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ORIGINAL INVESTIGATION

Effects of topiramate on the association between affect, cannabis craving, and cannabis use in the daily life of youth during a randomized clinical trial

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Abstract

Rationale Topiramate is an anticonvulsant currently under study for treating substance use disorders. Topiramate is thought to reduce substance use by attenuating craving and the rewarding effects of acute substance use through its concurrent GABAergic agonism and glutamatergic antagonism. Importantly, topiramate also impacts mood states central to many models of substance use. Despite this, little previous research has examined whether topiramate attenuates the respective associations of affect and craving with substance use.

Objectives We conducted a secondary analysis of 63 youths that exhibited heavy cannabis use, aged 15–24 years, who were randomized in a double-blinded 6-week clinical trial comparing the effects of topiramate (up to 200 mg/day) and placebo on cannabis use. Ecological momentary assessment data were leveraged to model the role positive affect, negative affect, and craving on use over the 6-week period and whether topiramate attenuated associations between these feeling states and cannabis use.

Results Findings showed that craving was positively associated with use at the within-person level, while positive affect was negatively associated with use at the between-person level. Topiramate appears to attenuate the negative association of between-person positive affect (i.e., average) and cannabis use. Specifically, those in the placebo condition exhibited this inverse association between average positive affect and use while those in topiramate condition did not. No other significant affect or affect × medication condition interactions were observed.

Conclusions These findings implicate craving and low positive affect as important risk factors for cannabis use in youth in treatment. Topiramate may attenuate this association for positive affect.

Keywords Ecological momentary assessment · Cannabis use · Positive affect · Craving · Youth · Topiramate

Some data reported in this study were presented in other published articles. Most notably, the treatment outcomes of this randomized controlled trial were published elsewhere (Miranda et al. 2017). In addition, previous versions of these analyses were presented at the Annual Collaborative Perspectives on Addiction, April 4–6, 2019, Providence, Rhode Island.

This article belongs to a Special Issue on Cannabis and Cannabinoids

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Cannabis is the most commonly used illicit drug among adolescents and young adults in the USA (Johnston et al. 2018) and confers risk for myriad adverse outcomes (Hall and Lynskey 2020; Silins et al. 2017). Roughly 1 in 7 youth who use cannabis will develop cannabis use disorder (CUD; SAMHSA 2019), and cannabis use accounts for the majority of substance use treatment admissions among youth (SAMHSA 2019). Current best practices for treating CUD rely on behavioral interventions (Aguinaldo et al. 2019) that demonstrate small to medium size effects in reducing youth cannabis use (Dennis et al. 2004). On the whole, these effects are weaker than those observed with adults, and many youth do not show sustained benefits (Davis et al. 2017; Jensen et al. 2011). Not surprisingly, recent reviews have stressed the need for improvements in the treatment of youth cannabis use (Aguinaldo et al. 2019; Squeglia et al. 2019).

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One way to improve cannabis treatment is to augment the best available psychosocial interventions with pharmacotherapy. Effective pairing of psychosocial intervention and pharmacotherapy requires understanding how medications work (Miranda and Treloar 2016; Squeglia et al. 2019). Few studies, however, have evaluated medications for treating CUD in youth. Prior work suggests that topiramate, a mixed GABA agonist and AMPA/kainite glutamate receptor antagonist, may help youth limit their cannabis use (Miranda et al. 2017). Specifically, topiramate reduced how many grams of cannabis youth smoked on using days but did not affect how often they smoked (Miranda et al. 2017). The current secondary analysis sought to advance our understanding of how topiramate impacts cannabis use by testing the hypothesis that it weakens the links between positive and negative affect and cannabis use as well as cannabis craving and cannabis use.

Affect figures prominently in most contemporary theoretical models of addiction (e.g., Baker et al. 2004; Buckner et al. 2013a; Koob and Le Moal 2001; Smith and Cyders 2016; Volkow et al. 2016). In line with structural models of affect that demonstrate that negative affect and low positive affect are distinct, yet related constructs (Clark et al. 1994), contemporary theoretical models of addiction suggest that individuals engage in cannabis and other substance use to alleviate negative affect or enhance positive affect. Perhaps the most compelling evidence for the role of affect comes from ecological momentary assessment (EMA) studies, which capture positive and negative affect and substance use multiple times a day in daily life. This work affords rich temporally sequenced data that elucidates within- and between-person associations between affect and substance use.

