BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026980
Article Type:	Protocol
Date Submitted by the Author:	29-Sep-2018
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Keywords:	Determinant, Compliance, Concordance, psychotropic drug, Mood stabilizer, MENTAL HEALTH

Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework: A Systematic Review Protocol

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Abstract

Introduction: People with bipolar disorder require long-term treatment but an estimated 40% of these people do not adhere to prescribed medication regimens. Non-adherence increases the risk of relapse, hospitalisation and suicide. Evidence syntheses report barriers to mental health treatment adherence but rarely delineate between modifiable and non-modifiable barriers. They also fail to distinguish between the patient perspective and that of other stakeholders such as clinicians despite their differing understanding and priorities about adherence. Facilitators of adherence, which are also important for informing adherence intervention design are also lacking from syntheses and few syntheses focus on bipolar medications.

This systematic review aims to identify modifiable barriers and facilitators (determinants) of medication adherence in bipolar disorder. We will also report and compare primary (participant reported) and secondary (author interpreted) determinants of medication adherence. A unique feature of this systematic review in the context of mental health is the use of the Theoretical Domains Framework to organise the literature identified determinants of medication adherence.

Methods, Synthesis and Result Presentation: The protocol adheres to Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) and ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ) guidelines. The review will include both qualitative and quantitative

studies exploring determinants of medication adherence in bipolar disorder. We will search following databases using a pre-planned strategy: CINAHL, Cochrane Library (CENTRAL), Embase, LiLACS, Medline, PsychINFO, PubMed without language or date restrictions. We will report the quality of included studies using bespoke Critical Appraisal Skills Programme (CASP) qualitative or Appraisal of Survey or Cochrane risk of bias tool. We will use framework synthesis using the Theoretical Domains Framework (TDF) as an *a priori* 'framework'. We will map literature identified determinants to the domains of TDF and report the results using ENTREQ guidelines and PRISMA statement.

Study registration number: PROSPERO CRD42018096306

Keywords

Determinant, compliance, concordance, psychotropic drug, mood stabilizer, mental health

Strengths and limitations of this study

- As the Theoretical Domains Framework (TDF) has been mapped to evidence-based behaviour change techniques, mapping determinants of medication adherence in bipolar disorder to the TDF offer significant utility for intervention development.
- This study will provide literature-identified barriers and facilitators (determinants) of medication adherence in bipolar disorder from the perspectives of patients, carers, healthcare professionals and other third parties such as researchers.
- No date and language restrictions on the review maximise comprehensiveness.
- Lack of data and quality of reporting may limit our ability to present determinants of adherence from perspectives of patients, carers, healthcare professionals and other third parties as clearly as we would like.
- Variation in the terms used to describe determinants of adherence may introduce a risk of mapping errors through misinterpretation of the reported barrier or facilitator.

Introduction

The lifetime prevalence of bipolar disorder is estimated at 1.4% of the UK adult population (1). Bipolar disorder featuring mood and activity level disturbance is a recurrent disorder and usually requires long-term maintenance therapy (1,2). However, an estimated 40% of people with bipolar disorder do not take their medication as prescribed (3). This non-adherence increases the risk of relapse, suicide and rehospitalisation (4,5). For example, the probability of hospitalisation in non-adherent patients with bipolar disorder is at least five times higher than adherent patients (6).

Adhering to prescribed medication regimes is a complex health behaviour which requires the patient to obtain the prescribed medication, have the physical and cognitive ability (practical function), and motivation (perceptual function) to take the medication. Furthermore, non-adherence may occur at initiation (i.e. patient may or may not start the treatment), implementation (i.e. patient may delay, omit or take extra doses during treatment) or persistence (i.e. patient may discontinue treatment after some time) phase (7). There are many reported barriers and facilitators (determinants) of medication adherence. For this review, a barrier is ed as "a circumstance that prevents the patient from taking their medication as prescribed", whereas a facilitator is "a circumstance that makes the process easy or easier" (8). We are calling these barriers and facilitators "determinants".

The challenges to successfully addressing non-adherence are to:

1. Accurately identify non-adherent patients
2. Determine individuals' determinants of medication adherence

3. Select the most appropriate individualised adherence intervention(s) underpinned by health psychology theory and empirical evidence (9,10).

There are various objective (e.g. drug plasma levels, pill counts and electronic monitoring of medication adherence such as medication event monitoring systems) and subjective (e.g. self-reported, carer or relative reported, clinician reported adherence rating scales) approaches to identifying patients not adhering to their prescribed medication for bipolar disorder (11). However, there are no validated tools for comprehensively eliciting from patients and/or their carers their individual determinants of adherence to their prescribed medication for bipolar disorder. There is also an absence of theory and evidence informed guidance for practitioners to work with patients in selecting the most effective interventions for identified determinants of an individual's non-adherent behaviour.

In order to generate such a tool, there is, therefore, a need to synthesize the available evidence regarding determinants of medication adherence in patients with bipolar disorder.

A recent systematic review (literature search restricted to 1990 - 2015) of adherence to antipsychotic medication in bipolar disorder and schizophrenia has provided a good overview of the likely barriers experienced by people with bipolar disorder (12). However, it failed to explore factors that might facilitate adherence and excluded studies involving medication other than antipsychotics, and therefore did not identify determinants of adherence to lithium and other mood stabilisers. This is a significant omission as lithium is considered the gold-standard first-line treatment for bipolar

disorder (1,13,14). The determinants of adherence may be different among patients taking lithium relative to other antipsychotics due to a variety of factors including regular blood test requirements of lithium, dietary restrictions and significant interactions with other medications. Thus, a systematic review without the date limits of the previous systematic review (12) is warranted to better represent the mood stabilisers which were the mainstay of treatment in the earlier decades not included in the previous review and to identify emerging research (15).

The dearth of adherence evidence syntheses in the mental health setting underpinned by health psychology theory (12,16–18) is of concern given its importance for informing intervention design and implementation (9,10). The Theoretical Domains Framework (TDF) is a comprehensive framework capturing 33 theories and 84 theoretical constructs related to behaviour change (19). The TDF comprises fourteen domains each of which has been coupled with evidence based behaviour change techniques (20). The TDF therefore offers an appropriate theory for underpinning an evidence synthesis of determinants of adherence as it will enable determinants to be linked to evidence-based behaviour change techniques. This in turn will inform the development of an adherence intervention to support practitioners and patients to work together in identifying an individual's key determinants of adherence and select the most appropriate evidence-based interventions.

The perspective of patients, carers and healthcare professionals often differ in terms of the determinants of medication adherence due to differing priorities and knowledge of the situation (16,21–24). For example, the healthcare professional is

generally the expert regarding how the medication should be taken whilst the patient and carer are the experts in the patient's lived experience of taking or trying to take the prescribed medication. Furthermore, some determinants are not modifiable such as sex, age and ethnicity, and therefore have no related specific evidence-based behaviour change techniques.

We will explore the modifiable determinants of medication adherence among patients with bipolar disorder from the perspectives of the patient, carer, health care professional and other third parties such as researchers.

Aim

To identify modifiable determinants of medication adherence in the treatment of bipolar disorder.

Objectives

- To compare primary (participant reported) and secondary (author interpreted) determinants of medication adherence.
- To describe the determinants of medication adherence from the perspectives of patients, carers, health care professionals and any other third parties.
- To map reported determinants of medication adherence to the domains of the Theoretical Domains Framework.

Method

This research protocol is based on ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ) (25) and Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) (26). The protocol is registered with PROSPERO- www.crd.york.ac.uk/PROSPERO/ - international prospective register of systematic reviews (Study registration number: PROSPERO CRD42018096306).

Figure 1 shows the PRISMA Flow Diagram and Figure 2 represents process and people involvement in the systematic review.

