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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
BACKGROUND 1
OBJECTIVES 4
METHODS 4
ACKNOWLEDGEMENTS 9
REFERENCES 9
APPENDICES 17
CONTRIBUTIONS OF AUTHORS 21
DECLARATIONS OF INTEREST 21
SOURCES OF SUPPORT 21
NOTES 22

[Intervention Protocol]

Pharmacological interventions for people with borderline personality disorder

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ABSTRACT

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

To assess the beneficial and harmful effects of pharmacological treatment for adolescents and adults with borderline personality disorder (BPD).

BACKGROUND

Description of the condition

Borderline personality disorder (BPD) is a condition first recognised in the 1960s (Gunderson 2009; Kernberg 1967; Kernberg 1975). Historically, the term BPD was coined by Adolph Stern to describe a condition in the 'borderland' between psychosis and neurosis (Stern 1938). Subsequent psychoanalytic contributions (especially that of Kernberg 1975) have reaffirmed this distinction, emphasising that the capacity to test reality remains grossly intact but is subject to subtle distortions, especially under stress.

According to current diagnostic criteria, BPD is characterised by a pervasive pattern of instability in affect regulation, impulse control, interpersonal relationships, and self-image (APA 2013; WHO 1993). Clinical hallmarks include emotional dysregulation, impulsive aggression, repeated self-injury, and chronic suicidal tendencies (Fonagy 2009; Lieb 2004). Whereas some authors have suggested that it is a variant of affective disorders (Akiskal 2004), others claim that it is only the causes of these diseases that partially overlap (Paris 2007). Despite the classification challenges in defining and delimiting the condition, BPD is still being widely researched. Its importance stems from the large amount of suffering of the persons concerned (Stiglmayr 2005; Zanarini 1998), debilitating functional impairments (Gunderson 2011a; Gunderson 2011b; Niesten 2016; Skodol 2002; Soetmann 2008b), and from

the significant impact it has on mental health services (Cailhol 2015; Hörz 2010; Soetmann 2008a; Tyrer 2015; Zanarini 2004a; Zanarini 2012). It is estimated that about 60% to 78% of BPD patients attempt suicide (Links 2009), though the rate of completed suicides is far less. Zanarini and colleagues found suicide rates of 4.5% during 16 years of follow-up (Zanarini 2015), whereas Stone 1993 reported a suicide rate of 8.5% after 16.5 years. Study estimates of the lifetime risk of suicide among patients with BPD range from 3% to 10% (Links 2009). Suicidal behaviour is reported to occur in up to 84% of patients with BPD (Goodman 2012; Soloff 2002), and comorbid mood disorders or substance use disorders are the most common risk factors associated with successful suicide attempts (Black 2004; Doyle 2016; Yen 2004).

The definition of BPD in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) Fifth Edition (DSM-5; APA 2013), Fourth Edition Text Revision (DMS-IV-TR; APA 2000) and Fourth Edition (DSM-IV; APA 1994) comprises nine criteria that cover the features mentioned above. At least five criteria should be met for a definite categorical BPD diagnosis to be made, and four criteria for probable diagnosis (see Appendix 1). In the alternative diagnostic classification system of the World Health Organization (WHO), the*International Classification of Diseases*, which is currently in its tenth edition (ICD-10; WHO 1993), the relating condition is referred to as "Emotionally unstable personality disorder (F60.3)", of which there is an impulsive type (F60.30) and a borderline type (F60.31: see Appendix 2). The latter essentially overlaps with the DSM-IV definition. There are 10 possible criteria defined that very closely reflect the DSM criteria, with the exception of one criterion which is not included in the DSM ("4. Difficulty in maintaining any course of action that offers no immediate reward"; WHO 1993). Out of 10 possible criteria at least five must be met, one of which must be "a marked tendency to quarrelsome behaviour and to conflicts with others, especially when impulsive acts are thwarted or criticised".

Overall, the prevalence of BPD in the general population is estimated to be about 1.5% (Torgersen 2012), with findings of single epidemiologic studies ranging between 0.6% (Coid 2006) and 2.7% (Trull 2010). In clinical populations BDP occurs frequently (Munk-Jørgensen 2010), with studies reporting a prevalence ranging from 9.3% to 46.3% and a mean point prevalence across studies of 28.5% (Torgersen 2012). Though BPD is predominantly diagnosed in women (75%; APA 2000), it is estimated to be equally frequent in men (Lenzenweger 2007; Ten Have 2016; Torgersen 2001; Torgersen 2012). BPD commonly co-occurs with mood disorders, substance misuse, eating disorders, post-traumatic stress disorder (PTSD), attention-deficit hyperactivity disorder (ADHD), and is also associated with other personality disorders (Coid 2006; Lenzenweger 2007; Stepp 2012; Storebø 2014; Tomko 2014).

Although the short- to medium-term outcome of BPD is poor, there is some evidence that long-term follow-ups show a more favourable course, with remission rates of about 85% to 88% within 10 years (Gunderson 2011b; Zanarini 2007). Here, however, remission only means that diagnostic criteria are not fulfilled and does not indicate the absence of any symptoms. Indeed, whereas acute symptoms - such as self-mutilation, help-seeking suicide threats or attempts and impulsivity - in most cases decrease with time, affective symptoms reflecting areas of chronic dysphoria, such as chronic feelings of emptiness, intense anger or profound abandonment, largely remain (Zanarini 2007). Therefore the majority of people with BPD still have significant levels of symptoms and experience severe and persistent impairment in social functioning (Kongerslev 2015; Ng 2016). Risk factors for a poorer long-term outcome are comorbid substance use disorders, PTSD, and anxiety cluster disorders (Zanarini 2005; Zanarini 2007), and also a family history of psychiatric disorder (especially mood disorders and substance use disorders), as well as demographic issues such as older age, longer treatment history, pathological childhood experiences, temperament issues, and adult psychosocial functioning (Chanen 2012; De Fruyt 2014; Kongerslev 2015; Zanarini 2007).

