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Behavioural and cognitive behavioural therapy for obsessive compulsive disorder (OCD) in individuals with autism spectrum disorder (ASD) (Protocol)

Elliott SJ, McMahon BM, Leech AM

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[Intervention Protocol]

Behavioural and cognitive behavioural therapy for obsessive compulsive disorder (OCD) in individuals with autism spectrum disorder (ASD)

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The main objective is to assess the effectiveness of behavioural and cognitive behavioural therapy for OCD in individuals with ASD.

BACKGROUND

Description of the condition

Obsessive compulsive disorder (OCD) is common in people with autistic spectrum disorders (ASD). OCD occurs worldwide, affects approximately 2 percent of the population and is associated with substantial impairment (Angst 2004, Kessler 2005). Onset is usually in childhood/early adulthood and the course is variable (Stewart 2004).

OCD is characterised by recurrent obsessional thoughts or compulsive acts. Obsessional thoughts are repeated stereotyped ideas, images, or impulses that are distressing, unsuccessfully resisted, but recognised as belonging to the individual. Compulsive acts comprise repeated stereotyped behaviours that are not inherently enjoyable or useful, are perceived as preventing some objectively unlikely event, and are recognised as pointless/ineffective. In ICD-10, symptoms must be present on most days for at least two weeks and be a source of distress or interfere with activities (WHO 1992). In DSM-V (APA 2013), OCD is no longer classed as an anxiety disorder. The DSM-V diagnostic criteria are similar to ICD-10, but specifiers are added for degrees of insight and presence/absence of tics.

Autism is characterised in ICD-10 by difficulties in the three areas of qualitative impairment in social interaction and communication and by restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities. Stereotyped behaviours may be movements or verbal utterances, or both (Casey 2007). The ICD-10 criteria for Asperger's syndrome are similar to that of Autism but they include a lack of significant delay in spoken/receptive language or in cognitive development.

DSM-V no longer separates Asperger's syndrome and autism, including both under the rubric, ASD. The diagnoses of As-

perger's syndrome and autism are therefore included under the umbrella of ASDs in this review as they share the same impairments (Macintosh 2004). Diagnostic criteria require deficits in two main areas, firstly, social communication/interaction and secondly, restricted, repetitive patterns of behaviour. Sensory difficulties are included under restricted, repetitive patterns of behaviour for the first time. Specifiers indicating severity/need for support and comorbidities are included. Autism is common, and a 2006 study in the USA showed that 0.9% of 310,000 children aged eight years were identified as having ASD (Rice 2009).

Both OCD and ASD are characterised by repetitive behaviours, which has led to questions about a possible association between the two disorders. Studies have found a high rate of OCD symptoms in the ASD population and these are associated with significant distress (Russell 2005). Russell and colleagues (Russell 2005) found a similar frequency of obsessions and compulsions in participants with OCD alone as in participants with high-functioning ASD, but those with OCD alone had more somatic obsessions and checking compulsions. A further study from the same institution (Mack 2010) found that children with ASD may experience similar levels of impairment from OCD symptoms as children with both Tourettes Syndrome and OCD and as children with OCD alone. It should be noted that these participants were drawn from a clinic specialising in treating patients with high levels of comorbidity. McDougle and colleagues (McDougle 1995) found that, compared to individuals with OCD alone, those with autism were less likely to have thoughts with aggressive, contamination, sexual, religious, symmetry, and somatic content.

A recent large meta-analysis of 31 studies of 2121 young people with ASD found that 17.4% with ASD met the criteria for OCD (Van Steensel 2011) and further studies have supported this finding (Leyfer 2006). Conversely, studies have also found that participants with OCD have autistic traits (Anholt 2010; Bejerot 2001; Ivarsson 2008; Stewart 2016). Kuno 2018 suggested that variations in white matter features may be associated with autistic traits in OCD. The fact that repetitive behaviours are characteristic in both OCD and ASD can lead to diagnostic confusion (Perez 2012) and either underdiagnosis or overdiagnosis. In OCD, repetitive behaviours are perceived as ego-dystonic (i.e. they are in conflict with a person's self-perception and are distressing) and are resisted. In ASD, repetitive behaviours that are not related to OCD are often pleasurable, not resisted, and are not usually distressing. In summary, both OCD and ASD are common disorders which often occur together. People with ASD have an increased incidence of OCD and people with OCD display traits of ASD. Difficulties in diagnosis of OCD in ASD may lead to a degree of overdiagnosis or underdiagnosis in the ASD group.

