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The Role of Personality Disorder in Pharmacological Intervention Clinical Trials for Adults with Major Psychiatric Disorders: A Systematic Review and Meta-Analysis Protocol

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PERSONALITY AND MAJOR PSYCHIATRIC DISORDERS

ABSTRACT

Introduction: Remission rates for several major psychiatric disorders remain relatively low despite available treatments, and many patients fail to respond adequately to these interventions. Evidence suggests that personality disorder may play a confounding role in poor outcomes. Although personality disorders are common in patients with other mental health disorders, it remains unknown whether personality disorder may affect treatment outcomes in those with major psychiatric disorders. We aim to review currently available evidence regarding the role of personality disorder on pharmacological interventions in clinical trials for adults with major psychiatric disorders.

Methods and analysis: A systematic search of PubMed, EMBASE, PsycINFO, and CINAHL databases will be conducted to identify clinical trials that have investigated pharmacological interventions in participants aged 18 years or older for a major psychiatric disorder (i.e., depressive disorders, bipolar spectrum disorders, and schizophrenia spectrum disorders) and include assessment of personality disorder. One reviewer will confirm whether studies meet the predetermined eligibility criteria. Established methods to assess methodological quality of data will be employed. A systematic review, and if heterogeneity permits, a meta-analysis will be completed. Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) will be adhered to.

Ethics and dissemination: As this systematic review will utilize published data, ethics permission will therefore not be required. This systematic review has been registered with PROSPERO. The outcomes of this systematic review will be published in a relevant scientific journal and presented at a research conference.

Registration details: CRD42018089279.

PERSONALITY AND MAJOR PSYCHIATRIC DISORDERS

Keywords: Personality disorders, clinical trial, depression, bipolar, schizophrenia, pharmacological interventions

Article summary:

- This systematic review will investigate an under-acknowledged clinical area.
- It will evaluate randomised clinical trials which have assessed the role of personality disorder in pharmacological intervention randomised clinical trials for adults with major psychiatric disorders.
- It will also explore a range of outcomes, including clinical subjective measures, clinical objective assessments, and patient-rated measures.
- A potential limitation of this study may be the paucity of information available, due to the novelty of the subject area, and as such may result in heterogeneity of available studies.

PERSONALITY AND MAJOR PSYCHIATRIC DISORDERS

INTRODUCTION

Major psychiatric disorders (i.e., depression, bipolar disorder, and schizophrenia) substantially contribute to the global burden of disease.[1] Significant progress has been made in developing treatments for major psychiatric disorders in recent years, however, this progress has concurrently been hampered by limited treatment effectiveness and adverse outcomes for many people.[2] For instance, remission rates from clinical symptoms remain at ~30% for patients with depression,[3] ~28% for bipolar disorder,[4] and ~37% for schizophrenia,[5] though notably, some studies report lower functional compared to symptom remission rates in schizophrenia.[6 7]

Recognising the potential risk factors implicated in the outcomes of major psychiatric disorders may assist in providing more targeted treatments, leading to better outcomes.[8] Clinical trials are considered the gold standard for evaluating the psychiatric treatments and associated outcomes, [9] due to their rigorous and established methods to measure clinical change. Such methods entail testing treatments in ideal or best-practice conditions, which result in strict eligibility criteria, often excluding patients with complex presentations[10] and psychiatric comorbidities.[11] Despite the strict criteria necessary for clinical trials, many patients with major psychiatric disorders do not respond effectively to the intervention being assessed[12 13]. As such, further investigation into the patient characteristics which may influence treatment outcomes in major psychiatric disorders is warranted.

One factor which may influence both disorder course and treatment outcome is personality disorder. Personality disorder refers to a constellation of persistent maladaptive patterns of behaviour and experiences that deviate from the expectations of the individual's culture, is stable and leads to distress or impairment.[14 15] Personality disorder is highly comorbid amongst clinical populations[16], and this comorbidity has important implications for

development, intervention, and treatment planning for major psychiatric disorders. [17 18] Previous epidemiological research has demonstrated that personality disorder affects the course of depression,[19 20] bipolar disorder,[21 22] and schizophrenia.[23-25] Moreover, other research has suggested that personality disorder may influence treatment outcomes in depression,[26-29] clinical and functional outcomes in bipolar disorder,[30 31] and symptomatology in schizophrenia.[32] Little attention, however, has focussed on the influence of personality disorder on treatment outcomes, defined as response to an intervention, in clinical trials for major psychiatric disorders. This is a major oversight considering that clinical trial outcomes have critical implications for treatment recommendations in major psychiatric disorders. Moreover, clinical trials depend on the assessment of change, and the failure to include and report on personality disorder in clinical trials may therefore omit an important mediator or moderator of study results.

Currently, the literature examining the role of personality disorder in clinical trials for major psychiatric disorders is scant and despite growing recognition that personality disorder should be considered in clinical settings, the role that personality disorder plays in pharmacological interventions for in major psychiatric disorders remains largely undefined. Given the paucity of information and inconsistent findings in relation to pharmacological interventions, the inclusion and evaluation of personality disorder in clinical trials assessing efficacy of interventions is warranted. As such, this review will investigate the role of personality disorder in pharmacological interventions trials for adults with major psychiatric disorders. To our knowledge no previous meta analyses have been conducted which report on the effect of personality disorder on pharmacological interventions for major psychiatric disorders in clinical trials.

Objectives

The aim of this systematic review is to:

1. Identify published studies which examine the treatment outcomes of major psychiatric disorders (defined as depressive disorders, bipolar spectrum disorders, and schizophrenia spectrum disorders) and which include assessment of personality disorder in clinical trials;
2. Appraise the quality of methodology employed in each of the clinical trials eligible for inclusion in this systematic review;
3. Collate the findings of the studies to be reviewed, including identifying any potential confounding and/or mediating factors in the relationship between personality disorders, depressive disorders, bipolar spectrum disorders, and schizophrenia spectrum disorders, and clinical and functional outcomes;
4. Perform sensitivity analyses, where indicated, to elucidate differences between (a) screening measures and structured clinical interview diagnoses of personality disorders, and (b) diagnostic criteria between different versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD). Sensitivity analyses will be determined once any heterogeneity between studies has been identified.
5. Produce a best evidence synthesis of the findings to describe and explore patterns. If sufficient data has been identified, and heterogeneity low, a meta-analysis will also be performed.

Methods and analysis

Eligibility criteria for studies to be included in this review:

This systematic review will include completed clinical trials of pharmacological interventions for depressive disorders, bipolar spectrum disorders, and schizophrenia spectrum disorders, as opposed to an intervention for personality disorder. For the purposes of this review, depressive disorders are defined as major depressive disorder and persistent

depressive disorder; bipolar spectrum disorders include bipolar I disorder, bipolar II disorder, cyclomythic disorder, and bipolar disorder not elsewhere classified or not otherwise specified; and schizophrenia spectrum disorders are defined as schizophrenia and schizoaffective disorder. Clinical trials conducted in adult populations (≥ 18 years) with depressive disorders, bipolar spectrum disorders, and schizophrenia spectrum disorders (based on structured interviews and defined by diagnoses based on any version of the DSM or ICD, inclusive of personality disorders (defined by any version of the DSM or ICD; or indicated by screening tools such as the Standardised Assessment of Personality, SAPAS),[33] any sex or nationality, and published in any year, are eligible to be included in this review. The primary outcome of this review will be an evaluation of the influence of personality disorder in major psychiatric disorder outcomes in clinical trials.

Treatment outcomes include clinical subjective outcomes (for instance, clinician rated questionnaire), clinical objective outcomes (for example, blood or urine test), and patient subjective outcomes (for example, self-reported symptom improvement), and may also include the assessment of functioning, quality of life, and adverse events.

Patient and Public Involvement:

Patient and public involvement was not sought for the design of this study; though patient experience of pharmacological treatments and clinical trials were considered in the development of the research question.

Criteria for Study Consideration for This Review

Clinical trials must be controlled (i.e., either by placebo or another intervention). Articles will need to be published in the English language. Articles that are cross-sectional, case-control or cohort by design, grey literature, theses, and/or conference presentations will not be included.

Search Strategy and Data Extraction

To identify applicable literature, an electronic search strategy using databases for medical, health, psychology, and the social sciences (PubMed, EMBASE via embase.com, PsychINFO via Ebsco, and CINAHL Complete via Ebsco) will be performed. We will apply the following medical subject headings (MeSH) to search all fields: ('personality disorders' AND 'clinical trial') AND ('mood disorders' OR 'bipolar and related disorders' OR 'schizophrenia spectrum and other psychotic disorders'). We will also include the key terms: ('schizoaffective' OR 'bipolar depression' OR 'mania'). Relevant truncation and wildcard symbols will be applied to each database.

One reviewer will apply the search strategy and ascertain studies eligible for inclusion by cross-checking against the pre-determined eligibility criteria, using a three-step method: (1) assessment of titles and abstracts, (2) assessment of full-text papers, and (3) hand-searching reference lists. A second reviewer will sanction 10% of each category of excluded studies. One further reviewer will confirm the eligibility of those identified studies. If there is disagreement regarding eligibility, an independent reviewer will determine the conclusive decision.

