



## Craving and opioid use disorder: A scoping review

Bethea A. Kleykamp<sup>a,\*</sup>, Marta De Santis<sup>b</sup>, Robert H. Dworkin<sup>a</sup>, Andrew S. Huhn<sup>c</sup>,  
 Kyle M. Kampman<sup>d</sup>, Ivan D. Montoya<sup>b</sup>, Kenzie L. Preston<sup>e</sup>, Tanya Ramey<sup>b</sup>, Shannon M. Smith<sup>a</sup>,  
 Dennis C. Turk<sup>f</sup>, Robert Walsh<sup>b</sup>, Roger D. Weiss<sup>g</sup>, Eric C. Strain<sup>c</sup>

<sup>a</sup> Department of Anesthesiology, School of Medicine and Dentistry, University of Rochester, USA

<sup>b</sup> National Institute on Drug Abuse, Bethesda, MD, USA

<sup>c</sup> Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD, USA

<sup>d</sup> Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

<sup>e</sup> Clinical Pharmacology and Therapeutics Research Branch, National Institute on Drug Abuse, Baltimore, MD, USA

<sup>f</sup> Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA, USA

<sup>g</sup> McLean Hospital, Harvard Medical School, Belmont, MA, USA

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### ABSTRACT

**Introduction:** The subjective experience of drug craving is a prominent and common clinical phenomenon for many individuals diagnosed with opioid use disorder (OUD), and could be a valuable clinical endpoint in medication development studies. The purpose of this scoping review is to provide an overview and critical analysis of opioid craving assessments located in the published literature examining OUD.

**Method:** Studies were identified through a search of PubMed, Embase, and PsychInfo databases and included for review if opioid craving was the focus and participants were diagnosed with or in treatment for OUD.

**Results:** Fifteen opioid craving assessment instruments were identified across the 87 studies included for review. The most common were the Visual Analog Scale (VAS, 41 studies), Desires for Drug Questionnaire (DDQ, 12 studies), Heroin Craving Questionnaire (HCQ, 10 studies), and Obsessive-Compulsive Drug Use Scale (OCDUS, 10 studies). Craving assessments varied considerably in their format, content, time frame, and underlying subscales, and only 6 of 15 had been psychometrically evaluated.

**Discussion:** This review identified a variety of opioid craving assessments, but few had been evaluated for their psychometric properties making it difficult to ascertain whether craving is being assessed optimally in studies of OUD. Thus, the development of a reliable and valid opioid craving assessment would be worthwhile and could be guided by recently published Food and Drug Administration Clinical Outcome Assessment (COA) guidelines. Importantly, a COA focused on opioid craving could be a valuable addition to research studies designed to evaluate novel treatments for OUD.

## 1. Introduction

The subjective experience of ‘craving’, defined as a strong desire or urge to use drugs, is closely associated with substance use and has been the focus of numerous research articles, expert panels, and conferences over the past 60 years (American Psychiatric Association, 2013; Anton and Drobos, 1998; Kozlowski and Wilkinson, 1987; O’Brien, 2005; Pickens and Johanson, 1992; Sayette, 2016; Shiffman et al., 2004; Skinner and Aubin, 2010; Tiffany et al., 2012; World Health Organization, 1955, 1992; Supplementary Materials, Appendix A). One of the earliest organized efforts to critically examine the role of craving in substance use was convened by the World Health Organization in

1954 (World Health Organization, 1955). The report resulting from that meeting acknowledged the importance of craving as it related to alcohol use, but ultimately recommended that the term ‘craving’ be eliminated from the scientific literature due to confusion arising from its various ‘everyday connotations’ (Supplementary Materials, Appendix A). Since that time there has been continued debate regarding the clinical utility of the concept of craving as it relates to substance use disorders (Kassel and Shiffman, 1992; Kozlowski and Wilkinson, 1987; Pickens and Johanson, 1992; Sayette et al., 2000; Tiffany and Wray, 2009, 2012).

However, despite these challenges, drug craving remains a salient and important patient-reported experience as reflected by a survey at a

\* Corresponding author at: University of Rochester, School of Medicine and Dentistry, 601 Elmwood Avenue, Rochester, NY 14642, USA.

E-mail address: [Bethea\\_Kleykamp@URMC.Rochester.edu](mailto:Bethea_Kleykamp@URMC.Rochester.edu) (B.A. Kleykamp).

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recent public meeting hosted by the Food and Drug Administration (FDA) in collaboration with the National Institute of Drug Abuse (NIDA) (see meeting slides located at [Food and Drug Administration, 2018a](#)). The survey found that 48% of attendees (patients diagnosed with opioid use disorder [OUD], and caregivers/advocates), reported that symptoms associated with opioid “cravings” had a significant impact on their daily life as compared to other less endorsed symptoms such as withdrawal (7%) or the health effects of opioids (33%). Corresponding with such reports is the designation of craving as a symptom of substance use disorders in the Diagnostic and Statistical Manual of Mental Disorders-5 diagnostic criteria ([American Psychiatric Association, 2013](#); [Hasin et al., 2013](#)) and recent remarks by former FDA Commissioner, Dr. Scott Gottlieb, that highlighted opioid craving as target of treatment for OUD ([Food and Drug Administration, 2018b](#)):

“...craving is an endpoint that the FDA has included in labeling for smoking cessation products, and the agency intends to provide assistance to develop a validated measurement of “craving” or “urge to use” illicit opioids to complement other endpoints and to determine how it supports the goal of sustained abstinence.”

Dr. Gottlieb’s suggestion that craving can serve as an endpoint in medication development studies has been discussed previously in the published literature and aligns with patient reports that this OUD symptom is a key factor in continued use of opioids ([Kosten, 1992](#); [Shiffman et al., 2004](#); [Tiffany et al., 2012](#)). However, before an outcome such as craving can be relied on to serve as a target of treatment, it is essential to clarify whether there are existing opioid craving assessments available for use in such studies. And importantly, such assessments must meet criteria for being reliable, valid, and sensitive to change should they be relied on as accurate approximations of a patient’s subjective experience of opioid craving. Thus, the purpose of this scoping review is to provide an overview and critical evaluation of existing assessments of opioid craving in the published literature to inform future work examining craving as a potential clinical endpoint in studies of OUD.

## 2. Method

The present article was designed to be a scoping review which is distinct from systematic reviews. Scoping reviews provide a ‘map’ of the existing literature to address broad research questions related to complex and heterogeneous bodies of literature, whereas systematic reviews address more pointed research questions ([Chang, 2018](#); [Peters et al., 2015](#); [Pham et al., 2014](#); [Tricco et al., 2018](#)). Both types of reviews are intended to be objective and transparent in their approach to research synthesis, with the overall aim of minimizing bias.