Description of the intervention

Treatments for OCD include psychological therapies, particularly cognitive behavioural therapy (CBT), as well as pharmacological therapies such as selective serotonin reuptake inhibitors (SSRIs) (Soomro 2008), and some antipsychotic medications (Komossa 2010). National Institute for Health and Care Excellence (NICE) guidelines recommend psychological therapies as the first-line treatment, especially for milder cases (NICE 2005; NICE 2013). In the general population, the central technique for treating OCD is Behaviour Therapy (BT) which includes Exposure and Response Prevention (ERP). ERP exposes the client to the anxiety provoked by his or her obsessional thoughts, then reduces and eliminates the use of rituals or repetitive behaviours that are performed by the client to reduce this anxiety. Relaxation therapy techniques are used to help to control the anxiety. Cognitive Therapy (CT) is often combined with BT/ERP. CT is based on the principal that certain thoughts fuel obsessions and compulsions, and aims to modify these thoughts. CBT is the psychotherapeutic intervention that combines CT and BT/ERP and is the primary intervention recommended by current NICE Guidance (NICE 2005). The use of CBT in adults and children with OCD is supported by meta-analyses (Gava 2009; O'Kearney 2006; Olatunji 2013). There is a large body of clinicians with knowledge of CBT, although shortfalls have been highlighted (Clark 2011). Importantly, there is little guidance on the use and adaption of this therapy for OCD with comorbid ASD.

How the intervention might work

As discussed above, evidence supports the use of ERP combined with CT for the treatment of OCD in the general population, during which repeated exposure to a feared stimulus, whilst refraining from rituals, leads to habituation to anxiety, and maladaptive thinking maintaining the disorder is diminished.

Concerns have been raised about the effectiveness of psychological therapies in people with ASD because of their differing cognitive processes (Hauck 1995), although other research has challenged this (Dahlgren 2003) and has confirmed that CBT may be helpful for anxiety disorders in children with ASD (Sofronoff 2005).

CBT is assumed to work in a similar way in people with ASD but may need adaptations. Five case reports of treatment of OCD with CBT in children and adolescents with ASD (Elliott 2014; Lehmkuhl 2008; Lord 1995; Nadeau 2014; Reaven 2010) highlight some of the adaptations that may be useful, including emphasising the behavioural aspects of CBT and relying more on concrete practical and verbal interventions than on discursive discussion. Specific techniques included high level of parental/teacher involvement, use of visual cues, charts and strategies, social stories, involvement of the patient in decision making and planning, use of simple coping statements, behavioural reward systems, psychoeducation, and simple relaxation exercises. Factors associated with a good outcome in these case reports included ego-dystonic nature of symptoms, motivation, ability to self-reflect and self-monitor, ability to externalise, verbal ability, and parental support. Family factors were also associated with good outcome in a randomised

controlled trial of CBT versus anxiety management for treatment of OCD with comorbid ASD (Murray 2014).

In a case-controlled study, Murray and colleagues (Murray 2014) compared efficacy of CBT for OCD in 44 young people, 22 with comorbid ASD and 22 without ASD, and found that people with ASD responded positively to CBT but showed lower response and remission outcomes than people without ASD. Russell and colleagues (Russell 2013) studied 46 adolescents and adults with comorbid ASD and OCD who were randomised for treatment with CBT or anxiety management, in this study the anxiety management approach was carefully constructed to ensure that any treatment effects were solely due to the CBT. The anxiety management included psychoeducation and general anxiety management techniques. The study found no statistically significant differences between the two groups (CBT or anxiety management) at the end of treatment in terms of symptom severity. There were twice as many responders in the CBT group compared to the anxiety management group but this difference was not statistically significant. In a study of 39 participants, 15 with ASD and OCD and 22 with OCD and no ASD, Tsuchiyagaito 2017 found that participants with OCD and ASD responded significantly less well to CBT and that the non-remission group had significantly smaller grey matter volume in the left dorsolateral prefrontal cortex. In a case series of intensive CBT for OCD in 9 adolescents with ASD, Iniesta-Sepulveda 2018 found that an intensive CBT approach for OCD was effective among adolescents with ASD. Kose 2018 and colleagues, in a review of the research, referenced the usefulness of modifications of the standard CBT protocol for individuals with OCD and ASD, such as parental involvement, use of visuals, personalised treatment metaphors, self-monitoring, positive reinforcement, and use of clear language and instructions.

Why it is important to do this review

As ASD is increasingly recognised in both adult and child populations, research on the efficacy of established models of treatment for mental disorder in individuals with ASD is increasing. Due to the high prevalence of OCD in ASD (Russell 2005) and the considerable distress and morbidity OCD symptoms cause, clinicians need to be aware of up-to-date information about evidence-based treatments in this population. CBT is well established as a first-line treatment for OCD in the general population (NICE 2005). CBT is likely to have a positive impact on OCD symptoms in the ASD population, but differing cognitive styles in individuals with ASD are likely to influence response to treatment with CBT and adaptation of CBT delivery will be required. Due to the growing interest in this area, it is hoped that future studies will more precisely clarify the efficacy of and helpful modifications to CBT for OCD in individuals with ASD.

