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ORIGINAL ARTICLE

# Open-label placebo reduces fatigue in cancer survivors: a randomized trial

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## Abstract

**Purpose** Cancer-related fatigue (CRF) is a common and challenging late effect for many cancer survivors. Clinical trials demonstrate robust placebo effects on CRF in blinded trials. Recently, open-label placebo (OLP) has been shown to improve a variety of symptoms in other populations. We conducted a randomized controlled trial to investigate the effect of OLP on CRF in cancer survivors, and to explore biologic and psychological correlates of placebo efficacy.

**Methods** Forty cancer survivors (92.5% female; mean age 47.3 years) were randomized to OLP or no treatment control. OLP participants were prescribed two placebo tablets twice daily, for 3 weeks. All participants completed assessments at Baseline, Day 8, and Day 22. The primary endpoint was change in CRF (FACIT-F), and secondary outcomes included exercise frequency, mood, and quality of life. We examined whether personality characteristics or a genetic variation important in dopamine catabolism (catechol-O-methyltransferase; COMT) affected the placebo response.

**Results** The OLP group reported significantly improved CRF at both Day 8 ($p = 0.005$) and Day 22 ($p = .02$), while the control group did not (ps > .05). CRF improvement differed by COMT genotype, but was not associated with personality characteristics. Marginal improvements were noted in the placebo group for some secondary outcomes (exercise frequency and quality of life), but not in the control group.

**Conclusions** Results demonstrate that even when administered openly, placebos improve CRF in cancer survivors and dopaminergic systems may be associated with this response. This novel research has meaningful implications for the use of OLP in symptom management for cancer survivors.

**Keywords** Open-label placebo · Cancer-related fatigue, cancer survivors · Genetics · Quality of life

Cancer-related fatigue (CRF) is one of the most commonly reported late effects of cancer treatment [1, 2]. Though the clinical presentation of CRF among cancer survivors is variable [3], symptoms usually include feelings of exhaustion, lack of energy, and loss of motivation [4] that cannot be easily explained by insufficient rest or an underlying medical condition [2]. Unlike general fatigue, symptoms of CRF are not clearly related to exertion and do not improve with rest [3]. As a result of CRF, patients can be trapped in a difficult cycle wherein their CRF symptoms discourage them from engaging in the very activities that could potentially improve fatigue and/or its associated symptoms, including physical and psychosocial treatments [5]. For many survivors, coping with CRF is difficult and frustrating because of its persistence and interference with daily activities [6], and negative impact on overall quality of life [7]. Despite significant efforts to understand the underlying mechanisms that cause CRF, its pathogenesis remains unclear and is believed to be complex and multifactorial [4, 8].

CRF treatment guidelines emphasize addressing potentially contributory medical conditions before considering exercise, cognitive-behavioral therapy, and other non-pharmacological

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treatments [2, 5, 9]. Stimulants have been shown effective for fatigue in other populations [10], but controlled trials find little benefit for post-treatment cancer survivors [9, 11], with several studies finding survivors assigned to both placebo and drug condition reporting significant improvements in fatigue [12, 13]. Given limited knowledge about what precisely causes CRF, clinicians are often unable to provide consistently effective therapy for patients suffering from CRF [14].

In clinical research, placebo effects are commonly viewed as nuisances to be managed by trial design and analysis [15], or a product of participant response bias [16]. However, a substantial body of research demonstrates placebo medications can ameliorate many symptoms, including pain, and nausea [15, 17, 18]. While placebos often affect patient perceptions of symptoms, they can also act on the same physiological systems as active agents to effect physical symptoms. For example, placebo effects on pain are associated with opioid receptor activation and blocked by opioid antagonists [19] and placebo administration to Parkinson's disease patients increases endogenous dopamine, the neurotransmitter targeted by conventional drug therapy [20]. Moreover, several studies suggest dopaminergic brain systems involved in motivation and reward play a significant role in the placebo response [19, 20]. Genetic variants in catechol-O-methyltransferase (COMT), an enzyme involved in dopamine clearance from the synaptic cleft, are associated with response to placebo [15, 21], indicating that individual differences in placebo responsiveness may be tied to differences in dopamine exposure [19, 20]. Specifically, individuals with genetic profiles associated with higher dopamine levels of have shown greater placebo response in studies of irritable bowel syndrome [21] and experimentally induced pain [22].

While placebos are most commonly administered in the context of some form of blinded administration, this may not be necessary for their effectiveness. Placebos are thought to exert therapeutic effects through activation of positive expectations (that could have developed through personal experiences, observational learning, information acquired from medical staff, and/or other resources such as the Internet) and classical conditioning mechanisms that are triggered within a clinical setting (e.g., swallowing a pill) [23, 24], neither of which require concealment. Psychological frameworks have been posited to explain the complex interaction of expectations and conditioning with the clinical situation, which can be further affected by factors such as the patient's genetics, and their personality [25]. Empirical support for open-label placebo (OLP) administration comes from recent studies reporting positive effects on irritable bowel syndrome [26], depression [27], and pain [18]. These studies supporting the efficacy of OLP, along with strong effects of placebo on CRF reported in blinded trials, led us to hypothesize that OLP administration would improve CRF in cancer survivors. In addition, we aimed to explore the potential impact of personality variables and genetic variation in COMT on the placebo effect.

