist of the NMDA receptor and has been explored as a pharmacologic strategy to enhance various exposure-based psychotherapies. D-cycloserine is not recommended as an adjunct to ERP/behavioral therapy for TR-OCD due to evidence of inefficacy from a large DBPC trial (Level 2, negative) (Kvale et al., 2020).

4.2.2.4. NMDA receptor modulators. N-acetylcysteine (NAC), a precursor to L-cysteine, alters the release of glutamate in the cortico-striatal brain circuitry by modulating the cysteine-glutamate antiporter (Afshar et al., 2012). It also increases the levels of glutathione, an antioxidant that modulates the AMPA and NMDA receptors. NAC is a prodrug of the amino acid cysteine and is an NMDA receptor modulator which may attenuate inflammatory response (Afshar et al., 2012). NAC is available over the counter and generally well-tolerated (Deepmala et al., 2015). Although the bulk of the NAC studies have been in moderate-to-severe OCD, in TR-OCD, the evidence for adjunctive NAC is mixed. One RCT in TR-OCD adults (n = 20 in the treatment arm) found no significant benefit of adjunctive NAC in reducing OCD severity after 16 weeks (Level 3) (Costa et al., 2017). Another RCT (n = 24 in treatment arm) showed positive results after 12 weeks of adjunctive NAC (Level 3) (Afshar et al., 2012). In the only network meta-analysis which included these two RCTs and excluded those examining moderate-to-severe OCD, NAC failed to demonstrate superiority over placebo (Level 2, negative) (Suhas et al., 2023). Therefore, the evidence supporting the benefit of adjunctive NAC remains preliminary and RCTs with larger sample sizes are necessary to elucidate possible smaller effect sizes as well as the therapeutic effects of different doses (Level 2, negative).

4.2.3. Serotonergic agents

The serotonergic hypothesis suggests that OCD may be characterized by dysfunction in serotonergic signaling (Zohar et al., 2004). This hypothesis is supported by pharmacologic challenge studies that found that the activation of 5-HT_{1D} and 5-HT_3 receptors, which reduce serotonin neurotransmission, exacerbated obsessive-compulsive symptoms (Zohar et al., 2004). Moreover, genetic studies suggest that OCD is characterized by a polymorphism of the 5-HT_{1D} gene (Zohar et al., 2004). As previously reported in these guidelines, SRIs are well-established first-line treatments for OCD. In TR-OCD, a potential second-line option is high-dose SSRIs, and potential third-line treatments examined in the literature include intravenous SRIs and other drugs which target serotonin including mirtazapine, inositol, and the anti-emetic agents ondansetron and granisetron.

4.2.3.1. SSRIs. A meta-analysis of 9 RCTs in populations mostly comprised of non-TR-OCD found that high dose SSRIs (WMD 3.9, 95 % CI 2.9–4.9, p < .001) are associated with a greater reduction in Y-BOCS scores in comparison to medium (WMD 1.8, 95 % CI 0.7–2.9, p = .001) and low doses (WMD 2.1, 95 % CI 1.0–3.1, p < .001) (Bloch et al., 2010). Two controlled studies investigating the so called “superdose” strategy for partial or non-responder patients found positive results and good tolerability for both sertraline (up to 400 mg) and escitalopram (up to 40 mg) (Level 2) (Ninan et al., 2006; Rabinowitz et al., 2008). Citalopram is an SSRI leading to increased levels of serotonin in the synaptic cleft due to gradual desensitization of terminal 5-HT autoreceptors. Intravenous (IV) citalopram is delivered using starting doses of 20 mg that are titrated to 80 mg/d. In TR-OCD, one study found that 69 % (n = 27) had at least a 20 % decrease in Y-BOCS scores after 21 days (Pallanti et al., 2002b). When responders were switched to oral citalopram at the maximum dose received intravenously, 92 % (n = 25) of these patients had a 35 % decrease in Y-BOCS scores after 63 days on the oral drug (Level 4) (Pallanti et al., 2002b). While the QT prolongation risk of citalopram has been deemed low, due to the use of above-therapeutic doses in the super dose strategy and given the lack of evidence of the

QT risk in a high dose strategy, it is recommended to use an SSRI other than citalopram for an abundance of caution.

4.2.3.2. Tricyclic reuptake inhibitors. Clomipramine is a tricyclic agent that potentially blocks the reuptake of NE and 5-HT, leading to an enhanced effect of these neurotransmitters in the brain (Benkelfat et al., 1989). Since some studies suggest that clomipramine is superior to its noradrenergic metabolite, desmethylclomipramine, at improving OCD symptoms (Mavissakalian et al., 1990a; Stern et al., 1980), IV clomipramine may be favoured over oral clomipramine because it optimizes the bioavailability of clomipramine, the more serotonergic compound (Fallon et al., 1992, 1998; Karameh and Khani, 2015). IV administration allows clomipramine to bypass the first pass hepatoenteric metabolism, leading to a higher plasma ratio of clomipramine to desmethylclomipramine (Fallon et al., 1992, 1998; Karameh and Khani, 2015). Pulse-loaded regimens typically deliver IV clomipramine over one to two sessions in doses ranging from 150 mg to 200 mg, whereas gradual dose regimens titrate IV clomipramine from 25 mg to 250 mg across 14 sessions. In TR-OCD, clomipramine has been used as an add-on treatment with success. To date, one RCT has found clomipramine + citalopram to be superior compared to quetiapine + citalopram (Level 3) (Diniz et al., 2010) and two open-label studies have reported significant improvements in Y-BOCS scores in patients treated with clomipramine + SSRI, one as augmentation (Level 4) (Marazziti et al., 2008) and one as combined treatment (Level 4) (Pallanti et al., 1999). On the other hand, one RCT demonstrated the superiority of IV clomipramine monotherapy (gradual dose) over placebo (Level 3) (Fallon et al., 1998), yet another RCT reported no significant difference in efficacy between adjunctive IV clomipramine (pulse-loaded) and oral clomipramine after 12 weeks, nor did IV pulse-loaded clomipramine demonstrate a clinically meaningful sustained response (Level 4, negative) (Koran et al., 2006).

4.2.3.3. SNRIs. Venlafaxine, used for MDD but also for anxiety, is a SNRI, when used at doses higher than its minimal effective dose for MDD. An open-label study using venlafaxine in TR-OCD reported response in 75.9 % of participants (Level 4) (Hollander et al., 2003b). However, in a randomized double-blind switch study using venlafaxine and paroxetine, where non-responders were switched to the alternative drug, the authors reported a 19 % and 56 % response rate in the venlafaxine and paroxetine groups, respectively, after 12 weeks (Level 3, negative) (Denys et al., 2004). A systematic case records report examining venlafaxine in treating TR-OCD found 29/65 patients responded (>35 % drop in Y-BOCS) to the drug at 4-month follow-up (Level 4) (Balachander et al., 2019).

Duloxetine, indicated for MDD, generalized anxiety disorder and chronic pain, is a SNRI when used at doses higher than its minimal effective for MDD. It has been investigated in a case series of four treatment resistant OCD patients and was found to significantly reduce Y-BOCS scores (>35 % score reduction) in 3/4 participants (Level 4) (Dell'Osso et al., 2008).

4.2.3.4. 5-HT3 Antagonists. Ondansetron and granisetron are 5-HT3 receptor antagonists that are used to treat nausea and vomiting associated with cancer treatment or surgery (Rao and Faso, 2012). Their use as augmentation agents in TR-OCD is supported by two RCTs (Sepehrmanesh et al., 2019; Sharafkhah et al., 2019). One RCT reported that ondansetron (n = 45) and granisetron (n = 45) were each superior to placebo (n = 45) as adjunctive treatments to SSRIs and antipsychotics (Level 2) (Sharafkhah et al., 2019). The other RCT reported that adjunctive ondansetron treatment for TR-OCD (n = 20) was more effective than placebo (n = 20) at improving Y-BOCS scores after 8 and 12 weeks (Level 3) (Sepehrmanesh et al., 2019). A recent network meta-analysis found augmentation with ondansetron to be the best treatment for TR-OCD (SMD -2.01, 95 % CI -3.19-(-0.83)) (Level 2), however, this study was associated with high risk of bias and low GRADE ratings (Suhas et al., 2023). Conversely, a large multicenter RCT (N = 130) using low dose ondansetron (0.5–0.75 mg/day) in TR-OCD was terminated due to lack efficacy (Transcept Pharmaceuticals, 2013) and expert clinical opinion on the use of ondansetron is generally negative. Adverse effects for these drugs are generally mild, including diarrhea, constipation, and headache (Sepehrmanesh et al., 2019; Sharafkhah et al., 2019). Since these drugs prolong the QTc interval, it is critical to carefully monitor patients who are at risk for arrhythmia or who are taking other medications that may prolong the QTc interval. Ondansetron and granisetron are recommended as third line for treatment resistant OCD.

4.2.3.5. 5-HT$_{1A}$ Antagonist. Pindolol, a beta-adrenergic blocker that enhances serotonergic signaling by antagonizing the presynaptic serotonin receptor 5HT1A, is unable to be recommended for TR-OCD (Sassano-Higgins and Pato, 2015). A meta-analysis (N = 4) reported that pindolol augmentation of SSRIs and clomipramine may be effective for improving OCD symptoms in patients with TR-OCD (Sassano-Higgins and Pato, 2015). However, when the analysis was restricted to only RCTs (n = 2 RCTs, both with n = 8 in the treatment arms), pindolol augmentation was associated with a non-statistically significant trend toward reduction of OCD symptoms (Level 2, negative) (Sassano-Higgins and Pato, 2015).

4.2.3.6. Mirtazepine. Mirtazapine acts by antagonizing the adrenergic alpha$_2$-autoreceptors and alpha$_2$-heteroreceptors on 5-HT neurons as well as by blocking 5-HT$_2$ and 5-HT$_3$ receptors (Anttila and Leinonen, 2001). Mirtazapine showed its efficacy (at a daily dose up to 60 mg) in an open-label followed by double-blind placebo-controlled discontinuation OCD trial (N = 30), where 50 % of the randomized sample had failed at least 1 trial of SRI (Koran et al., 2005b). Notably, a 33 % decrease in Y-BOCS scores was reported in the resistant population (n = 15) (Level 4) (Koran et al., 2005b).

4.2.3.7. Other serotonergic Agents. Inositol is a sugar that has been proposed to act as an intracellular modulator of serotonin receptor signaling (Rahman and Neuman, 1993). Support for inositol monotherapy in TR-OCD originates from a small double-blind, controlled crossover trial (N = 13) reporting that individuals taking inositol had reduced OCD symptoms after 6 weeks compared to placebo (Level 4) (Fux et al., 1996). In contrast, adjunctive inositol for TR-OCD has generated mixed results with an open-label study reporting improvement in only 30 % of participants (Seedat and Stein, 1999) and a small placebo-controlled trial (N = 10) reporting no significant treatment effect after 6 weeks in participants with failed SRIs treatments (Level 4, negative) (Fux et al., 1999).

Psilocybin modulates serotonergic signaling as it is a potent 5-HT$_{1A}$ and 5-HT$_{2A/2C}$ agonist (Yousefzadeh et al., 2020). Currently one small double-blind study (N = 9) and one case study have found positive results for psilocybin monotherapy (Level 4) (Moreno et al., 2006; Wilcox, 2014), while one case report also found psilocybin augmentation to improve OCD symptoms (Level 4) (Lugo-Radillo and Cortes-Lopez, 2021). Further research is needed to understand the safety, tolerability, and efficacy of using psilocybin in patients with TR-OCD. Due to safety concerns about using psilocybin outside of a structured treatment setting, we are unable to make a recommendation at this time.

Buspirone enhances serotonergic signaling, as it is a full and partial agonist for the presynaptic serotonin 5-HT$_{1A}$ autoreceptors and postsynaptic 5-HT$_{1A}$ receptors, respectively (Eison and Temple, 1986). In TR-OCD, while open-label studies reported positive results with adjunctive buspirone (Level 4) (Jenike et al., 1991; Markovitz et al., 1990), subsequent placebo-controlled studies did not find significant improvements in OCD symptoms for buspirone adjunctive to fluoxetine

(Grady et al., 1993), fluvoxamine (McDougle et al., 1993), or clomipramine (Pigott et al., 1992a) (Level 3, negative).

4.2.4. Opioids

4.2.4.1. Opioid receptor Agonists. Morphine is a full agonist of the mu-opioid receptor, which is highly concentrated in the striatal system, a region implicated in OCD pathophysiology (Koran et al., 2005a; Murrin et al., 1980). In TR-OCD, adjunctive oral morphine (pulse-dosed) was significantly more effective than placebo and the active comparator, lorazepam, in a small (N = 23) crossover RCT (Level 3) (Koran et al., 2005a). The morphine group reported symptom improvement the day after taking morphine and the effect lasted for 2–5 days (Koran et al., 2005a).

In TR-OCD, adjunctive therapy with buprenorphine (opioid receptor partial agonist [mu], receptor antagonist [kappa, delta]) has generated mixed results. Although positive results were reported by an open-label trial (Level 4) (Liddell et al., 2013), a placebo-controlled double-blind trial (N = 43) found that adjunctive buprenorphine was not significantly more effective than placebo after 12 weeks (Level 3, negative) (Ahmadpanah et al., 2017).

Similar to morphine, tramadol is also a mu receptor agonist and a SERT and NET inhibitor (Dayer et al., 1997). In TR-OCD, tramadol monotherapy has been reported to reduce OCD symptoms in a small open-label trial (Level 4) (Shapira et al., 1997). Caution should be observed for potential serotonin syndrome when tramadol is used as an adjunct to other SRI medication (Brown and Davies, 2016).

4.2.4.2. Opioid receptor Antagonists. Naltrexone (opioid receptor antagonist [mu, kappa]) requires further study for TR-OCD, as the evidence is restricted to a small double-blind crossover RCT (N = 10) that reported no significant difference in Y-BOCS score reductions between those receiving adjunctive naltrexone and placebo after 5 weeks (Level 3, negative) (Amiaz et al., 2008). This study also noted an increase in depressive and anxiety symptoms in the naltrexone group, therefore clinicians should be cautious when prescribing naltrexone and should be tracking patients' mood and anxiety symptoms during treatment.

4.2.5. Other agents

4.2.5.1. Cannabinoids. Data on cannabinoids in OCD remains limited. Case reports of treatment augmentation with dronabinol (tetrahydrocannabinol, THC), a partial CB1 and CB2 receptor agonist, report improvement on the Y-BOCS in patients with TR-OCD (Level 4) (Cooper and Grant, 2017; Schindler et al., 2008).

4.2.5.2. Statins. Statins are cholesterol lowering agents that have been found to alter dopaminergic activity throughout the striatum and to decrease dopamine levels in the prefrontal cortex (Akouchekian et al., 2018). In TR-OCD, while a double-blind, placebo-controlled trial (N = 64) reported improvement in OCD symptoms with adjunctive atorvastatin (Level 2) (Akouchekian et al., 2018), another RCT (N = 26) reported that adjunctive atorvastatin only improved obsessions, but not compulsions (Level 3) (Rahim and Sayyah, 2018).

4.2.5.3. Mood stabilizers. Lithium (enzyme modulator) upregulates Wnt/beta-catenin signaling by inhibiting GSK3beta, which modulates glutamatergic and inflammatory pathways (Vallee et al., 2021). Adjunctive lithium has been examined in TR-OCD, however, the evidence is limited to one small RCT which failed to show efficacy (Level 3, negative) (McDougle et al., 1991). While lithium is often used to treat bipolar disorder comorbid to OCD, it has not demonstrated efficacy for TR-OCD.

4.2.5.4. Eicosapentaenoic acid. Adjunctive omega-3 derivative eicosapentaenoic acid (EPA) has been studied in one preliminary placebo-controlled cross-over trial (N = 11) in participants who were not fully benefiting from their current OCD medication (Fux et al., 2004). The study reported no significant improvements in OCD symptoms in the EPA group compared to placebo (Level 4, negative).

4.2.6. Conclusion

When approaching treatment for OCD, patients should be considered treatment resistant to pharmacotherapy if they have failed at least two trials of adequately dosed SSRIs. The current TR evidence supports starting with adjunctive antipsychotics/serotonin-dopamine activity modulators, namely aripiprazole or risperidone, or with haloperidol; and secondarily, augmentation with the glutamatergic agent lamotrigine, augmentation with the NMDA receptor antagonist memantine, or using high-dose SSRIs. Unfortunately, the TR-OCD literature is limited by small studies as well as confusion over the manner in which this literature has been approached. Often studies of moderate-to-severe OCD are included in the TR literature and the definitions of resistance and refractory are inconsistent and often used interchangeably. Furthermore, it is unclear where these treatment resistant strategies best fit in the sequencing of OCD treatment, given the emerging evidence for neuromodulation modalities (Grassi et al., 2020). Nevertheless, achieving optimal dosing and duration of treatment should be two central tenets of a pharmacological treatment approach to OCD. The dosage of SSRIs required for an optimal response in OCD are usually higher than what is typically observed in depression or anxiety (Bloch et al., 2010; Menchon et al., 2019). The duration of the acute treatment is widely suggested to be 12 weeks (Dell'Osso et al., 2007), supported by several controlled trials where continued symptom improvement was demonstrated up to 12 weeks after treatment initiation (Menchon et al., 2019). Augmentation agents of SRIs should be tried for at least 8 weeks to determine the clinical benefit (Level 1) (Skapinakis et al., 2007).

RECOMMENDATIONS FOR PHARMACOLOGICAL MANAGEMENT OF TR-OCD

- **FIRST LINE:** Start with adjunctive medications for psychosis (antipsychotics), namely aripiprazole (Level 1
) or risperidone (Level 1
) or haloperidol (Level 2
) or augment with CBT/ERP (Level 1
).
- **SECOND LINE:** Next consider augmentation with lamotrigine (Level 1
) or memantine (Level 2
) or high-dose SSRI's (Level 2
).
  - o Augmentation of SRI should be at least 8 weeks before being able to ascertain the benefit of the intervention (Level 1) (Skapinakis et al., 2007).

4.2.7. Combining pharmacotherapy and psychotherapy in TR-OCD

While there are many studies examining the use and efficacy of medication, there are far fewer large studies examining the use of CBT with ERP in TR-OCD. Many of the studies involving CBT as a sole treatment have methodological problems including small numbers, usage of waitlist controls as a comparator arm, ignoring medication and stating that "medication was kept stable throughout the study", difficulty in blinding both participants and researchers, and possible researcher bias in favor of CBT (Reid et al., 2021). Even in the non-resistant group of patients, there are very few studies examining head-to-head efficacy of SSRI versus CBT or combination and even fewer examining this in a refractory group. In fact, most studies are performed in subjects with a range of severity and most exclude those with treatment refractory conditions, although it should be noted that the definition of "refractory" does vary between studies.

Sequential combination treatments of SRI and psychotherapy in refractory OCD. Numerous open-label studies have examined the addition of CBT/

ERP to SRIs in patients not responding to their current pharmacological treatment. These open-label studies found that the combination of these treatments significantly improves OCD symptoms, as noted by a >35 % drop in Y-BOCS scores at endpoint (Level 4) (Albert et al., 2003; Anand et al., 2011; Kampman et al., 2002; Simpson and Liebowitz, 1999; Tolin et al., 2004). One RCT found that patients randomized to the CBT/ERP + medication group (n = 56) had significantly greater improvements in symptom severity compared to the control group (stress management training - SMT) + medication) (n = 55). Most patients in the active group were responders (74 %) compared to just 22 % in the control group, suggesting that CBT/ERP has a robust effect as an augmenting intervention compared to other psychotherapeutic interventions (Level 2) (Simpson et al., 2008a). In another RCT, 100 adults who had only partially responded to adequate doses of SRIs were allocated to receive either augmentation with risperidone (n = 40), pill placebo (n = 20), or CBT/ERP (n = 40). The addition of CBT to the medication was found to be significantly better than the other two groups, with 80 % of patients who received the CBT demonstrating a reduction of at least 25 % on the Y-BOCS score compared to only 23 % for those receiving risperidone and 15 % for placebo (Level 2) (Simpson et al., 2013a). In conclusion, individuals with partial or non-response to SRIs may benefit from augmentation with CBT/ERP (Level 1). To date no studies have examined the sequential addition of SRI to psychotherapy in TR-OCD adult populations.

There are many naturalistic studies which identify patients with refractory OCD and examine the effect of adding intensive CBT to ERP (daily or weekly CBT/ERP sessions and behavioural interventions) either in the community or in an inpatient setting. The problem with these studies is that, being naturalistic, medication may also have been changed and optimized alongside the CBT interventions. For example, a study of a treatment resistant community sample where all patients had previously received a trial of CBT/ERP as well as a trial of SRI, found that in a total of 205 individuals, there was overall a significant reduction in OCD symptomatology when CBT/ERP was combined with existing medication (Boschen and Drummond, 2012). In an even more treatment resistant group who had received at least 2 adequate trials of SRI medication and 2 previous trials of CBT involving ERP and were significantly disabled to require inpatient help for their own health and safety, intensive CBT again resulted in significant improvement (Boschen et al., 2010). A recent naturalistic study demonstrated that significant gains in TR-OCD symptomatology were maintained up to one year following intensive inpatient treatment with combined medication (Nadeem et al., 2021).

4.2.8. Other non-pharmacological interventions

One RCT has examined the efficacy of aerobic exercise in TR-OCD (N = 56) (Abrantes et al., 2017). In this study, participants were randomized to augmentation with aerobic exercise or 12 sessions of health education. Although the proportion of responders was higher in the exercise group, no differences were found between the two groups on the primary outcome of change in Y-BOCS score (Level 3, negative). Interestingly, a follow-up analysis reported significant reductions in negative affect and a significant acute effect in the reduction of compulsions in the aerobic exercise group compared to control (Abrantes et al., 2019).

RECOMMENDATIONS FOR NON-PHARMACOLOGICAL INTERVENTIONS IN TR-OCD

❖ In patients with partial or non-response to SSRI, there is strong evidence to support adding CBT/ERP (Level 1).

4.3. Immunotherapy

Although there is growing evidence of the implication of dysfunction of both innate and adaptive immunity and a persistent low-grade inflammation in resistant OCD, the definitions of specific biomarkers with sensitivity and specificity adequate to address targeted treatment remain inconsistent (Gerentes et al., 2019). Blood levels of IL-1β, IL-6 and TNF-α have been reported as significantly higher in patients with OCD than in healthy controls, but to date research has only found a correlation between increased cytokine levels and the cognitive dysfunction symptoms of OCD (Karaguzel et al., 2019). Translocator protein density measured by distribution volume (TSPO VT) is increased in activated microglia and is considered a marker of neuroinflammation. TSPO levels have been correlated with OCD symptoms, and more specifically, with the severity of compulsions in 20 OCD medication-free patients, as measured with positron emission tomography (PET) imaging. The regional distribution of elevated TSPO (the translocator protein) in the cortico-striatal-thalamo-cortical circuit (CSTC) of adults with OCD (Attwells et al., 2017) also proves consistent with the autoimmune theory for OCD, highlighting the importance of investigating immunomodulatory therapies in adults and not only in PANDAS/PANS.

4.3.1. Immunotherapy studies

As detailed in Section 6.4.7, the treatment of PANDAS/PANS is associated with one negative RCT using an immune-modulating agent (K. A. Williams et al., 2016). Similarly, the immune-modulating agent Rituximab, which targets B-lymphocytes, was examined in an open-label pilot study, which included 10 adults with TR-OCD. Only one of ten patients responded (Level 4, negative) (Bejerot et al., 2023).

