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Research paper

A research agenda for bipolar disorder developed from a patients' perspective

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ABSTRACT

Background: Diagnosis and treatment of bipolar disorder is complex. Health care is supported by clinical guidelines, which are highly based on scientific evidence. However, such care does not necessarily correspond to preferred care according to patients. In order to narrow the gap between scientifically based guidelines and the patient's perceptions of the best clinical practice, additional research is needed. The aim of this study was to create a patient based research agenda for bipolar disorder to enhance the alignment between patients' needs and care system.

Methods: A mixed method study design was employed consisting of two phases: consultation and prioritization. In the consultation phase, six focus group discussions with patients (n = 35) were conducted to explore research needs according to patients, resulting in 23 research topics. Subsequently, these topics were prioritized by means of a questionnaire with patients (n = 219).

Results: Patients with bipolar disorder mentioned a variety of research topics covered by the following five themes: causes of disorder; pharmacotherapy; non-pharmacological treatment; diagnosis; and recovery & recovery oriented care. 'Etiology' was the topic with highest priority.

Discussion: The theme 'causes of disorder' is prioritized highest. We argue that this can be explained by the added value of an *explanatory framework* for appropriate treatment and recovery. The theme 'recovery & recovery oriented care' is currently underrepresented in actual research. It is argued that in order to bridge the knowledge and implementation gap, social science and health system research is needed in addition to biomedical research.

1. Introduction

Bipolar disorder (BD) is a psychiatric disorder characterized by episodes of depression and (hypo)mania. The estimated lifetime prevalence across Europe is 1.5–2%, with a lifetime prevalence of 1.3% for bipolar I disorder in the Netherlands (de Graaf, ten Have, van Gool, and van Dorsselaer, 2012). Globally, bipolar disorder is ranked sixth among the causes of Disability-Adjusted Life Years (DALY) between the ages of 15 to 44 years, is an important cause of a decline in the health-related quality of life (IsHak et al., 2012), and is associated with a high burden of social and occupational stress (Pini et al., 2005; Renes et al., 2014). Furthermore, it is a serious public health concern, as bipolar disorder often leads to hospitalization and therefore to high healthcare expenditure (Michalak et al., 2012). To limit these adverse consequences, timely diagnosis and adequate treatment are essential.

Clinical guidelines aim to optimize diagnosis and treatment and to improve outcomes. However, the underlying scientific evidence is not based on samples that represent the heterogeneous patient groups in real-life clinical practice (Concato et al., 2000; Henry et al., 2013; Newnham and Page, 2010; Williams and Garner, 2002). Moreover, interventions recommended in guidelines may not always be applicable in individual cases (Bensing, 2000; Henry et al., 2013), e.g. guidelines recommend monotherapy as maintenance therapy, while in practice many patients receive polypharmacy (Henry et al., 2013). Research agendas for increasing scientific evidence in health care are shaped primarily by clinical or pre-clinical researchers, policy-makers, national funding agencies, charitable foundations and the pharmaceutical industry (Broerse et al., 2010; Caron-Flinterman et al., 2007). Although these agents have much expertise to make decisions on relevant research topics, those that patients consider to be important may be

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unknown or neglected. It is increasingly argued that patients' involvement is essential in order to gain a full understanding of research needs for clinical practice (e.g. Abma and Broerse, 2010; Boote et al., 2002).

Three arguments for including patients in research are often mentioned – normative, instrumental and substantive (Broerse et al., 2010). The normative argument maintains that it is the right of end-users (e.g. patients) (Elberse et al., 2012) to be involved in (discussions on) research (Boote et al., 2002; Broerse et al., 2010; Entwistle et al., 1998; Patterson et al., 2014). The instrumental argument concerns greater support for research (Broerse et al., 2010), the acceptance of decisions and outcomes (Elberse et al., 2012), and improved clinical relevance (Abma and Broerse, 2010; Boote et al., 2002; Brett et al., 2014), therefore contributing to better outcomes for patients (Boote et al., 2002; Telford and Faulkner, 2004). The substantive argument considers that patients are experts on their illness, their needs for care, and their navigation of the mental healthcare system (Tait, 2005), while health professionals are experts on the disease, resulting in a different focus (Boote et al., 2002). Patients' experiential knowledge about their illness can complement that of health professionals (Broerse et al., 2010), and lead to different research priorities (Banfield et al., 2014; Caron-Flinterman et al., 2007; Elberse et al., 2012; Tallon et al., 2000).

