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Heart Rate Variability Biofeedback for Substance Use Disorder
A Randomized Clinical Trial

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IMPORTANCE Preliminary studies suggest heart rate variability biofeedback (HRVB) may reduce craving and negative affect in individuals with substance use disorder (SUD), but few studies have evaluated whether this translates into improved substance use outcomes, and no prior studies have examined second-generation wearable HRVB technology in this context.

OBJECTIVE To evaluate the effects of second-generation HRVB on negative affect, positive affect, craving, and alcohol and other drug (AOD) use in adults with SUD.

DESIGN, SETTING, AND PARTICIPANTS This phase 2 randomized clinical trial included 8 weeks of outpatient treatment. Recruitment was conducted virtually across the US from February 2023 to June 2024. Treatment-seeking adults with SUD were randomized to receive HRVB + treatment as usual (TAU) or TAU only.

INTERVENTION Eight weeks of HRVB.

MAIN OUTCOMES AND MEASURES The primary outcomes were negative affect, positive affect, craving, and substance use, assessed with ecological momentary assessment.

RESULTS Of 260 individuals assessed for eligibility, 120 were randomized to receive HRVB + TAU or TAU only. Among study participants (69 female participants of 115 [60.0%]; mean [SD] age, 46.18 [11.59] years), HRVB was associated with significant reductions in negative affect (*b*, −0.01; *z*, −3.21; *P* = .001) and craving (*b*, −0.01; *z*, −4.60; *P* < .001) over 8 weeks. In contrast, the control group experienced increases in both negative affect and craving. No differences were observed for positive affect. HRVB was also associated with a significantly lower proportion of AOD use days (odds ratio [OR], 0.36; 95% credible interval [CrI], 0.25-0.54), representing a 64% reduction in AOD use compared to controls. Treatment condition moderated the within-person relationship between craving and later AOD use (OR, 0.84; 95% CrI, 0.73-0.97), such that those receiving HRVB were less likely to use AOD following craving (*b*, −0.18; 95% CrI, −0.32 to −0.03).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, findings suggest second-generation HRVB can reduce negative affect, craving, and substance use among individuals in early recovery from SUD. HRVB appears to confer benefit in part by disrupting the association between craving and subsequent AOD use; these results support HRVB as a potentially efficacious treatment for SUD and warrant further investigation in phase 3 trials.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05454657

Visual Abstract

Supplemental content

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Addiction to alcohol and other drugs (AOD) kills more than 250 000 Americans annually[1,2] and exacts a prodigious economic toll of around $442 billion each year.[3] Given the enormous personal and public health burden of substance use disorder (SUD), helping individuals achieve SUD remission is one of the most important issues confronting clinical scientists today.

For individuals seeking SUD recovery, everyday experiences of negative affect like stress and anxiety and salient cues can serve as potent triggers for substance use that appear to be automatic, in the sense that they bypass individuals' conscious intentions not to use AOD.[4-7] One reason why intentional cognitive strategies sometimes fail to interrupt substance use behavior when triggers occur is that automatic visceral reactions in substance use urge states are usually not subject to cognitive control. Converging evidence strongly argues for the necessity of clinical interventions that act on automatic visceral mechanisms, particularly those that can be used in the moment to protect individuals from automatic capture by substance use triggers.[8]

Heart rate variability biofeedback (HRVB) is a biobehavioral intervention involving rhythmic breathing at resonance frequency that stimulates the baroreflex to potentially offset these vulnerabilities.[9,10] The autonomic normalization effected by resonance frequency breathing is believed to support cognitive control efforts by interrupting or dampening automatic visceral reactions that can unintentionally undermine treatment gains; in doing so, it supports reductions in negative affect and craving, as well as shifts in attention allocation and better decision-making.[11]

Resonance frequency breathing's capacity to help individuals better regulate affect and bolster cognitive control has garnered much excitement in addiction clinical science,[8,12-14] and preliminary studies suggest HRVB could be a valuable supplement to first-line addiction treatments.[8,11,15-21] In addition to the clinical benefits associated with HRVB, this intervention is particularly attractive because it is easy to learn, has no adverse effects, and has no contraindications.[8]

Studies using first-generation, clinic-based HRVB technology and methods focused on positive behavioral effects that accrued over weeks or months of regular resonance frequency breathing practice, with HRVB taught in the clinic and patients typically practicing between clinic sessions with a handheld HRVB device. However, regular practice, although beneficial, is likely to only partially mitigate the intense momentary bouts of emotion dysregulation that can trigger substance use in those in early SUD recovery. Conversely, brief practice of resonance frequency breathing ahead of psychosocial stress or in the midst of induced stress curbs physiological arousal, eases state anxiety, and strengthens cognitive control.[11,22,23] We have previously speculated that such bursts of resonance frequency breathing or HRVB could be a useful SUD treatment tool that helps individuals buffer salient triggers and urges to consume AOD in the moment.[8]

Recent technological advances have given rise to small lightweight biosensors that can support ambulatory HRVB with wearable devices, removing the need for expensive clinic-based HRVB equipment and cumbersome handheld HRVB practice devices. These second-generation HRVB devices also function as just-in-time interventions by prompting in-the-moment HRVB practice when autonomic arousal indicative of stress is detected. In addition to their potential for direct clinical benefit, the advent of these second-generation, wearable HRVB devices has profound implications for the accessibility and scalability of HRVB, as these devices are easy to use, affordable, commercially available, integrate with the end user's smartphone, and do not require a clinician to administer the intervention.

