

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

AUTHOR(S)

Bianca Kavanagh, Sharon Brennan-Olsen, Alyna Turner, Olivia Dean, Michael Berk, Melanie Ashton, Heli Koivumaa-Honkanen, Lana Williams

PUBLICATION DATE

01-05-2019

HANDLE

10536/DRO/DU:30121668

Downloaded from Deakin University's Figshare repository

Deakin University CRICOS Provider Code: 00113B

BMJ Open

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

Bianca E Kavanagh,[1] Sharon Lee Brennan-Olsen,[2,3] Alyna Turner,[1,4,5] Olivia M Dean,[1,4,6] Michael Berk,[1,4,6,7,8] Melanie M Ashton,[1,6,9] Heli Koivumaa-Honkanen,[10,11,12] Lana J Williams[1]

To cite: Kavanagh BE, Brennan-Olsen SL, Turner A, *et al*. 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. *BMJ Open* 2019;**9**:e025145. doi:10.1136/bmjopen-2018-025145

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-025145).

Received 3 July 2018
Revised 31 January 2019
Accepted 31 January 2019

Check for updates

© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Ms Bianca E Kavanagh; bianca.kavanagh@deakin.edu.au

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 (ie, 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% CIs. A random effects model will be employed and statistical heterogeneity will be evaluated using the I^2 statistic. Prespecified subgroup analyses will be completed.

Ethics and dissemination As this systematic review will use 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.

Strengths and limitations of this study

- 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.

Trial registration number CRD42018089279.

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 WHO World Mental Health Surveys estimated PD prevalence rates to be 6.1% in a cross-national sample,[3] while the Australian National Survey of Mental Health and Well-being (2000) estimated prevalence to be 6.5%[4] using the same self-report scale. Other

BMJ Open: first published as 10.1136/bmjopen-2018-025145 on 1 May 2019. Downloaded from http://bmjopen.bmj.com/ on 13 May 2019 by guest. Protected by copyright.

prevalence rates using structured clinical assessments have estimated PD prevalence to be between 10.6%[5] and 21.8% in population-based samples.[6]

Despite these high prevalence rates, it has been argued that PDs do not receive the attention they warrant[7] and have largely been omitted from policy and research initiatives.[8 9] 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.[10] 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.[11] The omission of PDs at the population level has important repercussions for treatment programmes and healthcare planning,[8] including the development and trial of pharmacological interventions in randomised controlled trials (RCT). Consequently, while interventions for psychiatric disorders in general have 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.[12] 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 with switching to an antidepressant from another class) for depression.[13] 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 trialed.[13] 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 using a range of pharmacological treatments (ie, citalopram, bupropion, sertraline, nortriptyline, mirtazapine, lithium, tranylcypromine, venlafaxine),[14] as well as combination therapies,[15 16] have gained recent attention for the treatment of depression. Additionally, pharmacological interventions such as antiepileptics (eg, divalproex sodium and carbamazepine)[17 18] for the treatment of bipolar disorder have been confirmed in recent clinical trials.[19] 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.[20] For instance, remission rates from clinical symptoms remain at ~30% for patients with depression[14] and ~28% for bipolar disorder[21] for patients treated by pharmacological interventions. These remission rates highlight the complexity in treating acute mood disorders, and also emphasise 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.[22] PD is highly comorbid among clinical populations, and has particularly high incidence rates for patients with depression and bipolar disorder. For example, Zimmerman *et al* 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.[23] Zimmerman *et al* also found that even one borderline trait may have an adverse effect on outcomes.[23] Similar rates were found by Melartin *et al*, where 44% of patients with depression met also criteria for PD.[24] Moreover, Post *et al* 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.[25] These comorbidities are noteworthy considering that the presence of PD has potential to affect the course and treatment of the comorbid mood disorder.[23]

For example, previous epidemiological research has demonstrated that PD affects the course of depression. Specifically, Grilo *et al* demonstrated that patients with comorbid schizotypal, borderline or avoidant PD and depression had slower time to remission over a 24-month period compared with patients with depression only.[26] Similarly, Gunderson *et al* 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 10-year period was 50% slower for patients with this comorbity.[27] Research on PD and the course of bipolar disorder is less robust, however. In a clinical sample study, Garno *et al* demonstrated that patients with comorbid cluster B PD and bipolar disorder had significantly more lifetime suicide attempts than patients with bipolar disorder only.[28] Tamam *et al* 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 with patients with bipolar disorder only.[29]

