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Assessment of craving in opioid use disorder: Psychometric evaluation and predictive validity of the opioid craving VAS

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ABSTRACT

Background: This work evaluated the psychometric properties of the single-item Opioid Craving Visual Analog Scale (OC-VAS) for opioid use disorder (OUD).

Methods: Psychometric evaluation of the OC-VAS (range: 0–100 mm) was supported by Subjective Opiate Withdrawal Scale (SOWS) item 16 and total score, Clinical Opiate Withdrawal Scale (COWS) scores, and the 36-Item Short-Form Health Survey, using data from phase 3 study (NCT02357901; N = 487) participants who received randomized treatment and completed the OC-VAS at screening. Descriptive properties, test-retest reliability, construct validity, known-groups validity, and responsiveness were assessed. Interpretation of meaningful change and predictive validity were also explored.

Results: Descriptive properties for the OC-VAS at screening did not provide evidence of problematic floor/ceiling effects or missingness. The test-retest reliability was established by weekly intraclass correlations >0.70. At the screening and end of the study, the strong positive correlations between OC-VAS and SOWS Total/Item 16 score and the significant OC-VAS differences among COWS severity groups supported construct validity and known-groups (discriminating ability) validity, respectively. The associations between the changes in OC-VAS and in supporting measures/opioid use from screening to the end of the study demonstrated responsiveness and the ability to detect change in clinical status. During the induction and randomization treatment periods, significant relationships were identified between OC-VAS score and subsequent opioid use.

Conclusions: This psychometric evaluation of the OC-VAS performed on a large OUD patient population provides evidence to support its use to measure the severity of opioid craving and its ability to predict opioid use.

1. Introduction

Craving has been described as a core feature of substance use disorders (SUDs), including those associated with opioids, alcohol, nicotine, cannabis, cocaine, and other psychoactive drugs or substances (Kakko et al., 2019). Opioid craving has been characterized as a subjective sensation of 'urge to use' and can vary in intensity depending on whether the individual has been abstinent from drug use for a short or long time (6C43.2 Opioid dependence IN 2020a; Kleykamp et al., 2019b). In current addiction models, craving has been proposed as a critical driver of the addiction cycle arising from a range of neurobiological adaptations, including executive dysfunction; specifically, craving impedes self-control and promotes drug-seeking behavior (George and Koob, 2017; Kakko et al., 2019). The importance of craving as a central feature of opioid use disorder (OUD) is reflected in its inclusion in the diagnostic criteria for OUD, and in the classification of SUDs, in the *Diagnostic and Statistical Manual of Mental Disorders, Version 5* (DSM-5) (Opioid Use Disorder 2013). Craving also is included in the definition of opioid dependence in the recently updated 11th Revision of the International Classification of Diseases system (6C43.2 Opioid dependence IN 2020a).

The importance of craving as both a symptom and driver of addictive

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Table 1
Data sources, statistical methods and results, and Interpretations used in psychometric and predictive validity evaluation of OC-VAS.

Measurement Property/purpose	Evaluation Methods
Distributional characteristics	
Distributional characteristics/To evaluate possible response biases	**Data:** OC-VAS scores and supporting measures (SOWS Item 16, SOWS and COWS Total scores, SF-36 PCS and MCS) at screening, randomization baseline (day 1/week 1), week 25; missing values of OC-VAS were not imputed (data from supporting measures were also used to assess their distributional characteristics) **Analysis:** Distributional characteristics of OC-VAS scores using descriptive statistics **Statistics**: Mean, SD; quartile measures (median, Q1, Q3); and percentage of scores at floor (worst score = 100) and at ceiling (best score = 0)
Reliability	
Test-retest reliability/To evaluate consistency of scores for participants who experienced no change in SOWS Item 16 ("I feel like using now")	**Data:** OC-VAS scores of participants with no change in SOWS Item 16 ("I feel like using now") at 2 visits 1 week apart or 2 visits 4 weeks apart during week 2 – week 25 **Analysis:** Two-way mixed-effects ANOVA with absolute agreement for single measures was used to calculate test-retest ICCs (McGraw and Wong,1996) **Statistics:** ICCs for OC-VAS scores from 2 visits separated by 1 week (1-week ICCs) and by 4 weeks (4-week ICCs) **Interpretation**: Test-retest reliability established by ICCs≥ 0.70 (Nunnally and Bernstein, 1994)
Validity	
Construct validity/To evaluate relationships among multiple indicators of similar and dissimilar constructs and the extent to which they follow predictable patterns	**Data:** OC-VAS and supporting measures (SOWS Item 16, SOWS and COWS Total scores, SF-36 PCS and MCS) at screening and week 25 **Analysis:** Correlations between OC-VAS and supporting measures at screening and week 25 **Statistics:** Correlation coefficients ® **Interpretation:** Correlation strength, based on absolute value of *r* (Cohen, 1992) • ≥ 0.50 is considered strong • 0.30 – 0.49 is considered moderate • 0.10 – 0.29 is considered weak
Known-groups validity (discriminating ability)/To compare scores for hypothesized subgroups of interest to provide support for discriminating ability	**Data:** OC-VAS scores at screening and week 25 **Analysis:** ANOVAs to evaluate OC-VAS predicted based on withdrawal severity subgroups defined by COWS total score ("None," "Mild," "Moderate," "Moderately severe," "Severe"), employing the overall F-test and pairwise comparisons using the T2 method of Tamhane (which adjusts for potential heterogeneity of variances) (Tamhane, 1979) **Statistics:** LS mean OC-VAS scores according to COWS Total score categories and the differences in LS mean between the COWS Total score categories
Ability to detect change	
Responsiveness/To evaluate the extent to which scores can detect change in participants whose clinical status has changed	**Data:** 1. Change from screening to week 25 for OC-VAS scores and supporting measures (SOWS Item 16, SOWS and COWS total scores, SF-36 PCS and MCS) 2. COWS total scores change from screening to week 25 in score category **Analyses:** 1. Correlations between changes in OC-VAS and supporting measures 2. ANOVAs for change in OC-VAS predicted by the change of COWS Total score severity category ("Improved," "Stable," "Worsened"), employing the overall F-test and pairwise comparisons using the T2 method of Tamhane (which adjusts for potential heterogeneity of variances) (Tamhane, 1979) **Statistics:**

(*continued on next page*)

Table 1 (*continued*)