4.3.2. Inflammatory-modifying agents

Studies examining the role of inflammation in TR-OCD are premised on findings that acute lipopolysaccharide-induced inflammation; (1) increases CNS histamine, (2) decreases CNS serotonin (via inhibitory histamine receptors), and (3) prevents SSRIs from effectively increasing extracellular serotonin (Hersey et al., 2021). It has been postulated that anti-inflammatories may enhance the activities of SSRIs when used adjunctively (Hersey et al., 2021). Inflammatory-modifying interventions for TR-OCD have included minocycline and NAC (Celecoxib, a COX-2 inhibitor has also been examined in moderate-to-severe OCD). Although these medications are not effectively able to cross the blood-brain barrier, they have been tested as treatments in double-blind RCTs due to their ability to both modulate glutamate and act on inflammatory processes (see the NMDA Receptor Modulator Section above). Unfortunately, these studies had small samples and did not consistently measure inflammatory markers, so conclusions about their effect on inflammation in TR-OCD are limited. Therefore, at this stage in the literature, the inflammatory hypothesis in OCD requires further elucidation, particularly in TR-OCD.

5. Neurostimulation and neuromodulation

There is increasing evidence that psychiatric disorders are associated with pathological activity in discrete neural circuits in the brain (Gordon, 2016). Stimulating neuroanatomical targets has been found to be effective in the treatment of depression and neurological diseases associated with the emergence of depressive symptoms. A putative shared universal brain circuit has been recently identified for OCD (Li et al., 2021). This conceptualization provides a basis for understanding how positive clinical changes can occur trans-therapeutically across diverse treatments, such as psychotherapy, pharmacotherapy, and brain stimulation, based on the degree to which each modality can alter the functional activity of discrete brain circuits (Giacobbe et al., 2009). Furthermore, ongoing developments in neurocircuitry models of psychiatric disorders provide the theoretical basis for understanding and facilitating the development of novel approaches for those with severe and difficult-to-treat forms of illness.

Transcranial and direct-to-brain therapeutic modalities represent promising therapeutic options for those with treatment resistant OCD. The remainder of this section will explore the basis of these

interventional approaches, the existing data for these treatments for treatment resistant OCD, their side-effects/tolerability, and clinical recommendations (Hassan et al., 2020).

5.1. Non-invasive techniques

5.1.1. Transcranial magnetic stimulation (TMS)

One of the most promising neurostimulation techniques is Transcranial Magnetic Stimulation (rTMS). Research on the neurobiology of OCD indicates dysfunction in the orbitofrontal-striatal-pallido-thalamic circuitry (Rapinesi et al., 2019) and most of the research undertaken with TMS in OCD targets this circuitry. This network includes the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), and anterior cingulate cortex (ACC), the supplementary motor area (SMA) and pre-supplementary motor area (pre-SMA), and the basal ganglia. Traditional TMS protocols involve repetitive TMS (rTMS), which delivers repeated magnetic pulses to stimulate superficial cortical regions over multiple sessions using a figure-of-eight coil or a circular coil. A newer subtype of TMS, known as deep repetitive TMS (dTMS) uses special H-coils to target deeper regions of the brain than rTMS and has recently received FDA approval for treating OCD. Another subtype of TMS, known as Theta Burst Stimulation (TBS) delivers theta wave pulses to the brain in 3-min sessions, and could eventually deliver similar overall total stimulation in shorter periods of time with accelerated treatment. In all subtypes of TMS, a coil positioned on the scalp produces repetitive magnetic pulses over cortical areas. The magnetic field produces electrical currents in the brain, stimulating or inhibiting brain structures. Depending on the protocol and devices used, TMS may be deep or superficial, and inhibitory or excitatory. Several types of coils are used in TMS, and they vary in size, format, focality, and depth reach. While optimization studies and the FDA recommend 20 min of 1–10 Hz stimulation per session, TBS recommendations are 600 pulses for a 3-min session (Blumberger et al., 2018). Stimulus intensity for all types of TMS is based on resting motor threshold (RMT), which is the minimum intensity to contract a patient's contralateral thumb or toe. Each patient has their own RMT, and the stimulus intensity is calculated as a percentage of this RMT. The stimulus intensity is defined in each TMS protocol; generally, 110 %–120 % of RMT in repetitive TMS and 80–120 % for intermittent theta burst stimulation (iTBS) (Blumberger et al., 2018). Stimulus frequency can be low frequency (LF) which is ≤ 1 Hz, or high frequency (HF) which is ≥ 5 Hz.

Treatments with TMS are generally recommended for treatment resistant OCD patients who would be eligible only after failed treatments with both an SRI and CBT/ERP. Insurance plans in the US require demonstration of treatment resistant OCD before payment for such services, although further research is needed to determine whether or not, from a risk versus benefit standard, sequencing TMS earlier would be beneficial. The requirement of treatment resistance may not be required for TMS in other jurisdictions.

5.1.1.1. Safety of TMS. TMS is a neurostimulation technique with an overall low risk of side effects and adverse reactions. The most common side effects are mild transient headache, local pain, neck pain, toothache, and paresthesia. Syncope, transient hearing changes, and burns on the scalp were also reported as rare side effects (Rossi et al., 2009). The most feared adverse event associated with TMS is seizure, but recent studies show that the risk of seizures is very low, less than 1 %. Alcohol use, brain injury, sleep deprivation, epilepsy, medications such as bupropion, and other diagnoses/situations may increase the risk of TMS-induced seizures. There are no significant differences in risk of seizures between repetitive TMS, Theta Burst Stimulation, or accelerated TMS. The seizure rates for medications used for treatment of OCD and TMS are comparable (Stultz et al., 2020). Meta-analyses showed that there were no significant differences in dropout rates between the sham and active TMS groups, including protocols with TMS over the DLPFC, SMA, MPFC/ACC, and OFC (Liang et al., 2021; Trevizol et al., 2016).

5.1.1.2. rTMS. More than two dozen RCTs (Alonso et al., 2001; Arumugham et al., 2018; Badawy et al., 2010; Carmi et al., 2019, 2018; Das, 2015; Dutta et al., 2021; Elbeh et al., 2016; Gomes et al., 2012; Haghighi et al., 2015; Harika-Germaneau et al., 2019; Hawken et al., 2016; Jahangard et al., 2016; Kang et al., 2009; W. Liu et al., 2021; Ma et al., 2014; Mansur et al., 2011; Mantovani et al., 2010; Naro et al., 2019; Nauczyciel et al., 2014; Pelissolo et al., 2016; Prasko et al., 2006; Ruffini et al., 2009; Sachdev et al., 2007; Sarkhel et al., 2010; Seo et al., 2016; Shayganfard et al., 2016; Zhang et al., 2019) have been conducted for rTMS in OCD within the last 20 years. When comparing active TMS and sham stimulation, some trials (Carmi et al., 2018; Elbeh et al., 2016; Gomes et al., 2012; Haghighi et al., 2015; Hawken et al., 2016; Ma et al., 2014; Seo et al., 2016; Shayganfard et al., 2016) clearly demonstrated superiority of the active treatment, but most of the trials (Alonso et al., 2001; Arumugham et al., 2018; Badawy et al., 2010; Carmi et al., 2019; Das, 2015; Dutta et al., 2021; Harika-Germaneau et al., 2019; Jahangard et al., 2016; Kang et al., 2009; W. Liu et al., 2021; Mansur et al., 2011; Mantovani et al., 2010; Naro et al., 2019, p. 20; Nauczyciel et al., 2014; Pelissolo et al., 2016; Prasko et al., 2006; Ruffini et al., 2009; Sachdev et al., 2007; Sarkhel et al., 2010; Zhang et al., 2019) failed to show statistically significant differences between treatment groups. Many of these studies had small sample sizes (Alonso et al., 2001; Arumugham et al., 2018; Badawy et al., 2010; Carmi et al., 2018; Das, 2015; Dutta et al., 2021; Elbeh et al., 2016; Gomes et al., 2012; Haghighi et al., 2015; Harika-Germaneau et al., 2019; Hawken et al., 2016; Jahangard et al., 2016; Kang et al., 2009; W. Liu et al., 2021; Mansur et al., 2011; Mantovani et al., 2010; Naro et al., 2019; Nauczyciel et al., 2014; Pelissolo et al., 2016; Prasko et al., 2006; Ruffini et al., 2009; Sachdev et al., 2007; Sarkhel et al., 2010; Seo et al., 2016; Shayganfard et al., 2016) and varied in stimulation-relevant parameters (i.e. frequency and target), use of rTMS as a monotherapy or adjunctive therapy, as well as in their definitions of treatment resistance, limiting the interpretation and generalizability of rTMS research in OCD. Meta-analyses have attempted to combine data from these studies to identify promising targets and stimulation parameters associated with positive treatment outcomes (Berlim et al., 2013; Fitzsimmons et al., 2022; Liang et al., 2021; Perera et al., 2021; Rehn et al., 2018; Zhou et al., 2017). It has been observed that both cortical target and frequency (low frequency (LF) versus high frequency (HF)) influence the efficacy of rTMS on treatment outcome (Carmi et al., 2018; Elbeh et al., 2016; Fitzsimmons et al., 2022), however, some meta-analyses fail to consider these factors separately when evaluating different protocols, limiting their ability to guide TMS clinical practice (Perera et al., 2021; Rehn et al., 2018; Zhou et al., 2017). Further, most studies included TMS as an augmentation strategy rather than a monotherapy, since patients were already being treated with SSRIs and CBT prior to addition of TMS.

TMS avoids medication-induced side effects (i.e., sexual side effects, metabolic adverse events) and does not require individuals to be motivated to do exposure therapy or have risks associated with exposure and behavior therapy. On the other hand, TMS may be costly, time-consuming, and require maintenance therapy to maintain gains, although more research is needed on how to maintain these effects. There is some evidence that TMS may be more effective than augmentation strategies with risperidone, although this requires further study (Level 3◐) (Pallanti and Hollander, 2014).

Based on pooled data, it was shown that rTMS at the DLPFC (which is the standard target for depression) was the most effective at reducing OCD symptoms (Berlim et al., 2013; Fitzsimmons et al., 2022; Perera et al., 2021). Subgroup analysis based on frequency and cortical target was conducted in one meta-analysis, showing that LF-rTMS at the right DLPFC and HF-rTMS at the bilateral DLPFC were two of the most

efficacious stimulation location/frequency combinations (Level 1) (Fitzsimmons et al., 2022). The efficacy of rTMS when targeting these locations has also been supported by other analyses (Perera et al., 2021; Rehn et al., 2018; Zhou et al., 2017). While one meta-analysis found that targeting the left DLPFC produced significant improvements in OCD symptoms compared to sham (Zhou et al., 2017), other analyses failed to show a significant difference between the two groups (Level 1, negative) (Fitzsimmons et al., 2022; Perera et al., 2021; Rehn et al., 2018). When used as a monotherapy, HF-rTMS at the left DLPFC (LF not studied) was comparable to sham in an RCT (Level 3, negative) (Badawy et al., 2010). Likewise, monotherapy LF-rTMS at the bilateral pre-SMA (HF not studied) produced similar results (Level 3, negative) (Zhang et al., 2019). When evaluating the bilateral pre-SMA as a rTMS target, four meta-analyses found significant efficacy in improving OCD symptoms using LF-rTMS (Level 1) (Berlim et al., 2013; Fitzsimmons et al., 2022; Liang et al., 2021; Rehn et al., 2018). Although only one study conducted subgroup analysis based on frequency (Fitzsimmons et al., 2022), the RCTs included in the remaining meta-analyses were studies using LF only (Berlim et al., 2013; Liang et al., 2021; Rehn et al., 2018). OFC as a rTMS target was shown to have no significant improvements in OCD symptoms compared to sham when using LF-rTMS at either the right or left OFC (Level 1, negative) (Berlim et al., 2013; Fitzsimmons et al., 2022; Liang et al., 2021; Perera et al., 2021; Rehn et al., 2018).

While these meta-analyses have helped identify targets and stimulation parameters associated with positive treatment outcomes, the overall efficacy of rTMS and the optimal stage at which rTMS should be introduced to a patient is still uncertain (Pellegrini et al., 2022). Since it is expected that different degrees of treatment resistance may have an impact on the effectiveness of OCD treatments (Pellegrini et al., 2022), inadequate and varying definitions of treatment resistance used by studies may be a potential source of the high levels of heterogeneity seen across meta-analyses (I^2: 62 % (Perera et al., 2021); I^2: 73.5 % (Liang et al., 2021); I^2: 35.1 % (Fitzsimmons et al., 2022)). In fact, most meta-analyses investigating rTMS in OCD did not adequately define treatment resistance using a standardized criteria (Berlim et al., 2013; Liang et al., 2021; Ma and Shi, 2014; Perera et al., 2021; Rehn et al., 2018; Zhou et al., 2017). One of these studies performed a sub-analysis of TR-OCD RCTs and found that rTMS had a greater therapeutic effect in non-treatment resistant patients, however only two studies were included in the treatment resistant subgroup (Zhou et al., 2017). Similarly, a sub-analysis from another meta-analysis found rTMS (specifically LF-rTMS over the DLPFC) to be significantly more effective in non-TR-OCD patients compared to TR-OCD patients (Liang et al., 2021), however like other meta-analyses, a standardized definition of TR-OCD was not used. A more recent meta-analysis of 21 RCTs (N = 662) found 18 RCTs using rTMS in treatment resistant populations (note that treatment resistance was defined differently by each study but requiring participants to have started or failed at least 1 trial of SSRI) (Fitzsimmons et al., 2022). Although this study accounts for many of the differences in methodologies between studies through subgroup analyses, it still shows a high level of heterogeneity (I^2: 35.1 % in Fitzsimmons et al., 2022). Interestingly, the subgroup analysis performed by this meta-analysis showed no differences in treatment effect in treatment resistant and non-treatment resistant patients, which may be due to lack of studies in the non-treatment resistant subgroup (Fitzsimmons et al., 2022). In an attempt to explain some of the heterogeneity of rTMS research in OCD, one meta-analysis used a standardized criteria to define treatment resistance and examined the efficacy of rTMS in OCD patients with or without treatment resistance. Upon analysis, it was concluded that rTMS was largely effective for non-resistant OCD patients and should be used earlier in a patient's treatment plan instead of reserving it for TR-OCD cases (Pellegrini et al., 2022).

Despite room for improvement, the overall advancement of rTMS research in OCD over the past 20 years has led the FDA to approve several rTMS devices including the MagVenture cool DB80 coil, the NeuroStar Advanced Therapy, the Brainsway dTMS helmets, including the H7 coil for OCD, and the Magstim Horizon 3.0 (with or without dTMS). The Magstim coils and Brainsway H7 coil dTMS helmets have been approved by Health Canada. In Europe, Brainsway deep TMS and Magstim coils have the European Union Conformite Europeenne (EU CE) and United Kingdom Conformity Assessed (UKCA) approval.

5.1.1.3. dTMS. A systematic review examining RCTs using dTMS to treat OCD found dTMS to be effective in reducing OCD symptoms compared to sham conditions (Lusicic et al., 2018). Only two RCTs specific to dTMS were included in the review, both with similar protocols of adjunctive dTMS targeting the ACC and mPFC in treatment resistant patients (Carmi et al., 2018, 2019). One of these RCTs (N = 38) compared LF and HF conditions in dTMS and found HF (20 Hz) to be superior to both LF (1Hz) and sham conditions (Carmi et al., 2018), although further research is required before a frequency recommendation can be given (Level 3). A subsequent multi-site RCT (N = 99) of HF dTMS found dTMS to significantly reduce OCD symptoms compared to sham control, with 45.2 % of patients reporting response at 1 month follow-up (Level 2) (Carmi et al., 2019). Similarly, a review of 22 naturalistic clinical trials (N = 219) examining the efficacy of dTMS for OCD found a response rate of 72.6 % and a sustained 1-month response rate of 52.4 % (Roth et al., 2021). A recent network meta-analysis examining SRI-resistant OCD populations found dTMS to be significantly more effective than placebo (SMD -1.95, 95 % CI -3.25-(-0.65)) (Level 1) (Suhas et al., 2023). In contrast, two meta-analyses that compared the effectiveness of dTMS with other rTMS treatments did not find a significant effect of dTMS interventions (Level 1, negative) (Fitzsimmons et al., 2022; Perera et al., 2021). Despite using the same two RCTs, these differences in findings among analyses may be due to different imputed standard deviations (SD) which could introduce bias towards no effect (Fitzsimmons et al., 2022).

Currently the only FDA approved dTMS devices are the BrainsWay dTMS H7 coil and MagVenture Cool D-B80 coil. They were approved in 2018 and 2020 by the FDA, respectively, to be used as an adjunctive treatment in adults with OCD. Health Canada approved the Brainsway dTMS system for TR-OCD in 2021. Of note, the Brainsway dTMS H7 clinical trial incorporated an individualized behavioral exposure prior to stimulation, which is often not done in current clinical practice.

5.1.1.4. TBS. While there are currently no FDA or Health Canada approved devices for TBS in treating OCD, research has started examining both continuous TBS (cTBS) and intermittent TBS (iTBS) for treating OCD. A recent RCT (N = 32) using cTBS at the SMA as an adjunctive treatment for non-TR-OCD found significant improvements in OCD symptoms in the cTBS group compared to sham (Level 3) (Mukherjee et al., 2022). A few RCTs examining adjunctive cTBS in treatment resistant populations have been published, reporting no difference in OCD symptoms between the cTBS and sham conditions when targeting either the left OFC (Level 3, negative) (W. Liu et al., 2021), right OFC (Level 3, negative) (Dutta et al., 2021) or SMA (Harika-Germaneau et al., 2019) (Level 3, negative). Another small crossover RCT (N = 10) comparing adjunctive iTBS treatment at the left DLPFC in TR-OCD found significant improvements in OCD symptoms at 1-month post-treatment in 100 % of the sample with maintained improvements at 3 months post-treatment in 40 % of the sample (Level 4) (Naro et al., 2019). A small open-label study investigated 5 consecutive days of accelerated continuous TBS (cTBSmod) to the frontal-striatal circuit of 7 individuals with treatment refractory OCD, with a response rate of 71 % and no reported severe adverse events (Level 4) (Williams et al., 2021). Overall, due to the limited number of studies and small sample sizes, no specific brain region target or TBS

type (continuous versus intermittent) can be recommended at this time.

RECOMMENDATIONS FOR TMS

- ❖ rTMS and dTMS may be more efficacious in non-treatment resistant OCD populations and should be used earlier in the treatment algorithm (i.e. after failing SSRI and CBT) (Level 4).
  - o rTMS is efficacious as adjunctive LF-rTMS at bilateral pre-SMA (Level 1).
  - o rTMS is efficacious as adjunctive HF-rTMS at bilateral DLPFC (Level 1).
  - o rTMS is efficacious as adjunctive LF-rTMS at right DLPFC (Level 1)*.
- ❖ dTMS is most efficacious as adjunctive HF-dTMS at ACC and mPFC (Level 2).

*In the case of adjunctive rTMS at right DLPFC, LF stimulation is considered more efficacious.

5.1.2. Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique. It involves the application of low direct electrical currents on specific cortical areas for several minutes through strategically positioned anodal and cathodal electrodes, which induces localized polarity-dependent effects. Anodal stimulation induces cortical excitability, whereas cathodal stimulation decreases cortical excitability (Freire et al., 2020; Zaghi et al., 2010). Although the polarizing effects of tDCS are generally restricted to the area beneath the anode and cathode stimulation sites, the functional effects can reach a widespread network of cortical and subcortical regions that are connected to the targeted region (Keeser et al., 2011; Zaghi et al., 2010). This ability of tDCS to modulate a network is of particular interest considering the abnormal activity and connectivity within the orbito-fronto-striato-pallido-thalamic network described in patients with OCD (Lam et al., 2016).

Thus far, tDCS has been poorly studied for indications other than depression. Therefore, high-quality evidence concerning the therapeutic potential of tDCS in OCD is limited, consisting of 21 clinical trials conducted over the last 20 years. Among these, there are only 7 RCTs (Bation et al., 2019; Da Silva et al., 2021; Fineberg et al., 2023; Manche Gowda et al., 2019; Todder et al., 2017; Yekta et al., 2015; Yoosefee et al., 2020), in addition to 5 open-label studies (Bation et al., 2015; Dinn et al., 2016; Harika-Germaneau et al., 2020; Kumar et al., 2019; Najafi et al., 2017), 8 case reports (Alizadehgoradel et al., 2016; Da Silva et al., 2016; D'Urso et al., 2015; Hazari et al., 2016; Mondino et al., 2015; Narayanaswamy et al., 2014; Palm et al., 2017; Volpato et al., 2013), one case series (Thamby et al., 2021), and one comparative study (D'Urso, 2016).

When comparing adjunctive tDCS to sham stimulation in TR-OCD, three RCTs reported a significant reduction in OCD symptoms in the active group (note that treatment resistance was defined as participants to at least have failed 1 trial of SSRI) (Bation et al., 2019; Da Silva et al., 2021; Manche Gowda et al., 2019). Adjunctive tDCS using anodal stimulation of the left pre-SMA and cathodal stimulation of the right OFC produced significant improvements in OCD symptoms compared to sham (Level 3) (Manche Gowda et al., 2019). In another RCT (N = 43), targeting the SMA using monopolar cathodal adjunctive tDCS was also found to result in significant clinical benefit after 12 weeks of treatment (Level 3) (Da Silva et al., 2021). When evaluating the efficacy of adjunctive tDCS using cathodal stimulation of the left OFC and anodal stimulation over the right cerebellum, one RCT (N = 21) reported a significant reduction of OCD symptoms at endpoint compared to sham, though during the 1 and 3-month follow up assessments tDCS was not observed to have significant long-lasting positive effect (Level 3) (Bation et al., 2019). In non-treatment resistant patients, one RCT (N = 60) evaluating adjunctive tDCS using cathodal stimulation at the right OFC and anodal stimulation at the left DLPFC found that tDCS was comparable to sham at endpoint (Level 2, negative) (Yoosefee et al., 2020). Based on the compiled data from these 4 RCTs, in addition to 4 open-label studies (N = 241), a recent meta-analysis found tDCS to significantly improve OCD symptom severity on the Y-BOCS (MD 0.86, 95 % CI 0.61–1.11) (Level 1) (Pinto et al., 2023). Although two other RCTs have been conducted, their ability to evaluate the efficacy of tDCS is limited; one RCT did not report the clinical assessment of OCD symptoms before and after treatment (Yekta et al., 2015) and the other RCT only examined the immediate effect of a single tDCS session after an obsession-provoking stimulus (Todder et al., 2017).

An RCT (N = 20) evaluated the efficacy of tDCS as monotherapy for OCD, using cathodal stimulation at the left OFC or SMA. Results showed no significant improvements in OCD symptoms, though a greater effect was observed in the left OFC group, suggesting it as a target for further investigation (Level 3, negative) (Fineberg et al., 2023). One case report (Alizadehgoradel et al., 2016) in an OCD patient with no current psychotherapy or pharmacotherapy interventions reported that tDCS cathodal stimulation of the left OFC produced significant clinical benefits (Level 4). Another case report using tDCS monotherapy targeting the pre-SMA in a treatment resistant patient found that OCD symptoms worsened with anodal stimulation (Level 4, negative), while an improvement was observed after cathodal stimulation of the pre-SMA (Level 4).

The FEATSOC (Fineberg et al., 2023) study suggests that adjunctive tDCS, while not currently recommended, deserves further study due to portability of treatment and low cost, and that OFC stimulation may be superior to SMA stimulation, but requires continual treatment since effects are not long lasting. Further, while studies showed that tDCS was well tolerated, there were no studies examining safety and tolerability over long-term use (See Table 5a, 5b).

