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Research paper

Bipolarity in Older individuals Living without Drugs (BOLD): Protocol and preliminary findings

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ABSTRACT

Introduction: Although clinical guidelines regard prophylactic medication as the cornerstone of treatment, it is estimated almost half of patients with bipolar disorder (BD) live without medication. This group is underrepresented in research but can provide indispensable knowledge on natural course, resilience and self-management strategies. We aim to describe the clinical phenotype of patients diagnosed with BD who have discontinued maintenance treatment.

Methods: The mixed-methods BOLD study included 58 individuals aged 50 years and over with BD that did not use maintenance medication in the past 5 years. A preliminary, quantitative comparison of clinical characteristics between BOLD and our pre-existing cohort of >220 older BD outpatients with medication (Dutch Older Bipolars, DOBi) was performed.

Results: BD-I, psychiatric comorbidities, number of mood episodes and lifetime psychotic features were more prevalent in BOLD compared to DOBi. BOLD participants had a younger age at onset and reported more childhood trauma. BOLD participants reported fewer current mood symptoms and higher cognitive, social, and global functioning.

Limitations: Our findings may not be generalizable to all individuals diagnosed with BD living without maintenance medication due to selection-bias.

Conclusion: A group of individuals exists that meets diagnostic criteria of BD and is living without maintenance medication. They appear to be relatively successful in terms of psychosocial functioning, although they do not have a milder clinical course than those on maintenance medication. The high prevalence of childhood trauma warrants further investigation. Future analyses will examine differences between BOLD and DOBi per domain (e.g. cognition, physical health, psychosocial functioning, coping).

1. Introduction

Bipolar disorder (BD) is characterized by recurrent episodes of depression and (hypo)mania, usually alternated by periods of clinical remission (euthymia). After a first index episode, the risk of a subsequent mood episode is 44 % in the first year, and the median time to a next episode is 1.4 years (Radua et al., 2017). Clinical guidelines regard long-term prophylactic medication as the cornerstone of treatment (Kupka et al., 2015, Yatham et al., 2018). The international CANMAT/ISBD BD guideline recommends prophylactic treatment in

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"almost all individuals with BD" and "even after a first episode" in order to prevent subsequent affective episodes and possibly further cognitive decline (Yatham et al., 2018). As a consequence, clinicians often advise life-long pharmacotherapy for BD, since it is not clear in which conditions the maintenance treatment might eventually be safely tapered and stopped.

Yet, it is estimated that on average 43 % of patients with BD do not take their medication regularly or will stop taking prophylactic medication at some point (Chakrabarti, 2017). Also, maintenance medication cannot always prevent new episodes. A recent meta-analysis found that psychotropic monotherapy was more effective in preventing new BD episodes than placebo (odds ratio, OR = 0.42) (Nestsiarovich et al., 2022). However, the reported risk of recurrence was 31.4 % for active treatment versus 51.1 % for placebo, indicating that people on long-term medication still have a high risk of recurrence. In addition, the number needed to treat (NNT) was 8 for mania and 11 for bipolar depression, so for each person who benefits from long-term pharmacotherapy, 8–11 people do not (Nestsiarovich et al., 2022). Another review calculated that although discontinuation of medications for ⩾1 month significantly increased recurrence risk, 47.3 % of patients who discontinued pharmacotherapy for 6 months did not experience recurrence (Kishi et al., 2021). Especially in individuals of >50 years, this trade-off between efficacy and tolerability of medication is complex (Qureshi and Young, 2021) and often dependent on individual patient preferences (Rej et al., 2016).

Medication studies in BD mainly focus on clinical recovery (fewer recurrences) whereas patients often consider functional recovery as a more important treatment goal. Medication is a common and effective approach for managing the symptoms of BD (Nestsiarovich et al., 2022), but are often associated with side effects. These side effects can decrease quality of life and create difficulties in daily functioning (Ali et al., 2021). In the last decade, a large recovery movement has emerged in mental healthcare, which advocates person-centred care, greater self-determination for those with mental illnesses, and an enhanced focus on restoring functioning beyond psychiatric symptom reduction (Davidson, 2016). This movement has urged an increase in research on safe guided discontinuation of maintenance treatment and the development of medication-free treatment options in the fields of psychosis and depression (Alvarez-Jimenez et al., 2016; Bockting et al., 2018). In BD however, this research is very scarce.