## Methods

### Sample

Participants were recruited via oncologist referral, advertisements in the hospital, and by direct study staff approach at scheduled survivorship appointments between September 2015 and December 2016 at a cancer center. Individuals ($N = 263$) were screened for inclusion criteria: (1) ≥ 18 years of age, (2) no evidence of active disease, (3) ≥ 6-months post-cancer treatment, (4) score < 43 on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and (5) not being evaluated or treated for a medical cause of fatigue. One hundred and nineteen individuals were ineligible, and of the 144 eligible survivors, 57 declined participation, 47 expressed interest but did not respond to multiple enrollment invitations, and 40 consented and enrolled in the study. Twenty participants were randomized to each study condition (OLP and control) using a 1:1 allocation ratio (Fig. 1). Random allocation was achieved using a random number generator, in block sizes of 10, with the participant's condition assignment written in a sealed envelope. This procedure was performed by a research assistant (JEB). The trial concluded when no additional funding was available.

Participants were an average age of 47.3 years (range 22–74), primarily female (92.5%), married (62.5%), and non-Hispanic White (87.5%; Table 1). Participants were diagnosed with cancer an average of 9.3 years prior, most commonly with breast cancer (55.0%). Study procedures were approved by the hospital IRB and registered in the clinicaltrials.gov (NCT no. 02452710). All participants gave a written consent.

### Procedure

**Day 1 (Baseline)** Participants completed the questionnaires, and provided a saliva sample for genetic analysis or took a collection kit for mailed return, before meeting an investigator (ESZ, CJR) for a 15-min study initiation discussion. Following a written script (Appendix 1), investigators described the study rationale, possible impact of placebo on CRF, prior evidence of the impact of placebo on symptoms including fatigue, and answered participants' questions. Investigators and participants were blind to treatment assignment until the conclusion of the discussion, when participants opened a sealed envelope indicating their allocation. Participants assigned to OLP were given 120 placebo tablets, and verbal and written instructions to take two placebo tablets, twice a day for 22 days. Control participants were informed they would be mailed placebo tablets in 22 days. Placebos were small red tablets containing microcrystalline cellulose, FD&C Red 40 and ethyl alcohol, manufactured and labeled by an FDA-registered pharmacy. All participants were scheduled for follow-up phone appointments and provided written

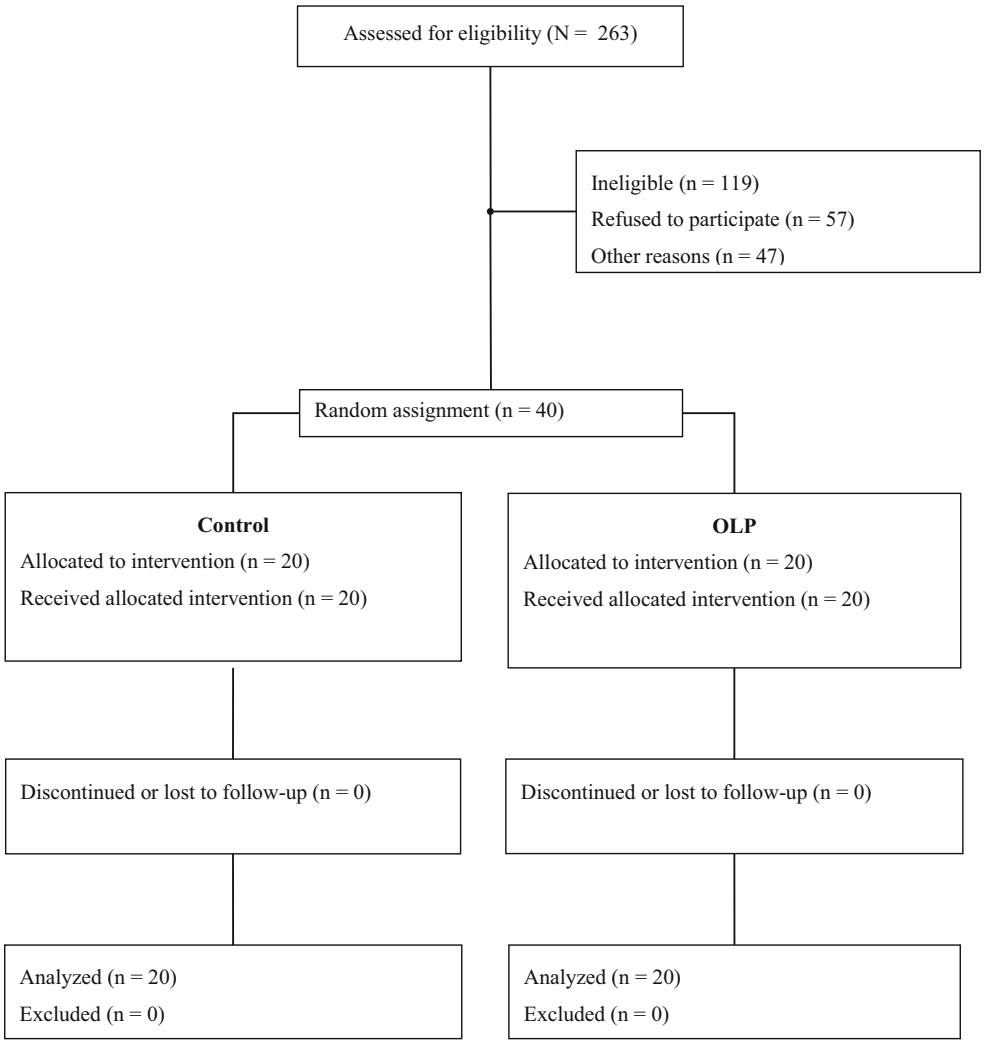


**Fig. 1** The CONSORT diagram

measures to complete at subsequent time points. Phone calls were conducted by research assistants (JEB, ALM) following written scripts (Appendix 2).

