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Mixed Methods Thematic Analysis of a Randomised Controlled Trial of Adjunctive Mitochondrial Agents for Bipolar Depression

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Objective: There is often a shortfall in recovery following treatment for an episode of bipolar disorder (BD). Exploration of participant's experience provides vital information to enhance statistical outcomes for novel therapy trials. This study used mixed-methods to explore participants' experience of a trial testing *N*-acetyl cysteine (NAC) and mitochondrially active nutraceuticals for BD depression.
Methods: Case report forms from a randomised controlled trial (RCT) of BD depression (n = 148) were analysed using a pragmatic adaption of grounded theory and thematic analysis.
Results: Thematic analysis of 148 study participants indicated numerous changes in participant experience over time. For example, perceived environmental stressors reported by participants decreased over the trial in both treatment groups. Quantitative analysis of the themes revealed more positive theme reports in the combination treatment arm compared to the placebo arm and there were more negative themes identified in the placebo arm, compared to the NAC arm.
Conclusion: This approach revealed additional results not elucidated in the primary quantitative analysis. This emphasises the value of mixed-methods research in capturing participants' experiences in RCTs and detecting possible latent benefits and risks. Such methods can detect latent target signals in novel therapy trials conducted in BD and generate novel hypotheses.

KEY WORDS: Bipolar disorder; Qualitative research; Mental disorders; Acetylcysteine; Neurosciences.

INTRODUCTION

Bipolar disorder (BD) is characterised by a fluctuation of mood states, ranging from depression through euthymia to hypomania or mania [1]. When symptomatic, those with BD spend up to 9% of their time in either the hypomanic or manic phase and up to 50% of their time in the depressed phase [2,3]. This discrepancy between time spent in the depressed state and hypomanic or manic states is further exacerbated by the poor efficacy of medications available to treat the depressed state [4-7]. Furthermore, there is a lack of development of new agents for depression by pharmaceutical companies, and many newer agents are merely analogues of off-patent agents [8].

There is an increase in placebo response rates in psychiatric clinical trials, and consequently, many novel agents have failed to show primary efficacy on quantitative rating scales [9]. However, secondary outcomes (including qualitative analysis) may provide rich in-

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formation on particular subgroups or symptoms that improved, not captured by the primary quantitative rating scales. Of note, psychiatric research still largely relies on quantitative data, despite its origins in the observational and qualitative work completed by Goffman in 1961 [10,11]. However, Whitley and Crawford [12] emphasise that qualitative research in psychiatric studies can offer insights into the diagnosis, prevention, treatment and management of disorders, by facilitating a deeper understanding of psychiatric conditions.

Qualitative methodologies and mixed-methods research designs have previously been implemented in clinical trials for schizophrenia [13] and autism [14]. These studies unearthed unexpected findings that had not been captured in the quantitative outcomes that went on to be validated by subsequent studies. A notable example can be seen in the mixed-methods study of the amino acid *N*-acetyl cysteine (NAC) in autism in children (n = 85) [14] with the NAC group qualitatively reporting decreased aggression and agitation, with improved calmness and verbal communications in comparison to the placebo group, a finding later validated by meta-analysis [14,15]. This approach closely aligns with the patient-centred treatment focus that has recently been adopted in the field of psychiatry [16].

A recent RCT has explored adjunctive NAC alone and in a combination treatment (CT) with additional nutraceutical agents targeting mitochondrial biogenesis [9] (compared to placebo) for bipolar depression. The primary trial [9] found no significant difference between either the NAC-alone or the CT group and placebo at the end of 16 weeks of treatment on the primary Montgomery Åsberg Rating Scale (MADRS) scores. However, when exploring the post-treatment discontinuation data (week 20) greater improvements over time were seen in the CT group compared to the placebo group on a number of mood and functioning scales, including the in MADRS $p < 0.031$, other symptom measures, functioning and quality of life.

The current study investigated the potential effects of two adjunctive therapies on bipolar depression by exploring qualitative data in case notes from a double-blind randomised controlled trial using previously validated mixed methods [9].

METHODS

Study Overview

The current study used the source documents from a 16-week, multi-site, double-blind RCT investigating the effects of mitochondrial agents NAC and nutraceuticals on participants with bipolar depression [9]. A mixed-methods qualitative approach was employed using a pragmatic combination of thematic analysis and grounded theory. This study received Deakin University ethics approval (reference number: 2012-138) and Barwon Health Human Research Ethics Committee approval (reference number 11/10).