### 2.1. Key questions

The current scoping review was designed to answer the following questions:

- 1 What assessments of opioid craving have been used in published studies of OUD?
- 2 Have assessments of opioid craving used in published studies been evaluated for their psychometric properties (i.e., reliability and validity)?
- 3 What are the research gaps and limitations related to currently available assessments of opioid craving and OUD?
- 4 Are there any existing reliable and valid assessments of opioid craving that can be recommended for use in studies of OUD and its treatment?

### 2.2. Search strategy

Evidence evaluated for this report was obtained from a search of the

PubMed, Embase, and PsychInfo databases through January 2019 (no restrictions were set on the start date of the search). Search terms included: (craving OR urge OR desire) AND (opioid OR opiate) AND (dependence OR disorder). The search strategy was reviewed by a medical librarian at the University of Rochester School of Medicine and Dentistry. The reference lists of retrieved articles were also manually searched for additional eligible studies.

### 2.3. Study selection and eligibility criteria

Studies were reviewed by BAK and included for review if they were published in English, participants were diagnosed with OUD\* or recovering from OUD (i.e., in treatment) and OUD was the primary substance use disorder among these patients. In addition, opioid craving had to be a focus of the study as determined by meeting the following criteria:

- 1 The title of the study included the term ‘craving’, and/or
- 2 The abstract: (a) listed opioid craving as a main outcome and/or (b) provided a name or description of the opioid craving assessment used in the study, and/or
- 3 The list of keywords included the term ‘craving’.

Studies were excluded if they: were conference abstracts or dissertations or examined craving for opioids in the absence of an OUD diagnosis (e.g., chronic pain patients; [Garland and Howard, 2014](#); [Priddy et al., 2018](#); [Wasan et al., 2009](#)). In addition, given the large body of the literature that has examined OUD and craving, studies with a sample size of less than 20 were excluded in order to manage the size of the literature review while still allowing the inclusion of a large number of studies ([Table 1](#) lists these excluded studies and the type of craving assessments reported in each).

### 2.4. Data extraction and summary of results

Data extraction was completed by BAK and a narrative/qualitative summary of findings for individual studies, as well as systematic reviews of opioid craving and OUD, was generated. The following information was collected:

- General study details (publication year, study sample size, patient population, geographical setting, financial support),
- Study design (trial, experimental, observational, psychometric, and secondary analysis);
- Opioid Craving assessment details
  - a Type (title/category of assessment)
  - b Format (number of items, response options/scale type)
  - c Content (language, wording, or prompts)
  - d Time frame (immediate, past day/week, or general craving)
  - e Psychometric evaluations

The following psychometric properties were also reviewed across assessments ([Leary, 2004](#)):

- Craving Subscales<sup>†</sup>

\* To be as inclusive as possible, studies that did not specify OUD diagnostic criteria (e.g., DSM-IV, DSM-5, American Psychiatric Association) were included if patients were described as opioid-dependent or in treatment for opioid dependence.

<sup>†</sup> Throughout the paper, the term ‘construct’ is used to refer to the underlying theoretical domains/dimensions associated with craving, while the term ‘sub-scale’ is used to refer to the specific underlying factor(s) associated with each craving assessment tool based on psychometric statistical analyses (e.g., factor analysis).

**Table 1**  
Excluded Studies (Sample Size N < 20) and Type of Craving Assessment.

First author (last name)	Year	Sample size	Craving Assessment	Content of Assessment
Badger	2007	13	Untitled	<b>NR</b>
Bolek	2016	19	VAS (single-item)	The participants responded to the question "How strong is your craving for heroin?". Responses were made on a continuous line between 0 (not at all) and 100 (very much so).
Daglish	2003	12	VAS (single-item)	<b>NR</b>
Dawe & Gray	1995	16	The Craving Questionnaire	The 'Craving Questionnaire' asked subjects to rate, on two 9-point scales (0-8), how strong was their desire to use heroin: (i) to take away unpleasant physical feelings (negative craving) and (ii) for its pleasant effect, (positive craving).
Farren & O'Malley	2002	13	OCBUS (labeled OCOS)	The scale was based on the Obsessive-compulsive Drinking Scale (Anton et al., 1996).
Greenwald	2002	14	HCQ (34-item version)	The HCQ was described as having five a priori (i.e. theory-derived) scales, each with nine items. These scales are Desire to Use Drug (e.g. "I want heroin so bad now I can almost taste it"), Intent to Use (e.g. "I am going to use heroin as soon as possible"), Anticipation of Positive Outcome (e.g. "I would feel so good and happy if I used heroin now"), Withdrawal Relief (e.g. "I would feel less sick now if I used heroin"), and Lack of Control (e.g. "I could not stop myself from using heroin if I had some here now").
Greenwald	2013	10	HCQ (10-item version)	Heroin craving was measured with a 10-item total score based on the HCQ full version (authors cited S.T. Tiffany, personal communication for the scale; November 23, 1999).
El Hage	2018	18	HCQ (number of items NR)	The HCQ had 5 underlying constructs: desire to consume, intention to use, anticipation of positive outcome, relief from withdrawal and dysphoria, and lack of control over use.
Hyman	2007	14	VAS (single-item)	Participants rated current intensity of desire to use opioids 0 (none at all) to 10 (more than ever).
Langerman	2001	8	NR	<b>NR</b>
Langleben	2012	15	Untitled	Opioid craving was assessed before and after each session with a ten-point (0-9) scale.
Mei	2010	15	Untitled	Assessed on a 10-point (0 to 9) scale (0 for least craving and 9 for strongest craving).
Metz	2017	11	VAS (single-item)	Generally described as assessing heroin craving.
Mirrn	1976	6	VAS (single-item)	Craving for heroin rated from none to very strong by bisecting a 100-cm line.
Mitchell	2004	14	NR	<b>NR</b>
Murphy	2018	18	Untitled	Likert-like subjective scales included 'do you feel you are ...', which was presented for 3 seconds before slides stating 'Craving?', 'followed by response options of 1 (not all), 2 (slightly), 3 (moderately) and 4 (extremely).
Sideroff	1978	19	VAS (single-item)	The VAS included labels for the middle 0-point ("Take it or leave it.") and a vertical arrow pointing toward +100 was labeled "increasing craving," while the arrow going toward -100 was labeled "increasing repulsion." In addition, the scale had space for responses to: "Where are you?," "With whom?," "What are you doing?," and the date.
Sideroff & Jarvik	1980	16	VAS (single-item)	Craving scale was a vertical line marked off in increments of 10, from -100 through 0 to 100; "0" was labeled "take it or leave it"; an arrow going up marked "increasing craving", and an arrow going down marked "increasing repulsion".
Sinha	2007	18	VAS (single-item)	A 10-pt visual analog scale.
Stine	2002	n = 17	VAS (two-items)	Participants responded to the question "Rate your desire for opiates" and the VAS response option was anchored at 6 points, labeled "not at all," "a little," "somewhat," "definitely," "very strong," "desire almost overpower." The other question, "If opiates were available I would," had a VAS response option anchored at 3 points, labeled "leave it alone," "consider using," and "definitely use." The results from both scales were averaged and used for data analysis.
Vasilev	2006	n = 19	VAS (single-item)	Scale included line anchors of 0 cm (no craving) and 10 cm (maximal craving).
Wang	2011	n = 14	VAS (single-item)	Assessed using a 0-10 visual analog scale, on which participants marked as 0 (not at all) to 10 (extremely high) in response to the question, "To what extent do you feel the urge to use heroin?" Craving ratings were obtained before and immediately after each imaging session.
White	2009	N = 12	VAS (single-item)	Assessed using a 100mm/visual-analogue scale that asks respondents to quantify their desire for heroin by marking a linear visual scale from 0 to 100, with 0 = no cravings and 100 = maximum heroin craving experienced.
Xiao	2006	N = 14	Untitled	<b>NR</b>