Evidence Synthesis

We will use the TDF as an *a priori* framework for our review. We will code the data extracted from the included studies to the domains of this framework. The deductive approach of this framework synthesis method (27–30) has the potential to restrict the nature of identified determinants. However, the comprehensive nature of the TDF should enable identification of all determinants relevant to behaviour change and any determinants which cannot be mapped to a TDF domain will still be extracted and mapped to new domains if appropriate (31). A further benefit of mapping determinants to the TDF is its linkage to behaviour change techniques (17). This early identification of relevant behaviour change techniques affords a substantial

advantage in terms of informing the design of theory and evidence-based medication adherence interventions for people prescribed medication for bipolar disorder.

Approach to searching, search strategy and data sources

We will employ a pre-planned search strategy to seek all relevant studies. Our search strategy will consist of three parameters: disease (bipolar disorder), treatment (medication) and outcome (adherence). Following a scoping exercise of search terms (on Pubmed, Medline and Embase) to define our search strategy, we decided to use the MeSH (Medical Subject Heading) terms "Treatment Adherence and Compliance", “Bipolar Disorder” AND "Psychotropic Drugs" for our search. We will adapt these search terms for the databases that do not permit MeSH terms or uses different MeSH terms.

We will search the following databases: CINAHL, Cochrane Library (CENTRAL), Embase, LiLACS, Medline, PsychINFO, Pubmed and the reference list of all included studies will be reviewed for any further relevant studies.

Study Inclusion criteria

We will include any primary studies (both qualitative and quantitative) explicitly reporting one or more determinants of medication adherence in the maintenance treatment of bipolar disorders from the perspective of patients, carers, clinicians or any other third parties. There will be no language or date restrictions. We will include studies of patients aged 18 years or over with bipolar disorder with or without other co-morbidities including dual diagnosis, other mental or physical health conditions to represent the real-world patient population. We will exclude reviews, letters,

editorials, commentaries, opinion pieces, clinical guidelines or general disease management articles and studies not in humans. We will also exclude studies involving short-term treatment of acute agitation or treatment other than medication such as psychotherapy.

Study screening methods

Screening of studies for inclusion in this review will involve three distinct stages:

I. Title Screening: After removal of duplicates using the reference manager software Mendeley, the remaining studies will be screened for their relevance to the review. Definite non-relevant studies will be excluded while relevant, or unclear studies will be retained for abstract screening.

II. Abstract Screening: Abstracts of the remaining studies, will be screened by the primary reviewer (AP) and a second reviewer independently to identify studies that potentially meet the inclusion criteria outlined above. Any disagreement between the two reviewers will be resolved through further discussion and referral to a third reviewer (DB) if there is a failure to achieve agreement.

III. Full Article Screening: Full articles will be reviewed independently by two reviewers using pre-defined inclusion/exclusion criteria. Any disagreement between two reviewers will be resolved through discussion or the involvement of the third reviewer. We will use appropriate statistics to report

the level of agreement between 1st and 2nd reviewers in both stages 2 and stage 3 of screening.

Within published syntheses of qualitative research there is often a lack of transparency about the search processes employed, with neither the search strategy nor databases detailed (25). For a comprehensive approach, we will use the PRISMA flowchart (see fig 1 below) for reporting the different phases of searching, screening and identifying studies for inclusion in the qualitative synthesis as recommended by ENTREQ (25).

<<<<Insert Figure 1 Here>>>>

Data extraction

Data related to determinants of adherence will be extracted verbatim from the included studies by two reviewers independently. We will extract the determinants of adherence from the results as well as discussion and conclusion sections to include both primary (participant reported) and secondary (author interpreted) determinants. If needed we will contact the corresponding author of the included study for any missing data.

We plan to use bespoke Microsoft Excel 2016 to screen retrieved studies and the computer software program Nvivo 12 (32) to extract data and to map the determinants of medication adherence to the domains of the TDF. Extracted information will include study characteristics (e.g. title, year of publication, country, population, number of participants, data collection methodology, analysis, and

research questions), determinants of medication adherence in patients with bipolar disorder. The lead reviewer (AP) and second reviewers will extract the data independently and any disagreement between reviewers will be resolved through discussion or the involvement of the third reviewer.

Mapping

We will map each extracted determinant to one of the following domains of the TDF: 1) Knowledge, 2) Skills, 3) Social Influences, 4) Memory, Attention and Decision Processes, 5) Behavioural Regulation, 6) Professional/Social Role and Identity, 7) Beliefs about Capabilities, 8) Belief about Consequences, 9) Optimism, 10) Intentions, 11) Goals, 12) Emotion, 13) Environmental Context and Resources and 14) Reinforcement. We will use constructs within the domains and construct definitions of the TDF (19) to inform mapping decisions. Any determinants that do not fit within the existing domains will organised into new domains as appropriate (31).

We will pilot mapping of the determinants from at least one study before embarking on full-scale mapping. Mapping will be led by two reviewers (AP and 2nd reviewer) independently. Any disagreement between reviewers will be resolved through discussion or the involvement of the third reviewer. We will report the level of agreement between two reviewers as well as resolutions to any discrepancies for transparency.

Quality assessment

No studies will be excluded based on quality as our aim is to identify determinants of medication adherence as comprehensively as possible. However, we will undertake a quality assessment for the purposes of characterising included studies. There is no gold standard tool for any study design, nor is there any widely accepted generic quality assessment tool that functions across multiple study types (33). We will use bespoke Critical Appraisal Skills Programme qualitative (CASP) (34), Critical appraisal of survey (35) and Cochrane risk of bias tool (36) to critically appraise qualitative studies, surveys and trials respectively. These tools meet the requirements of the study and provide key quality criteria such as validity, reliability and objectivity (37). Quality assessment will be carried out by two independent reviewers. Any disagreement between reviewers will be resolved through discussion and if necessary, referral to a third reviewer for arbitration.

<<<<Insert Figure 2 Here>>>>

Results

We will present the results as per the PRISMA flow diagram. We will report study and participants characteristics. We will describe the review findings in accordance with our objectives: including study comparison within and across studies; comparison of determinants from the perspectives of patients, carers and healthcare professionals; and mapping of those determinants to the domains of the TDF.

Quality assessment will be presented as a table using the questionnaires from the quality assessment tools namely, CASP qualitative (34), Appraisal of Survey (35) and Cochrane risk of bias (36).

Ethics and dissemination: Ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication.

Funding statement: This research is a part of the Clinical Doctoral Research Fellowship program funded by Health Education England / National Institute of Health Research. The funder has no role in the development of this protocol.

Competing interest statement: Mr Prajapati reports personal fees from Accession Healthcare Consulting Ltd for research participation, outside the submitted work.

Author's contribution: All authors helped conceive the study. AP and DB designed, wrote and reviewed the protocol. AP registered the study with PROSPERO. All other authors reviewed the protocol. All authors have approved the publication of this protocol.