Evaluation of Methodological Quality of Included Articles

To provide a comprehensive examination of the literature, methodological procedures will be applied to assess the quality of the studies. A best evidence synthesis of the included studies will summarise the findings, and quantitative approaches will be applied. Specifically, Consolidated Standards of Reporting Trials (CONSORT) guidelines will be utilised to evaluate the methodological quality of pharmacological intervention clinical trials.[34] Eligible literature will be scored as low, high, or unclear risk of bias using the criteria of the Cochrane Collaboration's "risk of bias" tool.[35] A modified scoring system from Higgins et al[35] to evaluate data extricated from included studies will be employed (Table 1). These factors include: random sequence generation, allocation concealment, blinding of participants and

personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Eligible studies will be independently scored by two independent reviewers. Should any discrepancy in scores be evident, a third independent reviewer will arbitrate the final judgement.

Presentation and Reporting of Results

This protocol adheres to PRISMA-P practice guidelines and the PRISMA-P checklist was used when writing this protocol.[36 37] The review will conform to PRISMA reporting guidelines;[38] and a PRISMA flow diagram will be utilised to depict study selection, numbers and reasons concerning included vs. excluded studies in the context of the pre-specified eligibility criteria. All eligible studies will have key information pertaining to major psychiatric disorders (i.e., depressive disorders, bipolar spectrum disorders, or schizophrenia spectrum disorders), personality disorder, and treatment outcomes identified, extracted and presented.

If low heterogeneity is identified, a meta-analysis will be performed. Heterogeneity will be determined using I^2, in accordance with suggestions from the Cochrane *Handbook for Systematic Reviews of Interventions*.[39] Heterogeneity will be quantified as low, moderate, or high with I^2 values of 25%, 50%, and 75%, respectively.[40] Heterogeneity of ≤50% will be considered low, and permit a meta-analysis. The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach will be utilised to summarise the findings and assess the quality of evidence for relevant outcomes.[41]

Where appropriate, subgroup analyses will be undertaken to determine any differences between major psychiatric disorders. Additionally, subgroup analyses will be performed based on the type of intervention assessed.

Dissemination

This review has been registered on PROSPERO (CRD42018089279). Results will be published in a peer-reviewed scientific journal, and results will be presented at relevant scientific conference/s.

Ethics

This review will only use published data, and as such, ethical approval is not required. Ethical and governance principles will be complied with, in respect to data management and the presentation and dissemination of findings.

Conclusion

To the best of our knowledge, this will be the first systematic review to investigate whether personality disorder influences the treatment outcomes for major psychiatric disorders in clinical trials. The findings of this review will contribute to the limited literature available on the role of personality disorder on treatment outcomes in those with major psychiatric disorder and will also provide information to inform clinical practice and health strategies.

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Author contributions

BEK conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. SLB developed the search strategy; and edited, revised, and approved the final version of this manuscript. AT conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. OMD conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. SLB developed the search strategy; and edited, revised, and approved the final

version of this manuscript. MB conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. MMA developed the search strategy; and edited, revised, and approved the final version of this manuscript. HK-H edited, revised, and approved the final version of this manuscript. LJW conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript.

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Competing interests statement

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Table 1.

Cochrane Risk of Bias Tool. Adapted from Higgins et al[35]

Bias domain	**Source of bias**	**Support for judgement**	**Judgment (assess as low, unclear, or high risk of bias)**
Selection bias	Random sequence generation	Describe the method used to produce the allocation sequence in satisfactory detail to permit assessment of whether it should yield comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in adequate detail to determine whether allocations could have been anticipated before or during trial enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and study personnel*	Describe the methods used, if any, to blind trial participants and researchers from information of which intervention participants received. Provide information concerning whether blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and study personnel during the study
Detection bias	Blinding of outcome assessment*	Describe all methods used, if any, to blind outcome evaluation from information of which intervention participants received. Provide information pertaining to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the extensiveness of outcome data for each main outcome, including attrition and exclusions from the analysis. Declare whether attrition and exclusions were stated, the numbers for each intervention group (in contrast with total randomised participants), details for attrition or exclusion were reported, and any re-inclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data

Reporting bias	Selective reporting	Decalre how selective reporting was assessed and what was found	Reporting bias due to selective outcome reporting
Other bias	Other bias	Anything else, ideally pre-specified	Bias due to problems not covered elsewhere

**Assessments should be made for each main outcome measure or class of outcomes*

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	N/A

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	11
Sponsor	#5b	Provide name for the review funder and / or sponsor	11
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	11
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	8
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

BMJ Open

The Role of Personality Disorder in Randomised Controlled Trials of Pharmacological Interventions for Adults with Mood Disorders: A Protocol for a Systematic Review and Meta-Analysis

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The Role of Personality Disorder in Randomised Controlled Trials of Pharmacological Interventions for Adults with Mood Disorders: A Protocol for a Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Remission rates for mood disorders, including depressive and bipolar disorders, remain relatively low despite available treatments, and many patients fail to respond adequately to these interventions. Evidence suggests that personality disorder may play a role in poor outcomes. Although personality disorders are common in patients with mood disorders, it remains unknown whether personality disorder affects treatment outcomes in mood disorders. We aim to review currently available evidence regarding the role of personality disorder on pharmacological interventions in randomised controlled trials for adults with mood disorders.

Methods and analysis: A systematic search of Cochrane Central Register of Controlled Clinical Trials (CENTRAL) via cochranelibrary.com, PubMed via PubMed, EMBASE via embase.com, PsycINFO via Ebsco, and CINAHL Complete via Ebsco databases will be conducted to identify randomised controlled trials that have investigated pharmacological interventions in participants aged 18 years or older for mood disorders (i.e., depressive disorders and bipolar spectrum disorders) and have also included assessment of personality disorder. One reviewer will screen studies against the predetermined eligibility criteria, and a second reviewer will confirm eligible studies. Data will be extracted by two independent reviewers. Methodological quality and risk of bias will be assessed using the Cochrane Risk of Bias Tool. A systematic review, and if sufficient evidence is identified, a meta-analysis will be completed.

Ethics and dissemination: As this systematic review will utilize published data, ethics permission will not be required. The outcomes of this systematic review will be published in a relevant scientific journal and presented at a research conference.

Registration details: This systematic review has been registered with PROSPERO (CRD42018089279).

Keywords: Personality disorders, randomised controlled trial, depression, bipolar disorder, pharmacological interventions

Article summary:

- This will be the first systematic review to examine personality disorder in randomised controlled trials of pharmacological interventions for mood disorders.
- Two independent reviewers will independently extract the data.
- The Cochrane Risk of Bias tool will be used to evaluate the quality of studies.
- The variety of tools to assess personality disorders and mood disorders may cause considerable heterogeneity.
- A potential limitation of this systematic review may be the paucity of evidence available, which may not permit a meta-analysis to be completed.

INTRODUCTION

Personality disorders (PD) are a group of mental disorders defined by a constellation of persistent, maladaptive patterns of behaviour and experiences, which markedly deviate from the expectations of the individual's culture, are stable over time, and lead to distress or impairment.[1 2] PDs are commonly manifested in disordered thoughts, affectivity, impulse control, and social and occupational functioning,[2] and have been recognised as common mental health conditions.[3] The World Health Organization (WHO) World Mental Health Surveys estimated PD prevalence rates to be 6.1% in a cross-national sample,[4] while the Australian National Survey of Mental Health and Wellbeing (2000) estimated prevalence to be 6.5%[5] using the same self-report scale. Other prevalence rates utilising structured clinical assessments have estimated PD prevalence to be between 10.6%[6] to 21.8% in population-based samples.[7]

Despite these high prevalence rates, it has been argued that PDs do not receive the attention they warrant[8] and have largely been omitted from policy and research initiatives.[9 10] For instance, the Global Burden of Disease Study (GBDS) highlighted that psychiatric disorders (namely, major depression, alcohol use, bipolar disorder, schizophrenia, and obsessive-compulsive disorder) substantially contribute to the global burden of disease.[11] However, the GBDS did not include PDs in its scope, and accordingly, true estimates of the disease burden of mental illness may have been underestimated.[12] The omission of PDs at the population level has important repercussions for treatment programmes and health-care planning,[9] including the development and trial of pharmacological interventions in randomised controlled trials (RCTs). Consequently, while interventions for psychiatric disorders in general has expanded in contemporary research, the recognition of PD in clinical and research contexts has been neglected.

Parallel to the exclusion of PD at the population level, significant progress has been

made in the development and confirmation of pharmacological treatments for mood disorders, but not PDs, in recent years. In particular, establishing effective interventions for depression, as the leading cause of disability worldwide, has been made a global priority.[13] Specific research recommendations put forward by the National Institute for Health and Care Excellence (NICE) recommend that RCTs are developed to test the efficacy of sequenced therapies (continuation of initial antidepressant compared to switching to an antidepressant from another class) for depression.[14] Psychotropic medications such as lithium (a mood stabiliser), antipsychotics (haloperidol, olanzapine, quetiapine, or risperidone) and combination therapies for the treatment of bipolar disorder have also been recommended to be trailed.[14] These clinical and research recommendations are made on the best available evidence, in which the influence of PD may not have been acknowledged.

