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Physical Activity as a Predictor of Clinical Trial Outcomes in Bipolar Depression: A Subanalysis of a Mitochondrial-Enhancing Nutraceutical Randomized Controlled Trial

L'activité physique comme prédicteur des résultats d'un essai clinique en dépression bipolaire : une sous-analyse d'un essai randomisé contrôlé d'un nutriceutique améliorant les mitochondries

Melanie M. Ashton, BSc, GDip[1,2,3], Mohammadreza Mohebbi, PhD[4], Alyna Turner, PhD[1,5], Wolfgang Marx, PhD[1,6], Michael Berk, MD, PhD[1,3,5,7,8], Gin S. Malhi, MD[9,10,11], Chee H. Ng, MBBS, MD[2], Sue M. Cotton, PhD[7,8], Seetal Dodd, PhD[1,5,7], Jerome Sarris, PhD[2,12], Malcolm Hopwood, MD[13], Brendon Stubbs, PhD[14,15], and Olivia M. Dean, PhD[1,3]

Abstract

Objectives: Individuals with bipolar disorder (BD) generally engage in low levels of physical activity (PA), and yet few studies have investigated the relationship between PA and change in BD symptom severity. The aim of this subanalysis of an adjunctive nutraceutical randomized controlled trial for the treatment of bipolar depression was to explore the relationship between PA, the active adjunctive treatments (a nutraceutical "mitochondrial cocktail"), and clinical outcomes.

Methods: Participants with bipolar depression were randomized to receive *N*-acetylcysteine alone, *N*-acetylcysteine with a combination of nutraceuticals (chosen for the potential to increase mitochondrial activity), or placebo for 16 weeks. Participants (n = 145) who completed the International Physical Activity Questionnaire–Short Form (IPAQ-SF; measured at Week 4) were included in this exploratory subanalysis. Assessments of BD symptoms, functioning, and quality of life were

[1] IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Deakin University, Geelong, Victoria, Australia
[2] Professorial Unit, The Melbourne Clinic, Department of Psychiatry, University of Melbourne, Richmond, Victoria, Australia
[3] The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia
[4] Biostatistics Unit, Faculty of Health, Deakin University, Geelong, Victoria, Australia
[5] School of Medicine and Public Health, Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW 2308, Australia
[6] Department of Rehabilitation, Nutrition and Sport, School of Allied Health, College of Science, Health and Engineering, La Trobe University, Bundoora, Victoria, Australia
[7] Centre of Youth Mental Health, University of Melbourne, Parkville, Victoria, Australia
[8] Orygen, Parkville, Victoria, Australia
[9] Academic Department of Psychiatry, Northern Sydney Local Health District, St Leonards, New South Wales, Australia
[10] Faculty of Medicine and Health, Department of Psychiatry, Northern Clinical School, University of Sydney, New South Wales, Australia
[11] CADE Clinic, Royal North Shore Hospital, Northern Sydney Local Health District, St Leonards, New South Wales, Australia
[12] NICM Health Research Institute, Western Sydney University, Westmead, New South Wales, Australia
[13] Professorial Psychiatry Unit, Albert Road Clinic, Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia
[14] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, United Kingdom
[15] Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom

Corresponding Author:
Melanie M. Ashton, BSc, GDip, IMPACT Strategic Research Centre, Deakin University, P.O. Box 281, Geelong, Victoria 3220, Australia.
Email: m.ashton@deakin.edu.au

completed at monthly visits up until Week 20. Generalised Estimating Equations were used to explore whether IPAQ-SF scores were a moderator of treatment received on outcomes of the study.

Results: Week-4 PA was not related to changes in Montgomery Åsberg Depression Rating Scale scores across the study until Week 20. However, participants who engaged in more PA and who received the combination treatment were more likely to have a reduction in scores on the Bipolar Depression Rating Scale ($P = 0.03$). However, this was not consistent in all domains explored using the IPAQ-SF. Participants who engaged in higher levels of PA also experienced greater improvement in social and occupational functioning and less impairment in functioning due to their psychopathology and improvement in quality of life at Week 20, irrespective of treatment.

Conclusions: This study provides novel evidence of the association between PA and reduction in BD symptoms in a nutraceutical clinical trial. However, further research assessing the potential synergistic effects of PA in BD is required.

Abrégé

Objectifs : Les personnes souffrant d'un trouble bipolaire (TB) ne s'adonnent généralement qu'à de faibles taux d'activité physique (AP), et pourtant, peu d'études ont recherché la relation entre l'AP et le changement de la gravité des symptômes du TB. L'objet de cette sous-analyse d'un essai randomisé contrôlé d'un adjuvant nutriceutique pour le traitement de la dépression bipolaire était d'explorer la relation entre l'AP, les traitements adjuvants actifs (un « cocktail mitochondrial » dans un nutriceutique), et les résultats cliniques.

Méthodes : Les participants souffrant de dépression bipolaire ont reçu de façon aléatoire soit la *N*-acétylcystéine seulement, soit la *N*-acétylcystéine avec une combinaison de nutriceutiques (choisis pour leur potentiel d'accroître l'activité mitochondriale), soit un placebo pendant 16 semaines. Les participants ($n = 145$) qui ont rempli la version abrégée du questionnaire d'activité physique international (IPAQ-SF; mesuré à la 4^{e} semaine) ont été inclus dans cette sous-analyse exploratoire. Les évaluations des symptômes de TB, du fonctionnement et de la qualité de vie ont été effectuées lors de visites mensuelles, jusqu'à la 20^{e} semaine. Des modèles linéaires mixtes ont servi à explorer si les scores à l'IPAQ-SF étaient un modérateur du traitement reçu dans les résultats de l'étude.

