

# BMJ Open 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 it is estimated that 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 patients' perspective and that of other stakeholders such as clinicians despite of their different 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 and Enhancing Transparency in Reporting the synthesis of Qualitative research (ENTREQ) guidelines. This review will include both qualitative and quantitative primary studies exploring determinants of medication adherence in bipolar disorder. We will search the following databases using a preplanned 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.

**PROSPERO registration number** CRD42018096306.

## 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.
- Variation in the terms that is 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.<sup>1</sup> Bipolar disorder, featuring mood and activity level disturbance, is a recurrent disorder and usually requires long-term maintenance therapy.<sup>1 2</sup> However, it is estimated that 40% of people with bipolar disorder do not take their medication as prescribed.<sup>3</sup> This non-adherence (generally described as taking less than 80% of prescribed doses of medication)<sup>4</sup> increases the risk of relapse, suicide and hospitalisation.<sup>5 6</sup> For example, the probability of hospitalisation of non-adherent patients with bipolar disorder is at least five times higher than that of adherent patients.<sup>7</sup>

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.<sup>8</sup> Furthermore, non-adherence may occur at initiation (ie, patient may or may not start the treatment), implementation (ie, patient may delay, omit or take extra doses during treatment) or persistence (ie, patient may discontinue treatment after some time) phase.<sup>9</sup> There are many reported barriers and facilitators (determinants) of medication adherence. For this review, a barrier is defined as ‘a circumstance that prevents the patients from taking their medication as prescribed’, whereas a facilitator is ‘a circumstance that makes the process easy or easier’.<sup>10</sup> We mention these barriers and facilitators as ‘determinants’.

The challenges to successfully address 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.<sup>11 12</sup>

There are various objective (eg, drug plasma levels, pill counts and electronic monitoring of medication adherence such as medication event monitoring systems) and subjective (eg, self-reported, carer or relative reported, clinician reported adherence rating scales) approaches to identify patients not adhering to their prescribed medication for bipolar disorder.<sup>13</sup> 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 synthesise 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.<sup>14</sup> 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.<sup>1 15 16</sup> 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<sup>14</sup> is warranted to better represent the mood stabilisers that were the mainstay of treatment in the earlier decades and not included in the previous review and to identify emerging research.<sup>17</sup>

The dearth of adherence evidence syntheses in the mental health setting underpinned by health psychology theory<sup>14 18–20</sup> is of concern given its importance for informing intervention design and implementation.<sup>11 12</sup> The Theoretical Domains Framework (TDF) is a comprehensive framework capturing 33 theories and 84 theoretical constructs related to behaviour change.<sup>21</sup> The TDF comprises 14 domains, each of which has been coupled with evidence-based behaviour change techniques.<sup>22</sup> 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.<sup>18 23–26</sup> For example, the healthcare professional is generally the expert regarding how the medication should be taken while 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 such as sex, age and ethnicity are not modifiable, 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.<sup>27</sup> We will explore the modifiable determinants of medication adherence among patients with bipolar disorder from the perspectives of the patient, carer, healthcare 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, while 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 identify both 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, healthcare 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)<sup>28</sup> and Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).<sup>29</sup> The protocol is registered with PROSPERO— [www.crd.york.ac.uk/PROSPERO/](http://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<sup>30–33</sup> 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 that cannot be mapped to a TDF domain will still be extracted and mapped to new domains if appropriate.<sup>34</sup> A further benefit of mapping determinants to the TDF is its linkage to behaviour change techniques.<sup>17</sup> This approach was successfully applied by Allemann and colleagues to match adherence interventions to determinants of patient adherence.<sup>27</sup> 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 under prescribed medication for bipolar disorder.

### Approach to searching, search strategy and data sources

We will employ a preplanned 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 use 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 further relevant studies.

### Study inclusion criteria

We will include any primary studies; both qualitative and quantitative for example, 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. There will be no date restrictions but we will include only the studies published in English language. We will include studies of patients aged 18 years and above with bipolar disorder with or without other comorbidities 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 involving 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,<sup>35</sup> 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 earlier. 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 predefined 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 first and second 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.<sup>28</sup> For a comprehensive approach, we will use the PRISMA flowchart for reporting different phases of searching, screening and identifying studies for inclusion in the qualitative synthesis as recommended by ENTREQ.<sup>28</sup>

### Data extraction and mapping

We will use the computer software program Nvivo V.12<sup>36</sup> 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  $\geq 80\%$  doses of prescribed medications, some studies report adherence in gradient terms (eg, good, moderate, low adherence and non-adherence).<sup>4</sup> Yet, in some cases (eg, in HIV), adherence means taking  $\geq 95\%$  doses of prescribed medications.<sup>36 37</sup> 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 (eg, 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<sup>21</sup> to inform mapping decisions. Any determinants that do not fit within the existing domains will be organised into 'Others' domain.<sup>34</sup>

Within Nvivo V.12, we will create four themes in line with the aim of this study:

1. Patient Perspective.
2. Carers Perspective.
3. HealthCare Professional Perspective.

### 4. Others Perspectives.

Within each theme we will create two subthemes (Barriers and Facilitators), and within each of these subthemes 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 was 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 first and second reviewers as we are dealing with nominal data, that is, agreement and 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 neither gold-standard tool for any study design nor is there any widely accepted generic quality assessment tool that functions across multiple study types.<sup>38</sup> We will use bespoke Critical Appraisal Skills Programme qualitative (CASP),<sup>39</sup> Critical appraisal of survey<sup>40</sup> and Cochrane risk of bias tool<sup>41</sup> 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.<sup>42</sup> 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

This systematic review is a part of the C-MAB project that include three patients and a carer as research advisory board members. Patient and public involvement (PPI) has influenced the study design with two notable recommendations: inclusion of the carer's perspective on medication adherence and differentiating between modifiable and 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.

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