Corresponding with the NICE guidelines, sequenced therapies utilising a range of pharmacological treatments (i.e., citalopram, bupropion, sertraline, nortriptyline, mirtazapine, lithium, tranylcypromine, venlafaxine),[15] as well as combination therapies[16 17] have gained recent attention for the treatment of depression. Additionally, pharmacological interventions such as antiepileptics (e.g., divalprox sodium and carbamazepine)[18 19] for the treatment of bipolar disorder have been confirmed in recent clinical trials.[20] These treatment developments echo recognition of the magnitude of mood disorders substantially contributing to the global burden of disease. However, the progress in treatment development has concurrently been hampered by limited treatment effectiveness and adverse outcomes for many people.[21] For instance, remission rates from clinical symptoms remain at ~30% for patients with depression[22] and ~28% for bipolar disorder[23] for patients treated by pharmacological interventions. These remission rates highlight the complexity in treating acute mood disorders, and also emphasises the potential that internal patient-related factors, such as PD, may contribute to the difficulty in finding effective pharmacological treatments.

Recognising the potential risk factors implicated in the outcomes of mood disorders may assist in providing more targeted treatments, leading to better outcomes.[24] PD is highly comorbid amongst clinical populations, and has particularly high incidence rates for patients with depression and bipolar disorder. For example, Zimmerman, Rothschild, and Chelminski (2005) estimated that 51.3% of community-based outpatients had a comorbid PD and major depressive disorder, and that the presence of this comorbidity was significantly associated with greater PD pathology.[25] Zimmerman et al. also found that even one borderline trait may have an adverse effect on outcomes.[25] Similar rates were found by Melartin et al. (2002), whereby 44% of patients with depression met also criteria for PD.[26] Moreover, Post et al. (2018) found that 65.9% of patients with bipolar disorder who were in a euthymic phase and 88.0% of patients who were in an acute depression state at the time of assessment met criteria for at least one PD.[27] These comorbidities are noteworthy considering that the presence of PD has potential to affect the course and treatment of the comorbid mood disorder.[25]

For example, previous epidemiological research has demonstrated that PD affects the course of depression. Specifically, Grilo et al. (2012) demonstrated that patients with comorbid schizotypal, borderline, or avoidant PD and depression had slower time to remission over a twenty-four month period compared to patients with depression only.[28] Similarly, Gunderson et al. (2011) found that the course of major depressive disorder was negatively influenced by the presence of borderline PD, in that the rate to remission over a ten-year period was 50% slower for patients with this comorbity.[29] Research on PD and the course of bipolar disorder is less robust, however. In a clinical sample study Garno et al. (2005) demonstrated that patients with comorbid Cluster B PD and bipolar disorder had significantly more lifetime suicide attempts than patients with bipolar disorder only.[30] Tamam, Ozpoyraz, and Karatas (2014) found that outpatients with comorbid PD and bipolar disorder had significantly greater psychopathology, more affective illness episodes, and a higher number of suicide attempts

compared to patients with bipolar disorder only.[31]

Other research has suggested that PD influences the treatment outcome of both depression[32 33] and bipolar disorder.[30 34] For example, in one meta-analysis it was found that comorbid PD and depression was associated with double the risk of poor treatment outcome (defined as less than 50% reduction in symptoms) compared to depression only, and that outcome was not affected by the type of intervention administered (with the exception of electroconvulsive therapy which showed no difference between groups).[10] Though the negative treatment outcomes did not diverge by the type of instrument used to measure depression, the authors did not state how the included studies assessed PD. Considering the aforementioned variance in prevalence rates resulting from differences in the assessment of PD (for example, assessment by screening tool compared to structured clinical assessment), this may have been an important oversight in relation to treatment outcomes. An earlier review by Mulder (2002) also investigated the influence of PD on treatment outcome in depression, and found that the majority of studies eligible for inclusion in the review reported worse treatment outcomes, compared to those with depression only. However, well-designed studies (for instance, studies which assessed PD via structured clinical interview and where treatment was controlled via standard treatment or random assignment into intervention groups) showed no difference in treatment outcome.

The treatment outcomes of comorbid PD and bipolar disorder have also been demonstrated. In a review, Beiling, Green, and Macqueen (2007) summarised that the presence of comorbid PD had a negative effect on treatment outcome in bipolar disorder.[35] However, the literature specific to pharmacological therapies included in the review was limited. In one retrospective study eligible for review, Abou-Saleh (1983) showed that patients with bipolar disorder who did not respond to lithium had traits of high neuroticism and low dominance,[36]

however this does not necessitate the presence of personality pathology. Gasperini et al. (1993) showed that patients with comorbid PD and bipolar disorder had a higher number of manic or depressive episode relapses, and this was particularly evident for patients with histrionic PD.[37] Moreover, Preston et al. (2004) retrospectively diagnosed borderline PD in two samples of patients with bipolar disorder who were trailing lamotrigine as a monotherapy. Both patient groups improved with treatment (response rates of 48% and 29% of patients with bipolar disorder and comorbid PD and bipolar disorder, respectively) though this difference was not statistically significant.[38]

Though previous research has suggested that PDs should be assessed in RCTs for patients with depressive and bipolar disorders,[10 35] there is limited evidence which has explored the mechanisms which underpin the poorer treatment outcomes for patients with comorbid PD. One possible explanation is that individuals may not recognise or admit personality psychopathology due to disruptions of identity and self-awareness. These disruptions are common features of PD and have crucial implications for the diagnosis of PD[39] and treatment of both the PD and comorbid disorder.[40] Previous research has demonstrated that despite the onset of PD occurring in late adolescence or early adulthood, patients do not tend to present for treatment until much later.[41] As such PDs may be left under-diagnosed and consequently untreated, affecting the therapeutic efficacy of the treatment for the comorbid mood disorder. In addition to this, some literature has suggested that individuals with PD, particularly borderline PD, are often non-compliant[42] or non-adherent with pharmacological treatments,[43] though this area has not been explored in depth. Poor therapeutic alliance is common in people with PD, driving adherence issues, treatment engagement, and self-efficacy. Non-adherence has important repercussions for the management of psychiatric disorders,[44] and these issues may consequently perpetuate symptomatology of PD and any comorbidities.

Furthermore, there is some evidence to suggest that PD may play a mediating role in the relationship between depression and treatment outcomes. For example Mulder et al. (2003) demonstrated that patients with comorbid PD and depression had poor treatment outcome with nortriptyline (a tricyclic antidepressant) compared to fluoxetine (an SSRI), and this was particularly evident in patients with borderline PD.[45] These results echo earlier research which demonstrated that patients with borderline PD respond poorly to tricyclic antidepressants, but moderately well to SSRIs [46-48] Though a lack of evidence does not permit discussion of the differences in treatment response between pharmacological interventions, literature suggests that both patients with PD and patients with comorbid PD and depression, have different treatment responses to patients without PD.

Despite this previous research, little attention, however, has specifically focussed on the influence of PD on treatment outcomes in RCTs of pharmacological interventions for mood disorders. This is a major oversight considering that RCT outcomes have critical implications for treatment recommendations in mood disorders. Moreover, RCTs depend on the assessment of change, and the failure to include and report on PD in RCTs may therefore omit an important mediator or moderator of study results. Given the paucity of information and inconsistent findings in relation to pharmacological interventions, the inclusion and evaluation of PD in RCTs assessing efficacy of pharmacological interventions is warranted. As such, this review will investigate the role of PD in RCTs of pharmacological interventions for adults with mood disorders, specifically depressive and bipolar spectrum disorders.

Objectives

The aim of this systematic review is to:

1. Identify published RCTs of pharmacological interventions for mood disorders (defined as depressive disorders and bipolar spectrum disorders), which also include an assessment of PD;
2. Appraise the quality of methodology employed in each of the RCTs eligible for inclusion in this systematic review;
3. Collate and provide a comprehensive synthesis of the evidence, to evaluate whether treatment outcomes differ for those with and without comorbid PD.

METHODS AND ANALYSIS

Eligibility criteria for studies to be included in this review

This systematic review will include completed RCTs of pharmacological interventions for depressive disorders and bipolar spectrum disorders, which also have a measure of PD. Importantly, this is distinct from RCTs which have specifically assessed an intervention for PD. For the purposes of this review, pharmacological interventions refer to any drug or exogenously administered substance given for the purpose of having an effect on mood disorder symptoms, including but not limited to, antidepressants, mood stabilisers, antiepileptics, and natural medicines. PDs include paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, obsessive-compulsive, PD-trait specified, dissocial, emotionally unstable, anankastic, anxious (avoidant), passive-aggressive, depressive, impulsive, affective, explosive, other-specific, PD unspecified, PD not elsewhere classified, and PD not otherwise specified. Depressive disorders include major depressive disorder, persistent depressive disorder, and dysthymia. Bipolar spectrum disorders include bipolar I disorder, bipolar II disorder, cyclomythic disorder, and bipolar disorder not elsewhere classified or not otherwise specified.