Although evidence is mixed, some EMA studies find that greater negative affect is associated with greater use within- and between-persons (e.g., Hussong 2007; Simons et al. 2014). For positive affect, evidence suggests that its association with use is discordant across the within- and between-person levels (Colder et al. 2010; Emery and Simons 2020; Simons et al. 2014). Studies of young adults consistently find a positive within-person association between positive affect and alcohol use (Colder et al. 2010; Dvorak et al. 2018; Emery and Simons 2020; Simons et al. 2010, 2014), such that higher positive affect at a moment or across a day is associated with higher drinking levels. Between-persons, however, lower average (or dispositional) positive affect is associated with high overall drinking levels (Colder & Chassin 1997; Emery and Simons 2020; Simons et al. 2014; Wills et al. 1999). Enhancing positive affect and coping with negative affect are common motives for youth to use cannabis (Fox et al. 2011; Patrick et al. 2016a). Using EMA, research shows that both positive and negative affect are associated with youth cannabis use (Buckner et al. 2012; Patrick et al. 2016b; Shrier et al. 2014) and relapse (Buckner et al. 2013b; Scott et al. 2018).

Despite evidence that topiramate acts a mood stabilizer (Marcotte 1998; McIntyre et al. 2002; Mowla and Kardeh 2011), no study to our knowledge has examined the relationship of topiramate and affect in the context of substance use. Additionally, although topiramate reduces cannabis use (Miranda et al. 2017) and reduces craving for alcohol (Johnson et al. 2003), whether it serves to decouple craving and cannabis use remains untested. The purpose of this secondary analysis was to test the hypothesis that negative affect and cannabis craving would exhibit positive associations with the likelihood of cannabis use and quantity of cannabis used on use days at both the within- and between-person levels. Positive affect was hypothesized to exhibit a positive prospective relationship with both the likelihood of cannabis use and quantity of cannabis used on use days at the within-person level and inversely associated with the likelihood of cannabis use and quantity of cannabis used on use days at between-person level. Data were culled from a parent randomized clinical trial (RCT) that tested topiramate for treating cannabis misuse in youth (Miranda et al. 2017).

We expected medication condition to moderate the relationships. Specifically, we hypothesized that medication condition would moderate the association between cannabis craving and cannabis use such that the relationship between craving and the likelihood of cannabis use and quantity of cannabis used on use days will be attenuated for youth in the topiramate condition and not in the placebo condition. Likewise, medication condition was hypothesized to moderate the association between negative affect and cannabis use such that the relationship between negative affect and the likelihood of cannabis use and quantity of cannabis smoked on use days will be attenuated for youth in the topiramate condition and not in the placebo condition. Lastly, medication condition was hypothesized to moderate the association between positive affect and cannabis use such that the positive within-person and negative between-person relationships between positive affect and the likelihood of cannabis use and quantity of cannabis smoked on a use day will be attenuated for youth in the topiramate condition and not in the placebo condition.

Method

Participants

Participants were 63 youths, ages 15 to 24 years ($M = 19.67$, $SD = 2.19$; 50.8% female). Fifty-five percent were White/Caucasian, 27% Black/African America, 5% American Indian/Alaskan Native, 3.2% Asian, 1.6% Native Hawaiian/Pacific Islander, 11.1% multiracial/another race, and 20.6%

reported their ethnicity to be Hispanic. To be eligible, participants had to use cannabis at least twice weekly in the past 30 days and endorse at least one symptom of DSM-IV-TR cannabis abuse or dependence (i.e., show clinically significant cannabis-related problems). Exclusion criteria were cannabis treatment in the past 30 days, mandated treatment, current Axis I psychopathology other than cannabis, alcohol, nicotine, or disruptive behavior disorders, actively suicidal or psychotic, and medical conditions or medications that contraindicated the pharmacotherapy. Females were excluded if they were pregnant, nursing, or unwilling to use birth control.

Study design and procedures

This RCT is registered at http://clinicaltrials.gov (NCT01110434) and described in greater detail elsewhere (Miranda et al. 2017). Participants were recruited from the community through advertising (e.g., flyers, stationed informational booths) for a 6-week double-blind, parallel group RCT testing the efficacy of topiramate (off-label use) versus placebo in treating cannabis use in youth. Interested volunteers completed a phone screen to ascertain preliminary eligibility, and those found tentatively eligible completed an in-person screening. Before enrollment, written informed consent was obtained from youths 18 years or older and the parents of minors; assent obtained from minors. Participants completed a baseline assessment of demographic and clinical characteristics. Psychiatric diagnoses, including CUDs, were derived using the Kiddie Schedule for Affective Disorders for School-Age Children (KSADS; Kaufman et al. 1997), a semi-structured interview based on DSM-IV-TR criteria. Topiramate was titrated to 200 mg/day over 4 weeks then stabilized for 2 additional weeks. In both conditions, participants received three sessions of an individually delivered behavioral intervention to enhance motivation and build skills to reduce cannabis use. Procedures were identical across conditions except for the medication administered. The Brown University Institutional Review Board approved the study protocol (no. 0903992676).