Résultats : À la 4^{e} semaine, l'AP n'était pas liée aux changements des scores à l'échelle de la dépression de Montgomery Åsberg dans toute l'étude jusqu'à la 20^{e} semaine. Toutefois, les participants qui faisaient plus d'AP et qui recevaient un traitement combiné étaient plus susceptibles d'avoir une réduction de leurs scores à l'échelle de dépression bipolaire ($P = 0.03$). Cependant, cela n'était pas constant dans tous les domaines explorés à l'aide de l'IPAQ-SF. Les participants qui se sont adonnés à des taux d'AP plus élevés ont aussi connu une plus grande amélioration du fonctionnement social et professionnel, et moins de déficience du fonctionnement en raison de leur psychopathologie et de la qualité de vie à la 20^{e} semaine, sans égard au traitement.

Conclusions : Cette étude apporte de nouvelles données probantes de l'association entre l'AP et la réduction des symptômes de TB dans un essai clinique nutriceutique. Il faut cependant plus de recherche pour évaluer les effets synergiques de l'AP dans le TB.

Keywords
physical activity, exercise, bipolar disorder, bipolar depression, mitochondrial agents, nutraceuticals, *N*-acetylcysteine

Introduction

Bipolar depression is often difficult to treat. One approach to optimize the effects of current therapeutics may be through lifestyle interventions such as engagement in physical activity (PA). Despite many known benefits of PA in the general population[1] and increasing evidence that individuals with other serious mental disorders such as schizophrenia[2] and major depression[3,4] can also benefit, limited research has investigated PA and symptom severity in bipolar disorder (BD; for reviews[5,6]).

To date, the literature is largely based on cross-sectional, prospective cohort, or small pilot studies, all of which suggest that engagement in PA improves mood and quality of life, but the evidence base is limited.[5,7-9] Individuals with BD engage in lower levels of PA, are less likely to meet recommended international guidelines for exercise (World Health Organization [WHO][10]), and are more likely to be sedentary versus age- and sex-matched controls.[11] Therefore, not surprisingly, people with BD demonstrate lower levels of cardiorespiratory fitness compared to healthy controls.[12,13] Previous research has suggested that increased PA is associated with better cognition in euthymic females with a diagnosis of BD.[14] Achieving an adequate level of PA has been included in the current National Institute of Health guidelines for treating BD, but only in the broad sense of improving general health.[15] In the general population, it is recommended that individuals achieve 150 min of moderate or 75 min of vigorous PA per week.[10] The literature to date in the general population has found that both continuous and interval aerobic PA at a moderate to high intensity can improve mitochondrial function.[16-

[19] An emerging evidence base also advocates that resistance training, specifically targeting the loading and strengthening of skeletal muscles, can also improve mitochondrial function.[19,20] While people with BD may have mitochondrial dysfunction,[21] it is unclear whether PA at moderate to high intensity at recommended guidelines such as those recommended by WHO[10] can influence mitochondrial function. PA is low-cost, safe, and tolerable and therefore could be an effective adjunct to improve response to treatment in BD; however, this has been largely unexplored. Therefore, we aimed to investigate whether PA was associated with changes in symptoms, functioning, and quality of life in BD. This study was embedded in a double-blind randomized controlled trial (RCT) evaluating the efficacy of adjunctive nutraceuticals for the treatment of bipolar depression. The adjunctive nutraceuticals were specifically selected due to their potential mitochondrial-enhancing properties,[22] and there may be a relationship between PA and the nutraceuticals via mitochondrial biogenesis.[23] There were three arms of the RCT: *N*-acetylcysteine (NAC) alone, a combination treatment (CT) of nutraceuticals including NAC and placebo.

We hypothesized that reported PA would be an effect modifier for the relationship between those receiving NAC alone or the CT, and an improvement on depression, functioning, and quality of life outcomes. We also hypothesized that PA in categorical terms, according to the scoring guide of the PA scale (low, moderate, and high), would be an effect modifier for the relationship between those receiving NAC alone or CT, and outcomes (detailed above). Finally, when utilizing data categorized by WHO recommendations, we hypothesized that PA (according to WHO recommendations) would be an effect modifier for the relationship between treatment with NAC alone or CT, and outcomes (detailed above).

Methods

Ethics

The study was run in accordance with International Council for Harmonisation Good Clinical Practices Guidelines.[24] Ethical approval was granted from Barwon Health Human Research and Ethics Committee (HREC), Northern Sydney Local Health District HREC, The Melbourne Clinic Research Ethics Committee and Deakin University HREC. The study is registered on the Australian and New Zealand Clinical Trial Registry (ACTRN12612000830897).

Trial Study Design

Participants ($n = 181$) who were randomized received the study medication for 16 weeks and visited study sites (Melbourne, Geelong, and Sydney) every 4 weeks for clinical interviews with a research assistant up until Week 20. Inclusion criteria were a diagnosis of BD, determined by the Mini-International Neuropsychiatric Interview 5.0[25] and a current moderate to severe depressive episode measured by a score $\geq$20 on the Montgomery Åsberg Depression Rating Scale (MADRS).[26] Full study protocol[16] and primary results[20] have been published previously.