Currently, despite a substantial volume of research on health care in the field of bipolar disorder, there is still a gap between research outcomes and clinical practice. In everyday clinical practice, questions commonly arise that research-based evidence cannot answer (Buckley et al., 2013), e.g. which type of treatment to offer to different subpopulations or which medication will be effective for an individual patient. This may result in treatment choices that are not evidence based. We argue that in order to enrich clinical practice with scientific knowledge, it is important to include patients in the agenda-setting process. In the Netherlands, a number of research agendas have been designed in collaboration with patients, researchers and health professionals, e.g. for asthma/COPD, burn wounds, congenital heart disease, and neuromuscular diseases (Broerse et al., 2010; Caron-Flinterman et al., 2005; Elberse, 2007; Elberse et al., 2012; Nierse et al., 2013). In the field of mental health, there have been initiatives to set research agendas that are general (e.g. Davison et al., 2017; Rose et al., 2008; Wykes et al., 2015) or specific to a disorder (e.g. Banfield et al., 2014; Jacobson et al., 2016), but to date there is no shared research agenda specifically for bipolar disorder. The aim of this study was to develop a research agenda for bipolar disorder from the perspective of patients.

2. Methods

The agenda-setting process consisted of two phases: consultation and prioritization (Abma and Broerse, 2010).

2.1. Phase 1. Consultation

To create a research agenda, both the research needs and the arguments for them are of interest. For this purpose, focus group discussions were conducted. This qualitative method was chosen to make it possible to gather data on participants' narratives (Green and Thorogood, 2009) and group norms, to generate feelings, experiences, and beliefs, and to trigger the participants by the views and experiences of their peers (Gray, 2014).

To recruit participants, questionnaires were sent to 100 randomly selected from a group of patients with BD who were treated at a specialized Dutch outpatient clinic (A) based at a large mental health institution, and who had indicated at an earlier occasion that they would be interested in participating in research. If they expressed an interest for this particular study, they were contacted to participate in a focus group. In addition, participants were recruited via the website of the Dutch patients' organization for Manic Depressive Patients and their Caregivers (VMDB). Inclusion criteria were: being diagnosed with bipolar disorder, being at least 18 years of age, and not currently in a severe mood episode.

The focus groups lasted 90–120 minutes and were facilitated by experienced moderators (BR & EM) to assist in formulating research themes. The structure of the focus groups was based on a guide, consisting of three parts. In the first part, the question addressed the challenges of living with BD and discussed among the participants. In the second part, aspirations for the future with regard to BD were discussed, based on a fictitious case of a young woman with BD who had not yet been diagnosed. Participants were asked to write down everything they hoped for this young woman in all life domains and for health care, after which these ideas were discussed among all participants. Using a 'vignette' offers a space to think outside the participants' own situation and so broaden the findings. This provided insight into possible needs for changes in health care, society and personal surroundings and stimulated solution-oriented thinking as the introduction for the third part, in which participants were asked to formulate research topics or questions they considered important in the field of BD. After each session a summary in which the research topics were clustered into themes was sent to the participants as a member check, to verify our interpretations of the discussions and our analysis.

The focus groups were transcribed and analyzed using the qualitative analysis software program MAXQDA 11.1.2. To identify and report patterns (or themes), a framework for thematic analysis by Braun and Clarke (2006), consisting of six phases, was used. First, we familiarized ourselves with the data by carefully reading the transcripts. Second, open coding was used to generate initial codes (i.e. research needs) from the data. Third, we looked for patterns throughout these codes and the themes as formulated in the summaries of the focus groups. These themes were further refined by looking for patterns throughout all the focus groups. Finally, the themes were named. The analyses were discussed by EM and BR. These analytical phases resulted in a list of 23 topics for research, clustered into five themes.