The detailed methodology for the overarching trial have been published elsewhere (www.anzctr.org.au; identifier: ACTRN12612000830897) [17,18]. In brief, the RCT included three trial sites Melbourne, Geelong and Sydney in Australia. Inclusion criteria included meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV) [19] criteria for bipolar disorder I, II or not otherwise specified and had a current acute depressive episode with a MADRS score > 20 [20]. All participants provided written informed consent before enrolment.

The participants were randomly assigned to treatment with NAC 2,000 mg, the CT or the placebo (study medications and placebos were supplied by Nutrition Care, Victoria Australia, BioCeuticals, New South Wales Australia and Catalent, Victoria Australia). The CT comprised NAC 2,000 mg, acetyl L-carnitine 1,000 mg, ubiquinone 200 mg, magnesium (as orotate 500 mg) 64 mg, calcium ascorbate dehydrate (equiv ascorbic acid 200 mg) 242 mg, cholecalciferol (equiv vitamin D3 250 IU) 12.5 μg, α-tocopherol (equiv natural vitamin E 50 IU) 60 IU, alpha-lipoic acid 150 mg, retinyl palmitate (equiv vitamin A 3,000 IU) 900 μg REIU, and vitamin B co-factors: biotin (vitamin H) (600 μg), thiamin hydrochloride (100 mg), riboflavin (100 mg), nicotinamide (200 mg), calcium pantothenate (100 mg), pyridoxine hydrochloride (100 mg), folic acid (800 μg), and cyanocobalamin (800 μg). The trial treatment was adjunct to the participants' usual treatment medications. The participants were assessed at baseline, 2 weeks, then every 4 weeks until the trial concluded at week 20 (four-week washout point). A total of six qualitative interviews were conducted. Participants included in the analysis had attended at least one post-baseline

interview.

Data Collection

In addition to the data collected using validated rating scales, detailed qualitative notes of participants' verbal descriptions and researchers' observations of the participants' affect were recorded in the trial source documents.

At each assessment, participants were initially asked one question, "How have you been feeling since I last saw you?" and then minimal open-ended prompting was used to help initiate conversation if needed such as "Can you describe what you mean by feeling flat?" Participants were also asked about their experience of health generally, while on the trial. The question asked was, "Do you have any specific worries or complaints about your health in general?"

The research source documents included researcher notes made both during and immediately after the interviews and contained the questions mentioned as well as any other comments noted by the researcher. Observations of the participant's behaviour, affect, and any change or persistence of symptoms was also noted. Transcripts were not returned to participants for comments or correction. A total of eight researchers conducted comprehensive research assessment interviews. The interviewers had extensive multi-step training and certification processes regarding the interview process and were given instructions regarding the qualitative question and to prompt with open-ended questions if necessary [18].

Thematic Analysis

The qualitative data points were entered into NVivo 12 [21]. Before data analysis and coding commencement, some *a priori* deductive themes were also developed based on the DSM-IV diagnostic criteria for BD [19]. These themes were chosen on an *a priori* basis to ensure any changes in BD symptomology were identified and formed the basis of the thematic analysis.

A pragmatic approach guided by principles from grounded theory and thematic analysis was used to analyse qualitative data. This was specifically based on the workings of Miles and Huberman [22], Miles *et al.* [23] and Saldaña [24] as per the protocol [13]. Adapted grounded theory techniques were used with inductive theme creation, as numerous combing/coding cycles were conducted, and reflective, analytical memos were created to help identify themes emerging from the data [23]. For example, mentions of Mood and Medications were a frequent and important topic among many of the participants' statements, subsequently becoming major themes. Additionally, this study included themes less frequently mentioned but were emerging and relevant to the research, such as Exercise.

The dataset was combed a total of four times until data and theme saturation was reached. Systematic coding began when no further themes emerged from the data, and it was initially completed by one investigator. The coding consisted of placing the participant's sentences into appropriate themes and sub-themes using NVivo 12. For example, the participant's response "I feel so much more energised" would be placed into the theme of Energy under the sub-theme of increased.