Participants received thorough instructions on how to use the handheld wireless electronic device (Omnia; Samsung Electronics, Ridgefield Park, NJ) to complete EMA with software developed for this study. Participants received $10/day for EMA compliance. The EMA program generated audible prompts for participants to complete brief ~ 2-min assessments at random times (i.e., random assessments) within 3-h blocks (e.g., 12 p.m. to 3 p.m.) throughout the 24-h day, except when they were unable to respond (e.g., driving, sleeping). Random assessments included measures of affect, craving, and situational factors. Participants also completed assessments before and after they used cannabis (i.e., begin and end use reports), in which they reported the amount of cannabis they used. These prompts provided information regarding the timing of participants' use.

EMA measures

Affect

At random and begin use reports, participants reported on positive (energized, excited, sociable, happy, relaxed) and negative (tense, sad, stressed) affect using 11-point scales (0 = not at all to 10 = extremely). Affect items were derived from the circumplex model of affect (Posner et al. 2005) and the Positive and Negative Affect Schedule–Expanded Form (Watson and Clark 1999). Previous research supports the internal consistency and criterion validity of these affective items assessed using EMA (Emery et al. 2020; Hoeppner et al. 2014). We calculated reliability of the positive and negative affect scales for this sample at the within- and between-person level using McDonald's omega (McDonald 2013) following procedures of Geldhof et al. (2014). McDonald's omega (ω) is an index of internal consistency that uses a factor analytic approach to partition the common variance among the items from the unique variance and determine the general factor saturation of the test. It is the ratio of the common variance to the total variance (common and unique; Dunn et al. 2014). Guidelines for ω follow those for Cronbach's alpha. The positive affect scale exhibited good reliability at both the within- ($\omega = 0.80$) and between-person ($\omega = 0.93$) levels. The negative affect scale also exhibited good reliability at both the within- ($\omega = 0.80$) and between-person ($\omega = 0.89$) levels.

Cannabis craving

At random and begin use reports, craving was assessed with a single-item of urge to use cannabis on an 11-point scale from 0 (no urge) to 10 (strongest ever). This measure is widely used in laboratory and EMA research (Emery et al. 2020; Miranda et al. 2008; Ray et al. 2010) and previous EMA work supports the criterion validity (Ramirez and Miranda 2014).

Cannabis use

Cannabis use at baseline was assessed using the 90-day Timeline Follow-Back (TLFB) Interview (Sobell and Sobell 1992). Cannabis use during the EMA period was assessed by participant-initiated cannabis use reports. Participants were instructed to self-initiate a begin-use report just before using any cannabis and an end-use report immediately after each cannabis use event (e.g., bowl, joint). At each end-use report, participants recorded the quantity of cannabis used in grams.

If participants shared cannabis with others, the total weight reported was divided by the number of users. Cannabis use outcomes were quantified in two ways: (1) the likelihood of use at a given moment (i.e., used = 1, did not use = 0) and (2) total grams used during use moments (i.e., quantity of use at a given moment).

Study medication

Topiramate capsules contained appropriate dosages of the study medication and placebo capsules contained pharmacologically inert filler. All capsules also contained 50 mg of riboflavin to assess medication compliance. Riboflavin concentrations were assessed at weekly visits with urine analysis. Two raters blind to randomization independently evaluated urine samples under ultraviolet light to determine the presence or absence of riboflavin (Del Boca et al. 1996). A third rater resolved discrepancies. Participants also provided blood samples at study weeks 3 and 6 for topiramate quantification in serum, which was dichotomized as present or absent for compliance purposes. Participants and study personnel in direct contact with participants were blind to treatment assignments. An independent compounding pharmacy provided topiramate and placebo capsules, which were identical in appearance. Capsules were packaged in 7-day blister cards and participants were instructed to take one morning and one evening dose.

Analysis plan and statistical power

To test the moderating effects of topiramate on the associations between affective states and cannabis use during the clinical trial, we estimated multilevel models (MLMs) with random intercepts using Stata 15 (StataCorp 2017). The data had a two-level structure in which moments (level 1 [L1]; within-person) were nested within persons (level 2 [L2]; between-persons). MLM accounts for the nonindependence of observations that results from the nesting of time-varying observations via momentary random assessments within persons (L1). The models contained within-person craving, negative affect, and positive affect at the previous moment predicting cannabis use at the next moment (i.e., lagged effects). These indicators were lagged within-day to focus on within-day next-moment associations and avoid lengthy between-day lags in analyses. Same-moment concurrent indicators were also included in the model to adjust for their effect, such that concurrent indicators could be interpreted as change in the indicator since the previous prompt. Random intercepts allowed levels of affect and craving to vary between participants. We also examined the inclusion of random slopes to account for variation across participants in the associations between the focal predictors and our outcomes. A random slope for craving was a significant addition to the likelihood model $\Delta\ \chi^2\ (2, N = 63) = 29.48\ (p < 0.001)$ and was retained. All other random slopes were not significant ($ps > 0.202$) and thus excluded for parsimony.