To our knowledge, only one report exists on medication-free individuals with BD, apart from neuroimaging studies. In a qualitative study, ten individuals diagnosed with BD who did not use medication were interviewed (Cappleman et al., 2015). The authors found that they had discontinued their medication intentionally and autonomously after an intensive decision-making process. This is contrary to the popular belief that non-adherence in BD is the result of an impulsive act, a lack of insight and/or inaccurate cognitions about medication (Cappleman et al., 2015).

According to (Dutch) patient and family support organizations for BD, a subgroup of BD patients exists that self-manage their illness without medication. This is confirmed by the Netherlands Mental Health Survey and Incidence Study (NEMESIS), in this population based study 51 % of individuals with BD had contact with Mental Health Care and 43 % used medication in the 12 months before the assessment (ten Have et al., 2022). As these medication-free individuals do not visit psychiatric treatment facilities, they are invisible to clinicians and therefore underrepresented in medical research. This is a lost opportunity, since they could provide indispensable knowledge on living with BD. In particular, their clinical phenotype is unclear: have they possibly been misdiagnosed in the past if one would apply the more stringent BD criteria of present-day, or do they represent a specific BD subtype with a milder clinical course with fewer recurrent episodes? And moreover, do they possess resilience, specific resources, or self-management strategies that could explain how they manage to live with their illness without medication?

To answer such questions, we have initiated the mixed-methods BOLD study (Bipolarity in Older individuals Living without Drugs), which focuses on individuals aged 50 years and over with BD that did not use medication for BD in the past 5 years. Our ultimate goal is to describe an extensive clinical phenotype of patients diagnosed with BD who may be able to safely and effectively discontinue maintenance treatment. In this report, we will describe the protocol of the BOLD study and present preliminary quantitative results.

2. Methods

2.1. Study design

The BOLD study is a sequential mixed-methods study, which included a quantitative assessment followed by semi-structured qualitative interviews in a subset of participants.

We included individuals of ≥50 years, because in older patients the illness course is more established and the risk of side effects is higher, which often results in specific personalized medical decision making. Also, the selection of older persons with BD enables a quantitative comparison to our previously collected cohort of >220 older BD patients with medication (Dutch Older Bipolars, DOBi, (Dols et al., 2014, Beunders et al., 2021)). The quantitative assessment battery of the BOLD study was similar to the baseline measurement from the DOBi protocol. DOBi included patients with BD aged 50 and over (for methods, see (Dols et al., 2014, Beunders et al., 2021)). In this way, the BOLD study sample could serve as a special medication-free control group for the DOBi study. For the BOLD study, two persons with lived experience (MvE, CN) and the chairman of the Dutch patient association for BD (HM) took active part in the research team and advised on the design of the study and recruitment of the individuals without medication, as we did not expect to find this group through mental health institutions only.

2.2. Participant recruitment

All participants of the DOBi study received treatment at GGZ inGeest, an outpatient mental health facility in Amsterdam, the Netherlands, at the time of inclusion. The total baseline sample of DOBi (wave 1 and 2) consists of 227 patients, of which only 5 (2.2 %) did not use maintenance medication for BD (Beunders et al., 2021).

BOLD participants were recruited by a call in the magazine and website of Plusminus (the Dutch patient association for BD), MIND (the largest Dutch online platform for mental health), and KenBiS (the Dutch Foundation for BD), through patient networks (e.g. Facebook group Petraetcetera, psychosenet.nl), social media, and at national and local patient information gatherings. Additionally, we placed a call in the weekly newsletter of the Dutch Association of Psychiatry (NVvP), which is received by the majority of Dutch psychiatrists and in the newsmagazine of The Dutch College of General Practitioners (NHG), requesting general practitioners to provide eligible patients. We also used snowball sampling, by asking included participants to share information on the study with acquaintances that might fulfil the inclusion criteria as well. If so, we asked these participants to share information on the BOLD study with their acquaintance. These in turn had to express interest in the study themselves by contacting the study coordinator (AB).

Inclusion criteria were: 1) individuals aged 50 or older, 2) with a diagnosis of BD by a health professional at least 5 years ago, 3) without using maintenance treatment for BD (mood-stabilizers, anti-psychotics, anti-convulsant, anti-depressive medication) for the past 5 years. Participants were allowed to have experienced mood episodes in the past 5 years and to currently use sleep medication. As the last medication use as well as formal BD diagnosis had to be at least 5 years ago, we were sure that all participants were aware of their (past) bipolar symptoms and psychiatric vulnerability for the full medication-free time period.

