Mindfulness-based Online Intervention to Improve Quality of Life in Late-stage Bipolar Disorder: A Randomized Clinical Trial

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Abstract

Objective

Adjunctive psychological interventions improve outcomes in bipolar disorder (BD), but people in latter stages likely have different clinical needs. The objective here was to test the hypothesis that for people with ≥ 10 episodes of BD, a brief online mindfulness-based intervention (ORBIT 2.0) improves quality of life (QoL) relative to a psychoeducation control.

Method

A rater-masked, pragmatic superiority randomized clinical trial compared ORBIT 2.0 with active control. Both interventions were 5-week coach-supported programs with treatment as usual continued. Inclusion criteria included age 18-65 years, confirmed diagnosis of BD, and history of ≥ 10 episodes. Measures were collected at baseline, post-intervention, and 3- and 6- month follow-ups. The main outcome was QoL, measured on the Brief Quality of Life in Bipolar Disorder (Brief QoL.BD) at 5 weeks, using intention-to-treat analyses.

Results

Amongst $N = 302$ randomized participants, the primary hypothesis was not supported (Treatment X Time $\beta = -0.69$, 95% CI [-2.69, 1.31], $p = 0.50$). The main effect of Time was not significant in either condition, indicating no improvement of either group. Recruitment was feasible, the platform was safe, both interventions were highly acceptable, but usage was suboptimal. *Post hoc* analyses found both interventions effective for participants not in remission from depression at baseline.

Conclusions

In people with late-stage BD, an online mindfulness-based intervention was not superior to psychoeducational control in improving QoL. Online delivery was found to be safe and acceptable. Future interventions may need to be higher intensity, address engagement challenges, and target more symptomatic individuals.

Public health significance statement

The present trial found that a low-intensity coach-supported mindfulness-based intervention (ORBIT 2.0) was not superior to a quality-matched psychoeducation control for improving quality of life in a late-stage bipolar disorder sample. However, both interventions were feasible, acceptable and safe, encouraging further efforts to improve this population's access to novel therapies through the web. Next generation approaches will be adaptive interventions, improving impact via strengthened engagement.

Keywords: bipolar disorder, quality of life, stage of illness, online, mindfulness

Some 50% of people diagnosed with bipolar disorder (BD) can be considered 'late-stage' (defined as a history of at least 10 mood episodes)[1]. This late-stage group carries a disproportionate burden of functional impairment, stigma, chronic depressive symptoms, relapse risk, and significantly impaired quality of life (QoL, Magalhães et al., 2012). Current adjunctive psychological treatments for BD decrease relapse through developing skills such as prodrome identification and medication adherence (Miklowitz et al., 2020), but this approach may be limited in late-stage BD, as relapse is more likely and can be unrelated to life events (Berk et al., 2012). For example, having experienced more than 12 episodes of BD predicts negative response to cognitive behaviour therapy (CBT, Scott et al., 2006).

Tailoring psychosocial intervention for late-stage BD

Inadequate response to treatment in late-stage BD has not been adequately addressed: Medication advice tends to be poorly supported by evidence, and little attention has been paid to stage-tailoring of psychosocial approaches (Berk et al., 2012). Informed by the recovery perspective on serious mental illness (Leamy, Bird, Le Boutillier, Williams, & Slade, 2011), we postulated that the symptom-focussed content of existing psychosocial interventions may be less beneficial in late-stage BD than a therapeutic focus on living well despite symptoms

[1] There is no agreed definition of late-stage, nor is there a consensus cut-point when number of episodes is used as a definition (see, Tremain, Fletcher, & Murray, 2019). The criterion of 10 or more episodes is the most common in the literature (e.g., Magalhães, Dodd, Nierenberg, & Berk, 2012).

(G. Murray et al., 2017). Specifically, we hypothesised that psychosocial intervention targeting QoL via mindfulness-based strategies had untapped potential for people with a poor trajectory of BD (G. Murray et al., 2017).

Mindfulness-based intervention to improve QoL in late-stage BD

The recovery perspective has encouraged research into patient-centered outcomes in mental health (e.g., Malhi et al., 2021). In BD research, the outcome receiving most attention is subjective QoL, understood as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"(WHOQUOL, 1995). The QoL construct represents the person's satisfaction with current circumstances and needs, and (unlike direct measures of the deeply personal recovery process itself) is a feasible nomothetic outcome for use in clinical trials (E. Morton, Michalak, & Murray, 2017). Importantly, patients with BD value subjective QoL as a treatment target (Sajatovic, Jenkins, Cassidy, & Muzina, 2009), and trajectories of QoL and symptom measures diverge over time (E Morton et al., 2015), highlighting the importance of adding QoL to common pathology-based measures of treatment outcome. As an outcome measure, QoL may be particularly relevant to late-stage BD: In other areas of medicine, patients not responding to routine care often receive interventions aimed at improving QoL despite symptoms (Berk et al., 2013).

The humanistic aims of 'third wave' or mindfulness-based interventions (MBIs, e.g., Hayes, Villatte, Levin, & Hildebrandt, 2011) are consistent with the recovery perspective, and the measurement of QoL outcomes. Mindfulness moderates the relationship between unavoidable distressing experiences and mental health outcomes (Bergomi, Strohle,

Michalak, Funke, & Berking, 2013), and is a well-being strategy employed by high functioning people with BD (G. Murray et al., 2011). We have argued that MBIs have potential to support skills that maximise QoL in late-stage BD (G. Murray et al., 2017). For example, the skill of non-judgemental awareness of present experience (as in Mindfulness-Based Cognitive Therapy [MBCT], Segal, Williams, & Teasdale, 2002) may reduce negative and positive rumination, a risk factor for relapse, and a challenge to multiple QoL domains (Deckersbach, Hölzel, Eisner, Lazar, & Nierenberg, 2014). Acceptance of extreme mood states (as contrasted with experiential avoidance) and commitment to behaviours in line with life-enriching personal values (e.g., Acceptance and Commitment Therapy [ACT], Herbert & Forman, 2011), may bolster self-esteem and QoL in a population whose chronic disorder has proven difficult to manage (Berk et al., 2012). Likewise, the ability to access self-compassion in the context of ongoing difficulties and past disappointments (e.g., Compassion-focused Therapy [CFT], Gilbert, 2014) may decrease self-stigma and support QoL. Consistent with these theoretical arguments, MBIs have shown BD-specific and transdiagnostic benefits for anxiety, depression, and QoL (Chu et al., 2018; Hofmann & Gomez, 2017). Both MBCT and ACT have emerging support as adjunctive therapy in severe mental illness populations generally (Xuan et al., 2020).