**Day 8 phone call** Participants were asked to complete the FACIT-F and Godin Leisure-Time Exercise Questionnaire (GLTEQ) and return them by mail. They also reported their FACIT-F responses verbally to a second research assistant blind to all study variables and group assignment. OLP participants were reminded about the importance of continued use of placebo tablets, and all participants were thanked for their continued participation, asked if they had questions, and encouraged to maintain study contact.

**Day 22 phone call** Participants completed the FACIT-F on paper and verbally as described above, before being asked to complete additional outcome measures (described below) and return them by mail. Control participants were reminded they would be mailed placebo tablets. No data were collected from participants after the Day 22 phone calls.

## Measures

**Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)** The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [28] is a 13-item self-report inventory widely used in studies of CRF [2, 12, 13, 29]. The FACIT-F inquires about fatigue over the prior week. Scores range from 0 to 52, with higher scores indicating less fatigue. The FACIT-F was assessed at Baseline, Day 8, and Day 22.

**Short Form-12** The Short Form-12 (SF-12) [30] is a 12-item self-report questionnaire commonly used to measure physical and mental health status in medical outcome research. The Physical and Mental Health Component Summary scores were used here. The SF-12 was assessed at Baseline and Day 22.

**Profile of Mood States–Short Form** The Profile of Mood States–Short Form (POMS-SF) [31] is a 35-item mood checklist. The Total Mood Disturbance score, assessed at Baseline and Day 22, was used here.

**Table 1** Demographic and medical characteristics of the sample

| | *M* | SD | *N* | % |
|---|---|---|---|---|
| Demographics | | | | |
| Age | 47.3 | 12.4 | | |
| Gender | | | | |
| Female | | | 37 | 92.5 |
| Male | | | 3 | 7.5 |
| Race/ethnicity | | | | |
| Caucasian | | | 35 | 87.5 |
| Hispanic | | | 2 | 5 |
| African American | | | 1 | 2.5 |
| Asian/Pacific islander | | | 1 | 2.5 |
| Other | | | 1 | 2.5 |
| Marital status | | | | |
| Married | | | 25 | 62.5 |
| Single | | | 12 | 30.0 |
| Divorced | | | 2 | 5 |
| Missing | | | 1 | 2.5 |
| Education | | | | |
| High school graduate | | | 7 | 17.5 |
| College graduate | | | 19 | 47.5 |
| Postgraduate | | | 14 | 35.0 |
| Employment status* | | | | |
| Full-time | | | 18 | 45.0 |
| Part-time | | | 11 | 27.5 |
| Disabled and unable to work | | | 4 | 10.0 |
| Unemployed | | | 13 | 30.9 |
| Medical characteristics | | | | |
| Years since cancer diagnosis | 9.3 | 9.6 | | |
| Cancer type | | | | |
| Breast cancer | | | 22 | 55.0 |
| Lymphoma | | | 11 | 27.5 |
| Leukemia | | | 3 | 7.5 |
| Other | | | 4 | 10.0 |

*Participants could choose more than one employment status

**Godin Leisure Time Exercise Quesitonnaire** The Godin Leisure Time Exercise Questionnaire GLTEQ [32] asks participants to respond to four items indicating how many times in an average week they participate in strenuous, moderate, and mild exercise. The GLTEQ was assessed at Baseline, Day 8, and Day 22.

**Balanced Inventory of Desirable Responding-Version 7** The Balanced Inventory of Desirable Responding-Version 7 (BIDR-7) [33] is designed to measure participants' tendency toward socially desirable responding, with high scores reflecting a tendency to overestimate or exaggerate positive attributes. The BIDR-7 was assessed at Baseline.

**Life Orientation Test-Revised** The Life Orientation Test-Revised (LOT-R) [34] is a six-item measure assessing generalized optimism previously used to examine optimism within cancer survivors [35]. The LOT-R was assessed at Baseline.

**Subjective change** Subjective change in fatigue and overall quality of life relative to baseline was assessed at Day 8 and Day 22 using single-item queries adapted from the Subjective Significance Questionnaire [36]. Participants were provided with seven response options, ranging from "Very much worse" to "Very much better."

**Genetics** Saliva samples were collected with an Oragene DNA (OG-500) test kit. DNA preps and genotyping were conducted using commercially available Taqman SNP genotyping assays for rs4680 and linked SNP, rs4818 were purchased from Applied Biosystems, and reads were obtained on COMT SNPs following the manufacturer's protocol on an Applied Biosystems 7900HT instrument, using SDS version 2.4 software.