Other research has suggested that PD influences the treatment outcome of both depression[30 31] and bipolar disorder.[28 32] 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 with 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).[9] Though the negative treatment outcomes did not diverge by the type of instrument used to measure depression, the authors did not state how

BMJ Open: first published as 10.1136/bmjopen-2018-025145 on 1 May 2019. Downloaded from http://bmjopen.bmj.com/ on 13 May 2019 by guest. Protected by copyright.

the included studies assessed PD. Considering the aforementioned variance in prevalence rates resulting from differences in the assessment of PD (eg, assessment by screening tool compared with structured clinical assessment), this may have been an important oversight in relation to treatment outcomes. An earlier review by Mulder [20]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 with those with depression only. However, well-designed studies (eg, 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. Similarly, one previous meta-analysis which looked at the efficacy of two or more pharmacotherapies in outpatients with depression and with or without comorbid PD found no significant differences between groups.[33]

The treatment outcomes of comorbid PD and bipolar disorder have also been demonstrated. In a review, Bieling *et al* summarised that the presence of comorbid PD had a negative effect on treatment outcome in bipolar disorder.[34] However, the literature specific to pharmacological therapies included in the review was limited. In one retrospective study eligible for review, Abou-Saleh showed that patients with bipolar disorder who did not respond to lithium had traits of high neuroticism and low dominance,[35] however this does not necessitate the presence of personality pathology. Gasperini *et al* 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.[36] Moreover, Preston *et al* retrospectively diagnosed borderline PD in two samples of patients with bipolar disorder who were trialing 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.[37]

Though previous research has suggested that PDs should be assessed in RCTs for patients with depressive and bipolar disorders,[9 34] 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[38] and treatment of both the PD and comorbid disorder.[39] 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.[40] As such PDs may be left underdiagnosed 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[41] or non-adherent with pharmacological treatments,[42] 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,[43] 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* demonstrated that patients with comorbid PD and depression had poor treatment outcome with nortriptyline (a tricyclic antidepressant) compared with fluoxetine (a selective serotonin reuptake inhibitor (SSRI)), and this was particularly evident in patients with borderline PD.[44] These results echo earlier research which demonstrated that patients with borderline PD respond poorly to tricyclic antidepressants, but moderately well to SSRIs.[45–47] 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 focused 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 aims of this systematic review are 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.

BMJ Open: first published as 10.1136/bmjopen-2018-025145 on 1 May 2019. Downloaded from http://bmjopen.bmj.com/ on 13 May 2019 by guest. Protected by copyright.

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, cyclothymic 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 Diseases (ICD)), and also include assessment of PD. PDs must be measured by structured or semistructured interviews including, but not limited to, the Structured Clinical Interview for DSM IV Axis II Personality Disorders,[48] the International Personality Disorder Examination,[49] the Iowa Personality Disorder Screen,[50] the Standardised Assessment of Personality-Abbreviated Scale,[51] or indicated by self-report tools such as the Dimensional Assessment of Personality Pathology,[52] the Personality Disorder Questionnaire-4,[53] the Wisconsin Personality Disorder Inventory-IV[54] or the DSM-IV and ICD-10 Personality Questionnaire.[55] 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 differ for those with and without PD. Treatment outcomes will be measured by validated assessment tools (eg, clinician-rated questionnaire) specific to the mood disorder and outlined in the RCT protocol (eg, the Montgomery-Asberg Depression Rating Scale,[56] 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 (eg, the Patient Global Impression-Improvement scale,[57] frequently used in RCTs) and assessments of quality of life and functioning (eg, the Quality of Life Enjoyment and Satisfaction Questionnaire[58] and Longitudinal Interval Follow-Up Range of Impaired Functioning Tool).[59] 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 are prespecified per protocol. The ITT approach includes all randomised participants in the final analysis, regardless of treatment non-compliance, protocol deviations and withdrawal[60]; however, a modified ITT method is also pertinent to this review due to its allowance of justified exclusion of participants from analysis (eg, only including participants in the final analysis who completed at least one postbaseline 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 have been identified in general, the authors will be contacted to obtain data.