Measurement Property/purpose	Evaluation Methods
	1. Correlation coefficient®(*r*) between changes in OC-VAS and supporting measures 2. Effect Size: ● Cohen's d. (LS mean difference in OC-VAS change from screening to week 25 between 2 COWS total score category change groups divided by the screening OC-VAS SD of the whole sample) ● Effect Size Estimate (ESE; mean change of OC-VAS from screening to week 25 divided by the OC-VAS SD at screening) ● Standardized Response Mean (SRM; mean change of OC-VAS from screening to week 25 divided by the change score SD) **Interpretation:** 1. Correlation strength, based on absolute value of *r* (Cohen, 1992) (see above construct validity section) • ≥0.50 considered strong • 0.30 – 0.49 considered moderate • 0.10 – 0.29 considered weak 1. Interpretation of effect sizes based on SDs (Cohen, 1992): • Approximately 0.20 represents small effect size • Approximately 0.50 represents moderate effect size • Approximately 0.80 represents large effect size
PRO responder Thresholds characterizing within-participant stability in the OC-VAS change scores To identify participants who experienced stability in opioid craving and to interpret OC-VAS changes from randomization to week 25	**Data:** Change in OC-VAS scores from randomization baseline (week 1 day 1) to week 25 **Analyses:** Anchor-based method: 1. The direction and magnitude of changes in SOWS Item 16 indicating improvement, stability, or worsening were used as anchors to assess changes in OC-VAS associated with each level of change in SOWS Item 16 2. The cumulative distribution function for change in OC-VAS was plotted for groups with various levels of change in SOWS Item 16 from randomization baseline to week 25 Threshold analysis of OC-VAS change (increase) from randomization baseline to week 25 to interpret OC-VAS change in terms of opioid usage (efficacy outcomes): 1. A range of potential thresholds for OC-VAS increases were assessed, in 5-mm increments from 5 mm to 45 mm 2. For each potential threshold, opioid use outcomes for BUP-XR-treated study participants with OC-VAS score increases $>$ or $\leq$ the threshold were plotted, including: • Reduction in proportion of participants with opioid use from randomization baseline to week 25 (proportion of participants with opioid use at week 25 minus proportion of participants with opioid use at week 1) • Group means for participants' percentage of opioid abstinence during the randomized period (week 1 day 1 to week 25) (defined as number of assessments negative for opioid use divided by the number of nonmissing assessments during week 1–25 for each participant)
Other validity **Predictive validity** Explore the association between OC-VAS and opioid use	**Data:** OC-VAS scores and opioid use assessments from screening to week 25 and opioid use assessed at week 1 –day 1 - week 25 visits **Analyses:** Logistic models (with or without adjustment for risk factors with opioid use [used vs not used]) as outcome and OC-VAS as explanatory variable

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Table 1 (*continued*)

Measurement Property/purpose	Evaluation Methods
	• Risk factors: age, gender, race (Black vs Other), injection route, lifetime opioid use (in years), employment status at screening, current tobacco, alcohol, or cocaine use at screening, COWS at visit 1) Run-in/induction phase (screening to randomization baseline): • Opioid use assessed at randomization (week 1 day 1 visit) as outcome • OC-VAS assessed at randomization or OC-VAS change from screening to randomization baseline as exploratory variables 2) Double-blind phase (post randomization baseline, from first randomized treatment to week 25; i.e., week 2–25 visits); robust sandwich variance estimates were used to obtain 95% CIs to account for statistical dependence of visits within participants • Logistic models were fit within participants treated with BUP-XR and with placebo separately • Next-week opioid use: weekly OC-VAS scores from weeks 2–24 as explanatory variable and opioid use assessed at next-week visit as the outcome • Same week opioid use: weekly OC-VAS scores from weeks 2–25 as explanatory variable and opioid use assessed at same visit as outcome • OC-VAS was parameterized as a continuous, ordinal categorical (=0, >0 – ≤20, >20), or binary (=0, >0) variable • The area under the receiver operating curves (ROCs) (i.e., c-statistic) was calculated to evaluate the ability of model/parameterization to differentiate opioid use from non-use

ANOVA, analysis of variance; COWS, Clinical Opiate Withdrawal Scale; ICC, interclass correlation coefficient; OC-VAS, Opioid Craving Visual Analog Scale; PRO, patient-reported outcome; SD, standard deviation; SF-36, 36-Item Short-Form Health Survey; SOWS, Subjective Opiate Withdrawal Scale.

behavior in limiting self-control has elevated the importance of its reduction as a critical treatment target and has renewed research focus on its role in addiction treatment and relapse (Kleykamp et al., 2019b). A critical need to facilitate a better understanding of craving is the development of a patient-reported assessment of craving for use in basic research, clinical trials, and the clinic (Kleykamp et al., 2019b). This need was reinforced by the US Food and Drug Administration (FDA) in a statement on the necessity for new approaches to OUD treatment (Statement from FDA Commissioner Scott Gottlieb 2018; OpioidUse Disorder 2020b).

A recent review of 85 studies (including observational, investigational, randomized-controlled, and other study types) that assessed patient-reported craving in the context of OUD found that 15 different assessments had been used to evaluate craving (Kleykamp et al., 2019a). A variety of assessment types was represented, ranging from single-item instruments to multi-factor assessments with 5–45 items. Of the 15 different assessments, only 6 have been psychometrically evaluated for reliability and/or validity. By far, the most commonly used assessment (in 41/85 studies) was a patient-reported outcome (PRO) measure using a visual analog scale (VAS) to capture the severity (or another aspect of craving). A VAS measure typically asks participants to record their response by selecting a point on a 100-mm line with the extremes marked as 0 and 100, resulting in scores reported on a 0–100 scale.

VAS assessments are commonly administered because of their ease of use and simple numerical scoring that can be treated as a continuous variable for statistical analyses (Goodyear and Haass-Koffler, 2020). These attributes also make VAS measures of OUD severity useful in the clinical setting, in part by facilitating analysis of trends during long-term treatment.

Buprenorphine and methadone have been shown to reduce craving in OUD patients (Fareed et al., 2010). The relationship between buprenorphine dose and craving suppression is thought to be determined by the level of occupancy at μ-opioid receptors in the brain (Greenwald et al., 2014). Specifically, heroin craving is negatively correlated with buprenorphine plasma levels and brain μ-opioid receptor occupancy (Greenwald et al., 2003).

Buprenorphine extended-release (BUP-XR; RBP-6000 [SUBLOCADE®]; Indivior Inc., North Chesterfield, VA) was designed to provide sustained exposure of buprenorphine over the entire monthly dosing interval and to deliver average buprenorphine plasma concentrations of 2−3 ng/mL or more and brain μ-opioid receptor occupancy ≥70% (Nasser et al., 2014), which is necessary to control both withdrawal and craving and block subjective drug-liking effects of illicit opioids (Jones et al., 2021). In a randomized, placebo-controlled, phase 3 study conducted in study participants with moderate or severe OUD (N = 504 randomized and treated), BUP-XR (2 dosing regimens) demonstrated significant improvement vs placebo on the primary efficacy outcome, participants' percentage abstinence from opioid use (NCT02357901) (Haight et al., 2019). In this study, the Opioid Craving VAS (OC-VAS) was administered electronically and change from baseline in the OC-VAS score from week 5 through week 24 was a secondary endpoint. Participants were asked to indicate the strength of craving for opioids on a 100-mm line, with 0 = no craving and 100 = strongest craving ever.

The phase 3 data provided the opportunity to conduct a psychometric evaluation of the OC-VAS to measure opioid craving severity and its ability to predict opioid use.