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Figure 1: PRISMA flow diagram

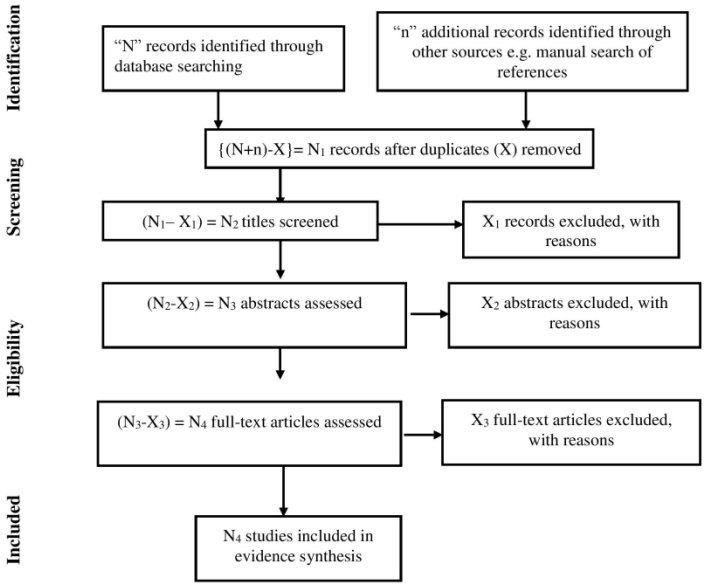

Figure 1 Prisma Flow Diagram

210x297mm (300 x 300 DPI)

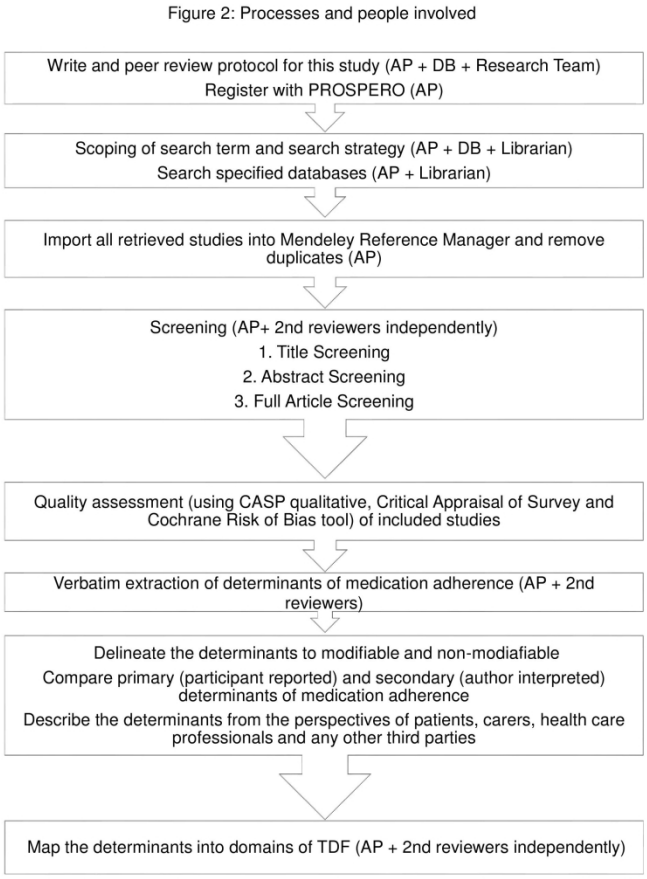

Figure 2 Process and People

210x297mm (300 x 300 DPI)

Table 1: Enhancing **tr**ansparency in reporting the synthesis of qualitative research: the **ENTREQ** statement

Reference: Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012;12(181). Available from: https://bmcmedresmethodol.biomedcentral.com/track/pdf/10.1186/1471-2288-12-181

No	Item	Guide and description	Reported on Manuscript Page no.
1	Aim	State the research question the synthesis addresses.	6
2	Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology *(e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis).*	7
3	Approach to searching	Indicate whether the search was pre-planned (*comprehensive search strategies to seek all available studies)* or iterative (*to seek all available concepts until they theoretical saturation is achieved).*	8

No	Item	Guide and description	Reported on Manuscript Page no.
4	Inclusion criteria	Specify the inclusion/exclusion criteria *(e.g. in terms of population, language, year limits, type of publication, study type).*	8-9
5	Data sources	Describe the information sources used (e.g. *electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO, Econlit), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists)* and when the searches conducted; provide the rationale for using the data sources.	8
6	Electronic Search strategy	Describe the literature search *(e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits).*	8-9
7	Study screening methods	Describe the process of study screening and sifting *(e.g. title, abstract and full text review, number of independent reviewers who screened studies).*	9

No	Item	Guide and description	Reported on Manuscript Page no.
8	Study characteristics	Present the characteristics of the included studies *(e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions).*	12
9	Study selection results	Identify the number of studies screened and provide reasons for study exclusion *(e,g, for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications t the research question and/or contribution to theory development).*	11
10	Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings *(e.g. assessment of conduct (validity and robustness), assessment of reporting (transparency), assessment of content and utility of the findings).*	13
11	Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings *(e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope* [25]*; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and*	13

No	Item	Guide and description	Reported on Manuscript Page no.
		interpretations, reporting).	
12	Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required.	13
13	Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale.	13
14	Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? *(e.g. all text under the headings "results /conclusions" were extracted electronically and entered into a computer software).*	11-12
15	Software	State the computer software used, if any.	12

No	Item	Guide and description	Reported on Manuscript Page no.
16	Number of reviewers	Identify who was involved in coding and analysis.	12
17	Coding	Describe the process for coding of data *(e.g. line by line coding to search for concepts).*	12
18	Study comparison	Describe how were comparisons made within and across studies *(e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary).*	11
19	Derivation of themes	Explain whether the process of deriving the themes or constructs was inductive or deductive.	7
20	Quotations	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation.	7

No	Item	Guide and description	Reported on Manuscript Page no.
21	Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. *new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct).*	7

Table 2 : PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol)

Reference: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. BMJ. 2015;349. Available from: https://www.bmj.com/content/349/bmj.g7647

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
Administrative information			
Title:			
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	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15
Amendments	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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	15
Introduction			

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
Methods			
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	8-9
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	12
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
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	11-12
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	12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11-12
Risk of bias in	14	Describe anticipated methods for assessing risk of bias of individual studies, including	13

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
individual studies		whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA
	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 I^2, Kendall's τ)	NA
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	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)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

BMJ Open

Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework (TDF): A Systematic Review Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026980.R1
Article Type:	Protocol
Date Submitted by the Author:	17-Dec-2018
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	Determinant, Compliance, Concordance, psychotropic drug, Mood stabilizer, MENTAL HEALTH

Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework (TDF): A Systematic Review Protocol

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Abstract

Introduction: People with bipolar disorder require long-term treatment but an estimated 40% of these people do not adhere to prescribed medication regimens. Non-adherence increases the risk of relapse, hospitalisation and suicide. Some evidence syntheses report barriers to mental health treatment adherence but rarely delineate between modifiable and non-modifiable barriers. They also fail to distinguish between the patient perspective and that of other stakeholders such as clinicians despite their differing understanding and priorities about adherence. Facilitators of adherence, which are also important for informing adherence intervention design are also lacking from syntheses and few syntheses focus on medications for bipolar disorder.

This systematic review aims to identify modifiable barriers and facilitators (determinants) of medication adherence in bipolar disorder. We also plan to report determinants of medication adherence from perspectives of patients, carers, healthcare professionals and other third parties. A unique feature of this systematic review in the context of mental health is the use of the Theoretical Domains Framework (TDF) to organise the literature identified determinants of medication adherence.

Methods, Synthesis and Result Presentation: The protocol adheres to Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) and ENhancing Transparency in REporting the synthesis of Qualitative research

(ENTREQ) guidelines. The review will include both qualitative and quantitative primary studies exploring determinants of medication adherence in bipolar disorder. We will search following databases using a pre-planned strategy: CINAHL, Cochrane Library (CENTRAL), Embase, LiLACS, Medline, PsychINFO, PubMed without date restrictions. We will report the quality of included studies. We will use framework synthesis using the Theoretical Domains Framework (TDF) as an *a priori* 'framework'. We will map literature identified modifiable determinants to the domains of TDF and report the results using ENTREQ guidelines and PRISMA statement.