The primary aim of the trial was to assess the efficacy of the two active arms of the study (NAC alone and CT) compared to placebo for treating depressive symptoms (measured by the MADRS) at Week 16. Primary results of the study at the primary endpoint were not significant at Week 16.[27] However, at Week 20 (4 weeks post–study medication discontinuation), CT was superior to placebo at improving the following outcome measures; changes in depression symptoms measured by the MADRS which was the primary outcome measure in the study; bipolar depression symptom severity measured by the Bipolar Depression Rating Scale (BDRS)[28]; Social and Occupational Functioning Assessment Scale (SOFAS),[29] a clinician-rated measure of functioning; The Longitudinal Interval Follow-Up Evaluation–Range of Impaired Functioning (LIFE-RIFT),[30] a clinician-rated measure of impairment in functioning from psychopathology and the Clinical Global Impressions Scales Bipolar Version–Improvement (CGI-I),[31] a 1-item clinician-rated scale measuring improvement. Participants also completed The Quality of life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF),[32] a self-report measure of quality of life. There was no significant relationship between CT versus placebo in regard to Q-LES-Q-SF scores, but this outcome was included in the subanalysis because of the association between PA and quality of life in BD.[13] Total possible scores for each outcome measure and indication of direction for improvement can be found in Supplemental Table 1.

PA

The International Physical Activity Questionnaire–Short Form (IPAQ-SF)[33] was administered at Week 4 to measure each participant's general level of PA. The IPAQ-SF is a 10-item self-report questionnaire where participants recall the number of days and minutes of vigorous activity, moderate activity, walking and sitting time, over the past 7 days. The IPAQ-SF has been used extensively in other mental health disorder populations and has acceptable validity and reliability.[34] The IPAQ-SF was administered at Week 4 to reduce participant burden at the baseline visit and to coincide with collection of dietary intake data. The IPAQ-SF was administered as secondary outcomes' data and has been included in the protocol[16]; however, this measure was inadvertently omitted from the trial registry.

Data were cleaned using IPAQ-SF recommendations[33] that include removing cases with missing values and removing cases with values too low (less than 10 min of activity per day). There was no missing data for vigorous, moderate activity, or walking. Two participants had missing values for the "time spent sitting" item. Both these participants remained in the analysis as this item is not used to calculate total scores or categorical scores. Minimum and maximum values were implemented to remove outliers. As a result, one

Table 1. Study Participants' Characteristics.

Characteristics	Placebo (n = 49)	NAC (n = 50)	CT (n = 46)	Total (n = 145)	Range	Median Cutpoint
Male gender, *n* (%)	17 (34.7)	18 (36.0)	16 (34.8)	51 (35.2)		
Age, *M* (*SD*)	45.88 (11.9)	45.0 (12.1)	47.7 (13.3)	46.1 (12.4)	21.3 to 72.0	
BMI, *M* (*SD*)	30.3 (7.9), n = 47	27.9 (6.3)	28.2 (6.8)	28.8 (7.0), n = 143	16.82 to 52.8	
Total weekly physical activity (MET-min), *M* (*SD*)	2,024.4 (2,477.8)	1,766.3 (2,433.2)	1,603.1 (1,718.9)	1,801.8 (2,239.3)	0 to 11,118.0	990.0
IPAQ categorical						
Low, *n* (%)	22 (44.9)	27 (54.0)	23 (50.0)	72 (49.7)		
Moderate, *n* (%)	13 (26.5)	11 (22.0)	14 (30.4)	38 (26.2)		
High, *n* (%)	14 (28.6)	12 (24.0)	9 (19.6)	35 (24.1)		
WHO recommendations						
No physical activity, *n* (%)	7 (14.3)	4 (8.0)	5 (10.9)	16 (11.0)		
Below WHO recommendations, *n* (%)	9 (18.4)	17 (34.0)	14 (30.4)	40 (27.6)		
Within WHO recommendations, *n* (%)	9 (18.4)	10 (20.0)	4 (8.7)	23 (15.9)		
Above WHO recommendations, *M* (*SD*)	24 (49.0)	19 (38.0)	23 (50.0)	66 (45.5)		
Minutes spent sitting per weekday, *M* (*SD*)	421.9 (236.6)	427.6 (251.6)	441.8 (239.9), n = 44	430.0 (241.4), n = 143	21 to 1,260	360.0

Note. Abbreviations: BMI = body mass index; CT = combination treatment; IPAQ = International Physical Activity Questionnaire; NAC: *N*-acetylcysteine.
$*P < 0.05$. $**P < 0.01$.

participant was removed for too few minutes (6 min) of activity. To normalize the data, the protocol suggests truncating each daily activity time to no more than 180 min. This rule was employed for five participants reporting vigorous activity, seven for moderate activity, and six for walking. Of note, one participant filled in the IPAQ-SF questionnaire at Week 8, not Week 4 but remained in the analysis.

Weekly metabolic equivalent of task (MET)-minute scores for each activity type were first calculated as follows:

- Vigorous activity, *minutes/week* = total minutes per week of vigorous activity × 8.0 METs
- Moderate activity, *minutes/week* = total minutes per week of moderate activity × 4.0 METs
- Walking, *minutes/week* = total minutes per week of walking × 3.3 METs

Each total activity-MET score was then summed to create a continuous total PA score.

In addition to total PA scores, a categorical value was produced for each participant. The categories were low, moderate, or high PA and were calculated for each participant in accordance with IPAQ-SF scoring protocol.[33] Within this protocol, participants' activity levels were deemed *high* if they engaged in at least 3 days of vigorous activity and achieving a total activity of at least 1,500 MET min/week, or a combination of all intensity levels for 7 days or more and achieving a total activity of at least 3,000 MET min/week. *Moderate* activity category was achieved if participants engaged in at least 20 min of vigorous activity for 3 days, or at least 30 min of walking and/or moderate activity for 5 days, or a combination of any activity level for 5 or more days and achieving a total activity of at least 600 MET-min/week. Lastly, participants' activities were categorized as *low* if they did not fit into either of the above categories. A summary of categorical scores for the sample can be found in Table 1.

The last item of the IPAQ-SF is "time spent sitting" and is used to assess participants' rates of sedentary behaviors. Sitting has been presented as a separate variable, measured in average minutes per typical weekday.