Search strategy

The PICO framework (ie, Populations/people/patient/problem, Intervention/s, Comparison, Outcome) was used 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

BMJ Open: first published as 10.1136/bmjopen-2018-025145 on 1 May 2019. Downloaded from http://bmjopen.bmj.com/ on 13 May 2019 by guest. Protected by copyright.

and CINAHL Complete via Ebsco) will be performed. We will apply the following medical subject headings, Emtree terms and keywords, where applicable, to search all fields: ('mood disorders' OR 'mood disorder' OR 'affective disorders' OR 'bipolar 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 the online supplementary tables. 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 predetermined eligibility criteria using the following method: first, 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 to 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[61]; 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. PD characteristics (type/s or cluster/s of PD 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).
6. Outcome characteristics (name of measurement scale, type of variable and reported inferential statistics including mean and SD 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.[62] The scoring system from Higgins *et al*[62] 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.

Heterogeneity of evidence will be determined using I^2 in accordance with suggestions from the Cochrane *Handbook for Systematic Reviews of Interventions*.[63] Heterogeneity will be quantified as low, moderate or high with I^2 values of 25%, 50% and 75%, respectively.[64] 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)[65] will be used 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.[66] For continuous data, we will calculate mean differences (MD) or standardised mean differences (SMD) with 95% CIs. For dichotomous data (eg, treatment responder/non-responder, adverse events), we will calculate risk ratios with 95% CIs. MDs will be used when the same scale has been used to measure treatment outcome, and SMDs will be used when different scales measure the same treatment outcome. Effect sizes will be calculated using Cohen's *d*. Sample sizes, SDs 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 SMD 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 PD subgroups (ie, PD vs no PD). A random effects model will be used and reported with 95% CIs 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

BMJ Open: first published as 10.1136/bmjopen-2018-025145 on 1 May 2019. Downloaded from http://bmjopen.bmj.com/ on 13 May 2019 by guest. Protected by copyright.

Table 1 Cochrane Risk of Bias tool. Adapted from Higgins *et al*[62]

Bias domain	Source of bias	Support for judgement	Judgement (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 reinclusions in analyses for the review.	Attrition bias due to amount, nature or handling of incomplete outcome data
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 prespecified	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.

differences between PDs (where data on specific PDs have been measured), their relationship to mood disorders and treatment outcomes:

1. Measurement of PD (ie, structured clinical interview compared with screening assessment).
2. Relation of PD clusters and/or specific PDs.
3. Relation of PD to treatment outcome of pharmacological agents (eg, 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 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) practice guidelines and the PRISMA-P checklist was used when writing this protocol.[67 68] The review will conform to PRISMA reporting guidelines[69]; and a PRISMA flow diagram will be used to depict study selection, numbers and reasons concerning included versus excluded studies in the context of the prespecified eligibility criteria. All eligible studies will have key information pertaining to mood disorders (ie, 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

BMJ Open: first published as 10.1136/bmjopen-2018-025145 on 1 May 2019. Downloaded from http://bmjopen.bmj.com/ on 13 May 2019 by guest. Protected by copyright.

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 both depressive and bipolar 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.

Author affiliations
[1]Deakin University, IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Geelong, Victoria, Australia
[2]Australian Institute for Musculoskeletal Science, University of Melbourne and Western Health, St Albans, Victoria, Australia
[3]Department of Medicine-Western Health, University of Melbourne, St Albans, Victoria, Australia
[4]University of Melbourne, Department of Psychiatry, Royal Melbourne Hospital, Parkville, Victoria, Australia
[5]School of Medicine and Public Health, The University of Newcastle, Callaghan, Victoria, Australia
[6]Florey Institute for Neuroscience and Mental Health, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia
[7]Centre of Youth Mental Health, University of Melbourne, Parkville, Victoria, Australia
[8]Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Victoria, Australia
[9]Professorial Unit, The Melbourne Clinic, Department of Psychiatry, University of Melbourne, Richmond, Victoria, Australia
[10]Institute of Clinical Medicine (Psychiatry), University of Eastern Finland, Kuopio, Finland
[11]Department of Psychiatry, Kuopio University Hospital, Kuopio, Finland
[12]Department of Psychiatry, Oulu University Hospital, Finland

Acknowledgements The authors acknowledge the library support from Blair Kelly, Deakin University.