RECOMMENDATIONS FOR tDCS

- ❖ There is no evidence to support tDCS monotherapy (Level 3, negative)
- ❖ Adjunctive tDCS is recommended as a third line treatment for TR-OCD (Level 3)
- ❖ There lacks evidence to support adjunctive tDCS, and therefore it is not recommended for non-TR-OCD (Level 2, negative)

5.1.3. Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) is the most ubiquitously available neurostimulation technique and has established efficacy for severe and refractory mood and psychotic disorders (Ali et al., 2019; Milev et al., 2016). However, the evidence of its efficacy in refractory OCD cases is still limited to case reports/series, case-control, and cohort studies (Fontenelle et al., 2015). In a review of 265 individuals who received ECT for OCD, clinical improvement was reported in 60.4 % of the cases in which individual responses to ECT were available. In this review, the response to ECT was more frequently seen in non-depressed patients, suggesting that the observed improvement may indicate the direct effects of ECT in modulating the CSTC and not simply attributable to the remissions of depressive symptoms, (Fontenelle et al., 2015). Similarly, a recent retrospective study of 21 OCD patients who received ECT yielded 57.1 % responders. Non-responders were more likely to report depressive symptoms and schizophrenia comorbidity, (Lou et al., 2022). There is a relatively low level of evidence (Level 4) for this modality and the current evidence is mixed. ECT may hold promise as a treatment for OCD but requires further study in the form of controlled trials in non-comorbid OCD populations. Risks of ECT include cognitive adverse events and the need for anesthesia.

5.2. Invasive techniques

5.2.1. Surgically invasive interventional treatments for refractory OCD

The following sections will summarize the extant knowledge on the clinical effectiveness and tolerability of two types of invasive techniques: ablative psychiatric neurosurgery (APN) and Deep Brain Stimulation (DBS) for treatment refractory OCD. It should be noted that these techniques are to be used in the most refractory patients with OCD as

these techniques are invasive and can have permanent effects. They should be used as a final resort for patients who have failed a reasonable number of treatments of adequate duration and intensity (including first- and/or second-line medications, an augmentation trial, and an adequate trial of CBT), have a long duration of the disorder (more than 5 years), and have extremely severe symptoms affecting their functioning, quality of life, and causing significant distress. Additionally, the definition of refractory OCD differs between studies, as seen throughout the OCD literature.

5.2.1.1. Ablative psychiatric neurosurgery. The use of APN for refractory psychiatric illness predates the advent of the SRIs (Volpini et al., 2017). There are 4 dominant APNs for OCD that have been described. Namely, capsulotomy, cingulotomy, subcaudate tractotomy, and limbic leucotomy (which is a combination of subcaudate tractotomy plus cingulotomy), with capsulotomy comprising more than 75 % of reported cases in the literature (Davidson et al., 2021). The theoretical basis behind the APNs for OCD is to ameliorate the pathological functional activity in the brain via image-guided surgical destruction of key nodes and structures in the circuits associated with OCD. The surgical techniques that have been employed to create the lesion have included thermocoagulation (Gong et al., 2019), gamma knife radiosurgery (Miguel et al., 2019), and MRI-guided focused ultrasound (MRgFUS) (Davidson et al., 2020).

Although there have not been RCTs using APN, there have been multiple open-label studies and case reports as well as meta-analyses. In a transdiagnostic meta-analysis of psychiatric outcomes pooled from 1414 patients from 43 studies employing the 4 surgeries, APN was associated with a very large effect size on improvement in obsessive-compulsive symptoms (g = 2.25, 95 % CI 1.79–2.71) (Davidson et al., 2021). The magnitude of the improvements seen in OC symptoms were larger than those seen for depression (g = 1.27, 95 % CI 0.94–1.60). The magnitude of effect for OCD was also greater than that for anxiety symptoms, however, given the overlap of confidence intervals, the effect is not significantly different (g = 1.76, 95 % CI 1.24–2.29). Adjusted effect sizes remained very large and statistically significant for OC symptoms after controlling for publication bias (Adjusted Hedge's g = 1.43, 95 % CI 0.92–1.95, p < .0001). Subgroup analyses comparing the clinical effects of the four APN techniques did not find statistical differences in the effect sizes between the types of surgeries for OCD. Another meta-analysis looking at categorical response rates and adverse events found a 55 % response rate (defined as ≥35 % reduction in Y-BOCS scores post-procedure) in a pooled sample of 21 studies with 459 patients who received APN for severe and refractory OCD (Lai et al., 2020). Broken down by APN procedure, the response rates at last follow-up (mean duration 45.4, range 7.6–142.0 months) were 59 % (95 % CI 54–65) for capsulotomy, 47 % (95 % CI 23–72) for limbic leucotomy, and 36 % (95 % CI 23–50) for cingulotomy. Based on this data, the authors concluded capsulotomy to be the most effective of the APN procedures, though the estimate of limbic leucotomy was not significantly different from capsulotomy. Controlled and head-to-head studies are required to definitively establish superiority due to the observational nature of the data.

The pooled total Y-BOCS score decreased from 33.1 (95 % CI 33.0–33.3) at baseline to 18.5 (95 % CI 17.8–19.2) at 12 months post-procedure and 19.3 (95 % CI 18.9–19.7) at last follow-up, demonstrating a durability of the effect in the long-term (Lai et al., 2020). Overall, the reported median incidence of severe or permanent adverse events was 0.5 % (range 0.3–2.3) and the median incidence of mild and transient adverse events was 1.0 % (range 0.3–14.9). The most commonly reported adverse effects were postoperative headache (14.9 % of adverse events), cognitive deficits (9.1 %), and behavior problems (8.1 %), which were transient. 11.6 % of the documented adverse events were classified as severe in nature, including personality changes (2.3 %), cognitive deficits (1.0 %), seizure (0.5 %), and intracerebral hemorrhage (0.3 %).

In two very recent studies, the long term clinical and safety outcomes and the efficacy of magnetic resonance-guided focused ultrasound (MRgFUS) capsulotomy was evaluated in patients with treatment refractory OCD (Level 4) (Chang et al., 2024; Hamani et al., 2024). In one study (N = 15), 67 % of patients were responders (≥35 % Y-BOCS reduction) two years after the procedure, showing decreased anxiety and depression, improved executive functioning, and no cognitive decline (Hamani et al., 2024). Lesion analysis indicated that medial left-sided lesions were associated with a stronger OCD symptom reduction (Hamani et al., 2024). In a longer-term study, patients were evaluated 10 years after MRgFUS capsulotomy, reporting an average 52.3 % decrease in Y-BOCS scores, with 2 of the 10 patients achieving full remission (Chang et al., 2024). In both studies, no serious adverse events were reported, including neurological deficits or suicidality.

Due to the evidence of APN being solely open-label studies, APN has level 4 evidence (Level 4). Overall, there are serious and possibly permanent adverse reactions that need to be discussed and weighed appropriately with the patient before deciding to use such invasive techniques to treat OCD.

5.2.1.2. Deep Brain Stimulation. DBS is a functional neurosurgery, which involves the implantation of electrodes under MRI guidance to discrete targets in the brain. Continuous, non-convulsive stimulation is delivered, powered by a pulse generator implanted under the skin, typically in the chest. The pulse generator also provides the means for the clinician to program the DBS settings, including turning it on or off, increasing the feasibility for RCTs to be performed. This technique requires careful patient selection, accurate placement of the electrode in the planned neuroanatomical target, and adequate programming of the implanted electrodes.

The effects of DBS on OCD have been evaluated in a number of sham-controlled trials and meta-analyses. One meta-analysis reported on 8 RCTs (n = 85) and 38 observational studies (n = 225) (Martinho et al., 2020). In the 8 RCTs included, DBS of the anterior limb of the internal capsule (ALIC) (n = 4 studies), Nucleus Accumbens (n = 2), Ventral Caudate/Ventral Striatum (VC/VS) (n = 1) and the Subthalamic Nucleus (n = 1), was superior to sham (difference in Y-BOCS = 7.8, 95 % CI 4.3–11.2) (Level 2). Receiving active stimulation was associated with a greater likelihood of achieving the Y-BOCS response criterion (51 % active DBS vs. 18 % sham DBS; OR: 2.4, 95 % CI 1.3–4.3). The effect increased when the open-label phases of treatment were added (difference in Y-BOCS at long-term follow-up = 15.0, 95 % CI 11.7–18.3). When the observational data was included, long-term follow-up response rate was 57.9 % and remission rate was 5.4 % at a mean of 33 months post-implantation. Illness severity at baseline was negatively correlated with response rate at long-term follow-up (Spearman p = −0.27, p = .001). Most common adverse events included hypomania/irritability, apathy, depression, and sleep disturbances, with a dropout rate of 0.13 per participant and a rate of 0.32 serious adverse events per participant (Martinho et al., 2020). The high rate of adverse events was attributed to an overrepresentation of transient events. The stimulation parameters found were on average: voltage 4.9 V, frequency 132 Hz, and pulse width 143 ms (Martinho et al., 2020). Another recent meta-analysis examining DBS for OCD in 25 studies found a significant pre-post treatment improvement in Y-BOCS scores (SMD 2.39, 95 % CI 1.91–2.87) (Cruz et al., 2022) (Level 2). Finally, a systematic review and meta-analysis examining the efficacy of DBS for TR-OCD included 34 studies (9 RCTs) (Gadot et al., 2022). At follow up, 66 % of patients were full responders to DBS therapy, and when examining efficacy compared to placebo, DBS was significantly more effective (Y-BOCS MD 13.46, 95 % CI 11.73–15.18) (Level 2). The most frequent non-serious and transient adverse events were hypomania (25.2 %), gastrointestinal upset (5.9 %), and worsening anxiety (5 %). Around 31 % of patients experienced at least one serious adverse event (SAE), with the most relevant being: device-related complications (8 %), postoperative

infection (4.4 %), postoperative seizure (3.6 %), and postoperative intracranial hemorrhage (~1.6 %) (Gadot et al., 2022). While DBS has meta-analytic evidence, it only reaches level 2 evidence due to the wide confidence intervals.

There have been a number of RCTs and large case series which provide further support for both the positive short- and longer-term effects of DBS for OCD. Denys et al. (2020) reported that in a large cohort of 70 patients, there was mean Y-BOCS reduction of 13.5 points (effect size 1.5, SD = 9.4) and 52 % of patients met the response criterion after 12 months of open-label active DBS of the ventral ALIC (Level 4). The most common adverse event was transient hypomania (39 %), which appeared to be independent of OCD response status, occurring in 42 % of responders and 35 % of non-responders (Denys et al., 2020). Long-term improvements were maintained in a report of a subset of 50 patients from this cohort who were on average 6.8 ± 3 years post-DBS (mean reduction in Y-BOCS = 15.2, 95 % CI 12.7–17.6), with a 50 % response rate and 14 % remission rate (Level 4) (Graat et al., 2020). In an independent multi-center study of 30 patients with OCD who received open-label DBS of the ALIC, a mean reduction of 42 % in Y-BOCS with a 60 % response rate was reported at 12 months post-surgery (Level 4) (Menchon et al., 2021). Tyagi et al. compared the effects of Ventral Capsule/Ventral Striatum (VC/VS) DBS and anteromedial Subthalamic Nucleus (amSTN) DBS in 6 patients who received a pair of electrodes in both targets (Level 4) (Tyagi et al., 2019). Patients entered a double-blind phase of 12 weeks of VC/VS or amSTN DBS, followed by an open-label 12-week phase of simultaneous VC/VS and amSTN stimulation (Level 4). Both VC/VS and amSTN significantly improved OCD symptoms to equal degrees and there was no added benefit of stimulation with the combined targets. The authors noted that VC/VS stimulation had a greater antidepressant effect.

More recently, the results of a RCT of DBS to the Bed Nucleus of the Stria Terminalis (BNST) was published (Level 4) (Mosley et al., 2021). The authors report a greater reduction in Y-BOCS scores in the blinded phase for those receiving active DBS compared to sham (MD 4.9 points, 95 % CI 0.8–8.9; p = .025). Following the double-blind period, at the end of the 1 year open-label period, the mean Y-BOCS reduction was 17.4 points and 7 of 9 participants were responders. Further replication is needed, but these promising results provide support for DBS for OCD (Level 4) (Wu et al., 2021).

5.2.1.2.1. Comparison of APN and DBS. In a recent meta-analysis comparing DBS to APN for patients with refractory OCD, comparable rates of efficacy were demonstrated between these two approaches. In an analysis of 38 studies, including 253 cases of DBS and 444 cases of APN, Hageman reported OCD response rates of 53 % and 48 % after 12–16 months, and 57 % and 56 % at follow-up for DBS and APN, respectively (Hageman et al., 2021). Meta-regression analyses combining all data to identify moderator variables related to outcome found that superior outcomes were associated with shorter duration of illness, younger age at the procedure, and lower baseline Y-BOCS score, irrespective of the technique employed (Hageman et al., 2021).

Comparing adverse events between these two surgical approaches, DBS was associated with statistically higher rates of impulsivity, agitation, and disinhibition than APN (16.7 vs. 2.6 per 100 patient years, p < .05) (Hageman et al., 2021). Higher rates of mania/hypomania (9.8 versus 2.7 % of sample, p = .055) and post-operative infection (5.2 versus 0.7 % of sample, p = .062) with DBS approaching near statistical significance. In a meta-analysis comparing the effects of APN to DBS on measures of quality-of-life derived utility scores, Kumar et al. reported a superiority of APN (difference of 0.022 quality adjusted life years), driven by the lower complication rates associated with APN and the fact that it is often an "one and done" surgical procedure, whereas DBS requires longer-term management of the device and replacement of the hardware (Kumar et al., 2019).

Taken together, the above suggests that both DBS and APN have comparable and durable long-term effects in ameliorating OCD, but DBS can be associated with treatment emergent hypomanic symptoms, although they are reversible after adjusting the stimulation parameters. However, due to the nature of these procedures and most notably the greater ease to conduct sham-controlled studies of DBS than APN, DBS has a higher degree of evidence, although APN seems to be associated with potentially better overall quality of life. Additionally, the meta-analyses for both APN and DBS are associated with low or very low GRADE ratings, primarily due to the lack of RCT evidence and blinding measures, most notably for APN, which limits the conclusions that can be made about either technique or their comparison. The clinical recommendation is that in the absence of any defined clinical or biological markers of response, the decision to choose APN or DBS should take into account that DBS is reversible and adjustable in its parameters; additionally, it should incorporate other ancillary factors including the availability of each procedure, the presence of baseline impulsivity or risk factors for bipolar spectrum illness, patient preference, the ability of the patient to maintain long-term engagement with the treating team, and the treating team's expertise with the surgical and psychiatric management of patients receiving these procedures.

5.3. Conclusion

This review of neuromodulation in OCD suggests that interventional approaches for treatment refractory OCD are efficacious, largely well-tolerated, and supports their ongoing use for patients not responsive to adequate trials of evidence-based pharmacotherapy and psychotherapy. The most robust evidence is for rTMS and DBS, supported by data from RCTs, meta-analyses, and controlled studies. Given the comparable response rates reported in the literature for rTMS, DBS, and APN, it can be hypothesized that each of these interventional approaches to OCD may be affecting similar changes to an OCD circuit, while differing in

Table 5a
Levels of evidence and lines of treatment for transcranial direct current stimulation (tDCS).

Treatment	Cathode	Anode	Current and Duration	Number of Sessions	Level of Evidence	Line of Treatment
Monotherapy tDCS in non-TR-OCD	**Left OFC or SMA**	**Right deltoid**	**2 mA for 20 min**	**4**		**unable to make recommendation**
Adjunctive tDCS in non-TR-OCD	**Right OFC**	**Left DLPFC**	**2 mA for 20 min**	**24**		**not recommended**
Adjunctive tDCS in TR-OCD	Left OFC	Right Cerebellum	2 mA for 20 min	10		third line
	Right OFC	Left pre-SMA	2 mA for 20 min	10		third line
	SMA	Left deltoid	2 mA for 30 min	20		third line

tDCS - transcranial Direct Current Stimulation; OFC - Orbitofrontal Cortex; SMA - Supplementary Motor Area; DLPFC - Dorsolateral Prefrontal Cortex; TR-OCD - Treatment resistant OCD.

Table 5b
Levels of evidence and lines of treatment for neurostimulation or neuromodulatory techniques in treatment resistant OCD.

Treatment Refractory OCD		
Technique	Level of Evidence	Line of Treatment
Electroconvulsive therapy (ECT)		third line
Ablative Psychiatric Neurosurgery (APN) (capsulotomy, cingulotomy, subcaudate tractotomy, limbic leucotomy)		third line
Deep Brain Stimulation (DBS)		third line
DBS at Bilateral ALIC (100–125 Hz)		third line
DBS at Bilateral STN (130 Hz)		third line
DBS at Bilateral Nacc (123–130 Hz)		third line
DBS at Bilateral VC/VS (115–133 Hz)		third line
DBS at Bilateral ALIC/Nacc (130–145 Hz)		third line
DBS at Bilateral BNST (130 Hz)		third line

Key Points
- Neuromodulation modalities for TR- OCD are efficacious, well-tolerated, and their use is supported for patients non- responsive to adequate trials of evidence-based pharmacotherapy and psychotherapy.
- The most robust evidence is for rTMS and DBS, supported by data from RCTs, meta-analyses, and controlled studies.
- Evidence for rTMS and dTMS is strongest for non-TR-OCD and should be used earlier in the treatment algorithm, (Fig. 1).
- Adjunctive tDCS is supported by Level 3 evidence in TR-OCD only.
- Given the comparable response rates reported in the literature for rTMS, DBS, and APN, each of these interventional approaches to OCD may be affecting similar changes to the OCD circuit, while differing in their degree of neuroanatomical invasiveness.
- Non-invasive options should be considered first among the interventional approaches, before progressing to the more invasive procedures.

RECOMMENDATIONS FOR APN AND DBS

- APN (Level 4) and DBS (Level 2) are recommended for treatment-refractory* OCD patients only as a third line treatment
- DBS may have more side effects than APN, but these were collected prospectively rather than retrospectively and may be reversible

ALIC - Anterior Limb of the Internal Capsule; STN - Subthalamic Nucleus; Nacc - Nucleus Accumbens; VC/VS - Ventral Caudate/Ventral Striatum; BNST - Bed Nucleus of the Stria Terminalis.
*Treatment refractory refers to the highest level of treatment resistance where patients do not respond to all available treatments, including three or more SRIs, as well as SRI augmentation with clomipramine and/or cognitive behavioural therapy (Fineberg et al., 2015).

their degree of neuroanatomical invasiveness. Non-invasive options, such as rTMS, may exert its effects at the cortical nodes of this circuit, whereas invasive surgical options are needed to target deeper subcortical structures which are inaccessible from direct influence by rTMS (Li et al., 2021). However, with regard to DBS, patients should be thoroughly informed of the pros and cons of this modality, including higher rates of adverse events and lower quality of life compared to APN.

In the absence of definitive clinical predictors of response or biomarkers to guide treatment selection, a stepwise approach is recommended. Non-invasive options should be considered first among the interventional approaches, before progressing to the more invasive procedures. The preponderance of the data supports the durability of the long-term positive clinical effects of DBS and APN. DBS has support from RCTs targeting the ALIC and BNST, although it has been associated with the emergence of transient hypomanic symptoms (Denys et al., 2020; Gadot et al., 2022; Martinho et al., 2020). APN of the ALIC has comparable response rates to DBS in meta-analytic studies (Hageman et al., 2021); however, APN currently lacks positive sham-controlled studies. Although the evidence is currently lacking to routinely recommend ECT for OCD, this treatment should be considered for patients with OCD with comorbid features such as mood disorders with psychosis, suicidality, and catatonia to specifically target these ECT responsive symptoms.

With further dissemination and greater availability of these therapeutic options, their delivery would ideally be provided as a dedicated interventional OCD care pathway within centers with expertise in the delivery of both non-invasive and invasive treatment options. The advantages of establishing an interventional care pathway model for refractory OCD would be to reduce the delay between treatments, to provide prospective and longitudinal assessment of the clinical features of an individual's OCD and comorbidities, and to progressively move patients through a series of treatments to help them achieve their optimal outcome.

5.3.1. *Treatment of adult obsessive-compulsive disorder*

6. Children and adolescents

6.1. *Clinical presentation*

The DSM-5 criteria for OCD are essentially the same in children and adolescents as they are in adults, however, there are important developmental differences in the typical symptom presentation in younger individuals. Children may be more likely to present with compulsions alone (Swedo et al., 1989), as obsessions are less prominent in younger children versus adolescents or adults (Selles et al., 2014). As noted in the DSM-5, young children may not be able to articulate the aims of compulsions, and in a substantial subgroup of children, compulsions are driven by a need to relieve a sense of unease or discomfort rather than responding to cognitive obsessions (Geller et al., 2021). Poor insight has been conventionally thought to be more typical of pediatric vs. adult OCD; however, a recent meta-analysis of a large sample of children and adolescents found that 89 % of participants had fair to excellent insight, but, as in previous studies, younger age was associated with poorer insight (Selles et al., 2018) (See Fig. 2).

OCD typically begins early in life. Some studies report the age of onset as a bimodal pattern, often with the first peak of incidence around age 10 and a second peak in the early 20s (Geller et al., 2021; Taylor, 2011); however, other studies have reported steady increases in incidence with age, with most cases presenting before 30 years old (Fineberg et al., 2013; Solmi et al., 2022). Regardless, multiple studies have identified that there is a higher proportion of males in populations of early onset OCD versus late onset OCD (Taylor, 2011). Earlier age at onset has been associated with an increased rate of OCD in first-degree relatives (Delorme et al., 2005; do Rosario-Campos et al., 2005; Nestadt

et al., 2000). However, family segregation was found to be high but independent of the age of onset in all patients with OCD in a nationwide three generation study (Steinhausen et al., 2013). For further information on the age of onset please see the Principles of Management Section (Section 2).

6.1.1. Family Accommodation

While family accommodation (FA) in the management of OCD in children and youth may provide temporary relief, it ultimately reinforces the OCD symptoms (Peris et al., 2008). Parental engagement in the child's OCD symptoms undermines the principles of CBT and ERP by preventing the fear extinction learning and habituation to anxiety required to overcome obsessional fears and compulsions. A recent comprehensive meta-analysis (Hermida-Barros et al., 2024) found moderate levels of FA in pediatric OCD cohorts and a positive correlation between FA and OCD severity, but baseline FA did *not* predict pre-to post-treatment change in OCD severity. FA decreased with both individual and family-focused cognitive behaviour therapy (Hermida-Barros et al., 2024).

6.1.2. Comorbidity in children

Comorbidity in children and adolescents with OCD is the rule rather than the exception. In a recent systematic review of comorbidity of OCD, 64 % of pediatric patients had at least one concurrent disorder (Sharma et al., 2021). Anxiety disorders are the most common co-occurring disorders in children and adolescents (mean 31 %, range 13 %–70 %) (Geller et al., 2000). Major depressive disorder is also relatively common in pediatric populations (17 %), though less so than in adult samples (40 %). Comorbidity with neurodevelopmental disorders, particularly tic disorders and ADHD, is also high, particularly in males. There is an increased rate of both OCD and tic disorders in the first-degree relatives of OCD probands with a family lifetime history of tics or OCD (Nestadt et al., 2000) and an increased frequency of tic disorders in the first-degree relatives of OCD probands compared to controls (Grados et al., 2001). It has been suggested that tic disorders are an alternative expression or phenotype of the familial OCD subtype (Grados et al., 2001). Furthermore, these children also seem to express a familial transmission triad of OCD, tic disorder, and ADHD (Leckman et al., 2010).

In patients with comorbid Tourette Syndrome (TS) and OCD there is a particular pattern of tic-related OCD symptoms that include symmetry obsessions and counting, “just right”, repeating, ordering, and arranging compulsions. For both diagnostic and treatment reasons, DSM-5 includes a tic-related specifier for individuals with OCD who have a current or past tic disorder.

Comorbidity with ADHD is also relevant, especially in children with OCD. A review of the literature reveals notable differences in ADHD-OCD co-occurrence rates reported in youth versus adult samples. Considerably higher co-occurrence rates are found in youth samples (unweighted mean = 19 %) relative to adult samples (unweighted mean = 9 %) (Abramovitch et al., 2015). Neurobiological similarities of OCD and ADHD are discussed in several reviews (Brem et al., 2014; Colzato et al., 2022).

