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ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

ORIGINAL ARTICLE

Naltrexone moderates the association of alcohol use and affect among adolescent drinkers in daily life

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Abstract

Background: Naltrexone is an efficacious medication for the treatment of alcohol use disorder in adults. As an opioid receptor antagonist, naltrexone blocks activation of the endogenous opioid system, which is involved in the affectively reinforcing properties of substance use. Few studies, however, have examined the moderating effect of naltrexone on the association between affect and alcohol use. Additionally, most existing research on naltrexone has been with adults in the human laboratory.

Method: We conducted a secondary analysis of ecological momentary assessment data from a randomized, double-blinded, placebo-controlled cross-over study that compared naltrexone (50 mg/daily) and placebo in 26 adolescents (15 to 19 years old) who exhibited problematic drinking patterns. Multilevel models tested whether naltrexone moderated associations of alcohol use with both positive and negative affect (PA, NA).

Results: Results indicated that, during naltrexone treatment, greater estimated blood alcohol concentration (eBAC) levels were associated with greater NA further into drinking episodes. In turn, greater NA after the first drink of an episode was associated with reduced subsequent eBAC values during naltrexone treatment. Low PA was also associated with lower subsequent eBAC levels in the naltrexone condition after the first drink.

Conclusions: These findings support the idea that naltrexone can disrupt the association between affect and alcohol use, effects that emerge later in drinking episodes. Greater attention to the effects of naltrexone on affect and reinforcement may help to tailor psychotherapy to maximize the benefits of naltrexone. However, in the present study, as most drink reports were in the first 2 h of the drinking episode and participants reported affect only at the first three end-drink reports of a drinking episode (limiting the number of drinks reported), we had reduced power to detect effects in the continuation phase. Thus, replication of the findings is needed using a design that assesses the impact of naltrexone across the entire episode.

KEYWORDS
adolescents, alcohol use disorder, ecological momentary assessment, naltrexone, reinforcement

INTRODUCTION

Naltrexone is an opioid receptor antagonist approved by the Food and Drug Administration to treat alcohol use disorder (AUD) in adults. It modestly but reliably increases abstinence, reduces alcohol consumption, and decreases relapse rates in adults who drink heavily (Jonas et al., 2014; Maisel et al., 2013). Human laboratory research finds that naltrexone reduces alcohol's hedonically pleasant subjective experiences of stimulation, with larger effects observed for individuals who drink heavily and those who experience alcohol problems compared to light drinkers (Ray et al., 2019). It also increases alcohol's subjective experiences of sedation and tension, with larger effects observed in light drinkers (Ray et al., 2019). Findings from the few studies that leveraged ecological momentary assessment (EMA) methods to examine whether these effects generalize to real-world settings largely show similar results. For example, Miranda et al. (2014) found naltrexone reduced stimulation and increased sedation during daily life drinking episodes among adolescents. Tidey et al. (2008) found that naltrexone decreased stimulation in daily life, but only in women.

These laboratory findings for subjective response suggest that naltrexone may reduce drinking, in part, through disrupting the affectively reinforcing properties of alcohol and altering the reciprocal relationship between affect and alcohol use (Ray et al., 2019; Sinclair, 2001). Few studies, however, have examined naltrexone's effect on affect and drinking in daily life. This was the goal of the current study.

Drinking to enhance positive affect (PA) and to reduce negative affect (NA) are commonly endorsed motives for consuming alcohol (Baker et al., 2004; Cooper et al., 2016; Koob & Le Moal, 2008) that imply that individuals use alcohol because it is affectively reinforcing to do so. As part of the reinforcement process, some individuals are theorized to develop a learned association, such that the link between affect and use becomes stronger as they continue to drink in response to affect and experience reward and/or relief following use. The endogenous opioid system is involved in emotion regulation and, thus, reinforcement processes (al'Absi, 2018; Pickar et al., 1982). It also plays a key role in the increase in PA and the reduction of NA following alcohol and other substance use (Gianoulakis, 2009; Roth-Deri et al., 2008; Trigo et al., 2010). By blocking opioid receptor activity, particularly β-endorphin at μ-receptors, naltrexone may acutely blunt changes in mood and disrupt the relationship between affect and alcohol use (Sinclair, 2001).

Only two studies, to our knowledge, have examined whether naltrexone alters the relationship between affect and alcohol use in daily life. Kranzler et al. (2004), in a daily diary study, found that naltrexone, compared to placebo, weakened the association for daily NA and PA with same-day drinking in adults. However, affect and alcohol use reports occurred at the same time, making the temporal ordering of affect and drinking unknown. Roos et al. (2021) found that, in young adults who endorse drinking for reward, naltrexone weakened the association of wake-time PA and alcohol craving. However, they did not directly examine the association of affect with alcohol use.

Several key gaps in the literature exist regarding the role of naltrexone in the link between affect and alcohol use. First, most work has been in the laboratory and existing daily life work examining naltrexone has not directly examined affect and alcohol use within-day and/or has not separately examined both PA and NA as recommended by current affect models (e.g., the circumplex model of affect; Posner et al., 2005). It is important to understand naltrexone's effect in the context of real-life affective experience. Second, no study, to our knowledge, has examined both naltrexone's effect on the association of affect with subsequent drinking and drinking with subsequent affect in the same participants. This temporal ordering of affect and alcohol use is important, as they represent distinct components of the hypothesized reinforcement process (i.e., increases in PA and reductions in NA following alcohol use; increases in alcohol use following low PA and high NA). Third, few studies have examined naltrexone in adolescent populations (De Sousa & De Sousa, 2008; Deas et al., 2005; Miranda et al., 2014; O'Malley et al., 2015). Unique developmental features of adolescents, including emotional lability (Larson et al., 2002; Shulman et al., 2016), and spikes in mood-driven risk behavior (Somerville et al., 2011), result in increased risk and unique substance use patterns that make them distinct from their adult counterparts (Chung & Jackson, 2019). Thus, there is a need to examine mechanisms of action of AUD interventions in adolescents.