OBJECTIVES

The main objective is to assess the effectiveness of behavioural and cognitive behavioural therapy for OCD in individuals with ASD.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled studies (RCTs), cross-over, cluster- and quasi-randomised controlled trials . Quasi-randomised trials will be included as it is expected that the literature will be sparse, but the results of these trials should be treated with caution given the suboptimal method of allocation.

We will include differing formats for delivery of CBT providing they otherwise meet criteria for inclusion in the review.

Types of participants

Participant characteristics

Participants of any age, both adult and paediatric, and of any race or gender will be included in the review.

Diagnosis

All participants will have received diagnoses from studies using validated tools based on standardised diagnostic criteria, such as ICD-10 (WHO 1992) or the DSM-IV or -5 (APA 2013) for both Autistic Spectrum Disorders (ASD) and OCD (including Asperger's syndrome in ICD-10). Participants who do not meet the full criteria for full syndrome autism or Asperger's syndrome, such as those with atypical autism or pervasive developmental disorder not otherwise specified, will not be included. Some studies of CBT for individuals with ASD may include other psychiatric diagnoses such as anxiety disorders, as well as OCD. These studies will be included as long as the diagnosis of ASD meets criteria described above and pre- and post-treatment measurements of OCD symptoms are included. Pretreatment measurement of OCD symptoms must also meet diagnostic criteria, as above.

Comorbidities

Studies will be included where the participants have comorbidities including other psychiatric disorders, neurodevelopmental disorder, and learning difficulties. It should be noted that the diagnosis of OCD may be problematic for those with more severe global

learning difficulties and it will therefore not be possible to include individuals in the analysis where global learning difficulty precludes a diagnosis of OCD.

Setting

Any setting for therapy will be included: inpatient, daypatient, or outpatient.

Types of interventions

Experimental interventions

Experimental interventions will include behavioural therapy (i.e. ERP and other BT techniques, such as graded exposure and relaxation therapy, breathing management, and distraction techniques, either alone or in combination) and CBT. ERP (exposure and response prevention) is a therapy that exposes the client to the anxiety provoked by his or her obsessional thoughts, then reduces or eliminates the use of rituals/repetitive behaviour performed by the client to reduce this anxiety. CBT is the psychotherapeutic intervention that combined CT and BT/ERP and is the primary intervention recommended by NICE (see Description of the intervention). Studies will be included where interventions are delivered in any format, for example, in groups or via the internet.

Comparator interventions

Comparator interventions will include no treatment, waiting list, attention placebo, psychological placebo, and treatment-as-usual.

Types of outcome measures

Primary outcomes

1. Efficacy outcome - change in core OCD symptomatology at end point (post-treatment) or follow-up compared to measures of symptomatology at baseline or remission from OCD status. This will be assessed by the severity of OCD symptoms as measured on a validated OCD symptom rating scale. Total scores on continuous measures will be used, including the Yale-Brown Obsessive Compulsive Scale (YBOCS) which is considered the 'gold standard' measure of OCD symptoms (Rosenfeld 1992), the children's version (CY-BOCS) (Storch 2004), the National Institute of Mental Health Global Obsessive Compulsive Score, and the Obsessive Compulsive Inventory-Revised (Foa 2002).
2. Adverse events outcome - total number of dropouts due to adverse effects.

Secondary outcomes

3. Quality of life, measured using recognised rating scales, for example, the World Health Organization Quality of Life index (WHO 1997).
4. Severity of depressive symptoms using a standardised scale, for example, the Beck's Depression Inventory (Beck 1961).
4. Severity of anxiety symptoms using standardised scales, for example, the Hospital Anxiety and Depression Scale (HADS, Zigmond 1982) and the child equivalent, the Childrens Depression Inventory (Kovacs 1985).
5. Level of behavioural difficulties using standardised scales, for example, the Child Behaviour Checklist (Achenbach 1983).

Timing of outcome assessment

Outcome measurement will be taken at end of treatment (within 2 weeks of the final treatment session) or at follow-up (within 6 weeks of final treatment session). If a study reports an outcome at several time points, we will select the latest time point, as long as it is within 6 weeks of the final treatment session.

Hierarchy of outcome measures

If studies use multiple measures and one of the measures is the YBOCS or CY-BOCS, then the YBOCS or CY-BOCS measure will be the measure included in the review, as this is considered the gold standard measure of OCD symptoms. If a study uses multiple measures not including the YBOCS, then the rating scale with the best assessed reliability and validity after peer discussion will be the one included in the review.