Study registration number: PROSPERO CRD42018096306

Keywords

Determinant, compliance, concordance, psychotropic drug, mood stabilizer, mental health

Strengths and limitations of this study

- As the Theoretical Domains Framework (TDF) has been mapped to evidence-based behaviour change techniques, mapping modifiable determinants of medication adherence in bipolar disorder to the TDF offer significant utility for intervention development.
- This study will provide literature-identified barriers and facilitators (determinants) of medication adherence in bipolar disorder from the perspectives of patients, carers, healthcare professionals and other third parties such as researchers.
- Lack of data and quality of reporting may limit our ability to present determinants of adherence from perspectives of patients, carers, healthcare professionals and other third parties as clearly as we would like.
- Variation in the terms used to describe determinants of adherence may introduce a risk of mapping errors through misinterpretation of the reported barrier or facilitator.

Introduction

The lifetime prevalence of bipolar disorder is estimated at 1.4% of the UK adult population (1). Bipolar disorder featuring mood and activity level disturbance is a recurrent disorder and usually requires long-term maintenance therapy (1,2). However, an estimated 40% of people with bipolar disorder do not take their medication as prescribed (3). This non-adherence (generally described as taking less than 80% of prescribed doses of medication) (4) increases the risk of relapse, suicide and rehospitalisation (5,6). For example, the probability of hospitalisation in non-adherent patients with bipolar disorder is at least five times higher than adherent patients (7).

Adhering to prescribed medication regimes is a complex health behaviour which requires the patient to obtain the prescribed medication, have the physical and cognitive ability (practical function), and motivation (perceptual function) to take the medication. Furthermore, non-adherence may occur at initiation (i.e. patient may or may not start the treatment), implementation (i.e. patient may delay, omit or take extra doses during treatment) or persistence (i.e. patient may discontinue treatment after some time) phase (8). There are many reported barriers and facilitators (determinants) of medication adherence. For this review, a barrier is defined as “a circumstance that prevents the patient from taking their medication as prescribed”, whereas a facilitator is “a circumstance that makes the process easy or easier” (9). We are calling these barriers and facilitators “determinants”.

The challenges to successfully addressing non-adherence are to:

1. Accurately identify non-adherent patients

2. Determine individuals' determinants of medication adherence

3. Select the most appropriate individualised adherence intervention(s) underpinned by health psychology theory and empirical evidence (10,11).

There are various objective (e.g. drug plasma levels, pill counts and electronic monitoring of medication adherence such as medication event monitoring systems) and subjective (e.g. self-reported, carer or relative reported, clinician reported adherence rating scales) approaches to identifying patients not adhering to their prescribed medication for bipolar disorder (12). However, there are no validated tools for comprehensively eliciting from patients and/or their carers their individual determinants of adherence to their prescribed medication for bipolar disorder. There is also an absence of theory and evidence informed guidance for practitioners to work with patients in selecting the most effective interventions for identified determinants of an individual's non-adherent behaviour.

In order to generate such a tool, there is, therefore, a need to synthesize the available evidence regarding determinants of medication adherence in patients with bipolar disorder.

A recent systematic review (literature search restricted to 1990 - 2015) of adherence to antipsychotic medication in bipolar disorder and schizophrenia has provided a good overview of the likely barriers experienced by people with bipolar disorder (13). However, it failed to explore factors that might facilitate adherence and excluded

studies involving medication other than antipsychotics, and therefore did not identify determinants of adherence to lithium and other mood stabilisers. This is a significant omission as lithium is considered the gold-standard first-line treatment for bipolar disorder (1,14,15). The determinants of adherence may be different among patients taking lithium relative to other antipsychotics due to a variety of factors including regular blood test requirements of lithium, dietary restrictions and significant interactions with other medications. Thus, a systematic review without the date limits of the previous systematic review (13) is warranted to better represent the mood stabilisers which were the mainstay of treatment in the earlier decades not included in the previous review and to identify emerging research (16).

The dearth of adherence evidence syntheses in the mental health setting underpinned by health psychology theory (13,17–19) is of concern given its importance for informing intervention design and implementation (10,11). The Theoretical Domains Framework (TDF) is a comprehensive framework capturing 33 theories and 84 theoretical constructs related to behaviour change (20). The TDF comprises fourteen domains each of which has been coupled with evidence based behaviour change techniques (21). The TDF therefore offers an appropriate theory for underpinning an evidence synthesis of determinants of adherence as it will enable determinants to be linked to evidence-based behaviour change techniques. This in turn will inform the development of an adherence intervention to support practitioners and patients to work together in identifying an individual's key determinants of adherence and select the most appropriate evidence-based interventions.

The perspective of patients, carers and healthcare professionals often differ in terms of the determinants of medication adherence due to differing priorities and knowledge of the situation (17,22–25). For example, the healthcare professional is generally the expert regarding how the medication should be taken whilst the patient and carer are the experts in the patient's lived experience of taking or trying to take the prescribed medication. Furthermore, some determinants are not modifiable such as sex, age and ethnicity, and therefore have no related specific evidence-based behaviour change techniques.

A literature review matching adherence interventions to determinants of adherence concluded that adherence interventions are often not congruent with the modifiable determinants of adherence (26). We will explore the modifiable determinants of medication adherence among patients with bipolar disorder from the perspectives of the patient, carer, health care professional and other third parties such as researchers. For the purpose of this systematic review we define modifiable as "any determinants (barriers or facilitators) of medication adherence that can be modified by the patient, carer or the prescriber to improve adherence. Modifiable in the context of an individual being able to effect the change themselves or in partnership with their carer or healthcare team within a short timeframe."

For example, knowledge about the condition / treatment can be changed within days or weeks. In contrast, whilst substance abuse can be changed over an extended period, a change is unlikely to be achievable within the timeframes acceptable for improving adherence.

This systematic review is a part of the Collaborative Medication Adherence in Bipolar disorder (C-MAB) project funded by Health Education England / National Institute of Health Research UK. The C-MAB project aims to develop a medication adherence tool for people with bipolar disorder. The tool is intended to both identify non-adherent behaviour and the individual's determinants of non-adherence. Following the systematic review we will develop the tool in the form of statements derived from the literature identified modifiable determinants of adherence. We will then refine the statements by conducting focus groups and interviews with patients with bipolar disorder and their carers to better understand and prioritise the literature identified modifiable determinants. After appropriate refinement, the tool will be tested with patients with bipolar disorder.

Aim

To identify modifiable determinants of medication adherence in the treatment of bipolar disorder.

Objectives

- To describe the modifiable determinants of medication adherence from the perspectives of patients, carers, health care professionals and any other third parties.
- To map reported modifiable determinants of medication adherence to the domains of the TDF.

Method

This research protocol is based on ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ) (27) and Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) (28). The protocol is registered with PROSPERO- www.crd.york.ac.uk/PROSPERO/ - international prospective register of systematic reviews (Study registration number: PROSPERO CRD42018096306).

Evidence Synthesis

We will use the TDF as an *a priori* framework for our review. We will map the extracted modifiable determinants of adherence from the included studies to the domains of the TDF. The deductive approach of this framework synthesis method (29–32) has the potential to restrict the nature of identified determinants. However, the comprehensive nature of the TDF should enable identification of all determinants relevant to behaviour change and any determinants which cannot be mapped to a TDF domain will still be extracted and mapped to new domains if appropriate (33). A further benefit of mapping determinants to the TDF is its linkage to behaviour change techniques (17). This approach was successfully applied by Allemann and colleagues to match adherence interventions to patient determinants of adherence (26). This early identification of relevant behaviour change techniques affords a substantial advantage in terms of informing the design of theory and evidence-based medication adherence interventions for people prescribed medication for bipolar disorder.

Approach to searching, search strategy and data sources

We will employ a pre-planned search strategy to seek all relevant studies. Our search strategy will consist of three parameters: disease (bipolar disorder), treatment (medication) and outcome (adherence). Following a scoping exercise of search terms (on Pubmed, Medline and Embase) to define our search strategy, we decided to use the MeSH (Medical Subject Heading) terms "Treatment Adherence and Compliance", “Bipolar Disorder” AND "Psychotropic Drugs" for our search. We will adapt these search terms for the databases that do not permit MeSH terms or uses different MeSH terms.

