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EMOTION AND ADDICTION (K MORIE, SECTION EDITOR)

Examining Associations Between Negative Affect and Substance Use in Treatment-Seeking Samples: a Review of Studies Using Intensive Longitudinal Methods

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Abstract

Purpose of Review Understanding dynamic relationships between negative affect and substance use disorder (SUD) outcomes, including craving, may help inform adaptive and personalized interventions. Recent studies using intensive longitudinal methods were reviewed to examine relationships between negative affect and the outcomes of either craving or substance use during and following SUD treatment.

Recent Findings Results on associations between negative affect and craving/substance use were mixed and difficult to synthesize, given methodological differences across studies. The strength and direction of these relationships varied across outcomes, subgroups, contexts, and time course.

Summary The current literature is mixed concerning negative affect and craving/substance use associations during and following SUD treatment. Researchers should increasingly recruit diverse individuals, for example, samples of varying racial and ethnic backgrounds and those reporting co-occurring disorders and polysubstance use. Experimental, qualitative, and person-specific methods will improve our understanding of relationships between negative affect and substance-related outcomes during SUD treatment.

Keywords Ecological momentary assessment · Daily diary · Intensive longitudinal methods · Substance use · Negative affect · Emotion

Introduction

Theoretical models of addiction imply that using substances to cope with negative affect is associated with poorer long-term substance use outcomes [1–3] and that substance use disorders (SUDs) become increasingly driven by negative reinforcement (i.e., using substances to relieve negative affect) over time [4–6]. Accordingly, SUDs often co-occur with disorders defined by high negative affect (e.g., depression, anxiety, posttraumatic stress disorder [PTSD]) [7, 8], and affective disorders are a risk factor for SUD [9]. Those with co-occurring disorders are more likely to experience greater SUD severity and impairment [10, 11] and to seek treatment [12]. Given the central role of negative affect in models of addiction, a large body of research has attempted to characterize the role of negative affect in predicting, moderating, and mediating SUD treatment outcomes to inform tailored, adaptive, and precision interventions.

The Role of Negative Affect in Substance Use Disorder Treatment

Generally, people who more frequently experience negative affect and who meet diagnostic criteria for affective disorders before and during treatment have poorer SUD treatment outcomes (e.g., more frequent/heavier substance use,

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greater craving) [13–15]. Those with higher trait negative affect also tend to respond better to specific SUD treatments, such as mindfulness-based relapse prevention (MBRP) [16] and acamprosate treatment for alcohol use disorder (AUD) [17]. However, the extent to which SUD treatment impacts negative affect is poorly understood. There is some evidence that average trait-level negative affect decreases during treatment [13], but negative affect has been understudied as a SUD treatment mechanism [13, 18].

A clearer understanding of negative affect during SUD treatment is needed to improve treatments. For example, it is unclear whether people with higher trait-level negative affect report greater cravings/substance use (a between-person effect) or if moments with higher state-level negative affect are associated with increased craving/substance use (a within-person effect). It could also be that individuals with higher trait-level negative affect experience increased craving and engage in more substance use during times of higher state-level negative affect or some person-specific or time-varying combination of these effects. The timescale connecting negative affect and craving or substance use is also unknown. For example, does the association between negative affect and craving or substance use change over minutes, hours, and/or cumulatively over extended periods? Time series analyses are needed to determine whether there are systematic trends in negative affect during treatment, including precipitous points of change that could inform adaptive interventions.

Using Intensive Longitudinal Methods to Understand the Role of Negative Affect in Substance Use Disorder Treatment

The use of intensive longitudinal methods, such as ecological momentary assessment (EMA) and daily diary methods, can improve our understanding of negative affect in SUD treatment [19]. These methods have several advantages over traditional, retrospective-based methods (e.g., self-report and calendar-based measures). Intensive longitudinal methods collect multiple observations within individuals over time, often multiple times within a day, using brief self-report measures. Measures can be administered randomly within the day (or within time blocks), at fixed times each day, or during user-initiated events in the individual's daily life [20]. Accordingly, these methods mitigate recall bias, increase ecological validity, and are better able to disentangle the temporality of constructs. Analytic techniques for analyzing intensive longitudinal data include, but are not limited to (1) multilevel modeling (MLM), which can help to understand the level of analysis (i.e., between- or within-person) at which a relationship occurs and the time course of change in an outcome [21], (2) time-varying effects modeling (TVEM), which can help understand how the strength of a relationship between variables differs across time [22], and (3) network-based methods, such as vector autoregression or group iterative multiple model estimation, which models the presence and magnitude of relationships between nodes for groups and specific individuals within groups [23, 24].

Given these methodological features, intensive longitudinal methods can provide information regarding the contexts during which negative affect is most likely to impact substance use outcomes [19, 25], such as when skills to reduce negative affect might be most beneficial during treatment. Measuring the relationships between negative affect and craving or substance use and how these relationships differ between individuals, within individuals, or between and within individuals can help determine who needs treatments that target negative affect explicitly (e.g., MBRP), when to deliver negative affect-specific strategies, and whether certain subgroups could benefit from skills targeting negative affect at critical moments during treatment. Person-specific or idiographic methods that use intensive longitudinal data can also be employed to model dynamics at the individual level, informing the design of tailored and personalized assessment and interventions [24, 26•]. For example, pre-treatment person-specific models could assess the strength of an individual's relationship between negative affect and substance-related outcomes to determine if they may benefit from treatments that target negative affect and/or guide the delivery of momentary interventions during contexts with stronger negative affect and substance use associations [27•]. Intensive longitudinal data could also be used as measurement-based care to give clients personalized feedback on relationships between negative affect and substance use [28, 29].

Previous Reviews and Meta-analyses and the Current Review

We reviewed intensive longitudinal studies that examined relationships between negative affect and substance-related outcomes among individuals in SUD treatment. Of note, a recent systematic review and meta-analysis [30••, 31•] synthesized findings on associations between negative affect and substance use in intensive longitudinal studies enrolling a broader range of samples. Specifically, findings from a systematic review focusing on the associations between affective states and cannabis use in daily life [31•] indicated that momentary and daily negative affect (particularly anger/hostility) were concurrently associated with cannabis use among samples experiencing significant levels of psychopathology (e.g., SUDs, personality disorders), but support for the negative reinforcement model of cannabis use was equivocal in community and college student samples. In a large-scale meta-analysis of participant-level data from 69 studies [30••], participants were not more likely to drink or

drink heavily on days with higher negative affect, including in college ($k = 19$), community ($k = 18$), and clinical samples ($k = 6$; e.g., those in SUD treatment, with personality disorders, chronic pain).

We aim to advance beyond these prior studies in three ways, including (1) explicitly study the negative affect and substance use association among those experiencing more severe SUDs who are seeking treatment, (2) examine multiple substances, and (3) examine substance use outcomes in addition to use (e.g., craving). Addressing these gaps will help to understand the role of negative affect in substance use maintenance during treatment to inform intervention targets related to negative affect. Accordingly, based on the current review, we discuss treatment implications and recommend future directions for research on negative affect and substance use outcomes.

Method

Search Strategy and Scope of Review

We searched PubMed and PsycINFO databases for peer-reviewed articles published between January 2017 and April 2022 that used intensive longitudinal methods to examine relationships between negative affect and substance-related outcomes during treatment. Search terms included the following combinations: ("ecological momentary assessment" OR "experience sampling" OR "intensive longitudinal" OR "daily diary") AND ("affect" OR "mood" OR "stress" OR "anxiety" OR "depression") AND ("substance use" OR "alcohol use" OR "cannabis use" OR "marijuana use" OR "craving" OR "cocaine use" OR "stimulant use"). We also conducted backward searching of references cited in relevant articles and searches of articles that have subsequently cited relevant articles. Google Scholar alerts using relevant keywords were also established to capture articles published between April 2022 to submission (July 2022).