2.2. Phase 2. Prioritization

The 23 research topics were used to design a questionnaire, which focused on (1) demographic characteristics, (2) prioritization, and (3) additional comments. To prioritize the topics, patients could distribute 25 points over the 23 topics as they wished, with no restrictions. A pilot questionnaire was tested by seven patients, who were recruited by random selection from patients who consecutively visited another specialized Dutch outpatient clinic (B) for routine appointments. This pilot study resulted in small adjustments, particularly of language, to clarify the research topics. The resulting questionnaire was then completed by two patient groups. The first group was recruited from patients who routinely attended the two specialized outpatient clinics (A and B) over a period of two weeks. Questionnaires could be anonymously returned either in print, or filled out online. For recruiting a second group, a link to the online questionnaire was posted on the website, Facebook page and in the newsletter of the Dutch patients' organization (www.vmdb.nl). For the online version we used SurveyMonkey, an online survey development software. The questionnaire was then open for eight weeks, results were received anonymously. Seventy-three percent of the people who started the online survey completed the questionnaire.

Statistical analyses were performed using SPSS version 23. The research topics were prioritized using descriptive statistics (total attributed points, means). For each topic, the total attributed points were calculated, enriched with the mean attributed points (total points divided by *all* respondents) and the range. In addition, the research themes were prioritized based on their total score, divided by the number of topics.

Ethical considerations

According to the Medical Ethical Committee of the VU University Medical Center, the Medical Research Involving Human Subjects Act

Table 1
Characteristics of respondents of the questionnaire.

Characteristics		Values
		Mean (SD)
Age		48.3 (1.3)
		N (%)
Sex	Men	62 (28.3)
	Women	157 (71.7)
Years of diagnosis	0–4 year	64 (29.2)
	5–14 years	81 (37.0)
	>15 years	70 (32.0)
	I don't know	4 (1.8)
Treatment	No	8 (3.7)
	Yes, general practitioner	9 (4.1)
	Yes, psychiatric clinic	165 (75.3)
	Yes, independent practitioner	18 (8.2)
	Other	19 (8.7)
Medication	Yes	198 (90.4)
	No	21 (9.6)

does not apply for this study. All participants confirmed their understanding of the aim of the research and approved the discussion being audio-taped. Anonymity of all participants was ensured.

3. Results

3.1. Characteristics of the participants

3.1.1. Consultation phase

In total, 35 participants (22 from outpatient clinics and 13 via the patients' organization) attended the six focus groups. The mean age of the participants was 51.6 years (27–66 years), of whom 48.5% were women. The groups varied from three to eight participants, and all groups included women and men.

3.1.2. Prioritization phase

In total, 219 patients completed the questionnaire. The characteristics of respondents of the questionnaire are shown in Table 1. The average age of the respondents was 48.3 (SD 11.3), of whom women account for 71% (n = 157). Almost all (96.3%) study participants are receiving some form of treatment – 90.4% of the respondents use medication for BD, and 49.7% have been diagnosed for less than 10 years.

3.2. Prioritization of the research agenda

Table 2 presents the research agenda for BD from the patients' perspective. All 23 research topics are presented in order of prioritization, based on the total attributed points. The research topic 'etiology' is most prioritized, with a total of 605 points and a mean score of 2.76. In total, 142 respondents attributed points to this topic, more than any of the other research topics. Furthermore, it is notable that both research topics addressing the side-effects of medication are ranked second and third and that both research topics clustered as 'cause of disorder', are in the top four.

The 23 research topics were clustered into five themes. The five themes in order of importance are: cause of disorder, pharmacological treatment, non-pharmacological treatment, diagnosis and recovery, and recovery-oriented care. In the top seven most important research topics, all five themes are represented. The emphasis (top four), however, is on the causes of disorder and pharmacological treatment.

In the following section the research themes are presented in order of prioritization.