Level 1 focal predictors were within-person lagged positive affect, negative affect, and craving. In addition to the focal predictors at L1, six orthogonal day of the week indicators and day in the study were included as covariates. The inclusion of day of the week addresses daily variation in mood and use as well as reduce potential serial auto-correlation across days (cf. Mohr et al. 2001). Inclusion of the number of days since initiating the study adjusts for change over time not associated with topiramate (e.g., psychosocial treatment effects). L2 focal predictors were between-person aggregates of the momentary affect and craving indicators and the effect of medication condition. L1 variables were centered within-persons by subtracting person-averages from momentary values (i.e., person-centered). L2 variables were centered by subtracting the overall sample-averages from person-level averages (grand-mean centered). In this context, person-centered variables reflect moment-to-moment deviations from a person's average level, and grand-mean centered variables reflect person deviations from the overall average for the sample.

Distinctions between person-average affect (e.g., dispositional positive affect) and cannabis craving (i.e., dispositional craving) from momentary states (e.g., a moment of high positive affect and/or craving) capitalized on the full richness of the EMA data by distinguishing dynamic, within-person changes in momentary affect or craving from between-person, individual differences in typical (i.e., dispositional) affect or craving level. EMA data also provides the advantage of temporal specificity. Affect was expected to vary within each person over time (L1; within-person), but also on average, from person to person (L2; between-persons). The inclusion of momentary and average indicators allowed for isolation of the within-person associations of affect and craving fluctuations with use from between-person, cross-sectional associations. An intercept-only model (without any predictors) estimated intraclass correlations (i.e., variability in predictors attributed to between-person effects [i.e., cross-sectional] relative to within-person influences [i.e., longitudinal]). We expected acute increases in affective states and craving at the previous moment to be associated with greater cannabis use at the next moment, and that topiramate would attenuate these associations. We also expected greater negative affect and craving and lower positive affect, in general, to be associated with greater cannabis use during the clinical trial, and that topiramate would attenuate these associations. To determine this, we first estimated main effect only models to test the hypothesized lagged effects of affect states on use and then added interactive effects with topiramate to test the hypothesized

moderation. Simple slopes were calculated for significant interactive effects to aid interpretation.

Power analysis was conducted via computer simulation, using the Monte Carlo feature of Mplus 8.5 (Muthén and Muthén 2017). Consistent with previous research, 50% of the variance in craving and affect was specified at the within-person level with the remaining variance specified at the between-person level (Emery and Simons 2020; Treloar and Miranda 2017). The focal effects of interest in this study are the interactions between affect/cannabis craving and medication. Unfortunately, previous research has not examined these associations using multilevel analyses. Thus, we conducted multiple Monte Carlo simulations with small effect sizes ranging $\beta = 0.05$ to $\beta = 0.35$ for the cross-level interaction effects on cannabis craving. Results of the power analysis using 10,000 replications indicated a sample of 63 individuals with 86 observations each would be sufficient powered to detect the hypothesized medication × affect or craving cross-level interactions on use for effects above 0.32. These models also indicated we would be powered to detect within-person effects of $\beta = 0.05$ or higher and between-person effects of $\beta = 0.26$ or higher. It is important to note that the final models will have more observations, especially tests of concurrent associations, and a series of covariates, which will account for additional residual variance not estimated in this model, effectively increasing power above what was seen here. Accordingly, we are adequately powered to detect any clinically meaningful effects found in these models.

Results

Descriptive statistics

See Table 1 for summary of descriptive statistics. Compliance with random assessments was calculated by dividing the total number completed by all participants by total number completed plus missed random assessments. There were 6,981 completed random assessments and 7,864 combined completed + missed random assessments; thus, compliance was 88.8%.

Participants in the placebo condition reported using cannabis on 42% of study days (372/900) and reported an average of 2.5 ($SD = 1.5$) grams per use day. In the topiramate condition, participants reported using cannabis on 40% of study days (431/1,070) and reported an average of 2.0 ($SD = 0.88$) grams per use day. Consistent with results reported elsewhere (Miranda et al. 2017), the topiramate group used less per use day than the placebo group (t (581.193) = 5.83, $p < 0.001$, $d = 0.43$), but there were no differences in number of use days during the trial (t (1906.45) = 0.77, $p = 0.440$).

As hypothesized, affect and craving varied between and within persons. The intraclass correlation was 0.50 for negative affect, 0.50 for positive affect, 0.36 for cannabis craving. This indicates that 50% of the variance in negative and positive affect was at the between-person level and the remaining 50% was due to moment-to-moment within-person fluctuations. For craving, 34% of the variance was at between-person level, whereas 64% was due to within-person moment-to-moment variability.

Predictors of use outcomes

Prior to examining the moderating effects of topiramate, we first estimated a MLM containing only main effects of focal variables and hypothesized covariates (i.e., day of the week, day in the study, medication condition). This allowed us to test the hypothesized association between the focal predictors and cannabis use before testing the moderating effects of medication. We then added interactions with medication group. Separate models were estimated for likelihood and quantity of cannabis use. See Table 2 for a summary of all main effects across both models.