Note: NR indicates that content of assessment was not report. Additional acronyms and abbreviations are as follows: Heroin Craving Questionnaire (HCQ); Obsessive Compulsive Drug Use Scale (OCBUS); Visual Analogue Scale (VAS).

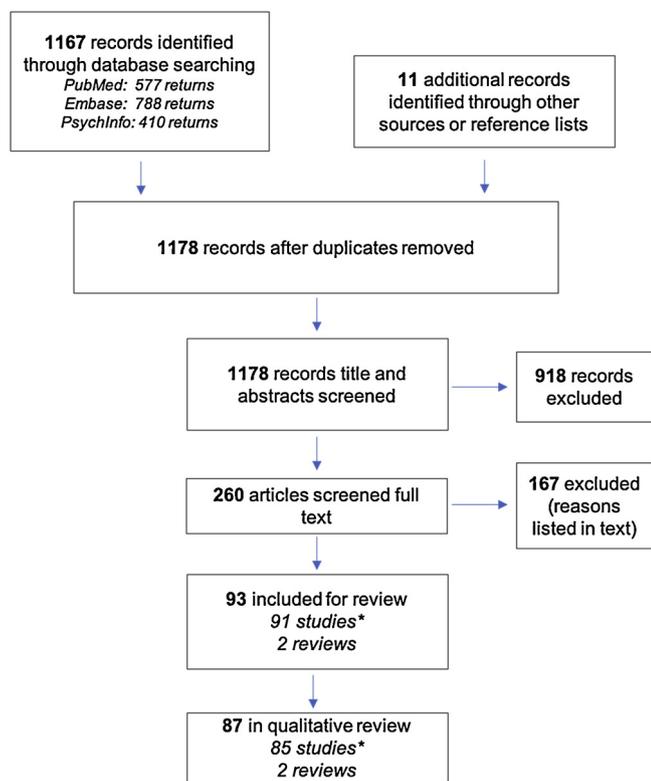


Fig. 1. PRISMA Flow Diagram.

Note: \*Twelve articles represented overlapping study samples and were combined, thereby reducing the final count of the studies included for review by 6 and resulting in a total of 85 studies and 2 reviews included for review.

- Reliability - internal consistency (usually tested statistically using Cronbach’s alpha) and consistency over time (test-retest)
- Validity - construct validity (convergent or discriminant validity with existing assessments); criterion-related or predictive validity, such as with illicit opioid use or time in treatment; and sensitivity (i.e., responsiveness) to change in craving over time or to differences between active and control or comparison treatments

A “study quality” evaluation (critical appraisal of studies included for review) was not included in the review in accordance with the best practice standards set forth by the Joanna Briggs Institute for scoping reviews (Peters et al., 2015).

**Table 2**  
Overview of Evidence – Number of Studies for each Assessment Type as a Function of Study Design.

	Experimental	Randomized-Controlled	Observational	Psychometric	Secondary Analysis	Total # of Studies
Visual Analogue Scale	13	16	9	3	0	41
Desires for Drug Questionnaire	3	3	2	4	0	12
Heroin Craving Questionnaire	3	4	2	1	0	10
Obsessive-Compulsive Drug Use Scale	3	2	3	2	0	10
Title of assessment not specified	6	2	1	0	1	10
Diary/ecological momentary assessment	0	2	3	0	1	6
Craving Beliefs Questionnaire	0	0	1	2	0	3
Brief Substance Craving Scale	1	0	1	0	0	2
Chinese Craving Scale	0	0	2	0	0	2
Opioid Craving Scale	0	0	0	0	2	2
Crav-Hero Inventory	0	0	0	1	0	1
Craving Rating Scale	0	1	0	0	0	1
Maudsley Craving Scale	0	1	0	0	0	1
Penn Craving Scale	0	0	0	1	0	1
Substance Craving Scale	0	0	1	0	0	1

Note: Values in table represent study counts for each assessment type (far left column) by study design (top row). The ‘Total’ column (far right) represents the total number of studies for each assessment type.

### 3. Results

#### 3.1. Overview

A total of 1178 studies were reviewed for inclusion at the title and abstract level, of which 918 were deemed ineligible (see Fig. 1 for PRISMA Flow Diagram). The remaining 260 articles were reviewed at the full text level of which 167 were excluded for the following reasons: opioid craving not a focus (n = 80), opioids or OUD not a primary focus (n = 46), sample size < 20 (n = 24; Table 1), insufficient details provided (n = 12), case studies or dissertations (n = 3), and article not in English (n = 2).

The remaining 93 publications (91 studies and 2 review papers) were then included for review. However, 12 of these reports overlapped such that they included the same craving assessments, patient population, and research teams (Dehgani-Arani et al., 2010; Dehgani-Arani et al., 2013; Dijkstra et al., 2007, 2008; Maremmanni et al., 2016, 2015; McHugh et al., 2014b, 2016; Preston et al., 2018, 2017; Zijlstra et al., 2008, 2009). These 12 reports were treated as duplicates and combined into 6 studies accounted for in Table 2 through 8 (highlighted with an \* asterisk symbol in Table 3). Thus, the final inclusion count for this scoping review was 85 studies (reduced by 6 from the original 91) and 2 review papers (Fareed et al., 2010, 2011).

#### 3.2. Individual studies of opioid craving and OUD

Individual studies included for review (n = 85) were published between 1986 and 2019, the majority (n = 55) were published in the last decade (2010–2019). Sample sizes ranged from 20 to 653 and most studies included patients primarily using heroin and/or currently in agonist treatment (i.e., methadone, buprenorphine, heroin-assisted treatment). A small subset of studies focused on craving related to prescription opioids (Ashrafioun, 2016; Back et al., 2015; Garland et al., 2013; Huhn et al., 2016; McHugh et al., 2014a, b; McHugh et al., 2016).