We will search the following databases: CINAHL, Cochrane Library (CENTRAL), Embase, LiLACS, Medline, PsychINFO, Pubmed and the reference list of all included studies will be reviewed for any further relevant studies.

Study Inclusion criteria

We will include any primary studies; both qualitative and quantitative e.g. focus groups, interviews and surveys; explicitly reporting one or more modifiable determinants of medication adherence in the maintenance treatment of bipolar disorders from the perspective of patients, carers, healthcare professionals or any other third parties. explicitly reporting one or more modifiable determinants of medication adherence in the maintenance treatment of bipolar disorders from the perspective of patients, carers, clinicians or any other third parties. There will be no date restrictions. We will include studies of patients aged 18 years or over with bipolar disorder with or without other co-morbidities including dual diagnosis, other mental or physical health

conditions to represent the real-world patient population. We will exclude reviews, intervention studies to improve adherence, case reports, letters, editorials, commentaries, opinion pieces, clinical guidelines or general disease management articles and studies not in humans. We will also exclude studies involving short-term treatment of acute agitation or treatment other than medication such as psychotherapy. Studies where effect of individual barriers/facilitators to adherence could not be isolated / extracted from composite measures (such as adherence rating scale) will be excluded.

Study screening methods

We will use computer software Covidence (34); an online systematic review program; for screening retrieved studies. Screening of studies for inclusion in this review will involve three distinct stages:

I. Title Screening: After removal of duplicates using the reference manager software Mendeley, the remaining studies will be screened for their relevance to the review. Definite non-relevant studies will be excluded while relevant, or unclear studies will be retained for abstract screening.

II. Abstract Screening: Abstracts of the remaining studies will be screened by the primary reviewer (AP) and second reviewers (CG, DB, FS, GM, JW and SS) independently to identify studies that potentially meet the inclusion criteria outlined above. Any disagreement between the two reviewers will be

resolved through further discussion and referral to a third reviewer (DB) if there is a failure to achieve agreement.

III. Full Article Screening: Full articles will be reviewed independently by two reviewers (AP, CG, DB, FS, GM, JW and SS) using pre-defined inclusion/exclusion criteria. Any disagreement between two reviewers will be resolved through discussion or the involvement of the third reviewer. We will use Cohen's kappa to report the level of agreement between 1st and 2nd reviewers.

Within published syntheses of qualitative research there is often a lack of transparency about the search processes employed, with neither the search strategy nor databases detailed (27). For a comprehensive approach, we will use the PRISMA flowchart for reporting the different phases of searching, screening and identifying studies for inclusion in the qualitative synthesis as recommended by ENTREQ (27).

Data extraction and mapping

We will use the computer software program Nvivo 12 (35) to extract data and to map the modifiable determinants of medication adherence to the domains of the TDF. While medication adherence is generally described as taking ≥80% doses of prescribed medications some studies report adherence in gradient terms (e.g. good, moderate, low adherence and non-adherence) (4). Yet, in some cases (e.g. in HIV) adherence means taking ≥95% doses of prescribed medications (36)(36). Acknowledging this wide variation on definition of medication adherence we will report the definition used for adherence in included studies for transparency and comparison among studies.

Extracted information will include study characteristics (e.g. title, year of publication, country, study design, population, number of participants, definition and rate of adherence) and modifiable determinants of medication adherence in patients with bipolar disorder.

We will map each extracted determinant to one of the following domains of the TDF: 1) Knowledge, 2) Skills, 3) Social Influences, 4) Memory, Attention and Decision Processes, 5) Behavioural Regulation, 6) Professional/Social Role and Identity, 7) Beliefs about Capabilities, 8) Belief about Consequences, 9) Optimism, 10) Intentions, 11) Goals, 12) Emotion, 13) Environmental Context and Resources and 14) Reinforcement. We will use constructs within the domains and construct definitions of the TDF (20) to inform mapping decisions. Any determinants that do not fit within the existing domains will be organised into an "Others" domain (33).

Within Nvivo12 we will create four themes in line with the aim of the study:

1. Patient Perspective
2. Carers Perspective
3. HealthCare Professional Perspective
4. Others Perspectives

Within each theme we will create two sub-themes (Barriers and Facilitators) and within each of these sub-themes we will create 15 domains (14 TDF plus "Others").

Two reviewers will pilot data extraction and coding of determinants of adherence to the domains of TDF from four studies. For example, if the following text were extracted from a study "Forgetting to take medication or being careless at times about taking

medication was reported to be experienced by x participants", this would be coded to the TDF domain "Memory, attention and decision process". The reviewers will then compare and discuss their coding to generate consensus in interpretation of literature-identified determinants. After piloting, all data will be extracted by one reviewer and independently checked by second reviewer for completeness.

All extracted determinants will be independently mapped onto the 14 domains of the TDF or "Others" category by two reviewers. The two reviewers will meet and discuss their mapping regularly. Any disagreement in mapping will be resolved through discussion between the two reviewers and referral to a third reviewer as adjudicator if the two reviewers fail to agree. We will use Cohen's kappa to report agreement between the 1st and 2nd reviewers as we are dealing with nominal data i.e. agreement or not with the domain to which a determinant is mapped onto the TDF.

Quality assessment

No studies will be excluded based on quality as our aim is to identify determinants of medication adherence as comprehensively as possible. However, we will undertake a quality assessment for the purposes of characterising included studies. There is no gold standard tool for any study design, nor is there any widely accepted generic quality assessment tool that functions across multiple study types (37). We will use bespoke Critical Appraisal Skills Programme qualitative (CASP) (38), Critical appraisal of survey (39) and Cochrane risk of bias tool (40) to critically appraise qualitative studies, surveys and trials respectively. These tools meet the requirements of the study and provide key quality criteria such as validity, reliability and objectivity (41). Quality assessment will be carried out by two independent reviewers. Any

disagreement between reviewers will be resolved through discussion and if necessary, referral to a third reviewer for arbitration.

Patient and Public Involvement (PPI)

This systematic review is a part of the C-MAB project which include three patients and a carer as research advisory board members. PPI has influenced the study design with two notable recommendations: inclusion of the carer's perspective on medication adherence and differentiating between modifiable from non-modifiable determinants of medication adherence. Two PPI representatives (CG and RG) are listed as authors.

Ethics and dissemination: Ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication.

Funding statement: This research is a part of the Clinical Doctoral Research Fellowship program funded by Health Education England / National Institute of Health Research. The funder has no role in the development of this protocol.

Competing interest statement: No, there are no competing interest for any authors.

Author's contribution: All authors (AP, AD, AC, CG5, CG4, RG, GM, SS, FS, BM, MT, JW and DB) helped conceive the study, reviewed the protocol and provided intellectual critique. AP and DB designed and wrote the protocol. AP registered the study with PROSPERO. All authors (AP, AD, AC, CG5, CG4, RG, GM, SS, FS, BM, MT, JW and DB) have approved the publication of this protocol.