Search methods for identification of studies

Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR)

The Cochrane Common Mental Disorders Group (CCMD) maintains two archived clinical trials registers at its editorial base in York, UK: a references register and a studies-based register. The CCMDCTR-References Register contains over 40,000 reports of RCTs in depression, anxiety, and neurosis. Approximately 50% of these references have been tagged to individual coded trials. The coded trials are held in the CCMDCTR-Studies Register, and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual, using a controlled vocabulary (please contact the CCMD Information Specialists for further details). Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950 to 2016), Embase (1974 to 2016), and PsycINFO (1967 to 2016); quarterly searches of the Cochrane Central Register of Controlled Trials (

CENTRAL); and review-specific searches of additional databases. Reports of trials are also sourced from international trial registers via the WHO trials portal (the International Clinical Trials Registry Platform (ICTRP)), pharmaceutical company websites, and handsearching of key journals, conference proceedings, and other (nonCochrane) systematic reviews and meta-analyses.

Details of CCMD generic search strategies (used to identify RCTs) can be found on the Group's website, with an example of the core MEDLINE search displayed in Appendix 1.

The CCMDCTR is up-to-date as of June 2016 only, when the Editorial Group moved from the University of Bristol to the University of York.

Electronic searches

1. **Cochrane Specialised Register**

CCMD's Information Specialist will search the Group's specialised register (CCMDCTR) using the following terms (condition and population only):

(i) CCMDCTR-Studies Register: (Condition = *obsess** or *compulsi** or *OCD* or "*anxiety disorder**") and (Condition or Comorbidity = *autis** or *asperger**)

(ii) CCMDCTR-References Register: ((*obsess** or *compulsi** or *OCD* or "*anxiety disorder**") and (*autis** or *asperger** or *kanner** or *ASD* or *ASDs* or (*childhood* and *schizophren**) or (*pervasive* and *development** and *disorder**) or *PDD* or *PDDs*): ti,ab,kw,ky,mh,mc,emt

[Key to field tags. *ti:title; ab:abstract; kw:keywords; ky:other keywords; mh:MeSH headings; mc:MeSH check words; emt:EMTREE headings*]

We will screen the results for behavioural and cognitive behavioural interventions.

2. **Bibliographic Databases**

The information specialist will conduct complementary searches on the following bibliographic databases using keywords, subject headings, and search syntax appropriate to each resource:

- PsycINFO (Ovid) (all years) (Appendix 2);
- Cochrane Central Register of Controlled Trials (CENTRAL) (current issue);
- Medline databases (Ovid) (1946-current date);
- Embase (Ovid) (1974-current date);
- CINAHL (Cumulative Index to Nursing & Allied Health) (EBSCO)(1982-current date);
- Sociological Abstracts (Proquest) (1963-current date);
- Web of Science - Core Collection (all years);
- ERIC (Educational Resources Information Center) (Proquest) (1966-current date).

3. **International Trial Registries**

The information specialist will also conduct searches on international trial registries to identify unpublished and/or ongoing studies in the World Health Organization's trials portal (ICTRP) and ClinicalTrials.gov.

There will be no restrictions on date, language, or publication status applied to the searches. We will use translation services to access materials in nonEnglish languages to reduce the possibility of language bias.

We will check for retractions and errata once all included studies have been selected. We will also ensure that multiple (secondary) publications are matched to the parent study and not represented more than once in the analysis

Searching other resources

Grey Literature

We will search the following sources of grey literature:

- Electronic Theses Online Service (EThOS) - British Library, http://ethos.bl.uk/Home.do
- DART - Europe e-theses Portal, http://www.dart-europe.eu/basic-search.php
- Networked Digital Library of Theses and Dissertations (NDLTD), http://search.ndltd.org/
- PQDT Open - open access dissertations and theses, https://pqdtopen.proquest.com/search.html
- Proquest Dissertations & Theses Global, https://search.proquest.com/pqdtglobal/dissertations/
- Open Grey (http://www.opengrey.eu/)

Reference Lists

We will check the reference lists of all included studies and relevant systematic reviews to identify additional studies missed from the original electronic searches (for example unpublished or in-press citations).

Correspondence

We will contact trialists and subject experts for information on unpublished or ongoing studies or to request additional trial data.

Data collection and analysis

Selection of studies

Two review authors (SE and AL) will independently screen titles and abstracts for inclusion and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full text study reports/publications of potential inclusions and will examine them for compliance with eligibility criteria. Reasons for exclusion of ineligible studies will be identified and recorded. We will resolve any disagreement through discussion or, if required, we will consult a third author (BM). We will identify and exclude

duplicate records and we will collate multiple reports that relate to the same study so that each study, rather than each report, is the unit of interest of the review. It may be appropriate to correspond with the investigators, where appropriate, to clarify study eligibility. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of studies' tables.