Rigour

To counteract any biases, both coding investigators were blinded to treatment group allocation throughout the analysis, making this a double-blind qualitative analysis. Additionally, analyst triangulation or 'code checking' was conducted by a secondary investigator on 33% of the primary investigators' dataset, specifically week 20. A total of 26 themes were compared: some themes were expanded where appropriate and comprehensively discussed with the first investigator to ensure similar interpretations.

A high degree of reliability was found between the secondary and primary investigators' codes. Utilizing SPSS version 25 software (IBM Co., Armonk, NY, USA) [25], the average intraclass correlation coefficient was 0.924 with a 95% confidence interval from 0.880 to 0.952 ($F[19,19] = 13.449$, $p < 0.001$). Overall, the similarities between total theme frequency were 92%. Similarity of 80% agreement or above between coders is accepted as a sufficient agreement [24]. Therefore, this code check confirms the rigour and confirmability of the findings by the first investigator. Additionally, codes were checked and reviewed for appropriateness and accuracy by three senior researchers with content expertise.

Frequency Matrix Analysis

Upon completion of the qualitative analysis, the data was transformed into a frequency matrix for exploratory quantitative analysis. Appropriate individual themes were

Table 1. Descriptive statistics of illness and demographic features for all participants

Characteristics	Participants (n = 148)
Age	46.5 ± 12.3
Sex (female)	96 (64.9)
Age of first symptoms	19.3 ± 9.3
Age of diagnosis	35.4 ± 11.4
Duration of illness (in years)	25.3 ± 11.8
Duration since diagnosis (in years)	10.1 ± 8.3

Values are presented as mean ± standard deviation or number (%).

collapsed into two overarching themes, Positive Themes and Negative Themes. Positive themes included improvements in mood, symptoms and functioning and negative themes included a worsened or maintenance of negative moods, symptoms and functioning. Quantitative data analysis was conducted using SPSS version 25 (IBM Co.) [25]. Non-parametric Mann−Whitney *U* tests were conducted between two treatment groups (Placebo−NAC, Placebo−CT), for both Positive Themes and Negative Themes, at week 20. Participants were linked whilst maintaining blinding to their treatment groups by a senior researcher and once data analysis was completed, the researcher was unblinded to the treatment groups.

RESULTS

Participant Characteristics

A total of 679 participants were screened for eligibility in the overarching trial. Of these, 181 met criteria for inclusion and were enrolled in the study: 61 participants were randomly assigned to the CT group, 59 to NAC alone and 61 to placebo. Data from 148 participants who had post-baseline data at either Week 16 or Week 20 were included in the current analyses. Characteristic means and standard deviations of the final sample can be seen in Table 1.

Qualitative Results

Four major themes were identified. The first two were the *a priori* deductive themes of Hypomanic or Manic episode and Depressive episode, including the symptoms of BD (see Table 2). The two inductively derived major themes were Mood which related to the mood states experienced by the participants, (this theme differs from the mood episodes experienced in BD as it does not align with any symptoms outlined by the DSM-IV criteria but still pertains to the mood of the participant) and Environmental factors which addressed the participant's perceived protective factors and stressors throughout the trial. Table 2 displays the 24 inductive (emergent) themes that were utilised during NVivo coding. Detailed extracts of participant quotes across 7 themes (including 3 major themes) are displayed in Table 3.

Table 2. The two *a priori* deductive themes and its sub-themes as derived from the DSM-IV criteria, and the emergent inductive themes

A-priori deductive themes	Emergent inductive themes
Hypomanic or manic episode	Anxiety
Increased goal directed activities	Appetite
Decreased need for sleep	Cigarette use
Distractibility	Cognitive functioning
Elevation	Employment
Flight of ideas	Energy
Grandiosity	Enjoyment
Irritability	Environmental factors
Pressured speech	Exercise
Psychosis	Functioning
Delusions	Hostility
Hallucination	Insight
Risky behaviours	Investigational product responses
	Medications
Depressive episode	Mood
Fatigue/loss of energy	Motivation
Guilt/worthlessness	Other psychiatric symptoms
Insomnia or hypersomnia	Outlook on life
Issues concentrating or thinking	Physical health
Lack of interest or pleasure	Reflux present
Psychomotor agitation	Sleeping issues
Recurrent thoughts of death	Social relationship functioning
Depressed/sadness	Substance use
	Suicidality

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition.