In this phase 2 randomized clinical trial (RCT), we tested the efficacy of a second-generation, wearable HRVB device to mitigate negative affect, craving, and substance use in individuals in the first year of a current SUD recovery attempt, while also exploring positive affect. We hypothesized that over the 8-week study period, participants randomized to receive HRVB would report (1) less negative affect, (2) less AOD craving, and (3) less frequent AOD use. We also hypothesized a mechanistic effect, predicting that HRVB practice would disrupt a day-level positive association between AOD craving and subsequent AOD use. To our knowledge, the relationship between HRVB and positive affect has not previously been investigated in this population, so this aspect of the analysis was treated as exploratory.

Key Points

Question What is the efficacy of heart rate variability biofeedback (HRVB) in the treatment of substance use disorder (SUD)?

Findings In this randomized clinical trial that included 115 adults with SUD, those receiving HRVB experienced significant reductions in negative affect, craving, and alcohol and other drug use relative to controls. Mechanistic findings suggest that HRVB practice may disrupt moment-level associations between craving and substance use, highlighting its potential as an adjunctive SUD treatment.

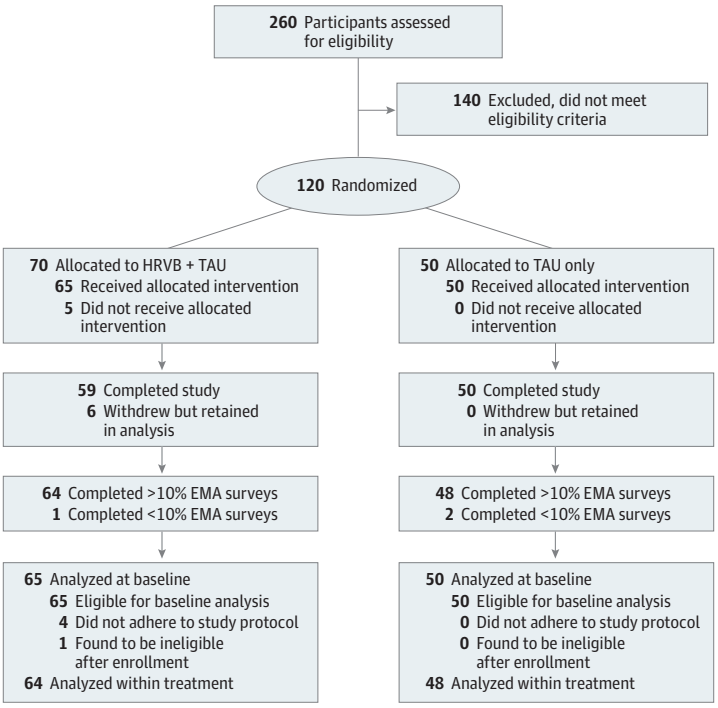
Meaning HRVB is a low-cost and accessible treatment that may support SUD recovery; future phase 3 trials are warranted.

Methods

We recruited 120 adults aged 18 years or older in their first year of a current abstinence-based SUD recovery attempt who were urn randomized using REDCap's Randomization Module[24] to receive either HRVB + treatment as usual (TAU) (n = 70) or TAU only (n = 50), with stratification by sex and SUD severity (see the eMethods in Supplement 2 for details). Individuals living anywhere in the US were invited to participate in this RCT, with baseline and end of treatment assessments conducted over video calls and HRVB equipment shipped directly to participants' homes.

The experimental group received 8 weeks of HRVB practice using the Lief HRVB Smart Patch and smartphone application (Lief Therapeutics) plus TAU. Participants were asked to wear the Lief Smart Patch for at least 8 hours per day and

Figure 1. Study CONSORT Diagram



EMA indicates ecological momentary assessment; HRVB, heart rate variability biofeedback; TAU, treatment as usual.

use it as needed in response to negative affect or cravings. The control group participated in 8 weeks of TAU only.

Both groups completed twice-daily ecological momentary assessments (EMAs) of affect and substance use over the 8-week study period. Participants were asked to report their stress, craving, confidence to remain abstinent from AOD for the rest of the day, sadness, guilt, nervousness, anger, happiness, calmness, energy levels, tiredness, and boredom in that moment, as well as any AOD use since the last survey.