People with BPD have difficulties achieving and maintaining vocational and social functioning over time (Zanarini 2010). Furthermore treatment-seeking people with personality disorders, such as BPD, pose a high economic burden on society (van Asselt 2007). Effective treatments could potentially decrease the high costs associated with the condition (Soetmann 2008a). The problem of deliberate self-harm is also a particular issue within this group (Ayodeji 2015; Kongerslev 2015; Linehan 1997; Rossouw 2012). In medical settings, people with BPD often present after self-harming behaviour or in suicidal crisis and are treated in emergency settings, often involving repeated psychiatric hospitalisations (Bender 2006; Cailhol 2015).

In summary, BPD is a condition that has been extensively studied. It has a major impact on health facilities, as those affected often present in crisis. The recovery from symptoms or functional impairment (or both) was previously considered likely for only a low percentage of people diagnosed with BPD. However, the long-term course is better than what was previously assumed, due to more favourable symptomatic recoveries (Zanarini 2012). Nonetheless, people with BPD continue to have considerable interpersonal and functional problems, and sustainable recovery appears difficult to attain (Biskin 2015; Kongerslev 2015; Rossouw 2012).

Description of the intervention

To date, all major treatment guidelines consider psychotherapy as the treatment of choice for BPD and assign drugs an adjunctive role (e.g. APA 2001; DGPPN 2009; Herpertz 2007; National Health and Medical Research Council 2013; NICE 2009). However, the large majority of people with BPD are prescribed psychotropic medications during the course of their illness. This may be the case in times of crisis, when people with BPD present to

mental health services with raised suicidality or parasuicidality, impulsivity-associated outbreaks, psychotic-like exacerbations, severe dissociations or aggravations of comorbid conditions (e.g. mood disorders), and when medications are used to achieve short-term stabilisation. Such crisis interventions will not be considered here but are subject to another Cochrane Review, which is currently being updated (Borschmann 2012).

In contrast to short-term crisis medication, up to 84.1% of people with BPD have been reported to use standing psychotropic medications (Bender 2001; Zanarini 2015), and as many as 92% have been reported to use any psychotropic medication for a non-specified period of time (Paton 2015). Indeed, it is a common finding that people with BPD are more likely to use psychotropic medications than people with other psychiatric conditions such as major depressive disorder (Bender 2001; Bender 2006), mood or anxiety disorders in general (Ansell 2007), or other personality disorders (Zanarini 2004a).

Studies across different countries show that antidepressants are the class of medication most often prescribed to BPD patients (Bender 2001; Knappich 2014; Makela 2006; Paton 2015; Sansone 2003; Zanarini 2015). Zanarini and colleagues found that 79.7% were taking antidepressant medication, followed by anxiolytics (46.6%), neuroleptics (38.6%), and mood stabilisers (35.9%) (Zanarini 2015). They also found that about 71% of people with BPD were using standing medications at six-year follow-up (Zanarini 2004a; Zanarini 2004b), and that they were still more likely to be using antidepressants, mood stabilisers, antipsychotics or anxiolytics than axis-II comparison participants at 16-year follow-up (Zanarini 2015). Polypharmacy is common, with reports of people with BPD taking, on average, 2.02 psychotropic medications at a time (Ansell 2007), and up to 28.6% taking four or more medications (Zanarini 2004a; Zanarini 2004b).

In summary, most BPD patients are taking psychotropic drugs for sustained periods of time, though medication is only regarded as an adjunctive to psychotherapy. Different classes of medication are used, with antidepressants being used most frequently, but there is no standard treatment. To date, any drug use in BPD is off-label (if not targeted at associated psychopathology such as depression or anxiety), but up to 82% of BPD patients without comorbid conditions receive pharmacotherapy to directly target BPD symptoms (Paton 2015).

How the intervention might work

To date, there is broad consensus about no single drug being able to substantially 'treat' BPD itself (e.g. APA 2001; Biskin 2012; National Health and Medical Research Council 2013).

In fact, drug treatment options are chosen with the intent to ameliorate distinct symptoms or symptom clusters (also called 'symptom domains') that a certain person with BPD may experience. These may either be symptoms specific to BPD (i.e. as defined in the diagnostic criteria) or BPD-unspecific ones, such as depression or anxiety, which are also common in BPD. A drug is mostly chosen due to its known efficacy in treating similar symptoms in other conditions (e.g. depression), or in conditions with putative similar underlying neurobiological features (e.g. impulsivity-related disorders). As a consequence, many different classes of drugs are used in BPD, depending on the individual clinical picture a person with BPD may experience (Bender 2001; National Health and Medical Research Council 2013; Zanarini 2015). As part of an integrated treatment plan, drug treatment may also be given with the intent to facilitate behaviourally-mediated learning processes as activated in a concurrent psychotherapy.