In close consultation with lived experience experts, our group therefore developed a new MBI designed to improve QoL in late-stage BD (see, G. Murray et al., 2015). The Online Recovery-focused Bipolar Individual Treatment (ORBIT), integrated content from MBCT, ACT and CFT. To circumvent well-recognised barriers to accessing psychosocial treatments worldwide (Leitan, Michalak, Berk, Berk, & Murray, 2015; Sevilla-Llewellyn-

Jones, Santesteban-Echarri, Pryor, McGorry, & Alvarez-Jimenez, 2018), ORBIT was designed as a bespoke online intervention. An open pilot trial found ORBIT to be feasible, safe and effective in improving QoL (G. Murray et al., 2015).

The present trial

We report findings of a pragmatic superiority randomized clinical trial (RCT) with a one-to-one allocation ratio comparing ORBIT 2.0 (a fully featured version of the piloted ORBIT intervention) with an appropriate online comparator (active psychoeducation control with identical user experience features). In both arms, treatment as usual continued throughout.

The primary hypothesis was: Relative to active control, ORBIT 2.0 would significantly improve QoL between baseline and end of treatment (5 weeks). Secondary hypotheses were: (i) QoL difference between groups will maintain over 6 months; (ii) ORBIT 2.0 will be associated with greater improvements in observer- and self-rated depression, and self-rated anxiety, (iii) ORBIT 2.0 will be associated with lower attrition. Because of the trial's innovations in target population (late-stage BD), modality (international online delivery), and user experience approach (lived experience videos), we also explored cross-arm outcomes (feasibility of recruitment, safety, acceptability, usage).

Method

Design

Design was a prospective, parallel group, rater-masked, pragmatic superiority RCT comparing ORBIT 2.0 with a quality-matched online active control condition (Psychoeducation). The trial was conducted by a multidisciplinary team of researchers, clinicians and lived experience experts (E. Michalak et al., 2015); it was prospectively registered on 23 June 2017 through ClinicalTrials.gov (NCT03197974) and the full protocol published (Fletcher, Foley, Thomas, et al., 2018). Swinburne University of Technology Human Research Ethics Committee approved the online trial (2016/289) with international recruitment. Trial objectives and protocol aligned with all aspects of Good Clinical Practice, the WHO Trial Registration Data Set (Version 1.2.1) and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The study setting was online, and participation in both arms occurred through a secure server housed at Swinburne University of Technology, Melbourne, Australia. Findings are reported according to Consolidated Standards of Reporting Trials eHEALTH criteria.

Participants

Inclusion/exclusion criteria were selected to balance the goal of maximising translatability, while minimising the risks of this first ever remote international delivery of a MBI for a late-stage BD population. Inclusion criteria were: Aged 18-65 years; confirmation of Diagnostic and Statistical Manual for Mental Disorders (Fourth edition, DSM-IV,

American Psychiatric Association, 1994)[2] diagnosis of BD (I, II or NOS) on the MINI International Neuropsychiatric Interview (Sheehan et al., 1998); history of 10 or more episodes of mania, hypomania or depression (self-assessment supported by semi-structured interview in the context of MINI phone assessment); under the care of a nominated medical practitioner (at least one contact in the past 12 months); sufficient English to provide informed consent and engage with the intervention; ready access to the internet, adequate internet literacy (assessed via purpose-built questionnaire). Exclusion criteria were: Experiencing a current episode of depression, hypomania or mania on the MINI; currently psychotic or actively suicidal (affirmative to items 3, 4 or 5 on Columbia Suicide Severity Rating Scale, Posner et al., 2011). Participants excluded on the grounds of a current mood episode were offered the option of being recontacted at a later time, and if then eligible were deemed 'delayed entry'. Recruitment was conducted primarily through social media sites and listservs. Participants indicated informed consent prior to baseline assessment by checking an online box.

Randomization

[2] When the protocol was developed, there were concerns that DSM-5's more stringent criteria for hypomanic and manic episodes may have improved diagnostic specificity at the cost of sensitivity (e.g., Machado-Vieira et al., 2017). Consequently, DSM-IV diagnosis was the inclusion criterion here, and we planned to explore the impact on diagnosis of adding the DSM-5 criterion that episodes must contain the symptom of increased activity. Post hoc analyses found that only two of 302 randomized participants (0.66%) did not meet the more stringent DSM-5 criteria, consistent with the position that activity changes are in fact core to the syndromes (Scott et al., 2017); removing these participants from analyses did not impact the pattern of findings.

Participants were sequentially allocated to intervention arms using a one-to-one ratio by predetermined permuted block randomisation (block size = 10); the permutation sequence for allocation within blocks was randomly generated by SAS Version 9.4, overseen by an off-site biostatistician (SJB) and coded into the website so randomisation was automated and free of potential allocation bias.

Intervention content

Coaching support was provided for the 5-week intervention active phase in both conditions. Both interventions were delivered in four modules, with new module content delivered sequentially each week over four weeks. The fifth week was an opportunity to consolidate skill development with the online coach. Participants could return to previous modules across the program at any time. To support ongoing generalisation of skills (and to mirror the planned website to be disseminated pending trial outcomes), participants retained access to the program for the 6-month follow-up (see for discussion of learning management decisions, Fletcher, Foley, & Murray, 2018; Fletcher, Foley, Thomas, et al., 2018; G. Murray et al., 2015).