Current study

The current study is a secondary analysis of data from a within-subjects cross-over design randomized clinical trial (RCT) first presented in Miranda et al. (2014), which did not examine affect. We examined whether naltrexone, compared to placebo, moderates the association of alcohol use with subsequent PA and NA, and PA and NA with subsequent alcohol use, in adolescents with alcohol-related problems. Our goal was to shed light on how naltrexone may disrupt learned associations that can increase the risk of AUD. As part of this, we also examined how naltrexone's moderation occurs over time before and during the drinking episode. Time is an important, but usually implicit, factor in reinforcement models, as reinforcement involves learning and learning requires time. The effect of naltrexone may differ based upon whether someone has initiated drinking, or how far into their drinking episode they are. We forward the following hypotheses:

Hypothesis 1 *In the naltrexone condition, higher estimated blood alcohol concentration (eBAC) levels would be associated with lower PA and greater NA than in the placebo condition (indicating reduced affective reinforcement). Incorporating the amount of alcohol consumed, time, and certain physiological factors, eBAC is more closely reflective of current intoxication than number of consumed drinks alone. We also included time since the initial drink as an additional predictor to examine whether the effect of naltrexone became more pronounced as a function of time spent drinking, independent of eBAC. It is unknown how quickly*

individuals taking naltrexone might report effects of naltrexone on their affect following alcohol use. The effects of naltrexone in the laboratory are relatively small (Ray et al., 2019) and may only be perceived over time.

Hypothesis 2 *In the placebo condition, lower PA and higher NA would be associated with increased subsequent eBAC levels, as a means of increasing PA or decreasing NA, respectively. These associations would be attenuated in the naltrexone condition. For this hypothesis, we also examined whether naltrexone's moderation of PA and NA's association with subsequent eBAC levels differed in the context of drink initiation (i.e., whether to start drinking) compared to continued alcohol consumption following initiation (Wycoff et al., 2020). We did this because naltrexone's influence may differ between the decision to initiate drinking versus choosing whether to* continue *to drink. For example, if naltrexone attenuates alcohol's effects on PA and NA (our first hypothesis), its effect on alcohol consumption may be more pronounced after drinking has begun and participants fail to experience the expected benefits of use.*

MATERIALS AND METHOD

Participants

Data for this secondary analysis were from an RCT of naltrexone in adolescents reported in Miranda et al. (2014). Participants were initially telephone screened (N = 461) and eligible youth came into the lab for additional screening. Study details were described to participants and their parents, if participants were younger than 18. Informed consent was obtained from participants older than 18 and parents of minors. Minors provided assent.

Twenty-eight participants were enrolled and randomized to treatment. Of these, one discontinued due to EMA burden and one discontinued due to naltrexone side effects, both participants withdrew before reporting alcohol use. Thus, there were 26 adolescents included in the present analyses. Of these, 21 completed both arms, one completed the naltrexone arm and discontinued during placebo. Four discontinued during the first arm but reported use prior to discontinuing. These four participants were not included in Miranda et al. (2014).

Adolescents were recruited from the community, were 15 to 19 years old, consumed alcohol at least twice weekly in the past 30 days, able to read simple English, and postpubescent. Participants were excluded if they had past alcohol treatment, past-30 day use of opiates, opioid use disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (American Psychiatric Association, 2010), positive urine toxicology screen for narcotics, amphetamines, sedative hypnotics or opiates, alcohol withdrawal (>10 on the Clinical Institute Withdrawal Assessment for Alcohol; Sullivan et al., 1989), were suicidal or psychotic, or medical conditions or medications that contraindicated taking naltrexone. Females were ineligible if pregnant, nursing, or unwilling to use birth control.

Procedure

Study design

This was a double-blind cross-over trial that compared naltrexone (25 mg first 2 days, 50 mg remaining days) and placebo. Participants were randomized to each condition for 8 to 10 days [M = 9.93, SD = 0.34] in counterbalanced order. Participants took one pill each of the first 2 days in a condition (corresponding to 25 mg in the naltrexone condition) and two pills each of the remaining days (50 mg naltrexone). Each condition was followed by a 4 to 11-day washout period (M = 4.52, SD = 1.72) to allow for clearance of naltrexone (Gonzalez & Brogden, 1988). Participants were contacted daily to assess for side effects. Procedures were identical across conditions, except for the medication administered. No instructions were provided to reduce or otherwise alter drinking habits. The Brown University Institutional Review Board approved this study.

EMA protocol

At baseline, adolescents were trained to complete EMA reports using a provided handheld device (Samsung Electronics) via custom software. Training included a manual that provided instructions on completing reports and reporting alcohol use in terms of standard drink volumes. Participants completed a pre-randomization EMA period of approximately 1 week (M days = 6.3, range = 5 to 13) to facilitate familiarity and compliance. Miranda et al. (2014) previously reported high compliance for participants.

Participants completed random assessments and alcohol-related reports. Random assessments were device-initiated prompts delivered once randomly within 3 h blocks. To reduce burden, random assessments did not occur when participants reported drinking. The program recorded if participants failed to respond within 2 min. Youths could "suspend" random assessments for up to 7 h when necessary (e.g., school, driving). Participants self-initiated begin- and end-drink reports directly before and after each standard drink, respectively. At the first begin-drink report and the first three end-drink reports of a drinking episode, participants additionally reported their current affect as described below. Participants did not report affect at end-drink reports beyond the first three to reduce burden.

Measures

Alcohol consumption

All begin-drink reports assessed: Whether the participant had already started consuming their drink and (if so) the number of minutes ago they started. All end-drink reports assessed: the number of min ago they finished the last drink, beverage type (i.e., "Beer," "Malt Liquor (Colt 45, etc.)," "Liquor (straight or mixed)," "Wine,"

"Wine Cooler," and "Fortified Wine,"), and ounces consumed (participants were instructed to include only ounces of liquor for a mixed drink). When participants reported any alcohol consumption ($n_{reports}$ = 222), they most often reported drinking beer (39.2%) or straight liquor (35.1%), followed by mixed drinks (15.8%), wine (8.1%), and malt beverages (1.8%).

Estimated BAC levels

To derive a more precise estimate of alcohol use, we calculated eBAC values for each observation using a formula well-suited for *ad lib* drinking (Hustad & Carey, 2005; Matthews & Miller, 1979). The formula incorporates sex, weight, the average population rate for metabolizing alcohol, time elapsed in hours (per EMA timestamps),[1] and cumulative number of standard drinks consumed. Previous work has found eBAC estimates to be reliable and valid, with eBAC correlated at 0.500 to 0.600 with BAC derived from venous and breath samples (Hustad & Carey, 2005). Rarely, the eBAC formula can produce an extreme and unlikely value associated with coma and death ($n_{observations}$ = 8). These values were winsorized to 0.250 g% (results did not differ when these observations were not winsorized).