A concept map of the major and select minor themes' code trees are presented in Figure 1, displaying both the themes and sub-themes. Minor themes Medications, Functioning and Outlook on life are displayed as notable themes due to their frequency and importance in the participant discussion through-out the trial.

Quantitative Results

The quantitative analysis of the frequencies of positive and negative themes between treatment groups at the end of trial week 20 are displayed in Table 4. There was a stat-

Table 3. Participant quotations and themes

Theme	Extracts of participant quotations
Depressive episode	1. "Feeling particularly flat, demotivated, lower energy and disinterested/anhedonic."
	2. "He is losing interest, finds it difficult to even derive pleasure from being with his son."
	3. "Feels no desire to do things with friends or family. No enjoyment for social activities or recreational activities."
	4. "She reports that she has been very depressed, no motivation, no energy, has been spending most of her time in bed or on the sofa watching movies, at times, not showering."
Mood	5. "Noted a significant improvement but attributes this as most likely related to usual seasonal fluctuation after depressive episode, though perhaps more speedy in recovery than usual."
	6. "Despite her recent drop in mood, has felt an improvement since commencing the trial, primarily in the severity and frequency of her low moods."
	7. "Her flatness and sluggishness were particularly marked at the start of the trial, and these have shifted."
	8. "Reports that in the last week she was sad because of the circumstances, her miscarriage, apart from that she was feeling good, not depressed."
	9. "While she was medically ill, in terms of her BD, she was actually feeling better, recuperating from physically being exhausted, she is happier."
	10. "Low mood seemed less severe at first usually worst days are at the start, but this time, was day 6 or 7. 'Shape' of episodes has changed."
	11. "She felt that, despite a resurgence of her depression a month ago, things have improved on the trial because it was the "softest" low she's had much "gentler" than in the past, and without really awful, intrusive thoughts she typically gets"
Environmental factors	12. "He presented today as fairly well and optimistic, partly in the context of being offered a new job (alleviating financial worries as his contract was almost up), and a work trip to the US which involved working with first-class academics and mentoring PhD & honours students."
	13. "On the weekend she phoned a good friend and went with her kids to see him. She also bumped into other old friends and had a good time."
	14. "She had a fight (last sunday) with her husband and this also affected her mood and left her anxious and tense several days."
	15. "Anxiety about future finances and capacity to work (recently turning down a new contract due to his depressive symptoms), and a "mental fog" that has again impaired his ability to read and concentrate."
Outlook on life	16. "He is looking for a place of his own, searching for his independence."
	17. "His outlook had also shifted back to a style more tinted with pessimism and hopelessness than had been apparent the previous month."
	18. "Anticipating future lows and feeling more anxious - affecting potential to work - bucking up, feeling a bit less optimistic in a way."
	19. "The key change for him this month was the shift in his outlook."
Other treatment, medication and physical health/illness	20. "I'm going to a medication review to help with my hypersomnia from the Seroquel."
	21. "Her Seroquel has been increased to 50 mg a day."
	22. "Mood is getting worse. He has been sleeping excessively and feeling quite fatigued. Energy is very low. Thinks that his previous admission where he had antidepressants lowered and left just on lithium is the cause. He is now restarting antidepressants. Mood is very flat."
	23. "Sleep and tremble are still a problem. May be affected by sleeping tablets Rivotril"
Insight	24. "He reported that he is feeling more aware and in control of his illness, noticing his anxiety triggers more easily, and readily engaging in strategies such as walking to manage these symptoms. He also sought to have his regular medication increased when needed, earlier in the course of the study, which he mentioned again today as he felt it was a sign of previously-absent initiative."
	25. "He has experienced a hypomanic episode since early February, but feels that the nature of this has changed compared to usual. He feels much more in control, has had better awareness of his irritable mood, has made an effort to continue to engage with his family, and has endeavoured to maintain routine to some extent despite sleep disturbances."