The studies included in this review used intensive longitudinal methods to examine relationships between negative affect, broadly defined (e.g., multiple negative affect states averaged, specific negative affect states, stress, PTSD symptoms), and substance use outcomes (e.g., craving, substance use frequency or intensity) among individuals in SUD treatment. All studies reviewed used intensive longitudinal methods (i.e., daily diary and/or EMA) to examine negative affect, though some studies used retrospective calendar-based methods to examine substance use outcomes. We also included three studies that did not explicitly recruit treatment-seekers but did use intensive longitudinal methods to examine mechanisms of SUD treatment (i.e., naltrexone for alcohol use [32]; topiramate for cannabis use [33, 34]). We did not review studies that only examined tobacco use outcomes to limit the scope of the review.

Results

Methodological Features of Reviewed Studies

The methodological features of the 32 reviewed studies are presented in Table 1. Overall, ten studies were conducted during alcohol treatment, 13 during opioid treatment, three during cannabis treatment, and six during SUD treatment, in which all substance types were included. Studies included randomized controlled trials of medications for SUDs or psychotherapy and naturalistic studies of individuals in outpatient or residential treatment. Most reviewed studies collected reports multiple times a day, including random or fixed reports (three to six per day) and user-initiated reports at times of drug use and high stress. However, five studies collected reports only once per day.

Negative affect and related symptom constructs were assessed using a variety of measures; 21 studies assessed averaged negative affective states or specific (e.g., anger, anxiety) negative affective states, often measured with adaptations of the Positive and Negative Affect Schedule [35, 36] or the circumplex model [37]. Fourteen studies assessed stress or stressful situations and often used single-item measures, though one study used an adaptation of the Perceived Stress Scale [38] and another used an adaptation of the Daily Inventory of Stressful Events [39]. Three studies examined PTSD symptoms, including adaptations of the PTSD Checklist (PCL)-5 and the PCL-Civilian Version [40–42]. Other measures assessed negative affect as a trigger for drug use [43], negative affect as a consequence of cannabis use [34], and negativity of events [44•, 45]. Several studies used measures of negative affect to calculate nuanced metrics, such as emotion differentiation (or the ability to identify one's specific emotions) across and within individuals [46•] and instability in and persistence of negative affect and stress [43, 47, 48].

Substance-related outcomes were most commonly assessed daily or momentarily via intensive longitudinal data reports. However, some studies examined substance use outcomes measured with more traditional methods, such as calendar-based methods [47, 47] and urine drug screens [38, 43, 49]. Many studies examined craving as a correlate of negative affect, often measured via a single item representing momentary or daily craving. Consumption outcomes included substance use occurrence/frequency, quantity (e.g., number of standard drinks, grams of cannabis consumed), and subtyping of substance-related profiles (e.g., subgroups based on whether abstinence was initiated before or during treatment or never during the treatment period; [50]).

Table 1 Methodological features of reviewed studies

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
Alcohol treatment studies							
[56]	126 young adults (aged 18–25) with at least 4 heavy drinking days in the prior 4 weeks. Not required to be motivated to reduce alcohol use. 31.7% female. 77.7% non-Hispanic white, 6.3% Black, 4.8% multiracial, 3.1% Asian, and 8% other racial/ethnic identity	Randomly assigned to either naltrexone or placebo for 8 weeks + brief motivational counseling for drinking reduction	Once daily reports (typically right after waking) for 8 weeks	Reported current negative affect, using 2 items: distressed, sad. Items rated from 1 (not at all) to 7 (extremely) and averaged	Drinking to intoxication (an estimated BAC ≥ .08 g%), based on daily reports of standard drinks and times stopped/started drinking	Between-person, within-person (daily)	Used MLM to examine: (1) the association between average negative affect and likelihood of drinking to intoxication, (2) daily deviations from average negative affect and the likelihood of same day drinking to intoxication, and (3) negative urgency as a moderator of the association between daily negative affect and likelihood of drinking to intoxication
[42]	65 adults with alcohol dependence and PTSD interested in reducing their drinking. 52.3% female. 26.2% Veterans. 43.1% African American, 40.0% non-Hispanic white, 4.6% Hispanic, 3.1% multiracial, 3.1% Native American, 1.5% Asian American, 4.6% other racial/ethnic identity	Randomized to a one-session active coping skills intervention for alcohol craving (cognitive restructuring or experiential acceptance) or an attention control about nutrition	Once daily reports (time NR) for 30 days after the intervention	Reported PTSD symptoms in the past 24 h using 12 items from the PCL-Civilian Version [74]. Items rated from 0 (not at all bothered) to 8 (bothered all the time) and averaged	Number of standard drinks consumed the previous day	Within-person (daily)	Used MLM to examine the association between daily deviations from average alcohol consumption and same-day PTSD symptoms

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[32]	26 non-treatment-seeking adolescents (aged 15–19). Consumed alcohol at least 2x/week in the past 30 days. 69% met criteria for AUD. 54% female. 69% white, 8% Black, 8% Asian, 4% Native American, 4% Pacific Islander, 8% no race reported. 15% Hispanic ethnicity, 81% non-Hispanic, 4% no ethnicity reported	Double-blind cross-over trial that compared naltrexone and placebo. Participants were randomized to each condition for 8 to 10 days in counterbalanced order with a 4–11–day washout between conditions	3 random reports over 3-h blocks throughout treatment + user-initiated prompts before and after each standard drink	Reported momentary negative affect using items adapted from the PANAS-X [35] and the circumplex model [37]: bored, tense, sad, stressed. Items rated from 0 (not at all) to 10 (extremely) and averaged	Estimated blood alcohol content (eBAC), based on momentary reports of ounces of ethanol consumed, time elapsed, sex, and weight	Between-person, within-person (daily, momentary)	Used MLM to examine: (1) the association between eBAC and same-moment negative affect, and whether treatment condition moderated this association, and (2) the association between momentary deviations from daily negative affect and next-moment eBAC, and whether treatment condition moderated this association
[47]	42 adults with AUD who had 2 weeks of abstinence before enrollment. 38.1% female. 73.8% White, 19.1% Black, 4.8% Asian, and 2.4% other or multiracial	Naturalistic study of individuals in their first year of a recovery attempt, including outpatient treatment for AUD (e.g., mutual help, individual treatment)	3 random reports per day + user-initiated prompts at times of high stress, craving, or alcohol use for 6 days	Reported momentary stress from 0 (no stress) to 10 (extreme stress). Calculated between-person stress variability using momentary stress reports	Percent days abstinence over the 90 days following the intensive longitudinal data collection period based on a calendar-based measure	Between-person	Used MLM to examine the effects of average stress and stress variability, as well as their interaction on percent days abstinent

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[46•]	42 adults with AUD who had 2 weeks of abstinence before enrollment. 38.1% female. 73.8% White, 19.1% Black, 4.8% Asian, and 2.4% other or mixed race	Naturalistic study of individuals in their first year of a recovery attempt, including outpatient treatment for AUD (e.g., mutual help, individual treatment)	3 random reports per day + user-initiated prompts at times of high stress, craving, or alcohol use for 6 days	Reported momentary negative affect using items adapted from the PANAS-X [35] and the circumplex model [37]: sadness, guilt, nervousness, tiredness, anger. Items rated from 0 (none) to 10 (extreme) and averaged. Negative affect was used to calculate person-level and momentary emotion differentiation [75] Reported momentary stress from 0 (no stress) to 10 (extreme stress)	Percent days abstinence over the 90 days following the intensive longitudinal data collection period, based on a calendar-based measure	Between-person, within-person (momentary)	Used MLM to examine: (1) the association between average emotion differentiation and percent days abstinent, and (2) momentary deviations from average negative affect and stress on same-moment emotion differentiation
[50]	72 adults with AUD, a treatment goal of abstinence, 14 + /21 + drinks/week consumed for women/men, 2 heavy drinking days/week for 4 consecutive weeks in the last 90 days. 12.5% female. 21.8% Veterans. 57.1% White, 31.2% African American, 11.7% other racial identity	Randomized to 12 weeks of prazosin or placebo + brief medication management counseling weekly	Once daily reports (in the morning) for 12 weeks	Reported yesterday's negative affect using 4 items: stress, anger, anxiety, and sadness. Items rated from 0 (no negative affect) to 8 (most severe negative affect). A latent, combined negative affect variable was examined, as well as each specific negative affect item	Based on daily drinking reports, classified: (1) those with continuous abstinence during the first 2 weeks of treatment (already abstainers), (2) those who initiated abstinence after the first 2 weeks of treatment (abstinence initiators), and (3) those who drank continuously throughout the trial (continued drinkers)	Between-person	Used multivariate latent growth curve models within a MLM framework to examine change in negative affect over the treatment period in the 3 drinking groups, separately (i.e., abstinence initiators, already abstainers, continued drinkers)