The studies were conducted in 18 countries with the majority in the United States (USA; 23 studies), China (14 studies), or Iran (9 studies). Additional countries (with study counts in parentheses) were as follows: Australia (1), Canada (1), France (1), Germany (1), Greece (1), India (1), Italy (3), Netherlands (6), Russia (2), Spain (2), Switzerland (6), Switzerland/Germany (1), Taiwan (4), Turkey (2), United Kingdom (6), and USA/Mexico (1).

Lastly, in terms of financial support, most of the studies reported funding from institutional or governmental organizations (e.g., the United States National Institutes of Health; National Natural Science Foundation of China). Only 2 studies reported funding from the private sector (i.e., Mundipharma Medical Company; Orexo US, Inc; Falcato

**Table 3**  
Evidence Table – Individual Studies Included for Review.

First Author Year	Title	N	Country	General Study Type	Craving Assessment
Almadi et al., 2018	Single high-dose buprenorphine for opioid craving during withdrawal	90	Iran	RCS	VAS
Ashrafoun, 2016	Prescription Opioid Craving: Relationship With Pain and Substance Use-Related Characteristics	106	USA	observational	DDQ
Back et al., 2015	Laboratory-induced stress and craving among individuals with prescription opioid dependence	75	USA	experimental	VAS
Barta et al., 2009	Craving and self-efficacy in the first five weeks of methadone maintenance therapy: a daily process study	21	USA	observational	BSCS
Bearn et al., 2009	Auricular acupuncture as an adjunct to opiate detoxification treatment: Effects on withdrawal symptoms	83	United Kingdom	RCS	MCS
Blanken et al., 2012	Craving and illicit heroin use among patients in heroin-assisted treatment	73	Netherlands	RCS	OCUDS
Blum et al., 2013	Acute effects of heroin on emotions in heroin-dependent patients	48	Switzerland	RCS	HCQ
Chang et al., 2011	Psychometric properties of the Chinese craving beliefs questionnaire for heroin abusers in methadone treatment	445	Taiwan	psychometric	CCBQ
Chang et al., 2016	Regional homogeneity changes between heroin relapse and non-relapse patients under methadone maintenance treatment: a resting-state fMRI study	40	China	observational	VAS
Charles et al., 2015	Attentional bias and treatment adherence in substitute-prescribed opiate users	44	United Kingdom	experimental	VAS
Childress et al., 1986	Conditioned responses in a methadone population. A comparison of laboratory, clinic, and natural settings	25 and 22	USA	experimental	not specified
Constantinou et al., 2010	Attentional bias, inhibitory control and acute stress in current and former opiate addicts	48	United Kingdom	experimental	VAS
Curran et al., 2001	Effects of methadone on cognition, mood and craving in detoxifying opiate addicts: A dose-response study	20	United Kingdom	RCS	HCQ
De et al., 2008	Assessment of differential doses of buprenorphine for long term pharmacotherapy among opiate dependent subjects	23	India	RCS	VAS
De Jong et al., 2006	Effects of craving self-report measurement on desire for heroin in opiate dependent individuals	56	Netherlands	experimental	VAS, OCUDS, and DDQ
De Jong et al., 2005	General anesthesia does not improve outcome in opiate antagonist detoxification treatment: A randomized controlled trial	272	Netherlands	RCS	VAS
De Vos et al., 1998	L-methadone and D,L-methadone in methadone maintenance treatment: A comparison of therapeutic effectiveness and plasma concentrations	40	Germany	RCS	Diary/EMA
Dehghani-Arani et al., 2010 and 2013*	Neurofeedback training for opiate addiction: improvement of mental health and craving	20	Iran	experimental	HCQ
Dijkstra et al., 2007 and 2008*	Prediction of withdrawal symptoms during opioid detoxification	272	Netherlands	observational	VAS, OCUDS, DDQ
Dürsteler-MacFarland et al., 2012	Alpha-synuclein and heroin craving in opiate-dependent patients on injectable heroin maintenance	42	Switzerland	experimental	VAS, HCQ
Elkader et al., 2009	Exploring the relationship between perceived inter-dose opioid withdrawal and patient characteristics in methadone maintenance treatment	90	Canada	observational	OCUDS
Evren et al., 2014	Predictors of outcome during a 6-month follow-up among heroin dependent patients receiving buprenorphine/ naloxone maintenance treatment	392	Turkey	observational	SCS
Falcato et al., 2015	Self-reported cravings for heroin and cocaine during maintenance treatment with slow-release oral morphine compared with methadone: A randomized, crossover clinical trial	157	Switzerland/Germany	RCS	VAS, HCQ (brief)
Fatseas et al., 2011	Cue-induced reactivity, cortisol response and substance use outcome in treated heroin dependent individuals	31	France	experimental	Not specified
Franken et al., 2002	Initial validation of two opiate craving questionnaires the obsessive-compulsive drug use scale and the desires for drug questionnaire	102	Netherlands	psychometric	VAS, OCUDS, DDQ
Fudala	Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone	326	USA	RCS	VAS
Garland et al., 2013	Attentional Bias For Prescription Opioid Cues Among Opioid Dependent Chronic Pain Patients	65	USA	experimental	OCUDS
Gerber et al., 2012	The impact of diacetylmorphine on hypothalamic-pituitary-adrenal axis activity and heroin craving in heroin dependence	28	Switzerland	experimental	HCQ
Gerra et al., 2006	Naltrexone and buprenorphine combination in the treatment of opioid dependence	34	Italy	observational	VAS
Ghorbani et al., 2019	The role of emotion dysregulation in the relation of childhood trauma to heroin craving in individuals with heroin dependence	330	Iran	observational	OCUDS
Hao and Zhao, 2000	A comparative clinical study of the effect of WeiniCom, a Chinese herbal compound, on alleviation of withdrawal symptoms and craving for heroin in detoxification treatment	42	China	RCS	CRS
Hassani-Abbarian et al., 2016	Validation for Persian Versions of “Desire for Drug Questionnaire” and “Obsessive Compulsive Drug Use Scale” in Heroin Dependents	131	Iran	psychometric	DDQ and OCUDS
Heberlein et al., 2012	Association of nerve growth factor and vascular endothelial growth factor with psychometric measurements of opiate dependence: Results of a pilot study in patients participating in a structured diamorphine maintenance program	48	Switzerland	observational	VAS, HCQ
Heberlein et al., 2011	Serum levels of BDNF are associated with craving in opiate-dependent patients	28	Switzerland	observational	VAS, HCQ

(continued on next page)

Table 3 (continued)