Eligible RCTs must be conducted in adult populations (≥ 18 years) with depressive disorders or bipolar spectrum disorders (based on structured interviews and defined by

diagnoses based on any version of the Diagnostic and Statistical Manual of Mental Disorders [DSM] or International Classification of Disease [ICD]), and also include assessment of PD. PDs must be measured by structured or semi structured interviews including, but not limited to, the Structured Clinical Interview for DSM IV Axis II Personality Disorders (SCID-II),[49] the International Personality Disorder Examination (IPDE),[50] the Iowa Personality Disorder Screen (IPDS),[51] the Standardised Assessment of Personality (SAPAS),[52] or indicated by self-report tools such as the Dimensional Assessment of Personality Pathology (DAPP),[53] the Personality Disorder Questionnaire (PDQ-4),[54] the Wisconsin Personality Disorder Inventory (WISPI-IV),[55] or the DSM-IV and ICD-10 Personality Questionnaire (DIP-Q).[56] We will also include studies which have assessed PD via chart review. RCTs conducted on any sex or nationality, and published in any year, are eligible to be included in this review.

The primary outcome of this review will be to evaluate the impact of PD on treatment outcomes in RCTs of pharmacological interventions for adults with mood disorders, namely depressive and bipolar spectrum disorders. Specifically, the main focus will be to determine whether treatment outcomes (assessed by mean change in symptom scores from baseline to the end of the RCT treatment phase) of the pharmacological intervention differs for those with and without PD. Treatment outcomes will be measured by validated assessment tools (for instance, clinician-rated questionnaire) specific to the mood disorder and outlined in the RCT protocol (for example, the Montgomery Asberg Depression Rating Scale [MADRS][57], commonly used in depression and bipolar disorder RCTs). The primary outcome of each RCT (as specified per protocol) will be examined regardless of the type of tool used to measure the outcome. In instances where RCTs have assessed multiple primary outcomes, highest priority will be given to clinician-rated assessments; and additional primary outcomes of the RCT, such as patient subjective evaluations, will be given subsequent priority.

Secondary outcomes of this review include, assessing the impact that PD has on patient subjective outcomes, such as self-reported mood disorder symptom improvement (for example, the patient global impression-improvement scale [PGI-I][58], frequently used in RCTs) and assessments of quality of life and functioning (for instance, the Quality of Life Enjoyment and Satisfaction Questionnaire [QLESQ][59] and Longitudinal Interval Follow-Up Range of Impaired Functioning Tool [LIFE-RIFT][60]). Evaluating the role that PD has on the occurrence of adverse events from pharmacological interventions will be given third priority.

Any RCT design will be considered eligible for this review. Specifically, the design of included RCTs may be double-blind, placebo-controlled or active-controlled; parallel group; or cluster design. The initial phase of cross-over design RCTs will also be eligible. RCTs which have included more than one pharmacological intervention arm will be included, and these data will be pooled.

No restriction on the length of the treatment phase of the RCT will be set. Included RCTs must follow the intention-to-treat (ITT), or a modified version of the ITT principle, where criteria for analysis is pre-specified per protocol. The ITT approach includes all randomised participants in the final analysis, regardless of treatment noncompliance, protocol deviations, and withdrawal,[61] however, a modified ITT method is also pertinent to this review, due to its allowance of justified exclusion of participants from analysis (for instance, only including participants in the final analysis who completed at least one post-baseline assessment). Articles will need to be published in the English language. Articles that are cross-sectional, case-control or cohort by design, grey literature, theses, and/or conference presentations will not be included.

Secondary analyses of primary RCT results which have examined the role of PD in relation to pharmacological interventions will also be included. In instances, where RCT protocols or primary outcome papers have stated that PD assessment was undertaken but not

reported on in the final analysis, or where missing data has been identified in general, authors will be contacted to obtain data.

Search Strategy

The PICO framework (i.e., Populations/people/patient/problem, Intervention/s, Comparison, Outcome) was utilised to develop the following search strategy. To identify applicable literature, a search strategy using databases for medical, health, psychology, and the social sciences (Cochrane Central Register of Controlled Clinical Trials [CENTRAL] via cochranelibrary.com, PubMed via PubMed, EMBASE via embase.com, PsycINFO via Ebsco, and CINAHL Complete via Ebsco) will be performed. We will apply the following medical subject headings (MeSH), Emtree terms, and key words, where applicable, to search all fields: ('mood disorders' OR 'mood disorder' OR 'bipolar and related disorders' OR 'bipolar depression' OR 'mania') AND ('personality disorders' OR 'personality disorder' OR 'personality') AND ('pharmacology' OR 'pharmacotherapy' OR 'drug trial' OR 'drug therapy') AND ('clinical trial' OR 'randomised controlled trial'). Relevant truncation and wildcard symbols will be applied to each database. Details of the search strategy are presented in supplementary appendix 1. A hand search of reference lists of existing reviews on this topic will also be completed.

One reviewer will apply the search strategy and ascertain studies eligible for inclusion by cross-checking against the pre-determined eligibility criteria, using the following method: (1) assessment of titles and abstracts to determine if the study satisfies the methodological inclusion criteria of: being an RCT, examining a pharmacological intervention, and being conducted on patients with a mood disorder; and (2) assessment of full-text papers. This method is being used ensure that RCTs which assessed PD, but did not report this in their title or abstract are not missed. A second reviewer will confirm 10% of the articles at each stage of

screening. If there is disagreement regarding eligibility, a third independent reviewer will determine the conclusive decision.

Data Management and Extraction

Data will be managed using Covidence;[62] an online reference management database. Covidence allows citation screening and review, handling of duplicate references, and extraction of study characteristics and outcomes using inclusion and exclusion criteria. Data will be extracted in accordance with the Consolidated Standards of Reporting Trials (CONSORT)[63] guidelines. Two reviewers will separately extract the data. Extracted information will include:

1. Study identification characteristics (first author's name, publication year, country/ies of RCT completion, sponsorship source);
2. Study design (type of disease group/s, number of study arms, primary and secondary outcomes, type of control, sample size, type of ITT analysis);
3. Intervention characteristics (type and dose of pharmacological therapy, length of treatment phase, and length of follow-up period);
4. Population characteristics (baseline demographic characteristics, group differences); and
5. Outcome characteristics (name of measurement scale, type of variable, and reported inferential statistics including mean and standard deviation for each time-point, and *p* value).

Evaluation of Methodological Quality of Included Articles

Eligible literature will be scored as low, high, or unclear risk of bias using the criteria of the Cochrane Collaboration's "Risk of Bias" tool.[64] The scoring system from Higgins et al[64] to evaluate data extricated from included studies will be employed (Table 1). These factors include: random sequence generation, allocation concealment, blinding of participants and

Table 1.

Cochrane Risk of Bias Tool[64]

Bias domain	**Source of bias**	**Support for judgement**	**Judgment (assess as low, unclear, or high risk of bias)**
Selection bias	Random sequence generation	Describe the method used to produce the allocation sequence in satisfactory detail to permit assessment of whether it should yield comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in adequate detail to determine whether allocations could have been anticipated before or during trial enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and study personnel*	Describe the methods used, if any, to blind trial participants and researchers from information of which intervention participants received. Provide information concerning whether blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and study personnel during the study
Detection bias	Blinding of outcome assessment*	Describe all methods used, if any, to blind outcome evaluation from information of which intervention participants received. Provide information pertaining to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the extensiveness of outcome data for each main outcome, including attrition and exclusions from the analysis. Declare whether attrition and exclusions were stated, the numbers for each intervention group (in contrast with total randomised participants), details for attrition or	Attrition bias due to amount, nature, or handling of incomplete outcome data

		exclusion were reported, and any re-inclusions in analyses for the review	
Reporting bias	Selective reporting	Declare how selective reporting was assessed and what was found	Reporting bias due to selective outcome reporting
Other bias	Other bias, preferably pre-specified	Describe any critical concerns about bias which has not been covered in the other domains in the tool	Bias due to problems not covered elsewhere

**Assessments should be made for each main outcome measure or class of outcomes*

personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Eligible studies will be independently scored by two independent reviewers. Should any discrepancy in scores be evident, a third independent reviewer will arbitrate the final judgement.

Heterogeneity of evidence will be determined using I^2, in accordance with suggestions from the Cochrane *Handbook for Systematic Reviews of Interventions*.[65] Heterogeneity will be quantified as low, moderate, or high with I^2 values of 25%, 50%, and 75%, respectively.[66] Heterogeneity of <50% will be considered low and will allow the inclusion of the study to the systematic review and meta-analysis.

The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)[67] will be utilised to summarise the findings and assess the quality of evidence and strength of recommendations for relevant outcomes. The following factors will be used to determine the quality of the evidence and will be graded as high, moderate, low, or very low: limitations of comprehensive design and execution; inconsistency or heterogeneity; indirectness; imprecision; and publication bias. Recommendations based on GRADE may include the suggestion to include assessment of PD in RCTs, or the use of particular pharmacological interventions for patients with PD and a comorbid mood disorder.

Data Synthesis and Statistical Analyses

Data will be analysed using RevMan.[68] For continuous data, we will calculate mean differences (MDs) or standardised mean differences (SMDs) with 95% confidence intervals. For dichotomous data (for instance, treatment responder/non-responder, adverse events), we will calculate risk ratios with 95% confidence intervals. MDs will be used when the same scale has been used to measure treatment outcome, and SMDs will be utilised when different scales

measure the same treatment outcome. Effect sizes will be calculated using Cohen's *d*. Sample sizes, standard deviations, and *p* values will be stated.

