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Research Article

DOES OCCASIONAL CANNABIS USE IMPACT ANXIETY AND DEPRESSION TREATMENT OUTCOMES?: RESULTS FROM A RANDOMIZED EFFECTIVENESS TRIAL

Jonathan B. Bricker, Ph.D.,[1,2]* Joan Russo, Ph.D.,[2] Murray B. Stein, M.D., M.P.H.,[3] Cathy Sherbourne, M.D.,[4] Michelle Craske, Ph.D.,[5] Trevor J. Schraufnagel, B.S.,[2] and Peter Roy-Byrne, M.D.[2]

This study investigated the extent to which occasional cannabis use moderated anxiety and depression outcomes in the Collaborative Care for Anxiety and Panic (CCAP) study, a combined cognitive-behavioral therapy (CBT) and pharmacotherapy randomized effectiveness trial. Participants were 232 adults from six university-based primary care outpatient clinics in three West Coast cities randomized to receive either the CCAP intervention or the usual care condition. Results showed significant ($P<.01$) evidence of an interaction between treatment group (CCAP vs. usual care) and cannabis use status (monthly vs. less than monthly) for depressive symptoms, but not for panic disorder or social phobia symptoms (all $P>.05$). Monthly cannabis users' depressive symptoms improved in the CCAP intervention just as much as those who used cannabis less than monthly, whereas monthly users receiving usual care had significantly more depressive symptoms than those using less than monthly. A combined CBT and medication treatment intervention may be a promising approach for the treatment of depression among occasional cannabis users. Depression and Anxiety 24:392–398, 2007.

Key words: *cannabis; depression; anxiety; treatment; primary care*

INTRODUCTION

Cannabis is the most widely used illegal drug among adults in North America and Western Europe [Farrell, 1999; Substance Abuse and Mental Health Services Administration (SAMHSA), 2002]. Recent scientific literature has examined the link between adult cannabis use and two of the most common mental disorders: anxiety and depression [Chen et al., 2002; Katerndahl and Realini, 1999; Lynskey et al., 2004; Sbrana et al., 2005]. This empirical literature has reported that adults with anxiety or depression use cannabis at rates two to eight times higher than the general population [Katerndahl et al., 1999; SAMHSA, 1998]. Specifically, use of cannabis among the general adult population is 8% [SAMHSA, 1998]. By contrast, depending on the frequency and severity of cannabis use and anxiety symptoms, recent studies show that the prevalence of cannabis use among those with anxiety, most notably panic and social anxiety, has usually ranged from 22%

[1]Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, Washington
[2]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington
[3]Departments of Psychiatry and Family and Preventive Medicine, University of California, San Diego, San Diego, California
[4]RAND Corporation, Santa Monica, California
[5]Department of Psychology, University of California, Los Angeles, Los Angeles, California

*Correspondence to: Jonathan B. Bricker, Ph.D., Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, 1100 Fairview Avenue North, M2-C826, PO Box 19024, Seattle, WA 98109. E-mail: jbricker@u.washington.edu

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to 29% [Agosti et al., 2002; Katerndahl and Realini, 1999; Sbrana et al., 2005], though rates as high as 60% have been observed among those with panic symptoms [Dannon et al., 2004]. Regarding depression and cannabis use, cannabis use among those with depressive symptoms ranges from 17% to 40% [Chen et al., 2002; Lynskey et al., 2004; SAMHSA, 1998]. This comorbidity evidence suggests that a significant portion of adults with anxiety or depression are cannabis users.

Given this significant comorbidity, a growing concern among scientists and clinicians is that these individuals may be difficult to treat effectively. They are more clinically complex, and continued cannabis use may interfere with treatment of the anxiety and depression [Raphael et al., 2005]. Indeed, few guidelines specifically address anxiety and depression interventions for those who use cannabis [Hall and Pacula, 2003]. To help address this important knowledge gap, our aim in this article is to understand the extent to which recent cannabis use might impact the effective treatment of adult anxiety and depression. Pursuing this aim is important for several reasons. For example, if there is little or no improvement in anxiety or depression among cannabis users, then such evidence could stimulate the development of interventions tailored to the specific challenges of treating anxiety or depression with co-occurring cannabis use. On the other hand, if an intervention can be identified that leads to the substantial improvement in anxiety or depression, even for those with co-occurring cannabis use, then this evidence would show that such an intervention could be potentially promising for helping this population of patients.