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Table 1: Enhancing **tr**ansparency in reporting the synthesis of qualitative research: the **ENTREQ** statement

Reference: Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012;12(181). Available from: https://bmcmedresmethodol.biomedcentral.com/track/pdf/10.1186/1471-2288-12-181

No	Item	Guide and description	Reported on Manuscript Page no.
1	Aim	State the research question the synthesis addresses.	6
2	Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology *(e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis).*	7
3	Approach to searching	Indicate whether the search was pre-planned (*comprehensive search strategies to seek all available studies)* or iterative (*to seek all available concepts until they theoretical saturation is achieved).*	8

No	Item	Guide and description	Reported on Manuscript Page no.
4	Inclusion criteria	Specify the inclusion/exclusion criteria *(e.g. in terms of population, language, year limits, type of publication, study type).*	8-9
5	Data sources	Describe the information sources used (e.g. *electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO, Econlit), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists)* and when the searches conducted; provide the rationale for using the data sources.	8
6	Electronic Search strategy	Describe the literature search *(e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits).*	8-9
7	Study screening methods	Describe the process of study screening and sifting *(e.g. title, abstract and full text review, number of independent reviewers who screened studies).*	9

No	Item	Guide and description	Reported on Manuscript Page no.
8	Study characteristics	Present the characteristics of the included studies *(e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions).*	12
9	Study selection results	Identify the number of studies screened and provide reasons for study exclusion *(e,g, for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications t the research question and/or contribution to theory development).*	11
10	Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings *(e.g. assessment of conduct (validity and robustness), assessment of reporting (transparency), assessment of content and utility of the findings).*	13
11	Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings *(e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope* [25]*; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and*	13

No	Item	Guide and description	Reported on Manuscript Page no.
		interpretations, reporting).	
12	Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required.	13
13	Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale.	13
14	Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? *(e.g. all text under the headings "results /conclusions" were extracted electronically and entered into a computer software).*	11-12
15	Software	State the computer software used, if any.	12

No	Item	Guide and description	Reported on Manuscript Page no.
16	Number of reviewers	Identify who was involved in coding and analysis.	12
17	Coding	Describe the process for coding of data *(e.g. line by line coding to search for concepts).*	12
18	Study comparison	Describe how were comparisons made within and across studies *(e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary).*	11
19	Derivation of themes	Explain whether the process of deriving the themes or constructs was inductive or deductive.	7
20	Quotations	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation.	7

No	Item	Guide and description	Reported on Manuscript Page no.
21	Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. *new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct).*	7

Table 2 : PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol)

Reference: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. BMJ. 2015;349. Available from: https://www.bmj.com/content/349/bmj.g7647

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
Administrative information			
Title:			
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	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15
Amendments	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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	15
Introduction			

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
Methods			
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	8-9
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	12
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
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	11-12
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	12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11-12
Risk of bias in	14	Describe anticipated methods for assessing risk of bias of individual studies, including	13

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
individual studies		whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA
	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 I^2, Kendall's τ)	NA
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	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)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

BMJ Open

Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework (TDF): A Systematic Review Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026980.R2
Article Type:	Protocol
Date Submitted by the Author:	02-Jan-2019
Complete List of Authors:	Prajapati, Asta; Norfolk and Suffolk NHS Foundation Trust, Pharmacy; University of East Anglia, Pharmacy Dima, Alexandra; University of Lyon Clark, Allan; Norwich Medical School Gant, Claire Gibbons, Chris; Harvard Medical School, Faculty of Medicine Gorrod, Richard Mosa, George; Norfolk and Suffolk NHS Foundation Trust Scott, Sion; University of East Anglia, Pharmacy Song, Fujian; University of East Anglia, Teague, Bonnie; Norfolk and Suffolk NHS Foundation Trust, Research Twigg, Michael; University of East Anglia, School of Pharmacy Wilson, Jon Bhattacharya, Debi; University of East Anglia, School of Pharmacy
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	Determinant, Compliance, Concordance, psychotropic drug, Mood stabilizer, MENTAL HEALTH

Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework (TDF): A Systematic Review Protocol

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1= Norfolk and Suffolk NHS Foundation NHS Trust, 2 = University of East Anglia, 3= University of Lyon, 4 = Harvard University, 5 = Patient and carer representatives

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Abstract

Introduction: People with bipolar disorder require long-term treatment but an estimated 40% of these people do not adhere to prescribed medication regimens. Non-adherence increases the risk of relapse, hospitalisation and suicide. Some evidence syntheses report barriers to mental health treatment adherence but rarely delineate between modifiable and non-modifiable barriers. They also fail to distinguish between the patient perspective and that of other stakeholders such as clinicians despite their differing understanding and priorities about adherence. Facilitators of adherence, which are also important for informing adherence intervention design are also lacking from syntheses and few syntheses focus on medications for bipolar disorder.

This systematic review aims to identify modifiable barriers and facilitators (determinants) of medication adherence in bipolar disorder. We also plan to report determinants of medication adherence from perspectives of patients, carers, healthcare professionals and other third parties. A unique feature of this systematic review in the context of mental health is the use of the Theoretical Domains Framework (TDF) to organise the literature identified determinants of medication adherence.

Methods and analysis: The protocol adheres to Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) and ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ)

guidelines. The review will include both qualitative and quantitative primary studies exploring determinants of medication adherence in bipolar disorder. We will search following databases using a pre-planned strategy: CINAHL, Cochrane Library (CENTRAL), Embase, LiLACS, Medline, PsychINFO, PubMed without date restrictions. We will report the quality of included studies. We will use framework synthesis using the TDF as an *a priori* 'framework'. We will map the literature identified modifiable determinants to the domains of TDF.

Ethics and dissemination: Ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication.

Study registration number: PROSPERO CRD42018096306

Keywords

Determinant, compliance, concordance, psychotropic drug, mood stabilizer, mental health

Strengths and limitations of this study

- As the Theoretical Domains Framework (TDF) has been mapped to evidence-based behaviour change techniques, mapping modifiable determinants of medication adherence in bipolar disorder to the TDF offer significant utility for intervention development.
- This study will provide literature-identified barriers and facilitators (determinants) of medication adherence in bipolar disorder from the perspectives of patients, carers, healthcare professionals and other third parties such as researchers.
- Lack of data and quality of reporting may limit our ability to present determinants of adherence from perspectives of patients, carers, healthcare professionals and other third parties as clearly as we would like.

- Variation in the terms used to describe determinants of adherence may introduce a risk of mapping errors through misinterpretation of the reported barrier or facilitator.

Introduction

The lifetime prevalence of bipolar disorder is estimated at 1.4% of the UK adult population (1). Bipolar disorder featuring mood and activity level disturbance is a recurrent disorder and usually requires long-term maintenance therapy (1,2). However, an estimated 40% of people with bipolar disorder do not take their medication as prescribed (3). This non-adherence (generally described as taking less than 80% of prescribed doses of medication) (4) increases the risk of relapse, suicide and rehospitalisation (5,6). For example, the probability of hospitalisation in non-adherent patients with bipolar disorder is at least five times higher than adherent patients (7).

Adhering to prescribed medication regimes is a complex health behaviour which requires the patient to obtain the prescribed medication, have the physical and cognitive ability (practical function), and motivation (perceptual function) to take the medication (8). Furthermore, non-adherence may occur at initiation (i.e. patient may or may not start the treatment), implementation (i.e. patient may delay, omit or take extra doses during treatment) or persistence (i.e. patient may discontinue treatment after some time) phase (9). There are many reported barriers and facilitators (determinants) of medication adherence. For this review, a barrier is defined as “a circumstance that prevents the patient from taking their medication as prescribed”,

whereas a facilitator is “a circumstance that makes the process easy or easier” (10). We are calling these barriers and facilitators “determinants”.

The challenges to successfully addressing non-adherence are to:

1. Accurately identify non-adherent behaviour

2. Determine individuals’ determinants of medication adherence

3. Select the most appropriate individualised adherence intervention(s) underpinned by health psychology theory and empirical evidence (11,12).

There are various objective (e.g. drug plasma levels, pill counts and electronic monitoring of medication adherence such as medication event monitoring systems) and subjective (e.g. self-reported, carer or relative reported, clinician reported adherence rating scales) approaches to identifying patients not adhering to their prescribed medication for bipolar disorder (13). However, there are no validated tools for comprehensively eliciting from patients and/or their carers their individual determinants of adherence to their prescribed medication for bipolar disorder. There is also an absence of theory and evidence informed guidance for practitioners to work with patients in selecting the most effective interventions for identified determinants of an individual’s non-adherent behaviour.