ORBIT 2.0. Consistent with Mental Health Research Network good practice guidelines and the principles of consumer engagement in clinical research (National Institute for Health Research, 2013), ORBIT 2.0 was developed in partnership with individuals with lived experience of BD (specifically, the CREST.BD community advisory group in Canada (see, E. Michalak et al., 2015)and the ORBIT community advisory group in Australia}. The intervention addressed five overlapping skills drawn from ACT, MBCT and CFT: mindfulness (self-awareness, mindfulness as a tool for emotion regulation), values and

committed action (identifying personal values as a guide to action), acceptance (of negative experiences, contrasted with struggling), self-compassion (cultivating self-compassion in the context of ongoing symptoms and previous disappointments), and defusion (creating distance from unproductive thoughts, emotions and sensations, particularly as it applies to depressive and hypo/manic symptoms). Content across the 5 weeks is summarised in Table 1 (see supplementary Table 1 for more detail).

INSERT TABLE 1 ABOUT HERE

Psychoeducation. Psychoeducation was a meaningful comparator because it is an effective adjunctive treatment for BD (Malhi et al., 2021) and readily translated into web format (Smith et al., 2011). The medical and symptom-based content of Psychoeducation also provides an important contrast to the recovery focus of ORBIT 2.0. Based on an evidence-based face-to-face intervention (Colom, Vieta, & Scott, 2006), the psychoeducational active control condition presented factual information about BD medications and treatments, mood monitoring, recognising triggers and early warning signs, and strategies to stay well. Material was organised into four modules (Bipolar and You, Treatments, Knowing the Signs, and Staying Well), followed by the consolidation of week 5 (see Table 2 and online supplementary Table 2). Online activities included training in, and a digital tool to support daily mood monitoring: Participants were encouraged to visit the site daily to utilise this tool.

INSERT TABLE 2 ABOUT HERE

User experience design

Following best practice in persuasive system design (Kelders, Kok, Ossebaard, & Van Gemert-Pijnen, 2012; Tremain, McEnery, Fletcher, & Murray, 2020), both websites contained features including dialogue support (praise from coach and discussion board moderator, email reminders), social support (social facilitation through discussion threads) and primary task support (best practice principles for modularisation of content, personalisation of progress, self-monitoring, and rehearsal). Video, audio, images, text, and exercises (online and offline) were coherently organised into materials congruent with the known aesthetic preferences of people with BD (see Figure 1 and recruitment video vimeo.com/232425652).

INSERT FIGURE 1 ABOUT HERE

Coaching support improves adherence to web interventions (Malhi et al., 2021), is valued by people BD (Todd, Jones, & Lobban, 2013), and was provided in both conditions. Communication with coaches was asynchronous via email: Participants could send as many emails as they liked to their coach and would receive one response per week. Completed onsite activities could also be shared with the coach for feedback (through one-touch website functionality). Coaches were honors-trained psychology students, currently completing Clinical PhD training. They were supervised by the trial executive group, led by a senior clinical psychologist. In preparation for the coaching role, coaches were paid for 5 days to familiarise themselves with content of the websites. Comprehensive, distinct coaching

manuals were developed for each intervention. Manuals included an explicit description of the role and aims of the coach, risk management flow chart, principles of email communication (based on our previous work training students in this role as part of a federally-funded online psychology clinic), template emails as a starting point for developing responses to each weekly module of the program, FAQs and common concerns (available on request).

Peer support was offered via moderated online forums and the ability for users to connect privately with each other via a secure-messaging system embedded in the website. Forums were designed to develop a sense of online community, and were moderated by trained and clinically supervised consumers with lived experience of BD. Forum moderators also seeded discussion threads with encouraging tips.

Participants could complete modules at their own pace: content within modules was 'chunked' allowing exploration in briefer or longer individual sessions of line engagement, depending on personal preferences. Weekly content commenced with a brief video and exercise introducing the topic, followed by exercises to be completed online and offline. Topics were introduced using interview-style unscripted videos (primarily presented by multiple lived experience experts), supported by text, reflective exercises, and downloadable audio files and handouts. Participants could comment publicly on videos (via comments feed) and share privately-completed exercises with their coach and other users of the website.

Videos on the home page provided an orientation to the site, to the progressive roll out of content, and tips for active engagement. Emails from coaches were also used to support participants' understanding of the progressive content release and the broad aims of each

week's content. Participants were encouraged to log in to the site at least once a week and to progress through the new content as it was delivered. It was recommended that they spend a minimum of 1-2 hours each week on the program to get the most out of participation. Participants were reminded that, while coach support was available for 5 weeks, they retained access to the site during the 6-month follow-up.

Measures

Outcome measures were collected at T0 (baseline), T1 (completion of 5-week intervention), T2 (3 months post-baseline) and T3 (6 months post-baseline). At each time point, assessment entailed phone (e.g., clinician-rated MADRS) and online (e.g., self-report Brief QoL.BD) measures. All randomized participants completed both forms of assessment at baseline, but follow-up completion differed for telephone and online assessment components. To focus on the self-report primary outcome measure, attrition was operationalised on the basis of online measure completion. Clinician-rated assessments were conducted over the phone by trained assessors unaware of treatment allocation and monitored for inter-rater reliability. Self-report assessments were completed online via a secure encrypted online survey platform (Qualtrics). Participants were emailed to arrange a time for phone assessments and to prompt completion of online assessments. The MINI was conducted by phone at baseline to confirm eligibility, establish comorbid diagnoses and record demographic variables. Participants were reimbursed for completing assessments ($25USD Virtual Visa card per assessment), and we aimed to follow and assess all participants regardless of usage to support intention-to-treat analyses (Fletcher, Foley, Thomas, et al., 2018).