### Statistical analysis

The primary analysis of change in CRF was conducted using paired *t* tests comparing Day 8 and Day 22 FACIT-F scores to baseline scores in each of the study groups (OLP or control). This approach was also used to test the effect of OLP on SF-12, POMS-SF, and GLTEQ measures. Responses to subjective improvement items were dichotomized and the proportion of participants reporting any improvement in fatigue and quality of life in the two study groups was compared using chi-square tests. To examine whether placebo response was associated with response bias and optimism measures, correlations between these variables and fatigue change scores at Day 8 and Day 22 were calculated. For genetic analyses, after insuring the Hardy–Weinberg equilibrium for both SNPs was met ($p > .05$) [37], a gene dosage model was used to investigate effects of increasing numbers of COMT minor alleles (rs4680, G and rs4818, G) on change in fatigue from Baseline to Day 8 and Day 22, while controlling for Baseline CRF in a linear regression. Effects of age (continuous), sex (male versus female), and race (Caucasian versus all others) did not modify the COMT effects and were not included in the final model. Gene-placebo treatment interaction effects were tested using a gene dose by treatment arm interaction term. Statistical analyses were performed using IBM SPSS Statistics 24.

## Results

### Cancer-related fatigue

The OLP group reported significantly improved CRF reflected in FACIT-F change scores from Baseline to Day 8

(mean = 5.4, $p < .01$, $d = .70$), and from Baseline to Day 22 (mean = 4.3, $p < .05$, $d = .57$), while the control group did not (Baseline to Day 8 mean = 1.7, $p > .05$, $d = .31$; Baseline to Day 22 mean = 1.2, $p > .05$, $d = .22$) (Table 2, Fig. 2). The proportion of participants reporting subjective improvement in CRF was significantly larger in the OLP group compared to the control group at Day 8 (45.0% versus 15.0%, $p < .05$), but not at Day 22 (42.1% versus 20.0%, $p > .05$). FACIT-F change scores at Day 8 and Day 22 were not significantly correlated with measures of social desirability (BIDR-7) or optimism (LOT-R) in either the placebo or no treatment control groups ($p > .05$).

## Mood, physical activity, and quality of life

At Day 22, there were no significant differences from baseline on the SF-12 Mental Component Summary, or the POMS-SF Total Mood Disturbance scale in either the OLP or control groups. On the SF-12 Physical Component Summary scale, the control group reported a small but non-significant decrease in functioning (mean = 1.8, $p > .05$), while the OLP group reported a slight improvement that approached, but did not reach statistical significance (mean = 2.6, $p = .09$, $d = .43$). More OLP than control participants reported their subjective quality of life was better at Day 8, with results approaching statistical significance (35.0% versus 10.0%; $p = .06$), but not at Day 22 (35.0% versus 20.0%; $p > .05$). Furthermore, OLP participants reported marginal increase in frequency of mild exercise over the past week (GLTEQ) compared with control participants (mean = 0.9 times/week, $p = .09$, $d = .42$ versus mean = 0.1 times/week, $p = .84$, $d = .05$), but not moderate (mean = 0.5 times/week, $p = .39$, $d = .21$ versus mean = 0.2 times/week, $p = .48$, $d = .17$) or strenuous exercise frequency (mean = increase 0.1 times/week, $p = .52$, $d = .16$ versus mean = decrease 0.4 times/week, $p = .74$, $d = .08$).

## COMT genetic effects

Genetic variations at COMT rs4818 and rs4680 were not associated with Baseline FACIT-F scores (Table 3). However,

**Table 2** Study outcomes by intervention condition

| | Statistics | | | | | | Change over time | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | Day 8 | | Day 22 | | Baseline to Day 8 | | Baseline to Day 22 | |
| | *M* | SD | *M* | SD | *M* | SD | *d* | *p* | *d* | *p* |
| FACIT-F | | | | | | | | | | |
| Control ($n = 20$) | 25.80 | 9.33 | 27.50 | 11.11 | 27.00 | 10.81 | 0.31 | 0.19 | 0.22 | 0.34 |
| Placebo ($n = 20$) | 28.40 | 9.59 | 33.80 | 9.70 | 32.70 | 11.10 | 0.70 | 0.005 | 0.57 | 0.02 |
| SF-12 (Mental Health Subscale)* | | | | | | | | | | |
| Control ($n = 20$)[a] | 42.88 | 8.15 | – | – | 43.52 | 7.30 | – | – | 0.18 | 0.48 |
| Placebo ($n = 20$)[b] | 41.89 | 9.16 | – | – | 39.80 | 9.92 | – | – | 0.29 | 0.24 |
| SF-12 (Physical Health Subscale)* | | | | | | | | | | |
| Control ($n = 20$)[a] | 43.47 | 9.48 | – | – | 41.32 | 7.83 | – | – | 0.34 | 0.18 |
| Placebo ($n = 20$)[b] | 46.85 | 13.60 | – | – | 49.87 | 13.59 | – | – | 0.43 | 0.09 |
| POMS (Total Mood Disturbance)* | | | | | | | | | | |
| Control ($n = 20$)[a] | 19.90 | 13.60 | – | – | 22.29 | 16.83 | – | – | 0.20 | 0.43 |
| Placebo ($n = 20$)[c] | 23.84 | 14.57 | – | – | 23.53 | 19.33 | – | – | 0.03 | 0.89 |
| Godin Leisure-Time Exercise Questionnaire | | | | | | | | | | |
| Mild exercise | | | | | | | | | | |
| Control ($n = 19$)[b] | 2.00 | 1.94 | 2.50 | 2.28 | 2.17 | 1.50 | 0.22 | 0.35 | 0.05 | 0.84 |
| Placebo ($n = 20$)[b] | 3.08 | 2.99 | 2.88 | 2.87 | 3.86 | 2.76 | 0.06 | 0.81 | 0.42 | 0.09 |
| Moderate exercise | | | | | | | | | | |
| Control ($n = 19$)[b] | 1.97 | 1.86 | 2.07 | 2.13 | 2.17 | 1.92 | 0.19 | 0.40 | 0.17 | 0.48 |
| Placebo ($n = 20$)[b] | 2.03 | 2.41 | 2.43 | 3.16 | 2.50 | 2.85 | 0.17 | 0.46 | 0.21 | 0.39 |
| Strenuous exercise | | | | | | | | | | |
| Control ($n = 19$)[b] | 1.21 | 1.62 | 1.28 | 1.79 | 0.78 | 1.40 | 0.07 | 0.75 | 0.16 | 0.52 |
| Placebo ($n = 20$)[b] | 1.3 | 1.92 | 1.03 | 1.69 | 1.39 | 1.85 | 0.3 | 0.19 | 0.08 | 0.74 |