In addition to the validated exploration of the IPAQ scale, further analysis was conducted using WHO recommendations. This was completed to provide preliminary data for guidelines and clinical practice and to provide real-world advice to patients. To explore these data in relation to WHO recommendations, total PA data in MET-min/week were categorically scored. These additional categories were utilized to aid direct interpretation of the results to participant adherence to WHO recommendations as outlined below. This quick interpretation allows results from this study to be easily translated into policy and clinical care.

1. *No PA*—All activity < 10 min duration (equivalent of 0 MET-min/week).
2. *Below WHO recommendations*—Less than 150 min of moderate activity or 75 min of vigorous activity per week.

Equivalent of energy expenditure between 0 and 600 MET-min/week (not inclusive).

3. *Within WHO recommendations*—At least 150 min of moderate activity or 75 min of vigorous activity per week. Equivalent of energy expenditure between 600 and 1,200 MET-min/week (inclusive).
4. *Exceeding WHO recommendations*—WHO recommends for greater health benefits, at least 300 min of moderate activity and 150 min of vigorous activity. Equivalent of energy expenditure greater than 1,200 MET-min/week.

Statistical Analysis

Generalized estimating equations (GEE) were used to assess whether PA (as a total score, categorical value, and according to WHO recommendations) were predictors of outcomes from the nutraceutical RCT (MADRS, BDRS, SOFAS, LIFE-RIFT, Q-LES-Q-SF, and CGI-I scores). Each predictor was assessed individually including an exploration of each of the treatment arms (NAC alone or CT) compared to placebo across the study up until Week 20. By using GEE, the analyses are able to take into account the longitudinal nature of data (i.e., measurement autocorrelation in follow-ups). The primary outcome of the study followed a modified intention-to-treat analysis whereby participants with post–baseline data were included in the analysis.[27] First, the original RCT analyses were replicated by including treatment arms as a nominal factor, log of follow-up time as a covariate, and the two-way interaction between log(time) and treatment arms was replicated, followed by including each predictor (each PA score) in a separate model to evaluate whether it is a predictor of outcomes. The latter model contained treatment arms as a nominal factor, log of follow-up time as a covariate, predictor of interest, all possible two-way interactions and the three-way interactions between treatment arms, log of follow-up time, and the predictor of interest. Three-way models evaluated the effect of each predictor on the outcome measure, across time in the study, for each treatment arm. Treatment by PA two-way interactions explored the role of the predictor for each of the study, independent of time. Each model utilized Baron and Kenny[35] criteria guidelines as first described by Kraemer et al.[36] Each model for each of the predictors is described below.

Categorical PA

We took into account the ordinal nature of PA categories when modeling the IPAQ-SF as low, moderate, and high. The model included a fixed-effect treatment group and categorical (ordinal) PA, and logarithm of time as covariates, all two-way interactions and the three-way interactions. As above, three-way interactions were then removed to explore two-way interactions. Total PA was also assessed as a continuous score, details of which are outlaid in Supplemental Material.

PA According to WHO Recommendations

PA according to WHO recommendations was assessed as nominal data and included in the model as a factor. The initial model included a fixed-effect treatment group and PA according to WHO recommendations, and logarithm of time as covariate, all two-way interactions and all three-way interactions. After this model was run for each outcome, three-way interactions were then removed to explore all two-way interactions for each outcome.

The *P* value for all overall three-way interactions were reported alongside Wald χ^2 statistic (used to measure parameter effects). In addition, for each treatment group (NAC alone or CT), three-way interactions were reported with *P* value and Wald χ^2 statistic, alongside their corresponding β coefficients and 95% confidence intervals (CIs) to measure association.

After examining three-way and two-way interactions of interest for each predictor, the data were then further explored for nonspecified predictors. Nonspecified predictors demonstrated a relationship with change in the outcome measure independent of what treatment was received and time. Each model for nonspecified predictors included the main effects of treatment group, the predictor, and logarithm of time. This model assesses for nonspecified predictors as it explores the predictors' response in the sample as a whole (combining all treatment groups).

The GEE technique was implemented for model estimation using an unstructured working correlation matrix and a robust variance estimator.[37] Statistical analyses were completed using IBM® SPSS® Statistics for Windows, Version 25.[38]

Results

Participants

Of the 181 participants in the clinical trial, 33 participants were excluded from the analysis for not having any post–baseline data, 2 participants excluded for missing IPAQ-SF data, and 1 participant excluded due to insufficient activity (less than 10 min activity). Therefore, 145 participants were included in the current analysis. The average age of the sample was 46.14 years ($SD = 12.38$), ranging from 21 to 72 years of age, and 51% were male. Participants were randomized to receive NAC ($n = 50$), CT ($n = 46$), and placebo ($n = 49$). A full list of study sample characteristics can be found in Table 1.

Analysis of Predictors

Change scores were calculated for each outcome measure (except CGI-I that self-evidently had no baseline data available). Mean change (Week 20 minus baseline scores) for each outcome variable per treatment group is shown in Supplemental Table 2. On average, participants in all treatment arms improved across all outcome measures. As CGI-I

Table 2. IPAQ Scores Categorized into Low, Moderate, and High According to IPAQ-SF Guidelines as a Predictor of Mean Change Scores for Each Treatment Arm.