This study was approved by the institutional review board at Mass General Brigham (2022P001496). The trial protocol is available in Supplement 1. This study followed Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Participants

Inclusion criteria were (1) being aged 18 years or older, (2) owning a smartphone, (3) having English proficiency, (4) having a *DSM-5* diagnosis of alcohol use disorder and/or an SUD for a drug other than alcohol, and (5) being in the first year of a current SUD recovery attempt with a goal of total AOD abstinence. Exclusion criteria were (1) history of severe cardiac arrhythmia and (2) active psychosis. Participants were assumed to have varying degrees of SUD treatment involvement and were not asked to change any ongoing SUD or other mental health treatments.

We recruited 120 participants (70 experimental, 50 controls) (**Figure 1**), with informed consent provided through the REDCap electronic consent module.[24] Five experimental group participants were excluded from the baseline analyses (n = 115): 4 failed to comply with the study protocol, and 1 was found to be ineligible after study enrollment. An additional 3 participants were excluded from the within-treatment EMA analyses because they completed less than 10% of surveys (final within-treatment group = 112 participants [64 experimental, 48 controls]). Six participants in the experimental group withdrew from the study; no participants withdrew from the control group. Available data for participants who withdrew were included in the analyses (eMethods in Supplement 2). No adverse events were reported.

HRVB Delivery

The Lief HRVB system used here includes a wearable Smart Patch with an embedded electrocardiogram monitor and accelerometer and a companion smartphone application. The Lief system has 3 key functions. First, it supports end user–initiated HRVB practice using haptic or in-application breathing cues driven by the wearer's dynamic HRV. Second, it works as a just-in-time intervention by monitoring autonomic arousal via the electrocardiogram signal and prompts the wearer to engage in brief, approximately 2-minute bursts of HRVB when autonomic arousal indicative of stress is detected. Third, a web-based, remote patient monitoring dashboard tracks adherence to HRVB exercises and HRVB's effects on heart rate and HRV.

To maximize ecological validity of this study and also to ensure participants understood and could use the Lief HRVB equipment, the same optional HRVB phone coaching offered to regular Lief subscribers was made available to experimental group participants.

Experimental group participants were asked to practice for 5 minutes at 2 scheduled times each day of their choosing, with

the ability to push the practice to later in the day if needed. They were also asked to do at least 5 minutes per day of HRVB practice in the moment when negative affect or craving arose or in response to just-in-time prompts to do brief bursts of HRVB when the device sensed autonomic arousal indicative of stress.

Measures

Baseline Measures

Participant demographic characteristics were assessed via self-report using the demographic section of the Global Appraisal of Individual Needs (GAIN).[25] Participants were formally assessed for SUD using the Structured Clinical Interview for *DSM-5*.[26] Baseline past 90-day AOD use was assessed with timeline follow-back.[27] Baseline measures of negative affect included the Perceived Stress Scale-4[28,29] and the PROMIS 6a Anxiety and Depression scales.[30]

HRVB Engagement

HRVB practice was automatically logged by the Lief device. As a benchmark of intervention engagement, we accepted 50% or greater daily practice adherence to the study practice target of 15 minutes per day, inclusive of scheduled and self-initiated HRVB practice.

EMA Within Treatment Measures

Affect Negative affect was represented by sadness, guilt, nervousness, tiredness, stress, and anger. Positive affect was represented by happiness, calmness, and energy. Measures of momentary negative and positive affect were calculated as the mean of the respective negative and positive affect items rated on an 11-point scale (0 = not at all, 10 = extreme) at each moment. These scores were then aggregated into survey-, day-, and person-average composite scores for negative and positive affect. Previous research supports the criterion validity of these affective items assessed using EMAs[31] (see the eMethods in Supplement 2 for more affective measure details).

Craving Craving was assessed using a single item rated on an 11-point scale from the EMA survey (0 = not at all, 10 = extreme). This measure is widely used in laboratory and EMA research, with support for criterion validity.[32,33] This was then averaged into day- and person-level mean scores.

AOD Use An EMA was used to assess AOD use since the last survey (yes/no). This is a well-established approach to measuring AOD use in EMA protocols, with support for criterion validity.[34,35] This was then aggregated into a day-level (yes/no) indicator.

Statistical Analysis

Within-Treatment Analyses

To test the hypothesized effects of HRVB on negative affect, positive affect, craving, and AOD use, as well as the moderating effects of HRVB on the associations between craving and AOD use during the clinical trial, we estimated a series of multilevel models with random intercepts using Stata version 18 (StataCorp).[36]

Day-Level Associations Between HRVB and Negative Affect, Positive Affect, and Craving

We tested the effects of HRVB on negative affect, positive affect, and craving using 3 multilevel models with unstructured variance-covariance matrices. Study day (L1, within-person model) predicted each outcome while controlling for day of the week; treatment condition and sex (L2, between-person model) were included as predictors. Key effects included the L2 main effect of treatment and cross-level interactions between study day and treatment condition. Outcomes were continuous, and significant interactions were probed using simple slopes to examine how study day's association with each outcome differed by condition (HRVB = 1, control = 0). Unstandardized regression coefficients (*b*) are reported.