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

Funding BEK is supported by an Australian Government Research Training Program Scholarship and an Australian Rotary Health Ian Scott PhD Scholarship. SLB-O is supported by an NHMRC Career Development Fellowship (APP1107510). OMD is supported by a NHMRC R.D. Wright Biomedical Research Fellowship (APP1145634). MB is supported by an NHMRC Senior PrincipalResearch Fellowship (APP1059660 and APP1156072). MMA is supported by Australian Rotary Health/Ian Parker Bipolar Research Fund PhD Scholarship and the ASBDD/Lundbeck PhD Neuroscience Scholarship. HK-H is supported by Kuopio University Hospital. LJW is supported by an NHMRC Career Development Fellowship (APP1064272).

Competing interests SLB-O has received speaker fees from Amgen Australia and Pfizer Australia, and grant/research support from the University of Melbourne, Deakin University, Arthritis Victoria, Arthritis Australia, Australian Association of Gerontology and the City of Greater Geelong. AT has received travel or grant support from the NHMRC, AMP Foundation, National Stroke Foundation, Hunter Medical Research Institute, Helen Macpherson Smith Trust, Schizophrenia Fellowship NSW, SMHR, ISAD and the University of Newcastle. OMD has received grant support from the Brain and Behavior Foundation, Simons Autism Foundation, Stanley Medical Research Institute, Deakin University, Lilly, NHMRC and Australasian Society for Bipolar and Depressive Disorders (ASBDD)/Servier. MB has received grant support from NIH, Simons Autism Foundation, Cancer Council of Victoria, CRC for Mental Health, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma and Servier. MMA has received grant/research support from Deakin University, Australasian Society for Bipolar Depressive Disorders, Lundbeck, Australian Rotary Health, Ian Parker Bipolar Research Fund, Cooperative Research Centre for Mental Health and Rotary Club of Geelong. HK-H has received grant/research support from University of Eastern Finland and Kuopio University Hospital. LJW has received grant/research support from Eli Lilly, Pfizer, The University of Melbourne, Deakin University and the NHMRC.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES

1. Gawda B, Czubak K. Prevalence of Personality Disorders in a General Population Among Men and Women. *Psychol Rep* 2017;120:503–19.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-5*. Fifth edition. Washington, DC, 2013.
3. Huang Y, Kotov R, de Girolamo G, *et al*. DSM-IV personality disorders in the WHO World Mental Health Surveys. *Br J Psychiatry* 2009;195:46–53.
4. Jackson HJ, Burgess PM. Personality disorders in the community: a report from the Australian National Survey of Mental Health and Wellbeing. *Soc Psychiatry Psychiatr Epidemiol* 2000;35:531–8.
5. Lenzenweger MF. Epidemiology of personality disorders. *Psychiatr Clin North Am* 2008;31:395–403.
6. Quirk SE, Berk M, Pasco JA, *et al*. The prevalence, age distribution and comorbidity of personality disorders in Australian women. *Aust N Z J Psychiatry* 2017;51:141–50.
7. Eskedal GA, Disorders P. and Treatment: A Therapeutic Conundrum. *J Adult Dev* 1998;5:255–60.
8. Quirk SE, Williams LJ, Chanen AM, *et al*. Personality disorder and population mental health. *Lancet Psychiatry* 2015;2:201–2.
9. Newton-Howes G, Tyrer P, Johnson T. Personality disorder and the outcome of depression: meta-analysis of published studies. *Br J Psychiatry* 2006;188:13–20.
10. Lopez AD, Murray CC. The global burden of disease, 1990-2020. *Nat Med* 1998;4:1241–3.
11. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. *Lancet Psychiatry* 2016;3:171–8.
12. World Health Organization. Depression Fact Sheet: World Health Organization. 2017. Updated 22 Mar 2018 http://www.who.int/news-room/fact-sheets/detail/depression (Accessed 16 Oct 2018).
13. National Institute for Health and Care Excellence. *Depression in adults: Recognition and Management: National Institute for Health and Care Excellence*, 2009.
14. Rush AJ, Trivedi MH, Wisniewski SR, *et al*. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163:1905–17.
15. Malhi GS, Ng F, Berk M. Dual-dual action? Combining venlafaxine and mirtazapine in the treatment of depression. *Aust N Z J Psychiatry* 2008;42:346–9.
16. Thomas SJ, Shin M, McInnis MG, *et al*. Combination therapy with monoamine oxidase inhibitors and other antidepressants or stimulants: strategies for the management of treatment-resistant depression. *Pharmacotherapy* 2015;35:433–49.
17. Bowden CL, Calabrese JR, McElroy SL, *et al*. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry* 2000;57:481–9.
18. Weisler RH, Kalali AH, Ketter TA. SPD417 Study Group. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *J Clin Psychiatry* 2004;65:478–84.
19. Goodwin FK, Jamison KR. *Manic-depressive illness: bipolar disorders and recurrent depression*: Oxford University Press, 2007.
20. Mulder RT. Personality pathology and treatment outcome in major depression: a review. *Am J Psychiatry* 2002;159:359–71.