MET-Categorical	Placebo Low	CT	NAC	Placebo Moderate	CT	NAC	Placebo High	CT	NAC	CT Interaction[a] β Coefficient (95% CI)	Interaction Test *P* Value	NAC Interaction[a] β Coefficient (95% CI)	Interaction Test *P* Value
MADRS change													
Mean (*SD*)	−12 (10.1)	−14.1 (9.5)	−15.1 (10.8)	−4.9 (11.2)	−18.7 (7.6)	−15.4 (10.8)	−14.8 (12.2)	−22.5 (3.5)	−10.6 (8.1)	−0.02	$\chi^2(1) < 0.01$	2.8	$\chi^2(1) = 3.8$
n	20	18	19	10	11	7	10	2	9	(−2.9 to 2.8)	$P = 0.987$	(−0.01 to 5.6)	$P = 0.051$
BDRS change													
Mean (*SD*)	−9.5 (9.8)	−10.2 (10.3)	−13.4 (9.7)	−2.1 (12.4)	−17.1 (7.9)	−13.8 (9.3)	−11.7 (9.3)	−21.0 (2.8)	−9.2 (7.2)	0.2	$\chi^2(1) = 0.01$	2.9	$\chi^2(1) = 3.9$
n	19	16	19	8	11	6	10	2	9	(−2.7 to 3.0)	$P = 0.917$	(0.03 to 5.7)	$\mathbf{P = 0.047}$
SOFAS change													
Mean (SD)	12.7 (12.9)	17.3 (12.7)	13.3 (10.6)	2.6 (12.7)	17.5 (14.5)	14.5 (14.5)	14.7 (12.0)	12.5 (7.8)	13.0 (11.2)	−0.7	$\chi^2(1) = 0.1$	−0.2	$\chi^2(1) = 0.01$
n	19	18	18	9	11	6	10	2	9	(−4.8 to 3.4)	$P = 0.736$	(−3.8 to 3.5)	$P = 0.932$
LIFE-RIFT change													
Mean (*SD*)	−2.3 (4.4)	−3.7 (5.0)	−3.7 (3.7)	−0.8 (3.6)	−5.6 (3.8)	−4.7 (2.5)	−3.7 (4.2)	−4.0 (1.4)	−3.6 (2.0)	−0.1	$\chi^2(1) = 0.01$	0.5	$\chi^2(1) = 0.7$
n	19	16	19	8	11	6	10	2	9	(−1.5 to 1.3)	$P = 0.909$	(−0.7 to 1.8)	$P = 0.417$
Q-LES-Q change													
Mean (*SD*)	12.7 (23.4)	16.7 (18.0)	18.1 (18.1)	<0.01 (15.0)	23.1 (19.8)	17.1 (10.0)	21.8 (18.0)	26.8 (12.6)	15.9 (23.7)	−1.8	$\chi^2(1) = 0.5$	−5.2	$\chi^2(1) = 3.1$
n	19	18	19	9	11	7	9	2	9	(−6.7 to 3.2)	$P = 0.486$	(−11.0 to 0.6)	$P = 0.077$
CGI-I Week 20[b]										0.2	$\chi^2(1) = 0.4$	0.05	$\chi^2(1) = 0.03$
n	20	18	19	9	11	7	10	2	9	(−0.4 to 0.8)	$P = 0.546$	(−0.5 to 0.6)	$P = 0.864$

Note. Abbreviations: BDRS = Bipolar Depression Rating Scale; CGI-I = Clinical Global Impression Improvement; CT = combination treatment; LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation–Range of Impaired Functioning Tool; MADRS = Montgomery Åsberg Depression Rating Scale; NAC = N-acetylcysteine; SOFAS: Social and Occupational Functioning Scale.

[a]Three-way interaction between potential predictor, time and treatment group, reference group was placebo.

[b]As CGI-I is not administered at baseline, mean score change has not been measured. High and low levels of each predictor were determined by median split.

represents a single score of change from baseline, mean Week-20 CGI-I scores per treatment group are summarized in Supplemental Table 3. On average, research clinicians rated participants as improving across the study. For all models with a significant interaction, age, sex and body mass index were explored as potential confounders, and no factors had a statistically significant impact on the relationships.

PA as a Categorical Variable

PA scores on the IPAQ-SF were categorized as low, moderate, or high using scale recommendations. From the whole sample, 49.7% of participants were categorized as engaging in low weekly PA, 26.2% engaging in moderate weekly PA, and 24.1% engaging in high weekly PA. A visual representation of data has been included in Supplemental Figure 1b.

Categorical PA was not significantly associated with scores for MADRS, SOFAS, LIFE-RIFT, Q-LES-Q-SF, or CGI-I (see Table 2). There was a three-way interaction between taking NAC and engaging in high exercise and participant's BDRS outcomes. Compared to placebo, participants receiving NAC and engaging in a high amount of exercise showed an increase in BDRS scores, indicating a worsening of symptoms across the trial. For every one-level increase in level of PA (i.e., level of PA according to IPAQ-SF categorical scores), mean BDRS on NAC further increased by 2.85 (95% CI, 0.03 to 5.7) units when compared with placebo group with similar PA level. There were no significant two-way interactions between treatment received and categorical PA.

WHO Recommendations

PA scores were represented in terms of WHO recommendations. From the whole sample, 11% engaged in no weekly PA, 27.6% engaged in weekly PA under the WHO recommendations, 15.9% engaged in weekly PA within the WHO recommendations, and 45.5% engaged in weekly PA greater than, or, exceeding the WHO recommendations. A visual representation of data has been included in Supplemental Figure 1c.

Results of the effect modification analysis are shown in Table 3. PA according to WHO recommendations was not significantly associated with scores for MADRS, SOFAS, LIFE-RIFT, Q-LES-Q-SF, or CGI-I. There was a significant three-way interaction between treatment received, PA according to WHO recommendations, and time. Participants who were randomized to receive CT and engaged in more PA had a greater reduction in BDRS scores, indicating an improvement in symptoms. For every one-level increase in PA (i.e., level of PA categorized according to WHO recommendations), mean BDRS in the combination therapy group further decreased by 2.15 (95% CI, −4.07 to −0.23) units when compared with the placebo group with similar PA levels. There were no significant two-way interactions between treatment received and PA in terms of WHO recommendations.