BD, bipolar disorder.

istically significant difference between placebo and NAC groups in total Negative themes ($p < 0.044$) with increased frequency occurring in the placebo group, specifically within themes of depressed mood, fatigue, cognitive functioning decrease, hostility, irritability, anxiety and sleeping issues. Statistical significance was found between placebo vs. CT group with more Positive themes ($p < 0.047$) specifically in themes of Environmental protective factors: general and interpersonal, improved functioning, mood improved, and optimism having higher frequencies in the CT group. However, comparisons of the placebo vs. CT group, in Negative themes and placebo vs. NAC in

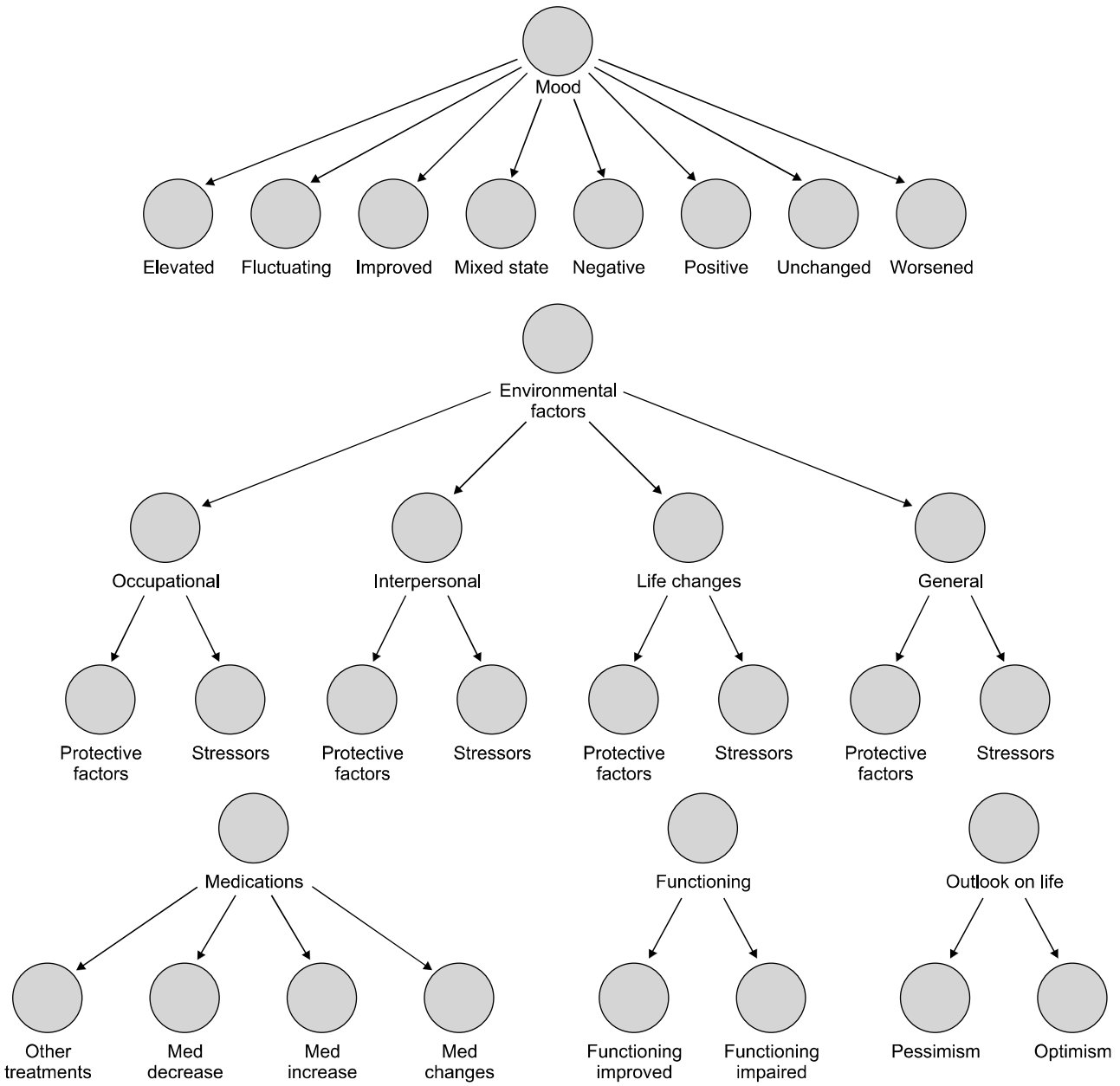

Fig. 1. Code tree concept map displaying mood, environmental factors, medications, functioning and outlook on life themes. Below each theme the associated sub-themes are shown.