Data extraction and management

Data will be extracted by two authors (SE and AL) independently and collated on a data extraction form which will be piloted on at least one study in the review. Disagreements will be resolved by discussion and through consultation with a third author (BM), if necessary. Data will be entered into Excel or Access before one author (SE) transfers data to Revman.We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second author (AL) will spot-check study characteristics for accuracy against the trial report. Information collected on the data extraction form will include:

1. Details of participants: mean age, age range, sex, severity of condition, diagnostic criteria (validity of participants' diagnoses of ASD or OCD prior to study (based on the use of validated tools based on standardised diagnostic criteria such as the ICD-10 (WHO 1992) or the DSM-V (APA 2013)), inclusion and exclusion criteria.
2. Methods: study design, total duration of study, number of study centres and location, study setting, withdrawals, date of study.
3. Types and application of interventions for study and comparison groups.
4. Outcome measures including primary and secondary outcomes and time point data collected including post-treatment measures.
5. Notes: funding for trial, and notable conflicts of interest.

Main comparisons

CBT in individuals with OCD and ASD will be compared with non active comparators.

Assessment of risk of bias in included studies

Methodological quality of bias, or both, will be assessed for each included study by two authors (SE and AL) using the Cochrane 'Risk of bias' tool (Higgins 2017). We will resolve any disagreements by discussion or by involving a third author (BM).

The following areas will be evaluated.

1. Sequence generation;
2. Allocation concealment;
3. Blinding of participants and personnel;
4. Blinding of outcome assessment;
5. Incomplete outcome data for main outcomes or class of outcomes: this will include whether reasons for missing outcome data were recorded and whether the reasons for the missing data were likely to be related to outcome;
6. Selective outcome reporting: this will ensure all preselected outcomes were exclusively and completely reported on and could be entered into a meta-analysis;
7. Other sources of bias: for example, discrepancies in the level of therapist qualification, treatment fidelity, manualisation of therapy, and researcher conflict of interest.

Assessment of studies will be made using the 'Risk of bias' tool using the following three categories: low, unclear, and high. A supporting quotation from the study report together with a justification for our judgement in the 'Risk of Bias' table will be provided. The authors of included studies will be contacted for further information, where necessary, and this will be noted in the 'Risk of Bias' table. 'Risk of bias' data will be presented graphically and described in the text. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary.

Measures of treatment effect

1. Dichotomous data: We will analyse dichotomous data as odds ratios (ORs). Where risk ratios are provided in the studies, we will convert to odds ratios using the formula:
odds = risk divided by 1- risk.(Sackett 1997)
2. Continuous data: If data are continuous, the mean difference (MD) will be used for continuous outcomes on the same scale. The standardised mean difference (SMD) will be used to measure the treatment effect if, as is likely, different rating scales will be used in different studies. Data will be entered as a scale with a consistent direction of effect.

There may not be sufficient studies to undertake meta-analysis. In the event that sufficient studies are found, we will ensure that the studies are suitable for meta-analysis, i.e. that the treatments, participants, and the underlying clinical question are similar enough for pooling. The I^2 statistic will be calculated to quantify inconsistency between studies (see discussion under Assessment of heterogeneity).

The review may include studies using both change from baseline and final value scores. Both types will be combined in a meta-analysis using the (unstandardised) mean difference method in Revman, taking care to use appropriate means and standard deviations for each study. As the means and standard deviations of both types of study may differ substantially, they will be placed in separate subgroups for clarity. The standard deviations of change from baseline studies may not be reported and may need to be imputed.

Skewed data, reported as medians or interquartile ranges, will be presented in narrative form.

Unit of analysis issues

These will be managed using appropriate statistical analyses from the *Cochrane Handbook for Systematic Reviews of Interventions*, chapters 9.3 and 16.

Cluster randomised controlled trials

In cluster RCTs, participants within any one cluster tend to respond similarly, thus, the data of individuals within a cluster cannot be assumed to be independent of the other individuals within the same cluster. If these studies are analysed as if the unit of allocation had been the individual participant, then a unit of analysis error may occur leading to false positive conclusions, overly narrow confidence intervals, and the study will receive more weight than is appropriate in the meta-analysis. Risk of bias in cluster RCTs will be reviewed for each study looking at possible recruitment bias, baseline imbalance between clusters, loss of complete clusters from a trial, and incorrect statistical analysis. When both cluster- and individually-randomised trials are included in a meta-analysis, possible differences between the intervention effects being estimated will be considered.
Appropriate statistical advice will be taken when analysing cluster RCTs or including them in meta-analysis.

Cross-over trials

Cross-over trials are unlikely to be used in this area due to the long duration of response to CBT which would lead to carry-over effects. However, if cross-over trials are included, we will avoid carry over-effects by including data from only the first period.
If cross-over trials are to be combined with parallel group trials in a meta-analysis, consideration will be given to the differences between the two types of trial, e.g. shorter intervention periods or less severe illness in cross-over trials. Cross-over trials will therefore be meta-analysed separately irrespective of whether they are also combined together with parallel group trials. We will explicitly state how we have dealt with data from cross-over trials in any meta-analysis and will conduct a sensitivity analysis to investigate the robustness of our conclusions if cross-over trials are not included. We will seek statistical support in this area.