A meta-analysis will be undertaken if more than two eligible studies are identified. This meta-analysis will be performed based on the standardised mean difference approach (specifically, the mean symptom change of the mood disorder, between participants with and without comorbid PD) using the Cohen's *d* test. A random-effects model will be used and reported with 95% confidence intervals and a *p* value. To determine the robustness of the meta-analysis outcome, sensitivity analyses will also be conducted.

Subgroup analysis:

Subgroup analysis will be performed where the evidence is heterogeneous ($I^2 \geq 50$). The following subgroup analyses have been decided *a priori* and include analysis of differences between PDs (where data on specific PDs have been measured), their relationship to mood disorders, and treatment outcomes:

1. Measurement of PD (i.e., structured clinical interview compared to screening assessment);
2. Relation of PD clusters and/or specific PDs;
3. Relation of PD to treatment outcome of pharmacological agents (for example, comparison of comorbid PD and mood disorder with mood disorder only, and its association with antidepressant efficacy).

Presentation and Reporting of Results

This protocol adheres to PRISMA-P practice guidelines and the PRISMA-P checklist was used when writing this protocol.[69] [70] The review will conform to PRISMA reporting guidelines;[71] and a PRISMA flow diagram will be utilised to depict study selection, numbers and reasons concerning included vs. excluded studies in the context of the pre-specified eligibility criteria. All eligible studies will have key information pertaining to mood disorders

(i.e., depressive disorders or bipolar spectrum disorders), PD, and treatment outcomes identified, extracted and presented.

Patient and Public Involvement

Patient and public involvement was not sought for the design of this study; though patient experience of pharmacological treatments and RCTs were considered in the development of the research question.

Ethics and Dissemination

This review will only use published data, and as such, ethical approval is not required. Ethical and governance principles will be complied with, in respect to data management and the presentation and dissemination of findings. This review has been registered on PROSPERO (CRD42018089279). Results will be published in a peer-reviewed scientific journal, and results will be presented at relevant scientific conference/s.

Conclusion

To the best of our knowledge, this will be the first systematic review to investigate whether PD influences the treatment outcomes for mood disorders in RCTs. The findings of this review will contribute to the limited literature available on the role of PD on treatment outcomes in those with mood disorders and will also provide information to inform clinical practice and health strategies.

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Author contributions

BEK conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. SLB-O developed the search strategy; and edited, revised, and approved the final version of this manuscript. AT

conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. OMD conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. MB conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. MMA developed the search strategy; and edited, revised, and approved the final version of this manuscript. HK-H edited, revised, and approved the final version of this manuscript. LJW conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript.

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Competing interests statement

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Supplementary Table 1. Search Strategy for Cochrane CENTRAL.

	Search Terms
#1	"mood disorders" [All text]
#2	"mood disorder" [All text]
#3	"bipolar and related disorders" [All text]
#4	"bipolar depression" [All text]
#5	"mania" [All text]
#6	#1 or #2 or #3 or #4 or #5
#7	"personality disorders"
#8	"personality disorder"
#9	"personality"
#10	#7 or #8 or #9
#11	"pharmacology" [All text]
#12	"pharmacotherapy" [All text]
#13	"drug trial" [All text]
#14	"drug therapy" [All text]
#15	#11 or #12 or #13 or #14
#16	"clinical trial"
#17	"randomised controlled trial"
#18	#16 or #17
#19	#6 and #10 and #15 and #18

Supplementary Table 2. Search Strategy for PubMed.

	Search Terms
#1	"personality disorders" [All fields]
#2	"personality disorder" [All fields]
#3	"personality" [All fields]
#4	#1 or #2 or #3
#5	"clinical trial" [All fields]
#6	"randomized controlled trial" [All fields]
#7	#5 or #6
#8	"mood disorders" [All fields]
#9	"mood disorder"
#10	"bipolar and related disorders" [All fields]
#11	"bipolar depression" [All fields]
#12	"mania" [All fields]
#13	#8 or #9 or #10 or #11 or #12
#14	"pharmacology" [All fields]
#15	"pharmacotherapy" [All fields]
#16	"drug trial" [All fields]
#17	"drug therapy" [All fields]
#18	#14 or #15 or #16 or #17
#19	#4 and #7 and #13 and #14

Supplementary Table 3. Search Strategy for Embase.

	Search Terms
#1	'personality disorder' [All fields]
#2	'personality' [All fields]
#3	#1 or #2
#4	'clinical trial' [All fields]
#5	'randomized controlled trial'[All fields]
#6	#4 or #5
#7	'mood disorders' [All fields]
#8	'bipolar and related disorders' [All fields]
#9	'bipolar depression' [All fields]
#10	'mania' [All fields]
#11	#7 or #8 or #9 or #10
#12	'pharmacology' [All fields]
#13	'drug therapy' [All fields]
#14	#12 or #13
#15	#3 and #6 and #11 and #14

Supplementary Table 4. Search Strategy for PsycInfo.

	Search Terms
#1	"personality disorders" [All text]
#2	"personality disorder" [All text]
#3	"personality" [All text]
#4	#1 or #2 or #3
#5	"clinical trial" [All text]
#6	"randomized controlled trial" [All text]
#7	#5 or #6
#8	"mood disorders" [All text]
#9	"mood disorder"
#10	"bipolar and related disorders" [All text]
#11	"bipolar depression" [All text]
#12	"mania" [All text]
#13	#8 or #9 or #10 or #11 or #12
#14	"pharmacology" [All text]
#15	"pharmacotherapy" [All text]
#16	"drug trial" [All text]
#17	"drug therapy" [All text]
#18	#14 or #15 or #16 or #17
#19	#4 and #7 and #13 and #18

Supplementary Table 5. Search Strategy for CINAHL Complete.

	Search Terms
#1	"personality disorders" [All text]
#2	"personality disorder" [All text]
#3	"personality" [All text]
#4	#1 or #2 or #3
#5	"clinical trial" [All text]
#6	"randomized controlled trial" [All text]
#7	#6 or #7
#8	"mood disorders" [All text]
#9	"mood disorder"
#10	"bipolar and related disorders" [All text]
#11	"bipolar depression" [All text]
#12	"mania" [All text]
#13	#8 or #9 or #10 or #11 or #12
#14	"pharmacology" [All text]
#15	"pharmacotherapy" [All text]
#16	"drug trial" [All text]
#17	"drug therapy" [All text]
#18	#14 or #15 or #16 or #17
#19	#4 and #7 and #13 and #18

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3

Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	20
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Sources	#5a	Indicate sources of financial or other support for the review	21
Sponsor	#5b	Provide name for the review funder and / or sponsor	21
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	21
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	11
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication	14

		status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	14
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary file
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	15
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	14
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	15
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	15

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	15
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	18
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	15
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	16
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16

Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	18

BMJ Open

The Role of Personality Disorder in Randomised Controlled Trials of Pharmacological Interventions for Adults with Mood Disorders: A Protocol for a Systematic Review and Meta-Analysis

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The Role of Personality Disorder in Randomised Controlled Trials of Pharmacological Interventions for Adults with Mood Disorders: A Protocol for a Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Remission rates for mood disorders, including depressive and bipolar disorders, remain relatively low despite available treatments, and many patients fail to respond adequately to these interventions. Evidence suggests that personality disorder may play a role in poor outcomes. Although personality disorders are common in patients with mood disorders, it remains unknown whether personality disorder affects treatment outcomes in mood disorders. We aim to review currently available evidence regarding the role of personality disorder on pharmacological interventions in randomised controlled trials for adults with mood disorders.

Methods and analysis: A systematic search of Cochrane Central Register of Controlled Clinical Trials (CENTRAL) via cochranelibrary.com, PubMed via PubMed, EMBASE via embase.com, PsycINFO via Ebsco, and CINAHL Complete via Ebsco databases will be conducted to identify randomised controlled trials that have investigated pharmacological interventions in participants aged 18 years or older for mood disorders (i.e., depressive disorders and bipolar spectrum disorders) and have also included assessment of personality disorder. One reviewer will screen studies against the predetermined eligibility criteria, and a second reviewer will confirm eligible studies. Data will be extracted by two independent reviewers. Methodological quality and risk of bias will be assessed using the Cochrane Risk of Bias Tool. A systematic review, and if sufficient evidence is identified, a meta-analysis will be completed. Meta-analysis will be conducted using the standardised mean difference approach and reported with 95% confidence intervals. A random-effects model will be employed and statistical heterogeneity will be evaluated using the I^2 statistic. Pre-specified subgroup analyses will be completed.

Ethics and dissemination: As this systematic review will utilize published data, ethics permission will not be required. The outcomes of this systematic review will be published in a relevant scientific journal and presented at a research conference.

Registration details: This systematic review has been registered with PROSPERO (CRD42018089279).

Keywords: Personality disorders, randomised controlled trial, depression, bipolar disorder, pharmacological interventions

Article summary:

- This will be the first systematic review to examine personality disorder in randomised controlled trials of pharmacological interventions for mood disorders.
- Two independent reviewers will independently extract the data.
- The Cochrane Risk of Bias tool will be used to evaluate the quality of studies.
- The variety of tools to assess personality disorders and mood disorders may cause considerable heterogeneity.
- A potential limitation of this systematic review may be the paucity of evidence available, which may not permit a meta-analysis to be completed.