Table 4. Differences in overall positive and negative frequencies between treatment groups at week 20

Statistical analysis	Placebo vs. NAC	NAC vs. Placebo	Placebo vs. CT	CT vs. Placebo
Theme	Negative totals	Positive totals	Negative totals	Positive totals
Time point	Week 20	Week 20	Week 20	Week 20
Mann−Whitney *U*	511.500	658.000	702.500	563.500
Wilcoxon W	1,141.500	1,478.000	1,443.500	1,304.500
Z	−2.014	−0.448	−0.577	−1.985
Asymp. Sig. (2-tailed)	0.044	0.654	0.0564	0.047

CT, combination treatment; NAC, *N*-acetyl cysteine.

Positive themes were statistically non-significant (see Table 4). Notable changes over time in individual themes can be seen in Supplementary Table 1 (available online) as raw coding frequencies.

DISCUSSION

The current study aimed to explore the effects of the mitochondrial agents NAC and selected nutraceuticals in BD depression, using a double-blind mixed methods analysis of data from an RCT. This approach, which is underutilised in early phase RCTs not only enhances the capacity to detect latent signals in data further but directly draws upon the participants' own experience which aligns with patient-centred treatment. In particular, these methods could allow detection under double-blind conditions of clinical signals that may have been undetected by the chosen rating instruments. Such methods could uncover unexpected signals of efficacy in various domains as well as other potential safety issues. The quantitative analysis of the collapsed themes found the placebo group had significantly more Negative theme reports compared to the NAC-alone group at the end of the trial. There was no significant difference found between these groups in the Positive themes. There were significantly more Positive themes in the CT group compared to the placebo group. No difference was found between the CT group and placebo group in the Negative theme reports. Similarities were found between the quantitative and qualitative findings, specifically in the increase of positive themes in both NAC and CT treatment groups: functioning improved, optimism and mood improved. However, statistically, qualitative themes of employment started and enjoyment increased did not differ in frequency between groups.

Qualitative analysis of the individual themes revealed rich and interesting results. Change over time, between week 2, 16 and 20 on several themes were found in the active treatment groups. These include themes of employment started, enjoyment increased, optimism and functioning improved in the NAC group, and mood improved in the CT group. These frequencies (Supplementary Table 1; available online) were all higher at week 20 compared to week 2. These results are reflected in the qualitative data; an example of participant responses can be seen in the extracts below and further quotes can be found in Table 3 extracts 9, 12, 13, and 16.

"She reports that there has been an improvement in the way she's been feeling. Her mood has lifted a bit. She does not feel as bad and not as often"

"Started work as nurse in aged care on a casual basis yesterday. Enjoyed it and looking forward to continuing."

"Feeling good about her life and future plans."

These findings are comparable to the primary and secondary findings from the primary RCT, which showed an increase in the Global Assessment of Functioning, Social and Occupational Functioning Scale, and Quality of Life Scale over time [9]. Additionally, such findings are in line with a number of other bipolar NAC trials [26-28], which suggested significantly improved clinical outcomes in depression, functioning and quality of life within the NAC groups.

A large proportion of participants also mentioned other treatments, medications and physical health/illnesses. Mentions of these themes in all groups and at all-time points represent the participants' experiences of comorbid illnesses or physical health complaints, specifically, raw data from Supplementary Table 1 (available online) displays themes other treatments and physical health/illness are both higher in the placebo group compared to the NAC and CT groups. These include reports of seeking out or receiving other treatments and medications, for example, a chiropractor, cognitive behavioural therapy or mood stabilisers. In particular, the challenges of medication decision making, side effects and physical illness were widely discussed by most participants. These results highlight the medical comorbidities that accompany BD and are consistent with a recent paper by Forty and colleagues which found increased rates of asthma, diabetes, elevated lipids, hypertension and more in a BD population group compared to unipolar depression and healthy controls [29]. These commonly discussed theme results emphasise the importance of acknowledging medical comorbidities and other medication schedules in the treatment of BD. Examples of participants experiences can be seen below and in Table 3 extracts 21−24.

"He feels that his coping ability and self-belief have improved and despite a few "hiccups" as he calls them, he has improved significantly since the start of the study. However, this is also in the context of increased mirtazapine."