2. Methods

2.1. Study description and participants

The psychometric evaluation was based on a 6-month phase 3, randomized, double-blind, placebo-controlled, parallel-group study of BUP-XR efficacy and safety in participants with moderate to severe OUD, conducted at 36 US treatment centers (NCT02357901) (Haight et al.,

Table 2
Distributional characteristics of the OC-VAS and supporting psychometric measures in randomized participants with a screening OC-VAS.

Psychometric Measures	At Screening	At Screening (with Week 25[a])	At Randomization Baseline (Week 1–Day 1)	At Week 25	Change from Screening to Week 25
OC-VAS, n	487	285	480	285	285
Mean (SD)	57.58 (28.94)	57.23 (29.11)	6.87 (13.24)	9.45 (18.83)	−47.8 (33.04)
Median (min, max)	63.0 (0, 100)	62.0 (0, 100)	3.0 (0, 98)	0.0 (0, 96)	−51.0 (−100, 49)
Ceiling (OC-VAS=0), n (%)	16 (3.3)	12 (4.2)	132 (27.5)	143 (50.2)	
Floor (OC-VAS=100), n (%)	19 (3.9)	10 (3.5)			
SOWS total, n	487	285	480	285	285
Mean (SD)	15.77 (14.33)	15.59 (13.98)	4.04 (5.70)	4.27 (8.04)	−11.3 (15.21)
Median (min, max)	11.0 (0, 60)	11.0 (0, 60)	2.0 (0, 41)	0.0 (0, 52)	−8.0 (−60, 25)
SOWS item 16 (I feel like using now), n	487	285	485	285	285
Mean (SD)	2.43 (1.33)	2.46 (1.35)	0.44 (0.63)	0.45 (0.84)	−2.01 (1.59)
Median (min, max)	3.0 (0, 4)	3.0 (0, 4)	0.0 (0, 4)	0.0 (0, 4)	−2.0 (−4, 4)
Ordinal category, n (%)					
Not at all	48 (9.9)	29 (10.2)	299 (61.6)	205 (71.9)	
A little	86 (17.7)	51 (17.9)	166 (34.2)	49 (17.2)	
Moderately	98 (20.1)	51 (17.9)	13 (2.7)	18 (6.3)	
Quite a bit	117 (24.0)	68 (23.9)	6 (1.2)	10 (3.5)	
Extremely	138 (28.3)	86 (30.2)	1 (0.2)	3 (1.1)	
COWS total, n	484	282	475	282	282
Mean (SD)	5.69 (5.76)	5.62 (5.65)	2.15 (2.44)	2.13 (3.18)	−3.48 (6.18)
Median (min, max)	4.0 (0, 26)	4.0 (0, 25)	1.0 (0, 13)	1.0 (0, 17)	−2.0 (−24, 13)
SF-36 PCS, n	487	285	478	285	285
Mean (SD)	47.84 (9.04)	47.44 (9.14)	52.13 (7.70)	53.53 (7.17)	6.09 (8.30)
Median (min, max)	49.0 (20, 66)	49.1 (20, 66)	53.9 (25, 66)	55.4 (22, 66)	5.0 (−17, 28)
SF-36 MCS, n	487	285	478	285	285
Mean (SD)	41.98 (11.80)	42.77 (11.99)	47.30 (9.28)	51.89 (8.88)	9.12 (12.38)
Median (min, max)	42.3 (12, 66)	43.8 (12, 66)	49.0 (13, 68)	54.9 (11, 66)	8.7 (−29, 47)

COWS, Clinical Opiate Withdrawal Scale; OC-VAS, Opioid Craving Visual Analog Scale; SD, standard deviation; SF-36, 36-Item Short-Form Health Survey; SOWS, Subjective Opiate Withdrawal Scale.
[a] The screen values for participants who had nonmissing values for both screen and week 25 visits.

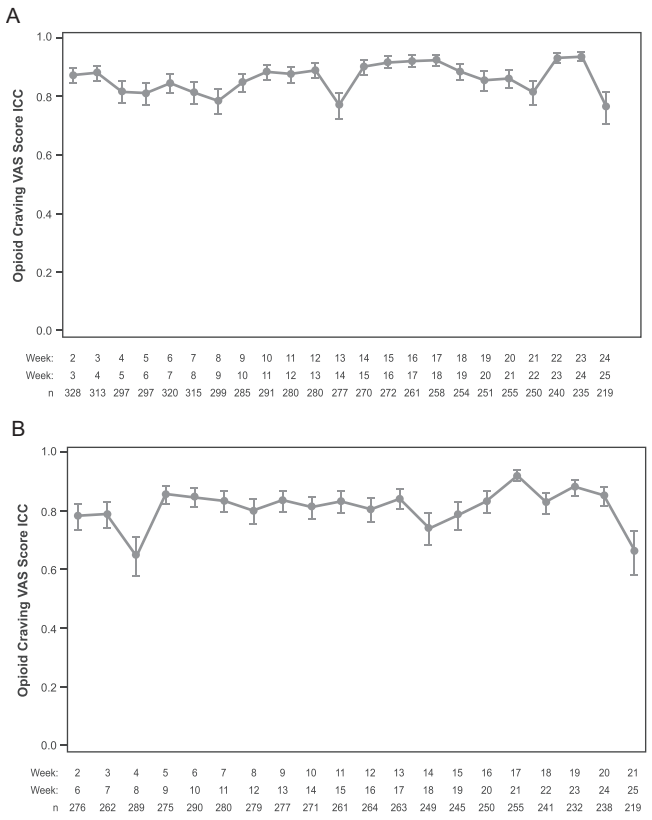

Fig. 1. Test-retest reliability: interclass correlation coefficients for comparisons of OC-VAS scores separated by 1 week or 4 weeks after randomization baseline to Week 25. A) Interclass correlation coefficients for visits 1 week apart (1-week ICCs). B) Interclass correlation coefficients for visits 4 weeks apart (4-week ICCs).

Table 3
Correlations between opioid craving VAS and supporting measures.

Supporting Measure	Correlation with Opioid Craving VAS		
	Screening	Week 25	Change from Screening to Week 25
SOWS Item 16 ("I feel like using now")	0.66*	0.79*	0.69*
SOWS Total	0.57*	0.65*	0.59*
COWS Total	0.43*	0.48*	0.46*
SF-36 PCS	−0.21*	−0.36*	−0.25*
SF-36 MCS	−0.24*	−0.36*	−0.25*

COWS, Clinical Opiate Withdrawal Scale; MCS, Mental Component Summary score; PCS, Physical Component Summary score; SF-36, 36-item Short-Form Health Survey; SOWS, Subjective Opiate Withdrawal Scale; VAS, visual analog scale.

* $P < 0.01$ test for null hypothesis of correlation r = 0.

2019). Full inclusion and exclusion criteria can be found in Haight et al. (2019). Key inclusion criteria were study participants should have a diagnosis of moderate or severe OUD based on DSM-5 criteria for the 3 months immediately before signing the informed consent form; be seeking medication-assisted treatment of OUD, and have no current diagnosis (other than OUD) requiring chronic opioid treatment.