*Measure not given at Day 8

[a] At Day 22, $n = 17$; [b] At Day 22, $n = 18$; [c] At Day 22, $n = 19$

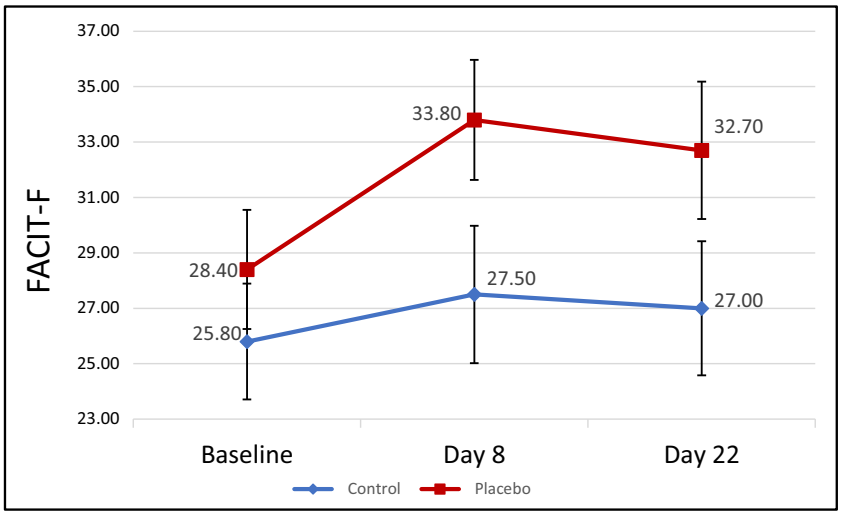


**Fig. 2** Changes in fatigue scores in the control and open-label placebo conditions

analyses examining the effect of treatment condition on fatigue as a function of COMT rs4818 showed a significant interaction, for both Day 8 ($P_{interaction} = .02$) and Day 22 ($P_{interaction} = .04$) change scores indicating that improvement on fatigue following OLP intervention differed by COMT genotype (Table 3). In rs4818 CC homozygotes, participants expected to have highest dopamine levels, OLP and control groups had similar modest improvements in Day 8 FACIT-F scores (2.0 and 1.8 points), but in GC heterozygotes (expected to have intermediate dopamine levels) Day 8 FACIT-F improvements were much larger for the OLP than control groups (9.3 versus 0.5 points). Of note, in the rs4818 GG homozygote group (expected to have the lowest dopamine levels), the pattern was not consistent, though the small number of