Exclusion criteria were: 1) severe personality disorder as the main diagnosis, 2) insufficient command of the Dutch language, 3) mental

retardation (IQ below 70), 4) dementia (Mini Mental State Examination (MMSE (Folstein et al., 1975)) below 18), or 5) a highly unstable psychiatric condition (e.g., current compulsory admission).

2.3. Quantitative data collection

We collected quantitative data on multiple domains of functioning (clinical BD characteristics, cognitive functioning, social functioning, physical health, coping, and personality traits). Data collection took place between September 2020 and December 2022. All individuals that expressed interest received an invitational phone call with the study coordinator (AB) to screen for eligibility. After the participant met inclusion criteria and provided written consent the assessment started.

First, a clinical assessment was performed by a trained psychologist (TK) or (resident) psychiatrist (AB; AD) through a video call. This entailed a semi-structured diagnostic interview based on the DSM-IV-TR (MINI-plus (Sheehan et al., 1998)) including confirmation of a bipolar disorder diagnosis, age at onset, presence of psychiatric comorbidities, calculation of the Bipolar Index (Sachs, 2004), psychiatric functioning (validated GAF-p (Spitzer et al., 1996)), and social functioning (validated SOFAS (APA., 2013)). During this video call, a questionnaire on somatic illnesses, smoking, alcohol use and medication use (somatic, psychotropic, and over the counter) was also assessed. Second, an extensive package of self-report questionnaires was filled in by the participant at home. These included among other items: sociodemographic features, illness history, and family history from the validated QBP-NL (Questionnaire for Bipolar Illness, Dutch translation (Leverich et al., 2001; Suppes et al., 2001)) and a scale for depressive symptoms (Center for Epidemiologic Studies Depression scale, CES-D (Radloff, 1977)) (see Appendix 1 for the full list of questionnaires). Third, a visit on site or at the participant's home was planned for an extensive neuropsychological assessment (NPA), including the MMSE and a broad range of neuropsychological tests measuring multiple cognitive domains (attention, (working) memory, executive functioning, language), performed by a trained psychologist. During this visit, manic symptoms with the Young Mania Rating Scale (YMRS (Young et al., 1978)) and measurements of blood pressure, waist circumference, height and weight, and frailty were also assessed. Finally, blood was drawn for laboratory measurements of the lipid spectrum, glucose, creatinine, TSH, including biobank storage (cells, plasma and serum). See Appendix 1 for the full list of measurements.

2.4. Qualitative data collection

In a subset of participants, we performed semi-structured qualitative interviews in order to explore personal experiences and perspectives. The aim was to better understand the potentially complex processes underlying the decision to refrain from using medication and the experience of living with bipolarity without medication.

All of the 58 participants from the quantitative research sample were asked if they were interested in undergoing an additional qualitative interview. However, it was only feasible for a subset of BOLD participants to participate. Consenting participants were selected using 'convenience sampling' until 'meaning saturation' was reached, i.e. when there is enough data to 'understand it all'. Hennink et al. (Hennink et al., 2017) show this usually occurs after ±16–24 participants. 'Meaning saturation' is more profound and preferred to 'data saturation', which refers to the situation in which no new themes or topics are emerging anymore (Hennink et al., 2017). Each qualitative interview was performed by two interviewers: a researcher (AB) or trained medical student (MS) paired with a person with lived experience (MvE or CN).

2.5. Participant contribution

For the quantitative part ($N = 58$): one clinical assessment by video call (1,5 h), plus the self-report questionnaires at home (2 h) plus one visit for the neuropsychological assessment and physical measurements (2–3 h, on site or at home) plus one visit for the blood draw (0.5 h). For the qualitative part (subset of 20 participants): one additional visit (2–3 h, on site or at home). Participants received financial compensation for each site visit and for travel costs.

2.6. Ethical issues

All participants gave written informed consent for the quantitative data collection as well as for the qualitative interview. Separate consent was obtained for participation in the biobank. The study was approved by the Medical Ethics Committee of the Amsterdam UMC, location VU University Medical Center, Amsterdam, the Netherlands.