To date, only one study has examined whether cannabis use might impact adult anxiety intervention outcomes. This study compared the effectiveness of paroxetine treatment for panic disorder (PD) in adult patients with and without recent cannabis use, showing that both groups had significant and similar improvement in their panic symptoms [Dannon et al., 2004]. However, this study was limited by its lack of a comparison group and small sample size ($n = 66$). Regarding depression, no treatment studies have examined to what extent cannabis use might impact adult depression intervention outcomes. The only related studies have focused on depression treatment outcomes among a sample of adolescent cannabis users [Cornelius et al., 2005; Riggs et al., 1997]. These studies also lacked comparison groups and had small sample sizes (*n*s ranged from 8 to 10). In summary, a research study is needed that uses a comparison group and a larger sample size to examine the extent to which recent cannabis use might impact the effective treatment of adult anxiety and depression.

The Collaborative Care for Anxiety and Panic (CCAP) trial is a three-site primary care study designed to examine the clinical effectiveness of a combined cognitive-behavioral therapy (CBT) and medication intervention compared with usual care provided by six university-based primary care clinics in three West Coast cities [Roy-Byrne et al., 2005]. Important anxiety and depression outcomes of the CCAP intervention were marked reductions in (1) "core" panic symptoms [as measured by the Anxiety Sensitivity Index; ASI; Reiss et al., 1986] and (2) depression symptoms [as measured by the Center for Epidemiologic Studies Depression Scale; CES-D; Radloff, 1977]. The CCAP trial also included social phobia symptom outcome data, which is especially pertinent to this study, because those with social phobia symptoms have the highest proportion of recent cannabis use of any of the anxiety disorders [29%; Agosti et al., 2002].

The effectiveness design of the CCAP trial allowed it to include participants with recent (i.e., monthly) cannabis use. However, the CCAP trial excluded those who met DSM-IV criteria for current cannabis abuse or dependence: (1) because the primary purpose of the CCAP trial was to test the effectiveness of an anxiety treatment and (2) because of concerns that such high levels of usage could severely limit patient participation. Nonetheless, given the paucity of studies and importance of the topic, the inclusion of monthly cannabis users in the CCAP trial provides this study with a unique opportunity to examine the following question: To what extent does recent cannabis use moderate the following outcomes of the CCAP intervention: (1) core panic symptoms (i.e., anxiety sensitivity), (2) social phobia symptoms, and (3) depression symptoms?

METHODS

STUDY POPULATION

Participants for the CCAP randomized treatment trial [Roy-Byrne et al., 2005] were 232 individuals with PD who were recruited from university-affiliated primary care clinics in Los Angeles, San Diego, and Seattle. Eligible participants (1) were between 18 and 70 years old; (2) met DSM-IV criteria for PD, with at least one panic attack in the past week; (3) spoke English; (4) had telephone access; and (5) stated a willingness to accept a combined treatment of anti-anxiety medication and CBT. Because this CCAP intervention was a treatment effectiveness trial, psychiatric and medical comorbidities were not reasons for exclusion, except those that were potentially life threatening (i.e., suicidal ideation, terminal medical illness) or those expected to limit patient participation severely (e.g., current substance abuse or dependence, psychosis, dementia, pregnancy). Patients receiving psychiatric disability benefits or those already seeing a psychiatrist or cognitive behavioral therapist were excluded

PROCEDURES

We recruited participants in clinic waiting rooms using a validated two-question PD screener [Stein

et al., 1999]. Referrals from clinic physicians were also actively solicited. All positive screened or referred patients were administered the Composite International Diagnostic Interview [CIDI; World Health Organization (WHO), 1997] over the phone by a trained research assistant to determine eligibility. The research assistant, blind to the randomization scheme, then gave eligible subjects' names to a study coordinator, who randomized subjects using alternating assignment, stratified within site by comorbid major depression and referral status [referred vs. screened; Roy-Byrne et al., 2000]. Once randomized, and consistent with the effectiveness design, neither patients, therapists, nor primary care physicians (PCPs) were blind to assignment.

Participants were randomized to receive either the CCAP intervention or usual care condition. The CCAP intervention had two main components: (1) a CBT psychological treatment and (2) a psychiatric medication treatment. The CBT psychological treatment component of the CCAP intervention utilized a trained behavioral health specialist (BHS) to deliver six face-to-face sessions of CBT for PD, as well as associated anxiety and depression symptoms [Barlow & Craske, 2000; Craske and Barlow, 2000]. The BHS interventionists had ongoing supervision meetings with a study psychiatrist and a study psychologist to discuss clinical treatment issues.