Affect

At all included assessments, participants reported the extent to which they felt five PA states (energized, excited, sociable, happy, relaxed) and four NA states (bored, tense, sad, and stressed) on an 11-point Likert-type scale (0 = *not at all* to 10 = *extremely*). Items were averaged to create indices of PA and NA. Items were derived from the circumplex model of affect (Larsen & Diener, 1992; Posner et al., 2005) and the Positive and Negative Affect Schedule-Expanded Form (PANAS-X; Watson & Clark, 1999). Previous research supports the internal consistency and validity of these EMA items (Emery et al., 2020).

Drinking episode phase

For analyses examining the association of affect with subsequent alcohol use, we categorized assessments into one of two different phases: *initiation* (occasions where the initiation or first drink of a drinking episode was possible) and *continuation* (occasions after a drinking episode had begun and continuation of the episode was possible; Wycoff et al., 2020). Observations were coded as part of the initiation phase if they took place at *non-drinking occasions* (i.e., on non-drinking days or prior to drinking on drinking days), where drink initiation was possible but did not occur, or were the *first begin-drink or first end-drink report* of an episode (i.e., the initial drink). Observations were part of the continuation phase if they were begin- or end-drink reports that came after the initial drink. For example, if a participant completed a random assessment and begin- and end-drink reports for three drinks, the random assessment and first set of begin- and end-drink reports would be coded as part of the initiation phase. The second and third sets of begin- and end-drink reports would be coded as part of the continuation phase. Phase was then included as an additional predictor in models examining the association of PA and NA with subsequent alcohol use and interactions with phase facilitated tests of whether naltrexone's moderation differed in terms of starting drinking compared to continuing to drink after starting.

Analytic approach

We used multilevel modeling with restricted maximum likelihood estimation with the PROC MIXED procedure in SAS® 9.4 (SAS Institute, 2014). Models accounted for the nesting of occasion-level reports within days, which were nested within persons. Models also accounted for the fact that occasion-level reports were spaced unevenly within day and person. Models had three levels (moment, day, and person) and included person- and day-level random intercepts. Degrees of freedom were calculated using the Kenward–Roger approximation. To interpret interactions, simple slopes were calculated (Bauer et al., 2007; Preacher et al., 2003). We conducted two sets of analyses examining, first, the association of alcohol use with affect after alcohol initiation and, second, the association of prior affect with subsequent alcohol use.

Does naltrexone moderate the association of alcohol consumption with affect (consumption$_t$→affect$_t$)?

In separate models, we examined the association of current eBAC value with same-moment PA and NA and whether condition moderated this. These analyses only included observations that took place over drinking episodes (i.e., begin- and end-drink reports). Following Carpenter et al. (2019), drinking episodes were defined as beginning at the start of the first begin-drink report and ending either at the final drink-related report of that study day or when eBAC returned to 0.000 g%, whichever occurred first. Any drinking that occurred after eBAC returned to 0.000 g% was considered part of a new secondary drink episode. To avoid carryover effects of alcohol, secondary drink episodes were removed from the data ($n_{episodes}$ = 4; $n_{observations}$ = 14). Within episodes, time of observations ranged from 0 (the first begin-drink report) to 423 min (M = 41, SD = 65), but there were few that occurred after 300 min (5 h; $n_{observations}$ = 4) and these were censored. The final number of observations included in this set of analyses, following exclusions, was 352 over 112 drinking episodes.

In these models, PA and NA were the dependent variables, respectively. Same-moment eBAC value, time elapsed since the initial drink (in hours), treatment condition (i.e., placebo vs. naltrexone), and their interactions were the independent variables. Same-moment eBAC values, as opposed to previous-moment eBAC values, were

included because these models were focused on the pharmacological effects of alcohol on affect at the moment of a given eBAC level. The models are temporally ordered, however, because affect was reported in end-drink reports, after drinking occurred. The inclusion of time elapsed made it possible to examine whether any moderating effect of naltrexone was immediate or only appeared later in the episode.

Does naltrexone moderate the association of affect with next-moment alcohol consumption ($affect_{t-1}$→$consumption_t$)?

We examined, in separate models, the association of PA and NA with next-moment eBAC values. These analyses included observations from all days (N = 1,690).[2] Estimated BAC value was the dependent variable. Previous-moment occasion-level affect (PA or NA), treatment condition, drinking episode phase (initiation or continuation), and their interactions were the independent variables. Previous-moment (i.e., lagged) affect indicators were created within day, with no carry-over from the previous day. Thus, the first observation for each day was not included in models, but contributed lag information. After exclusions already mentioned, the majority of observations in the final dataset (n = 1,559) were in the initiation phase, which reflects that participants were not drinking at most assessments, and the remainder (n = 131) were in the continuation phase.[3]

The effect of primary interest was the three-way interaction of previous-moment occasion-level affect, treatment condition, and drinking episode phase. This allowed us to examine whether the association for occasion-level PA and NA with subsequent alcohol consumption varied between condition and between the initiation versus the continuation of the drinking episode (see Drinking Episode Phase). While our focus was on previous-moment occasion-level affect, which was centered on the participant's day mean, we also included same-moment occasion-level affect to adjust for autoregression over time. Additionally, day- (person-mean centered) and person-level (sample-mean centered) affect adjusted for the fact that occasions were nested within days, which were nested within people (Curran & Bauer, 2011).

Finally, all models in both sets of analyses included covariates to adjust for possible contextual and person-level effects. Covariates were the hour of day for each report, the day of the week, day in the study, the order of treatment condition (i.e., placebo-naltrexone, naltrexone-placebo), and age.

Power considerations

In each set of analyses, we were primarily interested in a three-way interaction that involved condition, eBAC or previous-moment affect, and a measure of time (time elapsed or drinking episode phase). Given the within-subjects cross-over design, with condition nested within participants, the present interactions in all analyses are roughly equivalent to a two-level cross-level interaction with 52 observations at level 2. For analyses examining $consumption_t$→$affect_t$, there were about 14 assessments per person. For analyses examining $affect_{t-1}$→$consumption_t$, there were about 65 assessments per person. Based on simulation work (Arend & Schäfer, 2019), we had power to detect large effects when examining $consumption_t$→$affect_t$ and medium to large effects when examining $affect_{t-1}$→$consumption_t$. However, for $affect_{t-1}$→$consumption_t$, we had reduced power to detect effects in the continuation phase, given the smaller number of observations. Given existing gaps in the literature, especially in regard to adolescents, we found this sufficient power to examine these interactions, although replication of findings will be important.