INTRODUCTION

Personality disorders (PD) are a group of mental disorders defined by a constellation of persistent, maladaptive patterns of behaviour and experiences, which markedly deviate from the expectations of the individual's culture, are stable over time, and lead to distress or impairment.[1 2] PDs are commonly manifested in disordered thoughts, affectivity, impulse control, and social and occupational functioning,[2] and have been recognised as common mental health conditions.[3] The World Health Organization (WHO) World Mental Health Surveys estimated PD prevalence rates to be 6.1% in a cross-national sample,[4] while the Australian National Survey of Mental Health and Wellbeing (2000) estimated prevalence to be 6.5%[5] using the same self-report scale. Other prevalence rates utilising structured clinical assessments have estimated PD prevalence to be between 10.6%[6] to 21.8% in population-based samples.[7]

Despite these high prevalence rates, it has been argued that PDs do not receive the attention they warrant[8] and have largely been omitted from policy and research initiatives.[9 10] For instance, the Global Burden of Disease Study (GBDS) highlighted that psychiatric disorders (namely, major depression, alcohol use, bipolar disorder, schizophrenia, and obsessive-compulsive disorder) substantially contribute to the global burden of disease.[11] However, the GBDS did not include PDs in its scope, and accordingly, true estimates of the disease burden of mental illness may have been underestimated.[12] The omission of PDs at the population level has important repercussions for treatment programmes and health-care planning,[9] including the development and trial of pharmacological interventions in randomised controlled trials (RCTs). Consequently, while interventions for psychiatric disorders in general has expanded in contemporary research, the recognition of PD in clinical and research contexts has been neglected.

Parallel to the exclusion of PD at the population level, significant progress has been

made in the development and confirmation of pharmacological treatments for mood disorders, but not PDs, in recent years. In particular, establishing effective interventions for depression, as the leading cause of disability worldwide, has been made a global priority.[13] Specific research recommendations put forward by the National Institute for Health and Care Excellence (NICE) recommend that RCTs are developed to test the efficacy of sequenced therapies (continuation of initial antidepressant compared to switching to an antidepressant from another class) for depression.[14] Psychotropic medications such as lithium (a mood stabiliser), antipsychotics (haloperidol, olanzapine, quetiapine, or risperidone) and combination therapies for the treatment of bipolar disorder have also been recommended to be trailed.[14] These clinical and research recommendations are made on the best available evidence, in which the influence of PD may not have been acknowledged.

Corresponding with the NICE guidelines, sequenced therapies utilising a range of pharmacological treatments (i.e., citalopram, bupropion, sertraline, nortriptyline, mirtazapine, lithium, tranylcypromine, venlafaxine),[15] as well as combination therapies[16 17] have gained recent attention for the treatment of depression. Additionally, pharmacological interventions such as antiepileptics (e.g., divalprox sodium and carbamazepine)[18 19] for the treatment of bipolar disorder have been confirmed in recent clinical trials.[20] These treatment developments echo recognition of the magnitude of mood disorders substantially contributing to the global burden of disease. However, the progress in treatment development has concurrently been hampered by limited treatment effectiveness and adverse outcomes for many people.[21] For instance, remission rates from clinical symptoms remain at ~30% for patients with depression[22] and ~28% for bipolar disorder[23] for patients treated by pharmacological interventions. These remission rates highlight the complexity in treating acute mood disorders, and also emphasises the potential that internal patient-related factors, such as PD, may contribute to the difficulty in finding effective pharmacological treatments.

Recognising the potential risk factors implicated in the outcomes of mood disorders may assist in providing more targeted treatments, leading to better outcomes.[24] PD is highly comorbid amongst clinical populations, and has particularly high incidence rates for patients with depression and bipolar disorder. For example, Zimmerman, Rothschild, and Chelminski (2005) estimated that 51.3% of community-based outpatients had a comorbid PD and major depressive disorder, and that the presence of this comorbidity was significantly associated with greater PD pathology.[25] Zimmerman et al. also found that even one borderline trait may have an adverse effect on outcomes.[25] Similar rates were found by Melartin et al. (2002), whereby 44% of patients with depression met also criteria for PD.[26] Moreover, Post et al. (2018) found that 65.9% of patients with bipolar disorder who were in a euthymic phase and 88.0% of patients who were in an acute depression state at the time of assessment met criteria for at least one PD.[27] These comorbidities are noteworthy considering that the presence of PD has potential to affect the course and treatment of the comorbid mood disorder.[25]

For example, previous epidemiological research has demonstrated that PD affects the course of depression. Specifically, Grilo et al. (2012) demonstrated that patients with comorbid schizotypal, borderline, or avoidant PD and depression had slower time to remission over a twenty-four month period compared to patients with depression only.[28] Similarly, Gunderson et al. (2011) found that the course of major depressive disorder was negatively influenced by the presence of borderline PD, in that the rate to remission over a ten-year period was 50% slower for patients with this comorbity.[29] Research on PD and the course of bipolar disorder is less robust, however. In a clinical sample study Garno et al. (2005) demonstrated that patients with comorbid Cluster B PD and bipolar disorder had significantly more lifetime suicide attempts than patients with bipolar disorder only.[30] Tamam, Ozpoyraz, and Karatas (2014) found that outpatients with comorbid PD and bipolar disorder had significantly greater psychopathology, more affective illness episodes, and a higher number of suicide attempts

compared to patients with bipolar disorder only.[31]

Other research has suggested that PD influences the treatment outcome of both depression[32 33] and bipolar disorder.[30 34] For example, in one meta-analysis it was found that comorbid PD and depression was associated with double the risk of poor treatment outcome (defined as less than 50% reduction in symptoms) compared to depression only, and that outcome was not affected by the type of intervention administered (with the exception of electroconvulsive therapy which showed no difference between groups).[10] Though the negative treatment outcomes did not diverge by the type of instrument used to measure depression, the authors did not state how the included studies assessed PD. Considering the aforementioned variance in prevalence rates resulting from differences in the assessment of PD (for example, assessment by screening tool compared to structured clinical assessment), this may have been an important oversight in relation to treatment outcomes. An earlier review by Mulder (2002) also investigated the influence of PD on treatment outcome in depression, and found that the majority of studies eligible for inclusion in the review reported worse treatment outcomes, compared to those with depression only. However, well-designed studies (for instance, studies which assessed PD via structured clinical interview and where treatment was controlled via standard treatment or random assignment into intervention groups) showed no difference in treatment outcome.

The treatment outcomes of comorbid PD and bipolar disorder have also been demonstrated. In a review, Beiling, Green, and Macqueen (2007) summarised that the presence of comorbid PD had a negative effect on treatment outcome in bipolar disorder.[35] However, the literature specific to pharmacological therapies included in the review was limited. In one retrospective study eligible for review, Abou-Saleh (1983) showed that patients with bipolar disorder who did not respond to lithium had traits of high neuroticism and low dominance,[36]

however this does not necessitate the presence of personality pathology. Gasperini et al. (1993) showed that patients with comorbid PD and bipolar disorder had a higher number of manic or depressive episode relapses, and this was particularly evident for patients with histrionic PD.[37] Moreover, Preston et al. (2004) retrospectively diagnosed borderline PD in two samples of patients with bipolar disorder who were trailing lamotrigine as a monotherapy. Both patient groups improved with treatment (response rates of 48% and 29% of patients with bipolar disorder and comorbid PD and bipolar disorder, respectively) though this difference was not statistically significant.[38]

Though previous research has suggested that PDs should be assessed in RCTs for patients with depressive and bipolar disorders,[10 35] there is limited evidence which has explored the mechanisms which underpin the poorer treatment outcomes for patients with comorbid PD. One possible explanation is that individuals may not recognise or admit personality psychopathology due to disruptions of identity and self-awareness. These disruptions are common features of PD and have crucial implications for the diagnosis of PD[39] and treatment of both the PD and comorbid disorder.[40] Previous research has demonstrated that despite the onset of PD occurring in late adolescence or early adulthood, patients do not tend to present for treatment until much later.[41] As such PDs may be left under-diagnosed and consequently untreated, affecting the therapeutic efficacy of the treatment for the comorbid mood disorder. In addition to this, some literature has suggested that individuals with PD, particularly borderline PD, are often non-compliant[42] or non-adherent with pharmacological treatments,[43] though this area has not been explored in depth. Poor therapeutic alliance is common in people with PD, driving adherence issues, treatment engagement, and self-efficacy. Non-adherence has important repercussions for the management of psychiatric disorders,[44] and these issues may consequently perpetuate symptomatology of PD and any comorbidities.

Furthermore, there is some evidence to suggest that PD may play a mediating role in the relationship between depression and treatment outcomes. For example Mulder et al. (2003) demonstrated that patients with comorbid PD and depression had poor treatment outcome with nortriptyline (a tricyclic antidepressant) compared to fluoxetine (an SSRI), and this was particularly evident in patients with borderline PD.[45] These results echo earlier research which demonstrated that patients with borderline PD respond poorly to tricyclic antidepressants, but moderately well to SSRIs [46-48] Though a lack of evidence does not permit discussion of the differences in treatment response between pharmacological interventions, literature suggests that both patients with PD and patients with comorbid PD and depression, have different treatment responses to patients without PD.