Multiple treatment groups

For all multi-arm studies, we will assess:
- Which intervention groups are relevant to the systematic review;
- Which intervention groups are relevant to the meta-analysis;
- How the study will be included in the meta-analysis if two or more groups are relevant.

All intervention groups of a multi-intervention study will be mentioned in the table, 'Characteristics of Included Studies', either in the 'interventions' cell or the 'notes' cell. Detailed descriptions will be provided only for intervention groups relevant to the review, and only these groups will be used in analysis. If a study has more than one treatment group that satisfies the inclusion criteria, as long as interventions are similar and are compatible with the groups set out above, they will be combined in a single group. Interventions which are different from each other will not be grouped together.
To avoid risk of bias, the following questions will be asked about each study:
- Are the data presented for each of the groups to which participants were randomised?
- Are reports of the study free of suggestions of selective reporting of comparisons of intervention arms for the same outcomes?

When including more than one group from a study, we will ask if the study can provide independent comparisons or whether comparisons have intervention groups and participants in common (this may occur due to double counts of participants in shared intervention groups).

Dealing with missing data

Initially, we will contact the original investigators to request the missing data. We will review patterns of missing data and discuss their origins, i.e. we will examine patterns in the data to assess the most likely mechanism of missingness.
i. Data are missing completely at random (i.e. missingness not related to any observed/non-observed variables);
ii. Missing data may be related to observed or nonobserved variables but are ignorable because they are not related to actual values or outcomes;
iii. Missing data are actually related to the value of the outcome.

Missing data at random

We will deal with missing data, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions,* 16.1.2 (Higgins 2011), by one of the following options:
Where it is likely that data are missing completely at random or are ignorable (as in i. and ii. above), we will ignore it. It is probable that most missing data will not fall in this category. The advantage of this approach is that it will allow us to discount instances where missing data are unlikely to have an impact on the outcome of the study. The danger of this course of action is misinterpreting data as missing at random when there are in fact systematic underlying reasons. This may lead to over- or under-estimates of the effect size. Little's test may be useful for testing the assumption of data missing completely at random for multivariate, partially observed quantitative data (Little 1988).
We will deal with missing dichotomous data through an intention-to-treat (ITT) analysis, where we assume that participants who drop out after randomisation have a negative outcome. We also plan to calculate best/worse case scenarios for the clinical response outcome, where we will assume that dropouts in the active treatment group have positive outcomes and those in the control group

have negative outcomes (best case scenario), and that dropouts in the active treatment group have negative outcomes and those in the control group have positive outcomes (worst case scenario).

Where there is missing continuous data we will use imputation, for example using the last-observation-carried-forward (LOCF) and multiple imputation, if these data are reported by the trial authors.

If standard deviations (SDs) are missing, we will attempt to obtain these data by contacting trial authors. If SDs are not available from trial authors, we will calculate these from P values, t-values, confidence intervals, or standard errors, if these are reported in the trials.

We will bear in mind that due to the unacknowledged uncertainty of imputed values and results, confidence intervals may be too narrow and this will be addressed in the discussion section. We will perform a sensitivity analysis to assess how sensitive the results are to reasonable changes in assumptions made. We will address the potential impact of missing data in the discussion section or our review.

Assessment of heterogeneity

In our assessment of heterogeneity, we will take account of the I^2 measure which describes the variability in effect estimates due to heterogeneity rather than sampling error (chance).and is quoted as a percentage. The handbook states that I^2 of 0% to 40% might not be important, an I^2 of 30% to 60% may represent moderate heterogeneity, an I^2 of 50% to 90% may represent substantial heterogeneity, and an I^2 of 75% to 100% considerable heterogeneity. Our interpretation of I^2 will take into account the magnitude and direction of effects and the strength of evidence for heterogeneity (for example, the P value from the Chi^2 test).

Due to the nature of the studies in the meta-analysis, it is likely that treatment effects will vary according to effect modifiers as well as participant characteristics. For example, in studies of CBT in the general population, it is notable that the quality of the CBT delivery can be inconsistent between practitioners and participant characteristics can affect the quality of CBT delivery, although this does not appear to affect outcome (Boswell 2013). However, amongst other factors such as heterogeneous participant groups, this should be taken into account as a possible cause of clinical heterogeneity and we will apply a random-effects model to the data.

If there is substantial heterogeneity between studies, we will discuss the results of studies in a descriptive format, and meta-analysis will not be attempted.