All outcome measures were gold standard or best-available psychometrically sound instruments. Primary outcome measure was total score on the 12-item brief version of the disorder-specific self-report Quality of Life in Bipolar Disorder (QoL.BD, Erin E Michalak & Murray, 2010) instrument. The QoL.BD and Brief QoL.BD are validated, widely-used measures of subjective QoL, with established psychometric properties including evidence of sensitivity to change (e.g., E. E. Michalak et al., 2019; Emma Morton, Murray, N.Yatham, Lam, & Michalak, 2021). The Brief QoL.BD, carved from the full 56-item Qol.BD for repeated measures use, covers 12 factor-analytically derived domains (Physical, Sleep, Mood, Cognition, Leisure, Social, Spirituality, Finance, Household, Self-esteem, Independence, and Identity). Items are scored on a 5-point Strongly Disagree - Strongly Agree Likert scale, giving a theoretical range of 12 – 60. In the validation sample, Cronbach's α for the total score was 0.87 (*SD* = 8.76), giving a reliable change of 3.16 points. The Brief QoL.BD has been validated for online use and shown superior sensitivity to change in clinician-rated symptoms compared to commonly used generic QoL measures, including sensitivity to effects of psychological intervention in BD (Emma Morton et al., 2021).

Secondary outcome measures included Montgomery-Asberg Depression Rating Scale (MADRS, Montgomery & Asberg, 1979), an instrument demonstrating high inter-rater reliability (0.89-0.97); the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR, Rush et al., 2003) (internal reliability $\alpha = 0.87$); and the Anxiety scale of the Depression Anxiety Stress Scales (DASS-21, Lovibond & Lovibond, 1993) ($\alpha = 0.87$). Masked assessors were research assistants with at least an undergraduate degree in

psychology or related discipline, trained by an assessment expert (EEM) to standard on the MINI, YMRS, and MADRS.

Attrition was measured as loss to follow-up at T1 (see Figure 2). Safety of the interventions was measured as serious adverse reactions, i.e., serious adverse events (death, suicide attempt, or life-threatening behavior requiring or prolonging hospitalization, persistent or significant disability or incapacity) primarily related to participation in the trial. Occurrence of serious adverse reactions was tracked through adverse event self-reports systematically collected at each follow-up timepoint, and incidentally (e.g., reports from treating clinicians, assessors, coaches or trial staff, forum posts etc.).

Acceptability was measured at T1 via self-report (e.g., 'recommend to others with BD', online supplementary Table 4). Optimal exposure to the program was operationalised as accessing all four content modules ('intended usage'), and usage was further explored in number of modules accessed, number of logins and T1 self-report of satisfaction with engagement.

The trial was assessor-masked, with participants necessarily aware of the treatment they were receiving. Assessors were physically separated from team members aware of allocation, and participants were regularly reminded not to disclose elements of the intervention they were receiving. Assessors were to be replaced if they became aware of participant's allocation before or early in an assessment interview - no instances of this occurred. Analysis of assessors' guesses about treatment allocation found correct estimates at chance-level - 52.3%, 54.1%, and 48.8%, respectively, at T1 (n = 235 assessments), T2 (n = 222) and T3 (n = 211). Participants were necessarily aware of the treatment they received.

Prior to commencing recruitment for the present trial, the positive pilot findings for the ORBIT MBI had been published (G. Murray et al., 2015, see above). To minimise participant expectancy effects here, we therefore re-allocated the label ORBIT to the trial as a whole: Recruitment for the ORBIT trial characterised it as a comparison of two different interventions targeting QoL in late-stage BD, and the two websites to which participants were randomized were both named ORBIT.

Inter-rater reliability across the four assessors was measured on 50 randomly selected assessments at approximately 3-month intervals throughout the trial (approximately 5% of all assessments). Interviewers rated audio recordings of the MADRS and YMRS, with two-way random effects models finding intraclass correlations of 0.93 ($F(49,49) = 26.13$, $p < 0.0001$) and 0.86 respectively ($F(49,49) = 13.20$, $p < 0.0001$).

Risk Minimisation, Monitoring and Management

Risk management procedures were informed by our experience with digital interventions for BD (e.g., Lauder et al., 2013; Leitan et al., 2015; E. E. Michalak et al., 2019; G. Murray et al., 2015; Thomas et al., 2016) and consultation with the community advisory groups. Risk management was explicitly devolved to participants and their local clinical networks. The informed consent statement explained that the nominated medical practitioner or local emergency department remained the participant's first point of contact. Both the pre-registration page and informed consent statement highlighted participants' central role in their own safety and wellbeing, emphasising that the website does not act as an emergency service, and that the website was not monitored in real time. Participants were informed that

their local providers would retain responsibility regarding suicide risk (Fletcher, Foley, Thomas, et al., 2018).

The risk minimisation approach involved inclusion/exclusion criteria, cautions at relevant points of the intervention (e.g., meditation exercises), and provision of on-site links to international emergency resources (e.g., unsuicide.wikispaces.com). To minimise impact of any adverse events, being under the care of a medical practitioner was an inclusion criterion, and participants consented to this professional potentially being contacted by the researchers as part of a 'red flag decision tree' (below).

Adverse events were monitored via questions at post-test and follow-up time points; any adverse events incidentally identified (through forum posts, assessments, or participant contact with coaches, assessors or trial staff) were also logged. Severity of any adverse events, and causal relationship to the trial were assessed through participant self-report and logged. Adverse events were reviewed at monthly executive meetings. Serious adverse events suspected or known to be related to participation in the trial ('serious adverse reactions') were to be reported to Swinburne University of Technology Human Research Ethics Committee. Participants were to be withdrawn if their participation compromised clinical care as determined by the study's executive committee.