First Author Year	Title	N	Country	General Study Type	Craving Assessment
Heinz et al., 2006	Heroin and cocaine craving and use during treatment: Measurement validation and potential relationships	101	USA	psychometric	VAS, HCQ (brief and full version)
Huhn et al., 2016	Ecological momentary assessment of affect and craving in patients in treatment for prescription opioid dependence	73	USA	observational	Diary/EMA
Huhn et al., 2018	Prefrontal cortex response to drug cues, craving, and current depressive symptoms are associated with treatment outcomes in methadone-maintained patients	29	USA	experimental	VAS
Hulse et al., 2010	Risk Factors for Craving and Relapse in Heroin Users Treated with Oral or Implant Naltrexone	69	Australia	RCS	Not specified
Ilgem et al., 2008	The effect of stress on craving for methadone depends on the timing of last methadone dose	41	USA	experimental	Not specified
Jafari et al., 2017	Craving and drug reward: A comparison of celecoxib and ibuprofen in detoxifying opiate addicts	32	Iran	RCS	DDQ
Jones et al., 2018	The PPARγ Agonist Pioglitazone Fails to Alter the Abuse Potential of Heroin, But Does Reduce Heroin Craving and Anxiety	30	USA	RCS	Not specified and VAS
Kowalczyk et al., 2018	Using ecological momentary assessment to examine the relationship between craving and affect with opioid use in a clinical trial of clonidine as an adjunct medication to buprenorphine treatment	108	USA	secondary analysis	Diary/EMA
Kowalczyk et al., 2015	Clonidine Maintenance Prolongs Opioid Abstinence and Decouples Stress From Craving in Daily Life: A Randomized Controlled Trial ...	118	USA	RCS	Diary/EMA
Krupitsky et al., 2016	Anhedonia, depression, anxiety, and craving in opiate dependent patients stabilized on oral naltrexone or an extended release naltrexone implant	306	Russia	RCS	VAS
Krupitsky et al., 2002	A pilot study of memantine effects on protracted withdrawal (syndrome of anhedonia) in heroin addicts	67	Russia	RCS	VAS
Küçükkarapinar et al., 2018	Assessing the validity and reliability of the Turkish versions of craving beliefs and beliefs about substance use questionnaire in patients with heroin use disorder: demonstrating valid tools to assess cognition-emotion interplay	296	Turkey	psychometric	CBQ
Li et al., 2015	Predicting subsequent relapse by drug-related cue-induced brain activation in heroin addiction...	69	China	experimental	VAS
Lin et al., 2018	The association between the level of plasma oxytocin and craving among former heroin users	77	Taiwan	observational	CCS
Lin et al., 2012	Association between cholesterol plasma levels and craving among heroin users	70	Taiwan	observational	CCS
Liu et al., 2013	Scopolamine detoxification technique for heroin dependence: A randomized trial	91	China	RCS	VAS
Liu et al., 1999	Drug dependence and abuse potential of tramadol	219	China	observational	VAS
Malcolm et al., 2018	Changes in Withdrawal and Craving Scores in Participants Undergoing Opioid Detoxification Utilizing Ibogaïne	50	USA/Mexico	experimental	BSCS
Marenmani et al., 2015 and 2016*	An inventory for assessing the behavioural covariates of craving in heroin substance use disorder...	114	Italy	psychometric	Crav-Hero Inventory
McHugh et al., 2014a	Assessing craving and its relationship to subsequent prescription opioid use among treatment-seeking prescription opioid dependent patients	360	USA	secondary analysis	OCS
McHugh et al., 2014b and 2016*	Cue-induced craving in dependence upon prescription opioids and heroin and Cue-induced craving to paraphernalia and drug images in opioid dependence	50	USA	experimental	OCDSU
Moeini et al., 2019	The Effects of Oxytocin on Withdrawal, Craving and Stress Response in Heroin-Dependent Patients: A Randomized, Double-Blind Clinical Trial	58	Iran	RCS	VAS, DDQ
Mohammadzadeh et al., 2018	The comparison of impulsivity and craving in stimulant-dependent, opiate-dependent and normal individuals	40	Iran	observational	CBQ
Moran et al., 2018	Sex differences in daily life stress and craving in opioid-dependent patients	182	USA	observational	Diary/EMA
Nava et al., 2006	Relationship between plasma cortisol levels, withdrawal symptoms and craving in abstinent and treated heroin addicts	42	Italy	observational	VAS
Nikolaou et al., 2017	Severity of Withdrawal Symptoms, Plasma Oxytocin Levels, and Treatment Outcome in Heroin Users Undergoing Acute Withdrawal	57	Greece	observational	VAS
Northrup et al., 2015	Opioid withdrawal, craving, and use during and after outpatient buprenorphine stabilization and taper: A discrete survival and growth mixture model	653	USA	secondary analysis	OCS
Powell et al., 1993a	Can opiate addicts tell us about their relapse risk? Subjective predictors of clinical prognosis	43	United Kingdom	secondary analysis	Not specified
Powell et al., 1993b	Subjective craving for opiates: evaluation of a cue exposure protocol for use with detoxified opiate addicts	21	United Kingdom	experimental	Not specified
Preston et al., 2017 and 2018*	Before and after: craving, mood, and background stress in the hours surrounding drug use and stressful events in patients with opioid-use disorder	158	USA	observational	Diary/EMA
De Quirós Aragón et al., 2005	Evaluation of a group cue-exposure treatment for opiate addicts	24	Spain	experimental	Not specified
Ren et al., 2009a	Abnormal pain response in pain-sensitive opiate addicts after prolonged abstinence predicts increased drug craving	100	China	experimental	VAS
Ren et al., 2009b	Diurnal variation in cue-induced responses among protracted abstinent heroin users	80	China	experimental	VAS
Shi et al., 2009a	Effect of rapamycin on cue-induced drug craving in abstinent heroin addicts	60	China	RCS	VAS
Shi et al., 2009b	Tetradotoxin reduces cue-induced drug craving and anxiety in abstinent heroin addicts	45	China	RCS	VAS

(continued on next page)

Table 3 (continued)