2.7. Preliminary quantitative data analysis

For the first analysis in this report, we compared clinical BD characteristics (e.g. BD severity) of a subgroup of older BD persons without medication (BOLD participants, $N = 58$) to older BD individuals on maintenance medication (DOBi participants, $N = 222$). To this aim, selected quantitative data were added to the DOBi database. This explorative analysis compared the following: demographic characteristics, bipolar disorder diagnosis, clinical characteristics, current psychiatric symptoms, psychiatric comorbidities, and current use of psychotropic medication. First, descriptive analyses were performed by calculating percentages or mean, standard deviation, range or median, and interquartile range. Differences in continuous variables were tested with Mann-Whitney U tests (as most variables were not-normally distributed), dichotomous variables with 2-sided Fisher's exact tests, and categorical variables with more than two categories with 2-sided Fisher-Freeman-Halton Exact tests. A p-value of <0.05 was considered statistically significant. Data were analysed using the Statistical Package of the Social Sciences (SPSS, version 28.01.0, SPSS Inc., Chicago, IL).

2.8. Planned future analyses

Future analyses of the collected data will compare individuals with medication (DOBi) and without (BOLD) in the following domains: 1) cognitive functioning (using data from the neuropsychological assessment); 2) social functioning (using the SOFAS, as well as network size and social activities); 3) physical health (comorbidities and frailty); 4) coping and personality traits. These analyses will be more in depth, will include all relevant data, and take into account relevant confounders. Future studies in this medication-free BD sample will also investigate the extent of resilience; the personal attitudes and perspectives on illness, and coping strategies by using data from the quantitative and qualitative interviews. With the qualitative analysis we hope to answer questions such as: how and why did someone decide to (stop or) not start with medication for BD? Are there specific self-management strategies that contributed to recovery and resilience?

3. Results

3.1. Inclusion of participants

A total of 104 individuals were screened for eligibility, of which 32 were excluded (see Fig. 1). Out of 72 eligible patients, 14 (19 %) refused to consent and participate in the study. The most common reason for refusing after approaching the research team for participation was that the participants felt that the study set-up was too much designed from a mental health care perspective that they could no longer relate to. The following quote from an eligible individual that refused participation illustrates this: "*I have come a long way; I have talked with many psychiatrists and I can no longer relate to a DSM diagnosis as it does not reflect how I feel. I think this study is important, but the questionnaires are based on the DSM framework and I just feel overwhelmed by even looking at them*". Some