The rationale for using selective serotonin reuptake inhibitors in the treatment of BPD is that the serotonergic system has repeatedly been shown to be associated with low prefrontal serotonergic transmission in BPD (Herpertz 2007). The putative actions of atypical neuroleptics are also thought to impact the serotonergic system through a high 5HT1a receptor affinity and 5HT2a receptor antagonism. Therefore, atypical antipsychotics can be expected to have a stabilising effect on mood and anxiety, but also impulsivity and aggression (Herpertz 2007). Mood stabilisers are also used due to their stabilising effects on affective symptoms (Herpertz 2007). In recent years, omega-3 fatty acids (polyunsaturated fatty acids; PUFAs) have come into the focus of attention, as PUFAs deficiencies have been identified in many mental illnesses, and they have been assigned a role in impulsivity, mood and even suicidality (Gören 2011; Pompili 2017). Sedatives, such as benzodiazepines, are also commonly used in clinical practice with the intent to improve sleep, or decrease anxiety or agitation (Martinho 2014). However, the use of such agents is critical, due to their self-harming and addictive potential and also due to their well-known and unfavourable impact on learning processes as, for example, intended by psychotherapy (Hunter 2000; Westra 2002). And finally, the neuropeptide oxytocin has received attention in recent years, because oxytocin is supposed to lead to better emotion recognition and more trust in other people (Bakermans-Kranenburg 2013). It may, therefore, help people with BPD overcome hypersensitivity to perceived social threat (Meyer-Lindenberg 2011).

Why it is important to do this review

BPD poses a major burden, both personal (Soetmann 2008b) and financial (Soetmann 2008a), on those directly affected and their relatives. In 2008, the US House of Representatives passed a House Resolution naming the month of May BPD Awareness Month (110th Congress 2007 to 2008). This underlines the large public health problem of BPD. Despite its frequent use in clinical practice, and research activities on this topic in the last three decades, any medication in BPD is off-label. All the more, patients and carers must be able to make informed decisions on the basis of the up-to-date evidence (Ingenhoven 2015; Paris 2015; Silk 2015). This Cochrane Review aims to systematically identify, investigate, and

integrate the current state of high-quality evidence on the topic of pharmacotherapy in BPD.

This is a new protocol for a new review, which will update and replace the Cochrane Review first published in 2010 (Stoffers 2010). As no published protocol seems to exist, we considered it necessary to write and publish a protocol before conducting this review. The Stoffers 2010 review came to the conclusion that the then available evidence indicated beneficial effects for some drugs (i.e. second-generation antipsychotics, mood stabilisers and omega-3 fatty acids), but that the overall quality of the evidence was not robust enough to draw any reliable conclusions. In the meantime research has continued in the field, and new findings may change findings of the previous review. Therefore an update of this review seems both appropriate and timely (Garner 2016).

OBJECTIVES

To assess the beneficial and harmful effects of pharmacological treatment for adolescents and adults with borderline personality disorder (BPD).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Patients of all ages, in any setting, with a formal diagnosis of BPD according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) Third Edition (DSM-III; APA 1980), Third Edition Revised (DSM-III R; APA 1987), Fourth Edition (DSM-IV; APA 1994), Fourth Edition Text Revision (DSM-IV-TR; APA 2000), and Fifth Edition (DSM-5; APA 2013)), with or without comorbid conditions.

We will require at least 70% of study participants to have a formal diagnosis of BPD. We will also include studies involving subsamples of BPD patients providing data on these patients are available separately. We will not include studies that focus on people with mental impairment, organic brain disorder, dementia, or other severe neurologic diseases, should there be any.

Types of interventions

Any drug or defined combination of drugs administered at any dosage, prescribed to treat the disorder or its symptoms, compared to a placebo or active comparator drug(s). We will include studies that pair drugs with an adjunctive intervention (e.g. psychological therapies), providing this is given to participants in both the intervention and control arm, and the pharmacological intervention is unique to the treatment group.

A drug must have been prescribed continuously for a minimum duration of two weeks for the study to be eligible for our review. In addition, we will judge the actual duration required for inclusion in light of the specific mode of action of the drug. Medication must have been used to treat the disorder or symptoms thereof.

Types of outcome measures

Outcomes can either be self-rated by patients or observer-rated by clinicians. We will include only adequately validated measures (plus spontaneous reporting of adverse events).

Primary outcomes

1. BPD severity, as assessed by, for example, the Zanarini Rating Scale for Borderline Personality Disorder (Zan-BPD; Zanarini 2003), the Borderline Personality Disorder Severity Index (BPDSI-IV; Arntz 2003), or the Clinical Global Impression Scale for Borderline Personality Disorder Patients (CGI-BPD; Perez 2007).
2. Self-harm, in terms of the proportion of participants with self-harming behaviour, or as assessed by, for example, the Deliberate Self-harm Inventory (DSHI; Gratz 2001) or the Self-harm Behavior Questionnaire (SHBQ; Guttierez 2001).
3. Suicide-related outcomes, as assessed by, for example, the Suicidal Behaviours Questionnaire (SBQ; Osman 2001) or the Beck Scale for Suicidal Ideation (BSSI; Beck 1979) or in terms of the proportion of patients with suicidal acts.
4. Functioning, as assessed by, for example, the Global Assessment Scale (GAS; Endicott 1976), the Global Assessment of Functioning Scale (GAF; APA 1987) or the Social Functioning Questionnaire (SFQ; Tyrer 2005).

Secondary outcomes

1. Anger, as assessed by, for example, the "Hostility" subscale of the Symptom Checklist-90-Revised (SCL-90-R; Derogatis 1994), or the State-Trait Anger Expression Inventory (STAXI; Spielberger 1988).
2. Affective instability, as assessed by, for example, the relevant item or subscale on the Zan-BPD (Zanarini 2003), CGI-BPD (Perez 2007) or BPDSI-IV (Arntz 2003).
3. Chronic feelings of emptiness, as assessed by, for example, the relevant item or subscale on the Zan-BPD (Zanarini 2003), CGI-BPD (Perez 2007) or BPDSI-IV (Arntz 2003).

4. Impulsivity, as assessed by, for example, the Barrett Impulsiveness Scale (BIS; Barrett 1995), or the Anger, Irritability and Assault Questionnaire (AIAQ; Coccaro 1991).