RESULTS

Descriptive statistics

A slight majority of participants were female (N = 14; 54%), the remaining were male (N = 12; 46%). Mean age was 18.2 (SD = 1.2), with four participants under 18 and the remaining 18 or 19. Most participants were White (N = 18; 72%). Two participants were Black (8%), two were Asian (8%), one was Native American (4%), and one was Pacific Islander (4%). Two did not report their race. Four participants (16%) reported Hispanic ethnicity, 21 (84%) reported non-Hispanic ethnicity, and 1 did not report. Most (N = 18; 69%) met diagnostic criteria for AUD via the Kiddie Schedule for Affective Disorders for School-Age Children (Kaufman et al., 1997). Participants endorsed an average of 3.5 (SD = 2.5; median = 3, range = 0 to 8) AUD symptoms.[4] In terms of symptom count, two participants (7.7%) met for 0 symptoms, 4 (15.4%) met for 1 symptom, 8 (30.8%) met for 2 to 3 symptoms, 6 (23.1%) met for four to five symptoms, and 6 (23.1%) met for six or more symptoms. At baseline, participants completed a 90-day timeline follow-back interview (Sobell & Sobell, 1992). Participants reported drinking on an average of 26.1% (SD = 9.6%) of the 90 days prior to entering the study, of which 48.4% were heavy drinking days (females ≥4 drinks; males ≥5 drinks; SD = 28.1%). On drinking days, participants reported an average of 4.3 standard drinks (SD = 4.1, range = 2 to 8.9).

All participants reported at least one drinking episode and, across the 112 recorded drinking episodes, participants reported a total of 332 standard drinks. Across the placebo condition, mean NA was 2.48 (SD = 1.46), mean PA was 5.88 (SD = 1.50), mean eBAC (drinking episode assessments) was 0.068 g% (SD = 0.058 g%), average peak eBAC was 0.117 g% (SD = 0.084 g%), and the mean number of standard drinks per drink episode was 3.01 (SD = 2.65). Across the naltrexone condition, mean NA was 2.57 (SD = 1.49), mean PA was 5.62 (SD = 1.76), mean eBAC (drinking episode assessments) was 0.056 g% (SD = 0.044 g%), average peak eBAC was 0.090 g% (SD = 0.073 g%), and the mean number of standard drinks per drink episode was 2.35 (SD = 1.58).

ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

TABLE 1 Parameter estimates for multi-level models of the association of estimated blood alcohol concentration (eBAC), treatment condition (condition), and time elapsed since initial drink (time) with positive and negative affect

	Positive affect				Negative affect			
	Est.	95% CI	*t*	*p*	Est.	95% CI	*t*	*p*
Intercept	6.14	[4.88, 7.39]	9.83	<0.001	2.05	[1.05, 3.05]	4.09	<0.001
Condition	0.16	[−0.35, 0.67]	0.62	0.535	−0.08	[−0.53, 0.37]	−0.36	0.719
eBAC	0.83	[−1.78, 3.45]	0.63	0.531	0.25	[−2.31, 2.81]	0.19	0.848
Time	0.12	[−0.08, 0.33]	1.19	0.235	0.02	[−0.17, 0.22]	0.25	0.804
eBAC × condition	1.41	[−3.96, 6.78]	0.52	0.606	−4.96	[−10.21, 0.30]	−1.86	0.064
Time × condition	0.45	[−1.17, 2.06]	0.54	0.589	−1.78	[−3.35, −0.21]	−2.23	0.027
eBAC × time	−0.04	[−0.31, 0.22]	−0.31	0.753	−0.22	[−0.48, 0.04]	−1.68	0.095
eBAC × time × condition covariates	**−2.72**	**[−6.94, 1.5]**	**−1.27**	**0.205**	**7.76**	**[3.64, 11.89]**	**3.71**	**<0.001**
Study day	0.001	[−0.03, 0.04]	0.05	0.959	−0.01	[−0.04, 0.02]	−0.74	0.463
Weekday								
Sunday	−0.22	[−0.79, 0.36]	−0.74	0.460	0.67	[0.14, 1.20]	2.49	0.013
Monday	0.88	[−0.63, 2.38]	1.15	0.251	−0.14	[−1.47, 1.19]	−0.21	0.831
Tuesday	−0.65	[−1.66, 0.35]	−1.28	0.202	0.84	[−0.06, 1.73]	1.85	0.067
Wednesday	−0.92	[−2.01, 0.16]	−1.68	0.095	1.13	[0.16, 2.11]	2.30	0.023
Thursday	−0.65	[−1.51, 0.21]	−1.50	0.137	0.92	[0.17, 1.67]	2.43	0.017
Friday	−0.12	[−0.58, 0.34]	−0.54	0.594	0.06	[−0.35, 0.47]	0.27	0.786
Hour of day	0.01	[−0.02, 0.03]	0.68	0.498	0.004	[−0.02, 0.02]	0.37	0.715
Order	0.62	[−0.81, 2.05]	0.91	0.374	−0.83	[−1.88, 0.22]	−1.64	0.116
Age	0.39	[−0.24, 1.03]	1.28	0.214	−0.11	[−0.59, 0.37]	−0.46	0.647

Note: $N = 26$ individuals, 352 observations used. Degrees of freedom were calculated using the Kenward–Roger approximation. CI, confidence interval. Time refers to number of hours and minutes since the initial end-drink report. The reference for condition was placebo and the reference for weekday was Saturday. Order refers to order in which participants received the two treatment conditions. Age was sample centered. Effect of primary interest in bold.