Despite this previous research, little attention, however, has specifically focussed on the influence of PD on treatment outcomes in RCTs of pharmacological interventions for mood disorders. This is a major oversight considering that RCT outcomes have critical implications for treatment recommendations in mood disorders. Moreover, RCTs depend on the assessment of change, and the failure to include and report on PD in RCTs may therefore omit an important mediator or moderator of study results. Given the paucity of information and inconsistent findings in relation to pharmacological interventions, the inclusion and evaluation of PD in RCTs assessing efficacy of pharmacological interventions is warranted. As such, this review will investigate the role of PD in RCTs of pharmacological interventions for adults with mood disorders, specifically depressive and bipolar spectrum disorders.

Objectives

The aim of this systematic review is to:

1. Identify published RCTs of pharmacological interventions for mood disorders (defined as depressive disorders and bipolar spectrum disorders), which also include an assessment of PD;
2. Appraise the quality of methodology employed in each of the RCTs eligible for inclusion in this systematic review;
3. Collate and provide a comprehensive synthesis of the evidence, to evaluate whether treatment outcomes differ for those with and without comorbid PD.

METHODS AND ANALYSIS

Eligibility criteria for studies to be included in this review

This systematic review will include completed RCTs of pharmacological interventions for depressive disorders and bipolar spectrum disorders, which also have a measure of PD. Importantly, this is distinct from RCTs which have specifically assessed an intervention for PD. For the purposes of this review, pharmacological interventions refer to any drug or exogenously administered substance given for the purpose of having an effect on mood disorder symptoms, including but not limited to, antidepressants, mood stabilisers, antiepileptics, and natural medicines. PDs include paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, obsessive-compulsive, PD-trait specified, dissocial, emotionally unstable, anankastic, anxious (avoidant), passive-aggressive, depressive, impulsive, affective, explosive, other-specific, PD unspecified, PD not elsewhere classified, and PD not otherwise specified. Depressive disorders include major depressive disorder, persistent depressive disorder, and dysthymia. Bipolar spectrum disorders include bipolar I disorder, bipolar II disorder, cyclomythic disorder, and bipolar disorder not elsewhere classified or not otherwise specified.

Eligible RCTs must be conducted in adult populations (≥ 18 years) with depressive disorders or bipolar spectrum disorders (based on structured interviews and defined by

diagnoses based on any version of the Diagnostic and Statistical Manual of Mental Disorders [DSM] or International Classification of Disease [ICD]), and also include assessment of PD. PDs must be measured by structured or semi structured interviews including, but not limited to, the Structured Clinical Interview for DSM IV Axis II Personality Disorders (SCID-II),[49] the International Personality Disorder Examination (IPDE),[50] the Iowa Personality Disorder Screen (IPDS),[51] the Standardised Assessment of Personality (SAPAS),[52] or indicated by self-report tools such as the Dimensional Assessment of Personality Pathology (DAPP),[53] the Personality Disorder Questionnaire (PDQ-4),[54] the Wisconsin Personality Disorder Inventory (WISPI-IV),[55] or the DSM-IV and ICD-10 Personality Questionnaire (DIP-Q).[56] We will also include studies which have assessed PD via chart review. RCTs conducted on any sex or nationality, and published in any year, are eligible to be included in this review.

The primary outcome of this review will be to evaluate the impact of PD on treatment outcomes in RCTs of pharmacological interventions for adults with mood disorders, namely depressive and bipolar spectrum disorders. Specifically, the main focus will be to determine whether treatment outcomes (assessed by mean change in symptom scores from baseline to the end of the RCT treatment phase) of the pharmacological intervention differs for those with and without PD. Treatment outcomes will be measured by validated assessment tools (for instance, clinician-rated questionnaire) specific to the mood disorder and outlined in the RCT protocol (for example, the Montgomery Asberg Depression Rating Scale [MADRS][57], commonly used in depression and bipolar disorder RCTs). The primary outcome of each RCT (as specified per protocol) will be examined regardless of the type of tool used to measure the outcome. In instances where RCTs have assessed multiple primary outcomes, highest priority will be given to clinician-rated assessments; and additional primary outcomes of the RCT, such as patient subjective evaluations, will be given subsequent priority.

Secondary outcomes of this review include, assessing the impact that PD has on patient subjective outcomes, such as self-reported mood disorder symptom improvement (for example, the patient global impression-improvement scale [PGI-I][58], frequently used in RCTs) and assessments of quality of life and functioning (for instance, the Quality of Life Enjoyment and Satisfaction Questionnaire [QLESQ][59] and Longitudinal Interval Follow-Up Range of Impaired Functioning Tool [LIFE-RIFT][60]). Evaluating the role that PD has on the occurrence of adverse events from pharmacological interventions will be given third priority.

Any RCT design will be considered eligible for this review. Specifically, the design of included RCTs may be double-blind, placebo-controlled or active-controlled; parallel group; or cluster design. The initial phase of cross-over design RCTs will also be eligible. RCTs which have included more than one pharmacological intervention arm will be included, and these data will be pooled.

No restriction on the length of the treatment phase of the RCT will be set. Included RCTs must follow the intention-to-treat (ITT), or a modified version of the ITT principle, where criteria for analysis is pre-specified per protocol. The ITT approach includes all randomised participants in the final analysis, regardless of treatment noncompliance, protocol deviations, and withdrawal,[61] however, a modified ITT method is also pertinent to this review, due to its allowance of justified exclusion of participants from analysis (for instance, only including participants in the final analysis who completed at least one post-baseline assessment). Articles will need to be published in the English language. Articles that are cross-sectional, case-control or cohort by design, grey literature, theses, and/or conference presentations will not be included.

Secondary analyses of primary RCT results which have examined the role of PD in relation to pharmacological interventions will also be included. In instances, where RCT protocols or primary outcome papers have stated that PD assessment was undertaken but not

reported on in the final analysis, or where missing data has been identified in general, authors will be contacted to obtain data.

Search Strategy

The PICO framework (i.e., Populations/people/patient/problem, Intervention/s, Comparison, Outcome) was utilised to develop the following search strategy. To identify applicable literature, a search strategy using databases for medical, health, psychology, and the social sciences (Cochrane Central Register of Controlled Clinical Trials [CENTRAL] via cochranelibrary.com, PubMed via PubMed, EMBASE via embase.com, PsycINFO via Ebsco, and CINAHL Complete via Ebsco) will be performed. We will apply the following medical subject headings (MeSH), Emtree terms, and key words, where applicable, to search all fields: ('mood disorders' OR 'mood disorder' OR 'bipolar and related disorders' OR 'bipolar depression' OR 'mania') AND ('personality disorders' OR 'personality disorder' OR 'personality') AND ('pharmacology' OR 'pharmacotherapy' OR 'drug trial' OR 'drug therapy') AND ('clinical trial' OR 'randomised controlled trial'). Relevant truncation and wildcard symbols will be applied to each database. Details of the search strategy are presented in supplementary appendix 1. A hand search of reference lists of existing reviews on this topic will also be completed.

One reviewer will apply the search strategy and ascertain studies eligible for inclusion by cross-checking against the pre-determined eligibility criteria, using the following method: firstly, assessment of titles and abstracts to determine if the study satisfies the methodological inclusion criteria of: being an RCT, examining a pharmacological intervention, and being conducted on patients with a mood disorder; and subsequently, assessment of full-text papers. This method is being used ensure that RCTs which assessed PD, but did not report this in their title or abstract are not missed. A second reviewer will confirm 10% of the articles at each stage

of screening. If there is disagreement regarding eligibility, a third independent reviewer will determine the conclusive decision.

Data Management and Extraction

Data will be managed using Covidence;[62] an online reference management database. Covidence allows citation screening and review, handling of duplicate references, and extraction of study characteristics and outcomes using inclusion and exclusion criteria. Two reviewers will separately extract the data. Extracted information will include:

1. Study identification characteristics (first author's name, publication year, country/ies of RCT completion, sponsorship source);
2. Study design (type of disease group/s, number of study arms, primary and secondary outcomes, type of control, sample size, type of ITT analysis);
3. Personality disorder characteristics (type/s or cluster/s of personality disorder studied);
4. Intervention characteristics (type and dose of pharmacological therapy, length of treatment phase, and length of follow-up period);
5. Population characteristics (baseline demographic characteristics, group differences); and
6. Outcome characteristics (name of measurement scale, type of variable, and reported inferential statistics including mean and standard deviation for each time-point, and *p* value).

Evaluation of Methodological Quality of Included Articles

Eligible literature will be scored as low, high, or unclear risk of bias using the criteria of the Cochrane Collaboration's "Risk of Bias" tool.[63] The scoring system from Higgins et al[63] to evaluate data extricated from included studies will be employed (Table 1). These factors include: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and

Table 1.