Safety monitoring drew on three sources of information: online assessments at each time point, phone assessments at each time point, and incidental participant communications through discussion boards and coach emails. Criteria for action were QIDS Q2 $\geq$ 2 (online assessment); MADRS $\geq$ 15, YMRS $\geq$ 15, MADRS Q10 $\geq$ 4 (phone assessment); red flag content posted on discussion board or in email to coach. Actions to be taken in each case

were mapped on a red flag decision tree (online supplement, Appendix 2). Actionable red flag events noticed by the research staff were triaged to the on-call senior clinician who would then conduct a risk assessment by phone and develop a safety plan. All trial staff were comprehensively trained on protocol procedures.

Statistical Analyses

Sample size was determined by power analysis using G*Power 3, conducted on the primary endpoint of Brief QoL.BD score at T1. Based on our pilot study (intent-to-treat d = 0.52), a between-group effect size of d = 0.4 was conservatively estimated. This small-to-moderate effect size is comparable to effect sizes found for adjunctive CBT on a range of outcomes in BD (Szentagotai & David, 2010), and was considered a clinically important difference given the new intervention is low intensity and high access. A sample size of 200 (100 per group) provides at least 80% power (1-β) to detect a small-moderate effect d = 0.4 at two-tailed α = 0.05. Attrition was conservatively estimated at 33% based on rates in the pilot study and an earlier RCT of an online intervention for BD (Lauder et al., 2013), suggesting 300 randomized participants were required for a final sample of 200.

Statistical analyses were conducted using Stata in accordance with the International Conference on Harmonisation E9 statistical principles; analyses of the primary hypothesis were conducted offsite by [NAME MASKED FOR REVIEW], masked to treatment allocation. Analyses were conducted using mixed effects modelling repeated measures with planned comparisons (Gueorguieva & Krystal, 2004). Treatment effects were estimated using intention-to-treat: In the primary analysis, all randomized participants and available data were analysed. Four sensitivity analyses were conducted, (i) Complete case analysis used only

cases with all relevant assessments; (ii) Single imputation intention-to-treat analysis replaced missing data points with the last valid value (last value carried forward, LVCF), (iii) Multiple imputation intention-to-treat analysis using the chained equations method (scores imputed using 50 resamples, imputing from baseline variables age, gender, diagnosis, number of episodes, depression symptoms, country of residence and delayed entry into the trial), (iv) Per protocol analysis was restricted to participants who completed all relevant assessments and who used the intervention as intended (accessed all four modules). To investigate QoL outcomes across the full 6 months, mixed model analyses using T0, T1, T2 and T3 scores were undertaken (using linear growth model and planned pairwise comparisons). The analytic approach to the primary outcome was replicated for QIDS-SR, MADRS and DASS-21 Anxiety scale at immediate post-test and across 3- and 6-month follow-up; drop-out prediction was analysed at 5-weeks only.

Results

Feasibility and Participant Flow

Recruitment commenced 19th September 2017, randomisation target was reached 28th November 2018 (N = 302 randomized), and follow-up data collection completed 6th July 2019. Figure 2 shows participant flow from registration. There were no protocol violations.

INSERT FIGURE 2 ABOUT HERE

Descriptive Findings

With the exception of a trend for elevated MADRS scores in the Psychoeducation arm, $t(300) = 7.12$, $p = 0.05$), groups did not differ significantly at baseline (Table 3). In both groups BD I was the modal diagnosis, and female gender predominated (as found in other BD trials). By design, average number of episodes was high, participants had a long history of BD, and rapid cycling was relatively common. Past suicide attempts were also reported frequently. Currently, however, mean MADRS and YMRS scores were in the remission range, and self-reported baseline anxiety was in the mild range relative to community samples.

INSERT TABLE 3 ABOUT HERE

Across the > 150 person years of the trial, six serious adverse events were recorded - four participants were hospitalised once, and one participant was hospitalised twice; none of these events were attributed primarily to trial participation (one serious adverse event was

described as partly attributable to participation, see online supplement Appendix 4). Three red flags for risk arose: in each case, the participant was telephoned by the on-call clinician, their safety confirmed, and a serious adverse event ruled out.

Both interventions were highly acceptable. In response to single-item feedback questions at T1, Agree or Strongly Agree were modal responses to, 'recommend to others with BD' (95.8%, 87.8% Agree/Strongly Agree for ORBIT 2.0 and Psychoeducation respectively), 'feel more positive and hopeful about managing BD' (77.1%, 70.1%), 'taught skills that will help with future problems' (81.4%, 69.1%), 'kept interest and attention' (79.0%, 73.2%). A single item question at T1 found both arms were associated with subjective improvement in QoL ('minor improvement' the modal response). Trends for greater acceptability in the ORBIT 2.0 condition were not significant (see online supplementary Table 4).

Usage data showed non-optimal exposure to both interventions. Across both groups, only 41.7% (n = 126 participants) accessed all four modules (intended usage), and only a minority (n = 61, 25.3%) reported engaging with the program as much as they would have liked. A free text question found that barriers to engagement were similar across groups (principally lifestyle and illness factors). Unexpectedly, participants in Psychoeducation more commonly engaged with the program as intended (n = 79 [52.7%], *cf.* n = 47 [30.9%] in ORBIT 2.0, $\chi^2(1) = 14.68$ $p < .001$), accessed more modules (M = 2.99, SD = 1.29 *cf.* M = 2.45, SD = 1.34 in ORBIT 2.0, $F(1,300) = 12.75$, $p < .001$) and logged in more frequently (M = 19.78, SD = 19.61 *cf.* M = 14.07, SD = 12.37 in ORBIT 2.0, $F(1,300) = 9.19$, $p < .001$). Similarly, self-report of 'having been able to engage as much as you would like' was higher

in Psychoeducation (n = 41 [33.3%], *cf.* n = 20 [16.9%] in ORBIT 2.0, $\chi^2(1) = 8.55$, p = .003).

Hypothesis Testing

Baseline Brief QoL.BD scores (Table 4) were comparable to those found in our pilot study and published cohort studies (Emma Morton et al., 2021). Loss to follow-up at 5 weeks (17.9%) was lower than expected, and (as tested by χ^2 and t-test) unrelated to any of the baseline variables shown in Table 3. Contrary to hypothesis, attrition at T1 was similar across arms (20.4% ORBIT 2.0 versus 15.3% Psychoeducation, $\chi^2(1) = 1.32$, $p > .05$).