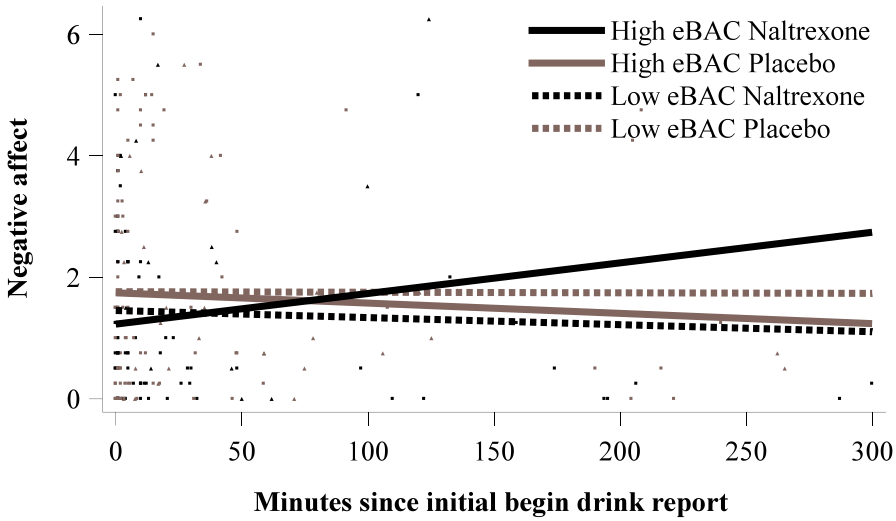

FIGURE 1 The interaction of estimated blood alcohol concentration and medication condition predicting negative affect over time in the drinking episode. *Note*: Estimated blood alcohol concentration (eBAC) values were dichotomized such that values at or below 0.020 g% were in the low group and values at 0.091 g% or higher were in the high group. Squares represent low and triangles high eBAC values

TABLE 2 Parameter estimates for multi-level models of the association of previous-moment affect (positive or negative), treatment condition (condition), and phase (drink initiation vs. continuation) with estimated blood alcohol concentration

	Positive affect				Negative affect			
DV: eBAC	**Est.**	**95% CI**	***t***	***p***	**Est.**	**95% CI**	***t***	***p***
Intercept	0.56	[−0.06, 1.17]	1.79	0.075	0.45	[−0.17, 1.06]	1.42	0.157
Condition	−0.11	[−0.40, 0.19]	−0.70	0.482	−0.11	[−0.40, 0.18]	−0.74	0.462
Previous-moment affect	0.27	[0.14, 0.40]	4.03	<0.001	−0.22	[−0.35, −0.08]	−3.13	0.002
Phase	6.64	[6.03, 7.25]	21.36	<0.001	6.69	[6.10, 7.28]	22.29	<0.001
Affect × condition	−0.13	[−0.32, 0.05]	−1.40	0.161	0.14	[−0.06, 0.34]	1.38	0.167
Phase × condition	−3.15	[−4.14, −2.17]	−6.28	<0.001	−3.09	[−4.03, −2.15]	−6.42	<0.001
PM affect × phase	0.46	[−0.22, 1.15]	1.33	0.185	−0.75	[−1.40, −0.11]	−2.29	0.022
PM affect × phase × cond. covariates	**1.70**	**[0.70, 2.71]**	**3.31**	**0.001**	**−1.70**	**[−2.68, −0.73]**	**−3.43**	**0.001**
Same-moment affect	0.16	[0.06, 0.26]	3.11	0.002	−0.18	[−0.28, −0.08]	−3.63	<0.001
Day-level affect	0.27	[0.12, 0.43]	3.44	0.001	−0.23	[−0.38, −0.07]	−2.82	0.005
Person-level affect	−0.13	[−0.24, −0.02]	−2.36	0.027	0.11	[−0.02, 0.24]	1.72	0.098
Study day	−0.01	[−0.03, 0.02]	−0.43	0.664	−0.001	[−0.02, 0.02]	−0.10	0.917
Weekday								
Sunday	0.39	[−0.09, 0.86]	1.58	0.114	0.43	[−0.05, 0.91]	1.77	0.077
Monday	0.29	[−0.23, 0.81]	1.10	0.273	0.23	[−0.29, 0.74]	0.87	0.386
Tuesday	0.06	[−0.46, 0.59]	0.24	0.810	0.02	[−0.50, 0.54]	0.08	0.936
Wednesday	−0.07	[−0.61, 0.47]	−0.25	0.801	−0.14	[−0.67, 0.39]	−0.51	0.609
Thursday	−0.01	[−0.44, 0.43]	−0.02	0.980	0.01	[−0.43, 0.44]	0.03	0.974
Friday	0.10	[−0.30, 0.49]	0.47	0.639	0.04	[−0.35, 0.44]	0.21	0.830
Hour of day	−0.01	[−0.03, 0.002]	−1.73	0.083	−0.01	[−0.03, 0.01]	−1.08	0.282
Order	0.06	[−0.30, 0.42]	0.36	0.723	0.05	[−0.33, 0.43]	0.27	0.792
Age	0.03	[−0.12, 0.18]	0.39	0.703	−0.004	[−0.16, 0.15]	−0.05	0.957

Note: $N = 26$ individuals, 1,690 observations. Degrees of freedom calculated using the Kenward–Roger approximation. CI, confidence interval. The reference for condition was placebo, for phase was drink initiation, and for weekday was Saturday. Order refers to order participants received the two treatment conditions. Age was sample centered. Effect of primary interest in bold. PM, previous moment.

Does naltrexone moderate the association of alcohol consumption with affect (consumption$_t$→affect$_t$)?

We first examined the association of eBAC, condition, and time since the start of the drinking episode with PA and NA (Table 1). For PA, there were no significant interactions or main effects for eBAC level, condition, or time. For NA, there was a significant three-way interaction of eBAC level, condition, and time. This positive interaction indicates that higher eBACs were associated with greater NA in the naltrexone, compared to placebo, condition, but only further into the drinking episode. To better visualize this, we plotted NA over time by eBAC dichotomized into high (≥80th percentile; 0.091 g%) and low (≤20th percentile; 0.020 g%) values (Figure 1).[5] At high eBAC values, naltrexone was associated with increases in NA further into the episode. The simple slope was significant ($b = 0.35$, $p = 0.030$). At low eBAC, naltrexone was not associated with NA ($b = -0.14$, $p = 0.099$). Placebo was not associated with NA at low ($b = 0.01$, $p = 0.907$) or high eBAC ($b = -0.07$, $p = 0.345$).

Does naltrexone moderate the association of affect with next-moment alcohol consumption (affect$_{t-1}$→consumption$_t$)?