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[59]	153 adults seeking treatment to moderate their drinking. Estimated average weekly consumption of 15 + standard drinks/week or 12–15 standard drinks/week and 2 + binge drinking days for women, 24 + standard drinks/week or 14–25 standard drinks/week and 2 + binge drinking days for men. 68.6% female. 90.8% non-Hispanic white, 6.5% Hispanic/Latino, 2.7% other racial/ethnic identity	Randomized to a stepped care intervention including a combination of brief advice/feedback, motivational interviewing, and/or behavioral self-control therapy	3 reports per day in the morning (6am–12 pm), afternoon (12–6 pm), or evening (5–11 pm) for 84 days	Reported whether they were in a context (in setting vs. not in setting) where they "felt especially upset, tense, stressed, or angry"	Momentary reports of craving from 0 (no desire or craving/urge) to 8 (extreme desire or craving/urge)	Within-person (momentary)	Used MLM to examine the momentary association between being in a negative affective context and the presence and intensity of craving
[57]	43 Dutch adults enrolled in outpatient treatment for AUD following detoxification and residential treatment. 30.2% female. Race/ethnicity NR	Naturalistic study of individuals in outpatient treatment (i.e., group or individual therapy with or without medication) following detoxification and 6 weeks of residential treatment	3 random reports per day + user-initiated reports during "an acute increase in the urge to drink or an occasion when they felt that they came to the brink of drinking without actually doing so" for 4 weeks	Reported momentary negative affect using 5 items from the PANAS—SF [36] (e.g., "I feel upset right now"). Items rated from 1 (not at all) to 5 (extremely) and average was taken Reported momentary stress using the item "I feel stressed right now" from 1 (not at all) to 7 (extremely)	Craving was assessed using the item "In the past hour I felt an urge (craving) to drink" from 1 (not at all) to 7 (very much)	Between-person, within-person (momentary)	Used MLM to examine: (1) the association between average negative affect and craving, and (2) trait mindfulness as a moderator of the association between momentary deviations in average negative affect and same-moment craving

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[58]	43 Dutch adults enrolled in outpatient treatment for AUD following detoxification and residential treatment. 30.2% female. Race/ethnicity NR	Naturalistic study of individuals in outpatient treatment (i.e., group or individual therapy with or without medication) following detoxification and six weeks of residential treatment	3 random reports per day + user-initiated reports during "an acute increase in the urge to drink or an occasion when they felt that they came to the brink of drinking without actually doing so" for 4 weeks	Reported momentary negative affect using 5 items from the PANAS—SF [36] (e.g., "I feel upset right now"). Items rated from 1 (not at all) to 5 (extremely) and averaged Reported stress using 2 items examined separately: "I feel stressed right now" and "In the past hour I felt stressed." Items rated from 1 (not at all) to 5 (extremely)	Craving was assessed using the item "In the past hour I felt an urge (craving) to drink" from 1 (not at all) to 7 (very much)	Within-person (momentary)	Used MLM to examine: 1) cross-sectional associations between momentary deviations in average negative affect and stress (independent variables) and same-moment assessment type (i.e., random vs. temptation) and craving intensity (dependent variables), and 2) prospective associations between momentary deviations in average negative affect and stress (independent variables) and next-moment assessment type and craving (dependent variables)

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[39]	Participants with AUD entering outpatient treatment recruited for two separate studies Study 1: $N=85$. 36.5% female. 50.6% African American, 48.2% white, 1.2% other racial/ethnic identity Study 2: $N=28$. 39.3% female. 64.3% African American, 32.1% white, 3.6% other racial/ethnic identity	Study 1: Randomized to prazosin or placebo + one hour per week of 12-step facilitation behavioral treatment. Focused on the first two weeks of treatment Study 2: One hour per week for 8 weeks of 12-step facilitation behavioral treatment, without any control condition	Study 1: Once daily in the evening for 2 weeks Study 2: Once daily in the evening for 8 weeks	Study 1: Reported if stressful events happened that day (yes/no) using 3 items from the Daily Inventory of Stressful Events [76] (e.g., having or nearly having an argument or disagreement). Reports were combined to represent 0 (no daily stressor) or 1 (daily stressor occurred) Study 2: Reported stressors experienced since yesterday's report (yes/no), including: work/education, home/family, finances, etc. Reports were combined to represent 0 (no daily stressor) or 1 (daily stressor occurred)	Study 1: Reported craving using: "Right now, I could really use a drink" and "Right now, the idea of a drink is appealing." Items rated from 0 (definitely false) to 4 (definitely true) and averaged. Reported number of standard drinks daily Study 2: Craving was measured using a single item "Right now I could really use a drink" rated from 1 (strongly disagree) to 100 (strongly agree). Reported number of standard drinks daily	Between-person, within-person (daily)	Used multilevel structural equation modeling (MSEM) to examine the mediating effect of craving right now on the association between same-day stress and next day drinking and number of standard drinks
Opioid treatment studies							
[54]	211 adults with OUD receiving buprenorphine or methadone treatment. 22% female. 68% non-white racial identity	Participants received methadone or buprenorphine treatment. Attended clinic 2–7 days per week, depending on the treatment arm	3 random reports per day + user-initiated reports when participants used drugs or felt "more stressed, overwhelmed, or anxious than usual" + end of day. Reported for up to 16 weeks during treatment starting 2 weeks after medication initiation	During random reports, reported momentary stress using a single item from 1 (not at all) to 5 (extremely). During user-initiated reports, reported stress using a single item from 1 (not bad at all) to 10 (the worst you've ever felt)	Reported momentary opioid craving using a single item from 1 (not at all) to 5 (extremely). Averaged reports across day to calculate a daily craving score	Between-person	Used growth mixture modeling to identify longitudinal, daily trajectories of craving during treatment and conducted chi-square tests to examine differences in the average number of event-contingent stress reports per day between craving-trajectory subgroups

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[53•]	211 adults with OUD receiving buprenorphine or methadone treatment. 22% female. 68% non-white racial identity	Participants received methadone or buprenorphine treatment. Attended clinic 2–7 days per week, depending on the treatment arm	3 random reports per day + user-initiated reports when participants used drugs or felt "more stressed, overwhelmed, or anxious than usual" + end of day. Reported for up to 16 weeks during treatment starting 2 weeks after medication initiation	During random reports, reported momentary stress using a single item from 1 (not at all) to 5 (extremely). During user-initiated reports, reported stress using a single item from 1 (not bad at all) to 10 (the worst you've ever felt). Recoded to the same 5-point scale and averaged across day to calculate a daily stress score	Reported momentary opioid and cocaine craving using a single item from 1 (not at all) to 5 (extremely) Average daily rate of drug use (i.e., number of drug use reports divided by number days with reports)	Between-person, within-person (momentary)	Used growth mixture modeling to identify longitudinal, daily trajectories of stress during treatment and conducted chi-square tests to examine differences in craving and daily rates of drug use between stress-trajectory subgroups Used MLM to examine whether changes in stress in the hours (up to 10 h) before a drug use event differed by stress-trajectory subgroups
[48]	224 adults with OUD receiving buprenorphine or methadone treatment. 23.2% female. 64.3% African American, 33.0% white, 0.4% Asian/Pacific Islander, 0.4% more than one race, 1.8% unknown	Participants received methadone or buprenorphine treatment and attended clinic 5–7 days per week + incentives for providing drug use reports that matched urine drug screen results, with greater incentives for negative urine drug screens/abstinence	3 random reports per day + user-initiated reports (e.g., drug use) + end of day reports for up to 30 weeks during treatment, but only the first 6 weeks were analyzed	Reported momentary negative affect using: fatigued, worn out, afraid, annoyed, angry, hopeless, on edge, sad, discouraged, resentful, exhausted, uneasy. Items rated from 1 (not at all) to 5 (extremely) and averaged	Reported opioid use during random, event-contingent, and end-of-day prompts and these were used to calculate the proportion of days using opioids across the 6 study weeks	Between-person	Used a MLM within a dynamic structural equation modeling framework to calculate two person-level indices: (1) intra-individual variances (iSD^2) to assess variability in negative affect, and (2) autocorrelations (AR1) to assess the stability of negative affect Used beta regression to examine associations between negative affect variability and stability and proportion of opioid use days, controlling for average negative affect