5. Interpersonal problems, as assessed by, for example, the Inventory of Interpersonal Problems (IIP; Horowitz 1988), or the relevant item or subscale of the Zan-BPD (Zanarini 2003), CGI-BPD (Perez 2007) or BPDSI-IV (Arntz 2003), or SCL-90-R (Derogatis 1994).

6. Abandonment, as assessed by, for example, the relevant item or subscale on the Zan-BPD (Zanarini 2003), CGI-BPD (Perez 2007) or BPDSI-IV (Arntz 2003).

7. Identity disturbance, as assessed by, for example, the relevant item or subscale on the Zan-BPD (Zanarini 2003), CGI-BPD (Perez 2007) or BPDSI-IV (Arntz 2003).

8. Dissociation and psychotic-like symptoms, as assessed by, for example, the Dissociative Experience Scale (DES; Bernstein 1986), or the Brief Psychiatric Rating Scale (BPRS; Overall 1962).

9. Depression, as assessed by, for example, the Beck Depression Inventory (BDI; Beck 1961), or the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery 1979).

10. Attrition, in terms of patients lost after randomisation in each group.

11. Adverse effects, as measured by use of standardised psychometric rating scales such as the Systematic Assessment for Treatment Emergent Events (SAFTEE; Levine 1986), laboratory values or spontaneous reporting.

Search methods for identification of studies

Electronic searches

We will search the electronic databases and trials registers listed below to identify relevant trials.

1. Cochrane Central Register of Controlled Trials (CENTRAL; current issue), in the Cochrane Library, which includes the Cochrane Developmental, Psychosocial and Learning Problems Specialised Register
2. MEDLINE Ovid (1948 onwards)
3. Embase Ovid (1980 onwards)
4. CINAHL EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1980 onwards)
5. PsycINFO Ovid (1806 onwards)
6. ERIC EBSCOhost (Education Resources Information Center; 1966 onwards)
7. BIOSIS Previews Web of Science Clarivate Analytics (1969 onwards)
8. Web of Science Core Collection Clarivate Analytics (1900 onwards)
9. Sociological Abstracts ProQuest (1952 onwards)
10. LILACS (Latin American and Caribbean Health Science Information database; all available years; lilacs.bvsalud.org/en)
11. OpenGrey (www.opengrey.eu)
12. Copac National, Academic and Specialist Library Catalogue (COPAC; copac.jisc.ac.uk)
13. ProQuest Dissertations and Theses A&I (1973 onwards)
14. DART Europe E-Theses Portal (www.dart-europe.eu/basic-search.php)
15. Networked Digital Library of Theses and Dissertations (NDLTD; www.ndltd.org)
16. Australian New Zealand Clinical Trials Registry (ANZCTR; www.anzctr.org.au/BasicSearch.aspx)
17. ClinicalTrials.gov (clinicaltrials.gov)
18. EU Clinical Trials Register (www.clinicaltrialsregister.eu/ctr-search/search)
19. ISRCTN Registry (www.isrctn.com)
20. UK Clinical Trials Gateway (www.ukctg.nihr.ac.uk/#popoverSearchDivId)
21. WHO International Clinical Trials Registry Platform (ICTRP; who.int/ictrp/en)

The search strategy for MEDLINE is in Appendix 1 and we will modify it for other databases using the appropriate syntax and controlled terms. We will not limit our searches by language, year of publication, or type of publication. We will seek translation of the relevant sections of non-English language articles.

Searching other resources

We will handsearch relevant journals including the Journal of Personality Disorders; the American Journal of Psychiatry; JAMA Psychiatry; British Journal of Psychiatry; ACTA Psychiatrica Scandinavica; Journal of the American Academy of Child and Adolescent Psychiatry; Personality Disorders: Theory, Research and Treatment; and the Journal of Clinical Psychiatry. Additionally, we will contact researchers working in the field by email, to ask for unpublished data. We will also trace cross-references from relevant literature. Finally, we will search for unpublished data on the websites of the United States Food and Drug Administration (FDA; www.fda.gov) and the European Medicines Agency (EMA; www.ema.europa.eu/ema).

Data collection and analysis

We will conduct this review according to guidelines set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and perform the analyses using the latest version of Review Manager 5 (RevMan 5), Cochrane's statistical software (Review Manager 2014).

Selection of studies

Six review authors (JMSW, OJS, BAV, MLK, JTM, SSN) will work in three pairs and independently screen titles and abstracts of all records retrieved by the searches; we will resolve uncertainty or disagreement by consensus. For records that could be eligible RCTs, we will obtain the full-text report and assess it for eligibility based on the inclusion criteria (Criteria for considering studies for this review). Review authors will discuss disagreements, and if they cannot reach an agreement they will consult a third review author (ES or KL). We will list apparently relevant RCTs that do not fulfil the inclusion criteria with reasons for exclusion in the 'Characteristics of excluded studies' tables. We will use Covidence software to keep track of appraised trials and decisions. To ensure transparency of study selection, we will provide a flow chart in accordance with the PRISMA statement, to show how many records have been excluded and for what reason (Moher 1999).

Data extraction and management

All review authors will extract data. Review authors will work in pairs and will complete the data collection form independently to ensure accuracy. We will resolve disagreements by discussion or use an arbiter (ES) if required. JMSW and OJS will enter the data into RevMan 5 (Review Manager 2014). In those cases where there are not enough data or data are unclear in the published trial reports, we will contact the trial authors, requesting them to supply the missing information. We will develop data extraction forms to facilitate standardisation of data extraction.