Hoarding, saving, and collecting rituals affect up to 25 % of youth with OCD. These youth show more frequent obsessions and compulsions across a broad range of dimensions and higher rates of tic disorders and indecision (Højgaard et al., 2019). In a recent study, CBT treatment response was not adversely impacted by hoarding symptoms in youth (Højgaard et al., 2019). Moreover, unlike in adults, there is no evidence that hoarding in youth is linked to a more severe clinical picture or higher functional impairment (Rozenman et al., 2019).

Multiple studies employing factor or cluster analysis of OCD symptoms have suggested that OCD is a heterogeneous condition with multiple subtypes or “dimensions” such as contamination, symmetry, or forbidden thoughts. However, the results of these studies have been inconsistent, and the validity of these dimensions has been questioned (Cameron et al., 2019). More meaningful symptom structures may be identified by a recent network analysis of symptoms (Cervin et al., 2021) and may prove useful for subtyping subjects for treatment trials and translational investigation using genetic or other approaches (Cervin et al., 2021; Strom et al., 2021).

6.2. PANDAS/PANS

A subtype of OCD has been described in the literature that begins in childhood or adolescence and is characterized by an acute and dramatic onset of OCD with a putative post-infectious, immune-mediated onset and inflammatory pathophysiology (Swedo et al., 1998). Originally this subtype was linked with group A beta-hemolytic streptococcal infections (GABHS), which had led to the subtype designation of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS). This designation has since been broadened to include other infections, and potentially other non-infectious causes, leading to the designation Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) (Swedo et al., 2012). Cases of PANS are defined as a clinical syndrome by sudden onset and rapid escalation of OCD symptoms or severely restricted food intake, in addition to two other neuropsychiatric symptoms from the following categories: (1) anxiety, (2) emotional lability, (3) aggression-irritability or oppositional behavior, (4) behavioral (developmental) regression, (5) deterioration in school performance, (6) sensory and motor abnormalities including new onset of motor tics, and (7) somatic signs and symptoms including sleep problems, enuresis, or urinary frequency (Swedo et al., 2012). Nosological validity of these entities remains controversial (Gilbert et al., 2018; Kurlan et al., 2008) and there are no validated diagnostic biomarkers. Recent studies point to significant methodological heterogeneity and a lack of robust replication of initial immunological findings despite some supporting evidence from animal (Yaddanapudi et al., 2010) and epidemiological (Orlovska et al., 2017) studies. Recent reports from one group have identified antibody binding to striatal anticholinergic interneurons with changes in these interneurons’ activity (Frick et al., 2018; Xu et al., 2021). PANDAS/PANS may represent just one example of a broader class of immune- or inflammatory-mediated neuropsychiatric illness (Brown and Meyer, 2018) but much work remains to be done to understand and validate these disorders as subtypes of pediatric OCD with a specific etiology.

6.3. Measuring symptom severity in youth

6.3.1. OCD symptoms

A number of clinician-rated and self-report scales can be used to assess OCD symptoms in youth and to monitor response to treatment over time (Tables 6–1). The gold standard measure for assessing OCD symptoms in youth and monitoring treatment response over time is the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (Scahill et al., 1997), a 10-item severity scale administered as a semi-structured interview. The total score ranges from 0 to 40, with scores ≥30 indicating severe illness (Cervin et al., 2022). Although the CY-BOCS Total Severity score has demonstrated sensitivity to evidence-based treatments (either pharmacotherapy or CBT) (Rapp et al., 2016), the CY-BOCS-II was recently developed to address some of its limitations, specifically its non-linear scalar characteristics and the heavily weighted resistance and control scores. Initial evaluation of the CY-BOCS-II in a small sample of children and adolescents (n = 102) suggested that it has strong psychometric properties (Storch et al., 2019) and it is likely that the CY-BOCS-II will ultimately replace the CY-BOCS as the core clinician measure of OCD severity. There are multiple self- or parent-report symptom measures for OCD in children and adolescents (Tables 6–1). While these measures have been studied as potential screening measures, they are not a substitute for a thorough clinical diagnostic evaluation (Tables 7a, 7b, 6b).

6.3.2. Other measures

Clinicians may also consider including additional measures to assess family accommodation, functional impairment, and quality of life. The Child Obsessive-Compulsive Impact Scale-Revised (COIS-R) may be useful for measuring functional impairment related to OCD across multiple domains (Piacentini et al., 2007). Family functioning is frequently disrupted by children within the nuclear family unit and can be assessed by the OCD Family Functioning scale, measuring how families accommodate their child's OCD symptoms (Stewart et al., 2017). Family accommodation measures include Family Accommodation Scale for Obsessive-Compulsive Disorder – Interviewer-Rated (FAS-IR) (Calvocoressi et al., 1999) and the Family Accommodation Scale for Obsessive-Compulsive Disorder – Self Rated Version (FAS-SR)/Patient Rated Version (FAS-PR) (Pinto et al., 2013).

6.4. Treatment of pediatric OCD

6.4.1. Disorder- and context-related treatment considerations

Comprehensive psychoeducation for children and adolescents as well as their parents or caregivers should take place at the beginning of treatment using understandable and age-appropriate language and can be supported by written information. Caregivers should be motivated to positively support the treatment and understand the influence of their own behavior on OCD symptoms in their children. In addition, children and adolescents are infrequently affected only by OCD. Often youth suffer from comorbid disorders that also require parental support and treatment intervention. In such cases, each disorder should be treated according to guidelines promulgated for that specific illness. Exposure treatment should also be provided in the child's natural environment, i.e. in a home setting with structured “homework” assignments, under the guidance of a clinician.

6.4.2. Early treatment initiation

Based on previous follow-up outcome studies, early detection and initiation of treatment were the most important positive prognostic factors (Walitza et al., 2020). There is little empirical data addressing the issue of optimal treatment intensity and duration. Most well-controlled studies on treatment report active treatment periods of approximately 12–14 weeks (Level 1●) (Sanchez-Meca et al., 2014; Skarphedinsson et al., 2015a).

CBT/ERP and SSRIs are both highly effective according to meta-analyses, umbrella, and systematic reviews (Level 1●) (Cervin et al., 2023; Correll et al., 2021; O'Kearney et al., 2006; Uhre et al., 2020). While CBT is often recommended as the first-line intervention, SSRIs may also be introduced early in treatment either alone as initial treatment or in combination with CBT (see Section 6.4.6 for combination therapy)(Level 1●). There are several reasons why CBT may be preferred as the initial stand-alone treatment including its generally high acceptability with both youth and parents, robust effect sizes with high fidelity ERP, and concerns regarding potential medication adverse events. However, reports from the one-year Nordic Long Term OCD Treatment Study (NordLOTS) showed that one third of youth did not meaningfully engage with CBT (Torp et al., 2015). Therefore, medications which are also effective and do not differ statistically from CBT as sole treatments in the most careful meta-analytic studies are a reasonable first treatment option. Several RCTs have found both SSRI and CBT groups had a reduction in OCD symptom severity, with no significant difference between the groups (Level 2◔) (Asbahr et al., 2005; Fatori et al., 2018; Pediatric OCD Treatment Study (POTS) Pediatric OCD Treatment Study Team, 2004). Choices are to some degree determined by parental (and youth) preferences, the availability of skilled CBT therapists locally (less limiting with remote telehealth CBT providers), and the need to address concurrent psychiatric illness. Reasons to consider early treatment with medication include severe OCD symptoms, comorbid major depression or other mood disorder, multiple concurrent anxiety disorders, chronic tic disorders exacerbated by anxiety, and limitations imposed by other practical difficulties accessing CBT. Recommendations regarding pharmacotherapy initiation are found below.

Given that the number of total CBT hours appears to have a significant impact on effect size, as does the rigor and fidelity of CBT interventions (Sanchez-Meca et al., 2014), we recommend treatment of at least 12–14 weeks of weekly CBT in standard outpatient settings (expert consensus, Level 4◔) but note that brief and intensive outpatient treatment programs (IOP) may be equally effective according to studies reported for adults with OCD and preliminary studies in children and adolescents (Level 3◐) (Wolters et al., 2021). Abbreviated standardized CBT approaches (10 visits with 7 active ERP sessions) have also shown strong efficacy (Level 2◔) (Storch et al., 2016).

6.4.3. Defining treatment response and remission

There has been no universal definition of remission in treatment trials for children. In 3 of 12 studies examined in one meta-analysis (Kotapati et al., 2019), remission was defined as a total CY-BOCS score $\leq$11 at the end of treatment. Response criteria for the CY-BOCS have also differed across treatment studies, with scale score reduction rates varying from 25 % to 40 % (Level 1●) (Kotapati et al., 2019). A recent meta-analysis and systematic review of 21 RCTs (N = 1234) examining treatment response and remission in pediatric OCD used a two-stage, random-effects meta-analysis model to identify the optimal cutoff for remission was a post-treatment CY-BOCS score of $\leq$12 (sensitivity 82 %, specificity 85 %) plus Clinical Global Impression - Improvement (CGI-I) scale score of $\leq$2 (much or very much improved). They found the optimal cutoff for response was a 35 % CY-BOCS reduction from baseline to post-treatment (sensitivity 84 %, specificity 82 %) plus a CGI-I scale score of $\leq$2 (much or very much improved) (Level 1●) (Farhat et al., 2021).

6.4.4. Cognitive behavioural therapy for OCD in children and adolescents

Cognitive behavioural therapy (CBT) with exposure and response prevention (ERP) is the first-choice psychotherapeutic treatment for children and adolescents diagnosed with OCD (Level 1●). However, when interpreting this literature, it is important to note that the use of waitlist controls as comparators contrasts markedly with the rigorous participation requirements of medication trials (which may enhance placebo response and thus diminish effect sizes). Several meta-analyses have clearly indicated the high efficacy of CBT for pediatric OCD (Cervin et al., 2023; Sanchez-Meca et al., 2014; Skarphedinsson et al., 2015a; Uhre et al., 2020). One meta-analysis (Uhre et al., 2020) included 5 trials comparing CBT with waitlist control, 4 trials comparing CBT and placebo (relaxation techniques or pill placebo), and 3 trials comparing CBT with SSRIs (see section below). Compared with waitlist control and placebo, CBT significantly reduced OCD severity (Level 1●). Efficacy of CBT with ERP is particularly well-founded on methodologically strong and qualitatively good meta-analyses, reviews, and controlled randomized trials (e.g. Pediatric OCD Treatment Study (POTS) Pediatric OCD Treatment Study Team, 2004) (Level 1●). For example, standardized protocol-driven individualized CBT was found to be significantly more effective than waitlist and placebo conditions in a meta-analysis (Level 1●) (Skarphedinsson et al., 2015a). However, CBT monotherapy was equal in efficacy to other active control conditions including SSRIs and modifications of CBT such as abbreviated CBT protocols, intensive individual CBT, group-based CBT, and family-based CBT (Level 1●). This meta-analysis also showed comparable, non-significantly different efficacy of combined treatment (SSRI + CBT/ERP) compared to CBT monotherapy (Level 1●). Another meta-analysis (Sanchez-Meca et al., 2014) reported an effect size of d = 1.704 for combined CBT + medication treatment, d = 1.710 for CBT alone, and d = 0.745 for medication alone, showing that combination treatment and CBT alone were better than medication alone (Level 1●),

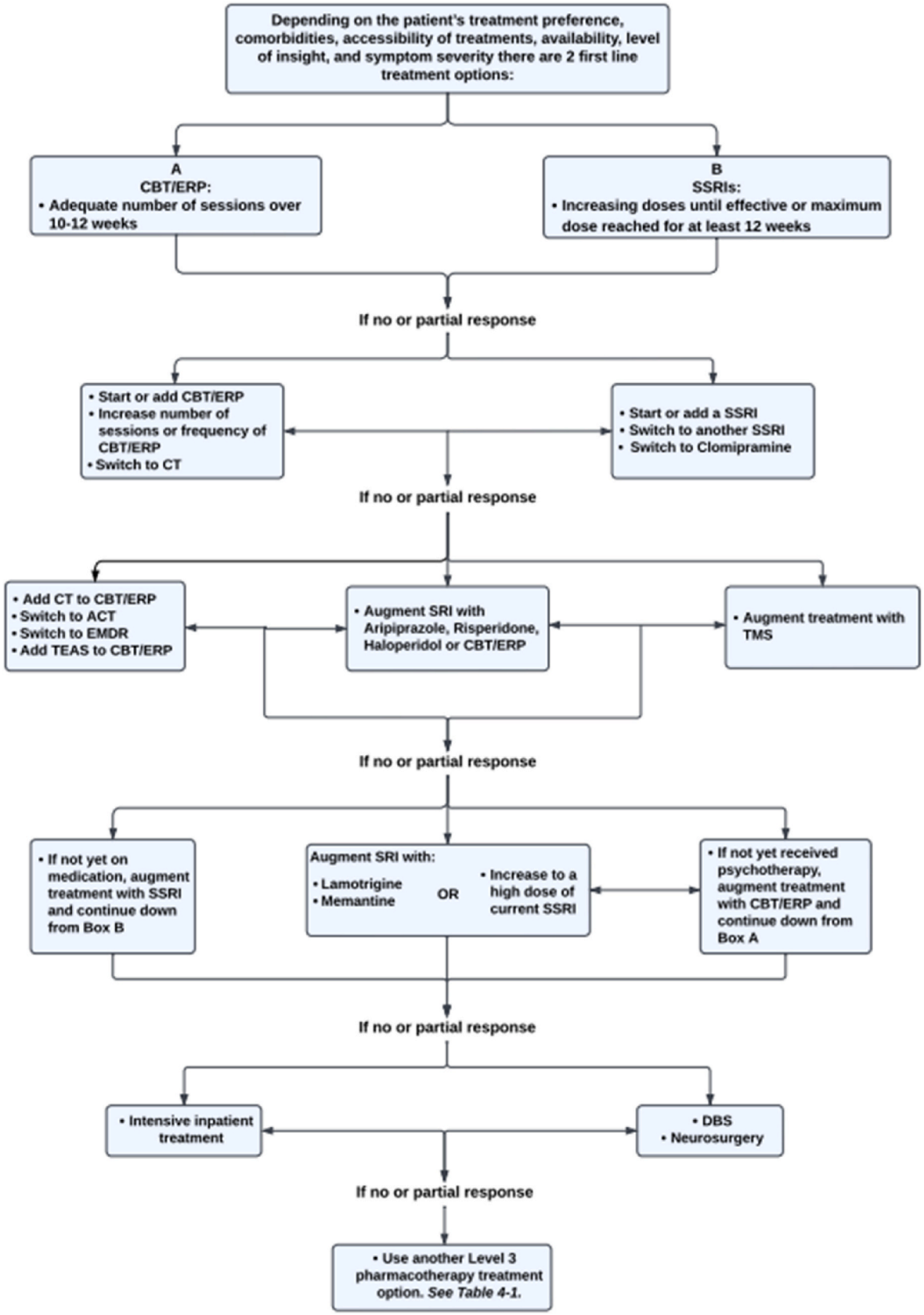

Fig. 1. Algorithm for Adult OCD treatment: One or more treatment options in each box can be tried before moving to the next step/box. ACT = Acceptance and Commitment Therapy; CBT/ERP = Cognitive Behavioural Therapy with Exposure and Response Prevention; CT = Cognitive Therapy; DBS = Deep Brain Stimulation; DLPFC = Dorsolateral Prefrontal Cortex; dTMS = deep Transcranial Magnetic Stimulation; EMDR = Eye Movement Desensitization and Reprocessing; rTMS = repetitive Transcranial Magnetic Stimulation; SMA = Supplementary Motor Area; SSRI = Selective Serotonin Reuptake Inhibitor.

with no difference in efficacy of combination and CBT monotherapy treatment (Level 1). Furthermore, CBT significantly reduced co-occurring depression, anxiety, and psychosocial functional impairment (Sanchez-Meca et al., 2014). However, the conclusions of this meta-analysis are limited due to the study having no risk of bias assessment or discussion of the impact of the risk of bias, reducing the trustworthiness of the findings. A recent network meta-analysis (Cervin et al., 2023) found in-person CBT did not significantly differ from SRIs (MD 3.07, 95 % CI -0.07-6.20) or combined treatment (in person CBT + SRIs) (MD -1.20, 95 % CI -5.29-2.91), but was significantly more efficacious than waitlist (MD 11.10, 95 % CI 8.97–13.23) and pill placebo (MD 7.66, 95 % CI 4.25–11.06) as well as various other psychotherapeutic modalities (Level 1) (Cervin et al., 2023). The one- and three-year NordLOTS studies provide a semi-structured, flexible, expanded CBT protocol using booster sessions based on clinical need that should be considered an updated standard of care for youth with OCD, beyond initial protocols (Højgaard et al., 2017). Of note, inherent in psychotherapy literature is a lack of blinding due to the nature of psychotherapy delivery.

6.4.4.1. Efficacy and effectiveness of CBT and fCBT (family-based CBT). Several small RCTs and non-RCTs have studied family-based CBT (fCBT) in children and adolescents, however, few allow for a strong conclusion of the efficacy of fCBT in comparison to other treatments with no family involvement, as treating pediatric OCD will always include at least some familial involvement, especially for young children. The efficacy of fCBT is seen in a study of very young patients aged 3–8 years (Lewin et al., 2014), with the experimental group (n = 17) receiving 12 sessions of CBT/ERP with intensive family involvement over 6 weeks compared to a control group receiving treatment as usual (n = 14). The authors found a significant reduction in obsessive-compulsive symptomatology (d = 1.69) with high stability over a 3-month period (Level 4). Another controlled study (Piacentini et al., 2011) compared outcomes between children and adolescents aged 8–17 years with a primary OCD diagnosis receiving treatment for 14 weeks of CBT/ERP with structured family intervention (n = 49) to a control group receiving psychoeducation and relaxation training (n = 22) with parental review and discussion for the last 15 min of every session. The differences between the treatment and control groups in this study were not significantly different, showing a non-superiority of fCBT (p = .14) (Level 2, negative) (Piacentini et al., 2011). Methodological limitations in control groups for these two small controlled studies (Lewin et al., 2014; Piacentini et al., 2011), especially that some parents in control groups were receiving some parent-oriented intervention (parent management training, psychoeducation), limits the utility of these studies as a basis for whether to recommend fCBT. In a larger study, one hundred forty-seven children aged 5–8 years were randomized to either family-based CBT or family-based relaxation therapy (Freeman et al., 2014). After 14 weeks of treatment, remission was observed in 72 % of patients in the fCBT treatment group and 41 % in the relaxation group, with a moderate between-group effect size of 0.84 (95 % CI 0.62–1.06) (Level 2). This study indicates that family-involved CBT is more effective than family-involved relaxation training. Several small case series and open trials have shown large effect sizes of fCBT ranging from 2.13 to 2.56 (Farrell et al., 2010; Ginsburg et al., 2011; Storch et al., 2010a), including one study (Storch et al., 2010) seeing this large of an effect when delivering intensive fCBT (14 sessions in 3 weeks) (Level 4).

In a meta-analysis, it was concluded that there were larger mean effect sizes for included studies with moderate to high parental involvement (d = 2.195 and 2.044, respectively) compared to those with low parental involvement (d = 1.308) (Sanchez-Meca et al., 2014). The authors noted that this conclusion should be interpreted with caution due to the low number of studies (N = 8) included in the analysis, and additionally, the quality of the meta-analysis has some concerns as it lacks a risk of bias assessment or discussion of how the risk of bias in the included studies affects the analysis and conclusions. Overall, family-based CBT has several RCTs and open studies showing efficacy (Level 2) (Sanchez-Meca et al., 2014) and parental involvement should be encouraged for most patients whenever possible, despite two studies that show no effect of parental "dose" (Level 1) (Reynolds et al., 2013; Rosa-Alcazar et al., 2019).

A preliminary treatment option that has shown efficacy in pediatric anxiety disorders is the "Supportive Parenting for Anxious Childhood Emotions" (SPACE) Program. In contrast to child-oriented CBT/ERP, exclusive support of parents is the focus of SPACE. SPACE works entirely through parents (by reducing family accommodation) and does not require *any* direct child participation, making it feasible to implement even when a child cannot or will not collaborate with treatment. A recent randomized controlled trial (Storch et al., 2024) included a large proportion of primary OCD cases (~50 %) and found outcomes for OCD specifically that are comparable to those that have been reported in trials of ERP (Level 4). Data from completed but unpublished RCTs further support the efficacy of SPACE for anxiety and OCD and show outcomes comparable to CBT/ERP (Gee et al., 2024).

6.4.4.2. Efficacy of CBT in a group setting. Very few studies of low

Table 6a
Pediatric OCD outcome measures.

Scale	Indication	Number of Items/ Comments
Observer-Rated		
Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (Scahill et al., 1997)	OCD symptom inventory and severity	Symptom checklist + 10 item severity rating Additional items for Insight, Avoidance, Indecision, Pathological Responsibility, Slowness, and Pathological Doubt that are not used in total score
Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) II (Storch et al., 2019)	OCD symptom inventory and severity	Symptom checklist + 10 item severity rating Additional items for Insight, Avoidance, Indecision, Pathological Responsibility, Slowness, and Pathological Doubt that are not used in total score
Self-Rated		
Obsessive Compulsive Inventory-Child Version (OCI-CV-R) (Abramovitch et al., 2022)	OCD symptom inventory and severity	21 item severity rating Scores ≥6 show 86 % sensitivity and 76 % specificity with OCD diagnosis
Children's Florida Obsessive-Compulsive Inventory (C-FOCI) (Storch et al., 2009)	OCD symptom presence and severity	17 item symptom checklist + 5 item severity rating for each (if applies) Developed as a brief screening tool
Children's Obsessive-Compulsive Inventory-Revised (ChOCI-R) (Uher et al., 2008)	OCD symptom presence and severity	20 item symptom ratings + 12 item impairment rating. Pearson's correlation with CY-BOCS r = 0.55
Child Assessment of Beliefs Scale, parent- and child-report versions (Eisen et al., 1998)	A measure of insight based on the adult Brown Assessment of Beliefs Scale (BABS) adapted for pediatric use	5 item Likert severity scale (0 = good insight, 4 = no insight)
Toronto Obsessive-Compulsive Scale (Lambe et al., 2021; Park et al., 2016)	OCD Symptom Inventory and Severity	21 item severity rating Both parent and self-report versions available Symptoms count scores ≥2 show 87 % sensitivity and 93 % specificity with OCD diagnosis

Table 6b
Lines of treatment and levels of evidence for psychotherapy treatments in pediatric OCD.

Intervention	Level of Evidence	Line of Treatment
Cognitive Behavioural Therapy with Exposure Response Prevention (CBT/ERP)	●	first line
Family-based CBT (fCBT)	◔	first line
Group CBT	◐	second line
Webcam-delivered CBT	◐	second line
Internet-delivered CBT (ICBT)	◔	second line
Telephone-delivered CBT	◔	second line

RECOMMENDATIONS FOR PSYCHOTHERAPY IN PEDIATRIC OCD

- ❖ CBT with ERP, in person, is the first line psychotherapeutic treatment (Level 1●).
- ❖ Family involvement in CBT is recommended as first line treatment (Level 2◔).
- ❖ A typical course of CBT is 12–14 weekly sessions, in outpatient settings (Level 4◴).
- ❖ Internet, telephone (Level 2◔) or webcam (Level 3◐) delivered CBT are second line alternatives.