We next examined the associations of previous-moment affect, condition, and drinking episode phase (i.e., initiation vs. continuation) with eBAC level (Table 2). For PA, there was a significant three-way interaction of previous-moment PA, condition, and phase.[6] To better visualize this interaction, we plotted the association of eBAC level and PA by condition in the initiation (Figure 2A) and continuation (Figure 2B) phase. Simple slopes reveal that, in the initiation phase, there was a significant association between PA and subsequent eBAC for placebo ($b = 0.003$, $p < 0.001$), but not naltrexone ($b = 0.001$, $p = 0.060$). In the continuation phase, greater PA was associated with greater subsequent eBAC in both conditions, but the association was stronger in the naltrexone ($b = 0.02$, $p < 0.001$) than placebo condition ($b = 0.01$, $p = 0.033$). This is primarily a result of the fact that, in the naltrexone condition, moments of low PA were associated with low eBAC values.

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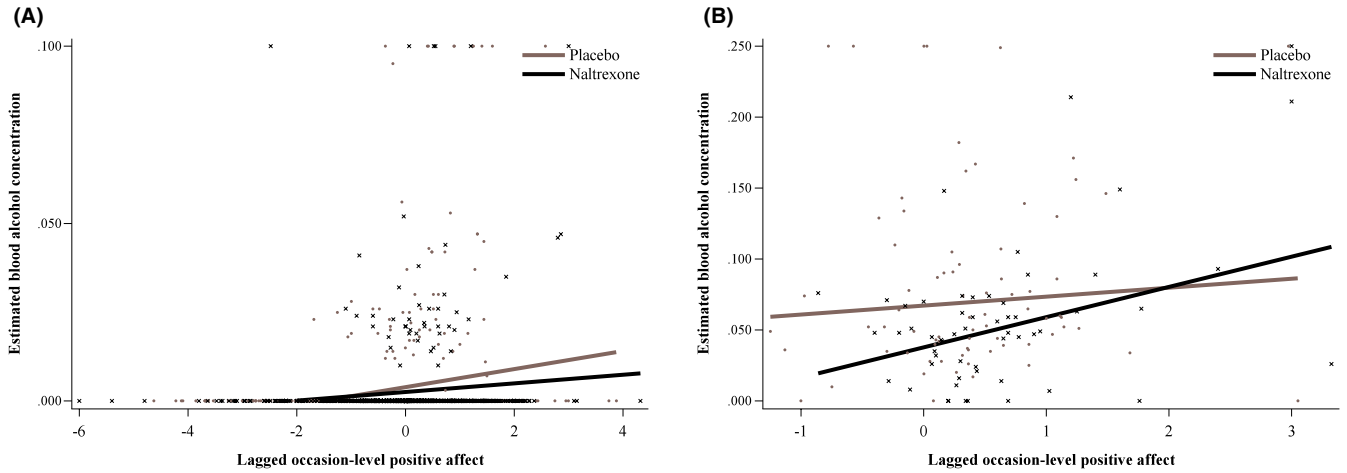

FIGURE 2 The interaction of lagged occasion-level positive affect and medication condition predicting estimated blood alcohol concentration (eBAC) at initiation of drinking (A) and continuation of the drinking episode (B). *Note*: eBAC values are winsorized to 0.100 g% instead of 0.250 g% in (A) to better visualize the interaction

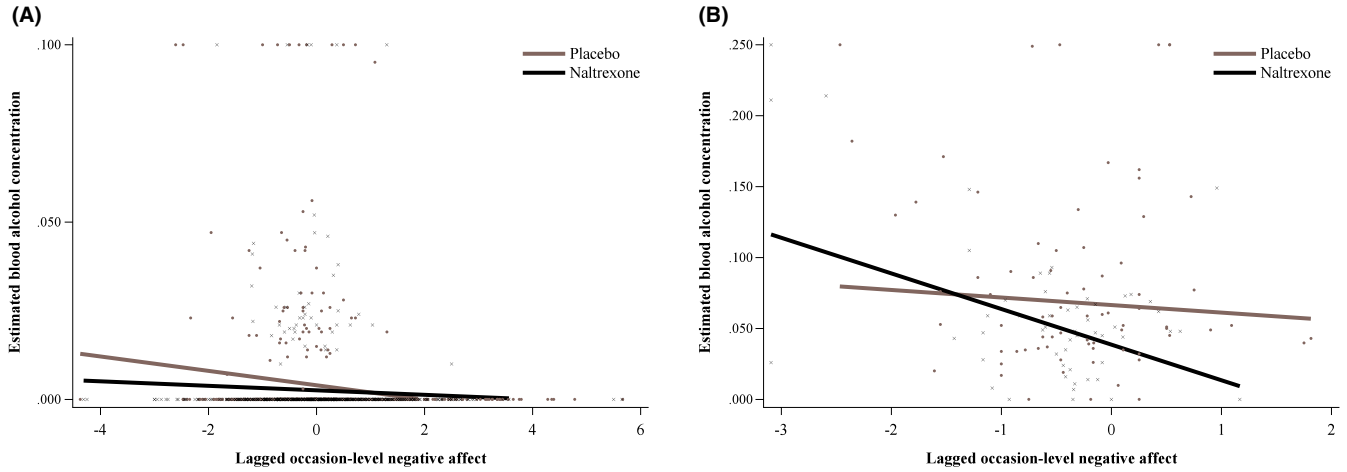

FIGURE 3 The interaction of lagged occasion-level negative affect and medication condition predicting estimated blood alcohol concentration at initiation of drinking (A) and continuation of the drinking episode (B). *Note*: eBAC values are winsorized to 0.100 g% instead of 0.250 g% in (A) to better visualize the interaction

For NA, there was a significant interaction of previous-moment NA, condition, and phase.[7] To better visualize this, we plotted the association of eBAC level and NA by condition in the initiation (Figure 3A) and continuation (Figure 3B) phase. Simple slopes reveal that, in the initiation phase, greater NA was associated with reduced subsequent eBAC in the placebo ($b = -0.22$, $p = 0.002$) but not the naltrexone condition ($b = -0.08$, $p = 0.311$). In the continuation phase, greater NA was associated with reduced subsequent eBAC in both conditions, but, as can be seen, the association was stronger in the naltrexone ($b = -2.53$, $p < 0.001$) than placebo condition ($b = -0.97$, $p = 0.002$).[8,9]

DISCUSSION

Few studies have examined the effects of naltrexone in either adolescents (De Sousa & De Sousa, 2008; Deas et al., 2005; O'Malley et al., 2015) or the context of daily life drinking and only one study to our knowledge has done both (Miranda et al., 2014). Few studies have also examined whether naltrexone attenuates the relationship between affect and alcohol use in daily life (Kranzler et al., 2004). Additionally, no study has examined how the effects of naltrexone may differ based on time before and during the drinking episode. We examined whether naltrexone, compared to placebo, moderated the association of NA and PA with subsequent alcohol use, and vice versa, in the daily life of adolescents engaging in problem drinking. Overall, findings suggested moderation effects of naltrexone, though effects differed by NA versus PA and varied in important ways across time.