Assessment of reporting biases

A comprehensive search will be undertaken for studies that meet the eligibility criteria for the review. Multiple sources will be searched including grey literature and trial registries to reduce publication bias. Given an adequate number of studies, we will test for publication bias by visual inspection of funnel plots. Generally, for sufficient power, at least 10 studies are needed for a funnel plot. However, the number needed depends on the size of the studies and on the treatment effect. For continuous outcomes with intervention effects measured as mean differences, we will use Egger's test to test for funnel plot asymmetry. However, Egger's test should not be used if there are fewer than 10 studies in the meta-analysis (Egger 1997). Thorough analysis of outcomes and the time to follow-up, as presented in each paper, will be undertaken to minimise outcome bias.

Data synthesis

Given adequate data, we will include details of outcome data in the form of summary tables, forest plots, and meta-analyses, including comparisons and subgroup analyses.

Meta-analysis will only be carried out if there are sufficient studies and if they are sufficiently similar. Studies should be sufficiently similar to be combined in a meta-analysis - i.e. the treatments, participants and the underlying clinical question are similar enough for pooling (see Measures of treatment effect). Meta-analysis may technically be undertaken with only 2 studies (Valentine 2010) but the heterogeneity between the studies should be taken into account. The Cochrane Handbook suggests that I^2 above 50% may represent substantial heterogeneity (Cochrane 2011). Therefore we will not complete meta-analysis if I^2 is over 50%. If there are a small number of heterogenous studies (as is likely), then analysis will be narrative, in the form of a structured summary of the studies' characteristics and findings.

If meta-analysis is carried out, we will use a random-effects model for the data, as we anticipate significant heterogeneity between studies, although if there are a very small number of studies, then it will not be possible to predict Tau^2 with a sufficient level of precision and a fixed-effect model may be the only viable option. The use of a random-effects model allows for differences in the true effect sizes in different studies depending on certain characteristics of these studies, for example, whether individuals have a learning disability or normal intelligence.

Data are likely to be continuous given the nature of the research question. If some data are dichotomous, as long as the assumptions, firstly, that the continuous measurements follow a logistic distribution and, secondly, that variability of outcomes are the same for treated and control participants, then the odds ratios will be expressed as Standardised Mean Differences (SMD) (SMD = square root of 3 divided by pie multiplied by the log of the odds ratio).

Given the discussion in the above two paragraphs, the inverse-variance random-effects model in Revman will be used .

Participants with a learning disability are likely to be excluded from trials not looking at this population specifically, so the presence of learning disability is expected to be a study level covariate. If the above is not possible, then a narrative presentation will be used.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses should be interpreted with caution. If more than one study can be included in an analysis, we will undertake a subgroup analysis based on the outcome of CBT treatment for OCD in individuals with ASD according to the following variables:

1. Age: i.e. individuals who are greater than or equal to 18 years versus less than 18 years as family/parental involvement may be a positive component and may be more readily available for participants less than 18 years, and, in addition, children and adults may differ in their responses to therapy.
2. Presence or absence of global intellectual disability verified by appropriate testing of intelligence and functioning in the study as therapy may be more challenging in those with intellectual disabilities.
3. Number or sessions; i.e. four or more sessions attended versus fewer than four sessions attended, as individuals attending fewer than four sessions are not likely to experience the full treatment effect.
4. Comorbid conditions; for example, clinically significant depression, as this may affect compliance with treatment and motivation.
5. Mode of delivery of intervention; i.e. individual or group sessions as there may be differences in efficacy between the two modalities.
6. If there are a large enough number of studies, we will consider a subgroup analysis to assess modification of treatment effects by type of non active comparator.
7. If it is clear that studies have used BT/ERP alone and not CBT, then a subgroup analysis will be undertaken to assess whether outcomes differ between BT/ERP alone and CBT.

Sensitivity analysis

Where there is unclear or high risk of bias, we plan a priori a sensitivity analysis based on the following criteria:

1. Extent of dropouts: studies of CBT indicate high dropout rates (Bados 2007; Hans 2013). Sensitivity analysis will be carried out excluding studies with dropouts of over 50%.
2. Outcome reporting bias: the problem of outcome reporting bias has been highlighted in behavioural intervention studies (Wiltshire 2017). Sensitivity analysis will be carried out excluding studies with a high risk of outcome reporting bias.
3. Allocation concealment: sensitivity analysis will be carried out excluding studies with a high risk of bias for this domain. Due to the nature of psychological therapies, allocation concealment from participants and personnel is difficult, especially if the control group is a 'wait-list group' or 'no treatment' group.
4. Sensitivity analysis will be carried out excluding quasi-randomised studies due to the risk of systemic bias in quasi-randomised trials.

Further issues may be identified throughout the process of conducting the review, which are appropriate for a sensitivity analysis.