The second main component of the CCAP intervention was medication managed by the PCP using a medication algorithm [Roy-Byrne et al., 1998]. A consulting psychiatrist at each study site relayed specific medication recommendation to the participant's PCP via the BHS.

Participants had to complete the six CBT sessions within the first 3 months of the study. Six follow-up telephone "booster" sessions, each lasting 15–30 minutes, were scheduled the rest of the year at 6- to 12-week intervals to monitor clinical status, reinforce cognitive-behavioral skills and prescribed use of medications, and make further treatment recommendations, if needed. Because the purpose of the CCAP intervention was to treat panic and associated anxiety and depression, there was no intervention on participants' current substance use.

Using methods previously used by the large, multicenter collaborative panic efficacy study [Barlow et al., 2000], expert CBT Master's-level or newly graduated doctoral-level psychologists independently rated 63 separate BHS sessions, randomly selected across the six CBT sessions, for adherence to content (rated 1–7), overall competency (rated 0–8) to deliver the treatment, and session length. Average adherence was 4.1 ($SD = 0.74$) and average competency was 4.4 ($SD = 1.9$), indicating adequate adherence and competency in these newly trained BHSs. Session lengths ranged from 45 to 60 minutes. There were no cross-site differences in the BHS ratings of adherence and competency, nor did the medication recommendations provided by study psychiatrists differ across sites, based on an independent analysis of concordance across pairs of sites for case descriptions for one of every six intervention patients.

Participants randomized to the usual care control group received treatment as usual (typically pharmacotherapy) from their PCP without psychiatric consultation, and may have received referrals from their PCP to specialty mental health providers.

All assessments of the participants, including measures of participants' core panic symptoms, social phobia symptoms, and cannabis use, were conducted via telephone-administered questionnaires by trained research assistants. These research assistants were blind to participants' intervention status. All assessments were conducted at baseline, as well as 3, 6, 9, and 12 months after baseline. Study procedures are described in further detail in Roy-Byrne et al. [2005] and Craske et al. [2002].

All study procedures were approved by the Institutional Review Boards of all three participating universities (University of California, Los Angeles and San Diego, University of Washington, Seattle).

MEASURES

Core panic symptoms were assessed by the 16-item Anxiety Sensitivity Index [ASI; Reiss et al., 1986; across the baseline, 3-, 6-, 9-, and 12-month measures, the average $\alpha = .91$], on which participants' overall discomfort with anxious cognitions, behaviors, and physical sensations is rated on a scale from 1 (*Very little*) to 5 (*Very much*), with higher scores reflecting higher levels of anxiety sensitivity. A sample item is: "It scares me when I feel shaky." Past research has shown that the ASI has good psychometric properties [Rapee and Medoro, 1994; Zinbarg et al., 1999].

Social phobia symptoms were assessed by the 5-item Social Phobia subscale of the Fear Questionnaire [SP; Marks & Matthews, 1979; across the baseline, 3-, 6-, 9-, and 12-month measures, the average $\alpha = .85$], on which participants' phobic avoidance of a variety of social situations (e.g., talking to people in authority) is rated on a scale from 0 (*Would not avoid it*) to 8 (*Always avoid it*), with higher scores reflecting higher levels of social phobic symptoms. A sample item is: "How much do you avoid talking to people in authority because of fear or unpleasant feelings?" Past research has shown that the SP subscale has good psychometric properties [Van Ameringen et al., 2004; Van Zuuren, 1988].

Depression symptoms were assessed by the 20-item Center for Epidemiological Studies—Depression Scale [CES-D; Radloff, 1977; across the baseline, 3-, 6-, 9-, and 12-month measures, the average $\alpha = .94$], which rated participants' depressive symptoms for the past 7 days on a scale from 1 (*Rarely or none of the time*) to 4 (*Most or all of the time*), with higher scores reflecting higher levels of depressive symptoms. A sample item is: "I had crying spells." There is empirical evidence that

the CES-D has good psychometric properties [Hann et al., 1999; Radloff, 1977].