3.3. Understanding the research themes

3.3.1. Causes of disorder

This research theme was seen as the greatest priority by patients with bipolar disorder. When discussing the causes of the illness, two aspects for research were of particular importance, namely the *etiology* and *the triggers* responsible for developing a depressive or manic episode. Many participants indicated that they would appreciate research on genetic influences and brain processes to increase their understanding of the mechanisms underlying the symptoms they experience and because it will have a positive influence on pharmacological treatment, the process of diagnosis, and developing interventions to prevent relapse. In addition to the pathophysiological mechanisms behind the disorder, many participants wanted research on the triggers for a depressive or manic episode:

> *… you can also look at the external causes. So, what are the triggers? I really want research done on what you can do [to prevent or respond to triggers], to decrease the use of medication. If we know what the triggers are for developing a depressive or manic episode, you can work on those triggers. That is only possible if you recognize them in time.* (Woman, aged 49)

Some participants gave examples of triggers that might influence a relapse, namely stress, travelling, lifestyle, and the effects of physical illnesses. They wanted research on the influence of these aspects on developing a depressive or manic episode.

3.3.2. Pharmacotherapy

The research theme pharmacotherapy was ranked second. Participants of the focus groups formulated six research topics that were clustered as 'pharmacotherapy'. First, they believed that finding the right medication that effectively treats the individual patients can be time-consuming and so called for research on the development of new medication that is better targeted. One participant explained:

> *Research on medication. There is a wide variety of medicines […]. You need to wait three months for a pill to start working. Then I think, come on, I am depressed now, I just want it to work quickly. After three months you come back because it still doesn't work and then you get another pill and again you have to wait three months before [you know if] it starts working. And then it is six months later. I think come on. So I believe it to be important to do research so that the effect is known sooner.* (Man, aged 50)

The side-effects of pharmacotherapy were a second major issue. Many of them had struggled to find medication in which the positive effects outweigh the negative, resulting in the need for research on medication with fewer side-effects. One of the participants indicated this as follows:

> *Medication and side-effects. I am searching [for the right medication] and sometimes it drives me crazy. I once gained 12 kg and sex is changing due to medication. Sometimes you start to think that you can solve it by taking [illicit] drugs.* (Woman, aged 27)

These challenges were experienced by the majority of the participants, leading them to doubt the usefulness of and need for medication, which resulted in a need for research on the value of medication:

> *Yes, yes, of course there is a huge aversion to medication, mainly because of the side-effects. And maybe taking medication is inescapable. If that is the case, it would be nice to know.* (Man, aged 51)

In addition, some participants wanted research on the medication's mechanism of action, and of the effect of lithium on sport performance.

3.3.3. Non-pharmacological treatment

The research theme 'non-pharmacological treatment' was ranked third and comprised three research topics. The need for non-pharmacological treatment came out clearly in discussing aspirations

Table 2
Research Agenda for Bipolar Disorder according to patients, presenting research topic and corresponding research theme; prioritization is based on total attributed points. The mean is calculated by total points divided by all participants (n = 219). The number of attributed points is the number of respondents that attributed points the that topic.