Day-Level Associations Between HRVB and AOD Use

We examined the effect of HRVB on AOD use using a bayesian logistic multilevel model with an unstructured variance-covariance matrix. Study day (L1, within-person model) predicted same-day AOD use, controlling for day of the week; treatment condition and sex (L2, between-person model) were included as predictors. Key effects included the L2 main effect of treatment and cross-level interactions between study day and treatment condition. AOD use was binary (1 = any use reported in either survey). Significant interactions were explored via posterior marginal estimates of group-specific effects.

We tested whether HRVB moderated the within-day link between craving and AOD use using a bayesian logistic multilevel model with an unstructured variance-covariance matrix. Craving from the first survey (L1; lagged within-person) predicted AOD use in the second survey (binary: 1 = use). At L2 (between-person), predictors included treatment condition and person-level averages of negative affect, positive affect, and craving. The key effect was the cross-level interaction between earlier-day craving (L1) and treatment condition (L2) predicting later-day AOD use. This was tested in 2 models: (1) using group assignment (HRVB = 1, control = 0) and (2) using minutes of HRVB practice (controls coded as 0).

P values were 2-tailed, with $P < .05$ considered significant.

Results

Participant Characteristics

Participants' demographic and AOD severity characteristics are detailed in **Table 1**. Briefly, the sample (N = 115) included 69 female participants (60.0%), with overall mean (SD) participant age of 46.18 (11.59) years and most participants having severe SUD (109 [94.8%]). Groups were similar on all pretreatment assessment measures at pretreatment baseline.

EMA compliance was 75.2%. Within-study treatment activities are reported in eTable 1 in Supplement 2. Within-

Table 1. Pretreatment Baseline Sample Demographic, Substance Use, and Substance Use Disorder (SUD) Characteristics

Characteristic	No. (%)		
	HRVB + TAU (n = 65)	TAU only (n = 50)	Combined (N = 115)
Age, mean (SD), y	46.18 (12.08)	46.18 (11.04)	46.18 (11.59)
Sex			
Female	40 (61.5)	29 (58.0)	69 (60.0)
Male	25 (38.5)	21 (42.0)	46 (40.0)
Race and ethnicity[a]			
American Indian or Alaskan Native	1 (1.5)	2 (4.0)	3 (2.6)
Asian	2 (3.1)	0	2 (1.7)
Black or African American	7 (10.8)	4 (8.0)	11 (9.6)
White or European American	51 (78.5)	44 (88.0)	95 (82.6)
Other[b]	4 (6.2)	0	4 (3.5)
Hispanic ethnicity	4 (6.2)	6 (12.0)	10 (8.7)
Education			
<High school	2 (3.1)	3 (6.0)	5 (4.4)
High school diploma or GED	6 (9.2)	8 (16.0)	14 (12.2)
Some college	13 (20.0)	13 (26.0)	26 (22.6)
Junior college or associate's degree	8 (12.3)	8 (16.0)	16 (13.9)
Bachelor's degree	15 (23.1)	10 (20.0)	25 (21.7)
Master's degree	11 (16.9)	7 (14.0)	18 (15.7)
Other professional degree	3 (4.6)	1 (2.0)	4 (3.5)
Doctoral degree	7 (10.8)	0	7 (6.1)
Employment			
Yes	45 (69.2)	38 (76.0)	83 (72.2)
No	20 (30.8)	12 (24.0)	32 (27.8)
Health insurance			
No insurance	1 (1.5)	3 (6.0)	4 (3.5)
Medicaid or Medicare	32 (49.2)	26 (52.0)	58 (50.4)
TRICARE	2 (3.1)	1 (2.0)	3 (2.6)
Private insurance, with SUD coverage	19 (29.2)	12 (24.0)	31 (27.0)
Private insurance, without SUD coverage	0	2 (4.0)	2 (1.7)
Private insurance, don't know if I have SUD coverage	10 (15.4)	6 (12.0)	16 (13.9)
Don't know if I have insurance	1 (1.5)	0	1 (0.9)
Substance use disorder severity			
Mild	1 (1.5)	2 (4.0)	3 (2.6)
Moderate	1 (1.5)	2 (4.0)	3 (2.6)
Severe	63 (96.9)	46 (92.0)	109 (94.8)
Substance endorsed as primary			
Alcohol	44 (65.7)	26 (54.2)	70 (60.9)
Benzodiazepines	1 (1.5)	1 (2.0)	2 (1.7)
Cannabis	2 (3.0)	3 (6.3)	5 (4.4)
Cocaine	3 (4.5)	5 (10.4)	8 (7.0)
Methamphetamine	9 (13.4)	8 (16.7)	17 (14.8)
Opioids	8 (11.9)	5 (10.4)	13 (11.3)
Days since last AOD use, mean (SD)	100.48 (101.97)	112.02 (104.92)	105.27 (102.86)
Days using alcohol in past 90 d, mean (SD)[c]	8.34 (16.05)	10.50 (19.34)	9.28 (17.51)
Days using drugs other than alcohol in past 90 d, mean (SD)[c]	7.80 (19.32)	6.88 (18.26)	7.40 (18.79)
Taking medication for alcohol use disorder	6 (9.2)	8 (16.0)	14 (12.2)
Taking medication for opioid use disorder	7 (10.8)	7 (14.0)	14 (12.2)
Perceived Stress Scale score, mean (SD)	14.83 (2.97)	14.20 (3.30)	14.56 (3.12)
PROMIS Anxiety 6a, mean (SD)	16.20 (5.76)	16.35 (5.19)	16.26 (5.50)
PROMIS Depression 6a, mean (SD)	14.71 (6.48)	13.72 (5.47)	14.28 (6.06)