We assessed recent cannabis use at baseline using the following question: "During the past month, how often would you say you have smoked cannabis, on average?" [Burnam et al., 1995]. Study participants who indicated that they used at least once during the past month (but no more than once a week) were classified, for simplicity, as "monthly" cannabis users. In contrast, those who indicated not using at all in the past month were classified, also for simplicity, as "less than monthly" cannabis users. (Note that less than monthly cannabis use includes any frequency of use that is less than monthly. Also note that those who used more than once a week were excluded from the study due to concerns that such high levels of usage could severely limit patient participation.) To increase accurate responding, before answering this question, participants were told that this "information is kept confidential and will not be shared with your doctor or health plan."

STATISTICAL ANALYSES

Analyses were intent-to-treat, with all randomized patients used in all analyses. The sample was divided into two groups: (1) those reporting monthly (but less than weekly) cannabis use at baseline ($n = 29$) and (2) those reporting less than monthly use ($n = 203$). Both χ^2 tests with corrections for continuity and *t*-tests were used to compare the cannabis user and nonuser groups on pertinent demographics and anxiety sensitivity, social phobia, and depression at baseline. Demographic factors significantly associated with recent cannabis use were included as covariates in the regression models.

To determine whether the core panic, social phobia, and depression treatment outcomes were moderated by recent cannabis use, random coefficient hierarchical models [Hedeker and Gibbons, 1996] were fit to the data for each of the following dependent outcome variables at 3-, 6-, 9-, and 12-month follow-up: (1) ASI, (2) SP scale, and (3) CES-D. Mixed effect linear regressions were used for each of these three continuous outcome measures. In the regression models, the intercept (participants) were random coefficients, whereas all other effects were fixed. A model was fit that contained one three-way interaction between treatment group (CCAP vs. usual care), time (3- vs. 6- vs. 9- vs. 12-month measures) and cannabis use status (use vs. nonuse). In the event of a nonsignificant three-way interaction, a model would be refit with all three two-way interactions between time (3- vs. 6- vs. 9- vs. 12-month measures), study group (CCAP vs. control), and cannabis use status (monthly vs. less than monthly). Each insignificant two-way interaction was eliminated from the model until only significant interactions were included (or none, if there were no significant two-way interactions). We also conducted analyses examining the main effects of treatment group, time, and cannabis use. The appropriate baseline levels of (1) ASI, (2) SP scale, and (3) CES-D were included in all models. Sensitivity analyses were also conducted without the use of any covariates.

RESULTS

DEMOGRAPHIC AND BASELINE CLINICAL CHARACTERISTICS

The demographic and baseline clinical characteristics of monthly and less than monthly cannabis users are reported in Table 1. With the exception of employment status, the monthly cannabis users tended to have lower social and economic status than those who used less than monthly. Specifically, it can be seen that study participants who had used cannabis monthly (1) had a lower income (i.e., gross income less than

TABLE 1. Demographic and baseline anxiety/depression of monthly and less than monthly cannabis users

Characteristic	Less than monthly $N = 203$ N (%) or M (SD)	Monthly $N = 29$ N (%) or M (SD)	Test statistics $T(230)$ or $\chi^2(1)$
Demographics			
Washington site	98.0 (48.3%)	20.0 (69.0%)	3.56[a]
Female	141.0 (69.5%)	15.0 (51.7%)	2.86
Caucasian	137.0 (67.5%)	17.0 (58.6%)	0.54
Age in years	41.5 (11.1)	39.3 (12.4)	1.00
Low income	58.0 (28.7%)	14.0 (48.3%)	3.66[a]
Employed	115.0 (56.7%)	14.0 (48.3%)	0.42
At least high school education	160.0 (78.8%)	17.0 (58.6%)	4.66*
Married	57.0 (28.2%)	3.0 (10.3%)	3.34[a]
Baseline anxiety and depression			
Anxiety sensitivity	33.0 (12.7)	35.8 (9.0)	−1.12
Social phobia	18.3 (10.0)	23.8 (10.5)	−2.72**
Depression	26.7 (14.0)	32.1 (13.7)	−1.93[a]

[a]$P < .06$, *$P < .05$, **$P < .01$.

$6,500 per year), (2) were less likely to have at least a high school education, and (3) were less likely to be married. Monthly cannabis users were also more likely to be from the Washington State site, which included a large public hospital serving lower income patients. It is noteworthy that the monthly and less than monthly users were similar in age, gender, and race. Finally, a similar percentage ($P>.05$) of all monthly and less than monthly cannabis users were assigned to the CCAP intervention and usual care control groups, respectively.