Top	Topic	Research theme	Total points	Mean	Range	SD	Number of attributed points
1	Etiology	Causes of disorder	605	2.76	0–25	3.68	142
2	Development of medication with fewer side-effects	Pharmacological treatment	415	1.89	0–20	2.58	124
3	Long-term side-effects of medication	Pharmacological treatment	388	1.77	0–25	2.67	125
4	Triggers for onset of mood episode	Causes of disorder	365	1.67	0–10	2.08	122
5	Recognition early warning signs of BD	Diagnosis	342	1.56	0–10	1.96	122
6	Development of medication that is better targeted	Pharmacological treatment	335	1.53	0–20	2.35	110
7	*Re*-integration in society	Recovery & recovery-oriented care	305	1.39	0–10	2.14	107
8	Development of new non-pharmacological therapies	Non-pharmacological treatment	295	1.35	0–10	1.91	113
9	Effectiveness current non-pharmacological therapies	Non-pharmacological treatment	263	1.20	0–15	1.90	106
10	Increase of social acceptance	Recovery & recovery-oriented care	235	1.07	0–10	1.70	99
11	Designing a patient-centered care approach	Recovery & recovery-oriented care	215	0.98	0–25	2.12	92
12	Knowledge improvement GP	Diagnosis	209	0.95	0–10	1.66	88
13	Self-management strategies	Recovery & recovery-oriented care	191	0.87	0–10	1.58	88
14	Positive aspects BD	Recovery & recovery-oriented care	181	0.83	0–10	1.63	90
15	Development diagnostic tool	Diagnosis	162	0.74	0–8	1.54	76
16	Collaboration system practitioners (incl. alternative medicine)	Recovery & recovery-oriented care	145	0.66	0–10	1.56	75
17	Development therapies to support caregivers	Non-pharmacological treatment	140	0.64	0–10	1.31	79
18	Impact of diagnosis	Recovery & recovery-oriented care	135	0.62	0–5	1.15	82
19	Mechanism of action of medication	Pharmacological treatment	132	0.60	0–7	1.24	73
20	Treatment options for co-morbidity	Recovery & recovery-oriented care	130	0.59	0–10	1.39	69
21	Need for medication	Pharmacological treatment	121	0.55	0–6	1.17	73
22	Adequate referral system	Diagnosis	98	0.45	0–10	1.36	58
23	Effect of lithium on sports	Pharmacological treatment	68	0.31	0–5	0.99	52

BD: bipolar disorder; GP: general practitioner.

concerning treatment for a fictitious woman who will be diagnosed with BD in 2025:

> *I would advise her to do mindfulness training. It helped me a lot. I am really sad that 20 years ago it did not exist.* (Woman, aged 50)

> *Yes, me too [had use of mindfulness]. And I did cognitive behavioral therapy, that was really important for me as well. I would advise her to start with that.* (Man, aged 55)

> *What I do believe is important, is that she can talk, therapeutically, with a psychologist, so that you can talk about the fears and shame you experience.* (Man, aged 51)

Most participants wanted research to be conducted on the effectiveness of a variety of non-pharmacological treatments. Second, they wanted that new treatments focus more on non-pharmacological than on pharmacological interventions. Third, they would appreciate research on the development of therapy focused on caregivers.

3.3.4. Diagnosis

The research theme 'diagnosis' was ranked fourth. Four research topics fitted this theme. In the focus groups, participants described the process of timely recognition and diagnosis as problematic. For them, the problem is the considerable delay between seeking help and being correctly diagnosed with bipolar disorder. According to participants, reasons for this delay are the presence of co-morbidity, the fact that BD often starts with depressive episodes, and limited knowledge about the disorder. As one participant said:

> *Yes, I have been with my general practitioner for a long time. He prescribed pills himself, which he should never have done. It was the wrong medication. He did not diagnose me correctly.* (Man, aged 55)

For some participants this delay meant not receiving any diagnosis for 10 to 20 years, for others it meant being misdiagnosed before being correctly diagnosed with BD and hence receiving inadequate or no treatment during that period. The following quote illustrates a severe consequence of delay in diagnosis:

> *I have been sick for three years, because I could not be diagnosed. It was cyclic, rapid cycling. I did not function at my job and because of that, I had a nervous breakdown.* (Man, aged 64)

Thus, the shared opinion was that research should improve the diagnostic process; research needs to be conducted on early warning signs of BD, a diagnostic test that is more effective in detecting BD, how to improve the knowledge of general practitioners and how to develop an adequate referral system to reduce the delay in diagnosis.