In order to generate such a tool, there is, therefore, a need to synthesize the available evidence regarding determinants of medication adherence in patients with bipolar disorder.

A recent systematic review (literature search restricted to 1990 - 2015) of adherence to antipsychotic medication in bipolar disorder and schizophrenia has provided a good overview of the likely barriers experienced by people with bipolar disorder (14). However, it failed to explore factors that might facilitate adherence and excluded studies involving medication other than antipsychotics, and therefore did not identify determinants of adherence to lithium and other mood stabilisers. This is a significant omission as lithium is considered the gold-standard first-line treatment for bipolar disorder (1,15,16). The determinants of adherence may be different among patients taking lithium relative to other antipsychotics due to a variety of factors including regular blood test requirements of lithium, dietary restrictions and significant interactions with other medications. Thus, a systematic review without the date limits of the previous systematic review (14) is warranted to better represent the mood stabilisers which were the mainstay of treatment in the earlier decades not included in the previous review and to identify emerging research (17).

The dearth of adherence evidence syntheses in the mental health setting underpinned by health psychology theory (14,18–20) is of concern given its importance for informing intervention design and implementation (11,12). The Theoretical Domains Framework (TDF) is a comprehensive framework capturing 33 theories and 84 theoretical constructs related to behaviour change (21). The TDF comprises fourteen domains each of which has been coupled with evidence based behaviour change techniques (22). The TDF therefore offers an appropriate theory for underpinning an evidence synthesis of determinants of adherence as it will enable determinants to be linked to evidence-based behaviour change techniques. This in turn will inform the development of an adherence intervention to support practitioners and patients to work

together in identifying an individual's key determinants of adherence and select the most appropriate evidence-based interventions.

The perspective of patients, carers and healthcare professionals often differ in terms of the determinants of medication adherence due to differing priorities and knowledge of the situation (18,23–26). For example, the healthcare professional is generally the expert regarding how the medication should be taken whilst the patient and carer are the experts in the patient's lived experience of taking or trying to take the prescribed medication. Furthermore, some determinants are not modifiable such as sex, age and ethnicity, and therefore have no related specific evidence-based behaviour change techniques.

A literature review matching adherence interventions to determinants of adherence concluded that adherence interventions are often not congruent with the modifiable determinants of adherence (27). We will explore the modifiable determinants of medication adherence among patients with bipolar disorder from the perspectives of the patient, carer, health care professional and other third parties such as researchers. For the purpose of this systematic review we define modifiable as "any determinants (barriers or facilitators) of medication adherence that can be modified by the patient, carer or the prescriber to improve adherence. Modifiable in the context of an individual being able to effect the change themselves or in partnership with their carer or healthcare team within a short timeframe."

For example, knowledge about the condition / treatment can be changed within days or weeks. In contrast, whilst substance abuse can be changed over an extended period, a change is unlikely to be achievable within the timeframes acceptable for improving adherence.

This systematic review is a part of the Collaborative Medication Adherence in Bipolar disorder (C-MAB) project funded by Health Education England / National Institute of Health Research UK. The C-MAB project aims to develop a medication adherence tool for people with bipolar disorder. The tool is intended to both identify non-adherent behaviour and the individual's determinants of non-adherence. Following the systematic review we will develop the tool in the form of statements derived from the literature identified modifiable determinants of adherence. We will then refine the statements by conducting focus groups and interviews with patients with bipolar disorder and their carers to better understand and prioritise the literature identified modifiable determinants. After appropriate refinement, the tool will be tested with patients with bipolar disorder.

Aim

To identify modifiable determinants of medication adherence in the treatment of bipolar disorder.

Objectives

- To describe the modifiable determinants of medication adherence from the perspectives of patients, carers, health care professionals and any other third parties.
- To map reported modifiable determinants of medication adherence to the domains of the TDF.

Method

This research protocol is based on ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ) (28) and Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) (29). The protocol is registered with PROSPERO- www.crd.york.ac.uk/PROSPERO/ - international prospective register of systematic reviews.

Evidence Synthesis

We will use the TDF as an *a priori* framework for our review. We will map the extracted modifiable determinants of adherence from the included studies to the domains of the TDF. The deductive approach of this framework synthesis method (30–33) has the potential to restrict the nature of identified determinants. However, the comprehensive nature of the TDF should enable identification of all determinants relevant to behaviour change and any determinants which cannot be mapped to a TDF domain will still be extracted and mapped to new domains if appropriate (34). A further benefit of mapping determinants to the TDF is its linkage to behaviour change techniques (17). This approach was successfully applied by Allemann and colleagues to match adherence interventions to patient determinants of adherence (27). This early identification of

relevant behaviour change techniques affords a substantial advantage in terms of informing the design of theory and evidence-based medication adherence interventions for people prescribed medication for bipolar disorder.

Approach to searching, search strategy and data sources

We will employ a pre-planned search strategy to seek all relevant studies. Our search strategy will consist of three parameters: disease (bipolar disorder), treatment (medication) and outcome (adherence). Following a scoping exercise of search terms (on Pubmed, Medline and Embase) to define our search strategy, we decided to use the MeSH (Medical Subject Heading) terms "Treatment Adherence and Compliance", “Bipolar Disorder” AND "Psychotropic Drugs" for our search. We will adapt these search terms for the databases that do not permit MeSH terms or uses different MeSH terms.

We will search the following databases: CINAHL, Cochrane Library (CENTRAL), Embase, LiLACS, Medline, PsychINFO, Pubmed and the reference list of all included studies will be reviewed for any further relevant studies.

Study Inclusion criteria

We will include any primary studies; both qualitative and quantitative e.g. focus groups, interviews and surveys; explicitly reporting one or more modifiable determinants of medication adherence in the maintenance treatment of bipolar disorders from the perspective of patients, carers, healthcare professionals or any other third parties

explicitly reporting one or more modifiable determinants of medication adherence in the maintenance treatment of bipolar disorders from the perspective of patients, carers, clinicians or any other third parties. There will be no date restrictions but we will only include the studies published in English language. We will include studies of patients aged 18 years or over with bipolar disorder with or without other co-morbidities including dual diagnosis, other mental or physical health conditions to represent the real-world patient population. We will exclude reviews, intervention studies to improve adherence, case reports, letters, editorials, commentaries, opinion pieces, clinical guidelines or general disease management articles and studies not in humans. We will also exclude studies involving short-term treatment of acute agitation or treatment other than medication such as psychotherapy. Studies where effect of individual barriers/facilitators to adherence could not be isolated / extracted from composite measures (such as adherence rating scale) will be excluded.

Study screening methods

We will use computer software Covidence (35); an online systematic review program; for screening retrieved studies. Screening of studies for inclusion in this review will involve three distinct stages:

I. Title Screening: After removal of duplicates using the reference manager software Mendeley, the remaining studies will be screened for their relevance to the review. Definite non-relevant studies will be excluded while relevant, or unclear studies will be retained for abstract screening.

II. Abstract Screening: Abstracts of the remaining studies will be screened by the primary reviewer (AP) and second reviewers (CG, DB, FS, GM, JW and SS) independently to identify studies that potentially meet the inclusion criteria outlined above. Any disagreement between the two reviewers will be resolved through further discussion and referral to a third reviewer (DB) if there is a failure to achieve agreement.

III. Full Article Screening: Full articles will be reviewed independently by two reviewers (AP, CG, DB, FS, GM, JW and SS) using pre-defined inclusion/exclusion criteria. Any disagreement between two reviewers will be resolved through discussion or the involvement of the third reviewer. We will use Cohen's kappa to report the level of agreement between 1st and 2nd reviewers.