Assessment of risk of bias in included studies

All review authors will assess the risk of bias using Cochrane's tool for assessing risk of bias (Higgins 2017). For each included trial, data extractors will independently evaluate each risk of bias domain - Appendix 4 - as being at low, unclear (uncertain) or high risk of bias, resolving disagreements by discussion. We will categorise trials that have a low risk of bias in all domains at low risk of bias overall, and we will consider trials with one or more unclear or high risk of bias domains as trials at high risk of bias overall. Given the risk of overestimation of beneficial intervention effects and underestimation of harmful intervention effects in RCTs with unclear or inadequate methodological quality (Kjaergard 2001; Lundh 2012; Moher 1998; Savović 2012a; Savović 2012b; Schulz 1995; Wood 2008), we will assess the influence of risk of bias on our results (see Sensitivity analysis).

Measures of treatment effect

Dichotomous data

We will summarise dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We will calculate the risk difference (RD) and the number needed to treat for an additional beneficial outcome (NNTB) or for an additional harmful outcome (NNTH) if there is a significant effect of the intervention.

Continuous data

For continuous data, we will compare the mean score between the two groups to give a mean difference (MD) and present this with 95% CIs. We will use the overall MD, where possible, to compare the outcome measures from trials. We will estimate the standardised MD (SMD) where different outcome measures are used to measure the same construct in the trials. We will calculate SMDs using end-scores at post-treatment results and, in a separate analysis, follow-up data. We will bundle follow-up data in six-month steps. Where the direction of a scale is opposite to most of the other scales, we will multiply the corresponding mean values by −1 to ensure adjusted values. If the trials do not report means and standard deviations but report other values like t-tests and P values, we will try to transform these into standard deviations.
Our first choice will be to calculate effect sizes on the basis of intention-to-treat (ITT) data. If means and standard deviations from an ITT analysis and missing values that were replaced are available, we will use these data. In other cases, we will conduct the analysis using only the available data.
We will perform all calculations using the latest release of RevMan 5 software (Review Manager 2014).

Unit of analysis issues

Repeated observations

We will calculate study estimates on the basis of post-treatment group results. We will conduct separate analyses for data from different points of measurement (i.e. we will use the last measurement where post-treatment follow-up data at six-month intervals is available). We will not use interim observations.

Cluster-randomised trials

Where trials have used cluster randomisation, we anticipate that investigators will have presented their results after appropriately controlling for clustering effects (robust standard errors or hierarchical linear models). If it is unclear whether a cluster-randomised trial has used appropriate controls for clustering, we will contact the investigators for further information. Where appropriate controls have not been used, we will request and reanalyse individual participant data using multilevel models that control for clustering. If individual participant data are not available, we will look for information on intraclass correlation coefficients to adjust for the potential clustering effects. Following this, we will analyse effect sizes and standard errors in RevMan 5 (Review Manager 2014),

using the generic inverse method (Higgins 2011b). If there is insufficient information to control for clustering, we will enter outcome data into RevMan 5 (Review Manager 2014), using individuals as the units of analysis, and conduct a sensitivity analysis to assess the potential biasing effects of inadequately controlled cluster-randomised trials (Donner 2002); see Sensitivity analysis.

Cross-over trials

We plan to include data from randomised cross-over studies up to the point of first cross-over (first period only) (Curtin 2002). We will not consider outcomes from subsequent periods due to the likelihood of carry-over effects from the preceding treatment(s). We will not combine repeated observations on participants in one meta-analysis.

Studies with multiple treatment groups

If a trial compares more than two intervention groups, we will include all pair-wise comparisons as long as they are not subject to the same meta-analysis. If a trial includes two arms of different doses of a certain drug that are tested against placebo, we will combine the experimental groups into a single group, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, making a single, pair-wise comparison (Higgins 2011b). Thus we will avoid including the same group of participants twice in the same meta-analysis.

Adjustment for multiplicity

We will adjust the P values and CIs for multiplicity due to the many secondary outcome comparisons following the method described by Jakobsen 2014b.

Dealing with missing data

We will try to obtain any missing data, including incomplete outcome data, by contacting trial authors. We will report this information in the 'Risk of bias' tables.

We will evaluate the methods used to handle the missing data in the publications and to what extent it was likely that the missing data influenced the results of outcomes of interest. For preference, we will calculate effect sizes on the basis of ITT data. If only available data are reported, we will calculate effect sizes on this basis. Where dichotomous data are not presented on the basis of ITT data, we will add the number of participants lost in each group to the participants with unfavourable results, acting on the assumption that most patients with BPD do not get lost at random. For continuous outcomes, we will discuss each trial's methodology for dealing with missing continuous data (e.g. last observation carried forward or modified ITT approach). We will use per protocol analysis, as available from the trial reports (that is, results are based on the number of patients at follow-up).

If data are not reported in an immediately usable way, we will consult a statistician.

We will assess results derived from statistically processed data in sensitivity analyses. See Sensitivity analysis.

Assessment of heterogeneity

We will assess studies for clinical homogeneity with respect to type of pharmacological interventions, setting and control groups. We will take into account the number of studies and study characteristics, such as duration, dose and participants, to judge if heterogeneity is more probable due to clinical (i.e. explainable factors) or to unknown factors. In case of substantial heterogeneity, we will make up subgroups according to study characteristics, such as study size, duration, dose or participants, and discuss the most apparent sources of heterogeneity. We will evaluate methodological heterogeneity by comparing the design of trials. See Subgroup analysis and investigation of heterogeneity.

We will investigate statistical heterogeneity within a certain comparison by visual inspection of the graphs and the I^2 statistic (Higgins 2003). We will judge I^2 values between 0% and 40% to indicate little heterogeneity, between 30% and 60% to indicate moderate heterogeneity, between 50% and 90% to indicate substantial heterogeneity, and between 75% and 100% to indicate considerable heterogeneity (Deeks 2017). We will also assess statistical heterogeneity by Chi^2 test ($P < 0.10$) and tau^2 – an estimate of between-study variability.