Regarding baseline characteristics, the monthly cannabis users reported being more anxious and depressed than the less than monthly users. Specifically, the monthly cannabis users reported significantly higher ($P<.01$) levels of social phobia and nearly significantly ($P<.06$) higher levels of depression. Although not reaching statistical significance, monthly users reported higher levels of anxiety sensitivity.

INTERVENTION EFFECT MODIFICATION BY CANNABIS USE

There was a non-significant ($P>.05$) three-way interaction between treatment group (CCAP vs. usual care), time (3- vs. 6- vs. 9- vs. 12-month measures), and cannabis use status. Therefore, reported in column two of Table 2 are the results of the test for effect modification (i.e., "moderation") of the CCAP intervention by monthly cannabis use. As can be seen, there was no evidence of an interaction between treatment group status and cannabis use status for panic (i.e., anxiety sensitivity) or social phobia scores. For example, monthly cannabis users in the control group had social phobia scores [adjusted $M = 19.64$; 95% confidence interval (CI) = 16.35–22.92] that were not significantly different, as reported as an average of their 3-, 6-, 9-, and 12-month study outcome assessments, from those who used less than monthly (adjusted $M = 18.16$; 95% CI = 16.79–19.52). (Note the overlap in the 95% confidence intervals for these two groups' scores). Monthly cannabis users in the intervention group also had social phobia scores (adjusted $M = 15.93$; 95% CI = 12.55–19.32) that were not significantly different, as reported as an average of their 3-, 6-, 9-, and 12-month study outcome assessments, than scores of those who used less than monthly (adjusted $M = 13.18$; 95% CI = 11.89–14.8).

There was significant ($P<.01$) evidence that of an interaction between treatment group and cannabis use status for depression. As illustrated in Figure 1, in the control group, monthly cannabis users reported significantly higher levels of depression (adjusted $M = 28.54$; 95% CI = 24.20–32.87) than those who used less than monthly (adjusted $M = 21.73$; 95% CI = 19.92–23.55), as reported as an average of their 3-, 6-, 9-, and 12-month study outcome assessments. In contrast, both monthly and less than monthly cannabis users in the CCAP intervention group reported similar levels of depression in their treatment outcome assessments (monthly users' adjusted $M = 17.58$; 95% CI = 13.04–22.11; less than monthly users' adjusted $M = 18.94$; 95% CI = 17.21–20.66).

OTHER INTERACTIONS AND THE MAIN EFFECTS

Also, it is noteworthy that there was a significant interaction ($P<.01$) between cannabis use status (monthly vs. less than monthly) and time relative to anxiety sensitivity. Specifically, among the monthly cannabis users, anxiety sensitivity scores followed a differential pattern of statistical significance at 3 months ($P=.90$), 6 months ($P<.01$), nine months ($P<.05$), and 12 months ($P=.06$), controlling for baseline anxiety sensitivity scores, intervention group membership, and income level. At each time point, the means showed that the monthly cannabis users'

TABLE 2. *Z* scores for interactive (and direct) effects of CCAP intervention and cannabis use on anxiety sensitivity, social phobia, and depression

	Intervention X cannabis use	CCAP intervention	Cannabis use
Anxiety sensitivity	−0.23	−4.98***	−0.13
Social phobia	0.49	−5.69***	1.56
Depression	−2.61**	−2.34*	2.95**

*$P<.05$, **$P<.01$, ***$P<.001$.

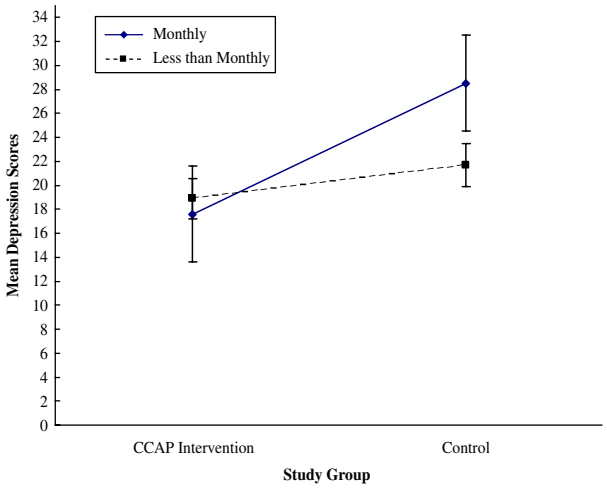

Figure 1. Mean and 95% CIs for CES-D scores in the CCAP intervention and control groups, according to whether participants used cannabis monthly. *Note.* CES-D scores represent the average of all scores across the 3-, 6-, 9-, and 12-month assessments, adjusted for baseline scores and participant income level.

group reported higher anxiety sensitivity scores than the less than monthly cannabis users' group.