INSERT TABLE 4 ABOUT HERE

As shown in Tables 4, 5 and Figure 3, no support was found (in primary or sensitivity analyses) for the hypothesised superiority of ORBIT 2.0 over Psychoeducation at immediate post-test for the primary outcome. There was also no support for the prediction that ORBIT 2.0 would be associated with increased QoL relative to Psychoeducation when analysed across all four time points (Treatment X Time observed data β = -0.15*,* 95% CI [-0.85,0.55], p = 0.67; see online supplementary Table 9, online supplementary Figure 6). Data in Table 5 also show that the main effect of Time was not significant. Analysed separately, neither intervention was associated with significant QoL.BD change (ORBIT 2.0: M = 0.10, SD = 8.20, *d.f.* = 120, p = 0.89; Psychoeducation: M = 0.47, SD = 8.43, *d.f.* = 126, p = 0.53).

INSERT TABLE 5 ABOUT HERE

INSERT FIGURE 3 ABOUT HERE

Analyses of secondary outcomes found no support for the predicted benefits of ORBIT 2.0 over Psychoeducation for MADRS (Treatment X Time observed data $\beta = 2.42$, 95% CI [0.34, 4.51], $p = 0.02$[3]), QIDS-SR ($\beta = 0.42$, 95% CI [0.71,1.55], $p = 0.46$) or DASS-21 Anxiety at 5 weeks ($\beta = -0.05$, 95% CI [-0.70,0.59], $p = 0.87$; see online supplementary Tables 6-8, online supplementary Figures 3-5). Nor were benefits seen in secondary outcomes across the full 6 months of the trial (for MADRS, QIDS-SR, DASS-21 Anxiety, respectively, Treatment X Time observed data: $\beta = 0.21$, 95% CI [-0.46, 0.88], $p = 0.54$; $\beta = 0.03$, 95% CI [-0.38,0.43], $p = 0.90$; $\beta = 0.11$, 95% CI [0.71,1.55], $p = 0.36$; see online supplementary Tables 10-12, online supplementary Figures 7-9).

INSERT FIGURE 4 ABOUT HERE

Interaction with Depression Remission at Baseline

[3] This unexpected benefit of Psychoeducation over ORBIT 2.0 on MADRS (observed data T0-T1) was not replicated in sensitivity analyses, or across follow-up (T0-T3), and may reflect Type I error in the context of multiple testing (see online supplement Appendix 6).

Motivated by evidence for the sample being relatively well at baseline (Table 3), *post hoc* analyses investigated baseline MADRS remission status (remitted MADRS < 10, not remitted MADRS ≥ 10, see Hawley, Gale, Sivakumaran, & Hertfordshire Neuroscience Research, 2002) as a categorical moderator of treatment outcome. Figure 4 demonstrates a robust moderation effect, which was statistically significant at each time point (β = 12.1, 9.48-14.72, $p < 0.00001$, see online supplementary Table 13). For those participants not in remission from depression at baseline (n = 100) both treatments were associated with robust QoL improvements that were maintained across follow-up; for those in remission (n = 202), Time was not significant in either condition (online supplementary Table 14). The same pattern was found when baseline MADRS was investigated as a dimensional moderator of outcome: greater improvement in QoL.BD scores was strongly associated with higher MADRS at baseline, $F(30, 217) = 3.07$, $p < .001$. Treatment group did not impact the moderation effect.

Discussion

The results of this pragmatic superiority RCT did not support the hypothesis that, amongst people with a long history of BD, a low-intensity coach-supported online MBI (ORBIT 2.0) is superior to a quality-matched active control (Psychoeducation) in improving QoL at immediate post-intervention, or across 6-month follow-up. Similarly, relative to Psychoeducation, there was no support for predicted benefits of ORBIT 2.0 for depression (self- or clinician-rated) or self-rated anxiety. The null finding was not due to failure of the ORBIT 2.0 intervention to separate from an effective control condition – neither intervention generated statistically significant improvements on QoL or the secondary outcomes. Recruiting a late-stage sample was feasible, and attrition was lower than expected in both conditions. No safety concerns were identified, and self-report measures of acceptability suggested both interventions were highly valued. However, most participants reported that they did not use the intervention as much as they would have liked. *Post hoc* analyses suggested that both interventions generated sustained benefits in QoL amongst individuals symptomatic at baseline. Findings have implications for the content, form, and target of future psychosocial treatments for late-stage BD.

Intervention Content

To our knowledge, this is the first large-scale RCT to deliver MBI in an online format for BD. A recent systematic review and meta-analysis of in-person MBCT for BD irrespective of stage (7 non-RCTs, 3 RCTs with treatment-as-usual controls, aggregate N = 240) found some evidence of benefit for depression and anxiety symptoms (Xuan et al., 2020). However, interventions reviewed by Xuan et al were not low intensity (typically c.20 hours face-to-face). The disappointing findings for the ORBIT 2.0 here suggest that more

intensive packages of treatment will need to be developed to deliver these subtle offerings online (with consequent challenges to engagement, see below)

Objective and subjective measures of usage favoured Psychoeducation, and contrary to prediction, attrition was not lower in the ORBIT 2.0 arm. These findings suggest that, contrary to our rationale for stage-tailored recovery-focused intervention (above), psychoeducation remains valued in a sample with more than 20 years' experience of BD. Most participants experienced a new diagnosable episode during follow-up (ORBIT 2.0: 56.5%, Psychoeducation: 60.3%), so psychoeducation content (focused on relapse prevention) may remain an important component of treatment in late-stage BD.