BMJ Open: first published as 10.1136/bmjopen-2018-025145 on 1 May 2019. Downloaded from http://bmjopen.bmj.com/ on 13 May 2019 by guest. Protected by copyright.

21. Tohen M, Waternaux CM, Tsuang MT. Outcome in Mania. A 4-year prospective follow-up of 75 patients utilizing survival analysis. *Arch Gen Psychiatry* 1990;47:1106–11.
22. Hengartner MP, Yamanaka-Altenstein M. Personality, Psychopathology, and Psychotherapy: A Pre-specified Analysis Protocol for Confirmatory Research on Personality-Psychopathology Associations in Psychotherapy Outpatients. *Front Psychiatry* 2017;8:9.
23. Zimmerman M, Rothschild L, Chelminski I. The prevalence of DSM-IV personality disorders in psychiatric outpatients. *Am J Psychiatry* 2005;162:1911–8.
24. Melartin TK, Rytsälä HJ, Leskelä US, *et al*. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. *J Clin Psychiatry* 2002;63:126–34.
25. Post RM, Leverich GS, McElroy S, *et al*. Prevalence of axis II comorbidities in bipolar disorder: relationship to mood state. *Bipolar Disord* 2018;20:303–12.
26. Grilo CM, Sanislow CA, Shea MT, *et al*. Two-year prospective naturalistic study of remission from major depressive disorder as a function of personality disorder comorbidity. *J Consult Clin Psychol* 2005;73:78–85.
27. Gunderson JG, Stout RL, McGlashan TH, *et al*. Ten-year course of borderline personality disorder: psychopathology and function from the Collaborative longitudinal personality disorders study. *Arch Gen Psychiatry* 2011;68:827–37.
28. Garno JL, Goldberg JF, Ramirez PM, *et al*. Bipolar disorder with comorbid cluster B personality disorder features: impact on suicidality. *J Clin Psychiatry* 2005;66:339–45.
29. Tamam L, Ozpoyraz N, Karatas G. Personality disorder comorbidity among patients with bipolar I disorder in remission. *Acta Neuropsychiatr* 2004;16:175–80.
30. Shea MT, Widiger TA, Klein MH. Comorbidity of personality disorders and depression: implications for treatment. *J Consult Clin Psychol* 1992;60:857–68.
31. Mulder RT. The influence of personality on the treatment outcome of psychopathology. *World Psychiatry* 2011;10:116–7.
32. Strakowski SM, Stoll AL, Tohen M, *et al*. The Tridimensional Personality Questionnaire as a predictor of six-month outcome in first episode mania. *Psychiatry Res* 1993;48:1–8.
33. Kool S, Schoevers R, de Maat S, *et al*. Efficacy of pharmacotherapy in depressed patients with and without personality disorders: a systematic review and meta-analysis. *J Affect Disord* 2005;88:269–78.
34. Bieling PJ, Green SM, Macqueen G. The impact of personality disorders on treatment outcome in bipolar disorder: A review. *Personal Ment Health* 2007;1:2–13.
35. Abou-Saleh MT. Platelet MAO, personality and response to lithium prophylaxis. *J Affect Disord* 1983;5:55–65.
36. Gasperini M, Scherillo P, Manfredonia MG, *et al*. A study of relapses in subjects with mood disorder on lithium treatment. *Eur Neuropsychopharmacol* 1993;3:103–10.
37. Preston GA, Marchant BK, Reimherr FW, *et al*. Borderline personality disorder in patients with bipolar disorder and response to lamotrigine. *J Affect Disord* 2004;79–297–303.
38. Balsis S, Loehle-Conger E, Busch AJ, *et al*. Self and informant report across the borderline personality disorder spectrum. *Personal Disord* 2018;9:429–36.
39. Cloninger CR, Svrakic DM, Personality disorders. *The Medical Basis of Psychiatry: Springer*, 2008:471–83.
40. Zanarini MC, Frankenburg FR, Hennen J, *et al*. The longitudinal course of borderline psychopathology: 6-year prospective follow-up of the phenomenology of borderline personality disorder. *Am J Psychiatry* 2003;160:274–83.
41. Sansone RA, Bohinc RJ, Wiederman MW. Borderline personality symptomatology and compliance with general health care among internal medicine outpatients. *Int J Psychiatry Clin Pract* 2015;19:132–6.