**Table 3** Changes in the FACIT-F score by COMT rs4818 and rs4680 genotype

| | | Baseline | Day 8 | Change Day 8 | Change between groups | Gene-treatment $P_{interaction}$[1] | Day 22 | Change Day 22 | Change between groups | Gene-treatment $P_{interaction}$[1] |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | *M* (SD) | *M* (SD) | *M* (SD) | *M* | *p* | *M* (SD) | *M* (SD) | *M* | *p* |
| rs4818 | | | | | | | | | | |
| C/C | | | | | 0.2 | 0.02 | | | 0.4 | 0.04 |
| Control | 6 | 25.7 (10.0) | 27.7 (12.6) | 2.0 (7.1) | | | 28.8 (11.8) | 3.2 (7.0) | | |
| Placebo | 8 | 30.1 (8.2) | 31.9 (11.1) | 1.8 (4.9) | | | 33.8 (9.5) | 3.6 (3.9) | | |
| G/C | | | | | 8.8 | | | | 5.9 | |
| Control | 8 | 23.9 (10.8) | 24.4 (12.0) | 0.5 (6.2) | | | 24.9 (11.8) | 1.0 (4.6) | | |
| Placebo | 10 | 26.4 (11.3) | 35.7 (9.7) | 9.3 (8.3) | | | 33.3 (13.3) | 6.9 (8.3) | | |
| G/G | | | | | 7 | | | | 13 | |
| Control | 3 | 28.7 (10.4) | 32.7 (11.5) | 4.0 (3.0) | | | 29.7 (11.9) | 1.0 (6.2) | | |
| Placebo | 1 | 36.0 (0.0) | 33.0 (0.0) | − 3.0 (0.0) | | | 24.0 (0.0) | − 12.0 (0.0) | | |
| rs4680 | | | | | | | | | | |
| G/G | | | | | 0.5 | 0.59 | | | 1.4 | 0.44 |
| Control | 5 | 32.0 (10.8) | 35.8 (11.2) | 3.8 (2.5) | | | 33.3 (12.1) | 1.3 (5.1) | | |
| Placebo | 4 | 25.7 (11.1) | 30.0 (3.6) | 4.3 (7.5) | | | 28.3 (5.1) | 2.7 (16.2) | | |
| G/A | | | | | 4.9 | | | | 4.5 | |
| Control | 8 | 25.9 (9.8) | 26.8 (11.3) | 0.9 (6.1) | | | 26.8 (11.3) | 0.9 (5.5) | | |
| Placebo | 13 | 29.5 (8.1) | 35.4 (9.1) | 5.8 (8.7) | | | 34.9 (9.8) | 5.4 (6.4) | | |
| A/A | | | | | 5.6 | | | | 1.2 | |
| Control | 4 | 20.0 (7.9) | 19.2 (7.8) | − 0.8 (4.9) | | | 20.8 (8.7) | 0.8 (5.6) | | |
| Placebo | 3 | 26.8 (14.8) | 31.5 (15.1) | 4.8 (5.7) | | | 28.8 (17.8) | 2.0 (3.2) | | |

[1] Gene-treatment $P_{interaction}$ determined using a term corresponding to the product of gene dose and treatment arm in a linear regression model

individuals in these groups makes their results more difficult to interpret. For the rs4680 genotype, fatigue change scores showed a similar pattern with larger placebo effects in AA and GA groups (expected to have high and intermediate dopamine levels, respectively) compared to GG homozygotes expected to have the lowest dopamine levels, though these differences were not statistically significant.

## Discussion

Our findings demonstrate that OLP can significantly improve CRF symptoms in cancer survivors compared with a no treatment control. The efficacy of OLP on CRF in this study was similar to the efficacy reported in pharmacotherapy trials of active agents [12, 13], with moderate to large effect size changes in fatigue. These data are consistent with reports of positive effects of OLP for other medical symptoms [18, 26, 27, 38], and demonstrate that concealment is not necessary for placebo to produce a clinically meaningful effect. We are aware of only one prior study that recently reported similar positive effects of OLP on CRF in survivors [39]; the fact that studies using different CRF measures in different samples report similar effects strongly supports the reliability of the findings. Beyond improvements in CRF, the effect of OLP on quality of life and activity in the study were more modest and not statistically significant. Moderate changes in physical health function and exercise that approached statistical significance suggest these outcomes should be studied further in trials with larger sample sizes and longer duration. Increasing physical activity is widely endorsed as a key component for treating CRF [2, 9], but initiating physical activity in a deconditioned oncology population can be extremely difficult [40]. If OLP could increase exercise initiation, it could potentially help survivors benefit from exercise recommendations.

We had hypothesized OLP response could be tied to personality differences but found no association between optimistic expectations and self-enhancement bias and placebo response. Personality variables that could be associated with OLP responsiveness should continue to be investigated, but our results suggest that general tendencies to expect the best outcome or to present one's self in the best light may not be among them. We also hypothesized OLP response would be tied to genetic variation in COMT genotype. Studies have reported OLP response is more robust in individuals with rs4680 genotypes associated with higher dopamine levels [21, 22]. In our data, this association was not statistically significant, but was observed at a statistically significant level for the rs4818 genotype. The rs4818 genotype has been previously associated with variability in cancer patients need for pain medication, but not with response to placebo [41], suggesting these genetic variations should be further studied for their potential association with oncology patients' response to treatments more broadly. Although this study is limited by the number of participants, especially those with specific genotypes, results support continued exploration in larger studies of the genetic effects of COMT and other genes thought to modify response to placebo.

It is noted this study had limited power to detect small differences which may account for the lack of significant findings on most secondary outcomes. Similarly, with a limited follow-up period, it is unclear if observed fatigue improvements would be maintained over time, or if effects not observed in a 3-week period would emerge. Given the unusual nature of the study, we took steps to promote participant engagement by increasing understanding of the study rationale, and adhering to self-administered placebo. As there were no study dropouts, we believe these procedures were successful, but they could limit generalizability of our conclusions. The placebo response is a complex mind-body phenomenon likely effected by many factors, including experience, situational context, interpersonal relationships, and expectations. Whether OLP would affect CRF if it were not provided in the same supportive context is an important question to be addressed in future studies.