Eligible participants entered an open-label run-in/induction (dose adjustment) phase of 7–14 days of treatment with buprenorphine-naloxone sublingual film to achieve daily buprenorphine doses ranging from 8 mg to 24 mg. Participants with a Clinical Opiate Withdrawal Scale (COWS) score of ≤12 and an OC-VAS score of ≤20 mm at the end of the run-in/induction phase were eligible for randomization into the double-blind phase. They were then randomly assigned to

Table 4
Known-groups analysis based on COWS classifications at screening and week 25 and effect size of changes in OC-VAS from screening to week 25.

Screening			
COWS Total Score Categories (score range)[a]	**n**	**OC-VAS Score Least Squares Mean, mm (SE)**	
No withdrawal (0–4)	260	47.7 (1.65)	
Mild (5–12)	156	64.6 (2.14)	
Moderate (13–24)	64	78.4 (3.34)	
Moderately severe (25–36)	4	83.7 (13.34)	
Severe (>36)	0	–	
ANOVA/Comparisons	**Least Squares Mean Difference (95% CI)**	***F/t (df)***	**Adjusted *P*-value**
Overall	–	29.80 (3, 480)	<0.0001
No withdrawal vs Mild	−16.9 (−24.1, −9.8)	−6.27 (480)	<0.0001
No withdrawal vs Moderate	−30.7 (−40.5, −20.9)	−8.25 (480)	<0.0001
Mild vs Moderate	−13.8 (−24.2, −3.3)	−3.48 (480)	0.0033
Week 25			
COWS Total Score Categories (score range)[a]	**n**	**OC-VAS Score Least Squares Mean, mm (SE)**	
No withdrawal (0–4)	229	5.7 (1.12)	
Mild (5–12)	52	22.0 (2.36)	
Moderate (13–24)	5	48.4 (7.60)	
ANOVA/Comparisons	**Least Squares Mean Difference (95% CI)**	***F(df1, df2)/t (df)***	**Adjusted *P*-value**
Overall	–	32.96 (2, 283)	<0.0001
No withdrawal vs Mild	−16.3 (−22.60, −10.06)	−6.26 (283)	<0.0001
No withdrawal vs Moderate	−42.7 (−61.14, −24.24)	−5.56 (283)	<0.0001
Mild vs Moderate	−26.4 (−45.47, −7.25)	−3.31 (283)	0.0031
Change from Screening to Week 25			
Change in COWS Total Score Severity Categories[a]	**n**	**OC-VAS Score Change Least Squares Mean, mm (SE)**	
Improved	104	−60.7 (3.00)	
Stable	153	−44.0 (2.47)	
Worsened	25	−14.4 (6.11)	
ANOVA/Comparisons	**Cohen's d**	***F(df1, df2)/t (df)***	**Adjusted *P*-value**
Overall	–	25.46 (2, 279)	< 0.0001
Improved vs Stable	−0.57	−4.30 (279)	< 0.0001
Improved vs Worsened	−1.59	−6.81 (279)	< 0.0001
Stable vs Worsened	−1.02	−4.50 (279)	< 0.0001
Effect Size Estimate (SD of screening score)	**−1.6 (29.16)**		
Standardized Response Mean (SD of change score)	**−1.4 (33.11)**		

ANOVA, analysis of variance; CI, confidence interval; COWS, Clinical Opiate Withdrawal Scale; OC-VAS, Opioid Craving Visual Analog Scale; SD, standard deviation; SE, standard error.

P-values were adjusted using the T2 method of Tamhane

Effect size calculations:

1. Cohen's d: LS mean difference in OC-VAS change from screening to week 25 between 2 COWS total score category change groups divided by the screening OC-VAS SD of the whole sample
2. Effect Size Estimate (ESE): mean change in OC- VAS from screening to week 25 divided by the OC-VAS SD at screening.
3. Standardized Response Mean (SRM): mean change of OC- VAS from screening to week 25 divided by the change score SD.

[a] COWS categorical score ranges based on Wesson and Ling (Wesson and Ling, 2003).

receive up to 6 monthly injections of BUP-XR 300/300 mg (6 monthly injections of 300 mg), BUP-XR 300/100 mg (2 monthly injections of 300 mg followed by 4 monthly injections of 100 mg) or volume-matched placebo. All randomized participants also received weekly individual drug counselling (IDC) (Haight et al., 2019).

2.2. Assessments

The OC-VAS is a single-item visual analog PRO scale. Participants were provided a computerized tablet that displayed a 100-mm line with 0 at the left end and 100 at the right end and asked: "With zero (0) meaning 'No Craving At All' and 100 meaning 'Strongest Craving Ever' please indicate the point on the line that represents your current state." Supporting measures used in the psychometric evaluation of the OC-VAS included the PRO instruments Subjective Opiate Withdrawal Scale (SOWS) with all items rated on a scale of 0–4 (Handelsman et al., 1987) and the Physical Component Score (PCS) and Mental Component Score (MCS) from the 36-item Short-Form Health Survey (SF-36) (Ware et al., 2007); as well as the clinician-reported outcome instrument Clinical Opiate Withdrawal Scale (COWS) (Tompkins et al., 2009; Wesson and Ling, 2003). OC-VAS, SOWS, COWS, and opioid use were assessed at screening, randomization baseline (week 1 Day 1 visit), and weekly visits throughout the study (weeks 2–25). Assessments at injection visits were performed before the BUP-XR/placebo injection. Opioid abstinence (no opioid use) for a visit was defined as negative urine drug screen (UDS) for opioids and self-reports negative for illicit opioid use assessed at the same visit. SF-36 was assessed at screening, randomization baseline, before each subsequent injection, and at the week 25 visit (i.e., following intervention).

2.3. Statistical methods

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). These analyses were performed on data derived from all randomized participants who received at least one dose of BUP-XR or placebo with a screening OC-VAS; each analysis included all available assessment values from the designated time points. Consistent with the original phase 3 study analyses, results from 15 participants at one study site (site 20) were excluded from the analyses due to extensive protocol violations (Haight et al., 2019). Missing OC-VAS responses were reported and examined but not imputed. Psychometric evaluations were conducted in accordance with the FDA guidance on PRO assessments (Guidance for industry, 2009). The source data, analysis methodology, and outcome measures/interpretations used for evaluations of OC-VAS distributional characteristics, reliability, validity, ability to detect a change, and predictive validity properties are summarized in Table 1. Methods used to explore meaningful change thresholds are described.

3. Results

3.1. Analysis population

A total of 487 (96.6% of randomized treated) participants completed the OC-VAS at screening and had at least one assessment after screening, and constituted the psychometric analysis sample; of these, 285 (58.5%) completed the OC-VAS at screening and week 25. Characteristics of participants with an OC-VAS score at each time point used in this analysis are summarized in the Supplemental Table.