3.3.5. Recovery and recovery-oriented care

The last theme is 'recovery and recovery-oriented care'. Eight research topics addressing this theme emerged from the discussions. Participants struggled with self-acceptance and social acceptance. Self-acceptance was described as accepting their own limitations and of being chronically ill and in need of medication. According to most participants, self-acceptance is linked with social acceptance. Acceptance is important for social recovery, for example being able to return to work. According to participants, the complexity of the re-integration process is exacerbated by the fluctuating course of the disorder. This challenge is explained by a participant:

> *If you are diagnosed with bipolar disorder and you are not able to work, you are declared unfit for work. […] when you are declared fit for work again and a year later something happens that makes you stressed again you can go back to the UWV*[1] *to apply for sickness benefit again. [….] I have sort of a trauma due to all this hassle at the UWV. Only looking at the forms makes me nauseous.* (Woman, aged 34)

To recover, participants advocated a recovery-oriented care system, with better collaboration between various disciplines and departments and between the standard and alternative care systems, especially for those who suffer from co-morbid disorders. Second, some patients struggled with the limited availability of emergency services when they are in crisis. Third, the system could be improved if it was focused on customized care and the stimulation of self-management rather than focused primarily on the illness.

> *What happens is, you get a diagnosis and then the illness will be treated,*

[1] UWV (Uitvoeringsinstituut Werknemersverzekeringen) is a Social Security Agency in the Netherlands.

while I would benefit a lot more from solving the problems that I experience at that moment. (Man, aged 46)

Customized care entails making patients' needs the starting point of the treatment and could result in tailor-made support regarding lifestyle, psychological treatment, sport, nutrition and the social environment.

These challenges resulted in associated research needs on (1) topics that contribute to their personal, social and functional recovery, and (2) ways to design a recovery-oriented healthcare system. For the first, participants explained the need for research on awareness programs and school programs to increase public acceptance and on the policy of the social security agent regarding the re-integration process, but also on the impact of the diagnosis on the patients and their social environment and on the positive aspects of bipolar disorder. The second includes research on a patient-centered healthcare system, the organization of a flexible care system for people with co-morbid disorders, the attention to self-management in treatment and collaboration in order to improve cooperation between a range of (alternative) practitioners.

4. Discussion

In order to bridge the knowledge gap (Elberse et al., 2012) and the implementation gap (Tallon et al., 2000) between research and clinical practice, it is important to include patients in the agenda-setting process. In this study, patients with bipolar disorder currently treated in specialized outpatient mental health facilities and/or being a member of the patients' organization set a research agenda including 23 topics covering five major research areas.

Our results are confirmed by a mental health research agenda established by service users from the UK (Rose et al., 2008) and an Australian research agenda for mood disorders (Banfield et al., 2014). Patients in both the UK and Australian project preferred topics that resemble our theme of recovery-oriented care, namely improving re-integration, accessibility of care, social understanding of mental illness and customized care (Banfield et al., 2014). Other topics are similar too, namely the impact of the diagnosis (Banfield et al., 2014; Rose et al., 2008), the GP's knowledge (Banfield et al., 2014), side-effects of medication (Banfield et al., 2014), effectiveness of complementary therapies and the need for medication (Banfield et al., 2014; Rose et al., 2008) and causes, such as genetic and environmental factors (Banfield et al., 2014; Rose et al., 2008). Due to the similarities with the UK research agenda for mental health service users in general, it could be suggested that these themes are important for the broader mental health field, as stated by Banfield et al. (2014).

It is interesting to see whether the research themes prioritized in this project correspond to the current European research agenda for bipolar disorder. To stimulate European-wide research on BD, to improve its management and to gain understanding of the underlying mechanisms, centers from six European countries joined forces in a European Network of Bipolar Research Expert Centre (ENBREC) (Henry et al., 2013), and its research program can be seen as a current European research agenda on bipolar disorder. In this network, special attention is paid to diagnostic tools, cognitive functions, biomarkers, genetics, treatment optimization, and neuro-imaging. These research topics fit the categories 'diagnosis', 'causes of disorder' and 'pharmacotherapy' in our study. In addition, ENBREC will address the implementation of psycho-education, which fits our category of non-pharmacological treatment. Interestingly, recovery and recovery-oriented care initiatives are not mentioned in the ENBREC research projects. This particular gap between current research and patients' priorities is confirmed by Michalak et al. (2016), who found that in the field of BD, the focus of current research is mainly on 'genetics', 'neurobiology' and 'clinical phenomenology', despite patients' need for research on recovery, lifestyle and psychosocial factors. In addition, a similar gap was found in the British ROAMER project on mental health priorities in Europe, where service users emphasized social rather than biomedical interventions, e.g. the research priorities on the quality of health services and the development of alternative therapies (Robotham et al., 2016; Wykes et al., 2015), and in an Australian initiative that found research topics highly prioritized by patients with BD (e.g. individualized care, effective coping strategies and evidence on effective therapies), were underrepresented in the literature (Banfield et al., 2011).