First Author Year	Title	N	Country	General Study Type	Craving Assessment
Shi et al., 2007	Long-term methadone maintenance reduces protracted symptoms of heroin abstinence and cue-induced craving in Chinese heroin abusers	70	China	experimental	VAS
Shi et al., 2008	PET imaging of dopamine transporter and drug craving during methadone maintenance treatment and after prolonged abstinence in heroin users	31	China	observational	VAS
Shi et al., 2018	Effects of extended-release naltrexone on the brain response to drug-related stimuli in patients with opioid use disorder	24	USA	experimental	Not specified
Strasser et al., 2010	Effects of a single 50% extra dose of methadone on heroin craving and mood in lower- versus higher-dose methadone patients	28	Switzerland	RCS	VAS and HCQ
Tabatabaei-Jafari et al., 2014	Patterns of brain activation during craving in heroin dependents successfully treated by methadone maintenance and abstinence-based treatments	40	Iran	experimental	DDQ
Tsui et al., 2014	Craving predicts opioid use in opioid-dependent patients initiating buprenorphine treatment: A longitudinal study	147	USA	psychometric	DDQ and Penn Craving Scale
Tsui et al., 2016	Chronic pain, craving, and illicit opioid use among patients receiving opioid agonist therapy	105	USA	observational	Not specified
Verdejo-García et al., 2012	Effect of craving induction on inhibitory control in opiate dependence	58	Spain	experimental	DDQ
Wang et al., 2003	Inhibition by peripheral electric stimulation of the reinstatement of morphine-induced place preference in rats and drug-craving in heroin addicts	117	China	experimental	VAS
Wang et al., 2014	Reduced responses to heroin-cue-induced craving in the dorsal striatum: effects of long-term methadone maintenance treatment	47	China	experimental	VAS
Webster et al., 2016	Efficacy and safety of a sublingual buprenorphine/naloxone rapidly dissolving tablet for the treatment of adults with opioid dependence: A randomized trial	313	USA	RCS	VAS
Woolley et al., 2016	The effects of intranasal oxytocin in opioid-dependent individuals and healthy control subjects: A pilot study	33	USA	RCS	VAS
Yen et al., 2016	Heroin craving and its correlations with clinical outcome indicators in people with heroin dependence receiving methadone maintenance treatment	314	Taiwan	psychometric	VAS and DDQ-CM (Chinese Versions)
Zhao et al., 2012	Cue-induced craving and physiological reactions in recently and long-abstinent heroin-dependent patients	81	China	experimental	VAS
Ziaaddini et al., 2015	Trial of tramadol plus gabapentin for opioid detoxification	59	Iran	RCS	VAS
Zijlstra et al., 2008 and 2009*	Neurobiological substrates of cue-elicited craving and anhedonia in recently abstinent opioid-dependent males	29 and 30	Netherlands	experimental	DDQ and OCDUS

Note: Sample size (N) represents total sample size (sometimes including control groups that were not diagnosed with OUD. Asterisk (\*) represents overlapping studies that have been combined; only 1 title was provided for each. Craving Assessments (last column) are described in detail in Tables 2–5. Acronyms and abbreviations are as follows: Brief Substance Craving Scale (BSCS); Chinese Craving Scale (CCS); Craving Beliefs Questionnaire (CBQ); Crav-Hero Inventory; Craving Rating Scale (CRS); Desires for Drug Questionnaire (DDQ); Diary/Ecological Momentary Assessment (EMA); Heroin Craving Questionnaire (HCQ); Maudsley Craving Scale (MCS); Obsessive Compulsive Drug Use Scale (OCDUS); Opioid Craving Scale (OCS); Penn Craving Scale (PCS); Randomized Controlled Study (RCS); Substance Craving Scale (SCS); Visual Analogue Scale (VAS). The titles of some publications have been shortened for brevity.

**Table 4**  
Overview of Multi-Factor Craving Assessments.

Assessment Name	Scale	Item Number	Time Frame	Number of Studies (references)
Brief Substance Craving Scale (BSCS)	Likert-like (5 point)	3-4	Past 24 hours	2 Barta et al., 2009; Malcolm et al., 2018
Chinese Craving Scale (CCS)	Likert-like (4 point)	10	Not Specified	2 Lin et al., 2012, 2018
Craving Beliefs Questionnaire (CBQ)*	Likert-like (7 point)	10 (Chang et al version included 19 items)	General	3 Chang et al., 2011; Küçükkarapinar et al., 2018; Mohammadzadeh et al., 2018
Crav-Hero Inventory*	Likert-like (5 point)	13	Immediate and Past Week	1 Maremmani et al., 2016, 2016
Craving Rating Scale (CRS)	varied (0-9 scale)	3	Past day	1 Hao and Zhao, 2000
Desires for Drug Questionnaire (DDQ)*	VAS (0-100)	15	Immediate	12 Ashrafioun, 2016; De Jong et al., 2006; Dijkstra et al., 2007/ 2008; Franken et al., 2002; Hassani-Abharian et al., 2016; Jafari et al., 2017; Moeini et al., 2009; Tabatabaei-Jafari et al., 2014; Tsui et al., 2014; Verdejo-Garcia et al., 2012; Yen et al., 2016; Zijlstra et al., 2008/ 2009
Heroin Craving Questionnaire (HCQ)*	Likert-like (7 point)	45	Immediate	10 Blum et al., 2013; Curran et al., 2001; Dehghani-Arani et al., 2010/2013; Dürsteler-MacFarland et al., 2012; Falcato et al., 2015; Gerber et al., 2012; Heberlein et al., 2011, 2012; Heinz et al., 2006; Strasser et al., 2010
Maudsley Craving Scale (MCS)	not reported	8	Previous day	1 Beam et al., 2009
Obsessive Compulsive Drug Use Scale (OCDUS)*	VAS (0-100)	13	Past week	10 Blanken et al., 2012; De Jong et al., 2006; Dijkstra 2007/2008; Elkander et al., 2009; Franken et al., 2002; Garland et al., 2013; Ghorbani et al., 2019; Hassani-Abharian et al., 2016; McHugh et al., 2016/2014b; Zijlstra et al., 2008/2009
Opioid Craving Scale (OCS)	VAS (0-10)	3	Immediate and Past Week	2 McHugh et al., 2014a; Northrup et al., 2015
Penn Craving Scale (PCS)*	Likert-like (7 point)	5	Past week	1 Tsui et al., 2014
Substance Craving Scale (SCS)	Likert-like (7 point)	5	Past week	1 Evren et al., 2014

Note: Above details are approximated from descriptions reported in studies included for review and sometimes vary including the number of items per assessment (e.g., DDQ can range from 2 to 15 items and OCDUS can range from 10 to 13 items). In addition, as noted in the text of the report (see section 3.3.3), some studies have adjusted the parameters of scales/assessments and thus are not identical to those listed in the table. Asterisk (\*) indicates scales that were examined for psychometric properties among studies reviewed. NA = not applicable.

et al., 2015; Webster et al., 2016, respectively).

### 3.3. Study design

The 85 studies included a variety of study designs and could be generally classified into each of the following, as represented in Tables 2 and 3: experimental studies (n = 27), randomized-controlled studies (n = 25), observational studies (n = 21), psychometric studies (n = 8), and secondary analyses of pre-existing data sets (n = 4).

### 3.4. Characteristics of opioid craving assessments

#### 3.4.1. Type

Overall, there were 15 types of craving assessments represented across the 85 studies reviewed (as listed below; see also Tables 2–8). Table 2 provides an overview the craving assessments (as listed below) as a function of the type of study design for which they were included.

- 1 Visual Analogue Scale (VAS): 41 studies
- 2 Desires for Drug Questionnaire (DDQ): 12 studies
- 3 Heroin Craving Questionnaire (HCQ): 10 studies
- 4 Obsessive-Compulsive Drug Use Scale (OCDUS): 10 studies
- 5 Title of assessment not specified: 10 studies
- 6 Diary/ecological momentary assessment\* (EMA): 6 studies

\*Diary/EMA studies utilized hand-written diaries or mobile health technologies to assess craving in real time in participants' natural environment (see Table 5).