Total PA Scores

Total PA, as a continuous score, was not significantly associated with MADRS, SOFAS, LIFE-RIFT, Q-LES-Q-SF, or CGI-I scores (see Supplemental Table 4). There was, however, a significant three-way interaction between participants taking CT and engaging in more PA and participant's BDRS outcomes. Compared to placebo, participants receiving CT and engaging in a high amount of exercise showed a decrease in BDRS scores at Week 20 indicating an improvement in symptoms across the trial. For every 10% increase in participants' total MET score, BDRS scores decreased by 0.09 (95% CI, −1.8 to −0.1) units. There were no significant two-way interactions between treatment received and log-transformed total PA.

Nonspecified Predictors' Analysis

Results of the nonspecified predictors of outcomes analysis can be found in Table 4. Total PA was not significantly related to MADRS or CGI-I outcomes. Total PA was a significant nonspecified predictor of SOFAS, LIFE-RIFT, and Q-LES-Q-SF scores at Week 20, irrespective of treatment received. For every 10% increase in participants' total MET score, SOFAS scores increased by 0.06 (CI, 0.01 to 1.31) units, LIFE-RIFT scores decreased by 0.02 (95% CI, −0.41 to −0.08) units, and Q-LES-Q-SF scores would increase by 0.09 (95% CI, 0.13 to 1.80) units.

Categorical PA did not significantly predict Week-20 MADRS scores. Higher PA categories, according to the IPAQ-SF scoring protocol, was a nonspecified predictor of SOFAS, LIFE-RIFT, CGI-I, and Q-LES-Q-SF. Higher activity levels were more likely to be associated with slightly improved scores for these measures, regardless of treatment received. For every one-level increase in level of PA according to IPAQ-SF categorical scores (i.e., moderate to high), mean SOFAS scores at Week 20 increased by 2.27 (95% CI, 0.24 to 4.30) units, mean LIFE-RIFT scores decreased by 0.67 (95% CI, −1.23 to −0.11) units, mean Q-LES-Q-SF scores increased by 2.39 (95% CI, 0.03 to 4.75) units, and mean CGI-I scores decreased by 0.16 (95% CI, −0.31 to −0.01) units.

PA according to WHO recommendations was not associated with Week-20 MADRS or CGI-I scores. Higher PA categories, according to WHO recommendations, was a nonspecified predictor of SOFAS, LIFE-RIFT, and Q-LES-Q-SF. Higher activity levels were more likely to be associated with slightly improved scores for these measures, regardless of treatment received. For every one-level increase in level of PA according to WHO recommendations (i.e., from below to within recommendations), mean SOFAS scores at Week 20 increased by 1.80 (95% CI, 0.35 to 3.25) units, mean LIFE-RIFT scores decreased by 0.71 (95% CI,

Table 3. Physical Activity According to WHO Recommendations as a Predictor of Mean Change Scores for Each Treatment Arm.

MET–WHO	Placebo	CT	NAC	Placebo	CT	NAC	Placebo	CT	NAC	Placebo	CT	NAC	Overall Three-Way Interaction Test	Interaction[a] β Coefficient	Interaction Test	Interaction[a] β Coefficient	Interaction Test
	No Physical Activity			Below WHO Recommendations			Within WHO Recommendations			Exceeding WHO Recommendations			*P* Value	(95% CI)	*P* Value	(95% CI)	*P* value
MADRS change																	
Mean (*SD*)	−11.3 (14.5)	−9.0 (13.9)	−15.0 (7.2)	−14.1 (5.0)	−14.8 (9.1)	−14.9 (10.1)	−3.0 (11.2)	−15.3 (7.1)	−18.0 (13.7)	−13.0 (11.1)	−19.9 (7.0)	−10.4 (8.5)	$\chi^2(2) = 3.3$	−0.8	$\chi^2(1) = 0.6$	1.1	$\chi^2(1) = 1.0$
n	7	3	4	8	12	12	8	4	7	17	12	12	$P = 0.19$	(−2.8 to 1.2)	$P = 0.440$	(−1.1 to 3.2)	$P = 0.319$
BDRS change																	
Mean (*SD*)	−14.1 (11.0)	<0.01 (14.1)	−14.5 (11.1)	−12.1 (7.5)	−9.9 (9.8)	−12.9 (9.3)	−0.6 (11.1)	−16.8 (5.1)	−15.0 (11.1)	−8.5 (10.2)	−18.1 (7.5)	−9.8 (10.5)	$\chi^2(2) = 6.2$	−2.2	$\chi^2(1) = 4.8$	−0.1	$\chi^2(1) < 0.01$
n	7	2	4	7	11	12	7	4	6	16	12	12	$\mathbf{P = 0.046}$	(−4.1 to −0.2)	$\mathbf{P = 0.028}$	(−2.2 to 2.0)	$P = 0.951$
SOFAS change																	
Mean (*SD*)	15.3 (16.0)	7.0 (15.9)	19.8 (10.1)	13.9 (11.3)	18.0 (11.3)	12.9 (8.9)	1.6 (11.3)	16.0 (15.4)	9.7 (16.8)	12.1 (12.4)	18.9 (13.4)	13.7 (10.5)	$\chi^2(2) = 1.4$	1.7	$\chi^2(1) = 1.4$	0.8	$\chi^2(1) = 0.4$
n	7	3	4	7	12	11	8	4	6	16	12	12	$P = 0.504$	(−1.1 to 4.5)	$P = 0.243$	(−1.8 to 3.4)	$P = 0.546$
LIFE-RIFT change																	
Mean (SD)	−3.0 (4.5)	<0.01 (7.1)	−3.5 (5.1)	−3.7 (3.5)	−3.7 (4.2)	−3.4 (4.0)	−0.4 (4.7)	−5.0 (4.1)	−4.7 (2.0)	−2.3 (4.2)	−5.7 (4.2)	3.9 (4.0)	$\chi^2(2) = 0.8$	−0.4	$\chi^2(1) = 0.8$	−0.1	$\chi^2(1) = 0.03$
n	7	2	4	7	11	12	7	4	6	16	12	12	$P = 0.666$	(−1.3 to 0.5)	$P = 0.382$	(−1.0 to 0.8)	$P = 0.866$
Q-LES-Q change																	
Mean (SD)	13.8 (22.2)	10.1 (14.5)	24.6 (11.4)	19.4 (23.7)	18.8 (16.2)	16.4 (18.9)	−3.1 (16.0)	17.0 (11.9)	13.8 (15.8)	14.2 (20.9)	23.7 (22.8)	17.9 (21.1)	$\chi^2(2) = 1.3$	1.3	$\chi^2(1) = 0.5$	−1.0	$\chi^2(1) = 0.2$
n	7	3	4	7	12	12	7	4	7	16	12	12	$P = 0.512$	(−2.5 to 5.1)	$P = 0.496$	(−5.1 to 3.1)	$P = 0.640$
CGI-I Week 20[b]													$\chi^2(2) = 0.8$	−0.2	$\chi^2(1) = 0.7$	<0.01	$\chi^2(1) < 0.01$
n	7	3	4	8	12	12	8	4	7	16	12	12	$P = 0.67$	(−0.6 to 0.2)	$P = 0.402$	(−0.4 to 0.4)	$P = 0.999$