Table 1 Correlation matrix and descriptive statistics

Variable	*M*	*SD*	1	2	3	4	5	6	7
1. Sex									
2. Age	19.67	2.18	−0.06						
3. Negative affect	1.45	1.16	0.07	−0.09					
4. Positive affect	5.12	1.56	−0.12	0.15	−0.11				
5. Craving	3.80	2.46	0.02	−0.19	0.07	0.34**			
6. Use moments	0.42	0.26	0.02	−0.07	0.18	0.19	0.35**		
7. Grams used	0.83	0.74	0.14	−0.16	−0.21	−0.13	0.38**	0.87	
8. Cannabis dependence	0.60	0.49	0.05	−0.17	−0.05	−0.28*	0.08	0.22	0.27*

Note. $N = 63$. Sex (men = 0, women = 1). Use moments = proportion of use moments. Grams used = average grams used during use moments. All variables are at the person-level. Positive affect, negative affect, craving, use moments, and grams used are person-mean aggregates from EMA data. *$p < 0.05$, **$p < 0.01$

Table 2 Multilevel main effects only models of cannabis use

Variable	Likelihood model			Quantity model		
	OR	*SE*	*p* value	*β*	*SE*	*p* value
Within-person (L1; time-varying)						
Lagged negative affect	1.01	0.040	0.760	0.031	0.023	0.172
Lagged positive affect	1.05	0.042	0.255	0.041	0.022	0.063
Lagged craving	**1.15**	**0.031**	**< 0.001**	**0.134**	**0.023**	**< 0.001**
Concurrent negative affect	**0.90**	**0.037**	**0.011**	−0.057	0.30	0.058
Concurrent positive affect	1.08	0.044	0.063	0.022	0.050	0.656
Concurrent craving	**1.09**	**0.024**	**< 0.001**	**0.174**	**0.054**	**0.001**
Monday	1.30	0.232	0.139	0.019	0.022	0.400
Tuesday	0.98	0.180	0.897	0.011	0.017	0.503
Wednesday	0.96	0.178	0.815	−0.012	0.017	0.473
Thursday	0.89	0.165	0.536	−0.023	0.019	0.228
Friday	1.10	0.195	0.583	0.003	0.022	0.901
Saturday	1.02	0.185	0.930	−0.017	0.023	0.464
Day in the study	**0.98**	**0.005**	**< 0.001**	−0.007	0.020	0.749
Between-person (L2; time-invariant)						
Negative affect	1.14	0.154	0.329	−0.016	0.191	0.934
Positive affect	0.87	0.098	0.232	**−0.456**	**0.182**	**0.012**
Craving	0.98	0.070	0.736	0.019	0.258	0.941
Medication condition	0.88	0.271	0.688	−0.227	0.147	0.123

General note. *OR*, odds ratio. *β*, standardized coefficients. Boldface denotes significance. Level 1 variables were person-centered and level 2 variables were grand-mean centered. Sunday was the reference group for day of the week indicators. Medication condition (topiramate = 1, placebo = 0). Likelihood model note. $N = 63$. Level 1 observations = 5,453. Quantity model note. $N = 59$. Level 1 observations = 2,351

Likelihood model

Consistent with our first hypothesis, at the within-person level (L1), youths were more likely to use at the next moment if the previous moment was characterized by greater craving ($OR = 1.15$, $p < 0.001$). Contrary to expectations, neither lagged negative affect ($OR = 1.01$, $p = 0.760$) nor lagged positive affect ($OR = 1.05$, $p = 0.255$) were significant prospective predictors of the likelihood of use at the next moment. As for concurrent effects, craving was positively ($OR = 1.09$, $p < 0.001$), negative affect was inversely ($OR = 0.90$, $p = 0.011$), and positive affect was not associated ($OR = 1.07$, $p = 0.063$) with the likelihood of use at the same moment. At the between-person level (L2), average craving ($OR = 0.98$, $p = 0.736$), average negative affect ($OR = 1.14$, $p = 0.329$), positive affect ($OR = 0.87$, $p = 0.232$), and medication condition ($OR = 0.88$, $p = 0.688$) were all unrelated to an increased proportion of use moments during the trial.

To test the hypothesized moderating effects of topiramate, we modeled the interaction of medication condition with our three focal variables (i.e., negative affect, positive affect, and craving) on the likelihood of use at both levels. Contrary to our hypothesis, there were no significant cross-level interactions between medication condition and lagged negative affect ($OR = 1.02$, $p = 0.812$), positive affect ($OR = 1.09$, $p = 0.264$), or craving ($OR = 1.07$, $p = 0.126$). Similarly, there were no significant interaction effects at the between-person level for medication condition and average negative affect ($OR = 0.71$, $p = 0.178$) or craving ($OR = 0.85$, $p = 0.221$). Average positive affect, on the other hand, was moderated by medication ($OR = 1.56$, $p = 0.037$). Simple slopes by medication condition were investigated to better quantify this interaction. As shown in Fig. 1, simple slopes revealed that in the placebo group ($n = 26$, $b = -0.037$, $p = 0.025$), average positive affect was inversely associated with proportion of use moments, such that those with lower average positive affect had a higher proportion of use moments and those with higher positive affect used less frequently. This association was not evident in the topiramate group ($n = 37$, $b = 0.001$, $p = 0.907$). For full interaction model estimates see Table 3.