- 7 Craving Beliefs Questionnaire (CBQ): 3 studies
- 8 Brief Substance Craving Scale (BSCS): 2 studies
- 9 Chinese Craving Scale (CCS): 2 studies
- 10 Opioid Craving Scale (OCS): 2 studies
- 11 Crav-Hero Inventory: 1 study
- 12 Craving Rating Scale (CRS): 1 study
- 13 Maudsley Craving Scale (MCS): 1 study
- 14 Penn Craving Scale (PRS): 1 study
- 15 Substance Craving Scale (SCS): 1 study

While most reports included a single type of craving assessment, there were several studies that included 2 or 3 assessments within the same study (e.g., Desires for Drug Questionnaire and Obsessive Compulsive Drug Use Scale; Franken et al., 2002; Hassani-Abharian et al., 2016). Thus, for this reason, the study counts listed below sum to a number greater than the 85 studies included for review. In addition, as represented below, the majority of the assessments were represented by acronyms in the published literature. The only exception is the Crav-Hero which was created by an expert panel and titled without an acronym, and as a consequence is reported as such throughout this paper (Maremmani et al., 2016, 2015).

#### 3.4.2. Format

The VAS, diary/EMA, and untitled assessments tended to be limited to 1 or 2 items (Tables 5–7), whereas the multi-factor assessments included between 5 and 45 items (Table 4). In terms of response options/scale type, VAS assessments were most commonly lines anchored from '0 to 10' or '0 to 100' with anchors such as "not at all" and "extremely"

**Table 5**  
Overview of Visual Analog Scales (VAS).

First Author Year	Scale Type	Time of assessment	Question/Prompt
Ahmadi 2018	0-10	past day	1) Rate your craving over the past day
Back 2015	0-10	immediate	NR
Chang 2016	0-10	NR	NR
Charles 2015	10 cm line	immediate	1) I would like to use drugs 2) I want to use drugs 3) I have an urge to use drugs
Constantinou 2010	0-10	immediate	NR
De 2008	NR	immediate	NR
De Jong 2005	0-100	NR	NR
De Jong 2006	0-100	immediate	NR
Dijkstra 2007/2008	0-100	NR	NR
Dürsteler-MacFarland 2012	0-100	immediate	NR
Falcato 2015	0-10	past week	1) How intense was your craving for [the drug in question] during the past 7 days?
Franken 2002	0-100	immediate	NR
Fudala 2003	0-100	Past day	NR
Gerra 2006	0-10	NR	NR
Heberlein 2011	100 mm line	NR	NR
Heberlein 2012	100 mm line	NR	NR
Heinz 2006	100 mm line	immediate	1) How much are you craving heroin/cocaine? 2) How much do you want heroin/cocaine? 3) How much do you need heroin/cocaine?
Huhn 2018	100 mm line	immediate	1) How much do you want to use right now? 2) How much do you want to avoid using right now? 3) How much control do you feel you have over using right now?
Jones 2018	0-100	NR	1) I want heroin.
Krupitsky 2002	NR	NR	NR
Krupitsky 2016	10pt scale	NR	NR
Li 2015	0-10	immediate	1) To what extent do you feel the urge to use heroin?
Liu 1999	100 mm line	NR	NR
Liu 2013	NR	NR	NR
Moeini 2019	NR	immediate	NR
Nava 2006	0-10	past day	NR
Nikolaou 2017	100 mm line	NR	NR
Ren 2009a	(0-100	immediate	NR
Ren 2009b	0-10	immediate	NR

**Table 5 (continued)**

First Author Year	Scale Type	Time of assessment	Question/Prompt
Shi 2007	1-10	immediate	1) How much do you feel the urge to use heroin?
Shi 2008	0-10	immediate	1) How much do you feel the urge to use heroin?
Shi 2009a	1-10	immediate	1) How much do you feel the urge to use heroin?
Shi 2009b	1-10	immediate	1) How much do you feel the urge to use heroin?
Strasser 2010	100 mm line	immediate	1) I have control over my behavior right now 2) I have the feeling that I am missing something right now 3) I have no desire for using something right now 4) I am experiencing unpleasant bodily feelings right now
Wang 2003	0-10	NR	NR
Wang 2014	0-10	immediate	NR
Webster 2016	0-100	NR	NR
Woolley 2016	10 cm line	Immediate	NR
Yen 2016	0-100	past week	1) How much did you crave/desire/want heroin in the preceding week?
Zhao 2012	0-10	immediate	1) How much do you feel the urge to use heroin?
Ziaaddini 2015	0-10	NR	NR

Note: NR, not reported.

(Table 5). In contrast, diary/EMA and multi-factor assessments most commonly included Likert-like response options (e.g., 5-point or 7-point scales) rather than VAS-type scales (Table 6). Untitled assessments represented in Table 7 did not have a consistent format.

### 3.4.3. Content

Tables 4 through 8 include details regarding the content across the various craving assessments. Most were in English; however, 13 studies explicitly stated that scales had either been originally developed in languages other than English (e.g., Dutch version of the DDQ and OCDUS; Franken et al., 2002) or translated to versions other than English (e.g., Chinese, Persian, Dutch; Hassani-Abhari et al., 2016; Yen et al., 2016). Not surprisingly, scale translation sometimes resulted in changes to the underlying factor structure and content/wording of assessments, as described in more detail in Section 3.3.5 (e.g., CBQ; Chang et al., 2011; Küçükkarapinar et al., 2018). Additionally, some studies included assessments that had been altered in some capacity from the original versions. For example, items were sometimes reworded to account for prescription opioid use rather than heroin use (OCDUS; Ashrafioun, 2016; Garland et al., 2013), while other studies used shortened versions of scales (e.g., 9-item version of the HCQ rather than the original, 45-item version; Blum et al., 2013; Gerber et al., 2012). There was only 1 study that addressed psychometric differences between shortened versus longer versions of assessments, as described in Section 3.3.5 (i.e., Heinz et al., 2006). Lastly, the content of the VAS, diary/EMA, and untitled craving assessments was not consistent across studies (Tables 5–7).