CBT = Cognitive Behavioural Therapy; ERP = Exposure Response Prevention; SSRI = Selective Serotonin Reuptake Inhibitor.

methodological quality are available on the efficacy of CBT in a group setting for youth. A randomized study compared individual family-based CBT (n = 24), group family-based CBT (n = 29), and waitlist (n = 24) for children and adolescents with OCD (Barrett et al., 2004). Both CBT conditions were significantly more efficacious than waitlist control ($p < .001$) and were not significantly different from each other (Level 3◐). The reduction of OCD symptom severity was maintained in both groups at the 6-month follow up. In a randomized study of 40 children and adolescents with OCD comparing group CBT with sertraline, both treatment regimens showed significant improvement with no significant differences in efficacy between treatments (Level 3◐) (Asbahr et al., 2005). In an open study of children 6–17 years (N = 43), all participants received group CBT/ERP and had a significant improvement in OCD symptom severity as assessed by both the Y-BOCS and Dimensional Y-BOCS (DY-BOCS) (Level 4◴) (Olino et al., 2011). A pilot study (N = 43) evaluating group family-based CBT (including a mix of both child group and parent group sessions) found a 45 % decrease in CY-BOCS scores pre-to post-treatment ($d = 0.92$, $t(37) = 5.93$, $p < .01$), with 60.5 % of participants responding to treatment (Level 4◴) (Farrell et al., 2012). Overall, the evidence for group CBT in children and adolescents is Level 3 (◐).

6.4.4.3. Technology-delivered remote CBT treatment. Several RCTs report the outcomes of technology-assisted CBT for children and adolescents with OCD, with substantial heterogeneity in the type of technique used. A randomized pilot trial compared video-teleconferencing (VTC)-delivered family-based CBT (fCBT) and clinic-based fCBT in 22 children 4–8 years old with OCD (Comer et al., 2017). Both groups had a significant reduction in CY-BOCS scores at post-treatment and the 6-month follow up, with no significant differences between the groups ($p = .09$) (Level 3◐). In a waitlist-controlled study (Storch et al., 2011), webcam-delivered CBT was superior to no intervention in reducing OCD symptoms in children and adolescents ($d = 0.82$) (Level 4◴). A recent RCT compared webcam/videoconference CBT (n = 30) to waitlist controls (n = 30) in youth and showed a robust response to webcam intervention (Level 4◴). The discontinuation rate in waitlisted youth was 30 % compared to only 7 % in the webcam group (Hollmann et al., 2022). Finally, an RCT with 72 adolescents with OCD comparing telephone CBT and in-person CBT reported that telephone CBT was similar in efficacy to in-person CBT and that their results were maintained at the 12-month follow-up (Level 2◔) (Turner et al., 2014).

Internet-delivered CBT (ICBT) provides CBT guidelines which are often self-directed but sometimes include therapist involvement. In a study (N = 67) comparing waitlist to therapist-guided ICBT, the ICBT group had significantly greater improvements ($d = 0.69$, 95 % CI 0.19–1.18, $p < .001$) (Level 4◴) (Lenhard et al., 2017). A later ICBT RCT using a stepped model of care suggested comparable improvements in the group that started with 16 weeks of ICBT (n = 74), and had in-person CBT if a non-responder by 3 months, and those who had in person CBT for 16 weeks (n = 78) followed by additional in person CBT if a non-responder (Level 2◔) (Aspvall et al., 2021). At the 3 month follow up, 54 % of the stepped care group and 71 % of the in-person CBT group were responders. However, at the study's primary endpoint (6 month follow up), there was no significant difference in Y-BOCS scores (MD 0.91, p for non-inferiority p = .02). This study indicates that stepped care is as effective as non-stepped care, where stepped care saves resources by using mainly ICBT, a less resource- and therapist-demanding modality than in person CBT.

In a recent network meta-analysis (Cervin et al., 2023), there was no significant difference between therapist-assisted webcam/telephone CBT and in-person individual CBT (MD 0.85, 95 % CI -2.51-4.21). ICBT was found to be better than waitlist, not significantly different from webcam/telephone CBT (MD 3.10, 95 % CI -7.76-1.56) and not as efficacious as in-person CBT (MD 3.95, 95 % CI 0.42–7.49) (Cervin et al., 2023). Although these interventions were evaluated in the Cervin meta-analysis, the level of evidence for each is based on the individual RCTs as each intervention has only one evidence-based, non-waitlist-controlled study. In general, a technology-based treatment strategy offers interesting opportunities, such as engagement with experts independent of the place of residence, both as an exclusive therapy approach and in the context of so-called "blended treatment". Overall, webcam-delivered CBT has level 3 (◐) evidence, and telephone- and internet-delivered CBT have level 2 (◔) evidence in pediatric OCD.

6.4.4.4. CBT versus medication. One recent meta-analysis (Uhre et al., 2020) revealed no difference in symptom reduction in a substantial sample (N = 146) of children and adolescents with OCD in three head-to-head comparative studies between CBT and SSRIs (Level 1●). It should be noted however that in this study the duration of CBT was limited to 14 sessions, i.e. acute treatment similar to medication trials. The efficacy and acceptability of pediatric OCD treatments was also examined in another recent network meta-analysis (Cervin et al., 2023). RCTs of various forms of CBT, SRIs, and various control conditions were compared to each other. In person CBT was superior to internet-delivered CBT, waitlist, relaxation and pill placebo (Level 1●) and equal in efficacy to both webcam- and telephone-delivered CBT and to SRIs alone (Level 1●). SRIs were found to be superior to pill placebo and waitlist only (Level 1●) (Cervin et al., 2023). Therefore, initial

Table 7a
Levels of evidence and lines of treatment for pharmacotherapy of OCD in the non-pregnant and pregnant population during the perinatal period.

Intervention	Level of Evidence Non-Perinatal	Level of Evidence Perinatal	Line of Treatment
SEROTONERGIC AGENTS			
Escitalopram	1	1	first line
Sertraline	1	1	first line
Citalopram*	1	1	first line
Fluvoxamine	1	1	first line
Fluoxetine	1	1	second line
Clomipramine	1	1	second line
Paroxetine	1	1	third line
Venlafaxine	1	not studied[a]	third line
DOPAMINERGIC AGENTS			
Risperidone**	1	1	second line
Aripiprazole**	1	not studied[a]	third line
Haloperidol**	1	not studied[a]	third line
Quetiapine**	0	1	unable to make a recommendation***
Olanzapine**	0	not studied[a]	unable to make a recommendation***
Paliperidone**	0	not studied[a]	not recommended
GLUTAMINERGIC AGENTS			
Lamotrigine **	1	not studied[a]	third line
Pregabalin**	1	not studied[a]	third line

* In non-perinatal populations, doses up to 30 and 50 mg/day have been effective in clinical trials, although doses higher than 20 mg/day have not been recommended due to the risk of QT prolongation and doses greater than 10 mg/day should be used carefully in patients older than 65 years of age. Regular electrocardiogram testing is recommended for doses higher than 20 mg in non-perinatal populations, and therefore caution should also be used when using while pregnant or during lactation.

** Medication has only been evaluated in these guidelines in the treatment resistant non-perinatal population, taken adjunctively to SSRIs.

*** Unable to recommend in the treatment resistant non-perinatal population due to low quality meta-analytic evidence and lack of efficacy.

[a] In the published CANMAT 2024 Clinical Practice Guideline for the Management of Perinatal Mood, Anxiety and Related Disorders (Vigod et al., 2025), the evidence for these agents was evaluated as Level 4 (1) during pregnancy and lactation for individuals who have O-C symptoms, but not necessarily OCD. In these OCD Guidelines, we have restricted the evidence to studies which have examined patients with OCD and not only O-C symptoms.

treatment should be with SRIs or CBT alone as they appear to be equally efficacious (Level 1) (Cervin et al., 2023; Uhre et al., 2020). See 6.4.2 above for details regarding choice of initial treatment, as well as 6.4.6 below for clinical contexts in which combination SRI + CBT treatment may be considered.

6.4.5. *Psychopharmacotherapy*

There are several indications for introduction of medication in youth affected by OCD but not universal agreement on the thresholds required. OCD resistant to CBT should prompt consideration of medication (Geller and March 2012; Ivarsson et al., 2015; NICE, 2005). As discussed above (Section 6.4.2), monotherapy with SSRIs may also be considered if symptom severity, comorbidities, lack of motivation, or logistical issues prevents meaningful active participation in CBT (Ivarsson et al., 2015; Weidle and Skarphedinsson, 2016).

The efficacy of SSRIs in children and adolescents with OCD versus placebo has been reported by several meta-analyses and RCTs, with overall rather moderate effect sizes (d = 0.46) (Level 1) (Cervin et al., 2023; Geller et al., 2003b; Ivarsson et al., 2015; Kotapati et al., 2019; Locher et al., 2017; Tao et al., 2022; Varigonda et al., 2016). A meta-analysis of 12 RCTs (Kotapati et al., 2019) found that all medications studied were superior to placebo, although some of the reported effects were small (Level 1). However, two studies in the meta-analysis had a very high risk of bias because of missing outcome data due to dropouts, and it was unclear in several studies if there was blinding of outcome assessors. In another recent meta-analysis, all medications studied were also superior to pill placebo, with mean differences ranging from 3.17 (sertraline) to 6.22 (escitalopram) (Tao et al., 2022). Based on meta-analytic evidence, clomipramine was found to be statistically superior to SSRIs through comparison with placebo, suggesting it may be more effective (Level 1) (Geller et al., 2003b; Varigonda et al., 2016). One meta-analysis of SRIs found the following effect sizes, expressed as standardized mean differences, in CY-BOCS scale scores between baseline and end of treatment in collated RCT's: fluoxetine 0.55, paroxetine 0.41, fluvoxamine 0.38, sertraline 0.33, clomipramine 0.69 (Geller et al., 2003b). A study from the Pediatric OCD Treatment Study Team (2004), published after this meta-analysis, also saw a greater effect of sertraline compared to pill placebo (p = .007) (Level 2). In a head-to-head comparison by a recent meta-analysis (Tao et al., 2022), clomipramine, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline were all found to be significantly superior to pill placebo. This meta-analysis includes studies not found in other meta-analyses (such as Geller et al., 2003a,b; Cervin et al., 2023) as the papers are non-English and therefore excluded from these English-only meta-analyses. Tao et al. conducted their own risk of bias assessment on all papers included in their meta-analysis and found unclear risk of bias in many criteria for almost all included studies. The authors of these guidelines could not further evaluate these individual studies as they were not in English. SSRI doses typically start at the low end of the dose range (see Tables 6–3) and slowly titrate up to the maximum effective dose as tolerated, with the American Academy of Child and Adolescent Psychiatry (AACAP) recommendation to dose increase every 3 weeks (Level 4) (Geller and March 2012). High doses of SSRIs have been associated with significantly greater improvement in symptom severity and likelihood of treatment response compared to lower doses in adults but not in youth (Bloch and Storch, 2015).

Overall, SSRIs have level 1 (1) evidence and are all equally considered first-line pharmacotherapies. The decision of which SSRIs to prescribe in children and adolescents should be based on the evidence available, side effect profiles, pharmacokinetic drug properties, pharmacogenomic findings (when available) and any other coexisting mental illnesses. More frequent adverse drug events (e.g., prolonged QTc intervals on ECG, dry mouth, sedation, constipation, etc.) and study discontinuations occurred with clomipramine than with SSRIs in some meta-analyses and reviews (Geller et al., 2003b; Gentile, 2011). As such, clomipramine is only recommended as a second-line medication in children and adolescents, with close monitoring when prescribed. See footnotes at the end of these guidelines (number 1) for regulatory guidelines for the USA and Europe.

6.4.5.1. Adverse effects of medication. A recent meta-review of 78 *a priori* selected adverse events from various psychotropic medications used for any psychiatric condition in children and adolescents found that of the medications for MDD examined, the SSRIs escitalopram and fluoxetine had the safest profiles in children and adolescents (Solmi et al., 2020). Common adverse drug reactions include headache, nausea, or dizziness. A widely observed side effect from SSRIs, particularly in pre-pubertal children, is known as “behavioral activation” which can prohibit upward titration of the dose to effective levels (Luft et al., 2018). Anxiety or disturbances in sexual function have also been reported, and this latter adverse event is especially important to discuss with adolescents. Serotonin syndrome, otherwise known as "serotonergic syndrome", may rarely occur at high doses or in interaction with other medications. Symptoms of serotonin syndrome include akathisia and tremors in mild cases, and mental status changes, hyperthermia, and

Table 7b
Levels of evidence and lines of treatment for comorbid OCD and ASD or OCD with RRBs.

Intervention	Level of Evidence	Line of Treatment
Comorbid OCD and ASD		
Fluoxetine		first line
Cognitive Behavioural Therapy (CBT)		second line
Memantine Augmentation		third line
Deep Brain Stimulation (DBS)		third line
Deep Transcranial Magnetic Stimulation (dTMS) Augmentation		third line
OCD with RRBs		
Fluvoxamine		first line
Risperidone Augmentation		third line

RECOMMENDATIONS FOR THE TREATMENT OF ASD-OCD COMORBIDITY

- Fluoxetine is the first-line pharmacotherapy treatment for ASD/OCD comorbidity (Level 3), while fluvoxamine is first-line for OCD and restricted, repetitive behaviours (Level 2).
- Augmentation with risperidone (Level 4) improves OCD symptoms in ASD.
- Pharmacological treatments should be started at low doses and titrated slowly in this population.
- Function-based CBT is first-line psychological treatment for ASD-OCD comorbidity (Level 3), which is modified for ASD including an extended number of treatment sessions, less focus on cognitive restructuring, and the use of caregiver-reported outcomes.

ASD – Autism Spectrum Disorder; RRBs – Restricted, repetitive behaviours.

rarely, myoclonus, in more severe cases (Boyer and Shannon, 2005). Furthermore, in studies of SSRI treatment of depressive disorders, suicidal ideation and suicidal behaviours have been observed more frequently with SSRI use than with placebo, with a number needed to harm (NNH) of 143 (Bridge et al., 2007). A meta-analysis analyzing SSRI/SNRI induced adverse effects in children and adolescents with only OCD/anxiety diagnoses did *not* show increased rates of suicidality (Strawn et al., 2015). Ideally, the initial prescription and treatment monitoring should be done by a clinician with experience in recognizing and treating OCD. If psychotherapy has been the primary treatment modality with partial or non-response, the psychotherapist should then work together with a clinician who has OCD medication prescribing expertise. If successful, treatment should be continued for a period of 12 months (Level 4) (Geller and March 2012; Wagner et al., 2003). If medication is discontinued, a gradual reduction in medication should be made over a period of months, as discontinuation phenomena may occur if the reduction is too rapid. These discontinuation symptoms may include, but are not limited to, headaches, tremors, nausea, sleep disturbances, and agitation, but rarely last more than two weeks and should be differentiated from clinical relapse which generally appears later.

6.4.6. *Combined CBT and SSRI treatment*

The combination of CBT and medication was found most effective in a large randomized controlled study (Pediatric OCD Treatment Study (POTS) Pediatric OCD Treatment Study Team, 2004) where remission was evident in 53.6 % of children receiving both CBT and sertraline, significantly better than monotherapy sertraline and monotherapy CBT (Level 2). A meta-analysis (Sanchez-Meca et al., 2014) of 18 controlled trials showed an effect size of d = 1.203 for CBT alone, d = 0.745 for medication alone, and the highest of d = 1.704 for combined treatment (Level 1). However, other studies, including a meta-analysis (Ivarsson et al., 2015) and a recent network meta-analysis (Cervin et al., 2023) report that combination therapy does not provide a significant gain over CBT alone (Level 1), but that the addition of CBT to drug monotherapy provides a substantial additional effect (Level 1). Additionally, when Ivarsson et al. performed an analysis of the POTS study, they found no superiority of combination treatment over CBT (MD 2.80, 85 % CI -7.55-1.95) (Level 2) (Ivarsson et al., 2015). A recent network meta-analysis (Tao et al., 2022) found that a combination of fluvoxamine and CBT as well as sertraline and CBT were superior to most SRI monotherapies examined and not significantly different from CBT monotherapy. Although in the Cervin network meta-analysis (Cervin et al., 2023), CBT alone was found to be equal in efficacy to CBT combined with SRIs (Level 1), the authors of the study noted that firm conclusions on this issue could not be made, given the few combination studies conducted to date. In clinical contexts, SRIs are frequently considered to be mediators of better CBT outcomes due to their anxiolytic effects and improved tolerance of ERP. Therefore, overall, there is evidence that combined treatment with CBT and SRIs may have an additive effect when compared to SRI alone but not to CBT alone (Level 1). Nevertheless, initiating combination therapy with SRIs and CBT may be considered as first-line treatment in cases where there is significant symptom severity or comorbidities, as is what is typically done in clinical practice (Level 1) (Cervin et al., 2023; Ivarsson et al., 2015; Sanchez-Meca et al., 2014; Tao et al., 2022).

RECOMMENDATIONS FOR COMBINATION TREATMENT IN PEDIATRIC OCD

- The combination treatment of SSRIs and CBT should be considered when there are moderate-to-severe symptom severity and/or comorbidities (Level 1, first line).

6.4.7. *Treatment of PANDAS/PANS-Associated OCD*

PANDAS or PANS infers an immune-mediated etiology and inflammatory pathophysiology with sudden onset but does not otherwise distinguish clinical correlates of OCD in these youth from that occurring in non-PANDAS/PANS affected youth. Conventional treatments aimed at typical OCD symptoms, including CBT and SSRIs, are considered helpful for children identified as having PANDAS/PANS. However, since there are no controlled studies of OCD that segregate PANDAS/PANS cases from non-PANDAS/PANS cases, the evidence is inconclusive (Sigra et al., 2018). With respect to antibiotics, the most commonly received antibiotics reported by parents of children with PANDAS/PANS include amoxicillin, azithromycin, and amoxicillin-clavulanate (Calaprice et al., 2017; Lepri et al., 2019). However, antibiotic treatment has emerged as effective only during active infections (Burchi and Pallanti, 2018). An RCT of intravenous immunoglobulin for PANDAS was safe and well tolerated, but was found, however, not significantly more effective than placebo (Level 3, negative) (Williams et al., 2016), despite substantial anecdotal evidence that it may be helpful in some cases (Calaprice et al., 2017). Other treatments that have been proposed but with insufficient evidence include: 1) therapeutic plasma exchange (TPE), with one open-label study in 10 children reporting significant improvements in PANDAS symptoms (Perlmutter et al., 1999) and similar findings in various case series/studies (Level 4) (Beşiroğlu et al., 2007; Latimer

et al., 2015); 2) non-steroidal anti-inflammatory drugs (NSAIDS, e.g. ibuprofen, naproxen, celecoxib), which are widely used (Calaprice et al., 2017) but with no high quality published evidence; 3) Short course of corticosteroids given during disease flares, so that symptoms improve more quickly, and patients achieve clinical remission sooner, with longer courses of corticosteroids possibly resulting in more durable remissions, however, due to concerns of tolerability and possible escalation of psychiatric symptoms, this option is not recommended (Level 4, negative) (Sigra et al., 2018) and; 4) tonsillectomy and adenoidectomy surgery (two observational studies suggesting lack of effectiveness) (Level 4, negative) (Sigra et al., 2018). Clinicians interested in learning more are recommended to consult a previously published set of expert consensus guidelines (Thienemann et al., 2017). In conclusion, it is important to emphasize that there is, as of yet, no scientifically supported evidence-based treatment for PANDAS/PANS cases of pediatric OCD and standard interventions for OCD are therefore considered first-line. Expert consensus guidelines suggest a basic panel of laboratory tests may be considered to assay for elevated white cell counts (CBC), anti-streptococcal antibodies (ASOT, anti-DNase B), inflammatory markers (high sensitivity C-reactive protein, erythrocyte sedictionation rate), and markers of auto-immune dysfunction (Immunoglobulin levels, ANA ± other auto-immune antibodies such as anti-neuronal and thyroid antibodies), to rule out any medical illness if the clinical picture fits a PANDAS/PANS presentation and standard interventions are unsuccessful (Thienemann et al., 2017). A trial of NSAIDS may be considered in suspected cases but treatment is empirical (Level 4). To summarize, the treatment of OCD with a PANDAS/PANS phenotype follows the same first-line guidelines (SSRIs and CBT-ERP), and immunomodulatory interventions (e.g., antibiotics, corticosteroids, IVIG, plasmapheresis) lack a clear evidence base and may best be restricted to research contexts or multidisciplinary specialized evaluation.

6.5. Clinical predictors of OCD severity and treatment response in youth

Clinical features of OCD may be important moderators of severity at ascertainment and may also be important moderators of treatment response and/or predictors of outcome. Moderators may also show differential effects for different treatments e.g. CBT vs. medication. Understanding these issues could inform clinical decision making if treatments are matched to individual clinical profiles. Unfortunately, little research has addressed this important issue in pediatric OCD to date and the extant research is often contradictory. Care must be taken in extrapolating data from adult OCD studies to affected youth.

A meta-analysis and review of OCD in youth examined 22 studies (N = 521) and showed that a longer duration of illness, a need for inpatient care, and an earlier age at onset predicted higher rates of persistence (Level 1) (Stewart et al., 2004). Failure to respond to first-line treatment interventions and specific comorbid illnesses were also associated with poorer long-term outcomes. A recent meta-analysis of 18 studies comprising of 1389 participants less than 18 years old at baseline reported a pooled remission rate of 62 % and found that shorter duration of illness predicted higher rates of remission (Level 1) (Liu et al., 2021). However, the NordLOTS study found that even in youth whose initial CBT treatment response was poor, a sustained treatment protocol led to a positive response in 90 % of enrolled participants, and clinical remission in 73 % at the 3-year follow-up (Level 2) (Melin et al., 2020).

Clinical variables most consistently evaluated in CBT outcome studies include initial OCD symptom severity (Garcia et al., 2010; Ginsburg et al., 2008; Rudy et al., 2014; Torp et al., 2015; Wilhelm et al., 2018), symptom dimensions (Wu et al., 2019), comorbidity (Garcia et al., 2010; Rech et al., 2020; Storch et al., 2008; Torp et al., 2015; Wilhelm et al., 2018), treatment expectancy (Lewin et al., 2011b), insight (Wilhelm et al., 2018), and functional impairment (Garcia et al., 2010), as well as measures of family accommodation (Garcia et al., 2010; Ginsburg et al., 2008; Merlo et al., 2009; Rudy et al., 2014), but findings have been too inconsistent to be reliably useful (Caporino and Storch, 2016). Demographic variables exploring outcome following CBT, including current age (Smárason et al., 2021; Torp et al., 2015) and gender (Rudy et al., 2014), have also shown inconsistent findings (Caporino and Storch, 2016; Wilhelm et al., 2018). A recent double-blind randomized controlled trial in 130 youth examined moderators of high-fidelity CBT and found several variables were associated with a decreased likelihood of achieving remission status, including higher family accommodation scores, higher impairment scores, higher depression scores, and higher externalizing scores. Lower insight was also found to be a negative predictor in a large naturalistic study of OCD youth in Denmark (Nissen and Parner, 2018). Avoidance behavior has been reported to be a negative predictor of response by several investigators, presumably because opportunities for fear extinction learning are limited (Nissen and Parner, 2018; Selles et al., 2020). One study found children with a first-degree relative with OCD did less well with CBT monotherapy when compared to children with no family history (i.e., sporadic cases) (Garcia et al., 2010). Additionally, children with a comorbid tic disorder responded more favorably to CBT monotherapy compared to those receiving other treatments, and less well to SSRI monotherapy compared to those without comorbid tics (March et al., 2007; McGuire et al., 2015). However, it is important to note these two moderators have not been consistently replicated (Caporino and Storch, 2016).

6.6. Treatment non-response

There is no agreed upon definition of treatment resistant or treatment refractory pediatric OCD. A definition the literature has used to describe both treatment resistance and refractoriness for pediatric OCD is an inadequate response to 2 trials of serotonin reuptake inhibiting drugs and prior CBT (Bloch and Storch, 2015; Krebs and Heyman, 2010). A review stated that these definitions are less stringent in the number of SRIs that need to be tried to be classified as resistant/refractory in pediatric OCD than found in adult OCD treatment resistance and refractoriness (see Section 4) (Younus et al., 2024). An adequate medication trial is defined as an optimal dose for an adequate duration (>8 weeks at maximal dose and at least 12 weeks total). Recommended doses are generally presented as a range, and optimal dosing generally means upward titration until maximal recommended doses are obtained *or* sufficient effect has been achieved at lower (sub-maximal) dose. Intolerance of medication may constrain the upward titration of an agent, which should be viewed as a failed trial and not necessarily treatment resistance to that agent.