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[52••]	73 adults with OUD (prescription opioids were the drug of choice) recruited from residential treatment following detoxification. 23.3% female. Race/ethnicity NR	Naturalistic study of individuals in residential treatment for OUD. Required to stay in treatment at least 30 days for study participation. All participants completed detoxification 10–14 days before the study	4 fixed reports per day (morning, midday, mid-afternoon, evening) for 12 days	Reported momentary negative affect using items adapted from the PANAS-X [35]: angry, irritable, lonely, sad, guilty, ashamed, anxious, stressed. Items were rated from 0 (not at all) to 100 (very) and averaged at the momentary and daily level	Reported craving using 3 items since the last data entry: "the idea of using drugs has intruded upon my thoughts," "I have missed the feeling drugs can give me," and "I have thought about how satisfying drugs can be." Items were rated from "strongly disagree" to "agree" and averaged at the momentary and daily level	Between-person, within-person (daily)	Used TVEM to examine: (1) the day(s) of treatment at which negative affect and craving were most strongly associated, and (2) the time of day within days at which negative affect and craving were most strongly associated
[62]	73 adults with OUD (prescription opioids were the drug of choice) recruited from residential treatment following detoxification. 23.3% female. Race/ethnicity NR	Naturalistic study of individuals in residential treatment for OUD. Required to stay in treatment at least 30 days for study participation. All participants completed detoxification 10–14 days before the study	4 fixed reports per day (morning, midday, mid-afternoon, evening) for 12 days	Reported momentary negative affect using items adapted from the PANAS-X [35]: angry, irritable, lonely, sad, guilty, ashamed, anxious, stressed. Items were rated from 0 (not at all) to 100 (very) and averaged at the daily level	Reported craving using 3 items since the last data entry: "the idea of using drugs has intruded upon my thoughts," "I have missed the feeling drugs can give me," and "I have thought about how satisfying drugs can be." Items were rated from "strongly disagree" to "agree" and averaged at the daily level	Between-person, within-person (daily)	Used MLM to examine: (1) the association between average negative affect and craving, (2) the association between daily deviations in average negative affect and same-day craving, and (3) daily deviations in average positive social events and negative social events as moderators of the association between daily negative affect and same-day craving

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[49]	108 adults with OUD seeking outpatient treatment. 21.3% female. Race/ethnicity NR	Randomized to clonidine or placebo for 12 weeks as an adjunctive medication to buprenorphine treatment. Participants attended clinic 7 days per week + weekly counseling sessions for up to 28 weeks + vouchers of increasing monetary value for opioid-negative urine drug screens	4 random reports per day for 12 weeks	Reported momentary negative affect using the following items that were examined separately: stressed, tired, bored, irritated. Items rated from 1 (YES!!!) to 4 (NO!!!). Examined each affective item separately, which were averaged over 2- to 3-day periods to match the urine drug screen period	Participants completed urine drug screens approximately every 3 days, so the outcome was urine drug screen positive or negative for opioids over the previous 48-to 72-h	Between-person, within-person (2 to 3 days)	Used MLM to examine: (1) the association between average negative affect and opioid use, (2) the association between deviations (at 2- to 3-day level of analysis) in average negative affect and same-period opioid use, and (3) whether treatment condition (clonidine or placebo) moderated these between-person and within-person associations
[51]	68 adults with OUD (prescription opioids were the drug of choice) recruited from residential treatment following detoxification. In the larger study ($N = 75$), 30% female. Race/ethnicity NR	Naturalistic study of individuals in residential treatment for OUD. Required to stay in treatment at least 30 days for study participation. All participants completed detoxification 10–14 days before the study	4 fixed reports per day (morning, midday, mid-afternoon, evening) for 12 days	Reported momentary negative affect using items adapted from the PANAS-X [35]: angry, irritable, lonely, sad, guilty, ashamed, anxious, stressed. Items were rated from 0 (not at all) to 100 (very) and averaged at the daily level	Reported craving using 3 items since the last data entry: "the idea of using drugs has intruded upon my thoughts," "I have missed the feeling drugs can give me," and "I have thought about how satisfying drugs can be." Items were rated from "strongly disagree" to "agree" and averaged at the daily level	Within-person (daily)	Used multilevel mediation model to test whether daily deviations in average negative affect mediated the association between daily deviations average sleep quality and same-day craving

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[63]	182 adults with OUD receiving buprenorphine or methadone treatment. 25.8% female. In men, 63.9% African American, 35.3% European American. In women, 70.2% African American, 27.6% European American	Participants received methadone or buprenorphine treatment. Attended clinic 5–7 days per week + weekly individual counseling	3 random reports per day + user-initiated reports when participants felt "more stressed, overwhelmed, or anxious than usual." Reported for up to 16 weeks during treatment starting 2 weeks after medication initiation	During random reports, reported momentary stress using a single item from 1 (not at all) to 5 (extremely). During user-initiated reports, reported stress using a single item from 1 (not bad at all) to 10 (the worst you've ever felt)	Reported momentary opioid and cocaine craving using a single item from 1 (not at all) to 5 (extremely)	Within-person (momentary)	Used MLM to examine: 1) the association between momentary stress severity and same-moment craving, 2) sex and the presence of drug cues (and their interaction) and moderators of the association between momentary stress severity and same-moment craving
[43]	309 adults with OUD receiving buprenorphine or methadone treatment. 22% female. 64% African American, 34% white, 2% Asian or more than one race	Participants received methadone or buprenorphine treatment. Attended clinic 2–7 days per week, depending on the treatment arm + incentives for providing drug use reports that matched urine drug screen results, with greater incentives for negative urine drug screens/abstinence. All participants were offered counseling	3 random reports per day + user-initiated reports when participants used drugs or felt "more stressed, overwhelmed, or anxious than usual" + end of day reports. Reported for up to 16 weeks during treatment starting 2 weeks after medication initiation	Reported momentary negative affect using several items (wording NR). Items rated from 1 (not at all) to 5 (extremely) and averaged. Calculated person-level average negative affect and variability in negative affect using root mean square of successive deviations (rMSSD) Reported momentary stress using a single item from 1 (not at all) to 5 (extremely). Calculated person-level average stress and variability in stress using rMSSD Reported negative affect as a trigger for drug use during drug use prompts for which options included (yes/no): boredom, stress, anger/frustration, anxiety/fear	Reported momentary opioid and cocaine craving using a single item from 1 (not at all) to 5 (extremely). Opioid and cocaine craving were combined Urine drug screens were provided 2–3 times per week and opioid and cocaine urine drug screens were examined in the present analysis	Between-person, within-person (momentary)	Used hierarchical clustering to examine patters of cocaine and opioid use during the treatment period and ANOVA to examine differences between clusters in: average negative mood, average stress, negative mood variability, stress variability, and average negative affect as a trigger for drug use Used TVEM to examine how associations between stress and next report craving varied depending on the amount of time elapsed since stress was measured; conducted separately by cocaine/opioid clusters identified in the hierarchical clustering analyses