'Summary of findings' table

We will create a 'Summary of findings' table for the comparison of CBT/BT versus non active comparators. The 'Summary of findings' tables will include the following outcomes: change in core OCD symptomatology at the end of treatment and at follow-up, total number of dropouts due to adverse events at the end of treatment, quality of life at the end of treatment and at follow-up, severity of depressive symptoms at the end of treatment, and severity of anxiety symptoms at the end of treatment. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using GRADEpro software (www.gradepro.org). We will justify all decisions to down or upgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review, where necessary.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CCMDCTR core MEDLINE Search

Core search strategy used to inform the Cochrane Common Mental Disorders Group's specialised register: OVID MEDLINE
A weekly search alert based on condition + RCT filter only
1. *[MeSH Headings]:*
eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/
2. *[Title/Author Keywords]:*
(eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati# ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.
3. *[RCT filter]:*
(controlled clinical trial.pt. or randomized controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomized controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)
4. (1 and 2 and 3)
Records are screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs are tagged to the appropriate study record.
Similar weekly search alerts are also conducted on OVID Embase and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

Appendix 2. PsycINFO and CENTRAL searches

OVID PsycINFO
PsycINFO will be searched (all years to date) using the following search strategy:
1. (obsess* or compulsi* or OCD).ti,ab,id.
2. OBSESSIVE COMPULSIVE DISORDER/
3. OBSESSIONS/
4. exp COMPULSIONS/
5. OBSESSIVE COMPULSIVE PERSONALITY DISORDER/
6. anxiety disorder*.ti,ab.id.
7. ANXIETY DISORDERS/
8. or/1-7

9. exp PERVASIVE DEVELOPMENTAL DISORDERS/
10. CHILDHOOD SCHIZOPHRENIA/
11. (autis* or asperger* or kanner* or ASD or ASDs).ti,ab,id.
12. (childhood adj3 schizophren*).ti,ab,id.
13. ((pervasive and development* and disorder*) or PDD or PDDs).ti,ab,id.
14. or/9-13
15. (comorbid* or co morbid* or co occur* or cooccur* or concurren*).mp.
16. COMORBIDITY/ or DUAL DIAGNOSIS/
17. or/15-16
18. treatment effectiveness evaluation.sh.
19. clinical trials.sh.
20. mental health program evaluation.sh.
21. randomly.ab.
22. randomi#ed.ti,ab,id.
23. (study or trial).ti.
24. ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask* or dummy)).mp.
25. (control* adj3 (trial* or study or studies or group*)).ti,ab,id.
26. treatment outcome.md.
27. (waitlist* or wait* list*).ti,ab,id.
28. ((convention* or standard) adj (treatment* or therap* or psychotherap*)).ti,ab,id.
29. ((treatment* adj2 usual) or TAU or ((routine or standard or usual) adj2 (care or medication*))).ti,ab,id.
30. ("no" treatment* or non treatment* or nontreatment* or minim* treatment* or untreated group* or untreated control* or without any treatment).ti,ab,id.
31. ("no" intervention* or non intervention* or without any intervention*).ti,ab,id.
32. (("no" adj (contact or therap*)) or non therap* or nontherap* or minim* therap* or pseudotherap* or therap* as usual or usual therap*).ti,ab,id.
33. (untreated adj3 (patients or participants or subjects or group* or control*)).ti,ab,id.
34. (receiv* nothing or standard control or reference group or observation* group).ti,ab,id.
35. or/18-34
34. (14 and (8 or 17) and 35)

Cochrane Central Register of Controlled Trials (CENTRAL)

CENTRAL will be searched (all years to date) using the following search strategy:
#1. (obsess* or compulsi* or OCD)
#2. MeSH descriptor OBSESSIVE COMPULSIVE DISORDER, this term only
#3. MeSH descriptor OBSESSIVE BEHAVIOR, this term only
#4. MeSH descriptor COMPULSIVE BEHAVIOR explode all trees
#5. (anxiety NEXT disorder*)
#6. MeSH descriptor ANXIETY DISORDERS, this term only
#7. (#1 or #2 or #3 or #4 or #5 or #6)
#8. MeSH descriptor CHILD DEVELOPMENT DISORDERS, PERVASIVE explode all trees
#9. (autis* or asperger* or kanner* or ASD or ASDs)
#10. (childhood NEXT schizophren*)
#11. ((pervasive and development* and disorder*) or PDD or PDDs)
#12. (#8 or #9 or #10 or #11)
#13. MeSH descriptor COMORBIDITY, this term only
#14. (comorbid* or co-morbid* or co-occur* or cooccur* or concurren*).mp.
#15. (#13 or #14)
#16. (#12 and (#7 or #15))
[Final Set= ASD and (OCD or Comordition)]

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None

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NOTES

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