The following studies are a mix of both children and adolescents with partial or no response to SRIs and CBT, capturing both resistant and refractory populations. While resistant and refractory are two different concepts, the authors of these studies do use them interchangeably, which is often seen in both adult and pediatric treatment literature. The Pediatric OCD Treatment Study (POTS) found that 25–33 % of children/adolescents did not experience a treatment response with first-line OCD treatments (SSRI or CBT) (Pediatric OCD Treatment Study (POTS) Pediatric OCD Treatment Study Team, 2004). For more severe cases or partial/non-responders, combined CBT and medication are commonly used by clinicians (Bloch and Storch, 2015), although no studies to date have examined its use specifically in children with treatment resistant OCD.

6.7. Treatment non-response interventions

In a clinical review examining RCTs of treatments for children with OCD (Bloch and Storch, 2015) the authors concluded that CBT was effective in children even when they had refractory OCD symptoms. Increasing the "dose" of CBT can be a useful strategy in youth who do not respond to standard weekly outpatient CBT. An RCT in 54 children and

adolescents (using the NordLOTS sample) who had partially or not responded to an adequate CBT/ERP trial compared continued/extended CBT versus adding treatment with sertraline to continued exposure practice ("CBT support") (Skarphedinsson et al., 2014). The results showed no difference in OCD symptoms between the two groups over 16 weeks, although both groups showed significant improvements in their symptom severity (50 % response rate in the continued CBT group vs. 45.4 % in the sertraline augmentation group) (Level 3). In a further follow-up of those who were non-responsive to an initial 14 sessions of CBT plus an additional 16 sessions of CBT, these CBT non-responders (N = 11) were then evaluated for the effect of adding sertraline (maximum dose 200 mg/d) to CBT support. After treatment with adjunctive sertraline (mean 164.2 days, SD 68.3), the CY-BOCS score reduced from 21.5 (SD 2.6) to 17.5 (SD 3.3) and two participants achieved >25 % CY-BOCS score reduction, with an overall within-group effect size of 1.19 (95 % CI 0.54–1.83) (Level 4) (Skarphedinsson et al., 2015a,b). The addition of an SSRI when there is non/partial response to CBT has been evaluated in several practice guidelines (Geller and March 2012; NICE, 2005), as well as in a systematic review and meta-analysis, however the meta-analysis was found to have large confidence intervals (Level 2) (Ivarsson et al., 2015). Therefore, for CBT non-responders or partial responders, adding an SSRI should be considered (Level 2), as well as increasing the dose of the CBT (Level 3).

For non/partial response to SSRIs, the only evidence points to intensive CBT (daily sessions for 3 weeks), which was found to significantly improve OCD symptoms in children who were partial or non-responsive to SRI treatment (Level 4) (Storch et al., 2010b), although augmentation with regular CBT/ERP should be tried first when there is non-response to SRIs due to its feasibility (Level 4).

There lacks literature on next step treatment in pediatric OCD when an individual fails combination treatment of both CBT and SSRIs. The only evidence in pediatric OCD of no response to a course of combined CBT and SSRI is from a retrospective chart review, which recommends switching to another SSRI while continuing with the CBT if possible (Level 4) (Krebs and Heyman, 2015). If a second SSRI also fails to be effective, despite adequate dosing over a sufficient period, other strategies for SSRI non-response should be tried given the lack of data in this population, such as clomipramine as an alternative, second-line, medication treatment option (Level 4) (Krebs and Heyman, 2015). If therapeutic doses of clomipramine do not result in a sufficient clinical response, then the evidence suggests combining SSRIs and clomipramine, with careful attention to potential CYP-450 hepatic enzymatic interactions (Level 4) (Geller and March 2012).

A strategy to optimize clomipramine blood levels has been proposed for pediatric TR-OCD (Fung et al., 2021). Following non or partial response to a trial of fluvoxamine, clomipramine is added. Fluvoxamine will then modulate the clomipramine:desmethylclomipramine ratio in the blood and optimize clomipramine concentrations (Level 4). Hardy and Walkup (2021) further recommend for those with severe OCD or many SSRI failures, starting with clomipramine and adding fluvoxamine if it fails may be best (Level 4) (Hardy and Walkup, 2021). Regardless, treatment with clomipramine requires close monitoring of blood levels and QT intervals, especially when combining it with fluvoxamine. Except for clomipramine, other tricyclic reuptake inhibitors are not effective and should not be used.

If the combination treatment continues to not provide adequate response despite changes in the SRI, the CBT arm of the treatment can also be adjusted, following the recommendations for CBT monotherapy non/partial response above (Level 4).

A cost-analysis study examining treatment-refractory OCD in a pediatric population used a hospital database with 264 care episodes to examine treatment effectiveness and costs. This chart review found that intensive outpatient (IOP) followed by partial hospital or day treatment, and CBT + medication were the most effective treatments in reducing OCD symptoms in treatment refractory children (Level 4) (Gregory et al., 2020).

6.7.1. *Medication augmentation strategies for treatment non-response*

There have been limited trials of augmenting medications in pediatric populations. The approach most supported and most common matches that of adult evidence-based trials that augment SSRIs with

Table 6c
Levels of evidence and lines of treatment for pharmacotherapy in pediatric OCD.

Pediatric OCD			
Intervention	Level of Evidence	Line of Treatment	Total Dose Range
Escitalopram*	●	first line	5–20 mg/day
Sertraline*	●	first line	25–200 mg/day (pre-adolescents) 50–300 mg/day (adolescents)
Fluoxetine*	●	first line	10–80 mg/day
Fluvoxamine*	●	first line	25–300 mg/day
Paroxetine*	●	second line**	5–60 mg/day
Clomipramine	●	second line	25–200 mg/day

RECOMMENDATIONS FOR PHARMACOTHERAPY IN PEDIATRIC OCD

- SSRIs are the first-line pharmacological treatment, particularly fluoxetine, sertraline, fluvoxamine, and escitalopram* (Level 1●), but not paroxetine (Level 1●), which is second line**
- SSRI dosing should start low and slowly increase every 3 weeks to the maximum tolerated dose (Level 4)
- Treatment trials involve gradually titrating to maximally tolerated dose or until sufficient effect has been achieved for at least 12 weeks to evaluate response
- Successful treatment should be maintained for 12 months (Level 4)

CBT - Cognitive Behavioural Therapy; SRI - Serotonin Reuptake Inhibitor; SSRI - Selective Serotonin Reuptake Inhibitor.
*While escitalopram was identified as having a high safety profile in children (Solmi et al., 2020), there are concerns regarding its risk of prolongation of the QT interval, making it recommended, however not before fluoxetine or sertraline.
**Paroxetine has strong evidence for its efficacy in children, however, is not FDA approved for OCD in children and adolescents, and has some concerns regarding its suicide risk, making it recommended as a second line treatment.
* Monotherapy with SSRIs should be considered as first-line treatment if there is significant symptom severity, comorbidities, lack of motivation or logistical and accessibility issues preventing the child's participation in CBT (Ivarsson et al., 2015; Weidle and Skarphedinsson, 2016).
** Paroxetine has strong evidence for its efficacy in children, however, is not FDA approved for OCD in children and adolescents and has some concerns regarding its suicidal ideation risk, making it recommended as a second line treatment.

second generation atypical antipsychotics (SGAs), most of which are serotonin-dopamine activity modulators (SDMs) (Bloch et al., 2006; Dold et al., 2015). However, RCT studies are sparse and the level of evidence of studies in children and adolescents is weak. One retrospective chart review (N = 48) investigated aripiprazole augmentation of SSRIs in children and adolescents with treatment resistant OCD (Level 4) (Ardic et al., 2016). The study reported significant reduction in symptom severity as per CY-BOCS and CGI-I/S ($p < .001$) after a 12-week trial. A case series (N = 39) reported that 59 % of patients who had not responded to at least two SRIs as monotherapy responded to aripiprazole augmentation (CGI-S = 3) (Level 4) (Masi et al., 2010). An open-label study (N = 16) similarly reported clinically significant improvements in children who had not responded to at least two SSRIs and CBT after a 12-week aripiprazole augmentation treatment (Level 4) (Ercan et al., 2015). A case series examining adolescents (N = 17) with TR-OCD found that risperidone augmentation in doses up to 2 mg significantly improved OCD symptom severity, with 5 patients reporting a drop of at least 25 % in Y-BOCS and 10 patients reporting a score drop between 10 and 25 % (Level 4) (Thomsen, 2004). A naturalistic comparative study treated 69 treatment resistant children and adolescents with either risperidone or aripiprazole augmentation. 56.5 % of patients were responders and no differences were found between the two augmentation groups (Level 4) (Masi et al., 2013). Dosing should always be kept as low as possible to minimize adverse effects (e.g. initiating risperidone at 0.5 mg/d or aripiprazole at 2 mg/d). If there is no response to augmentation after an adequate trial, the medication should be discontinued or switched. Trials using SGA augmentation are typically 8–12 weeks depending on titration schedules. Regular monitoring for development of a metabolic syndrome to include fasting blood sugars, hemoglobin A1C, and lipid studies should occur along with regular weight measurements.

A small number of studies have examined glutamatergic agents in pediatric populations. A case study of a 15-year-old girl with severe, treatment resistant OCD found augmentation of citalopram with 10 mg of memantine to significantly reduce CY-BOCS scores to a sub-clinical level, gains which were maintained at the 9-month follow-up (Level 4) (Hezel et al., 2009). Given its high tolerability and Level 2 evidence in adults, memantine augmentation of SRIs may be considered in adolescents who have not responded to other more established treatments for TR-OCD. There have been two small DBPCs of NAC augmentation of SSRIs in OCD, one trial augmenting SSRIs in patients who had failed only one trial of an SRI (i.e., not meeting definition of TR-OCD) resulted in improvement (Level 3) (Ghanizadeh et al., 2017), and another using NAC monotherapy, with both yielding negative results (Level 3, negative) (Li et al., 2020). One open-label trial of riluzole in 6 children who failed one adequately dosed SSRI trial (i.e. did not meet definition of treatment resistant OCD) found 4/6 children to be responders (>30 % decrease in CY-BOCS scores) (Level 4) (P. J. Grant et al., 2007) but a subsequent RCT failed to show superiority of riluzole over placebo (Level 3, negative) (Grant et al., 2014). As with adults, D-cycloserine is not recommended as an adjunct to CBT/ERP for OCD due to evidence of inefficacy from a large DBPC trial in children and adolescents (Level 2, negative) (Farrell et al., 2022).

Other treatments that have been tried in adult OCD have very limited evidence in pediatric OCD. One case study found augmentation of venlafaxine with 15 mg mirtazapine to significantly reduce CY-BOCS scores in a 14-year-old patient with TR-OCD (Level 4) (Aksu et al., 2020). A recent case series (N = 5) of IV ketamine use for adolescents who failed first-line treatments demonstrated OC symptom reduction immediately after ketamine infusion, however the effects were not maintained over the course of the 14-day study (Level 4) (Ishimuro et al., 2025). Single case studies examining lamotrigine (Naguy et al., 2016), methylphenidate (King et al., 2017), and clonazepam (Leonard et al., 1994) augmentation strategies have been successful, however there are no RCTs for these agents in pediatric OCD (Level 4).

To date no studies have examined other medications in treatment resistant pediatric populations.

There is insufficient evidence to confidently recommend any of these interventions for pediatric OCD with treatment non-response. Tables 6–4 outlines the recommendations for treatments which have been examined by some degree of evidence for clinical use in pediatric OCD that has not responded to a first line treatment.

6.8. Relapse prevention

Treatment with CBT should include relapse prevention strategies (e.g., booster sessions), as well as continued outpatient treatment after inpatient therapy (Bloch and Storch, 2015). The Nordic Long-term OCD Treatment Study (NordLOTS) initial sample included 269 children and adolescents. One hundred and fifty-five youth completed the one-year CBT study and of these, 16 % of responders had relapsed at the 6 or 12-month follow up assessment (Level 3). A parallel design was used to randomize CBT non-responders to either sertraline or additional protocol-driven CBT. At the three-year follow up, 90 % were considered to be responders (CY-BOCS ≤15) and 73 % were in remission (CY-BOCS ≤10) with no significant difference between extended CBT and medication treatment (Level 2) (Melin et al., 2020). In a double-blind randomized controlled withdrawal study following 12 weeks of open-label treatment with paroxetine, relapse rates varied from 32 % in youth with no comorbid illness to 59 % in youth with ≥3 comorbid psychiatric illnesses (Level 2) (Geller et al., 2003a). These high relapse rates provide evidence that, once response is achieved, treatment should continue for a minimum of 12 months. The long-term sertraline trial showed 66 % full and 28 % partial remission in children in the acute 12-week RCT and 45 % full and 33 % partial remission at 12-month follow-up of open-label treatment (Level 2) (Wagner et al., 2003).

In youth who have relapsed following medication withdrawal after successful treatment, SSRIs should be continued for at least 12 months after recovery and perhaps longer after multiple relapses (Krebs and Lewis, 2018). SSRI discontinuation is a reasonable strategy for youth with minimal or mild OCD symptoms over at least 12 months, where there are no concerns regarding comorbid illness and especially for those with access to further CBT as needed (Level 4) (Bloch and Storch, 2015). Although there are no discontinuation trials in pediatric OCD populations, this strategy is often used by clinicians as it takes into account the substantial portion of children whose OCD remits over time and reduces the cumulative lifetime exposure to SSRIs during sensitive developmental periods (Bloch and Storch, 2015). Appropriate follow-up over several months following discontinuation is recommended (Bloch and Storch, 2015). Parents and youth should be educated about the possible episodic course of the disorder and risk of relapse. Environmental stressors, family accommodation, avoidant coping styles, and other maladaptive reactions to stress were found to be predictors of OCD relapse (Level 3) (Steketee and Van Noppen, 2004). Learning to anticipate and avoid potential triggers alongside using the CBT tools learnt during treatment (which include relapse prevention techniques) can substantially reduce the risk of relapse (Krebs and Lewis, 2018).

Key Points

- Despite similar DSM-5 criteria to adults, children may be more likely to present with compulsions alone and may have poorer insight than adults.
- Early detection and treatment initiation improves prognosis.
- CBT/ERP and SSRIs are first-line treatments for children and adolescents with OCD.
- In person, individual CBT and individual webcam or telephone CBT appear to be equal in efficacy.
- Family-based CBT is supported by Level 2 evidence and parental involvement in all CBT is encouraged.
- Conventional OCD pharmacotherapies and psychotherapies are helpful for children presenting with PANDAS/PANS.
- Similar to adults, the pediatric literature lacks a consistent definition of treatment resistance.

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(*continued*)

- For TR-OCD in children and adolescents, pharmacotherapy is similar to that in adults, namely augmentation with second generation antipsychotics.
- There is also evidence to support increasing the dose of CBT for Paediatric TR-OCD cases.
- Pharmacological treatments should be continued for a minimum of 12 months. Continued access to CBT is also important.

6.8.1. Treatment of pediatric obsessive-compulsive disorder

7. Other Populations

7.1. Pregnancy and lactation

OCD has been found to be more prevalent in the third trimester of pregnancy and in the postpartum period, with 2 %–16 % of postpartum women thought to suffer from OCD (Fairbrother et al., 2021; Russell et al., 2013; Viswasam et al., 2019, 2021).

While the diagnosis of OCD is similar within and outside the perinatal period, there are some common symptoms perinatally. For example, contamination obsessions and cleaning compulsions may include issues related to the health and well-being not only of the mother, but also the pregnancy and/or the baby (Brakoulias et al., 2020). This can sometimes lead to situations where a mother is not comfortable accepting help from others for the baby, which can reduce the level of social support that she receives. Recurrent and intrusive irrational thoughts or images that a mother will harm their baby (both unintentionally and intentionally) are also quite common and can be extremely distressing (Viswasam et al., 2019).

The above symptoms can occur in OCD, but also in depression or in anxiety disorders, so diagnostic accuracy is important in order to guide treatment (Fairbrother et al., 2021). It is also very important to differentiate obsessions and compulsions from psychosis (e.g., postpartum psychosis, or depression with psychotic features) or other situations where there is a clear intent to harm the infant or where the patient expresses a rationale about why they would want to harm the infant (e.g., the baby is not mine, or the baby would be better off without me, or there is something very wrong with the baby), and from intense emotional dysregulation where there is a high risk for impulsive harm (i.e., risk for abuse or assault). While child protection is of utmost importance, misdiagnosing a mother with OCD as having a psychotic disorder can have negative implications for the mother, child, and family, particularly if a child is removed from the home unnecessarily (Challacombe and Wroe, 2013).

7.1.1. Therapies for OCD in pregnancy and lactation

To date no studies have examined potential differences in treatment response in postpartum OCD versus patients who have OCD at other periods in their lives (Brakoulias et al., 2020). Therefore, as in other stages of life, first-line treatments for OCD in pregnancy and lactation are either CBT/ERP or SSRIs (Brakoulias et al., 2020; Uguz, 2015). RCT evidence supporting such treatments in pregnancy and lactation is limited to a single RCT in patients with postpartum depression and anxiety symptoms that compared paroxetine monotherapy to CBT adjunctive to paroxetine (N = 35, including 11 with OCD) (Misri et al., 2004). Both groups demonstrated significant improvements in their Y-BOCS scores from baseline and there was no significant difference in the response rates (defined as ≥60 % Y-BOCS score decrease) between the groups (Misri et al., 2004). There is some other positive evidence from open-label trials, case series, and reports on the postpartum OCD population for the use of SSRIs, clomipramine, risperidone monotherapy, and adjunctive quetiapine (Level 4) (Arnold, 1999; Hertzberg et al., 1997; Misri and Milis, 2004; Sharma and Sommerdyk, 2015; Sichel et al., 1993). As there are limited treatment studies in the postpartum population with low levels of evidence, we would recommend following guidelines for general adult OCD (OCD not specific to a certain group or population) found in the treatment and treatment resistant OCD sections (Sections 3.1 and 4.0), while also taking into account the safety of medications in pregnancy and lactation.

Most SSRIs have reasonably reassuring safety profiles for use during pregnancy. Sertraline, escitalopram, citalopram, and fluvoxamine are the first choices for pharmacological treatment of OCD during pregnancy (Vigod et al., 2025). Second-line agents in pregnancy include clomipramine and fluoxetine, and third-line agents include paroxetine and venlafaxine (Vigod et al., 2025). Overall, SSRIs, SNRIs, and TCAs do not appear to significantly raise the risk of congenital malformations. However, some research suggests a small increase in cardiovascular malformations when SSRIs and SNRIs are taken during the first trimester (Vigod et al., 2025). Paroxetine has been linked to a slightly higher risk in some studies (De Vries et al., 2021; Grigoriadis et al., 2013; Lou et al., 2022; Turner et al., 2019). Persistent pulmonary hypertension of the newborn (PPHN) is uncommon but serious, affecting approximately 2 in 1000 infants, and exposure to SSRIs or SNRIs in the third trimester may raise this risk to 3 in 1000 infants (Vigod et al., 2025). Poor neonatal adaptation syndrome (PNAS) occurs in up to 30 % of newborns exposed to SSRIs and SNRIs but usually resolves within 2–3 days with supportive care and rarely leads to severe complications (Eleftheriou et al., 2024; Vigod et al., 2025). Research has not consistently linked fetal SSRI exposure to later physical health, neurodevelopmental, or psychiatric issues in adolescence (Rommel et al., 2020). Instead, it is hypothesized that these observed issues may be largely influenced by underlying genetic vulnerabilities shared between parent and child, as well as environmental factors related to parental mental illness (Vigod et al., 2025).

Lamotrigine is only used for OCD in cases of treatment resistance. For OCD treatment during pregnancy and lactation, lamotrigine has the most favorable reproductive risk profile of anticonvulsants (Pinheiro and Stika, 2020). However, maintaining therapeutic concentrations can be challenging, as its clearance can increase as early as 5 weeks gestation, potentially exceeding 200 % during pregnancy (Karanam et al., 2018). When antiepileptics are prescribed during pregnancy, folic acid supplementation of at least 0.4 mg/day is advised (Vigod et al., 2025). Antipsychotics do not seem to be linked to a heightened risk of congenital malformations, although some analyses (Huybrechts et al., 2016; Vigod et al., 2015) have associated risperidone with a slightly increased risk of cardiac defects. SDMs (antipsychotics), particularly olanzapine, and to a lesser degree, quetiapine, may contribute to an increased risk for metabolic complications including gestational diabetes and large-for-gestational age infants (Heinonen et al., 2022; Wang et al., 2021). Prenatal exposure to medications for psychosis may also be associated with temporary neurodevelopmental delays in infancy, but these typically resolve in the first one to two years (Poels et al., 2018). Currently, this does not appear to be associated with long-term health or development issues (Poels et al., 2018). Even in postpartum, risks in future pregnancies should be considered as the mother may either still be taking or need to recommence an SSRI during her next pregnancy.

SSRIs are generally regarded as acceptable for use in lactation, as small amounts are found in breastmilk. During lactation, the first-line recommendations are citalopram, escitalopram, fluvoxamine, and sertraline due to the reassuring safety data and the low infant dose of the latter two (Vigod et al., 2025). Second-line agents include clomipramine and fluoxetine, and third-line agents include paroxetine and venlafaxine (Vigod et al., 2025) There is ample evidence suggesting that there are very few adverse effects from lamotrigine exposure in lactation (National Institute of Child Health and Human Development, 2024). Olanzapine and quetiapine appear to have a favorable risk profile in lactation (National Institute of Child Health and Human Development, 2024).

Monotherapy treatment is recommended before the combined use of two or more agents, as the latter has been associated with a small

increased risk of adverse pregnancy and infant outcomes (Källén and Reis, 2012). Before prescribing multiple medications, clinicians should consider a higher dose of a single medication, or augmentation with psychotherapy if available (Level 4◔).

For nonpharmacological treatments there is similarly minimal perinatal specific data such that guidelines for psychological treatments outside the perinatal period should be followed. One RCT in postpartum patients with OCD (N = 34) compared time-intensive CBT to treatment as usual (TAU) (Challacombe et al., 2017). The study found that the time-intensive CBT group had greater Y-BOCS score reductions in comparison to the TAU group (48.4 % vs. 12.8 %, t = 4.27, p < .001) (Level 3◑). Notably, 17 participants were on stable doses of psychotropic medications throughout the study, including SSRIs, SNRIs, and SDMs (antipsychotics) as augmentative agents, and the TAU group was offered ICBT after the treatment period (Challacombe et al., 2017). A case series of postpartum patients with OCD (N = 6) reported that 12 h of intensive CBT reduced the Y-BOCS score of all patients after 2 weeks (Level 4◔) (Challacombe and Salkovskis, 2011). Case reports suggest that CBT, ERP, and ACT are effective at improving OCD symptoms in postpartum patients (Level 4◔) (Christian and Storch, 2009; Gershkovich, 2019; Grove et al., 2023). As little high-quality research has been done in this population, specific lines of treatment cannot be given to these therapies. Instead, clinicians should follow the guidelines for general OCD found in the treatment and treatment resistant OCD chapters (Sections 3.1 and 4.0). However, it is important to mention that when treating postpartum OCD, it may be beneficial to recommend time-intensive CBT if available. In the UK, comparable results were found between weekly and intensively delivered treatment (Oldfield et al., 2011). The shorter timeframe of time-intensive CBT may improve the accessibility of psychosocial treatment for new parents with young children and minimize the impact on the mother-infant relationship (Challacombe et al., 2017).

Clinical experience suggests that SSRI treatment may be preferred when the severity of OCD symptoms prevents the mother from engaging in ERP. Additionally, the competing demands and unpredictable schedule of infant care can make treatment options such as regular psychotherapy sessions more challenging (Brakoulias et al., 2020).