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[60]	182 adults with OUD receiving buprenorphine or methadone treatment. 25.8% female. 64.8% African America, 34.0% white	Participants received methadone or buprenorphine treatment. Attended clinic 5–7 days per week + weekly individual counseling	3 random reports per day + user-initiated reports when participants felt "more stressed, overwhelmed, or anxious than usual." Reported for up to 16 weeks during treatment starting 2 weeks after medication initiation	During user-initiated reports, reported stress using a single item from 1 (not bad at all) to 10 (the worst you've ever felt)	Reported momentary opioid and cocaine craving using a single item from 1 (not at all) to 5 (extremely)	Between-person, within-person (momentary)	Used MLM to examine the association between stress and opioid and cocaine craving and decomposed the variance into between-person and within-person components
[61]	182 adults with OUD receiving buprenorphine or methadone treatment. 26% female. 65% African America, 34.0% white, 1% multiracial	Participants received methadone or buprenorphine treatment. Attended clinic 5–7 days per week + weekly individual counseling	3 random reports per day + user-initiated reports when participants felt "more stressed, overwhelmed, or anxious than usual." Only random reports analyzed in the present analysis. Reported for up to 16 weeks during treatment starting 2 weeks after medication initiation	Reported momentary stress using a single item from 1 (not at all) to 5 (extremely)	Reported momentary opioid and cocaine craving using a single item from 1 (not at all) to 5 (extremely)	Between-person, within-person (momentary)	Used MLM to examine: (1) whether the average drug cue exposure moderated the association between average stress and cocaine and opioid craving, and (2) whether the presence of momentary drug cues moderated the association between momentary deviations in average stress and same-moment craving

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[38]	161 adults with OUD receiving buprenorphine or methadone treatment. 27.3% female. 64.8% African America, 33.0% white	Participants received methadone or buprenorphine treatment. Attended clinic 5–7 days per week + weekly individual counseling	3 random reports per day + user-initiated stress and drug reports + fixed end of day reports approximately one hour before bedtime. Present analysis focused on end of day reports. Reported for up to 16 weeks during treatment starting 2 weeks after medication initiation	Reported current day's perceived stress using 5 items from the Perceived Stress Scale [77] (e.g., "Today, how often did you feel confident about your ability to handle your personal problems?"); items rated from a 0 (never) to 4 (very often) and averaged Endorsed (yes/no) which feelings they were experiencing during currently: angry/annoyed/afraid, sad/depressed. Examined each separately	Days that were cocaine- and opioid-positive on urine drug screens Days where a drug use event was reported	Within-person (daily)	Used MLM to examine associations between daily perceived stress and negative mood (independent variables) and same-day drug use events, opioid-positive urine drug screen, and cocaine-positive urine drug screen (dependent variables)
[64]	182 adults with OUD receiving buprenorphine or methadone treatment. 26% female. 65% African America, 34.0% white, 1% multiracial	Participants received methadone or buprenorphine treatment. Attended clinic 5–7 days per week + weekly individual counseling	3 random reports per day + user-initiated stress and drug reports. Reported for up to 16 weeks during treatment starting 2 weeks after medication initiation	Reported momentary negative affect using several items (wording NR). Items rated from 1 (not at all) to 5 (extremely) and averaged Reported momentary stress using a single item from 1 (not at all) to 5 (extremely)	Reported momentary opioid and cocaine craving using a single item from 1 (not at all) to 5 (extremely) Examined drug use events	Within-person (momentary)	Used MLM to examine: (1) the effect of time on stress in the hours leading up to a drug use event and in the hours after a drug use event, (2) the effect of time on negative affect in the hours leading up to a drug use event and in the hours after a drug use event, and (3) the effect of time on opioid and cocaine craving in the house leading up a stress event and in the hours after a stress event. Conducted exploratory analyses examining these associations separately by treatment (i.e., methadone or buprenorphine)

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
Cannabis treatment studies							
[33]	63 youth (aged 15–24) who reported cannabis use 2x/week in the last 30 days and one symptom of cannabis use disorder. 50.8% female. 55% white, 27% Black/African American, 5% American Indian/Alaskan Native, 3.2% Asian, 1.6% Native Hawaiian/Pacific Islander, 11.1% multiracial/another race. 20.6% Hispanic ethnicity	Randomized to topiramate or placebo for 6 weeks + 3 sessions of a behavioral intervention to enhance motivation and build skills to reduce cannabis use	Random prompts in 3-h blocks throughout the day + user-initiated prompts before cannabis use during 6 weeks of treatment	Reported momentary negative affect using items adapted from the PANAS-X [35] and the circumplex model [37]: tense, sad, stressed. Items rated from 0 (not at all) to 10 (extremely) and averaged	Cannabis use reports were used for any cannabis use and quantity (in grams)	Between-person, within-person (momentary)	Used MLM to examine: (1) the association between average negative affect and average likelihood of cannabis use and quantity of cannabis use, and (2) momentary deviations in average negative affect and next-moment cannabis use likelihood and quantity, and (3) treatment condition as a moderator of these associations
[65]	198 adults seeking treatment for cannabis use disorder. 42% female. 51% white, 28% Black, 14% Hispanic, and 7% other racial/ethnic identity	Randomized to the following 9-session treatment conditions: motivational enhancement therapy (MET) + cognitive behavioral therapy (CBT); MET + CBT + contingency management (CM); individualized assessment and treatment program (IATP); or IATP + CM	4 to 6 random reports a day during the following periods: 2 weeks before treatment started, 1 week mid-treatment, 1 week immediately post-treatment, and 1 week prior to the 8- and 14-month follow-ups	Reported momentary negative affect using items from the circumplex model [37]: unpleasant high-activation (nervous, angry) and unpleasant-low activation (bored, sad). Items were rated from 0 (not at all) to 4 (very much) and averaged at their respective scale	Cannabis use in the past hour from random reports	Within-person (momentary)	Using a Generalized Estimating Equations approach, examined the association between momentary negative affect and next-report cannabis use

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[34]	66 youth (aged 15–24) who reported cannabis use 2×/week in the last 30 days and one symptom of cannabis use disorder. 47.5% female. 57.5% white, 22.5% Black. 25.0% Hispanic/Latino ethnicity	Randomized to topiramate or placebo for 6 weeks + 3 sessions of a behavioral intervention to enhance motivation and build skills to reduce cannabis use	Random prompts in 3-h blocks throughout the day + user-initiated prompts before cannabis use during 6 weeks of treatment. This analysis focused on weeks 4–6 of reporting	Reported negative affect following cannabis use at the first cannabis use event on a given day, with the following items: tense, stressed. Rated from 0 (not at all) to 10 (extremely) and averaged	From user-initiated reported, examined cannabis grams at initial cannabis episode and total daily cannabis grams	Between-person, within-person (daily)	Used multilevel structural equation models to examine: (1) average negative affect following a cannabis use episode as a mediator of the association between treatment condition and average cannabis grams used, and (2) daily negative affect following the first cannabis use episode as a mediator of the association between grams used at the first episode and total grams used that day
SUD treatment studies — all substance types included							
[44•]	159 adults in outpatient addiction treatment in France. 59.7% with co-occurring mood or anxiety disorder. In those with co-occurring disorder, 37.5% female, 28.1% AUD, 26.6% OUD, 15.6% cannabis use disorder, 29.7% tobacco use disorder. In those without a co-occurring disorder, 29.5% female, 31.6% AUD, 16.8% OUD, 15.6% cannabis use disorder, 29.7% tobacco use disorder. Race/ethnicity NR	Naturalistic study of outpatient SUD treatment, including individual behavioral treatment with or without pharmacotherapy	4 random prompts per day for 14 days. The present analysis used data from days 2–13	Reported momentary sad and anxious moods (examined separately) using a 7-point Likert scale (anchors NR) Selected an event that had the greatest impact on them since their last prompt and rate its event negativity on a 7-point scale (anchors NR)	Rated maximum level of craving felt since the previous assessment from 1 (no desire) to 7 (extreme desire) Reported use of their primary substance and other substances since the last assessment	Within-person (momentary)	Used MLM to examine: (1) the association between momentary mood states and same-moment craving and substance use, (2) the association between momentary mood states and next-moment craving and substance use, and (3) whether these associations differed between those with and without co-occurring mood and anxiety disorders