Assessment of reporting biases

We will provide funnel plots for comparisons with sufficient primary studies and we will perform Egger's statistical test for small-study effects (Egger 1997). We will not use a visual inspection of the funnel plot if there are fewer than 10 studies in the meta-analysis, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2017).

Data synthesis

We will perform statistical analyses according to recommendations in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017). In carrying out the meta-analysis we will use the inverse-variance method, in order to give more weight to more precise estimates from studies with less variance (mostly larger studies). We will divide the doses and the controls into different comparisons, ensuring that the treatment comparisons are comparable and homogeneous. We will use the random-effects model for meta-analysis, since we expect some degree of clinical heterogeneity to be present in most cases, though not so substantial as to prevent pooling in principle. For trials with a high level of statistical heterogeneity, and where the amount of clinical heterogeneity makes it inappropriate to use these trials in

meta-analyses, we will provide a narrative description of the trial results. If we consider data pooling to be feasible, we will pool the primary studies effects and calculate their 95% CIs. If a trial provides more than one measure for the same outcome construct (e.g. several questionnaires for the assessment of depression), we will select the one used most often in the whole pool of included studies for effect size calculation, in order to minimise heterogeneity of outcomes in form and content. If a study reports data of two assessment instruments that are equally frequently used, two review authors will discuss the issue and choose the one which is, in its content, most appropriate for assessing BPD patients. We will prefer observer-rated measures as the primary analysis.

Subgroup analysis and investigation of heterogeneity

We will conduct a subgroup analysis to make hypotheses about the subgroups mentioned below.

1. Age (15 to under 18 years of age, 18 to 50 years of age, above 50 years of age)
2. Sex (male versus female)
3. Cormorbidity (patients with comorbidity versus patients without comorbidity)
4. Doses
5. Different setting (outpatient compared to inpatient)
6. Differences between different types of medication within the same class (for example, antipsychotic, antidepressant)

Heterogeneity-adjusted required information size and Trial Sequential Analysis

Trial Sequential Analysis (TSA) is a methodology that combines a required information size (RIS) calculation for a meta-analysis with the threshold for statistical significance (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008). TSA is a tool for quantifying the statistical reliability of the data in cumulative meta-analysis, adjusting P values for sparse data and for repetitive testing on accumulating data (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008).

Comparable to the a priori sample size estimation in a single randomised trial, a meta-analysis should include a RIS calculation at least as large as the sample size of an adequately powered single trial to reduce the risk of random error. TSA calculates the RIS in a meta-analysis and provides an alpha-spending boundary to adjust the significance level for sparse data and repetitive testing on accumulating data (CTU 2011; Wetterslev 2008), and consequently the risk of random error can be assessed. Multiple analysis of accumulating data when new trials emerge leads to repeated significant testing and hence introduces multiplicity, thus use of a conventional P value is prone to exacerbate the risk of random error (Berkey 1996; Lau 1995). Meta-analyses not reaching the RIS are analysed with trial sequential alpha-spending monitoring boundaries analogous to interim monitoring boundaries in a single trial (Wetterslev 2008). This approach will be crucial in future updates of the review. We will calculate an RIS on all outcomes in the review. If a TSA does not reveal significant findings (no crossing of the alpha-spending boundary and no crossing of the conventional boundary of P = 0.05) before the RIS has been reached, then the conclusion should either be that more trials are needed to reject or accept an intervention effect that was used for calculation of the required sample size or - in the case when the cumulated Z-curve enters the futility area - the anticipated effect can be rejected. We will calculate the a priori diversity-adjusted required information size (that is, number of patients required to detect or reject a specific intervention effect in the meta-analysis), and perform a TSA for the primary outcomes based on the following a priori assumptions.

1. The standard deviation of the primary outcome is 1.0.
2. An anticipated intervention effect equal to Hedge's g of 0.5.
3. A maximum type I error of 5% (alpha).
4. A maximum type II error of 20% (beta; equal to a minimum 80% power).
5. A priori anticipated 50% diversity (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009).

We will also calculate a post hoc, low bias, risk diversity-adjusted required information size (that is, the number of patients required to detect or reject a specific intervention effect in the meta-analysis), and perform a TSA for the primary outcomes based on the following estimated assumptions.

1. The standard deviation of the primary outcome in patients in the control group of trials with low risk of bias.
2. The estimated intervention effect in trials with low risk of bias.
3. A maximum type I error of 5% (alpha).
4. A maximum type II error of 20% (beta; equal to a minimum 80% power).
5. The estimated diversity in the trials included in the meta-analysis (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008).

'Summary of findings' tables

We will used the GRADE approach to construct a 'Summary of findings' table in which to document all review outcomes. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Considerations are due to: within-trial risk of bias; directness of the evidence; heterogeneity of the data; precision of effect estimates; and risk of publication bias (Andrews 2013a; Andrews 2013b; Balshem 2011; Brunetti 2013; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Mustafa 2013). When possible, we will use the MD or the RR, and we will use Trial Sequential Analysis (TSA) to rate

the imprecision (Jakobsen 2014a). We will report the four primary outcomes (BPD severity, self-harm, suicide-related outcomes, and mental health status) and the three secondary outcomes (interpersonal problems, attrition, and adverse events) in the 'Summary of findings' table for the main comparison (Atkins 2004).

Sensitivity analysis

We will assess the impact of heterogeneity on the overall pooled effect estimate by removing studies ('outliers') that are contributing to the heterogeneity. We will remove outliers one by one and assess the impact on the overall outcome.
We will conduct sensitivity analyses to determine whether findings are sensitive to the following.