Does naltrexone moderate the association of alcohol consumption with affect?

Examining the association of alcohol use with affect, findings were specific to NA. As hypothesized, higher eBAC was associated with

greater NA in the naltrexone condition, though this effect emerged relatively later in the drinking episode (keeping in mind that most drink reports were in the first 2 h of the episode). In contrast, NA did not change in the placebo condition. Naltrexone, then, may increase the aversiveness of drinking, but in a gradual fashion at elevated eBACs. This increase may be the result of naltrexone blocking alcohol's activation of the endogenous opioid system (Gianoulakis, 2009; Sinclair, 2001). While speculative, this effect may emerge gradually because the endogenous opioid system is only one of multiple systems involved in the rewarding effects of alcohol.

Does naltrexone moderate the association of affect with next-moment alcohol consumption?

Examining the association of affect with subsequent alcohol use, there were associations for both PA and NA. In part, findings build upon Kranzler et al. (2004), who found naltrexone moderated the association of daily PA and NA with alcohol use, but suggest greater complexity when examining associations within day.

PA was associated with subsequent eBAC level and this differed by condition in both phases. In the initiation phase, the positive association of PA and eBAC in the placebo condition was attenuated in the naltrexone condition. In the continuation phase, this association was stronger in the naltrexone condition. However, as can be seen in Figure 2B, the main difference between conditions in the continuation phase was at low levels of PA, which were associated with lower eBACs in the naltrexone condition. This provided partial confirmation for our hypothesis regarding PA and suggests that when adolescents taking naltrexone are experiencing low PA, they may reduce their drinking instead of continuing to use alcohol to try and lift their mood. In contrast, at higher levels of PA, participants in both conditions reached roughly equivalent eBACs. Thus, naltrexone had a "protective" effect at low levels of PA that disappeared at higher levels. In effect, it may be that if PA is already sufficiently elevated, it may be able to "override" the aversive effects of alcohol heightened by naltrexone.

Potentially related to the association of PA and naltrexone, recent work has found that individuals who endorse drinking for reward receive greater benefit from naltrexone (Mann et al., 2018; Roos et al., 2021; Witkiewitz et al., 2019). Although this recent work did not directly examine affective experience, individuals who endorse drinking for reward may be more prone to drink to increase their PA. Our results for PA in the initiation phase support in part the idea that naltrexone may reduce the degree to which individuals begin drinking due to reward.

Greater NA was associated with a lower eBAC at drink initiation in the placebo, but not the naltrexone condition. The effect for the placebo condition was largely at low levels of NA, which were associated with relatively higher eBAC values. In the continuation phase, NA was associated with lower subsequent eBAC in both groups, but the effect was stronger in the naltrexone condition. It is important to keep in mind that participants only reported affect during their first three end-drink reports of a drinking episode, meaning that it is unknown whether the effect for naltrexone would be present at higher eBACs. Few studies have examined the association of NA with the continuation of drinking. Wycoff et al. (2020) found positive associations between NA and both the initiation and continuation of alcohol use, but specifically for people who endorsed high coping motives. Future work is needed that incorporates both drinking motives and momentary affective experiences, both PA and NA, before and during drinking to understand the impact of naltrexone more fully on the drinking experience.

Though NA was associated with lower eBACs in both conditions, findings in the continuation phase suggest that, while taking naltrexone, participants were even less inclined to drink in response to NA. Although our models were not recursive, this effect may, in part, be due to the accumulating aversive effects of alcohol heightened by naltrexone following drinking. That is, when participants in the naltrexone condition experienced an increase in NA after alcohol use, this may have led them to reduce their drinking in response to NA. Over time, this may lead to a weakening of the learned association between affect and alcohol use, such that people lose the expectation that alcohol will reduce their NA. Ultimately, this may lead to extinction of the association for some people (Sinclair, 2001). This is speculative, as, again, our two sets of models were not sequenced in any way, and we did not examine how increases in NA in one drinking episode may be associated with reductions in drinking in response to NA in the next episode. Future research that unpacks these effects over time would help us to better understand how naltrexone's benefits may emerge. However, this work will need to consider over what time course effects should be expected (e.g., should changes in one drinking episode affect the next, or do effects accumulate over multiple episodes) and design an EMA protocol that is able to capture these effects. Despite limitations, however, the present study demonstrates that naltrexone moderates the association of NA and alcohol use, making alcohol less relieving and more aversive at relatively higher eBAC levels.

Clinical implications and limitations

The current study is notable for examining teenagers, especially given the unique features of affective processing during adolescence. Specifically, rapid changes in brain regions implicated in affective processing (Larson et al., 2002; Shulman et al., 2016) render youth's emotional experiences more reactive to their social environments (Schriber & Guyer, 2016; Somerville et al., 2011) and more difficult to effectively regulate (Moreira & Silvers, 2018; Silvers et al., 2012). In line with recent calls to better account for the role of affect in adolescent alcohol use (Cousijn et al., 2018; Ewing et al., 2016), our results suggest that naltrexone, in conjunction with complementary psychosocial intervention, may be particularly effective in managing the strong associations between PA and NA with alcohol use for youth seeking to reduce their alcohol use.

For example, a core component of cognitive behavioral therapy (CBT) for adolescent alcohol use is conducting functional analyses to highlight how an affective experiences predict alcohol use and change as a function of use (Hogue et al., 2020). For youth taking naltrexone, it may be helpful to receive psychoeducation, as part of CBT, noting that they may no longer receive the affective benefits of alcohol use. Psychoeducation may aid treatment in two ways by (1) preventing adolescents from attempting to "chase" the desired affective effects of alcohol use when taking naltrexone and (2) by teaching new skills (e.g., effective communication skills, cognitive restructuring) to better manage low PA and high NA.