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[66]	117 justice-involved men participating in a community-based SUD treatment problem. 76% on probation, 24% on parole. 78% African American/Black, 19% white, and 3% other racial/ethnic identity. 81% opioids as primary substance, 11% alcohol, 13% other substance	Naturalistic study of outpatient SUD treatment; all participants were referred to medication treatment for AUD or OUD	Once a day for 14 days following referral to outpatient medication treatment for AUD or OUD	Reported the number of stressors they had experienced since yesterday's report (yes/no), including about: an argument with someone, work or unemployment, money problems, health, probation/parole, legal issues, where they were living, transportation. Stressors were summed	Craving was assessed with the item "How strong is your craving to [drink, use illegal drugs]?" Items were rated from 0 (not at all strong) to 4 (extremely strong) Reported number of standard drinks and use of illegal drugs in the past 24 h	Within-person (daily)	Used MLM to examine: (1) the association between daily number of stressors and same-day number of standard drinks and use of illegal drugs, (2) the association between daily number of stressors and next-day number of standard drinks and use of illegal drugs, and (3) number of prior SUD treatment episodes as a moderator of these associations
[40]	32 adult, pregnant persons with prior trauma exposure enrolled in an integrated medical and SUD treatment program for prenatal, maternity, and newborn care. 75% current OUD, 16% medication remission OUD, 28% AUD, 31% cannabis use disorder, 34% sedative use disorder, 47% stimulant use disorder. 66% Hispanic, 28% non-Hispanic white, 13% American Indian/Native American, 3% African American/Black	Naturalistic study of an integrated medical and SUD treatment program for prenatal, maternity, and newborn care	Reported during 3 fixed reports a day based on participants schedules (upon waking, afternoon around 2 pm, before bedtime) for 28 days	Reported PTSD symptoms severity since the last report using items from the PCL-5 [78]. Items rated from 0 (not at all) to 5 (extremely) and averaged	Craving was assessed with the item "I have a desire to get high right now." Item rated from 1 (not at all) to 5 (extremely)	Between-person, within-person (momentary)	Used multilevel mediation models to examine: (1) average parental bonding as a mediator of the association between average PTSD symptoms average craving, and (2) momentary deviations in average parental bonding as a mediator of the association between momentary deviations in average PTSD symptoms and same-moment craving

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[41]	33 adult, pregnant persons with prior trauma exposure enrolled in an integrated medical and SUD treatment program for prenatal, maternity, and newborn care. 91% OUD, 64% non-opioid SUD. 78.8% white, 21.2% Native American, 3% African American. 66.7% Hispanic ethnicity	Naturalistic study of an integrated medical and SUD treatment program for prenatal, maternity, and newborn care. 91% receiving medications for OUD	Reported during 3 fixed reports a day based on participants schedules (upon waking, afternoon around 2 pm, before bedtime) for 28 days	Reported PTSD symptoms severity since the last report using items from the PCL-5 [78]. Items rated from 0 (not at all) to 5 (extremely) and averaged	Substance use (drug use, cannabis use, heroin use, alcohol use, cigarette use) since last report	Between-person, within-person (daily)	Used MLM to examine: (1) the association between average peak daily PTSD symptoms and average likelihood of drug use, cannabis use, and heroin use and average daily number of drinks/cigarettes, and (2) the association between daily deviations in average peak PTSD symptoms and same-day likelihood of drug use, cannabis use, and heroin use and number of drinks/cigarettes
[55]	43 adults who were admitted to SUD treatment and met at least one SUD symptom. In the larger study ($N=301$), 37% female. 72% African American, 19% white, 2% Hispanic, 7% multiracial/other racial/ethnic identity. 30% weekly alcohol use, 16% cocaine/stimulant use, 12% heroin/opioids, 12% cannabis, 2% other drugs	All participants were receiving outpatient or residential SUD treatment with or without medication. Randomized to the following conditions: (1) EMA only, (2) ecological momentary intervention (EMI) only, (3) both EMA and EMI, or (4) a control group. Those in the EMA only condition were included in this analysis	5 random prompts per day (between 6:00 am and midnight) for 6 months	Reported negative affect (yes/no) in the past 30 min using 10 items: stressed, upset, irritated, angry, worried, tense, depressed, sad or blue, nervous, anxious. Number of negative affective feelings was summed	Reported substance use in the past 30 min, since the last EMA, and before the last EMA/never for alcohol, cannabis, and other drugs. From these reports, calculated the % of the next 5 reports with substance use	Within-person (momentary)	Used chi-square Automatic interaction detector decision tress to identify the best predictors, interactions between predictors, and cut points (including negative affective feelings) for predicting the % of the next 5 reports with substance use

Table 1 (continued)

Citation	Overview of sample	Overview of treatment	Intensive longitudinal data collection protocol	Negative affect measure(s)	Substance use and craving measure(s)	Level(s) of analysis	Analytic method(s) and research question of interest
[45]	159 adults in outpatient addiction treatment in France. 30.1% AUD, 20.8% OUD, 22.0% cannabis use disorder, 27.0% tobacco use disorder. 32.7% female. Race/ethnicity NR	Naturalistic study of outpatient SUD treatment, including individual behavioral treatment with or without pharmacotherapy	4 random prompts per day for 14 days. The present analysis used data from days 2–13	Reported momentary sad and anxious moods (examined separately) using a 7-point Likert scale (anchors NR) Selected an event that had the greatest impact on them since their last prompt and rate its event negativity on a 7-point scale (anchors NR)	Rated maximum level of craving felt since the previous assessment from 1 (no desire) to 7 (extreme desire)	Within-person (momentary)	Used MLM to examine: (1) the association between momentary deviations in average mood states and same-moment craving, (2) the association between momentary deviations in average mood states and next-moment craving, and (3) whether these associations differed by primary SUD

All reported levels of analysis and analytic methods refer to questions regarding negative affect and substance-related outcomes relevant to the present review; some of the reviewed studies also used additional analytic methods at levels of analysis not reported in the table, but these methods did not relate to relationships between negative affect and substance use. *SUD* substance use disorder; *AUD* alcohol use disorder, *OUD* opioid use disorder, *PTSD* posttraumatic stress disorder; *NR* not reported, *MLM* multilevel modeling, *TVEM* time-varying effect modeling; *PANAS-X* Positive and Negative Affect Schedule – Expanded Form; *PANAS—SF* short form of the Positive and Negative Affect Schedule; *PCL* PTSD Checklist. This is an original table that has not previously been published

Lastly, most of the reviewed studies leveraged MLM to examine the associations between negative affect and substance-related outcomes between persons (i.e., the association between average negative affect and craving/substance use across the reporting period) or within persons (i.e., the association between daily/momentary negative affect and same-report or next-report craving/substance use). Several reviewed studies utilized multilevel mediation models or multilevel structural equation modeling to examine negative affect as a mediator of the association between a given factor (e.g., sleep quality) and substance-related outcomes [34, 51] or mediators (e.g., parental bonding, craving) of the association between negative affect and substance-related outcomes [39, 40]. Two studies used TVEM to examine the time course of relationships between negative affect and substance use [43, 52••]. Other analytic methods included latent variable modeling to examine the time course of change or subgroups of change in negative affect and substance use during treatment [50, 53•, 54] and chi-square automatic interaction detector decision trees to identify the best predictors, interactions between predictors, and cut points (including negative affect) in predicting substance-related outcomes [55].

Relationships Between Negative Affect and Craving or Substance Use in Alcohol Treatment

Between-Person Relationships

Studies examining average negative affect/stress levels and alcohol use demonstrated primarily null associations. Two naltrexone treatment trials that recruited adolescents and young adults demonstrated non-significant associations between average negative affect and the average likelihood of drinking to intoxication [56], as well as estimated blood alcohol level during drinking episodes [32]. Likewise, average negative affect and stress were not associated with drinking intensity or craving for individuals enrolled in outpatient AUD treatment [57], nor were average PTSD symptoms associated with drinking intensity following a brief intervention for co-occurring AUD and PTSD [42]. Only one study found a significant relationship between stress and substance use outcome, such that among individuals with AUD in two separate trials—one evaluating prazosin vs. placebo and the other delivering a behavioral intervention—average craving mediated the relationship between the proportion of stressful days and probability of drinking the next day [39].