42. Palmer NB, Salcedo J, Miller AL, *et al*. Psychiatric and social barriers to HIV medication adherence in a triply diagnosed methadone population. *AIDS Patient Care STDS* 2003;17:635–44.
43. Ekselius L, Bengtsson F, von Knorring L. Non-compliance with pharmacotherapy of depression is associated with a sensation seeking personality. *Int Clin Psychopharmacol* 2000;15:273–8.
44. Mulder RT, Joyce PR, Luty SE. The relationship of personality disorders to treatment outcome in depressed outpatients. *J Clin Psychiatry* 2003;64:259–64.
45. Soloff PH. What's New in Personality Disorders?: An Update on Pharmacologic Treatment. *J Pers Disord* 1990;4:233–43.
46. Norden MJ. Fluoxetine in borderline personality disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 1989;13:885–93.
47. Salzman C, Wolfson AN, Schatzberg A, *et al*. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. *J Clin Psychopharmacol* 1995;15:23–9.
48. First MB, Gibbon M, Spitzer RL, *et al*. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. Washington, DC: American Psychiatric Association, 1997.
49. Loranger AW, Sartorius N, Andreoli A, *et al*. The international personality disorder examination. The world health organization/ alcohol, drug abuse, and mental health administration international pilot study of personality disorders. *Arch Gen Psychiatry* 1994;51:215–24.
50. Langbehn DR, Pfohl BM, Reynolds S, *et al*. The Iowa Personality Disorder Screen: development and preliminary validation of a brief screening interview. *J Pers Disord* 1999;13:75–89.
51. Moran P, Leese M, Lee T, *et al*. Standardised Assessment of Personality - Abbreviated Scale (SAPAS): preliminary validation of a brief screen for personality disorder. *Br J Psychiatry* 2003;183:228–32.
52. Pukrop R, Gentil I, Steinbring I, *et al*. Factorial structure of the German version of the dimensional assessment of personality pathology-basic questionnaire in clinical and nonclinical samples. *J Pers Disord* 2001;15:450–6.
53. Hyler SE, Rieder RO, Williams JBW, *et al*. The personality diagnostic questionnaire: Development and preliminary results. *J Pers Disord* 1988;2:229–37.
54. Klein MH, Benjamin LS, Rosenfeld R, *et al*. The wisconsin personality disorders inventory: development, reliability, and validity. *J Pers Disord* 1993;7:285–303.
55. Ottosson H, Bodlund O, Ekselius L, *et al*. The DSM-IV and ICD-10 personality questionnaire (DIP-Q): Construction and preliminary validation. *Nord J Psychiatry* 1995;49:285–92.
56. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9.
57. Guy W. *ECDEU Assessment Manual for Pharmacology, Revised*. Rockville, MD: National Institute of Mental Health: US Department of Health, Education, and Welfare Publication (ADM), 1976.
58. Endicott J, Nee J, Harrison W, *et al*. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull* 1993;29:321–6.
59. Leon AC, Solomon DA, Mueller TI, *et al*. The Range of Impaired Functioning Tool (LIFE-RIFT): a brief measure of functional impairment. *Psychol Med* 1999;29:869–78.
60. Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res* 2011;2:109–12.
61. *Covidence Systematic Review Software, Veritas Health Innovation*. Melbourne, Australia. www.covidence.org
62. Higgins JP, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
63. Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. 2011: The Cochrane Collaboration. Available from. www.handbook.cochrane.org. (Updated Mar 2011)
64. Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
65. Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
66. Review Manager (RevMan) [program]. 5.3 version. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
67. Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
68. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4.1.
69. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.

BMJ Open: first published as 10.1136/bmjopen-2018-025145 on 1 May 2019. Downloaded from http://bmjopen.bmj.com/ on 13 May 2019 by guest. Protected by copyright.