Abbreviations: AOD, alcohol and other drug; GED, General Educational Development; HRVB, heart rate variability biofeedback; PROMIS, Patient-Reported Outcomes Measurement Information System; TAU, treatment as usual.

[a] Self-reported via a questionnaire.

[b] No participant endorsing "other" race indicated their racial identity.

[c] Inclusive of all participants regardless of primary substance.

study negative affect, positive affect, craving, and AOD use summary statistics are reported in eTable 2 in Supplement 2.

HRVB Engagement

Participants randomized to HRVB practiced a mean (SD) total of 8.95 (14.31) minutes per day during their time in the study. Measured via mean (SD), 7.04 (13.05) minutes of this practice was self-initiated (scheduled or ad hoc), and 1.91 (4.09) minutes was in response to prompts by the study device when autonomic arousal indicative of stress was detected.

On average, participants completed the target of 15 minutes of HRVB practice per day on 13.32 days, representing 24.0% of their total days enrolled in the study. Additionally, 24.2% of participants achieved at least 50% adherence to the daily practice target.

EMA Within-Treatment Daily Outcomes

Negative Affect

At the within-person level (L1), study day was positively associated with daily negative affect (*b*, 0.01; *z*, 4.75; *P* < .001), indicating that negative affect increased over time. At the between-person level (L2), treatment condition was not associated with average negative affect (*b*, -0.10; *z*, -0.30; *P* = .76). However, a significant cross-level interaction emerged (*b*, -0.01; *z*, -5.66; *P* < .001), consistent with our hypothesis. Simple slopes showed that negative affect increased over time in the control group (*b*, 0.01; *z*, 4.75; *P* < .001) but decreased in the HRVB group (*b*, -0.01; *z*, -3.21; *P* = .001) (**Figure 2**A, **Table 2**).

Positive Affect

At the within-person level (L1), we did not find a significant association between study day and daily positive affect (*b*, 0.01; *z*, 1.19; *P* = .23). At the between-person level (L2), treatment condition was not associated with person-level average positive affect over the clinical trial (*b*, 0.21; *z*, 0.76; *P* = .45) nor did we observe a cross-level interaction effect of treatment condition (*b*, 0.01; *z*, 1.38; *P* = .17).