Quantity model

At the within-person level, youth used more grams of cannabis if the previous moment was characterized by greater craving ($\beta = 0.134$, $p < 0.001$). Lagged negative ($\beta = 0.031$, $p = 0.172$) and positive affect ($\beta = 0.041$, $p = 0.063$) were not significant prospective predictors of use quantity at the next moment. Similarly, study day was not a significant predictor

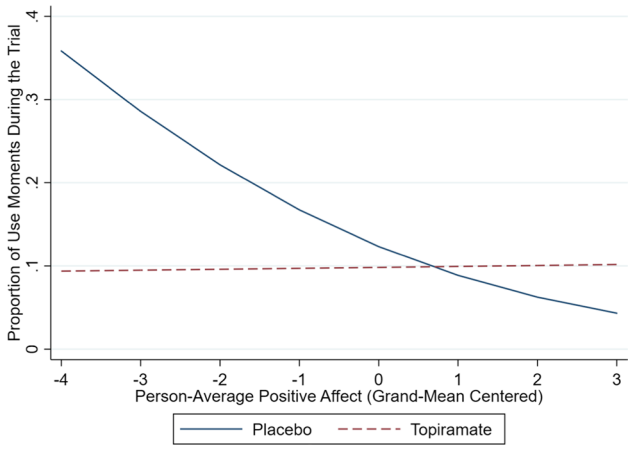

Fig. 1 Simple slopes of person-average positive affect predicting proportion of use moments during the trial by medication condition. Variables were averaged within-persons across the monitoring period (i.e., person-average). Person-average positive affect was centered at the grand-mean; thus, these values reflect a person's deviation from the overall average for the sample (i.e., 0)

of quantity used ($\beta = -0.007$, $p = 0.749$). Concurrent craving was positively ($\beta = 0.174$, $p = 0.001$) associated with quantity of cannabis used at the same moment. Neither concurrent negative affect ($\beta = -0.057$, $p = 0.058$) nor concurrent positive affect ($\beta = 0.022$, $p = 0.656$) were related to use at the same moment. At the between-person level, lower average positive affect ($\beta = -0.456$, $p = 0.012$) was associated with using more cannabis during the trial. Person-level average negative affect ($\beta = -0.019$, $p = 0.941$) and craving ($\beta = -0.016$, $p = 0.934$) were not associated with quantity used nor was medication condition ($\beta = -0.227$, $p = 0.123$).

To test the hypothesized moderating effects of topiramate in the quantity model, we estimated the interaction of medication condition with our three focal variables on the quantity of use at both levels. Contrary to hypothesis, we did not find support for cross-level interactions between lagged negative affect ($\beta = 0.042$, $p = 0.217$), positive affect ($\beta = 0.017$, $p = 0.668$), or craving ($\beta = 0.038$, $p = 0.284$) and medication condition. At the between-person level, neither average negative affect ($\beta = 0.127$, $p = 0.640$) nor craving

Table. 3 Multilevel interaction effects models of cannabis use

Variable	Likelihood model			Quantity model		
	OR	*SE*	*p* value	*β*	*SE*	*p* value
Within-person (L1; time-varying)						
Medication × lagged negative affect	1.02	0.075	0.812	0.042	0.034	0.217
Medication × lagged positive affect	1.09	0.083	0.264	0.017	0.039	0.668
Medication × lagged craving	1.07	0.005	0.442	0.038	0.035	0.284
Lagged negative affect	1.01	0.053	0.853	−0.001	0.038	0.976
Lagged positive affect	1.00	0.056	0.984	0.030	0.038	0.976
Lagged craving	**1.10**	**0.039**	**0.008**	**0.107**	**0.022**	**< 0.001**
Concurrent negative affect	**0.90**	**0.037**	**0.015**	−0.052	0.031	0.097
Concurrent positive affect	1.08	0.044	0.052	0.022	0.050	0.663
Concurrent craving	**1.09**	**0.024**	**< 0.001**	**0.170**	**0.054**	**0.002**
Monday	1.29	0.230	0.160	0.019	0.022	0.386
Tuesday	0.97	0.179	0.883	0.011	0.017	0.514
Wednesday	0.94	0.175	0.739	−0.013	0.018	0.449
Thursday	0.88	0.163	0.503	−0.025	0.019	0.200
Friday	1.09	0.193	0.614	0.002	0.022	0.935
Saturday	1.01	0.183	0.962	−0.018	0.023	0.439
Day in the study	**0.98**	**0.005**	**< 0.001**	−0.007	0.021	0.746
Between-person (L2; time-invariant)						
Medication × negative affect	0.71	0.182	0.178	0.127	0.271	0.640
Medication × positive affect	**1.56**	**0.331**	**0.037**	**0.591**	**0.223**	**0.008**
Medication × craving	0.85	0.115	0.221	−0.252	0.243	0.299
Negative affect	1.38	0.276	0.106	−0.175	0.334	0.600
Positive affect	**0.65**	**0.119**	**0.019**	**−0.999**	**0.286**	**< 0.001**
Craving	1.12	0.119	0.284	0.268	0.352	0.447
Medication condition	0.86	0.256	0.606	−0.221	0.132	0.094