"Current inpatient. Primary borderline personality

disorder. During visit, patient was very dysregulated and labile, with dissociative symptoms evident"

"Continued with my trauma therapy which has been so helpful and made a real difference in my mood. Trauma counselling and support group is really the main thing which has helped my mood and enjoyment"

Another notable finding is the participants' experiences of environmental factors and their effect on mood states. Exploratory results from the raw frequencies (Supplementary Table 1; available online) showed that participants experienced a lower aggregate frequency of general stressors, life change stressors, interpersonal stressors and occupational stressors at Week 20 than at Week 2 in the NAC group and less interpersonal stressors in the CT group at Week 20. The placebo group also shows less frequency in a number of environmental stressors across time. Examples of participants environmental factors experiences can be seen below and in Table 3 extracts 12−15.

"Her business (with her husband) is a cause for major stress, they are struggling financially, and she is helping (when she is well) as much as she can."

"He experienced a number of stressors over the trial including physical illness, relationship stressor, hectic work deadlines, the death of a friend, financial pressure and the decision to move house."

"He presented today as fairly well and optimistic, partly in the context of being offered a new job (alleviating financial worries as his contract was almost up)"

These results have captured valuable information on the lives of those with BD, including their resilience and stress regarding the environmental factors they face. These results are consistent with a recent meta-synthesis [30] of what people with BD experience as distressing. Warwick and colleagues identified five themes of Loss, Diagnosis, Relationships, Uncertainty and Threat. These themes align with the 26 total themes or the sub-themes of Environmental stressors from this analysis. Understanding the stressors and factors involved could assist with improving longer-term treatment outcomes. Most notably, the positive change over time in many of the themes could point to other pertinent factors in the participants' lives, such as the therapeutic environment of a clinical trial. Undergoing monthly check-ins with a trusted individual asking numerous questions about mood states over the past month, could increase insight and well-being, as shown below and in Table 3 extracts 25 and 26.

"He reported that he was happy to have taken part and that the impact of coming to regular appointments, having to review his symptoms and focussing on taking regular medication had helped with his awareness of the illness and generally felt more in control and open with those around him."

"Feels like her quality of life has improved over the course of the trial, with her motivation and energy in particular helping her achieve her goals. Her flatness and sluggishness were particularly marked at the start of the trial, and these have shifted"

The contrast between the deductive themes of the BD symptomology and the participant-centred inductive themes highlights the importance of mixed methods research in clinical trials. Open-ended qualitative questioning enabled the participants to discuss the effect of the trial on themes that were important in their lives such as lifestyle, employment, relationships, wellbeing and future goals.

This study is an *a priori* exploratory outcome of the overarching quantitative RCT and as such there are some overt limitations to the findings. Conducting qualitative analyses with previously-collected data does not have the rigour of the qualitative pragmatic approach. The amount of qualitative data varied, some records included a great depth of the participant's experiences, and some were very brief. This might also demonstrate variability between data collectors, in terms of background, experience, and bias that we are unable to control for in the analysis. Furthermore, the qualitative data collection approach utilised only three questions and limited researcher's observations, rather than a longer semi-structured interview and relied on interviewer notes rather than audiotaped interviews. Therefore, the scope of the responses is limited and less exploratory than most qualitative research, making this study less exploratory in nature compared to pure qualitative papers.

This blinded mixed methods study revealed a number of novel and unexpected findings. The NAC and CT groups showed an increase in the frequency of several themes (employment started, functioning improved, optimism and enjoyment increase) compared to the placebo

group. A decrease was also observed in environmental stressor themes of general, interpersonal, life changes and occupational in the NAC group. These results build upon the original RCT [9] and provide an in-depth qualitative analysis of the participants' experiences. The use of mixed methods may allow detection of potentially impactful measures such as occupational circumstances and subtleties of quality of life. Identifying the participant experiences, through the addition of a qualitative component can help to guide future research, encouraging more patient-centred research methods and create a way for participants to be involved in the research. Moreover, this study highlighted the importance of including qualitative data in the RCT analysis process, not only to interpret the data in its entirety but to discover novel findings that may be missed by the quantitative analyses, such as the influence of environmental stressors and the increased presence of comorbidities in the placebo group compared to both NAC and CT groups. Such mixed methods add depth to quantitative methods, especially in early phase clinical trials.

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■ Conflicts of Interest

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