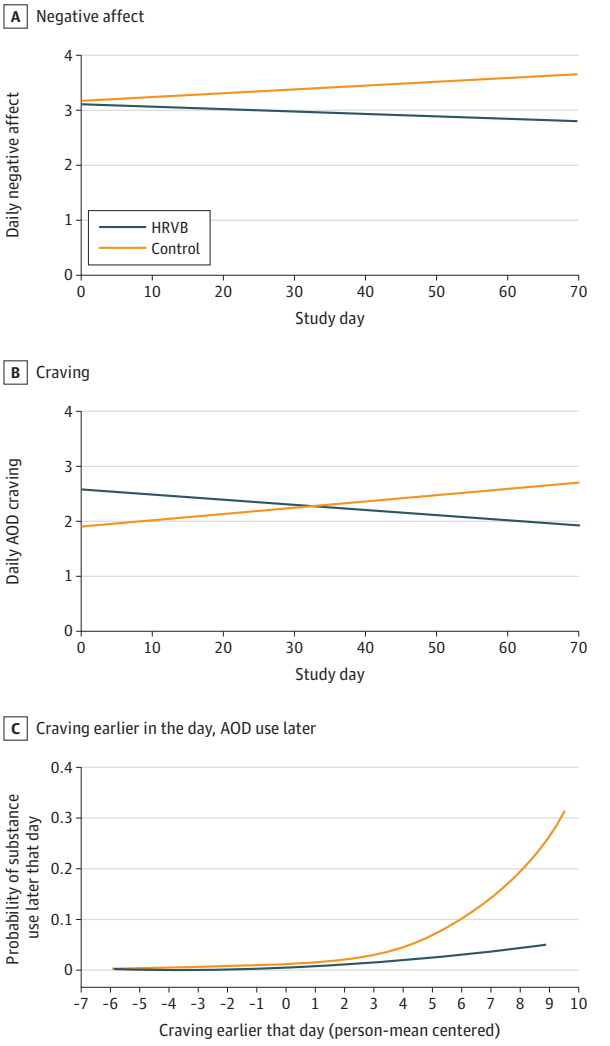
Craving

At the within-person level (L1), we found a positive association between study day and daily craving (*b*, 0.01; *z*, 5.30; *P* < .001) indicating that overall, craving increased over the clinical trial. At the between-person level (L2), treatment condition was not associated with person-level average craving over the trial (*b*, 0.64; *z*, 1.65, *P* = .10). However, consistent with our hypothesis, we observed a cross-level interaction effect (*b*, -0.02; *z*, -7.01; *P* < .001) of treatment condition (L2). As shown in Figure 2B, simple slopes revealed that in the control group, study day was positively associated with daily craving, such that AOD craving increased over the study period (*b*, 0.01; *z*, 5.20; *P* < .001), whereas it decreased in the HRVB group (*b*, -0.01; *z*, -4.60; *P* < .001).

AOD Use

At the within-person level (L1), we did not find study day to be associated with daily AOD use (odds ratio [OR], 1.01; 95% credible interval [CrI], 0.99-1.02). However, at the between-person level (L2), consistent with our hypotheses, we observed a strong effect of treatment group on the proportion of AOD use days over the clinical trial (OR, 0.36; 95% CrI, 0.25-0.54), indicating a 64% lower proportion of AOD use days in the HRVB group compared to control. However, inconsistent with our hypothesis, treatment group (L2) did not exhibit a

Figure 2. Effects of Treatment Condition on Negative Affect, Craving, and the Relationship Between Craving and Alcohol and Other Drug (AOD) Use Later in the Day



A, Cross-level marginal effects of treatment time × condition for negative affect, assessed using ecological momentary assessment (EMA), showing that in the control group, study day was positively associated with daily negative affect, such that negative affect increased over the study period, while for the heart rate variability biofeedback (HRVB) group, simple slopes revealed an inverse association with daily negative affect, such that negative affect systematically decreased over the trial period. B, Cross-level marginal effects of treatment time × condition for craving assessed using EMA showing that that in the control group, study day was positively associated with daily craving, such that AOD craving increased over the study period, whereas an inverse association with daily craving was observed in the HRVB condition, such that craving systematically decreased over the trial period. C, Treatment condition moderated the within-person association between craving earlier in the day and AOD use later that day, such that compared to the control group, for those in the HRVB group, craving was associated with lower AOD use.

Table 2. Multilevel Models of Daily Negative Affect, Positive Affect, Craving, and Alcohol and Other Drug Use[a]

	Daily negative affect model				Daily positive affect model				Daily craving model				Daily AOD use model	
Variable	*b*	*z*	SE	*P* value	*b*	*z*	SE	*P* value	*b*	*z*	SE	*P* value	OR (95% CrI)	PSD
Within-person model (L1)														
Study day[b]	0.01[c]	4.75[c]	.001[c]	<.001[c]	0.01	1.19	.001	.23	0.01[c]	5.30[c]	.002[c]	<.001[c]	1.01 (0.99-1.02)	.005
Monday[b]	0.10	1.57	.061	.12	−0.06	−0.95	.064	.34	−0.02	−0.21	.088	.84	0.95 (0.69-1.28)	.153
Tuesday[b]	0.19[c]	3.09[c]	.061[c]	.002[c]	−0.11	−1.73	.063	.08	−0.04	−0.43	.088	.67	0.59 (0.51-0.69)[c]	.045[c]
Wednesday[b]	0.14[c]	2.26[c]	.061[c]	.02[c]	−0.12	−1.94	.064	.05	0.03	0.29	.088	.77	0.86 (0.62-1.15)	.141
Thursday[b]	0.15[c]	2.42[c]	.061[c]	.02[c]	−0.09	−1.41	.063	.16	−0.01	−0.01	.087	.99	0.96 (0.86-1.08)	.060
Friday[b]	0.09	1.49	.061	.14	0.01	0.01	.063	>.99	0.12	1.41	.087	.16	1.72 (1.38-2.10)[c]	.187[c]
Saturday[b]	−0.05	−0.84	.061	.40	0.07	1.12	.063	.26	−0.09	−1.06	.087	.29	1.42 (1.14-1.72)[c]	.149[c]
Cross-level interaction														
Study day × treatment condition	−0.01[c]	−5.66[c]	.002[c]	<.001[c]	0.01	1.38	.002	.17	−0.02[c]	−7.01[c]	.003[c]	<.001[c]	1.00 (0.99-1.02)	.008
Between-person model (L2)														
Treatment condition	−0.10	−0.30	.321	.76	0.21	0.76	.278	.45	0.64	1.65	.389	.10	0.36 (0.25-0.54)[c]	.074[c]
Sex[d]	−0.74[c]	−2.31[c]	.319[c]	.02[c]	0.84[c]	3.05[c]	.276[c]	.002[c]	−0.40	−1.02	.307	.31	0.75 (0.61-0.92)[c]	.007[c]