3.2. OC-VAS psychometric evaluation

3.2.1. Distributional characteristics

At the screening, descriptive statistics for the OC-VAS (Table 2) showed no unexpected anomalies nor any evidence of problematic missingness. No evidence was found of extensive ceiling/floor effects; only 3.3% and 3.9% of participants, respectively, scored at the ceiling (VAS=0) and the floor (VAS=100). The participants with OC-VAS scores at screening and week 25 (N = 285) had a similar distribution.

OC-VAS scores at randomization baseline (after buprenorphine-naloxone run-in/induction phase) indicated significant improvement (ceiling: 27.5%) and were consistent with the randomization requirement for scores ≤ 20 mm. Week 25 OC-VAS scores indicated a substantial improvement from screening; the net change (SD) in mean score was −47.78 (33.04) mm, and 50.2% of participants were at the ceiling value of 0 mm. The large changes in OC-VAS scores from screening to week 25, along with the extensive variability in scores throughout the

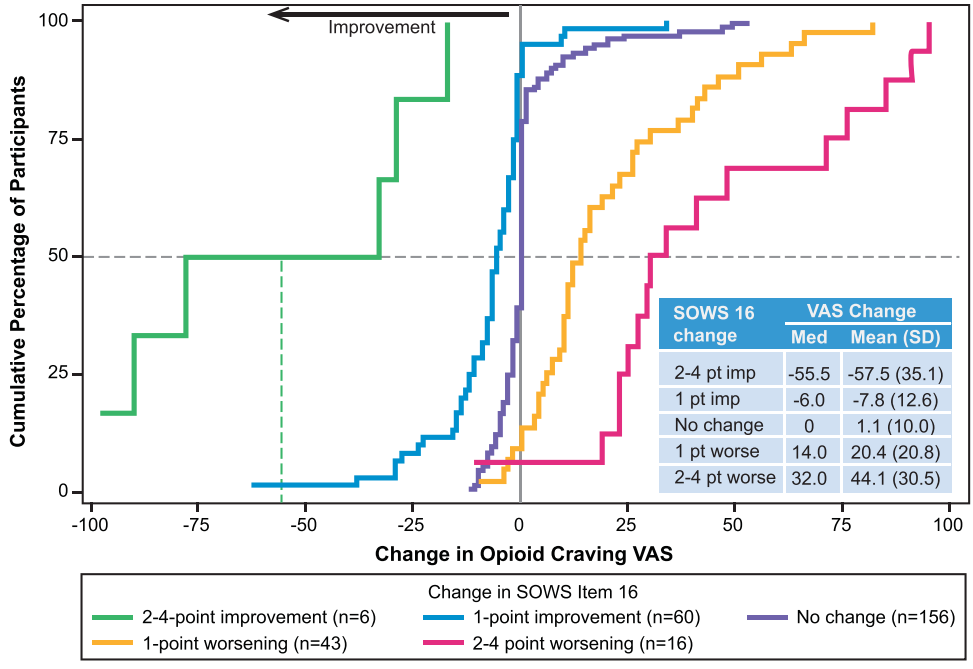

Fig. 2. Distribution function of change in OC-VAS scores from randomization baseline (week 1) to week 25, by response category to SOWS Item 16 ("I feel like using now").

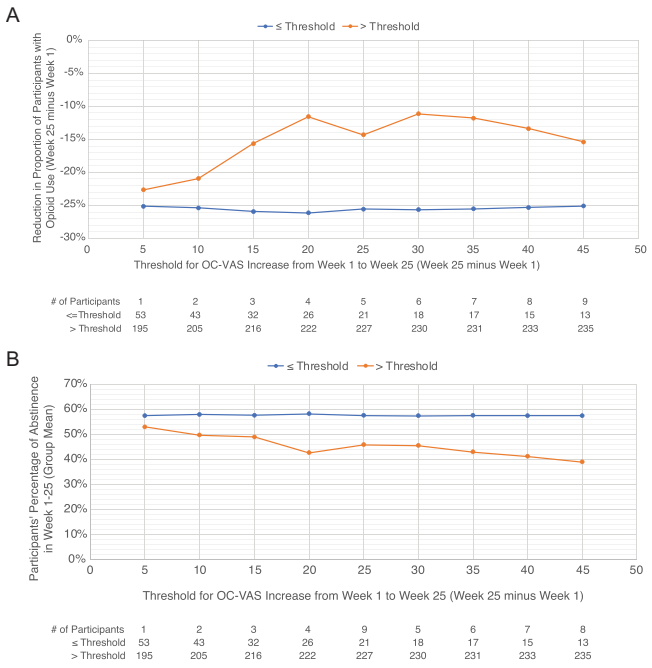

Fig. 3. A) Reduction in proportion of BUP-XR treated participants with opioid use from week 1 (randomization baseline) to week 25 by thresholds for OC-VAS increase from week 1 to week 25 (week 25 minus week 1). B) Group means of BUP-XR treated participants' percentage of opioid abstinence during week 1 (randomization baseline) to week 25 by thresholds for OC-VAS increase from week 1 to week 25 (week 25 minus week 1). OC-VAS, opioid craving visual analog scale. A range of potential thresholds for OC-VAS increases were assessed, in 5-mm increments from 5 mm to 45 mm. For each potential threshold, opioid use outcomes for BUP-XR-treated study participants with OC-VAS score increases $>$ or $\leq$ the threshold were plotted: A) Reduction in proportion of participants with opioid use from randomization baseline to week 25 (proportion of participants with opioid use at week 25 minus proportion of participants with opioid use at week 1); B) Group mean for participants' percentage of opioid abstinence during the randomized period (week 1 day 1 to week 25) (defined as number of assessments negative for opioid use divided by the number of nonmissing assessments during week 1–25 for each participant).