1. Decisions made during the review process (such as our assessment of the level of clinical heterogeneity).
2. Impact of bias (studies with low and high risk of bias).
3. Type of model used for analysis (repeating the analysis using the fixed-effect model to test the robustness of the results).
4. Type of data collection (for example, different ways to measure adverse events).
5. Imputed data (comparing the analyses with available outcome data with those using the intention-to-treat (ITT) approach).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. DSM diagnostic criteria for BPD (301.83)

DSM Third Edition (DSM-III; APA 1980) **301.83 BPD**	DSM Fourth Edition Text Revision (DSM-IV-TR; APA 2000) **301.83 BPD**	DSM Fifth Edition (DSM-5; APA 2013) **301.83 BPD**
Diagnostic criterion A 5 of the following are required 1. Impulsivity or unpredictability in at least 2 areas that are potentially self-damaging (e.	**Diagnostic criterion A** A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by	**Diagnostic criterion A** A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning

(*Continued*)

g. spending, sex, substance use, shoplifting, overeating, physically self-damaging acts) 2. A pattern of unstable and intense interpersonal relationships (e.g. marked shifts of attitude, idealization, devaluation, manipulation (consistently using others for one's own ends)) 3. Inappropriate, intense anger or lack of control of anger (e.g. frequent displays of temper, constant anger) 4. Identity disturbance manifested by uncertainty about several issues relating to identity, such as self-image, gender identity, long-term goals or career choice, friendship patters, values, and loyalties (e.g. 'Who am I', 'I feel like I am my sister when I am good') 5. Affective instability: marked shifts from normal mood to depression, irritability, or anxiety, usually lasting a few hours and only rarely more than a few days, with a return to normal mood 6. Intolerance of being alone (e.g. frantic efforts to avoid being alone, depressed when alone) 7. Physically self-damaging acts (e.g. suicidal gestures, self-mutilation, recurrent accidents or physical fights) 8. Chronic feelings of emptiness or boredom	early adulthood and present in a variety of contexts, as indicated by 5 (or more) of the following 1. Frantic efforts to avoid real or imagined abandonment (note: do not include suicidal or self-mutilating behavior covered in criterion 5) 2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation 3. Identity disturbance: markedly and persistently unstable self-image or sense of self 4. Impulsivity in at least 2 areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating) (note: do not include suicidal or self-mutilating behavior covered in criterion 5) 5. Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior 6. Affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, instability, or anxiety usually lasting a few hours and only rarely more than a few days) 7. Chronic feelings of emptiness 8. Inappropriate, intense anger or difficulty controlling anger (e.g. frequent displays of temper, constant anger, recurrent physical fights) 9. Transient, stress-related paranoid ideation or severe dissociate symptoms	by early adulthood and present in a variety of contexts, as indicated by 5 (or more) of the following 1. Frantic efforts to avoid real or imagined abandonment (note: do not include suicidal or self-mutilating behavior covered in criterion 5) 2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation 3. Identity disturbance: markedly and persistently unstable self-image or sense of self 4. Impulsivity in at least 2 areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating) (note: do not include suicidal or self-mutilating behavior covered in criterion 5) 5. Recurrent suicidal behavior, gestures or threats, or self-mutilating behavior 6. Affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, irritability, or anxiety of mood) usually lasting a few hours and only rarely more than a few days 7. Chronic feelings of emptiness 8. Inappropriate, intense anger or difficulty controlling anger (e.g. frequent displays of temper, constant anger, recurrent physical fights) 9. Transient, stress-related paranoid ideation or severe dissociative symptoms
Diagnostic criterion B If under 18, does not meet the criteria for Identity Disorder		

BPD: Borderline personality disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders

Appendix 2. ICD-10 research criteria for emotionally unstable personality disorder (F60.3)

F 60.30: ICD-10 Emotionally unstable personality disorder, impulsive type	F 60.31: Emotionally unstable personality disorder, borderline type
Diagnostic criterion A The general criteria of personality disorder (F60) must be met	**Diagnostic criterion A** The general criteria of personality disorder (F60) must be met
Diagnostic criterion B At least 3 of the following must be present, 1 of which is 2 1. Marked tendency to act unexpectedly and without consideration of the consequences 2. Marked tendency to quarrelsome behaviour and to conflicts with others, especially when impulsive acts are thwarted or criticized 3. Liability of outbursts of anger or violence, with inability to control the resulting behavioural explosions 4. Difficulty in maintaining any course of action that offers no immediate reward 5. Unstable and capricious mood	**Diagnostic criterion B** At least 3 of the symptoms mentioned in criterion B (F60.30) must be present, and in addition at least 2 of the following 6. Disturbances in and uncertainty about self-image, aims and internal preferences (including sexual) 7. Liability to become involved in intense and unstable relationships, often leading to emotional crises 8. Excessive efforts to avoid abandonment 9. Recurrent threats or acts of self-harm 10. Chronic feelings of emptiness