Within published syntheses of qualitative research there is often a lack of transparency about the search processes employed, with neither the search strategy nor databases detailed (28). For a comprehensive approach, we will use the PRISMA flowchart for reporting the different phases of searching, screening and identifying studies for inclusion in the qualitative synthesis as recommended by ENTREQ (28).

Data extraction and mapping

We will use the computer software program Nvivo 12 (36) to extract data and to map the modifiable determinants of medication adherence to the domains of the TDF. While medication adherence is generally described as taking ≥80% doses of prescribed medications some studies report adherence in gradient terms (e.g. good, moderate,

low adherence and non-adherence) (4). Yet, in some cases (e.g. in HIV) adherence means taking ≥95% doses of prescribed medications (37)(36). Acknowledging this wide variation on definition of medication adherence we will report the definition used for adherence in included studies for transparency and comparison among studies. Extracted information will include study characteristics (e.g. title, year of publication, country, study design, population, number of participants, definition and rate of adherence) and modifiable determinants of medication adherence in patients with bipolar disorder.

We will map each extracted determinant to one of the following domains of the TDF: 1) Knowledge, 2) Skills, 3) Social Influences, 4) Memory, Attention and Decision Processes, 5) Behavioural Regulation, 6) Professional/Social Role and Identity, 7) Beliefs about Capabilities, 8) Belief about Consequences, 9) Optimism, 10) Intentions, 11) Goals, 12) Emotion, 13) Environmental Context and Resources and 14) Reinforcement. We will use constructs within the domains and construct definitions of the TDF (21) to inform mapping decisions. Any determinants that do not fit within the existing domains will be organised into an “Others” domain (34).

Within Nvivo12 we will create four themes in line with the aim of the study:

1. Patient Perspective
2. Carers Perspective
3. HealthCare Professional Perspective
4. Others Perspectives

Within each theme we will create two sub-themes (Barriers and Facilitators) and within each of these sub-themes we will create 15 domains (14 TDF domains plus “Others”).

Two reviewers will pilot data extraction and coding of determinants of adherence to the domains of TDF from four studies. For example, if the following text were extracted from a study “Forgetting to take medication or being careless at times about taking medication was reported to be experienced by x participants”, this would be coded to the TDF domain “Memory, attention and decision process”. The reviewers will then compare and discuss their coding to generate consensus in interpretation of literature-identified determinants. After piloting, all data will be extracted by one reviewer and independently checked by second reviewer for completeness.

All extracted determinants will be independently mapped onto the 14 domains of the TDF or “Others” category by two reviewers. The two reviewers will meet and discuss their mapping regularly. Any disagreement in mapping will be resolved through discussion between the two reviewers and referral to a third reviewer as adjudicator if the two reviewers fail to agree. We will use Cohen’s kappa to report agreement between the 1st and 2nd reviewers as we are dealing with nominal data i.e. agreement or not with the domain to which a determinant is mapped onto the TDF.

Quality assessment

No studies will be excluded based on quality as our aim is to identify determinants of medication adherence as comprehensively as possible. However, we will undertake a quality assessment for the purposes of characterising included studies. There is no gold standard tool for any study design, nor is there any widely accepted generic quality assessment tool that functions across multiple study types (38). We will use bespoke Critical Appraisal Skills Programme qualitative (CASP) (39), Critical appraisal

of survey (40) and Cochrane risk of bias tool (41) to critically appraise qualitative studies, surveys and trials respectively. These tools meet the requirements of the study and provide key quality criteria such as validity, reliability and objectivity (42). Quality assessment will be carried out by two independent reviewers. Any disagreement between reviewers will be resolved through discussion and if necessary, referral to a third reviewer for arbitration.

Patient and Public Involvement (PPI)

This systematic review is a part of the C-MAB project which include three patients and a carer as research advisory board members. PPI has influenced the study design with two notable recommendations: inclusion of the carer's perspective on medication adherence and differentiating between modifiable from non-modifiable determinants of medication adherence. Two PPI representatives (CG and RG) are listed as authors.

Ethics and dissemination: Ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication.

Funding statement: This research is a part of the Clinical Doctoral Research Fellowship program funded by Health Education England / National Institute of Health Research. The funder has no role in the development of this protocol.

Competing interest statement: No, there are no competing interest for any authors.

Author's contribution: All authors (AP, AD, AC, CG5, CG4, RG, GM, SS, FS, BT, MT, JW and DB) helped conceive the study, reviewed the protocol and provided intellectual critique. AP and DB designed and wrote the protocol. AP registered the

study with PROSPERO. All authors (AP, AD, AC, CG5, CG4, RG, GM, SS, FS, BT, MT, JW and DB) have approved the publication of this protocol.

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Table 1: Enhancing **tr**ansparency in reporting the synthesis of qualitative research: the **ENTREQ** statement

Reference: Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012;12(181). Available from: https://bmcmedresmethodol.biomedcentral.com/track/pdf/10.1186/1471-2288-12-181

No	Item	Guide and description	Reported on Manuscript Page no.
1	Aim	State the research question the synthesis addresses.	6
2	Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology *(e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis).*	7
3	Approach to searching	Indicate whether the search was pre-planned (*comprehensive search strategies to seek all available studies)* or iterative (*to seek all available concepts until they theoretical saturation is achieved).*	8

No	Item	Guide and description	Reported on Manuscript Page no.
4	Inclusion criteria	Specify the inclusion/exclusion criteria *(e.g. in terms of population, language, year limits, type of publication, study type).*	8-9
5	Data sources	Describe the information sources used (e.g. *electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO, Econlit), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists)* and when the searches conducted; provide the rationale for using the data sources.	8
6	Electronic Search strategy	Describe the literature search *(e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits).*	8-9
7	Study screening methods	Describe the process of study screening and sifting *(e.g. title, abstract and full text review, number of independent reviewers who screened studies).*	9

No	Item	Guide and description	Reported on Manuscript Page no.
8	Study characteristics	Present the characteristics of the included studies *(e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions).*	12
9	Study selection results	Identify the number of studies screened and provide reasons for study exclusion *(e,g, for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications t the research question and/or contribution to theory development).*	11
10	Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings *(e.g. assessment of conduct (validity and robustness), assessment of reporting (transparency), assessment of content and utility of the findings).*	13
11	Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings *(e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope* [25]*; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and*	13

No	Item	Guide and description	Reported on Manuscript Page no.
		interpretations, reporting).	
12	Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required.	13
13	Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale.	13
14	Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? *(e.g. all text under the headings "results /conclusions" were extracted electronically and entered into a computer software).*	11-12
15	Software	State the computer software used, if any.	12

No	Item	Guide and description	Reported on Manuscript Page no.
16	Number of reviewers	Identify who was involved in coding and analysis.	12
17	Coding	Describe the process for coding of data *(e.g. line by line coding to search for concepts).*	12
18	Study comparison	Describe how were comparisons made within and across studies *(e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary).*	11
19	Derivation of themes	Explain whether the process of deriving the themes or constructs was inductive or deductive.	7
20	Quotations	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation.	7

No	Item	Guide and description	Reported on Manuscript Page no.
21	Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. *new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct).*	7

Table 2 : PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol)

Reference: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. BMJ. 2015;349. Available from: https://www.bmj.com/content/349/bmj.g7647

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
Administrative information			
Title:			
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	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 7
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15
Amendments	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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	15
Introduction			

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
Methods			
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	8-9
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	12
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
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	11-12
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	12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11-12
Risk of bias in	14	Describe anticipated methods for assessing risk of bias of individual studies, including	13

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
individual studies		whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA
	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 I^2, Kendall's τ)	NA
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	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)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13