Please refer to the other sections in the non-perinatal treatment of OCD for dosing information and safety considerations that can also be applied to the perinatal population given the lack of evidence in this field (Sections 3.1 and 4.0). Please also refer to the recently published CANMAT Perinatal guidelines (Vigod et al., 2025) and the FDA website (https://www.drugs.com/pregnancy/) for more in-depth evidence and recommendations on the safety of specific agents in the perinatal population during pregnancy and lactation.

RECOMMENDATIONS FOR TREATING OCD DURING PREGNANCY AND LACTATION

- There are no pharmacotherapy RCTs in postpartum OCD, only case series and open-label studies with SRIs (Level 4◔).
- Most SSRIs are considered low risk for use in pregnancy: with sertraline, citalopram, escitalopram, and fluvoxamine being preferred.
- SSRIs are generally low risk for use during lactation, as small amounts are found in breastmilk; lowest amounts are with sertraline, fluvoxamine, and paroxetine, however, paroxetine may have a greater risk of PPHN and cardiovascular malformations during pregnancy.
- If SSRIs alone are not efficacious during pregnancy, clomipramine and risperidone are safe to be used as an adjunctive to SSRIs.
- Monotherapy with a higher dose or adjunctive psychotherapy is recommended before combination pharmacotherapy (Level 4◔).
- CBT is beneficial in postpartum OCD (Level 3◑) with time-intensive CBT improving accessibility.
- Follow general adult OCD treatment guidelines, given lack of data for this population.

7.2. Older adults

In view of an aging population around the world, it is increasingly important to understand the specific issues related to the diagnosis and management of OCD in older adults. Although there is a need for further research in this area (Jazi and Asghar-Ali, 2020), the guidance below summarizes the relevant evidence to date.

7.2.1. Prevalence

Large studies have shown a lower prevalence of OCD in older adults of 0–0.8 % (Canuto et al., 2018; Dell'Osso et al., 2017a) compared to the prevalence in the general population ranging between 1.5 and 3.5 % (Ruscio et al., 2010). The prevalence is also lower than for depression or anxiety disorders in older adults, which is estimated between 1 and 42 % (Djernes, 2006) and 10–20 % (Beekman et al., 1998), respectively. Given the chronic course of OCD, this lower prevalence found in the elderly has been questioned by some studies, suggesting that the results may not reflect a true lower prevalence but instead loss to follow up due to predominance of other medical conditions, a lower degree of insight into symptoms, or symptoms becoming more egosyntonic (Dell'Osso et al., 2017a).

7.2.2. Presentation and onset

Despite the lower prevalence, studies show that OCD presents in older adults in equal severity to that of younger adults (Dell'Osso et al., 2017a; Fontenelle et al., 2003; Kohn et al., 1997). As older patients are more vulnerable to physical health issues, this group must be especially monitored for the risks OCD can bring, such as fluid and food restriction, toilet avoidance, and skin damage in washing rituals, among others (Jazi and Asghar-Ali, 2020). Case reports describe rare conditions, such as one report of scurvy in a 61-year-old, as a sequela of severe OCD (Vieira et al., 2009). Severe self-starvation and death have also been described (Jazi et al., 2016).

There are many similarities to younger patients with regards to OCD themes, the most common in both groups being contamination fears, pathological doubt, checking, and washing rituals (Kohn et al., 1997). However, there is evidence suggesting certain themes are more prominent in older adults, including the fear of having sinned, other obsessional themes of religious and moral scrupulosity (Calamari et al., 1994), and more ritualized hand washing. Conversely, elderly patients have fewer concerns around symmetry, 'need to know' obsessions, and counting routines (Kohn et al., 1997).

Several studies have shown that older adults with OCD have a later average age of onset than younger patients (Dell'Osso et al., 2017a; Kohn et al., 1997). For instance, one study of 416 people with OCD across Europe found the average onset age to be 29 years in older adults compared to an average onset of 18 years in adults with OCD (Dell'Osso et al., 2017a). Evidence suggests the age of OCD onset predicts a particular demographic and clinical profile, where those with later onset have a more relapsing-remitting course (J. E. Grant et al., 2007). Some studies suggest that women are more likely to develop late onset OCD (Flint, 1994), though the literature does not show a clear difference in rates between genders in the older age group (Jazi and Asghar-Ali, 2020).

7.2.3. Medical comorbidity

Given the majority of older adults with OCD will have had symptoms for decades (Byrne, 2002), and that OCD seldom begins in later life (Dell'Osso et al., 2016), it is vital to rule out any organic cause when the disease first presents around the approximate age of 50 (Dell'Osso et al., 2017a; Jazi and Asghar-Ali, 2020; Weiss and Jenike, 2000) with appropriate imaging and clinical examination.

Many case studies give examples of older adults who developed OCD that were then found to have brain pathology such as vascular lesions, infection, or neurodegeneration (Kumar et al., 2009; Matsui et al., 2007; Tonna et al., 2014; Weiss and Jenike, 2000). For example, an inpatient psychiatric department found that 5 of their 1000 patients with OCD first developed the condition as older adults (aged 56 and over). Of these individuals, 4 were found to have frontal lobe and caudate nuclei lesions (Weiss and Jenike, 2000). Another series of 5 case reports describes

Table 6d
Levels of evidence and lines of treatment for treatment non-response in pediatric OCD.

Treatment Non-Response in Pediatric OCD		
Intervention	Level of Evidence	Line of Treatment
Non-response to CBT/ERP		
Augmentation with SSRI		first line
Increase the dose of CBT/ERP		second line
Intensive outpatient treatment		third line
*Non-response to SSRI**		
Augmentation with CBT/ERP**		third line
Switch to another SSRI**		third line
Switch to clomipramine**		third line
Switch to intensive CBT		third line
Augmentation with aripiprazole		third line
Augmentation with risperidone		third line
Augmentation with riluzole		unable to make recommendation
Augmentation with D-Cycloserine (DCS)		unable to make recommendation

RECOMMENDATIONS FOR TREATMENT NON-RESPONSE TO FIRST INTERVENTIONS IN PEDIATRIC OCD

- There is no gold-standard definition of treatment resistance in pediatric OCD.
- If inadequate/no response to CBT/ERP:
  - **FIRST LINE:** Augment with an SSRI (Level 2).
  - **SECOND LINE:** Increase the dose (frequency or number of sessions) of CBT (Level 3).
- If inadequate/no response to an SSRI:
  - Based on currently available evidence, no recommendation is first or second line for non-response to SSRIs.
  - Clinicians may choose one of the following third-line treatments:
    Augment with CBT/ERP (Level 4) or aripiprazole (Level 4) or risperidone (Level 4), or switch to another SSRI (Level 4) or clomipramine (Level 4) or intensive CBT (Level 4).
- If inadequate response to initial combination treatment (SSRI + CBT), follow the treatment regiments for either inadequate CBT response or inadequate SSRI response.

CBT/ERP - Cognitive Behavioural Therapy with Exposure and Response Prevention; SSRI - Selective Serotonin Reuptake Inhibitor.
* Based on currently available evidence, no recommendation is first or second line for non-response to SSRIs.
** Recommendations which can also apply to SRI treatment adjustments when combination treatment provides no/partial response.

newly acquired OCD in adults over the age of 61 who were subsequently found to have basal ganglia lesions suggestive of a neurodegenerative pathophysiology. On this note, some case reports describe late onset OCD leading to neurological conditions such as progressive supranuclear palsy or Alzheimer's dementia later in life (Karnik et al., 2006; Mrabet Khiari et al., 2011).

However, there are case reports where OCD has developed at a late age without any medical cause. These examples have suggested a connection with the changes characteristic of later life, such as health problems or losses (Bhattacharyya and Khanna, 2004; Velayudhan and Katz, 2006). One study of 204 older adults also found a correlation between lower cognitive functioning and higher OCD symptom severity, which they believe is mediated by a correlation between higher awareness of ones' own thoughts, as measured by the cognitive self-consciousness self-report scale, and decreased cognitive functioning (Prouvost et al., 2016).

Other than the neurological concerns associated with late onset OCD, no other connection between older adults with OCD and any increased frequency of comorbid medical diseases or psychiatric poly-comorbidity has been found (Dell'Osso et al., 2017a).

7.2.4. Pharmacotherapy

When prescribing medication, it should be titrated slowly, beginning at 25–50 % of the starting dose for an antidepressant for a younger adult. This reflects age-related changes in hepatic and renal function, which can increase plasma concentration of medications and prolong half-lives. Regular follow-ups are necessary (Cassidy and Rector, 2008).

SSRIs should be the first line in pharmacological management of OCD in older adults (Dell'Osso et al., 2017a; Jazi and Asghar-Ali, 2020). Although clomipramine is also recommended in OCD, older patients are especially sensitive to the anticholinergic and cardiac side effects of tricyclic antidepressants (Cassidy and Rector, 2008). Case studies in geriatric OCD have reported successful reductions in OCD symptoms with adequate dosing of SSRIs and clomipramine (Austin et al., 1991; Bajulaiye and Addonizio, 1992; Calamari et al., 1994; Philpot and Banerjee, 1998). One open-label study (N = 12) found 8/12 older adults achieved a 50 % reduction in OCD symptoms after a 12-week trial on fluvoxamine (Level 4) (Wylie et al., 2000). The higher frequency of polypharmacy in the elderly should be considered especially if prescribing fluoxetine or paroxetine, which can lead to more drug interactions. Although paroxetine has been found to resolve OCD symptoms in the older adult population (Level 4) (Philpot and Banerjee, 1998), it is also generally not recommended as a first-line treatment in the older population due to its high anticholinergic burden (Wiese, 2011). Older adults will be especially sensitive to gastric bleeding (and gastroprotection should be given if already on an NSAID or aspirin) as well as SSRI-induced hyponatraemia through the syndrome of inappropriate antidiuretic hormone secretion. Female patients, with reduced renal function, medical comorbidity, and low body weight further increase the risk of hyponatraemia (Wiese, 2011). Serum sodium, electrocardiograms, and renal function should be regularly monitored in such patients especially after a dose change. Although the evidence for

SSRIs treatment in geriatric OCD are level 4 (), SSRIs (other than paroxetine) are considered a first-line treatment. Due to the health risks, paroxetine and clomipramine are considered a second-line treatment in geriatric OCD.

serotonin-dopamine modulators (SDMs)(antipsychotics) are most commonly used as augmentation of SSRIs, and a few case studies have reported the successful use of these medications as adjunctive therapy in older adults, such as fluoxetine being successfully augmented with olanzapine in a 77-year-old woman with chronic OCD (Jazi et al., 2016) and fluvoxamine augmented with aripiprazole and quetiapine in a 68-year-old man with severe OCD (Level 4) (Lozano-Vicario et al., 2020). However, side effects of SDMs are common, and older adults will be especially at risk, thus again careful titration is necessary. The older population have an increased risk of cerebrovascular events from SDMs (antipsychotics), which studies suggest is a dose-related side effect. Thus, the lowest dose necessary is recommended. Physically frail patients may need more frequent antipsychotic monitoring (Taylor et al., 2018). One case report in a 75-year-old woman with treatment resistant OCD found lithium augmentation to fluoxetine to significantly reduce her symptoms (Level 4) (Bajulaiye and Addonizio, 1992). Another case report found augmenting clomipramine with lamotrigine successfully treated a 59-year-old woman with treatment resistant OCD (Level 4) (Uzun, 2010). Adjunctive aripiprazole has level 4 evidence () and is considered a second-line treatment. Due to the small number of studies available, the levels of evidence of adjunctive treatments with lithium, lamotrigine, and olanzapine are all level 4 and they are considered third-line treatments in treating treatment resistant older adult OCD.

7.2.5. *Non-pharmacological treatments*

Cognitive behavioural therapy with exposure and response prevention (CBT/ERP) is the most studied form of psychological treatment for OCD (Dell'Osso et al., 2017a).

Evidence suggests that CBT is used much less frequently in older

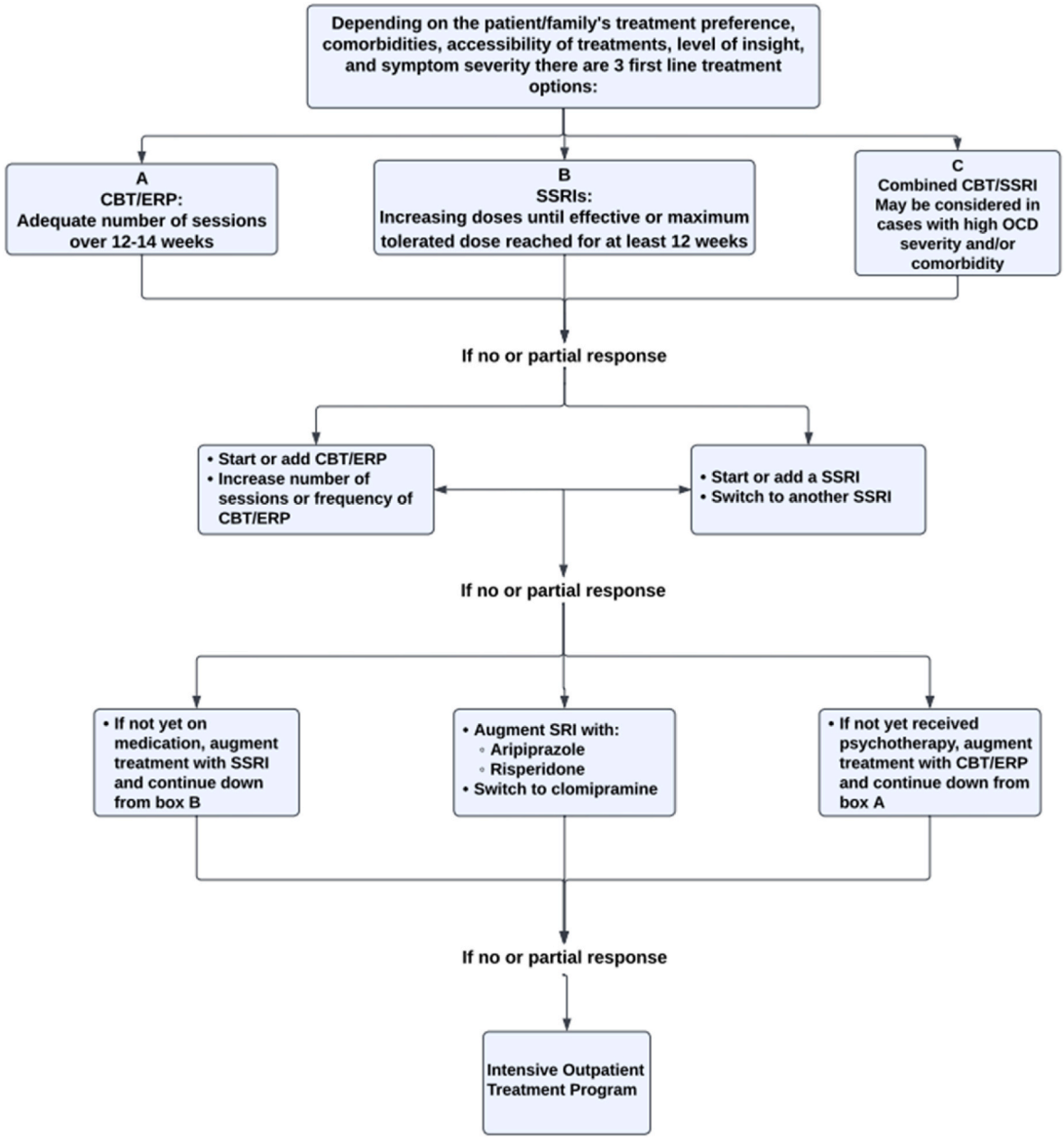

Fig. 2. Algorithm for Pediatric OCD treatment: One or multiple treatment options in each box can be tried before moving down to the next step/box. CBT/ERP = Cognitive Behavioural Therapy with Exposure and Response Prevention; SSRI= Selective Serotonin Reuptake Inhibitor.

people with OCD (P. J. Grant et al., 2007; Grenier et al., 2009). Older patients who have had CBT before might be reluctant to try a further course, or there may be physical health issues or cognitive impairment presenting a barrier (Dell'Osso et al., 2017a). Furthermore, as the availability of CBT has increased in recent years, elderly patients may not yet have had the chance of having treatment, or not had the financial means (Evans, 2007). Although there is little evaluation so far of CBT specifically in older people with OCD, case reports and a small open-label study (N = 20) describe successful treatment with CBT/ERP in older adult OCD (Level 4) (Calamari et al., 1994; Carmin et al., 1999; Jones et al., 2012). Multiple studies have also shown no correlation between treatment response and patient age (Franklin et al., 2000; Hoogduin and Duivenvoorden, 1988; King and Barrowclough, 1991). Adaptations to the delivery of CBT/ERP, such as virtual or home sessions and leniency in scheduling, may be beneficial for older adults (Carmin et al., 1999). However, CBT/ERP was not found useful in those patients with severe physical impairment, or moderate-to-severe intellectual impairment (Calamari et al., 1994; Dell'Osso et al., 2017a; Leng, 1985). CBT/ERP has level 4 evidence () in older adult OCD and is considered a first-line non-pharmacological treatment.

There are a few case reports of successful use of DBS in older patients to treat OCD (the individuals described were aged 58 and 60) (Level 4) (Mantione et al., 2014; N. R. Williams et al., 2016). To our knowledge, there are no specific studies exploring the effectiveness of rTMS or dTMS in the elderly. However, systematic reviews of rTMS have included studies with participants ranging from 18 to 75 years old. For more information concerning TMS and other neurostimulation techniques see the neurostimulation and neuromodulation chapter above (Section 5). As there are only case reports using DBS in geriatric OCD, its level of evidence is 4 () and it is considered a third-line treatment.

With regards to ECT, one case report describes an 81-year-old with TR-OCD who had 'significant remission' following ECT (Level 4) (Loi and Bonwick, 2010). Regarding surgical interventions such as APN, one case report compared two patients aged 18 and 64 with TR-OCD post radiofrequency capsulotomy. The 64-year-old improved gradually over 24 months (Y-BOCS score reducing from 30 to 8) whereas the 18-year--old improved quickly after surgery, scoring 0 on the Y-BOCS (Level 4) (Christensen et al., 2002). APN and ECT have level 4 evidence () for treating older adult OCD, and are both considered a third-line treatment, only used as a last resort in severe treatment resistant cases.

Although the studies are limited to open-label trials and case reports the first-line treatments, similar to a younger adult OCD population, would be SSRIs and CBT/ERP. As previously mentioned, when treating older adult OCD, clinicians may need to be more cautious and be aware of potential drug interactions, tolerability issues, and take into account the accessibility of different treatments.

RECOMMENDATIONS FOR THE TREATMENT OF OCD IN THE OLDER ADULTS

- There are no pharmacotherapy RCTs or CBT/ERP RCTs in OCD in older adults
- SSRIs, with the exception of paroxetine, are considered the first-line pharmacotherapy (Level 4)
- SSRIs should be titrated slowly, beginning at 25–50 % of the normal adult starting dose (Level 4)
- Serum sodium, electrocardiograms, and renal function should be regularly monitored
- CBT/ERP should be considered a first line psychotherapy treatment (Level 4)
- Follow general adult OCD treatment guidelines, given lack of data for this population

7.3. OCD and autism spectrum disorder (ASD)

OCD is the second most common comorbid disorder with autism spectrum disorder (ASD), and 2.6 %–37.2 % of children and adolescents with ASD have comorbid OCD (Postorino et al., 2018). Those with OCD also have a 13 times higher risk of having a comorbid ASD diagnosis than those without OCD. OCD may be underdiagnosed in children with ASD due to symptoms being viewed as a part of ASD, or ASD symptoms overshadowing presenting OCD symptoms (Martin et al., 2020). Individuals with comorbid ASD and OCD are more likely to be male, have an intellectual disability, and be younger at the time of OCD diagnosis (Martin et al., 2020). Additionally, those with both OCD and ASD have more severe compulsions and a lower level of obsessions, with severity of compulsions correlated with ASD symptom severity, and less insight (Barnard-Brak et al., 2021; Wikramanayake et al., 2018). The most endorsed ASD trait found in those with OCD is difficulty with flexibly shifting attention, with true diagnostic overlap also including poor social communication and decreased imagination (Wikramanayake et al., 2018). Increased ASD traits in those with OCD are also associated with greater functional impairment and higher levels of family accommodation (Richards et al., 2019). Hoarding behaviours are also higher in those with comorbid OCD and ASD, especially in those with greater social impairments, and in those who are female (La Buissonnière-Ariza et al., 2018).

Restricted, repetitive behaviours (RRBs) are a hallmark symptom of ASD. These behaviours are characterized by ritualistic and repeated motions or movements, lacking obvious function or purpose, although recent studies suggest it may help relieve anxiety (Jiujias et al., 2017). RRBs and OCD symptoms can be similar in that they both involve the compulsion of repeating certain behaviours and creating inflexible rituals around the behaviours (Santore et al., 2020). Although there are similarities in the presentation of RRBs and OCD symptoms, the former tends to involve more ordering and touching behaviours while the latter often includes more checking and counting behaviours (Santore et al., 2020). Although some studies show that when RRBs are interrupted it can lead to increased anxiety for individuals with ASD (Scahill et al., 2014), OCD compulsions stem from wanting to neutralize the distress caused by obsessive thoughts. Therefore, while it may be beneficial to study treatments geared at RRBs when wanting to treat OCD symptoms, clinicians must be aware of the difference in origin of these behaviours.

7.3.1. Therapies for OCD in ASD comorbidity

Individuals with comorbid OCD and ASD are more likely to be prescribed medications and to be in treatment for longer periods of time than those with only ASD or OCD (Doi et al., 2021; Martin et al., 2020). Psychological and pharmacological treatments for this population may need to be modified due to cognitive and executive processing difficulties, attentional issues, social and communication impairments, and lower language levels.

7.3.1.1. Psychological and psychosocial treatments. Individuals with both OCD and ASD are just as likely to receive CBT as those with just OCD, but are comparatively less likely to respond to it. They also experience treatment gains later than those with OCD alone and may need extended treatment sessions (Bedford et al., 2020). This could be due to ASD symptoms not responding to traditional CBT for OCD, and the need for alternative ways of presenting this intervention (Martin et al., 2020). As one of CBT's main goals is cognitive restructuring, cognitive inflexibility in those with ASD may make it difficult for them to consider alternative ways of thinking, negatively impacting outcomes. Individuals with ASD also struggle with emotion and thought recognition and reporting, which forces clinical researchers to rely on caregiver-reported outcomes. This, in accompaniment with executive functioning, cognition, and communication challenges, also impacts the success of traditional CBT in those with ASD, and those with comorbid ASD and OCD (Murray et al., 2015). A manualized autism-adapted CBT protocol for adolescents with OCD and comorbid ASD produced superior outcomes compared to a standard CBT protocol used in a comparable population (Level 4) (Jassi et al., 2021). Similar modifications have been made to internet-delivered CBT (Level 4) (Wickberg et al., 2022), intensive CBT, including CBT/ERP (Level 4) (Iniesta-Sepúlveda et al., 2018), and function-based CBT, with superior outcomes (Level 3) (Bedford et al., 2020; Vause et al., 2020).

7.3.1.2. Other psychosocial treatments. Dialectical behavior therapy (DBT) has emerged as a potential method of targeting emotion dysregulation in individuals with ASD (Ritschel et al., 2022), and early studies have found it to be feasible and beneficial (Bemmouna et al., 2021; Ritschel et al., 2022), with larger studies underway (Huntjens et al., 2020). It has not been examined in OCD or in comorbid OCD and ASD.

7.3.1.3. Pharmacological treatments. The only FDA-approved medications for symptoms of ASD are aripiprazole and risperidone, both of which are indicated for irritability in pediatric ASD (Marcus et al., 2009; McCracken et al., 2002). There are no medications approved to treat OCD symptoms in ASD.