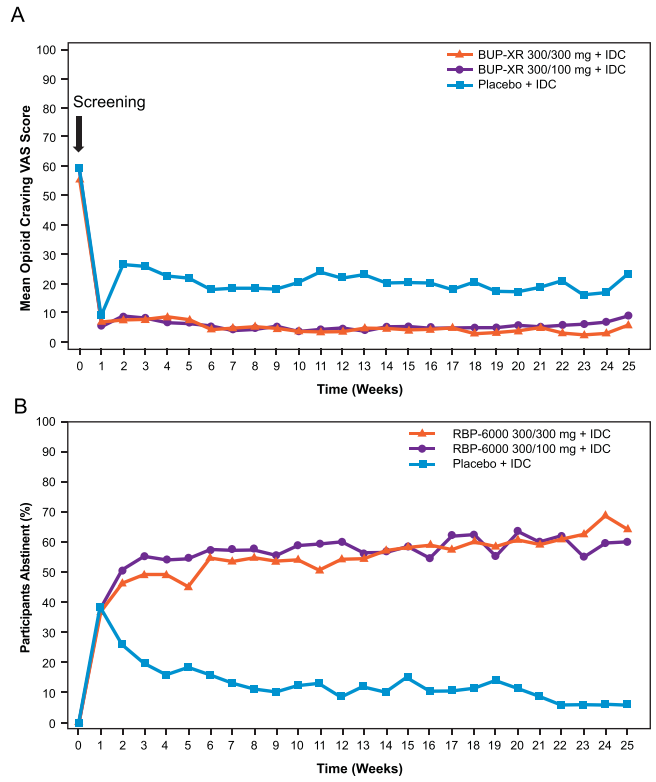

Fig. 4. Mean OC-VAS scores and proportion of abstinent participants, by treatment group, from screening to Week 25. A) Mean OC-VAS scores from screening to Week 25. B) Proportion of participants with no opioid use from screening to week 25. IDC, individual drug counseling. Key timepoints: Week 0: screening visit (before buprenorphine-naloxone run-in/induction phase). Week 1: week 1 day 1 visit, randomization baseline (end of buprenorphine-naloxone run-in/induction phase. Week 2: the first visit where both OC-VAS and opioid use were assessed after the first BUP-XR (RBP-6000) or placebo injection. OC-VAS and opioid use were assessed prior to the BUP-XR or placebo injection at injection visit. The proportion (%) of participants achieving abstinence was summarized by week using available data; participants with a missing opioid use assessment result at a specific visit were excluded from the percentage denominator for that visit.

study, provided adequate variability for assessing the psychometric properties.

3.2.2. *Descriptive statistics for supporting measures*

For all measures, distributions were similar between all participants at screening (N = 487) and those with results at screening and week 25 (n = 285 and COWS n = 282) (Table 2). Both the SOWS total and COWS total scores demonstrated similar patterns, dropping (indicating reduced severity) at randomization baseline and remaining stable through week 25. SOWS Item 16 ("I feel like using now") specifically asked participants to rate their desire to use opioids in 5 ordinal grades (Table 2). For SOWS, at the screening, 72.4% of the participants indicated a want of 'moderate' or above, with the majority rating relatively strong craving ("quite a bit" or "extremely"). At randomization baseline (post buprenorphine-naloxone sublingual film) and week 25 (post BUP-XR), most participants (95.8% and 89.1% respectively) indicated either no desire ("not at all") or "a little." Compared with the OC-VAS average scores within the individual desire categories at screening, the post-treatment distributions for "not at all," "a little," and "moderate" shifted to much lower average scores (mean OC-VAS: 21.02, 38.13, and 51.04 at screening vs 2.45, 10.35, and 30.92 at randomization baseline, and 1.96, 17.35, and 31.89 at week 25, respectively), and remained similar post-treatment for higher categories. SF-36 PCS and MCS scores, for which higher scores indicate better functioning, demonstrated improvement from screening to randomization baseline and remained stable or showed further improvement (SF-36 MCS score) at week 25. The magnitude of these changes was attenuated compared with changes in SOWS and COWS because of the small fraction of addiction-related items in the SF-36.

3.2.3. *Reliability*

Test-retest reliability was established, based on intraclass coefficients (ICCs) for 2 adjacent visits 1 week apart (1-week ICCs) and for 2 visits 4 weeks apart (4-week ICCs) during weeks 2–25, to demonstrate the consistency of OC-VAS among participants who showed no change in response to SOWS Item 16 ("I feel like using now"). The resulting 23 1-week ICCs and 20 4-week ICCs are plotted by week in Fig. 1**a** and **b**. All 1-week ICCs throughout the study were above 0.7 (range [value, (95% CI)]: 0.77 [0.71 – 0.82] to 0.94 [0.92 – 0.95]), the criteria for determining test-retest reliability throughout the study; the lowest 1-week ICCs (0.77) were at weeks 13 and 25. As expected, 4-week ICCs were somewhat lower (range 0.65–0.92) but remained above 0.7 except for weeks 4–8 and 21–25 (0.65 and 0.67, respectively). Results remained similar after excluding participants with OC-VAS= 0 at either of the 2 visits; 1-week and 4-week ICCs ranged from 0.78 to 0.96 and from 0.68 to 0.93, respectively.

3.2.4. *Validity*

Construct validity was established based on strong positive

Table 5
Evaluation of various methods for assessing OC-VAS predictive capability for next-week opioid use (Risk-Adjusted Models).

Treatment group (N)	Outcome: Ns of total/positive/negative assessments	Metrics for OC-VAS Change		Estimate (SE)	Odds Ratio (95% CI)	*P*-value	Area under ROC
Placebo (N = 87)	Next-week opioid use:	**Continuous**	**10-mm increase**	**0.49 (0.13)**	**1.64 (1.26, 2.12)**	**0.0002**	**0.898**
	Total n = 1024	3-level	>0–20 vs 0 mm	0.40 (0.37)	1.50 (0.72, 3.11)	0.2815	0.895
	Positive n = 901	category	>20 vs 0 mm	2.30 (0.55)	10.01 (3.41, 29.41)	<0.0001	
	Negative n = 123		>20 vs > 0–20 mm	1.90 (0.44)	6.69 (2.84, 15.78)	<0.0001	
		Binary	>0 vs 0	1.10 (0.42)	2.99 (1.30, 6.86)	0.0098	0.875
BUP-XR (N = 382)	Next-week opioid use:	Continuous	10-mm increase	0.05 (0.05)	1.05 (0.96, 1.15)	0.2656	0.644
	Total n = 6556	3-level	>0–20 vs 0 mm	0.46 (0.14)	1.59 (1.20, 2.09)	0.0011	0.658
	Positive n = 2804	category	>20 vs 0 mm	0.36 (0.24)	1.44 (0.90, 2.30)	0.1270	
	Negative n = 3752		>20 vs >0–20 mm	-0.10 (0.23)	0.91 (0.58, 0.1.43)	0.6736	
		Binary	**>0 vs 0**	**0.45 (0.14)**	**1.57 (1.20, 2.05)**	**0.0010**	**0.658**

BUP-XR, extended-release buprenorphine; OC-VAS, Opioid Craving Visual Analog Scale; ROC, receiver operating characteristic; SE, standard error.

correlations (≥0.5) between OC-VAS scores and instruments that measure similar constructs; specifically, SOWS Item 16 score ("I feel like using now") and SOWS total score at screening and week 25 (Table 3). OC-VAS scores also demonstrated significant, consistently moderate positive correlations with COWS total score. The strongest correlations (observed at week 25) were for SOWS Item 16 score, followed by SOWS total score and COWS total score. In contrast, OC-VAS scores demonstrated a weaker relationship with instruments that measure more dissimilar constructs. For example, correlation values between OC-VAS scores and the SF-36 PCS and MCS scores were weak to moderate, reflecting the anticipated weaker relationship and negative in sign due to the differences in scoring direction indicative of better outcomes. Together, these results provide convergent and divergent validity evidence for the OC-VAS. Results from the known-groups (discriminating ability) validity analysis are summarized in Table 4. ANOVAs for OC-VAS scores according to the COWS total score categories at screening and week 25 demonstrated highly significant results on the omnibus F-test ($P < 0.0001$) and for all pairwise comparisons across categorical severity levels for the COWS total score. All results for the known-groups comparison were in the anticipated direction, highly significant, and consistent at screening and week 25, demonstrating the ability of OC-VAS to discriminate between groups defined by the severity of withdrawal signs and symptoms.