General note. *OR*, odds ratio. *β*, standardized coefficients. Boldface denotes significance. Level 1 variables were person-centered and level 2 variables were grand-mean centered. Sunday was the reference group for day of the week indicators. Medication condition (topiramate = 1, placebo = 0). Likelihood model note. $N = 63$. Level 1 observations = 5,453. Quantity model note. $N = 59$. Level 1 observations = 2,351

($\beta = -0.252$, $p = 0.299$) were moderated by medication condition. However, positive affect was moderated by medication condition ($\beta = 0.591$, $p = 0.008$). We calculated simple slopes by medication condition to better quantify this interaction. As shown in Fig. 2, simple slopes revealed that in the placebo group ($n = 26$, $b = -0.114$, $p = 0.002$), average positive affect was inversely associated with average grams used, such that those with lower average positive affect used more and those with higher positive affect used less. This association was not evident in the topiramate group ($n = 37$, $b = 0.031$, $p = 0.200$). For full interaction model estimates see Table 3.

Discussion

Informed by contemporary models of addiction that posit affect (McCarthy et al. 2010) and craving (Tiffany and Wray 2012) are central to cannabis misuse, we examined within- and between-person associations among affect and cannabis craving with two metrics of cannabis use in the natural environment. Building on initial evidence that topiramate reduces alcohol craving and acts as a mood stabilizer (McIntyre et al. 2002; Mowla and Kardeh 2011), we also examined whether topiramate reduces youth cannabis use by attenuating affect-cannabis use and craving-cannabis use associations. Our findings add to the growing literature that a person's average level of positive affect is important to cannabis use. Moreover, the results suggest that topiramate may reduce how much cannabis youth use by blunting the relationship between person-level positive affect and cannabis use during treatment.

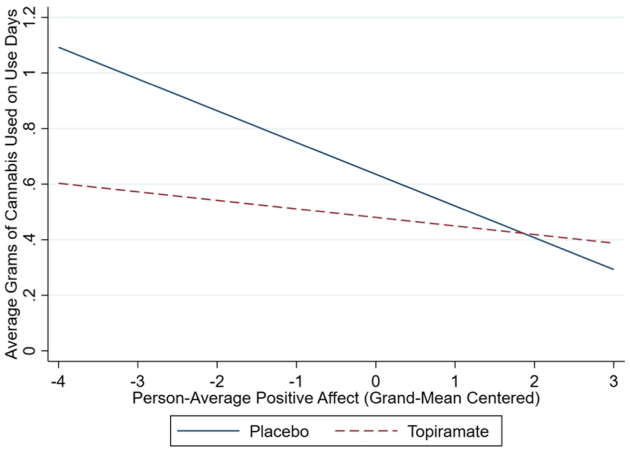

Fig. 2 Simple slopes of person-average positive affect predicting average grams used in use moments by medication condition. Variables were averaged within-persons across the monitoring period (i.e., person-average). Person-average positive affect was centered at the grand-mean; thus, these values reflect a person's deviation from the overall average for the sample (i.e., 0)

Inconsistent with our hypothesis, positive affect did not display divergent associations with cannabis use at the within- and between-person levels of analysis. At the within-person level, higher levels of positive affect at the previous moment were not associated with greater cannabis use at the next moment, though this association was in the expected direction and approaching significance. However, an individual's average (or dispositional) level of positive affect was inversely related to cannabis use at the between-person level. This pattern replicates prior work that shows positive affect's inverse between-person association with alcohol (Emery and Simons 2020) and cannabis (Emery et al. 2020).