On the other hand, a non-significant trend for greater acceptability of ORBIT 2.0 versus Psychoeducation suggests that personal recovery is also valued in this population. Much remains unknown about staging in BD (Tremain, Fletcher, et al., 2020), and the present findings suggest that the assumption of discrete stages with distinct needs may be an oversimplification. Equally, the data here - including remarkably similar impact of interventions with non-overlapping content (see Figure 3) - do not support a dichotomy between recovery-focused and clinically-focused treatments. Future online interventions may usefully combine 'third wave' with relapse-focused content to comprehensively address the needs of the late-stage population.

Effectiveness of Digital Intervention

The present findings contribute to a mixed picture for digital approaches to BD. In the only other adequately powered RCT, it was predicted that a full intervention combining online forum, psychoeducation and CBT tools would be superior to online forum plus psychoeducation, and forum-only control (Gliddon et al., 2019). Neither active condition

improved hypo/manic symptoms relative to control and, surprisingly, depression symptoms relative to control improved with online forum + psychoeducation but not with the fully featured intervention. The authors note challenges with engagement and present analyses showing engagement was positively associated with baseline depression scores (see below).

Present findings suggest three strategies to strengthen engagement with online treatment. Firstly, while acceptability findings suggest that the present attention to user experience (e.g., novel lived experience videos) was effective, suboptimal usage remains a challenge. Gamification and SMS prompts show promise to improve 'stickiness', as does explicit confrontation of the engagement challenge prior to presenting treatment content (Batterham et al., 2019). Engagement facilitation interventions use information (e.g., evidence about 'you get out what you put in') and motivational interviewing techniques ('what benefits would you like to see') to pre-empt low usage.

Secondly, *post hoc* analyses found baseline depression to be a robust moderator of outcomes. Participants with subsyndromal depressive symptoms showed large, sustained QoL improvement irrespective of allocation, while those in remission showed no change with time. These data suggest that future digital interventions for BD should select for moderate depressive symptoms at baseline to maximise effectiveness, potentially via deepened engagement with therapy content (Gliddon et al., 2019).

Finally, the email-based coaching approach used in both arms here was perceived less positively (rated positively by about half the participants) than other intervention elements. In line with the supportive accountability framework (Mohr, Cuijpers, & Lehman, 2011), coaching may be more effective if delivered synchronously via telehealth, and if coaches were perceived as more expert in BD (e.g., lived experience peers).

The interventions tested here were of brief duration and low intensity. In the late-stage BD population, remote digital delivery alone may be insufficient for behaviour change (especially if content/duration were to be increased as suggested above), and more intensive intervention models (e.g., blended face-to-face + internet treatments, Andersson, Titov, Dear, Rozental, & Carlbring, 2019) warrant investigation. Future research should also investigate whether lower intensity digital treatments like those tested here are beneficial for people in earlier stages of BD (G Murray, 2019). Stepped care approaches to BD are yet to receive systematic attention: the present findings may contribute to a research agenda.

Targeting Quality of Life

A recent review of treatment studies with QoL.BD as an outcome concluded that statistically significant improvement is rarely found (Emma Morton et al., 2021), and earlier research suggested that QoL change may be delayed relative to improvements in symptoms (G. Murray & Michalak, 2007). Research in other chronic illnesses suggests that QoL improvement is difficult, but can be supported by encouraging patients to first identify a specific condition-related issue upon which to focus behaviour change efforts (Anderson & Ozakinci, 2018). Here, suboptimal usage may be partly due to the interventions' abstract goal of generic QoL improvement. Future digital intervention could readily accommodate individual tailoring of QoL targets (G. Murray & Michalak, 2012): An adaptive digital intervention would personalise content to an individual's identification of sleep, for example, as a QoL domain warranting their immediate attention.

Limitations

Three limitations should be noted. First, in the absence of a treatment-as-usual control group, we cannot exclude the possibility that both treatments were protective against QoL

decline in this treatment-resistant sample. The decision to use a quality-matched comparator was driven by concerns that psychological treatment effects have been exaggerated by comparison with weak or nocebo controls (Cuijpers, 2017), and a three-arm trial was not feasible. Second, a consequence of the multiple innovations of ORBIT 2.0 (recovery-informed approach to therapeutic content and outcome measurement, low intensity online delivery, novel user experience features) is that the null findings are difficult to definitely explain and therefore address in future studies. Finally, on risk minimisation grounds for this first international trial, we excluded individuals who met criteria for any BD episode at baseline. This exclusion criterion limited the generalisability of findings, and possibly decreased our capacity to measure QoL benefit from the intervention as symptoms and episodes re-emerged with normative variability across follow-up.

Conclusions

Our primary hypothesis was not supported: compared to an active Psychoeducation control (theorised to be less relevant to the late-stage population), ORBIT 2.0 was not beneficial for primary or secondary outcomes across post-treatment or six-month follow-ups. However, online intervention for people in late-stage BD was found to be feasible, safe, and acceptable, encouraging further work. *Post hoc* analyses suggested that QoL-focused digital interventions should target more symptomatic individuals. Future digital interventions should combine symptom- and QoL-focused content. To maintain engagement with a higher intensity online intervention, known engagement barriers should be proactively addressed, and personalisation of QoL targets supported via adaptive intervention design.