This study had multiple strengths, including a within-subjects cross-over design, gold-standard randomization procedures, and the use of EMA to establish temporal ordering in daily life. To our knowledge, this is the first study to examine naltrexone's effect on both directions of the association of affect and alcohol in the same sample and is a secondary analysis of one of few studies to examine naltrexone in adolescents (most of whom were 18 or 19). Despite strengths, there were also limitations. First, while the use of a within-subjects cross-over design and EMA provides a large number of observations for the number of participants, the sample size was small, and the models were complex. We were powered to detect moderate-to-large effects; it will be important to replicate these findings in a larger sample. Second, a limitation of the cross-over design is the possibility of carryover effects for participants who first received naltrexone. Although the washout period was based on the clearance rate of naltrexone (Gonzalez & Brogden, 1988), it was relatively brief ($M = 4.52$ days) and blockade of at least some opioid receptors may persist for longer than 7 days (Lee et al., 1988). Condition order was included in models as a covariate, but we were not powered to test for interactions with this between-person factor. Potential concerns about possible carryover effects were further mitigated because the impact of a carryover effect would be to reduce differences between conditions (e.g., some participants in the placebo condition may still be experiencing the effects of naltrexone). Therefore, carryover would primarily be a potential concern only for naltrexone's effect on the association of eBAC on PA over the drinking episode.

Third, we were not able to test for causality in the relationship of affect and alcohol use. Fourth, while eBAC values were calculated using a valid and reliable formula (Hustad & Carey, 2005), the formula remains an estimate that relied upon participant self-report. However, self-reported EMA alcohol use reports compare favorably with transdermal biochemical verification (Simons et al., 2015). Fourth, treatment duration was short, potentially limiting the effect of naltrexone on drinking outcomes. Fifth, participants consisted of non-treatment-seeking adolescents, who may not fully reflect treatment-seeking adolescents. However, most participants met criteria for AUD, increasing the clinical applicability of the findings. Sixth, for analyses examining the association of affect with eBAC, there were relatively few observations in the continuation phase, most of which (81%) were in the first 2 h of the drinking episode. This suggests that the effect of naltrexone was apparent early in the episode and at relatively low eBACs. However, we had reduced power to detect effects in the continuation phase and, in particular, we are unable to make firm conclusions about whether this effect holds later on in drinking episodes. This is particularly the case because the EMA protocol was designed so that participants only reported affect at the first three end-drink reports of a drinking episode, which limits the number of drinks participants reported. Future work is needed to assess the impact of naltrexone across the entire episode.

In conclusion, this study provides evidence that naltrexone moderates the association of affect with alcohol use, and vice versa, in daily life. Overall, findings support the idea that naltrexone can disrupt the association of affect and alcohol use. Findings also depended on time, both in terms of whether an individual was having their first drink versus continuing to drink, and how far into a drinking episode they were. Findings suggest the potential value of greater attention on the affect-disrupting effects of naltrexone. This is particularly needed in the context of daily life and the range of affective experiences people, and especially adolescents, experience.

CONFLICT OF INTEREST

We have no conflict of interest to disclose.

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ENDNOTES

[1] For the first drink of an episode, if participants reported having already started their drink, the number of min ago they began drinking was added to time elapsed and included in the calculation of eBAC.

[2] As alcohol use is generally unlikely in the morning and early afternoon, we additionally ran this set of analyses only including observations that occurred between 5 p.m. and 4 a.m. This allowed us to examine whether the association of affect and subsequent use changed when restricting observations to times where drinking is more likely. Results did not differ from results from models where observations were not restricted.

[3] [3]There were relatively few observations in the continuation phase, which was, in part, due to the fact that participants only reported affect after their first three drinks. As a result, most observations (81%) and standard drinks (93%) were within the first 2 h of the initial drink. We conducted sensitivity analyses that restricted the continuation phase to the first 2 h of the episode and results did not change.

[4] AUD was assessed using DSM-IV-TR criteria and, thus, the craving criterion was not assessed. To more closely match DSM-5 AUD, we did not include the recurrent legal problems criterion.

[5] To determine percentile values, prompts where eBAC was 0.000 g% (e.g., begin drink reports) were excluded so the lines plotted more closely reflect high and low consumption drinking patterns. As can be seen in Figure 1, there were no high eBAC reports in the naltrexone condition after the 125th minute. We conducted sensitivity models with time restricted (i.e., censoring prompts after 100, 125, 150, and 200 min). Results did not change.

[6] There was also a negative two-way interaction of condition and phase and a positive main effect of phase. In the context of the three-way

interaction, these effects indicate that individuals generally reached lower eBAC levels in the naltrexone, compared to placebo, condition. Finally, there was a positive main effect of previous-moment PA. This indicates that, regardless of condition and phase, higher PA was associated with greater subsequent eBAC levels.

[7] There was also a negative two-way interaction of condition and phase and a positive main effect of phase, which indicates that individuals generally reached lower eBAC levels in the naltrexone, compared to placebo, condition. Finally, there was a negative two-way interaction of previous-moment NA and phase and a negative main effect of previous-moment NA. The main effect indicates that, regardless of condition and phase, higher NA was associated with lower subsequent eBAC levels, the two-way interaction indicates that this association was magnified in the continuation phase, and the three-way interaction indicates that this association was strongest in the continuation phase during the naltrexone condition.

[8] We additionally examined logistic models where dichotomous alcohol consumption (i.e., no use vs. any use) was the criterion, using PROC GLIMMIX with a logit function and a binomial distribution. This was primarily done to examine associations in the initiation phase, to address the fact that the majority of prompts were at non-drinking moments and, thus, had an eBAC value of 0.000g%, as well as the fact that there was less variance in eBAC values across days and individuals at the first end-drink report, as compared to the continuation phase of the episode. Logistic models found no significant interactions with treatment condition for NA or PA in the initiation phase.

[9] We conducted a sensitivity analysis for all four models to examine whether there were any differences due to the dosing schedule. We created a dichotomous indicator (0 = the first 2 days of the protocol and 1 = all remaining days) and added this to each model (specifying main effects and interactions). Results did not change, except in the model for PA predicting eBAC. The observed interaction of previous-moment PA, condition, and phase was specific to the period after the first 2 days of the protocol.

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