Note. Abbreviations: BDRS = Bipolar Depression Rating Scale; CGI-I = Clinical Global Impression Improvement; CT = combination treatment; LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation–Range of Impaired Functioning Tool; MADRS = Montgomery Åsberg Depression Rating Scale; NAC: *N*-acetylcysteine; SOFAS = Social and Occupational Functioning Scale.

[a]Three-way interaction between potential predictor, time and treatment group, reference group was placebo.

[b]As CGI-I is not administered at baseline, mean score change has not been measured. High and low levels of each predictor were determined by median split.

Table 4. Total Weekly Physical Activity, IPAQ Categorical Scores, and Physical Activity Categorized by WHO Recommendations as Nonspecified Predictors of Outcomes.

Predictor	β Coefficient (95% CI)	Main Effect
Total weekly physical activity		
MADRS	−0.2 (−0.6 to 0.3)	$\chi^2(1) = 0.6$, $P = 0.458$
BDRS	−0.1 (−0.5 to 0.2)	$\chi^2(1) = 0.5$, $P = 0.498$
SOFAS	0.7 (0.01 to 1.3)	$\chi^2(1) = 4.0$, $\mathbf{P = 0.046}$
LIFE-RIFT	−0.2 (−0.4 to −0.1)	$\chi^2(1) = 8.5$, $\mathbf{P = 0.004}$
Q-LES-Q	1.0 (0.1 to 1.8)	$\chi^2(1) = 5.2$, $\mathbf{P = 0.023}$
CGI-I	−0.01 (−0.1 to 0.04)	$\chi^2(1) = 0.1$, $P = 0.709$
IPAQ scores in categorical		
MADRS	−1.1 (−2.2 to 0.03)	$\chi^2(1) = 3.7$, $P = 0.056$
BDRS	−0.7 (−1.9 to 0.4)	$\chi^2(1) = 1.5$, $P = 0.218$
SOFAS	2.3 (0.2 to 4.3)	$\chi^2(1) = 4.8$, $\mathbf{P = 0.028}$
LIFE-RIFT	−0.7 (−1.2 to −0.1)	$\chi^2(1) = 5.6$, $\mathbf{P = 0.018}$
Q-LES-Q	2.4 (0.03 to 4.8)	$\chi^2(1) = 3.9$, $\mathbf{P = 0.047}$
CGI-I	−0.2 (−0.3 to −0.01)	$\chi^2(1) = 4.4$, $\mathbf{P = 0.036}$
Physical activity categorized by WHO recommendations		
MADRS	−0.6 (−1.5 to 0.3)	$\chi^2(1) = 1.5$, $P = 0.219$
BDRS	−0.4 (−1.3 to 0.4)	$\chi^2(1) = 1.0$, $P = 0.311$
SOFAS	1.8 (0.3 to 3.3)	$\chi^2(1) = 5.9$, $\mathbf{P = 0.015}$
LIFE-RIFT	−0.7 (−1.1 to −0.3)	$\chi^2(1) = 13.7$, $\mathbf{P < 0.001}$
Q-LES-Q	2.2 (0.5 to 4.0)	$\chi^2(1) = 6.0$, $\mathbf{P = 0.014}$
CGI-I	−0.1 (−0.2 to 0.1)	$\chi^2(1) = 1.1$, $P = 0.286$

Note. Abbreviations: BDRS = Bipolar Depression Rating Scale; CGI-I = Clinical Global Impression Improvement; CT = Combination Treatment; LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation–Range of Impaired Functioning Tool; MADRS = Montgomery Åsberg Depression Rating Scale; NAC = *N*-acetylcysteine; SOFAS: Social and Occupational Functioning Assessment Scale.
Bolded *p*-values highlight significant values.

−1.09 to −0.34) units, and mean Q-LES-Q-SF scores increased by 2.25 (95% CI, 0.45 to 4.04) units.

Discussion

The aim of this subanalysis of a nutraceutical RCT was to assess the relationships between PA, treatment received, and changes from baseline to Week 20 in outcomes measures for individuals with BD. Results suggest that there may be an association between PA and some of the depression and functioning outcomes of the study, but this was not consistent for all outcome measures.