Abbreviations: AOD, alcohol and other drugs; *b*, unstandardized coefficient; CrI, credible interval; OR, odds ratio; PSD, posterior standard deviation; *z*, *z* score, indicating how many standard deviations the coefficient deviates from zero.

[a] 112 Participants, 5437 observations.

[b] Orthogonal day of the week indicators represent that day's effect compared with the reference day (Sunday).

[c] Indicates significant effects.

[d] Sex (male = 1, female = 0).

cross-level interaction effect with study day (OR, 1.00; 95% CrI, 0.99-1.02).

Within-Day Association Between AOD Craving and AOD Use

By Group

As hypothesized, the HRVB group showed a significantly lower proportion of AOD use moments during the trial than the control group (OR, 0.74; 95% CrI, 0.58-0.94), reflecting a 26% difference. Treatment condition also moderated the within-day association between craving and later AOD use (OR, 0.84; 95% CrI, 0.73-0.97) (Figure 2C). In the HRVB group, higher craving was linked to lower subsequent AOD use (*b*, -0.18; 95% CrI, -0.32 to -0.03) compared to controls. See **Table 3** for full estimates.

By Minutes HRVB Practice

We did not find an association between minutes of HRVB practice and the proportion of use moments, nor did minutes of HRVB practice moderate the within-person association between craving earlier in the day and AOD use later that day (Table 3).

Discussion

This study extends previous clinical findings supporting the utility of HRVB for SUD. Here, HRVB was associated with lower negative affect, craving, and substance use. Per-protocol between-group differences were robust, with a 64% lower proportion of AOD use days in the HRVB group compared to controls. We also observed a potential mechanistic effect, with HRVB decoupling the relationship between AOD craving and subsequent AOD use.

Previous trials have reported HRVB's capacity to mitigate negative affect and craving in individuals with SUD,[11,15-21] but this study is among the first to show that this intervention gives rise to clinically meaningful reductions in AOD use. These findings are especially compelling given that most participants had severe SUD and suggests a benefit of complementing first-line SUD treatments with HRVB.

Notably, HRVB was associated with reduced AOD over the study period in our analysis by group, but not in our HRVB practice time model. This suggests that it may matter less how much patients practice overall and more how or when they use this treatment tool. This idea is supported by the fact that only 24% of experimental group participants achieved our benchmark for HRVB engagement (15 minutes of daily practice ≥50% of study days), as well as our novel finding that in-the-moment HRVB practice in response to AOD craving attenuated subsequent substance use. Taken together, these findings suggest HRVB may confer the most benefit when used strategically to manage acute bouts of craving. Future studies should seek to replicate these findings and also explore other potential HRVB mechanisms of behavior change.

Table 3. Bayesian Logistic Multilevel Models of Within-Day Alcohol and Other Drug Use[a]