Three studies also examined more complex negative affect–substance use relationships. Mean stress (measured over 6 days) from individuals with AUD engaged in community-based outpatient treatment during the first year of a recovery attempt was not associated with percent days abstinent 90 days later [47]. However, those with high levels of average stress and high levels of stress variability had lower percent days abstinent [47]. Among the same sample, lower average negative affect differentiation was associated with lower percent day abstinent but not drinking intensity [46•]. Finally, a subgroup analysis of individuals receiving prazosin or placebo for AUD revealed three subgroups: those with continuous abstinence during the first 2 weeks of treatment (already abstainers), those who initiated abstinence after the first 2 weeks of treatment (abstinence initiators), and those who drank continuously throughout the trial (continued drinkers) [50]. Already abstainers had the lowest levels of negative affect, and continued drinkers had the highest levels of negative affect, but neither group showed significant negative affect changes during treatment. Abstinence initiators were the only group to demonstrate gradual reductions in negative affect during treatment.

Within-Person Findings

Several studies among adults in various AUD treatments have demonstrated positive associations between negative affect and substance-related outcomes over time. Higher momentary negative affect and stress were associated with concurrent and prospective urges to drink among those in outpatient AUD treatment [58], particularly for those who experienced a lapse during treatment. Likewise, individuals with AUD in a trial examining stepped care demonstrated momentary associations between being in a negative affective context and the presence and intensity of craving [59]. At the daily level of analysis, positive associations between exposure to a stressful event on a given day and same-day craving and next-day likelihood of drinking and drinking intensity have also been identified among those in outpatient behavioral treatment (with or without adjunctive prazosin) [39]. Further, daily PTSD symptoms have been associated with greater than average alcohol consumption following a brief intervention for co-occurring AUD and PTSD [42].

Conversely, among adolescents/young adults receiving naltrexone, higher momentary negative affect was associated with lower daily odds of drinking to intoxication [56] and lower estimated blood alcohol levels during subsequent drinking events [32]. Analyses examining moderators of these negative relationships yielded interesting findings. Specifically, adolescents with higher trait negative urgency, a facet of impulsivity, showed positive associations between momentary negative affect and the daily likelihood of drinking to intoxication [56]. Naltrexone also moderated these associations, such that adolescents who received naltrexone versus placebo had a stronger positive relationship between estimated blood alcohol levels and subsequent negative affect and a stronger negative relationship between negative affect and subsequent estimated blood alcohol levels,

particularly at later stages of a drinking event [32]. These findings indicate that naltrexone might increase the aversive effects of alcohol.

Relationships Between Negative Affect and Craving or Substance Use in Opioid Treatment

Between-Person Relationships

Negative affect was often associated with substance use outcomes (particularly craving) for those with opioid use disorder (OUD). Individuals receiving buprenorphine or methadone for OUD and reporting higher stress overall reported greater cravings for heroin and cocaine [60, 61]. Those in a residential program for OUD also demonstrated positive associations between average negative affect and craving [62]. Although some findings indicate those in buprenorphine or methadone treatment (with or without adjunctive clonidine treatment) did not demonstrate significant associations between measures of negative affect (e.g., average levels, variability, stability) and substance use [43, 48, 49], greater variability in stress (but not average stress) was associated with more frequent cocaine- and opioid-positive urine drug screens [43].

Several studies of those in OUD treatment have leveraged latent variable mixture models to examine changes in negative affect and substance-related outcomes. Burgess-Hull and colleagues [53•] identified four stress trajectories over 16 weeks of buprenorphine or methadone treatment: (1) increasing stress, (2) moderate and stable stress, (3) low stress, and (4) declining then increasing stress. Those with increasing stress and moderate and stable stress demonstrated the highest rates of any drug use and greatest levels of opioid craving compared to the low-stress group. These analyses were replicated for craving trajectories. A low craving profile reported the lowest number of stress events, and the increasing then decreasing group reported the highest number of stress events [54].

Within-Person Findings

Within-person positive associations between measures of negative affect (e.g., negative events, stress) and opioid craving were consistently identified among individuals in residential treatment for OUD [51, 62] and those receiving buprenorphine or methadone treatment [60, 61]. Those with primary OUD also evidenced momentary associations between stress and cocaine craving [61, 63]. Moderator analyses suggest that momentary relationships between stress and opioid and cocaine craving are stronger in the presence of cues [61, 63] and that the daily relationships between negative affect and craving might be weaker on days with more frequent positive social events [62].

Researchers have also studied the time course of the negative affect-craving relationship. For example, Panlilio and colleagues [43] recruited individuals in buprenorphine or methadone treatment and found strong positive associations between stress and craving for 90 min following a stress event that was ranked moderate-to-extreme in severity; this association (and the presence of the time-sensitive peak) was stronger for those who used opioid and cocaine more frequently. Similarly, opioid and cocaine craving increased linearly in the 5 h before a self-initiated stress event [64]. Among those in residential treatment for OUD, negative affect-craving associations were stronger early in treatment and just before discharge than in the middle of treatment [52••]. Within the day, negative affect-craving associations were strongest during the afternoon [52••].

Only one research group examined within-person relationships between negative affect and consumption outcomes among those with OUD. Among individuals receiving buprenorphine or methadone, daily perceived stress/negative affect and drug use (e.g., opioid-positive urine drug screen, cocaine-positive urine drug screen, self-initiated drug use event) were significantly positively associated [38], and negative affect was higher during the 2–3 day collection period before an opioid-positive urine drug screens [49]. Interestingly, those receiving adjunctive clonidine (vs. placebo) treatment had higher levels of negative affect before submitting an opioid-positive urine drug screen [49]. Investigators concluded that clonidine dampened negative affect-craving associations at moderate, but not high, levels of negative affect [49]. Time course analyses identified linear increases in negative affect over the five hours before drug use was reported [64]; however, the time course of stress and drug use appears more complex. For example, one study found that stress increased linearly in the 8 h before a drug use event, but only for those with moderate and stable levels of stress (versus other stress profiles) [53•]. Alternatively, a second study found that stress was higher before a drug use event [64], but only in the 2 h preceding a drug use event.

Relationships Between Negative Affect and Craving or Substance Use in Cannabis Treatment

Between-Person Relationships

Two studies examined negative affect and substance-related outcomes in cannabis treatment [33, 34] among adolescents and young adults receiving psychosocial treatment and topiramate or placebo. Emery and colleagues [33] found that average negative affect was not associated with cannabis use frequency or quantity, and Treloar and colleagues [34] found average levels of feeling stressed/tense during a

cannabis use episode were not associated with the amount of cannabis consumed. Topiramate did not moderate associations in either study.

Within-Person Findings

Associations between negative affect and cannabis use outcomes within individuals over time were largely null or negative. Studies among adults receiving psychosocial interventions [65] and adolescents/young adults receiving psychosocial treatment and topiramate or placebo [33] showed that momentary negative affect did not predict subsequent cannabis use. Further, momentary negative affect was associated with a lower likelihood of concurrently using cannabis among adolescents/young adults receiving psychosocial treatment and topiramate or placebo but did not impact the amount of cannabis consumed [33]. Additionally, there were negative, bidirectional relationships between stress during cannabis use episodes and the amount of cannabis used later that day [34].

Relationships Between Negative Affect and Craving or Substance Use in SUD Treatment

Between-Person Relationships

Two studies examined between-person relationships among PTSD symptoms and substance use outcomes in SUD treatment, where all types of SUD were included in the samples. Both studies examined these relationships among pregnant persons with a trauma history in outpatient SUD treatment and demonstrated that average PTSD symptoms were not associated with levels of craving [40] or the likelihood of drug use or drinking quantity [41].

Within-Person Findings

Several studies examined within-person relationships between negative affect and craving across different substances and co-occurring disorders. Among adults in outpatient SUD treatment, higher momentary negative affect (e.g., sad mood, anxious mood, event negativity) was concurrently associated with higher momentary opioid craving, but not alcohol or cannabis craving [45]. Likewise, increases in daily stressors were associated with greater daily cravings for illegal drugs, but not alcohol, among legal system-involved men receiving SUD pharmacotherapy [66]. Similarly, among pregnant persons with trauma histories in SUD treatment, higher daily peak PTSD symptoms were associated with a greater likelihood of any drug use but were not associated with greater daily drinking intensity [41]. Momentary negative affect was concurrently and prospectively positively associated with greater craving for adults engaged in outpatient SUD treatment, but only among those without a co-occurring mood or anxiety disorder [44•]. Lastly, an analysis among those receiving outpatient SUD treatment using decision trees to predict future reports of substance use found that negative affect significantly predicted subsequent substance use, but only for those with no recent substance use reported [55]. One study examined a mediator of the relationship between PTSD symptoms and craving among pregnant persons with a trauma history in SUD treatment, and found a positive relationship between momentary PTSD symptoms and craving that was partially mediated by lower quality of momentary parental bonding [40].