Despite these limitations, our findings offer "proof-of-principle" for the efficacy of OLP to improve CRF, a common and vexing symptom. Placebo effects in medicine are often treated as nuisances complicating studies of "real" treatments, but our results support an emerging consensus that studying placebo effects can lead to better understanding of the complex psychophysiological factors affecting patients' symptoms and effective treatments [15, 19, 42]. The fact that placebos can be effective even without blinding should make this research easier to conduct, especially in medically vulnerably populations where blinding may not be acceptable. The efficacy of OLP also has meaningful clinical implications; more than half of community physicians report prescribing a treatment they believed to be placebo in the past year, but only 5% informed patients these treatments were placebo [43]. Results from our study and others [26, 27, 38] indicate physicians can openly disclose the true nature of placebos and still provide their benefit to patients. In the case of CRF, powerful effects of placebo are well known, but our study provides new evidence these positive effects may be obtained even when patients are aware they are taking a placebo. Given their association with deception and discredited medical treatments, it may be hard to imagine physicians prescribing placebo for CRF treatment. However, our findings suggest placebos may be outgrowing their status as "fake" treatments patients need to be deceived into taking, and on their way to becoming evidence-based treatments effective in managing CRF in cancer survivors.

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## Compliance with ethical standards

Study procedures were approved by the hospital IRB and registered in the clinicaltrials.gov (NCT no. 02452710). All participants gave a written consent.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## References

1. Cella D, Davis K, Breitbart W, Curt G, Fatigue C (2001) Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. J Clin Oncol 19(14): 3385–3391. https://doi.org/10.1200/JCO.2001.19.14.3385
2. Bower JE, Bak K, Berger A, Breitbart W, Escalante CP, Ganz PA, Schnipper HH, Lacchetti C, Ligibel JA, Lyman GH, Ogaily MS, Pirl WF, Jacobsen PB, American Society of Clinical Oncology (2014) Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. J Clin Oncol 32(17):1840–1850. https://doi.org/10.1200/JCO.2013.53.4495
3. Scott JA, Lasch KE, Barsevick AM, Piault-Louis E (2011) Patients' experiences with cancer-related fatigue: a review and synthesis of qualitative research. Oncol Nurs Forum 38(3):E191–E203. https://doi.org/10.1188/11.ONF.E191-E203
4. Horneber M, Fischer I, Dimeo F, Ruffer JU, Weis J (2012) Cancer-related fatigue: epidemiology, pathogenesis, diagnosis, and treatment. Dtsch Arztebl Int 109(9):161–171. https://doi.org/10.3238/arztebl.2012.0161
5. Kangas M, Bovbjerg DH, Montgomery GH (2008) Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. Psychol Bull 134(5):700–741. https://doi.org/10.1037/a0012825
6. Servaes P, Gielissen MF, Verhagen S, Bleijenberg G (2007) The course of severe fatigue in disease-free breast cancer patients: a longitudinal study. Psychooncology 16(9):787–795. https://doi.org/10.1002/pon.1120
7. Shi Q, Smith TG, Michonski JD, Stein KD, Kaw C, Cleeland CS (2011) Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's Studies of Cancer Survivors. Cancer 117(12):2779–2790. https://doi.org/10.1002/cncr.26146
8. Bruera E (2010) Cancer-related fatigue: a multidimensional syndrome. J Support Oncol 8(4):175–176
9. Howell D, Oliver TK, Keller-Olaman S, Davidson J, Garland S, Samuels C, Savard J, Harris C, Aubin M, Olson K, Sussman J, Macfarlane J, Taylor C, Sleep Disturbance Expert Panel on behalf of the Cancer Journey Advisory Group of the Canadian Partnership Against C (2013) A Pan-Canadian practice guideline: prevention, screening, assessment, and treatment of sleep disturbances in adults with cancer. Support Care Cancer 21(10):2695–2706. https://doi.org/10.1007/s00520-013-1823-6
10. Mendonca DA, Menezes K, Jog MS (2007) Methylphenidate improves fatigue scores in Parkinson disease: a randomized controlled trial. Mov Disord 22(14):2070–2076. https://doi.org/10.1002/mds.21656
11. Ruddy KJ, Barton D, Loprinzi CL (2014) Laying to rest psychostimulants for cancer-related fatigue? J Clin Oncol 32(18): 1865–1867. https://doi.org/10.1200/JCO.2014.55.8353
12. Spathis A, Fife K, Blackhall F, Dutton S, Bahadori R, Wharton R, O'Brien M, Stone P, Benepal T, Bates N, Wee B (2014) Modafinil for the treatment of fatigue in lung cancer: results of a placebo-controlled, double-blind, randomized trial. J Clin Oncol 32(18): 1882–1888. https://doi.org/10.1200/JCO.2013.54.4346
13. Bruera E, Yennurajalingam S, Palmer JL, Perez-Cruz PE, Frisbee-Hume S, Allo JA, Williams JL, Cohen MZ (2013) Methylphenidate and/or a nursing telephone intervention for fatigue in patients with advanced cancer: a randomized, placebo-controlled, phase II trial. J Clin Oncol 31(19):2421–2427. https://doi.org/10.1200/JCO.2012.45.3696
14. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P (2008) A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. J Natl Cancer Inst 100(16):1155–1166. https://doi.org/10.1093/jnci/djn250
15. Kaptchuk TJ, Miller FG (2015) Placebo effects in medicine. N Engl J Med 373(1):8–9. https://doi.org/10.1056/NEJMp1504023
16. Hrobjartsson A, Kaptchuk TJ, Miller FG (2011) Placebo effect studies are susceptible to response bias and to other types of biases. J Clin Epidemiol 64(11):1223–1229. https://doi.org/10.1016/j.jclinepi.2011.01.008
17. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M (2008) The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis 67(12): 1716–1723. https://doi.org/10.1136/ard.2008.092015
18. Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I (2016) Open-label placebo treatment in chronic low back pain: a randomized controlled trial. Pain 157(12):2766–2772. https://doi.org/10.1097/j.pain.0000000000000700
19. Zubieta JK, Stohler CS (2009) Neurobiological mechanisms of placebo responses. Ann N Y Acad Sci 1156:198–210. https://doi.org/10.1111/j.1749-6632.2009.04424
20. de la Fuente-Fernandez R (2009) The placebo-reward hypothesis: dopamine and the placebo effect. Parkinsonism Relat Disord 15(Suppl 3): S72–S74. https://doi.org/10.1016/S1353-8020(09)70785-0
21. Hall KT, Lembo AJ, Kirsch I, Ziogas DC, Douaiher J, Jensen KB, Conboy LA, Kelley JM, Kokkotou E, Kaptchuk TJ (2012) Catechol-O-methyltransferase val158met polymorphism predicts placebo effect in irritable bowel syndrome. PLoS One 7(10): e48135. https://doi.org/10.1371/journal.pone.0048135
22. Yu R, Gollub RL, Vangel M, Kaptchuk T, Smoller JW, Kong J (2014) Placebo analgesia and reward processing: integrating genetics, personality, and intrinsic brain activity. Hum Brain Mapp 35(9): 4583–4593. https://doi.org/10.1002/hbm.22496
23. Gollub RL, Kong J (2011) For placebo effects in medicine, seeing is believing. Sci Transl Med 3(70):70ps75
24. Petrie KJ, Rief W (2018) Psychobiological mechanisms of placebo and nocebo effects: pathways to improve treatments and reduce side effects. Annu Rev Psychol. https://doi.org/10.1146/annurev-psych-010418-102907
25. Rief W, Petrie KJ (2016) Can psychological expectation models be adapted for placebo research? Front Psychol 7:1876
26. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, Kowalczykowski M, Miller FG, Kirsch I, Lembo AJ (2010) Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One 5(12):e15591
27. Kelley JM, Kaptchuk TJ, Cusin C, Lipkin S, Fava M (2012) Open-label placebo for major depressive disorder: a pilot randomized controlled trial. Psychother Psychosom 81(5):312–314. https://doi.org/10.1159/000337053

28. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J (2005) Validation of the Functional Assessment Of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol 32(5):811–819
29. Alexander S, Minton O, Andrews P, Stone P (2009) A comparison of the characteristics of disease-free breast cancer survivors with or without cancer-related fatigue syndrome. Eur J Cancer 45(3):384–392. https://doi.org/10.1016/j.ejca.2008.09.010
30. Ware J (1993) SF-36 health survey: manual and interpretation guide. The Health Institute, Boston
31. Curran SL, Andrykowski MA, Studts JL (1995) Short form of the Profile Of Mood States (POMS-SF): psychometric information. Psychol Assess 7(1):80–83
32. Godin G, Shephard RJ (1985) A simple method to assess exercise behavior in the community. Can J Appl Sport Sci 10(3):141–146
33. Paulhus DL (1998) Paulhus deception scales (PDS): balanced inventory of desirable responding-7 user's manual. Multi-Health Systems, Inc., North Tonawanda
34. Scheier MF, Carver CS, Bridges MW (1994) Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol 67(6):1063–1078
35. Carver CS, Smith RG, Antoni MH, Petronis VM, Weiss S, Derhagopian RP (2005) Optimistic personality and psychosocial well-being during treatment predict psychosocial well-being among long-term survivors of breast cancer. Health Psychol 24(5):508–516. https://doi.org/10.1037/0278-6133.24.5.508
36. Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 16(1):139–144. https://doi.org/10.1200/JCO.1998.16.1.139
37. Rodriguez S, Gaunt TR, Day IN (2009) Hardy-Weinberg equilibrium testing of biological ascertainment for Mendelian randomization studies. Am J Epidemiol 169(4):505–514. https://doi.org/10.1093/aje/kwn359
38. Kam-Hansen S, Jakubowski M, Kelley JM, Kirsch I, Hoaglin DC, Kaptchuk TJ, Burstein R (2014) Altered placebo and drug labeling changes the outcome of episodic migraine attacks. Sci Transl Med 6(218):218ra215. https://doi.org/10.1126/scitranslmed.3006175
39. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR (2018) Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. Sci Rep 8(1):2784. https://doi.org/10.1038/s41598-018-20993-y
40. Brawley LR, Culos-Reed SN, Angove J, Hoffman-Goetz L (2003) Understanding the barriers to physical activity for cancer patients: review and recommendations. J Psychosoc Oncol 20(4):1–21
41. Rakvag TT, Ross JR, Sato H, Skorpen F, Kaasa S, Klepstad P (2008) Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain. Mol Pain 4(1):64. https://doi.org/10.1186/1744-8069-4-64
42. Tracey I (2010) Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. Nat Med 16(11):1277–1283. https://doi.org/10.1038/nm.2229
43. Tilburt JC, Emanuel EJ, Kaptchuk TJ, Curlin FA, Miller FG (2008) Prescribing "placebo treatments": results of national survey of US internists and rheumatologists. BMJ 337:a1938