	Per-protocol analysis			
	By treatment group		By minutes HRVB practice[b]	
Variable	OR (95% CrI)	PSD	OR (95% CrI)	PSD
Within-person model (L1)				
Lagged negative affect[c]	1.05 (0.91-1.19)	.074	0.97 (0.90-1.06)	.041
Lagged positive affect[c]	1.01 (0.88-1.15)	.071	0.93 (0.83-1.04)	.054
Lagged craving[c]	1.46 (1.31-1.63)[d]	.083[d]	1.31 (1.23-1.41)[d]	.046[d]
Monday[e]	0.59 (0.46-0.73)[d]	.070[d]	0.90 (0.81-0.96)[d]	.040[d]
Tuesday[e]	0.88 (0.71-1.08)	.094	0.80 (0.75-0.85)[d]	.026[d]
Wednesday[e]	1.06 (0.92-1.23)	.081	1.38 (1.28-1.52)[d]	.064[d]
Thursday[e]	1.04 (0.81-1.31)	.131	0.99 (0.91-1.09)	.045
Friday[e]	1.26 (1.11-1.40)[d]	.074[d]	1.49 (1.12-1.78)[d]	.175[d]
Saturday[e]	1.51 (1.20-1.84)[d]	.165[d]	1.42 (1.37-1.49)[d]	.032[d]
Study day[e]	0.99 (0.98-1.00)[d]	.005[d]	0.99 (0.98-1.00)	.005
Cross-level interactions				
Lagged craving × treatment condition[c]	0.84 (0.73-0.97)[d]	.063[d]	NA	NA
Lagged craving × practice time[c]	NA	NA	0.99 (0.99-1.00)	.001
Between-person model (L2)				
Average negative affect[f]	0.45 (0.32-0.58)[d]	.070[d]	0.59 (0.53-0.67)[d]	.036[d]
Average positive affect[f]	0.65 (0.43-0.91)[d]	.020[d]	0.68 (0.64-0.71)[d]	.018[d]
Average craving[f]	2.03 (1.69-2.42)[d]	.189[d]	1.97 (1.83-2.10)[d]	.068[d]
Treatment condition	0.74 (0.58-0.94)[d]	.093[d]	NA	NA
Practice time	NA	NA	1.00 (0.99-1.00)	.001
Sex[g]	1.65 (1.45-1.85)[d]	.102[d]	2.16 (1.77-2.67)[d]	.227[d]

Abbreviations: CrI, credible interval; HRVB, heart rate variability biofeedback; NA, not applicable; OR, odds ratio; PSD, posterior standard deviation.

[a] 112 Participants, 3998 observations.

[b] Controls coded as 0 for minutes HRVB practice model.

[c] Lagged = first survey of the day (9 AM-3 PM). AOD use = second survey of the day (3 PM-9 PM; used = 1, no use = 0).

[d] Significant effects.

[e] Orthogonal day of the week indicators represent that day's effect compared with the reference day (Sunday).

[f] Average = person-average over the sampling period.

[g] Sex: male, 1, female, 0.

We also examined potential effects of HRVB on positive affect. Null findings suggest that HRVB does not enhance positive affect in this population. However, further research is needed to draw definitive conclusions.

No adverse events were reported in this RCT. However, 6 participants in the experimental group—and none in the control group—withdrew from the study. While none cited HRVB practice as the reason for discontinuation (see eMethods in Supplement 2 for details), the higher attrition rate in the intervention group suggests that the daily practice requirements may have been burdensome for some. Future phase 3 trials should monitor dropout closely to better understand how treatment demands influence engagement and retention.

This was the first RCT to test second-generation wearable HRVB technology for SUD. The advent of wearable HRVB technology connected to intuitive smartphone applications is exciting. This technology reduces burden on patients and is likely more attractive than cumbersome first-generation HRVB practice devices. Though these second-generation devices offer many benefits, one downside is that they require connection to a smartphone to be fully functional, limiting their utility for people who do not own or use a smartphone.

Devices like the Lief Smart Patch used in this trial have an additional benefit of acting as a just-in-time intervention that can monitor HRV in real-time and prompt wearers to engage in brief bursts of HRVB practice when needed in the moment. While previous work indicates benefit associated with regular daily HRVB practice, it is also likely that this in-the-moment practice helps individuals manage acute bouts of emotion perturbation, such as craving. Future studies will ideally explore how the disaggregation of the craving and AOD use relationship observed in this study is being influenced by just-in-time prompts from such devices vs by individuals self-identifying craving states and proactively using HRVB to manage them.

Taken together, the present findings suggest HRVB can support SUD recovery in clinically meaningful ways and may be a valuable complement to first-line treatments. HRVB is particularly attractive as it can be delivered at low cost, has no contraindications, has no adverse effects, and is safe and easy to learn. Phase 3 RCTs are warranted.

Limitations

This study had numerous strengths, including an RCT design using urn randomization. There were, however, some limitations, including the modest sample size and lack of placebo group, both reflecting the phase 2 stage of this trial. Without a placebo group, it cannot be known how expectancy effects may have influenced study outcomes. Additionally, this study focused on individuals in the first

year of an abstinence-based SUD recovery attempt. Future studies should explore HRVB's utility for individuals who are currently using substances and are seeking to stop or reduce use. This study did not include follow-up. Future phase 3 trials should follow participants up longitudinally to assess the effects of HRVB following treatment. Finally, this study tested an a priori hypothesized moderation effect of HRVB on the craving and AOD use relationship but did not test for other possible mechanisms. Future studies on HRVB should extend this work and explore other potential mechanisms of behavior change.

Conclusions

This phase 2 RCT demonstrated that HRVB reduces negative affect, craving, and AOD use in individuals in early recovery from severe SUD. Mechanistic findings suggest that HRVB practice may disrupt moment-level associations between craving and substance use, highlighting its potential as an adjunctive SUD treatment. Given its apparent utility, safety, and low cost, future phase 3 trials should further explore HRVB treatment for SUD.

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