ICD-10: International Classification of Diseases - Tenth Edition

Appendix 3. Medline search strategy

1 Borderline Personality Disorder/
2 ((borderline or border-line) adj3 (state* or personalit*)).kf,tw.
3 ("Axis II" or "Cluster B" or flamboyant or "F60.3" or "F60.30" or "F60.31").kf,tw.
4 (idealization adj5 devaluation).kf,tw.
5 ((vulnerable or hyperbolic) adj3 temperament).kf,tw.
6 (((unstab* or instab* or poor or disturb* or fail* or weak or dysregulat*) adj3 (self* or impuls* or interperson* or identit* or relationship* or emotion* or affect*)) and (personality or character or PD)).kf,tw.
7 (impulsiv* adj5 (behavio?r or character or personalit*)).kf,tw.
8 (self adj3 (injur* or damag* or destruct* or harm* or hurt* or mutilat*)).kf,tw.
9 (suicidal adj3 behavio?r).kf,tw.
10 (feel* adj3 (empt* or bored*)).kf,tw.
11 (anger adj5 control*).kf,tw.
12 (risk-taking adj3 behavio?r).kf,tw.
13 or/1-12
14 randomized controlled trial.pt.
15 controlled clinical trial.pt.
16 randomi#ed.ab.
17 placebo.ab.
18 randomly.ab.
19 trial.ab.
20 groups.ab.
21 drug therapy.fs.
22 or/14-21
23 exp Animals/ not Humans/
24 22 not 23

25 13 and 24

Appendix 4. 'Risk of bias' domains and criteria for assigning judgements

Selection bias

Random sequence generation

1. **Low risk of bias.** The method used was adequate (e.g. computer-generated random numbers, table of random numbers) or was unlikely to introduce selection bias.
2. **Unclear risk of bias**. Information was insufficient for assessment of whether the method used could introduce selection bias.
3. **High risk of bias.** The method used was likely to introduce bias.

Allocation concealment

1. **Low risk of bias.** The method used (e.g. central allocation) was unlikely to bias allocation to groups.
2. **Unclear risk of bias.** Information was insufficient for assessment of whether the method used could bias allocation to groups.
3. **High risk of bias.** The method used (e.g. open random allocation schedule) could bias allocation to groups.

Performance bias (blinding of participants and personnel)

1. **Low risk of bias.** The method of blinding was described sufficiently and blinding was conducted in a satisfactory way.
2. **Unclear risk of bias.** Information was insufficient for assessment of whether adequate blinding was used and whether it was likely to introduce bias on the estimate of effect.
3. **High risk of bias**. No blinding or incomplete blinding.

Detection bias (blinding of outcome assessment)

1. **Low risk of bias.** The method of blinding was described and blinding was conducted in a satisfactory way.
2. **Unclear risk of bias.** Information was insufficient for assessment of whether the type of blinding used was likely to bias the estimate of effect.
3. **High risk of bias.** No blinding or incomplete blinding.

Attrition bias (incomplete outcome data)

1. **Low risk of bias.** Underlying reasons for missing data probably would not affect outcome measurement regarding effects of methylphenidate, as all missing data can be considered as missing at random or all data were reported.
2. **Unclear risk of bias.** Information was insufficient for assessment of whether missing data or the method used to handle missing data was likely to bias the estimate of effect.
3. **High risk of bias.** The crude estimate of effects could be biased given the reasons for the missing data, or the methods used to handle missing data are unsatisfactory.

Reporting bias (selective reporting)

1. **Low risk of bias.** The trial protocol was available and all prespecified outcomes of interest were reported.
2. **Unclear risk of bias.** Information was insufficient for assessment of whether selective outcome reporting could have occurred.
3. **High risk of bias.** Not all of the primary outcomes specified beforehand were reported or participants were excluded after randomisation.

Other potential sources of bias

Vested interest

1. **Low risk of bias.** The trial was not funded by any parties that might be considered to have a conflict of interest (e.g. a manufacturer of methylphenidate).
2. **Unclear risk of bias.** The source of funding was not clear.
3. **High risk of bias.** The trial was funded by parties that might have had a conflict of interest (e.g. a manufacturer of methylphenidate) or potential conflicts of interest were reported by trial authors.

Other sources of bias

1. **Low risk of bias.** The trial appeared to be free of other sources of bias.
2. **Unclear risk of bias.** Information was inadequate for assessment of other possible sources of bias.
3. **High risk of bias.** Other sources of bias were identified.

Seven of the above domains are specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We added an eighth domain - vested interest. Andreas Lundh and colleagues illustrate the many subtle mechanisms through which sponsorship and conflict of interest may influence intervention effects on outcomes. For more information, please see editorials by Bero 2013 and Sterne 2013, and the commentary by Gøtzsche 2015.

CONTRIBUTIONS OF AUTHORS

All of the authors contributed to writing this protocol. Jutta Stoffers-Winterling is the guarantor for the review.

DECLARATIONS OF INTEREST

Jutta M Stoffers-Winterling (JSW) is a board-certified psychologist ('Psychologische Psychotherapeutin', cognitive behaviour therapy), who has worked on a Dialectical Behaviour Therapy (DBT) ward, attended courses on DBT and Schema-Focused Therapy. JSW has been involved in the preparation of the World Federation of Societies of Biological Psychiatry Guidelines for the Treatment of Personality Disorders (Herpertz 2007).

Ole Jakob Storebø is an Editor with CDPLP.

Jessica T Mattivi's institution received a grant from the Federal Ministry for Education and Research (BMBF) for a systematic review on psychosocial interventions for self-harm in adolescents.

Birgit A Völlm - none known.

Signe Nielsen - none known.

Maja Lærke Kielsholm - none known.

Erlend G Faltinsen - none known.

Erik Simonsen - none known.

Klaus Lieb (KL) is an Editor with CDPLP. He is a board-certified cognitive behaviour therapist with a special interest in schema therapy. KL has been involved in the preparation of the World Federation of Societies of Biological Psychiatry Guidelines for the Treatment of Personality Disorders (Herpertz 2007).

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Internal sources

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External sources

- None, Other.

NOTES

This is a new protocol for a new review, which will replace the current published review: Stoffers J, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Pharmacological interventions for borderline personality disorder. Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD005653. DOI: 10.1002/14651858.CD005653.pub2.