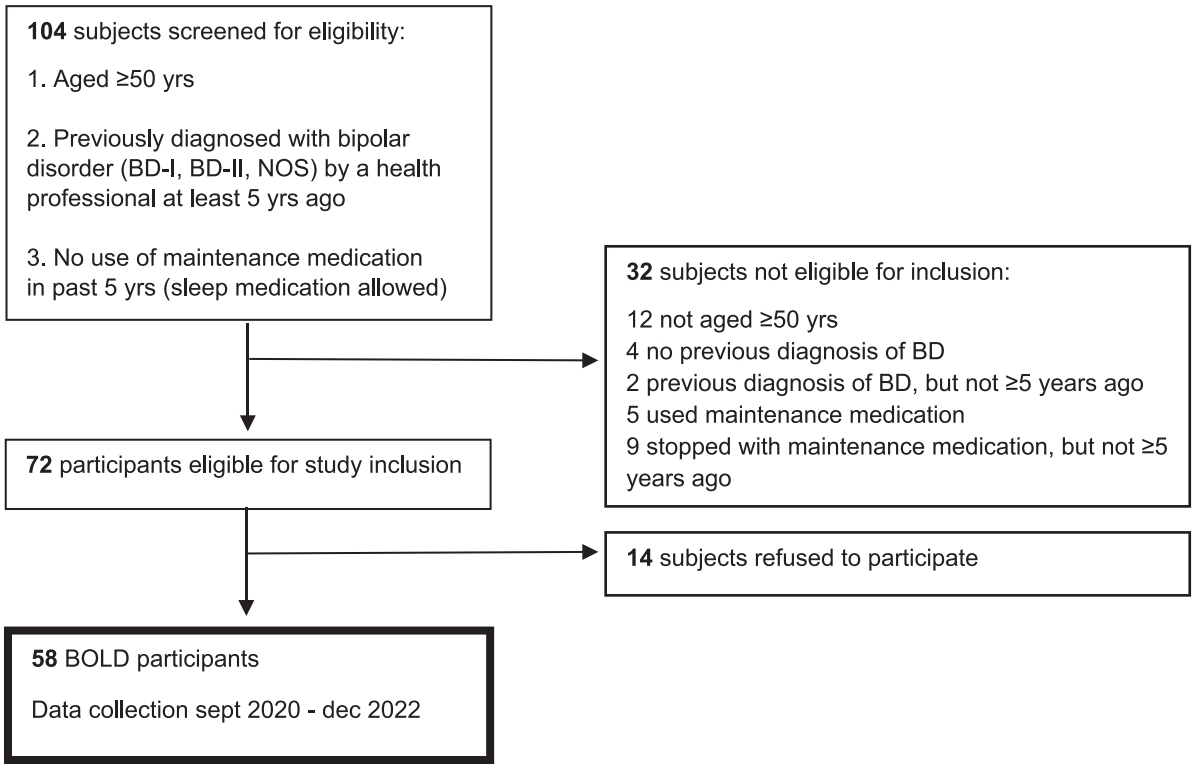

Fig. 1. Flow diagram of the study.

perceived the numerous questionnaires as a barrier, since they did not want to look back at their psychiatric history. Others did not perceive themselves as sufficiently mentally stable or could not invest enough time for the study. Ultimately, 58 participants were included in the BOLD study.

3.2. Demographic characteristics

BOLD participants were younger (62.0 versus 65.9, $p = 0.001$), more often highly educated (66.7 % versus 49.5 %, $p = 0.022$) and more often employed (43.9 % versus 28.2 %, $p = 0.034$) than DOBI patients (See Table 1). Approximately 60 % of both groups indicated to be in a steady relationship ($p = 0.537$).

3.3. BD diagnosis and psychiatric comorbidities

All BOLD participants met the DSM-IV-TR criteria for BD. At the time of assessment, BOLD participants were diagnosed for the first time by a health professional on average 21.2 years ago (SD 11.7, range 6–51, see Table 1). BD-I was more prevalent in BOLD (69 % versus 57.2 % in DOBi), whereas BD-II was more prevalent in DOBi (mean 42.3 % versus 27.6 % in BOLD, $p < 0.001$). The Bipolarity Index was higher in BOLD (mean 70 versus 66, $p = 0.043$). Rapid cycling did not occur more often in BOLD. Age at onset (for both mania and depressive episode) was higher in DOBi ($p < 0.001$) resulting in a longer mean illness duration in BOLD of 41.1 years versus 34.8 in DOBi ($p = 0.003$). The number of (hypo)manic episodes was higher in BOLD (median 10 versus 5 in DOBi, $p < 0.001$), but the number of depressive episodes did not differ. Episode density, defined as the number of mood episodes divided by the illness duration, was not different (mean 0.7 in DOBi versus 1.0 in BOLD, $p = 0.123$). Current or lifetime anxiety disorder was more prevalent in BOLD (43.1 % versus 17.7 % in DOBi, $p < 0.001$). Rates for current or lifetime alcohol dependence or abuse and substance dependence or abuse were similar between the two groups.

3.4. Clinical characteristics

Familial loading (defined as at least one parent with a history of depression, BD, or psychosis) was around 40 % in both groups. Of the BOLD participants, 81.8 % reported to have experienced emotional, physical or sexual abuse during childhood or adolescence, versus 48.1 % in DOBi ($p < 0.001$). History of psychiatric admissions or severe suicide attempts did not differ between the two groups. Lifetime psychotic features were more prevalent in BOLD (78.2 % versus 58.2 %, $p = 0.008$).

3.5. Current psychiatric symptoms

BOLD participants reported less current depressive and manic symptoms (resp. $p < 0.001$ and $p = 0.009$). Cognitive functioning, as measured with MMSE, was higher in BOLD (mean 28.8 versus 28.0, $p = 0.006$). Social functioning was higher in BOLD (mean 73.7 versus 63.8, $p < 0.001$) as was global functioning (mean 73.4 versus 64.2, $p < 0.001$).

3.6. Psychotropic medication use

As a result of the in- and exclusion criteria, none of the BOLD participants used any long-term mood stabilizing medication (lithium, anticonvulsant, antipsychotic, or antidepressant) at the time of assessment. Fifty participants provided their full history of psychotropic medication use. Based on these data, eight (15.4 %) participants never used maintenance medication in the past, of which four (7.7 %) never used any psychotropic medication and four did use sleep medication. The 42 participants that used maintenance medication in the past used these medications for an average duration of 7.9 years (SD 8.7, range 1–43). At the time of assessment, the average time of living without maintenance medication was 12.2 years (SD 7.1, range 5–39 years).