In regard to depression symptoms, PA was unrelated to change across the study from baseline to Week 20 on the primary outcome measure, the MADRS. However, for participants receiving CT, total PA significantly predicted changes in bipolar depression symptoms (measured by the BDRS). There was a robust relationship between participants receiving CT who exceeded WHO recommendations for PA. These participants showed a greater reduction in the BDRS depression symptoms, compared to participants receiving placebo at a similar level of PA, in a dose-dependent manner; however, the differences between the groups were minimal. In contrast, participants who received NAC and engaged in higher levels of PA demonstrated a worsening of their BD symptoms, but this was not consistent across all measures. After some types of strenuous, high intensity, or endurance PA, there is evidence of a short-term acute inflammatory response in some people[39-42] that adapts over time. Inflammation is a necessary part of muscular recovery from exercise, and anti-inflammatory medication such as NAC may be inhibiting this process.[43,44] There may be a delicate balance between anti-inflammatory use and benefits of exercise, potentially leading to the need for targeted and timed anti-inflammatory medication.[44] As use of NAC appears to demonstrate a worsening of BD symptoms for those in a high category of the IPAQ compared to placebo, this may be a demonstration of a disruption to this delicate balance and warrants further investigation. As the CT group demonstrates improvement on this same depression scale, there is potentially an element within the CT, which is protective and counteracting the negative effects of NAC. However, due to the exploratory nature of this subanalysis and the low number of participants, cautious interpretation is required.

It is possible that the combination of mitochondrial-enhancing PA and the mitochondrial-enhancing CT may be an important interaction for improving bipolar depression symptoms. This is in keeping with the hypothesis that BD is at its heart a mitochondrial disorder manifested by decreased biogenesis in depression and excess energy generation in mania.[21] Previous research has also found a reduction of depression (unipolar and bipolar) with PA at higher levels.[45] The potential for PA in BD is profound, given its positive effects on neuroplasticity,[46] hippocampal volume,[47] increasing brain-derived neurotrophic factor,[48] mitochondrial activity, and neurogenesis[23] potentially mediated by peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α.[49] These are all processes that are disturbed in BD, giving rise to the possibility that PA may improve symptoms of BD via improving mitochondrial dysfunction and neuroplasticity. The additional benefits of receiving CT and engaging in higher levels of PA may be achieved via synergistic effects on the pathway regulating mitochondrial energy generation, such as PGC-1α.[49,50]

There were no significant relationships between participants' PA, the treatment they received on the study and functional outcomes (LIFE-RIFT and SOFAS), quality of life (Q-LES-Q-SF), or clinician-rated improvement (CGI-I). However, there were relationships between the PA predictors and outcome measures, irrespective of what treatment they received. PA (including all variations on the scale) was a nonspecified predictor of improvement in social and occupational functioning (SOFAS), psychopathology-induced impairment of functioning (LIFE-RIFT), and quality of life (Q-LES-Q-SF) at Week 20. These results are in keeping with previous research suggesting improved outcomes for those who engage in more PA.[51] One interpretation could be a bidirectional relationship between functioning and PA. For instance, if a participant has adequate physical functioning levels, then they may have a greater motivation or ability to engage in PA. However, as PA is only measured once, we cannot determine causality.

Strengths of this study include the design of the double-blind adjunctive RCT adjunctive, allowing for robust clinical trial data. PA has been measured according to a validated scale with two possible outcome measures for interpretation (continuous weekly score and categorical weekly score).[33] This scale takes a conservative approach in truncating and removing data for less skew. In addition, PA has been categorized according to WHO recommendations allowing for real-world, practical interpretations and has implications for public health messages.

Results of this study should be cautiously interpreted due to its limitations. In particular, the phasic nature of BD may interact with PA levels of participants. Given the scale was administered at Week 4, we cannot guarantee the phase of BD that participants were in is consistent across the sample. In addition, there is no measure of activity later in the study to assess change in participants' level of PA. The disparity of energy expended in different states in BD highlights the potential for a bipolar-specific PA scale with population-specific standards. In terms of the PA Scale used (IPAQ-SF), limitations exist due to the nature of self-report and can be prone to error and recall bias.[52] In addition, the IPAQ considers the intensity of PA but does not record the types of exercise participants have engaged in. To reduce recall bias and to be able to review types of exercise, actigraphy could be used in addition to PA questionnaires.[52]

The nature of exploratory subanalyses in general poses further limitations. The RCT was powered for the primary outcome, that is, change in depression for the active treatment groups, which means the subanalysis is likely underpowered. Due to the small sample size of the data, there was insufficient power for a robust response to assess the categorical data measured from the IPAQ-SF scoring guide as nominal and as a factor within the model. PA is measured only once and as a covariate that is not directly being intervened, which limits interpretability of results. Lastly, the results presented in this subanalysis are statistically significant, but they represent small changes in outcome and thus small clinical significance. Future studies directly assessing the impact of PA programs should be powered to see greater changes in outcomes. Post hoc analyses always need to be interpreted with caution, as is the case for multiple comparisons.

Conclusion and Future Directions

Engaging participants to increase their activity may be a cost-effective way of improving treatment outcomes with additional health benefits for comorbid physical disorders This subanalysis of an adjunctive nutraceutical RCT adds some further support to the association between PA and mental health, and in particular, BD. PA measured at the beginning of this study was associated with functioning and quality of life at the end of the study. This subanalysis suggests that measures of PA may be useful when analyzing outcomes of a new treatment. Future research may clarify the potential adjunctive effects of higher PA and mitochondrial-enhancing therapies in treating bipolar depression symptoms, possibly through mitochondrial biogenesis.

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ORCID iD

Michael Berk, MD, PhD https://orcid.org/0000-0002-5554-6946

Supplemental Material

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