7.3.1.4. Selective Serotonin Reuptake Inhibitors (SSRIs). Although there is limited research into the pharmacological treatment of individuals with comorbid ASD and OCD, SSRIs have demonstrated reduction in OCD symptoms in both conditions (Bedford et al., 2020). SSRIs are used to treat RRBs and anxiety in ASD, and are observed to be well-tolerated, although they may cause activation, including insomnia, hyperactivity, and impulsivity.

Fluoxetine is one of the most studied SSRIs and is often prescribed to treat repetitive behaviours, irritability, anxiety, and depression in those with ASD (Hollander et al., 2005, 2012). Activation and agitation are the most predominant side effects, although these symptoms are minimized when fluoxetine is started at a low dose and titrated up slowly. Fluoxetine has also been studied in those with ASD and comorbid OCD, with significant improvement in OC symptoms (Level 3) (Reddihough et al., 2019). The use of fluvoxamine in those with ASD has mixed results (McDougle et al., 1996, 2000), with moderate treatment effects on RRBs in those with comorbid OCD (Level 2) (Zhou et al., 2021). Fluvoxamine has more side effects in children with ASD including agitation, aggression, and hyperactivity, and may be more appropriate for adults. Citalopram and escitalopram have both demonstrated efficacy in ASD and in OCD, but have not been examined in comorbid OCD and ASD (King et al., 2009, 2013; Owley et al., 2005, 2010; Simonoff et al., 2022; Skapinakis et al., 2021).

7.3.1.5. Serotonin/dopamine modulators. Risperidone and aripiprazole are the only two medications approved for the treatment of individuals with ASD, although only risperidone has been examined in OCD with RRBs. The target symptom of these medications is irritability, although they are also observed to be effective in reducing disruptive behaviours, including aggression and self-injury, which improves daily functioning and allows those with ASD to more effectively participate and benefit from educational and behavioral interventions. Although not a first-line treatment for OCD, SDMs (atypical antipsychotics) have been used as adjunctive augmentation in OCD with and without comorbid tics with some success in those that are non-responders to SSRIs and CBT (Veale et al., 2014). Risperidone adjunctive to SRIs has been successful in reducing RRBs as measured by the Y-BOCS in TR-OCD (Level 4) (McDougle et al., 2000; Pfanner et al., 2000).

7.3.1.6. Glutamatergic agents. Memantine, an NMDA receptor antagonist, has been studied in those with ASD and/or OCD due to its action on glutamate receptors. Preliminary results suggest that adjunctive memantine leads to greater reductions in CY-BOCS scores compared to placebo and is well-tolerated in children with ASD (n = 2), OCD (n = 4), and those diagnosed with both disorders (n = 1) (Level 4) (Niemeyer et al., 2022).

7.3.1.7. Additional ASD treatments. As the literature on treatments for comorbid ASD and OCD is limited, the following section gives an overview of beneficial treatments for ASD. These may be helpful in the treatment of ASD with comorbid OCD as many of these agents have been studied in reducing RRBs in ASD.

Valproate (divalproex sodium) has been evaluated as a treatment for irritability, aggression and compulsivity in children and adolescents with ASD (Hellings et al., 2005; Hollander et al., 2006, 2010). Methylphenidate was shown to improve symptoms of inattention and hyperactivity ASD (Antshel and Russo, 2019; Joshi and Wilens, 2022; Rodrigues et al., 2021; Sturman et al., 2017). Dextromethorphan (20 mg) combined with quinidine sulfate (10 mg) has shown reductions in irritability, repetitive behaviours, and aggression, and improved flexibility as well as global symptoms in ASD (Chez et al., 2020). IV oxytocin (single dose) was found to reduce repetitive behaviours in ASDs (Hollander et al., 2003e) and social cognition (Hollander et al., 2007), while intranasal oxytocin showed mixed results (Anagnostou et al., 2012; Guastella et al., 2010; Phaik Ooi et al., 2017; Sikich et al., 2021). Intranasal arginine vasopressin (AVP) also improved measures of various ASD symptoms including RRBs (Parker et al., 2019). Trichuris Suis Ova (TSO) (Hollander et al., 2020), targeting inflammation and immune dysfunction, was shown to improve rigidity and repetitive behaviours.

7.3.1.8. Neurostimulation. Deep brain stimulation (DBS) has been successful for those with treatment-refractory OCD and is also shown to reduce OCD and depressive symptoms in those with OCD and comorbid ASD when applied to the ventral anterior limb of the internal capsule (Level 4) (Graat et al., 2022). Case studies of DBS in individuals with only ASD showed significant improvement in aggression and self-injurious behaviours (Level 4) (Yan et al., 2022).

Deep transcranial magnetic stimulation (dTMS) targeting the bilateral dorsomedial prefrontal cortex (dmPFC), a brain region potentially involved in theory of mind and mentalization, in those with OCD resulted in significant reductions in repetitive behaviours in two case reports of dTMS augmentation in ASD with OCD comorbidity (Level 4) (Avirame et al., 2017; Carmi et al., 2019; Storch et al., 2021).

7.3.1.9. Summary. There is a high prevalence of undiagnosed ASD in individuals with OCD, with as high as 50 %, scoring above threshold on measures of autism traits (Wikramanayake et al., 2018). Although CBT and SSRIs are the first-line treatments for OCD, modifications need to be made in order to better target symptoms of ASD and reduce side effects. Medications for those with comorbid ASD and OCD should be started at low doses and titrated up slowly, and patients should be monitored for increased activation and mood instability. Additionally, CBT alone may be less effective for this population due to higher rates of intellectual disabilities and cognitive inflexibility, and lower adaptive functioning and verbal fluency. CBT may need to be modified to better fit this population, and adding social skills, mindfulness, emotion regulation, and DBT-informed interventions may be helpful. Families and caregivers should also be involved in intervention planning, as many individuals with ASD and OCD continue to be dependent as they enter adulthood, due to poorer adaptive functioning and daily living skills.

8. Future Directions and Knowledge Gaps

Despite significant advances in the treatment of OCD, there are numerous issues requiring further study and investigation. This chapter highlights some of the knowledge gaps that should inform future directions of research.

8.1. Gaps in diagnostic assessment and OCD nosology

Efforts continue to identify potential subtypes or dimensions of OCD and explore whether certain symptom patterns or neurobiological markers could differentiate subgroups of individuals with OCD. Studies on the specific brain circuitry, neurotransmitters, and genetic factors involved in the development and maintenance of OCD are also continuing. There is a need for further longitudinal studies to provide

information on risk factors, onset, and course of OCD for insight into the developmental trajectories of OCD.

Although OCD is diagnosed based on the severity of OC symptoms, the level of distress they cause, and their impact on an individual's daily functioning, illness severity of OCD can vary widely among individuals, and it fluctuates over time. Stepped care requires monitoring of the course and progression of illness and onward referral to the appropriate level of care to match the patient's needs. Although there may be exceptional circumstances that require the ability for individuals to be referred to any appropriate level of the model, the usual progression would be based on individuals 'stepping up' to a higher level of care with additional interventions, usually having received or been offered interventions at a lower level of the model. A clinical OCD staging or stepped care model aimed at preventing, where possible, progression of the illness, may be especially relevant for the early identification and management of subthreshold OCD. Staging models have been proposed but have yet to be implemented in regularity in clinical practice. Longitudinal naturalistic trials may be particularly helpful for the further development of these models and would address the proportion of cases staged as medium or high risk and eventually developing OCD. They can additionally be helpful for identifying predisposing or precipitating factors linked to transition to the full disorder. Further, interventional studies including testing of the effectiveness of low intensity CBT interventions in subsyndromal groups for relieving distress or preventing conversion into OCD would also be informative.

8.2. Previously identified knowledge gaps regarding first-line treatments of OCD

As identified in previous treatment guidelines (Koran et al., 2007; NICE, 2005), systematic reviews, and meta-analyses (Öst et al., 2015; Skapinakis et al., 2021), there are many treatment issues requiring further study. These evidence gaps include: 1) which acute monotherapy is best for both response and remission? (Hollander et al., 2003a, 2003b; Koran et al., 2007); 2) which treatment is best during long-term treatment? (Fineberg et al., 2018; Greist et al., 1995b; Stein et al., 2007b); 3) what is the best next sequential treatment for initial treatment non-remitters? (Öst et al., 2015; Simpson et al., 2013a; Skapinakis et al., 2021); 4) what is the best ranked overall sequence of treatments? (Guidi and Fava, 2020; Koran et al., 2007; Skapinakis et al., 2021); and 5) which patients do best with which treatments? Additionally, we need a further understanding of the heterogeneity effects of family history of OCD (Garcia et al., 2010) and cognitive flexibility (Fineberg et al., 2018) on treatment outcome, while controlling for the impact of prior treatment (Fineberg et al., 2018; Greist et al., 1995a; Öst et al., 2015; Skapinakis et al., 2021).

The superiority of medications versus psychotherapy as first-line monotherapy in OCD also remains equivocal, as more information is needed regarding the relative efficacy, risks and benefits, tolerability, and discontinuation rates for these treatments (Skapinakis et al., 2021). Furthermore, few studies have adequately evaluated the adverse effects associated with psychological therapies for OCD, making it difficult to compare the relative tolerability of these interventions. Comparison is also limited by the absence of sufficient information about the influence of different mediating or moderating factors on the outcomes of treatment of OCD with these modalities. There is emerging evidence that different subgroups of individuals with OCD might respond differentially to SRIs versus CBT. Further research into this may allow clinicians to better predict treatment outcomes at the level of the individual patient and allow for more personalized care. Finally, in terms of study methodology, very few trials have adequately compared CBT with SRIs on frequency and severity of adverse events using standardized instruments, and on measures of quality of life (Öst et al., 2016; Romanelli et al., 2014), and there is inconsistency in the reporting of treatment response (clinically meaningful reduction in symptoms) and remission rates in existing OCD trials (Mataix-Cols et al., 2016). These OCD guidelines have identified other gaps in knowledge specific to pharmacotherapy, psychotherapy, neuromodulation, treatment resistance, and pediatric OCD.

8.3. Knowledge gaps related to first-line pharmacotherapy

Other relevant gaps in knowledge concerning first-line pharmacotherapy include the issue of understanding SRI plasma levels as well as the use of pharmacogenetic testing. Although the literature has indicated greater anti-obsessional effect with high versus low or medium doses of SSRIs, how the anti-obsessional effect may correlate to SRI plasma levels remains unclear. Some reports found a correlation between plasma levels of fluvoxamine and clomipramine (as well as the N-desmethylclomipramine/clomipramine ratio) and OC symptom improvement (Marazziti et al., 2012; Mavissakalian et al., 1990a, 1990b), although a subsequent report found more mixed results (Marazziti et al., 2012). A better understanding of the relationship between SRI plasma levels and their anti-obsessional effect could be relevant for predictions of treatment response through pharmacogenetic testing. Indeed, if SRI plasma levels are related to OCD response, classifying patients according to their cytochrome enzymes status (e.g. CYP2D6/2C19/2B6 ultra-rapid, normal/intermediate or poor metabolizers) could guide the titration and dosing strategy for each patient in order to achieve the real "individual" maximum tolerable dose. Finally, while studies on depression showed that the SERT occupancy in the striatum needs to be approximately 80 % to confer therapeutic benefit in MDD (Furukawa et al., 2019; Meyer et al., 2004), little is known about the relation between the dose of SRIs, SERT occupancy, and treatment response in OCD.

Further study is also required regarding the duration of OCD pharmacotherapy. Most studies have been limited to a maximum of 2 years of follow-up. Since the available long-term studies on the natural course of OCD show a trend toward remission for most OCD patients (Fineberg et al., 2013; Skoog and Skoog, 1999), longer follow-up studies should investigate the role of SRIs in the long-term management of OCD patients. Also, while there is strong evidence of high relapse rates after SRI discontinuation, little is known about the re-trialing efficacy after SRI discontinuation. The limited available literature seems to suggest that patients who relapse after SRI discontinuation respond again when the same SRI is reinstated, but to a lower degree with respect to the acute treatment (Maina et al., 2001).

8.4. Knowledge gaps related to psychotherapy

Despite several decades of research and clinical experience with psychotherapeutic treatments for OCD, there remain multiple important gaps in knowledge in the field. CBT/ERP and CT have emerged as first-line psychotherapy treatments based on studies examining their (average) efficacy; yet, not everyone will respond to each, and clinicians do not know ahead of time which treatment may be best for any individual patient. While several studies have examined predictors and moderators of response to each of CT, CBT, and ERP (see meta-analysis Steketee et al., 2019), if a person is predicted to not respond well to one, this does not answer the question of what other treatment that person is likely to respond to. Further, there is insufficient mechanistic knowledge of how predictors affect treatment to enable modification of these factors at the individual level. Evidence-based strategies for such a personalized approach (not only for first-line treatments but for other treatment decisions such as augmentation for partial response, e.g.) are still lacking in the field. Another knowledge gap is how many CBT/ERP or CT sessions should be considered an "adequate trial" for outcomes including full response and treatment remission. Further, the empirical evidence of the efficacy of augmentation of CBT/ERP with medications (despite it being commonly done in clinical practice) needs to be established. The durability of the effects of CBT/ERP is also an area that needs further study, which would help determine if booster sessions

should be done regularly or only as needed. There is emerging evidence of efficacy of online-based cognitive behavioral therapies for the treatment of OCD (Hirschtritt et al., 2017). Internet-delivered CBT could potentially improve patients' access to this intervention (Luu et al., 2020). Studies using low-contact forms of internet-delivered CBT report improvements in OCD symptoms (Hoppen et al., 2021), although standards of administering digital modalities of CBT and their regulations still need to be developed. There is also a need to determine for which patients digitally delivered CBT may be beneficial and for which patients it might not be. Finally, the side effects of psychotherapy for OCD have not been adequately studied.

The current treatment literature is also limited by substantial methodological shortcomings. For example, 80 % of CBT trials allowed adult OCD subjects to enter the trial if they were on stable doses of antidepressants prior to screening, therefore most of these CBT studies should be considered augmentation or combination treatment studies. Further, very few CBT studies had a duration of greater than 16 weeks, making it impossible to draw conclusions about long term outcome of CBT in OCD (Geller et al., 2002). Although this is not an exhaustive list of knowledge gaps in psychotherapy for OCD, research that can address these questions could potentially improve the overall treatment experience, efficiency, and outcome.

8.5. Knowledge gaps related to treatment resistance

The most urgent knowledge gap in the treatment resistant literature involves establishing and adopting consistent, standardized criteria when describing treatment resistance and treatment refractoriness. At present, the literature is difficult to summarize as the definitions vary so broadly and are often mistakenly used interchangeably. The acceptance of using and implementing a universal treatment resistance definition is essential to move this area of research forward, as well as for clinicians who treat OCD. Augmentation of first-line pharmacotherapy with a pharmacological agent that typically acts via a different mode of action is currently the preferred treatment resistant strategy. It is unclear how long that a given augmentation strategy be used and at what dose to assess response, and if the patient does respond to augmentation, how long the augmentation agent needs to be used to maintain response. There are a number of augmentation strategies that have level 1 and 2 evidence of efficacy in treatment resistant OCD, with the recommended first line including aripiprazole, risperidone, haloperidol and CBT/ERP, and the second line including lamotrigine, topiramate, memantine, and high dose SSRI monotherapy, with rTMS also showing efficacy. However, there is no evidence-based literature as to which of these strategies should be tried first and in whom, and then which subsequent strategy should be used. There is a need to have adequately powered, head-to-head trials of these augmentation strategies to help answer these questions.

8.6. Knowledge gaps in OCD neuromodulation interventions

Non-invasive neuromodulatory interventions such as rTMS and transcranial direct tDCS hold promise as augmentation interventions for treatment resistant OCD (Fineberg et al., 2020). Further research on these interventions must examine what modalities and protocols are effective for which treatment groups so that a consensus can be reached on the protocols by clinicians hoping to adopt these treatments for their patients.

Specific evidence gaps for rTMS in OCD include: 1) whether monotherapy with rTMS is effective, since most studies to date have studied rTMS as an augmentation treatment added on to existing medication and/or psychotherapy (Fitzsimmons et al., 2022); 2) whether behavioural exposure is needed during TMS stimulation, since the multicenter dTMS study utilized this approach but most clinical TMS treatment does not implement exposure during stimulation (Carmi et al., 2018); 3) how often maintenance rTMS therapy is needed to maintain gains, and what is the optimal frequency of maintenance therapy (Pellegrini et al., 2022)?; 4) is the cost and time commitment for TMS justified in terms of its benefits compared to other treatments?; 5) what is the optimal sequencing of rTMS as a first-, second-, or third-line treatment, as some evidence suggests more robust response when administered earlier on in treatment (Pellegrini et al., 2022); and 6) is rTMS more effective than other augmentation treatments such as risperidone (Pallanti et al., 2016)?

DBS and APN are techniques used in severe treatment refractory cases. Further research is required to understand the pros and cons of these techniques and to have a better understanding of when these invasive techniques can and should be suggested (Alonso et al., 2015; Fineberg et al., 2020). The main knowledge gaps for optimizing the efficacy and safety of DBS in OCD include: 1) defining the optimal selection criteria for DBS, including those cases with comorbidities; 2) identifying biomarkers and clinical profiles capable of predicting the response to DBS; 3) establishing the best personalized anatomical target for each patient; 4) developing procedures to determine the optimal stimulation parameters for each individual case; 5) further elucidating the mechanisms of action; 6) given that invasive techniques are typically lifelong, there is a critical need to enhance understanding of their efficacy and safety over the long term.

8.7. Knowledge gaps related to pediatric OCD treatment

There are numerous gaps in our knowledge regarding etiology, pathophysiology, and optimal management of OCD in youth. Of these, perhaps the most salient is the putative subset of immune-driven inflammatory-mediated neuropsychiatric illness with OCD as a primary presentation, because it has major implications for alternate (immune modulating) treatment approaches. The construct of PANDAS/PANS will remain controversial until reliable biomarkers can be identified.

Other non-pharmacological treatments for pediatric OCD that have not been well studied but deserve evaluations are those that have been shown to be helpful for adults. For example, cognitive therapy and especially acceptance commitment therapy (ACT) which has been useful for certain kinds of obsessions where compulsions are not prominent. In youth with OCD associated with PTSD, eye movement desensitization and reprocessing (EMDR) may be useful.

With respect to pharmacology, an important issue is the optimal duration of treatment for the first episode. Some evidence suggests that treatment response increases beyond the 12 weeks typically used for RCTs. For example, in the one-year open-label pediatric OCD sertraline trial, CY-BOCS scale scores continued to fall substantially until week 26 (Cook et al., 2001). Therefore, the modest effect sizes seen for pharmacological trials likely underestimate the true effects of medications used over longer periods. Other medication augmentation strategies requiring investigation include 5-HT_3-receptor antagonists (ondansetron, granisetron), glutamatergic medications including memantine, d-cycloserine, troriluzole, and anti-epileptic drugs such as lamotrigine and valproate, which may also target glutamate pathways.

Finally, interventional neurology treatments such as deep TMS,

transcranial direct current stimulation (tDCS), and deep ultrasound may be useful options in severe and treatment refractory pediatric cases. However, treatment with DBS in children and adolescents has only been used in sparse cases in those suffering primarily from other conditions (such as Tourette's syndrome), and there are no RCTs of its use in OCD (Ashkan et al., 2021). The application of DBS in the pediatric OCD population raises specific ethical issues, concerning their capacity for assent, the lack of evidence on outcomes and possible unknown effects, and the potential for the disorder to improve with age (Muñoz et al., 2021).

8.8. Other knowledge gaps in OCD treatment and conclusion

There is also a great need to expand our knowledge in the areas of perinatal OCD, geriatric OCD, and in OCD with autism spectrum comorbidity. At present, clinicians are forced to extrapolate treatment data from either the adult or child literature, however, these populations have special characteristics which may require modified approaches.

In conclusion, these guidelines were developed with the goal of reviewing the current literature on OCD treatment and assisting clinicians in treating patients with OCD across the life span. These guidelines fulfill a need we identified by establishing clinical guidelines on the use of existing and new pharmacological and psychosocial interventions as well as augmentation therapies among various OCD populations and treatment resistant groups.

Key Points

- There is a need for further longitudinal studies to elucidate risk factors, onset and course of OCD to provide insight into developmental trajectories.
- Further development of stepped care models for OCD may be useful for early identification and management, based on data from longitudinal studies and clinical trials.
- There are multiple knowledge gaps related to first-line treatments including which treatments are best for acute monotherapy, long-term treatment and treatment non-remitters, as well as how these treatments are best sequenced.
- The use of pharmacogenetic testing and SRI plasma levels needs further refinement and there is a need for adequately powered trials in OCD treatment resistance.
- Methods of determining which psychological treatments may be best suited to which individuals is an important question, as well as how many sessions are optimal and the durability of these psychological treatments.
- Further studies are needed provide clarity on the most effective neuromodulation protocols using rTMS and tDCS, whether to use these agents as monotherapy or augmentation and where they best fit in the sequencing of OCD treatments.
- OCD treatment of children and adolescents is associated with numerous knowledge gaps including the use of psychotherapies such as ACT and EMDR, the optimal duration of pharmacological treatment and the appropriate use of interventional neurological treatments.
- More investigation of specific treatments in perinatal and geriatric OCD populations as well as OCD populations with comorbid ASD are required.

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Footnotes

1) In the United States, the FDA-issued approval for the treatment of OCD in children and adolescents currently exists for sertraline (ages 6 and above), fluvoxamine (ages 8 and above), fluoxetine (ages 7 and above), and clomipramine (ages 10 and above). In the European Union, several member states have approved sertraline (ages 6 and above) and fluvoxamine (ages 8 and above) for the treatment of pediatric OCD. Following a review and advisory from the European Medicines Agency (EMA) in April 2005 regarding increased risk for suicidality, the EMA concluded that SSRIs should not be used in children and adolescents "except in their approved indications" (European Medicines Agency, 2005). However, SSRIs including sertraline, fluvoxamine, citalopram, escitalopram, and fluoxetine are widely used off label in management of youth with anxiety, OCD, and depression. In Canada, no antidepressant medication is currently officially approved for use under the age of 18 (Korczak and Society, 2018).

Dedication

The authors wish to acknowledge Dr. Dan J. Stein and his larger-than-life contributions to the field of Obsessive-Compulsive and Related Disorders as well as psychiatry in general. His work significantly advanced our current understanding of the diagnosis, phenomenology, neurobiology and evidence-based treatments of OCD, as evidenced throughout these new treatment guidelines. He was a long-term member

of ICOCS and served as a Director of the organization, as well as numerous other international psychiatric societies and transnational initiatives such as DSM-5 and Enigma OCD. His friendship, quiet determination, curiosity, and brilliance will be greatly missed. We dedicate the CANMAT-ICOCS International Guidelines for the Management of Obsessive-Compulsive Disorder to Dr. Stein's memory.

Declaration of competing interest

All conflicts of interest (COI) forms for each author have been uploaded as a single file, under supplementary material. For some reason, it wouldn't allow us to upload them under the Declarations of Interest folder.

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Dr. Arun Ravindran reports a clinical trial with Biohaven Pharmaceuticals Inc.; consulting fees from AbbVie Pharmaceuticals Inc.; Advisory Boards for AbbVie Pharmaceuticals Inc. and Otsuka Pharmaceutical Co. Ltd.; and holds a leadership role in the Canadian Network for Mood and Anxiety Treatments (CANMAT).

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Dr. Naomi A Fineberg reports Research Grants from UK NIHR, UKRI and Orchard; Networking grants from COST Action; Honoraria from Global Mental Health Academy and Children and Screens; Travel expenses paid by ECNP, CINP, BAP and IFMAD; Is Chair of Trial Advisory Board for NIHR study into neuromodulation for depression; Holds position of National Clinical Lead for NHS England Severe OCD/BDD Service, is the secretary for ICOCS, and Co Chair for WPA Anxiety and OCD Section; Honorarium for editorial duties by Elsevier; has received research drug from Compass Pathways.

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Appendix A. Supplementary data

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