Regarding current medication, prescribed sleep medication was used by DOBi participants more often (44.3 % versus 27.6 %, $p = 0.024$). In

addition, 58.6 % of BOLD participants reported the use of any over the counter medication: 53.4 % used over the counter supplements and 12.1 % used over the counter psychoactive drugs (such as lithium muriaticum, melatonin, valerian, cannabidiol, and microdoses of LSD).

4. Discussion

4.1. Protocol

The main aim of the mixed-methods BOLD study is to describe a clinical phenotype of patients diagnosed with BD who may be able to safely and effectively discontinue maintenance treatment. We were able to include 58 individuals aged 50 years and older diagnosed with BD who did not use any maintenance medication for the past 5 years. All fulfilled DSM-IV-TR criteria for BD based on a clinical interview and confirmed with the MINI-Plus. This refutes the hypothesis that these individuals are able to live without medication because of a misdiagnosis in the past. Further quantitative and qualitative analysis of the BOLD data will investigate whether they possess resilience, specific resources or self-management strategies that could explain how they manage to live with their illness without medication.

4.2. Discussion of preliminary findings

A preliminary comparison of BOLD participants (no maintenance medication) with DOBi participants (on maintenance medication) showed that BOLD participants did not appear to have a milder course of BD. The percentage of BD-I, Bipolarity Index, prevalence of psychiatric comorbidities, number of mood episodes, and prevalence of lifetime psychotic features were all higher in BOLD than in DOBi participants. The percentage of lifetime psychotic features was higher in BOLD, indicating that some have struggled with at least one severe episode accompanied with psychotic symptoms. These data refute the hypothesis that individuals living with BD but without medication have got a milder clinical course and fewer recurrent episodes. The lower number of episodes and lifetime psychotic features in DOBi participants may be an indication of the effectiveness of the prophylactic medication or clinical support. Still, overall episode density was not different between the two groups, indicating that the number of mood episodes was similar throughout the life-span.

The age at onset was younger in BOLD participants. In previous reports, a younger age at onset was associated with a worse clinical course in terms of number of episodes (Geoffroy et al., 2013) and a history of abuse (Etain et al., 2008). Also in our BOLD sample, the lifetime number of mood episodes as well as the number of participants reporting a history of emotional, physical, or sexual abuse during childhood or adolescence were substantially higher than in DOBi. Perhaps, a younger age at onset gives more opportunities to acquire more adaptive coping and adequate self-management strategies and, as a result, a better functioning later in life. We plan to analyse these hypotheses using the qualitative interview data.

The difference in prevalence of childhood trauma between BOLD (81.8 %) and DOBi (48.1 %) was particularly large. Earlier studies in BD outpatients of adult age found prevalences of 61.8 % (Xie et al., 2018) and 36–39 % (Leverich et al., 2002). Childhood trauma and specifically emotional abuse has been associated with high levels of affective instability in BD (Hett et al., 2022). Childhood trauma can serve as a disease-modifier, as it is also associated with a higher number of mood episodes (Leverich et al., 2002). On the other hand, childhood trauma can also be a worthwhile therapeutic target (Hett et al., 2022). Interestingly, many individuals indicated during the screening phone calls that overcoming self-reported traumatic experiences was an explanation for the medication-free survival, a notion that warrants further exploration. Hopefully our qualitative analysis can shed more light on this.

Despite the higher number of mood episodes in the BOLD group, rates of suicide attempts or psychiatric admissions were not elevated, possibly indicating that episodes were milder and better self-manageable. Also, BOLD participants reported fewer current mood symptoms and higher cognitive, social, and global functioning. However, comorbid anxiety disorders were more frequent in BOLD. Several explanations are possible. First, the anxiety symptoms could be a result of the constant stress of recurrence when living without medication. Alternatively, BOLD participants could be able to live without medication due to their 'anxious' traits that enables them to prevent aggravation of mood symptoms on time. Third, the BOLD group of participants could form a special clinical phenotype of BD.

BOLD participants were younger, higher educated and more often employed. These factors may be protective and therefore associated with better outcomes (Anaya et al., 2016). However, we cannot rule out that this is a result of selection bias as white, employed, and higher educated people may have been more likely to find out about the BOLD study and to self-refer (Scanlon et al., 2021).