3.2.5. *Responsiveness and ability to detect change*

OC-VAS responsiveness was assessed to evaluate the extent to which OC-VAS scores can detect the change in participants who have changed in clinical status as defined by the SOWS and COWS scores. It was supported by strong positive correlations for change from screening to week 25 between OC-VAS score and SOWS Item 16/SOWS total score ($r = 0.69$, $r = 0.59$, respectively), with a moderate positive correlation to COWS total score ($r = 0.46$) (Table 3). Large effect size estimates were observed for OC-VAS change from screening to week 25 (Table 4). OC-VAS changes, expressed as an effect size estimate in units of SD of screening scores (−1.6) or as a standardized response mean in units of SD of change from screening to week 25 (−1.4), were categorized as strong, well above the threshold of 0.8. Participants, defined by their changes of COWS total score severity categories (improved, stable, worsened), were compared using the ANOVA F-test. Highly significant differences ($P < 0.0001$) in OC-VAS score changes were observed for the overall test and all 3 pairwise comparisons. The between-groups effect size estimates (Cohen's d values) range from −0.57 (moderate) to −1.59 (strong).

3.2.6. *PRO responder*

3.2.6.1. Defining meaningful OC-VAS change. A meaningful within-participant change was estimated using the SOWS Item 16 ("I feel like using now") as an anchor for observed OC-VAS changes. This anchor's appropriateness was evaluated by reviewing the relationship between changes on the OC-VAS and the anchor. For groups of participants defined by the change in SOWS Item 16 score from randomization baseline to week 25, a linear trend for the mean of OC-VAS change scores was observed, ranging from substantial improvement to no change to substantial worsening. OC-VAS score changes are plotted by SOWS Item 16 response-defined groups in Fig. 2; the clear separation between the SOWS Item 16 response-defined groups is evident.

3.2.6.2. Exploring the application of meaningful thresholds of OC-VAS change. As supportive evidence, meaningful thresholds of within-participant OC-VAS change were explored using the change in OC-VAS from randomization baseline to week 25 and change of participant opioid usage. Because randomization was based on attainment of relatively low opioid craving (OC-VAS ≤20 mm) and lack of clinically significant withdrawal symptoms (COWS total score ≤ 12) at the end of the run-in/induction phase, this analysis focused on maintenance or a worsening of craving (an increase in OC-VAS). A PRO responder would have OC-VAS change below the threshold, indicating maintenance of opioid craving. OC-VAS changes from randomization baseline to week 25 in study participants who received BUP-XR were evaluated against a range of thresholds for OC-VAS increase (5–45 mm in 5-mm increments). Participants were classified according to their OC-VAS increase on/below, or greater than a threshold. The reductions in the proportion of participants with opioid use from randomization baseline to week 25 and the mean of participants' percentage of opioid abstinence (the number of negative assessments divided by the number of non-missing opioid use assessments) during the randomized treatment were plotted for the cut-point subgroups. (Fig. 3). Participants with an OC-VAS increase greater than the threshold had a smaller opioid use reduction at week 25 and a lower percentage of opioid abstinence during treatment than participants with an OC-VAS change less than or equal to the threshold. The group difference increased for larger thresholds and was maximized at 20 or greater. This analysis identified a threshold of 20 mm as the lowest value that provided maximal separation for both opioid use outcomes. A ≤20-mm increase in OC-VAS from randomization to week 25 could be considered a threshold to indicate maintenance or stability of opioid craving that can translate to greater improvement in opioid abstinence.

3.2.7. *Predictive validity*

Investigation of the association between OC-VAS score and opioid use assessed at the same visit (same week) or the next visit (next week) was conducted separately for the run-in/induction phase (screening to randomization baseline) and the double-blind, randomized-treatment phase (post- first randomized treatment to week 25) (Fig. 4). These distinct intervention phases warranted separate investigations.

Mean OC-VAS scores were high at screening before falling to a low level at randomization baseline (after the run-in/induction phase). Placebo and BUP-XR participants diverged following the first BUP-XR/placebo injection of the double-blind phase. Specifically, placebo participants rose to 20–25 mm and BUP-XR participants remained at <10 mm during the entire double-blind phase (Fig. 4**a**). The proportion of participants achieving opioid abstinence demonstrated opposite trends, rising to near 40% at randomization baseline before falling and remaining low (~10%) among placebo participants, while rising and remaining high (~60%) among BUP-XR participants (Fig. 4**b**).

During the run-in/induction phase, the OC-VAS change from screening to randomization (week 1, the end of run-in/induction phase) significantly predicted the risk of opioid use at randomization. The odds ratio (OR) for opioid use (used vs not used) for a 10-mm OC-VAS reduction from screening to randomization was 0.91 (95% CI: 0.85, 0.97) and 0.88 (95% CI: 0.82, 0.94) after adjustment for baseline factors, suggesting that greater OC-VAS reduction from screening to randomization is associated with less opioid use at randomization.

During the randomized-treatment phase, where low OC-craving levels were maintained in the BUP-XR group, the associations between various OC-VAS parameterizations (continuous, 3-level ordinal categorical [=0, >0 – 20, >20], and binary [>0, =0]) and same week/next-week opioid use were evaluated. The models with same week opioid use as the outcome and the models with next-week opioid use yielded similar statistical inferences regarding the association between OC-VAS and opioid use. The risk-adjusted multivariate analysis for prediction of next-week opioid use in the BUP-XR and placebo groups is summarized in Table 5. The assessment providing the optimal predictive capability of OC-VAS differed between placebo-treated and BUP-XR-treated participants. For placebo-treated participants, the area under the receiver operating curve (ROC) using continuous OC-VAS is higher than the models using the other parameterizations. This suggests a significant linear association between OC-VAS and opioid use; OR (95% CI) of opioid use for a 10-mm OC-VAS increase is 1.64 (1.26 – 2.12). For BUP-XR-treated participants, the associations between opioid use and OC-VAS for all 3 OC-VAS parameterizations were much smaller than those observed in placebo-treated participants. The strongest association was for the binary OC-VAS parameterization; OR (95% CI) of opioid use for > 0 vs $= 0$ and for > 0–20 vs $= 0$ is 1.57 (1.20 – 2.05) or 1.59 (1.20 – 2.09), suggesting a similar association. The lower area under the ROC for the model with continuous OC-VAS also indicates that the association is unlikely to be linear. These predictive results were generally better than the SOWS Item 16 predictive analysis results (Table 5).

4. Discussion

This psychometric analysis of the OC-VAS performed on a relatively large and diverse OUD patient population provided evidence to support its distributional properties, test-retest reliability, construct validity (including convergent and divergent validity), discriminating ability (known-groups validity), and responsiveness. These results were based on comparisons using well-established assessments (e.g., SOWS, COWS, SF-36). Evaluation of the OC-VAS predictive validity established its ability to predict subsequent week opioid use, and OC-VAS was more sensitive than SOWS Item 16.