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Table 1: Content of ORBIT 2.0

Module	Content	Knowledge/skill development focus
1	Mindfulness	Rationale for mindfulness
		Types of mindfulness
		Developing a mindfulness practice
		Offline practice
2	Living meaningfully	Values as a guide to action: explanation and rationale
		How to use values to build a more meaningful life
		Integrating mindfulness into everyday life
		Offline practice
3	Self-compassion	Self-compassion: explanation and rationale
		Applying self-compassion in everyday life
		Making space for difficult experiences (flexibility, decreasing experiential avoidance)
		Progressing mindfulness skills through longer practices
		Offline practice
4	Navigating bipolar symptoms	Navigating depression: identifying ‘sticky’ thoughts
		Unhooking from sticky thoughts using mindfulness
		Adopting values-driven action in the face of depression

	Navigating hypomania and mania: identifying manicogenic thoughts and energetic states Ambivalence about unhooking from elevated states, and values as a basis for action choices Mindfulness and bipolar symptoms – returning to mindfulness in challenging times Maintaining mindfulness as a long-term exercise Offline practice: emotion-focused meditation
Week 5	Consolidation of content with online coach

Table 2: Content of Psychoeducation

Module	Content	Knowledge/skill development focus
1	Bipolar and you	What is bipolar disorder?
		Your experience of bipolar disorder
		Offline practice
2	Treatments	Medical treatments for bipolar disorder
		Other treatments
		Offline practice
3	Knowing the signs	Triggers
		Early warning signs
		Implementation
		Offline practice
4	Staying well	Taking action early
		Crisis plans
		Healthy habits
		Offline practice
Week 5	Consolidation of content with online coach	

Table 3. Baseline characteristics of 302 participants randomized at baseline

	ORBIT 2.0 (*n* = 152)	**Psychoeducation (*n* = 150)**
Age *M* (*SD*)	44.5 (10.9)	44.6 (12.4)
Female, No. (%)	105 (69)	108 (72)
Country of residence, No. (%)		
Australia	41 (27)	32 (21)
Canada	21 (14)	20 (13)
UK	27 (18)	21 (14)
USA	54 (36)	62 (41)
Other	9 (6)	15 (10)
Bipolar disorder diagnosis		
BD-I	125 (82)	117 (78)
BD-II	23 (15)	31 (21)
BD NOS	4 (3)	2 (1)
Clinical characteristics		
Number of episodes (*M*, *SD*)	88.9 (150.9)	97.8 (175.6)
Years since first hypo/manic episode (*M*, *SD*)	24.1 (11.7)	23.6 (12.7)

	ORBIT 2.0 (*n* = 152)	**Psychoeducation (*n* = 150)**
Rapid cycling (past 12 months), No. (%)	75 (49)	84 (56)
Family history of BD, No. (%)	80 (53)	86 (57)
Past suicide attempt, No. (%)	91 (60)	80 (53)
Current alcohol use disorder, No. (%)	10 (7)	9 (6)
Current substance use disorder, No. (%)	12 (8)	14 (9)
DASS-21 Anxiety (*M*, *SD*)	4.0 (3.4)	4.4 (3.8)
MADRS (*M*, *SD*)	7.4 (6.3)	9.0 (8.1)
YMRS (*M*, *SD*)	2.7 (3.7)	3.2 (3.8)
Delayed due to current mood episode, No. (%)	16 (11)	16 (11)

Abbreviations: DASS-21 Anxiety = Anxiety scale score of the Depression, Anxiety, Stress Scales; MADRS = Montgomery-Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale

Table 4. Brief QoL.BD score and sample size across timepoints

Timepoint	**ORBIT 2.0**		**Psychoeducation**	
	n	Brief QoL.BD *M* (*SD*)	*n*	Brief QoL.BD *M* (*SD*)
Baseline	152	40.24 (7.98)	150	39.23 (9.15)
5-week	121	40.36 (8.53)	127	40.36 (7.75)
3-month	113	40.57 (8.91)	125	40.24 (8.26)
6-month	114	41.67 (8.86)	118	41.04 (9.08)

Table 5. Results of mixed effect modelling across two waves (T0 – T1) with outcome of Brief QoL.BD

	ITT Observed data			**Complete case**			**ITT LVCF (single imputation)**			**ITT (multiple imputation)**			**Per protocol**		
	β	95% *CI*	*p*	*β*	95% *CI*	*p*	*β*	95% *CI*	*p*	*β*	95% *CI*	*p*	*β*	95% *CI*	*p*
Treatment [a]	1.02	-0.86, 2.89	0.29	0.37	-1.75, 2.48	0.73	1.02	-0.85, 2.88	0.28	-1.02	-0.89, 2.92	0.30	2.53	-0.61, 5.68	0.11
Time [b]	0.80	-0.61, 2.20	0.27	0.47	-0.97, 1.91	0.52	0.40	-0.80, 1.60	0.51	0.68	-0.74, 2.11	0.35	1.00	-0.91, 2.91	0.31
Treatment X Time	-0.69	-2.69, 1.31	0.50	-0.37	-2.44, 1.69	0.72	-0.32	-2.02, 1.37	0.71	-0.82	-2.86, 1.21	0.43	0.24	-2.86, 3.34	0.88
Constant	39.23	37.89, 40.56	<0.001	39.89	38.41, 41.37	<0.001	39.23	37.91, 40.55	<0.001	39.23	37.87, 40.58	<0.001	38.05	36.11, 39.99	<0.001

ITT = intention-to-treat, LVCF = last value carried forward

[a] Treatment reference = Psychoeducation

[b] Time reference = T0

Figure headings

Figure 1. User experience features of both websites

Figure 2. Consort diagram

Figure 2 caption: [a] Completed both phone and online components of assessment; [b] Includes loss to follow-up at any stage. Figure note 1: *N* = 32 ineligible/unknown: 3 excluded before interview because age > 65, remaining 29 did not meet inclusion criteria at assessment. Of these 29, 3 failed to complete baseline assessment (1 withdrawal, 2 could not be recontacted to complete assessment); 11 likely schizoaffective diagnosis; 3 did not meet criteria for BD; 4 < 10 episodes; 1 reduced capacity for consent; 3 language barrier; 1 no current medical practitioner; 3 whose participation was discouraged by their clinician. Figure note 2: *N* = 40 eligible but not randomised: 25 lost after delay; 5 did not complete online questionnaires; 1 withdrew prior to randomisation; 2 withdrew after delay; 6 could not be scheduled after delay; 1 did not finish baseline. Note 2: The *n* analysed in each condition is not a single figure, because it varies by analysis.

Figure 3. Brief QoL.BD change by treatment group at immediate post-test (observed data).

Figure 4. Brief QoL.BD change by treatment group and MADRS remission status at baseline (observed data).