4.3. Strengths and limitations

Our study set-up bridges the gap between psychiatric research and experience of individuals outside mental health care. For the first time, the BOLD study measures clinical, social, neurocognitive, and physical health characteristics of individuals that until now have been outside the scope of clinicians and therefore underrepresented in medical research.

One limitation is that it is difficult to determine how representative our BOLD sample is for individuals diagnosed with BD living without medication. Although the included participants mostly did not receive psychiatric treatment, we felt the need to confirm their DSM classification with a diagnostic interview and use validated scales to make a clinical comparison with BD patients using medication. Our aim was to include all individuals that were interested, but unfortunately various people told the lived experience researchers in our team (MvE, CN) or the chairman of the patient association for BD (HM) that the study was too much designed by the 'mental health care system'. These individuals did not want to participate because the study included a diagnostic clinical interview for confirmation of the DSM classification, whereas they did not believe in the classification of psychiatric disorders in general or felt they did not suffer from the illness anymore despite a history of (hypo)mania. Another objection to the study was that the (numerous) questionnaires put them off. Some stated they did not believe multiple-choice answers would do justice to their complex, personal life stories. For future research in individuals diagnosed with BD in the past but now living without medication, a diagnostic clinical interview may not be of added value, as all of our BOLD participants fulfilled these inclusion criteria. Such an interview may even be a barrier in understanding this special group and lead to selection-bias. Future studies could perhaps apply a recovery perspective, which advocates person-centred care and does not focus on specific DSM classifications. Another limitation is that our BOLD participants were self-referred for this study from all over the country and probably motivated to share their success story, in contrast to our DOBi sample that was recruited actively from our outpatient clinic. As a result of selection bias, functioning in BOLD participants may have been overestimated.

Another limitation is that the cross-sectional design of the study impedes conclusions on causality. The observed differences between DOBi and BOLD may be a consequence of absence of medication use or a necessary precondition for living with BD without medication. Larger naturalistic follow-up studies with individuals diagnosed with BD living with or without continuing medication are warranted for deeper insight on causality.

Despite therapeutic advantages, disability and poor outcomes for people diagnosed with BD are prevalent and possibly worse than in the pre-medication era (Huxley and Baldessarini, 2007). One hypothesis for the limited functional recovery in BD is that this is induced by psychotropic medication (Zarate Jr. et al., 2000). Therefore, longitudinal studies in medication-free individuals are warranted. Last, the

preliminary statistical analyses reported in this article were descriptive and did not control for potential confounders such as age and education level. The planned future analyses (see method section) will examine differences between BOLD and DOBi per domain (cognition, physical health, social functioning, global functioning, coping and personality) in more depth using all of the collected data and controlling for potential confounders.

4.4. Clinical implications

This study shows that a group of individuals exists that meets diagnostic criteria of BD but is living without medication. These people appear to be relatively successful in terms of psychosocial functioning, although they do not seem to have a milder clinical course than those on maintenance medication. Future studies should further explore psychotherapeutic options to enhance and optimize self-management and coping with mood instability. Next, the insights obtained from our mixed-methods study may change clinical guidelines for BD, improve shared-decision making regarding maintenance therapy, and improve psycho-education courses with novel self-management strategies. Health care providers should inform BD patients that although maintenance medication can be very effective, living without medication may be possible for a select group of individuals with BD. Starting or stopping maintenance medication in BD should always be the result of a shared-decision making process in which advantages and disadvantages are carefully considered.

CRediT authorship contribution statement

Alexandra J.M. Beunders: Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Writing – original draft. **Eline J. Regeer:** Conceptualization, Funding acquisition, Writing – review & editing. **Marieke van Eijkelen:** Conceptualization, Writing – review & editing, Data curation, Methodology. **Henk Mathijssen:** Conceptualization, Writing – review & editing. **Chris Nijboer:** Conceptualization, Writing – review & editing. **Sigfried N.T.M. Schouws:** Conceptualization, Data curation, Funding acquisition, Writing – review & editing. **Patricia van Oppen:** Conceptualization, Writing – review & editing. **Almar A.L. Kok:** Conceptualization, Data curation, Funding acquisition, Writing – review & editing. **Ralph W. Kupka:** Conceptualization, Funding acquisition, Writing – review & editing. **Annemiek Dols:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft.

Declaration of competing interest

None of the authors report a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.12.047.

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