Cochrane Risk of Bias Tool[63]

Bias domain	**Source of bias**	**Support for judgement**	**Judgment (assess as low, unclear, or high risk of bias)**
Selection bias	Random sequence generation	Describe the method used to produce the allocation sequence in satisfactory detail to permit assessment of whether it should yield comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in adequate detail to determine whether allocations could have been anticipated before or during trial enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and study personnel*	Describe the methods used, if any, to blind trial participants and researchers from information of which intervention participants received. Provide information concerning whether blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and study personnel during the study
Detection bias	Blinding of outcome assessment*	Describe all methods used, if any, to blind outcome evaluation from information of which intervention participants received. Provide information pertaining to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the extensiveness of outcome data for each main outcome, including attrition and exclusions from the analysis. Declare whether attrition and exclusions were stated, the numbers for each intervention group (in contrast with total randomised participants), details for attrition or	Attrition bias due to amount, nature, or handling of incomplete outcome data

		exclusion were reported, and any re-inclusions in analyses for the review	
Reporting bias	Selective reporting	Declare how selective reporting was assessed and what was found	Reporting bias due to selective outcome reporting
Other bias	Other bias, preferably pre-specified	Describe any critical concerns about bias which has not been covered in the other domains in the tool	Bias due to problems not covered elsewhere

**Assessments should be made for each main outcome measure or class of outcomes*

other sources of bias. Eligible studies will be independently scored by two independent reviewers. Should any discrepancy in scores be evident, a third independent reviewer will arbitrate the final judgement.

Heterogeneity of evidence will be determined using I^2, in accordance with suggestions from the Cochrane *Handbook for Systematic Reviews of Interventions*.[64] Heterogeneity will be quantified as low, moderate, or high with I^2 values of 25%, 50%, and 75%, respectively.[65] Heterogeneity of <50% will be considered low and will allow the inclusion of the study to the systematic review and meta-analysis.

The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)[66] will be utilised to summarise the findings and assess the quality of evidence and strength of recommendations for relevant outcomes. The following factors will be used to determine the quality of the evidence and will be graded as high, moderate, low, or very low: limitations of comprehensive design and execution; inconsistency or heterogeneity; indirectness; imprecision; and publication bias. Recommendations based on GRADE may include the suggestion to include assessment of PD in RCTs, or the use of particular pharmacological interventions for patients with PD and a comorbid mood disorder.

Data Synthesis and Statistical Analyses

Data will be analysed using RevMan.[67] For continuous data, we will calculate mean differences (MDs) or standardised mean differences (SMDs) with 95% confidence intervals. For dichotomous data (for instance, treatment responder/non-responder, adverse events), we will calculate risk ratios with 95% confidence intervals. MDs will be used when the same scale has been used to measure treatment outcome, and SMDs will be utilised when different scales measure the same treatment outcome. Effect sizes will be calculated using Cohen's *d*. Sample sizes, standard deviations, and *p* values will be stated.

A meta-analysis will be undertaken if more than two eligible studies are identified. This meta-analysis will be performed based on the standardised mean difference approach (specifically, the mean symptom change of the mood disorder, between participants with and without comorbid PD) using the Cohen's *d* test. This meta-analysis therefore requires treatment effects to have been reported (or where these data have been obtained) according to personality disorder subgroups (i.e., personality disorder vs. no personality disorder). A random-effects model will be used and reported with 95% confidence intervals and a *p* value. To determine the robustness of the meta-analysis outcome, sensitivity analyses will also be conducted.

Subgroup analysis:

Subgroup analysis will be performed where the evidence is heterogeneous ($I^2 \geq 50$). The following subgroup analyses have been decided *a priori* and include analysis of differences between PDs (where data on specific PDs have been measured), their relationship to mood disorders, and treatment outcomes:

1. Measurement of PD (i.e., structured clinical interview compared to screening assessment);
2. Relation of PD clusters and/or specific PDs;
3. Relation of PD to treatment outcome of pharmacological agents (for example, comparison of comorbid PD and mood disorder with mood disorder only, and its association with antidepressant efficacy).

Presentation and Reporting of Results

This protocol adheres to PRISMA-P practice guidelines and the PRISMA-P checklist was used when writing this protocol.[68 69] The review will conform to PRISMA reporting guidelines;[70] and a PRISMA flow diagram will be utilised to depict study selection, numbers and reasons concerning included vs. excluded studies in the context of the pre-specified eligibility criteria. All eligible studies will have key information pertaining to mood disorders

(i.e., depressive disorders or bipolar spectrum disorders), PD, and treatment outcomes identified, extracted and presented.

Patient and Public Involvement

Patient and public involvement was not sought for the design of this study; though patient experience of pharmacological treatments and RCTs were considered in the development of the research question.

Ethics and Dissemination

This review will only use published data, and as such, ethical approval is not required. Ethical and governance principles will be complied with, in respect to data management and the presentation and dissemination of findings. This review has been registered on PROSPERO (CRD42018089279). Results will be published in a peer-reviewed scientific journal, and results will be presented at relevant scientific conference/s.

Conclusion

To the best of our knowledge, this will be the first systematic review to investigate whether PD influences the treatment outcomes for mood disorders in RCTs. The findings of this review will contribute to the limited literature available on the role of PD on treatment outcomes in those with mood disorders and will also provide information to inform clinical practice and health strategies.

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Author contributions

BEK conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. SLB-O developed the search strategy; and edited, revised, and approved the final version of this manuscript. AT

conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. OMD conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. MB conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript. MMA developed the search strategy; and edited, revised, and approved the final version of this manuscript. HK-H edited, revised, and approved the final version of this manuscript. LJW conceptualised the research question; developed the search strategy; and edited, revised, and approved the final version of this manuscript.

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Competing interests statement

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Supplementary Table 1. Search Strategy for Cochrane CENTRAL.

	Search Terms
#1	"mood disorders" [All text]
#2	"mood disorder" [All text]
#3	"bipolar and related disorders" [All text]
#4	"bipolar depression" [All text]
#5	"mania" [All text]
#6	#1 or #2 or #3 or #4 or #5
#7	"personality disorders"
#8	"personality disorder"
#9	"personality"
#10	#7 or #8 or #9
#11	"pharmacology" [All text]
#12	"pharmacotherapy" [All text]
#13	"drug trial" [All text]
#14	"drug therapy" [All text]
#15	#11 or #12 or #13 or #14
#16	"clinical trial"
#17	"randomised controlled trial"
#18	#16 or #17
#19	#6 and #10 and #15 and #18

Supplementary Table 2. Search Strategy for PubMed.

	Search Terms
#1	"personality disorders" [All fields]
#2	"personality disorder" [All fields]
#3	"personality" [All fields]
#4	#1 or #2 or #3
#5	"clinical trial" [All fields]
#6	"randomized controlled trial" [All fields]
#7	#5 or #6
#8	"mood disorders" [All fields]
#9	"mood disorder"
#10	"bipolar and related disorders" [All fields]
#11	"bipolar depression" [All fields]
#12	"mania" [All fields]
#13	#8 or #9 or #10 or #11 or #12
#14	"pharmacology" [All fields]
#15	"pharmacotherapy" [All fields]
#16	"drug trial" [All fields]
#17	"drug therapy" [All fields]
#18	#14 or #15 or #16 or #17
#19	#4 and #7 and #13 and #14

Supplementary Table 3. Search Strategy for Embase.

	Search Terms
#1	'personality disorder' [All fields]
#2	'personality' [All fields]
#3	#1 or #2
#4	'clinical trial' [All fields]
#5	'randomized controlled trial'[All fields]
#6	#4 or #5
#7	'mood disorders' [All fields]
#8	'bipolar and related disorders' [All fields]
#9	'bipolar depression' [All fields]
#10	'mania' [All fields]
#11	#7 or #8 or #9 or #10
#12	'pharmacology' [All fields]
#13	'drug therapy' [All fields]
#14	#12 or #13
#15	#3 and #6 and #11 and #14

Supplementary Table 4. Search Strategy for PsycInfo.

	Search Terms
#1	"personality disorders" [All text]
#2	"personality disorder" [All text]
#3	"personality" [All text]
#4	#1 or #2 or #3
#5	"clinical trial" [All text]
#6	"randomized controlled trial" [All text]
#7	#5 or #6
#8	"mood disorders" [All text]
#9	"mood disorder"
#10	"bipolar and related disorders" [All text]
#11	"bipolar depression" [All text]
#12	"mania" [All text]
#13	#8 or #9 or #10 or #11 or #12
#14	"pharmacology" [All text]
#15	"pharmacotherapy" [All text]
#16	"drug trial" [All text]
#17	"drug therapy" [All text]
#18	#14 or #15 or #16 or #17
#19	#4 and #7 and #13 and #18

Supplementary Table 5. Search Strategy for CINAHL Complete.

	Search Terms
#1	"personality disorders" [All text]
#2	"personality disorder" [All text]
#3	"personality" [All text]
#4	#1 or #2 or #3
#5	"clinical trial" [All text]
#6	"randomized controlled trial" [All text]
#7	#6 or #7
#8	"mood disorders" [All text]
#9	"mood disorder"
#10	"bipolar and related disorders" [All text]
#11	"bipolar depression" [All text]
#12	"mania" [All text]
#13	#8 or #9 or #10 or #11 or #12
#14	"pharmacology" [All text]
#15	"pharmacotherapy" [All text]
#16	"drug trial" [All text]
#17	"drug therapy" [All text]
#18	#14 or #15 or #16 or #17
#19	#4 and #7 and #13 and #18

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3

Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	20
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Sources	#5a	Indicate sources of financial or other support for the review	21
Sponsor	#5b	Provide name for the review funder and / or sponsor	21
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	21
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	11
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication	14

		status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	14
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary file
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	15
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	14
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	15
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	15

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	15
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	18
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	15
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	16
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16

Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	18