Single-item measures have also assessed craving in other contexts, such as food craving (Sun and Kober, 2020), suggesting that craving can be measured effectively with only one question. Given the results, the OC-VAS may be beneficial in the clinic and in clinical trials to identify patients and participants who may be close to relapse and could eventually be used to inform treatment plan changes, such as decisions to increase the dose of buprenorphine or add another medication to help reduce craving. The utility of the OC-VAS in these settings is further supported by the results of the anchor-based analyses that suggest PRO responder analysis can identify stable participants with positive treatment responses.

Single-item VAS measures are a time-efficient and convenient method to assess craving at the present moment (Kleykamp et al., 2019a; Shiffman et al., 2004). However, it has been argued that the validity and reliability of single-item assessments in capturing multiple dimensions of opioid craving are less reliable compared with multiple-item assessments (eg, Desires for Drug Questionnaire, Heroin Craving Questionnaire) (Heinz et al., 2006; Kleykamp et al., 2019a; Sayette et al., 2000; Shiffman et al., 2004). A “one-size-fits-all” tool for clinicians to assess opioid craving may not be feasible (Kleykamp et al.; Shiffman et al.). For example, in early stages of recovery, single-item assessments may be helpful to tailor a patient’s OUD treatment by focusing on present craving and allow rapid collection of patient information in a difficult clinical environment (Kleykamp et al., 2019a; Sayette et al., 2000). Multiple-item craving assessments covering general craving across a wider range of circumstances may be more appropriate for patients who have been in recovery for a longer period (Kleykamp et al., 2019a). It has been proposed that investigations of craving and OUD could include both a single-item brief craving assessment, and a multi-factor assessment with demonstrated reliability and validity, depending on the goals of the study (Kleykamp et al., 2019a).

The VAS has been used to assess opioid craving in clinical trials of patients with OUD. In a trial of methadone-maintained patients, self-reported opioid craving as measured by a VAS correlated with opioid use and was used to develop a predictive model for continued opioid use (Huhn et al., 2019). Additionally, a VAS was used to compare craving for heroin and cocaine in opioid-dependent study participants receiving either slow-release oral morphine or methadone as maintenance treatment (Falcato et al., 2015), or opioid craving in opioid-dependent patients receiving extended-release implantable naltrexone with oral naltrexone and placebo (oral and implant) (Krupitsky et al., 2016). Clinical trials, currently in the recruiting stage, are also using the VAS to assess drug craving in OUD treatment and will add to the current level of evidence; these include vagal nerve stimulation (NCT04556552, phase 3), deep brain stimulation (NCT02440152, phase 2/3), glucagon-like peptide 1 receptor agonist (NCT04199728, phase 1/2), and a rapid induction procedure with naltrexone (NCT04762537). Findings from these and future clinical trials including VAS assessments of opioid cravings will be critical to the field of OUD. Evidence from a recent neurological imaging study confirmed, using functional magnetic resonance imaging, that withdrawal and craving are dissociable from neural cue reactivity, a negative correlation that may explain patients’ negative attitude toward opioid use and their ability to under-report craving symptoms even while seeking treatment for OUD (Shi et al., 2021).

The present analyses have some limitations. Because the OC-VAS was administered at scheduled site visits, the ratings may not represent participants’ experiences/feelings in the real world. This setting may lack the triggers/cues that induce craving in participants’ typical environment. Thus, although the study design allowed for a reasonable longitudinal assessment of tonic craving, it did not prospectively evaluate the effect of study medication on phasic craving. Research across SUDs has shown that both tonic and phasic craving predict use and outcomes (Hartwell and Ray, 2018; Kober and Mell, 2015). Despite this limitation, the predictive validity analyses demonstrated that OC-VAS assessments captured during a controlled clinic visit could predict illicit use of opioids in the same week or subsequent week. Furthermore, we used established measures for evaluating construct validity, such as COWS and SOWS, which are mainly measurements for withdrawal. Therefore, while these were not expected to perfectly align with OC-VAS, the strong correlation of OC-VAS with SOWS Item 16 supports the measurement of craving instead of withdrawal. Another potential limitation is that participants enrolled in a clinical trial may be more representative of OUD patients who are interested in seeking help compared with OUD patients who are resistant to treatment. Finally, a strong decline in opioid craving was observed in the placebo group of this analysis. This decline was likely due, at least in part, to the individualized drug counseling that was provided at each weekly visit for

each treatment group. Counseling was provided by trained, qualified individuals who were blinded to study treatment and UDS results, and counselors were tasked with inquiring about recent illicit drug use, identifying any urgent problems/challenges the patient was facing, and addressing the topic of focus that was most critical to the patient's current stage in recovery. Additionally, the placebo effect of volume-matched placebo injections likely played a role in reducing craving in the placebo group. Furthermore, the decline of opioid craving in the placebo group might also be related to their use of illicit opioids as self-medicating throughout the study (Haight et al., 2019).

Additional research is proposed to evaluate completion of the OC-VAS by patients within their normal, everyday environment rather than in a structured clinical setting. Utilizing a digital application of OC-VAS has the potential to inform clinicians quickly, thereby facilitating their assessment of the intensity, duration, and frequency of craving episodes that their patients are experiencing and providing useful prognostic information regarding the risk of relapse. The feasibility and acceptability of a smartphone app that used the VAS to assess craving was demonstrated in a study of individuals seeking treatment for substance use disorder (Zhang et al., 2019). The VAS was used to assess craving before and after the completion of training sessions for attention bias modification; the app had a 75% acceptance rate and was rated as extremely or very easy by 100% of participants who completed the questionnaires (Zhang et al., 2019).

5. Conclusion

In summary, the OC-VAS scale, unlike other measures of craving that can be complex and time consuming, is straightforward to use and can be easily administered within settings that are time-constrained (eg, medical appointments, real-world data collection). Additional studies are needed to determine the optimal frequency of administration of OC-VAS and can be designed based on the length of action of the drug being studied (ie, long versus short). The psychometric evaluation of the OC-VAS, its ability to predict opioid use, and its correlation with clinician-reported global measures support its use as part of a more comprehensive assessment of OUD patients and the effectiveness of OUD treatments.

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Brent Boyett: employee of Bradford Health Services Incorporated, shareholder of Pathway Healthcare Incorporated, global advisory board/adjudication committee member for Indivior Pharmaceuticals, served as site principal investigator for several RBP-6000 trials.

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Study design: PJF, SML, Study investigator: BB, KW (Oregon site), Enrolled study participants: BB, KW (Oregon site), Collection and assembly of data: LDM, LMN, YZ (RTI analysis plan), Data analysis: LDM, LMN, Data interpretation: All authors, Manuscript preparation: All authors, Manuscript review and revisions: All authors, Final approval of manuscript: All authors, Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved: All authors.

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Data Sharing Statement

The authors will not make data collected for the study available to others, including individual participant data and a data dictionary defining each field in the set.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2021.109057.

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