Finally, for the reader's information, the main effects of the treatment group and cannabis use status on anxiety and depression outcomes are also presented in columns three and four of Table 2. Note that there was no direct effect of time (all *P*s > .05) on the anxiety sensitivity, social phobia, and depression scores.

DISCUSSION

EFFECT MODIFICATION OF ANXIETY

The study found no evidence that monthly cannabis use moderated the core panic and social phobia outcomes in the CCAP intervention. Because the CCAP intervention had direct effects on lowering both anxiety and depression, this raises the question: Why would there be a significant interaction between treatment group and cannabis use status for depression but not anxiety? A significant portion of adults with anxiety or depression are cannabis users [Agosti et al., 2002; Chen et al., 2002; SAMHSA, 1998]. Moreover, the comorbidity between anxiety and depression is high, suggesting that both anxiety and depression may have common origins and/or symptoms [Means-Christensen et al., 2006]. Thus, cannabis use may very well moderate anxiety treatment outcomes as well as depression, but the current study simply did not have sufficient power to detect this moderation. Because only one prior study [Dannon et al., 2004] has examined whether cannabis use might impact adult anxiety intervention outcomes, it would be important for future research, with larger samples of cannabis users, to investigate further possible anxiety effect modification by cannabis use.

EFFECT MODIFICATION OF DEPRESSION

The significant effect modification of depression by cannabis use raises several interpretations. Monthly cannabis users receiving usual care (control group) had higher levels of depression than those who used cannabis less than monthly. But monthly cannabis users assigned to the CCAP intervention experienced significant reductions in their depression that were similar in magnitude to those of less than monthly cannabis users. These results suggest that monthly cannabis users' depression appeared to improve in the CCAP intervention just as much as for those who used cannabis less than monthly, whereas monthly users receiving usual care had significantly more depression symptoms than those who used less than monthly. In light of important concerns about the treatment of depression among cannabis users [Raphael et al., 2005], it is encouraging that occasional cannabis use did not appear to prevent positive changes in depression among those in the CCAP intervention. Thus, a clinical implication is that a combined CBT and medication treatment intervention (as was used in the CCAP intervention), may be a promising approach for the treatment of depression among occasional cannabis users. This possibility should be further evaluated in future empirical research.

OTHER LIMITATIONS

The implications of this study are tempered by several other limitations. In addition to the main limitations we already discussed, there was only one item for the cannabis use measure, and that item that was not biochemically validated. On the other hand, because cannabis use was gathered by self-report, it is possible that monthly users were using much more than they reported. Therefore, the current results may be underestimating the influence of cannabis use on anxiety and depression outcomes. To be conservative, it is important that the current results be interpreted as applicable only to patients with PD who use cannabis occasionally. And we believe that this is an important subgroup, because 22–29% of panic patients use cannabis [Agosti et al., 2002; Katerndahl and Realini, 1999]. Other limitations include the lack of an unintervened control group (as this was an effectiveness study) and the post hoc nature of the analysis.

Finally, as suggested by a reviewer, an interesting future question to explore is why the CCAP intervention had greater effectiveness than the usual care group. One possible reason is that participants in the CCAP intervention had a longer total time in therapy than those in usual care, which suggest that the effectiveness of the CCAP intervention could be attributed to the therapist's attention rather than to specific CBT methods. Total time in therapy is indeed greater in the CCAP intervention group than in the usual care group, because the CCAP intervention included both CBT and pharmacotherapy, whereas the usual care group typically received pharmacotherapy. A future evaluation of why the CCAP intervention was effective could be to add a comparison intervention group in which participants receive ongoing attention by a therapist, but not CBT.

CONCLUSION

There was no evidence of an interaction between the treatment group and cannabis use status for either social phobia or core panic symptoms. However, monthly cannabis users' depression symptoms improved in the CCAP intervention just as much as the symptoms of those who used cannabis less than monthly, whereas monthly cannabis users receiving usual care had significantly more depression symptoms than those who used less than monthly. A combined CBT and medication treatment intervention (as was used in the CCAP intervention), may be a promising approach for the treatment of depression among occasional cannabis users.

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