Discussion

Understanding the relationships between negative affect and substance-related outcomes may help identify mechanisms of treatment change and inform personalized interventions. We reviewed the recent literature on intensive longitudinal studies to examine associations between negative affect and substance-related outcomes among SUD treatment. Results were generally mixed and difficult to compare, given differences in methods and measurement. Nevertheless, we found more consistent relationships between negative affect measures and substance-related outcomes among those using a range of substances and in SUD treatment than a previous systematic review on cannabis use [31•] and a recent meta-analysis among primarily non-treatment-seekers drinking alcohol [30••]. These relationships tended to be stronger and more consistent at the within-person level of analysis than the between-person level, although findings were mixed at both levels of analysis.

The strength of these relationships varied across outcomes, subgroups, contexts, and time course. For example, positive associations between negative affect and substance-related outcomes appeared more consistent when measuring craving versus substance use, for those with OUD versus those with AUD or cannabis use disorder, during contexts when substance cues were present, and during specific periods (e.g., shortly following a stressor) or during specific phases of treatment (e.g., beginning or end vs. middle of treatment). Associations between negative affect and substance-related outcomes also varied based on individual-level differences (e.g., negative urgency, presence of a co-occurring psychiatric disorder).

Treatment Implications

The identified relationships between measures of negative affect and craving across substances suggest that these experiences often occur concurrently. In addition, some analyses found that substance craving prospectively influenced

negative affect [44•, 64], while others found that negative affect prospectively influenced craving [58], which has significant treatment implications. As previously mentioned, those with higher negative affect tend to respond well to MBRP [16]. MBRP and other acceptance-focused mindfulness-based interventions for craving might be particularly effective in decoupling the negative affect–craving association [67]. Another study identified that below-average ability in emotion differentiation was associated with fewer percent days abstinent [46•]. Together, results suggest that skills to identify and manage negative affect might be an effective technique for reducing substance use.

Our results also have implications for intervention timing development. Increasingly sophisticated technology-delivered interventions (e.g., just-in-time adaptive interventions; [68]) can be paired with intensive longitudinal methods to maximize treatment effectiveness. For example, one study demonstrated that positive relationships between negative affect and craving were strongest at the beginning and end of residential treatment [52••]. This suggests that interventions to manage negative affect may be most beneficial when an individual is starting a treatment program or nearing discharge. The afternoon appears to be a maximally impactful time to deliver intervention content [52••]. Providers and clients may wish to discuss with clients how levels of negative affect gradually reduce over time following initiation of abstinence [50], given that increased negative affect in the context of reduced substance use might be a concern for clients.

Future Research Directions

Greater attention to individual differences within study recruitment and reporting is needed. Across the studies described in this review, there was minimal consideration of differences in relationships between negative affect and substance-related outcomes across age, gender or sexual orientation status, and racial or ethnic characteristics. Additionally, there was minimal examination of medical comorbidities, such as chronic pain, despite chronic pain contributing to the initiation and maintenance of SUD (e.g., OUD; [69]), and demonstrated relationships between pain and negative affect [70]. As we move towards personalization and precision of assessment and interventions, we must first understand how the associations between negative affect and substance-related outcomes vary as a function of individual-level differences.

Additionally, few studies reported on co-occurring mood, anxiety, and trauma-related symptoms (outside of studies explicitly focused on co-occurrence; [42, 44•]), although co-occurrence is frequently reported among treatment-seeking populations (as discussed in Schulden & Blanco, 2021; [71]). Our review demonstrated mixed evidence regarding the magnitude, valence, and direction of relationships between negative affect and substance-related outcomes as a function of co-occurring disorders. Given the increasing implementation of integrated treatments for those with SUD and co-occurring psychiatric disorders, it is important to understand transdiagnostic factors that impact the association between negative affect and substance-related outcomes and focus on recruitment of individuals with SUD and co-occurring psychiatric disorders. Additionally, we call for explicit measurement of multiple substances and simultaneous use, as polysubstance use is often reported among those seeking treatments [72]. Intensive longitudinal methods can examine negative affective factors that drive poly- or simultaneous-use episodes.

Across reviewed studies, there was clear variability in negative affect measures (see Table 1), making it challenging to synthesize findings across studies. However, a notable strength of this review was the inclusion of more nuanced measures of negative affect, such as emotion differentiation, variability, and persistence. Additional research is needed to develop and strengthen our repertoire of negative affect measures and to improve our psychometric understanding of these more nuanced measures. Future work should leverage observational, experimental, qualitative, and person-specific methods to better understand the relationships between multiple measures of negative affect and substance-related outcomes. For example, reviewed research suggests that the associations between negative affect and substance-related outcomes varied significantly within individuals, across the day, and at different phases during treatment [53•]. As such, intensive longitudinal methods could use user-initiated prompts to assess substance-related outcomes at times with above-average negative affect (e.g., [60]) and with follow-up prompts to assess the time course of negative affect and substance-related outcomes. Likewise, experimental methods could randomize the intensity and/or schedule of assessments to better characterize the time course of the associations between negative affect and substance-related outcomes as they fluctuate over time and across treatment. Moreover, qualitative interviews with individuals with SUDs could help determine which negative affect measures use terminology most applicable and accessible to treatment-seeking populations and which indicators of negative affect (e.g., average vs. peak levels, specific constructs, or differentiation) are perceived to be the most tied to substance use [73•]. Finally, pairing qualitative interviews with person-specific methods and statistical models [26•] could increase our understanding of heterogeneity in the association between negative affect and substance-related outcomes (see [29] for an illustrative example). We recommend that future studies characterize the relationships between negative affect and substance-related outcomes using methods sensitive to

variance over time (e.g., time-varying effects model; [22]) and person-specific differences [23]).

Limitations of the Present Review

The present review was not systematic and limited to recent intensive longitudinal studies published in the last 5 years. Additionally, many reviewed findings came from the same parent studies, including all between-person studies on negative affect and cannabis use and all within-person studies on negative affect and opioid use. We chose to focus on individuals in SUD treatment as these individuals may most likely demonstrate relationships between negative affect and substance use [5, 12] and is an important population to study for the purposes of developing novel treatments. However, many studies focused on pharmacotherapies for SUD, which might attenuate negative affect and craving, thus impacting outcomes. Lastly, we focused on negative affect-related variables but did not examine other similar constructs that have received less attention in the field (e.g., low positive affect, anhedonia) and may also be associated with outcomes in SUD treatment. Some findings indicate that positive affect may play a more important role in substance use than negative affect [30••].

Conclusions

Understanding relationships between negative affect and substance-related outcomes during treatment may help inform personalized interventions. Results on the associations between negative affect and craving or substance use were generally mixed, and the strength and direction of these relationships varied across outcomes, subgroups, contexts, and time course. Our review indicated the need for interventions that target the negative affect-craving association (e.g., MBRP) and times when such interventions might be most effective (e.g., immediately before treatment discharge). Future research should increase attention to individual differences (e.g., race and ethnicity) and recruitment of individuals with co-occurring disorders and polysubstance use. Experimental, qualitative, and person-specific methods are needed to help understand the relationships between negative affect and substance-related outcomes during treatment.

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Declarations

Disclaimer Table 1 is an original table created by the authors of the manuscript and has not previously been published.

Conflict of Interest Dr. Katie Witkiewitz is a member of the Alcohol Clinical Trials Initiative Workgroup; its activities were supported by Alkermes, Dicerna, Ethypharm, Lundbeck, Mitsubishi, and Otsuka in the past 36 months. The other authors have no conflict of interest to declare.

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•• Of major importance

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