Low levels of dispositional positive affect is the defining feature of anhedonia—the impaired capacity to experience pleasure (Snaith et al. 1995). Anhedonia is associated with numerous adverse health consequences, such as increased risk for poor physical health and chronic pain (Pettit et al. 2001; Zautra et al. 2005); anxiety and depression (Durbin et al. 2005; Genĉöz 2002); and use of poor coping strategies (e.g., avoidance, isolation; Campos et al. 2004). Among adults, anhedonia contributes to substance use initiation, maintenance, and relapse (Garfield et al. 2014) and is most prominent during early stages of recovery (Martinotti et al. 2011) when relapse rates are the highest (Gossop et al. 2002). Anhedonia interferes with treatment by blunting the reinforcing effects of daily non-substance-related activities (Koob and Le Moal 2008) making it a key obstacle during this critical recovery period. While anhedonia is common among adolescents (Leventhal et al. 2015), its role in youth substance use is less clear than with adults, though there appears to be parallels. Indeed, the results from the present study add to the emerging line of studies that highlight the role of low positive affect in the development of heavy substance use (Emery and Simons 2020), maintenance of substance use disorder (Emery et al. 2020), and now interference with treatment in youth.

Importantly, our results suggest that pharmacotherapy, namely, topiramate, has the potential to ease the association of low positive affect and cannabis use. This effect may, in part, be responsible for the previously observed reductions in cannabis use in this sample (Miranda et al. 2017). Moderation analyses indicated that topiramate attenuated the relationship between low positive affect and use, which is consistent with topiramate's mood stabilizing properties (Marcotte 1998; McIntyre et al. 2002; Mowla and Kardeh 2011). This represents a previously untested mechanism by which topiramate confers benefit and the first study to our knowledge to reduce use by attenuating affect and substance use in youth. That said, this finding should be placed in context. The parent study determined that topiramate has limited utility in this population because of its side effect profile (Gray et al. 2018; Miranda et al. 2017). Alternative compounds with similar pharmacological properties may

exert similar effects without the tolerability issues seen with topiramate.

Negative affect did not exhibit any significant prospective or dispositional effects in our models. Instead, negative affect exhibited a small inverse concurrent effect on the likelihood of cannabis use. While contrary to our hypothesis and the intuitive nature of using to cope, this result is not entirely inconsistent with the larger EMA literature on negative reinforcement-based use in youth. It is not uncommon for EMA studies to report null (Dvorak and Simons 2014) or even inverse associations between negative affect and use (Dvorak et al. 2014; Simons et al. 2010). A growing body of literature suggests that for youth positive reinforcement (i.e., using to enhance positive feelings when they are low or increase their duration) is a leading mechanism facilitating increased use among youth (Chassin et al. 2013; Emery and Simons 2020; Howard et al. 2015). However, participants did not endorse high levels of negative affect during the trial. Thus, these findings may not generalize to youth with higher levels of negative affect.

Cannabis craving was a consistent prospective predictor of use during the clinical trial. This finding is in line with research that shows positive associations between increased craving and subsequent use or risk for relapse post-treatment (Bottlender and Soyka 2004; Flannery et al. 2003; Gordon et al. 2006; Rohsenow et al. 1994). In these analyses, topiramate did not attenuate the prospective association between cannabis craving and use at either the within- or between-person level. This finding is notable because craving has become an increasingly salient criterion for diagnosis and treatment of substance use disorders (American Psychiatric Association 2013; Hasin et al. 2013), and numerous strategies have been developed to help clients manage craving without use (Donovan and Marlatt 2005; Dulin and Gonzalez 2017; Monti 2002; Witkiewitz et al. 2005). Despite extensive research with adults, our knowledge about the role of craving in adolescent substance use remains limited to a small number of studies that almost entirely focused on alcohol (Deas et al. 2001, 2005; Martin et al. 1995; Ramirez and Miranda 2014; Tapert et al. 2003). This gap in knowledge is important given that cannabis is the most commonly used illicit drug among youth and adolescence is a key period in the development on substance use disorder (Johnston et al. 2018; Merikangas and McClair 2012; Swendsen et al. 2012). When placed in this context, our finding that cannabis craving systematically interferes with cannabis treatment in youth is noteworthy.

Several limitations of the current study should be noted. Although our analytic approach was rigorous, we disaggregated within- and between-person effects, and we controlled for contextual factors of import to longitudinal data; these data were from a proof-of-concept study with a small sample size and short duration of treatment, especially in terms of the length of topiramate treatment at the target dose (2 weeks). Additionally, participants were youth who exhibited frequent heavy cannabis use and symptoms of CUD. While this makes them good candidates for a combined pharmaco-psychosocial therapy approach, our results may not generalize across other ages or levels of use and misuse. Finally, this sample of youth was not clinically depressed (i.e., mood disorders were exclusionary), and so it remains unclear whether our findings regarding low positive affect would generalize to youth with co-occurring depression and cannabis misuse. It is possible these findings may be stronger in a sample of youth with co-occurring internalizing psychopathology, but this question requires further study.

On balance, using rigorous momentary assessment and statistical methods, our findings highlight the importance of craving in the frequency and quantity of cannabis use during treatment. In addition, this is the first study to examine affect as a potential mechanism by which topiramate affects cannabis use. Our findings add to mounting evidence supporting role of low positive affect in cannabis use and suggest that topiramate may impact this association.

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Declarations

Conflict of interest The authors declare no competing interests.

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