In the research agenda for bipolar disorder set out in this study, the themes most prioritized are 'causes of disorder' and 'pharmacological treatment' and the topic most prioritized is 'etiology'. We hypothesize there are two reasons for this. First, that generating an understanding of the etiology contributes to more acceptance and recovery. Schrank and Slade (2007) describe in their study on the concept of recovery in psychiatry that two components of recovery, 'self-identity' and 'symptom management', both benefit from 'knowing the illness' and 'developing an explanatory framework to understand the experience'. In addition, in a study about how patients successfully manage their bipolar disorder, Suto et al. (2010) found that one of the six strategies on managing BD was understanding the disorder, including its etiology. Second, we argue that it is prioritized highly because of the belief that understanding the etiology might provide patients with a clear direction towards the appropriate form of treatment. During the discussions it became clear that participants are often struggling with making sense of their treatment trajectory and deciding on its focus (pharmacological or non-pharmacological treatment), which for some participants depends on the etiology. We could therefore state that insights into the etiology of BD is supportive of the first step into the recovery process.

To further the previous discussion, we argue that it is relevant to acknowledge that the high ranking of research topics such as 'etiology', 'triggers for onset of episode', 'development of new medication with fewer side-effects' and 'long-term side-effects' could also be explained by the public view on what research entails; 'research' is often associated with basic science and interventional science and not with health system research. However, we would argue that the topics clustered in the theme 'recovery and recovery-oriented care' are indeed research topics, and that they may not currently be on e.g. the ENBREC agenda because they represent complex, unstructured, and often interdisciplinary issues, for which it is not clear which types of knowledge are needed (Schuitmaker, 2012). This makes it difficult to identify specific research questions related to these issues. Moreover, it may not be only biomedical research that is needed, but also social science research and health system research, fostering a more integrated perspective.

4.1. Limitations and recommendations for further research

Our study has some limitations. First, there was an over-representation of women and it is not known to what extent this could have influenced the results. Due to the sampling approach via Dutch outpatient clinics and the patient organization most of the sample received specialized treatment. More research is needed among untreated BD patients. Second, a patient-informed research agenda may contain topics that have been researched but of which patients are not aware. Some topics could, therefore, reflect implementation gaps of existing research rather than true research gaps, a phenomenon also described by Owens (2008) and Banfield (2014). In order to make this distinction, further research to compare previous research with the research topics prioritized by patients could provide insight. Third, it will also be relevant to include caregivers and health professionals in the agenda-setting process, since their perspectives could complement the patients' research agenda. Therefore, for future research we focus on including *all* end-users in order to obtain a shared research agenda for bipolar disorders.

In conclusion, our study contributes to the field of research agenda setting by including the perspectives of patients with bipolar disorder. This research agenda could steer funding agencies and researchers to

conduct research that is relevant to end-users. The next step in this process is to narrow the formulated research topics into specific research questions, without detracting from the complexity of topics addressed by patients. It will require a close collaboration between patients and researchers to increase our understanding and thereby effective diagnosis and treatment of bipolar disorder.

5. Conflict of interest

None.

6. Contributors

E.F.M contributed to the data collection, managed the analysis and wrote the first draft of the manuscript. B.J.R. designed the study, wrote the protocol, contributed to the data collection and provided critical revision of the manuscript. J.F.G.B contributed to the study design and critical revision of the manuscript. E.J.R contributed to the study conception, analysis and critical revision of the manuscript. R.W.K contributed to the study conception, acquisition of data and critical revision of the manuscript. All authors contributed to and have approved the final manuscript.

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