### 3.4.4. Time frame

As represented in Tables 4 through 7, respondents were prompted to report craving for different periods of time depending on assessment type, including: immediate/present moment craving (i.e., Crav-Hero

**Table 6**  
Overview of Diary/Ecological Momentary Assessment (EMA) Studies.

Reference	Prompts and Responses	Time frame
De Vos 1998	Participants rated their craving on a questionnaire that contained 6 questions: (1) 'Did you think about using?', (2) 'Did you feel stoned?', (3) 'Were you in control of your- self?', (4) 'Did you feel restless?', (5) 'Did you need dope quickly?', (6) 'Did you feel the need to use dope?'	immediate
Huhn 2016	Participants rated their frequency of craving 4 times daily as responses to the question "Since last data entry, how FREQUENT are your drug CRAVINGS?" on a 100- point touch point continuum, with anchors at "No Cravings" to "Very Frequent". Intensity of drug craving was measured 4 times daily as responses to the question "Since last data entry, how INTENSE are your drug CRAVINGS?" with responses anchored "No Cravings" through "Very Intense." For morning assessments, the stem for each item took the form of "Since waking" rather than "Since last data entry". The product of the frequency and intensity of drug craving was created for each individual at each time point, and an average daily craving score was created for each participant.	averaged daily score across 4 reports
Kowalczyk 2015	Participants rated their craving in response to an electronic diary prompt at 4 randomly chosen times during typical waking hours; at each prompt, the participant was asked to report on stress, craving, mood, and drug-related environmental cues. Participants answered stress, craving, and mood items with the response options "NO!!", "no??", "yes??", and "YES!!". Drug-related cues were assessed by asking whether the cue had been encountered in the hour before the prompt.	immediate
Kowalczyk 2018	Participants were asked to rate their craving for cocaine, heroin/opiates, or tobacco. The response options were "YES!!", "yes??", "no??", and "NO!!." These responses were coded with the values 4, 3, 2, and 1, respectively.	immediate
Moran 2018	Participants rated how much they craved opioids and cocaine on a 1 to 5 scale (1 = not at all; 5 = extremely)	immediate
Preston 2017/2018	Participants rated their craving in response to the following prompts: "Right now, do you crave heroin/other opiates (Percocet, oxycodone, etc.)? 1-5 (1 = not at all, 5 = extremely); note that when it was a random prompt the question was "Within 5 min of the ED beeping/since you got to your presentation location, did you crave heroin/other opiates (Percocet, oxycodone, etc.)?"	immediate

*Note.* When possible, the exact text used to describe craving assessments is included in the table as represented by quotations. None of the above assessment tools were described as containing underlying factors/constructs and are therefore assumed to assess craving as a unidimensional construct.

Inventory, DDQ, HCQ, OCS), craving in the past day or week (i.e., BSCS, Crav-Hero Inventory, MCS, OCS, OCDUS, PCS, SCS), and general craving with no specific time frame (CCS, CBQ, CRS). Sometimes the same assessment asked about craving across various time frames (i.e., Crav-Hero Inventory, OCS: immediate/present and past day or week). In contrast, VAS assessments most commonly assessed immediate or present moment craving rather than general craving or past day/week periods (Table 5). Similarly, EMA studies also focused on immediate craving and such assessments usually occurred at random prompts 2–5 times per day (Table 6). Untitled assessments (Table 7) were described with such limited detail that the particular time frame for most of these outcomes was difficult to determine.

#### 3.4.5. Psychometric evaluation of opioid craving assessments

Eight studies evaluated the psychometric properties associated with the following 6 assessments: CBQ, Crav-Hero Inventory, DDQ, HCQ, OCDUS, and PCS (see Table 8) (Chang et al., 2011; Franken et al., 2002; Hassani-Abhari et al., 2016; Heinz et al., 2006; Küçükkarapinar et al., 2018; Maremmani et al., 2016, 2015; Tsui et al., 2014; Yen et al., 2016). All of these studies examined the factor structure of 6 craving assessments and results revealed that various translations of the CBQ and DDQ, and a Dutch version of the OCDUS, were supported by 3-factor models (Chang et al., 2011; Franken et al., 2002; Küçükkarapinar et al., 2018; Yen et al., 2016). Four-factor models were found for the HCQ and a Persian version of the OCDUS (Hassani-Abhari et al., 2016; Heinz et al., 2006). Finally, a single factor was revealed for the

**Table 7**  
Overview of Untitled Opioid Craving Assessments.

Publication	Description
Childress 1986	Participants rated their "craving for opiates" on a 4-point scale.
Fatseas 2011	Participants rated their "Desire to use heroin" and "Likely to use if heroin would be available" on a 10-point scale.
Hulse 2010	Participants rated their craving using a "10-item survey using a Likert scale scored 1 to 7 with Strongly Disagree (1) and Strongly Agree (7). All items were worded such that a higher rating indicated higher craving level and items were summed to give a total score, with a possible range of 10 to 70 for non-missing data."
Ilgen 2008	Participants rated their present moment craving on a "scale of 0–10, with 0 being no craving for your methadone dose at all and 10 being the worst possible craving for your methadone dose"
Jones 2018	Participants reported their "Desire and Urge for heroin".
Powell 1993a	Participants rated their craving on a "9-point scale, on which 0 represented no desire at all for opiates and 8 represented the most intense craving imaginable."
Powell 1993b	Participants rated their craving on a 0-8 scale (assumed to be same assessment used in Powell et al., 1993a).
Shi 2018	Participants rated their craving on a scale ranging from 0 (none) to 9 (extremely).
Tsui 2016	Participants reported their craving: "On a scale of 0–10, please indicate how much craving you have experienced during the past week," with responses anchored at "0 = no craving at all" and "10-strongest craving ever". Participants were queried specifically about buprenorphine and methadone, as well as all other opioids (e.g., heroin, oxycodone, hydromorphone, etc.). Any response greater than zero for either question was considered positive for opioid craving; a dichotomous outcome (yes/no) was chosen as data were highly skewed and most subjects reported no craving (i.e., a score of "0")."
Quirós Aragón 2005	Participants rated their craving on a 0-100 point 'Craving Scale'.

*Note:* When possible, the exact text used to describe craving assessments is included in the table as represented by quotations. None of the above assessment tools were described as containing underlying factors/constructs and are therefore assumed to assess craving as a unidimensional construct.

**Table 8**  
Overview of Psychometric Studies.

Author Year	Population	Language	% male	Craving Assessment and Underlying Factors (as determined by factor analysis)	Reliability (results in parentheses)	Validity (results in parentheses)
Chang 2011	445 patients currently in methadone treatment	Chinese	87%	CBQ: 1) will power 2) compulsive behavior 3) negative coping	Internal consistency Cronbach's alpha by subscale: will power (0.88), compulsive behavior (0.81), negative coping (0.81) Test-retest reliability (tested for a subset of participants) ICC by subscale: will power (0.76), compulsive behavior (0.51), negative coping (0.64)	NR
Franken 2002*	102 patients currently in treatment (methadone or abstinence)	Dutch	80%	DDQ: 1) desire and intention 2) negative reinforcement 3) control OCDUS: 1) thoughts and interference 2) desire and control 3) resistance to thoughts and intention	Internal consistency DDQ* Cronbach's alpha by subscale: desire (0.81), negative reinforcement (0.84), control (0.37) and OCDUS* Cronbach's alpha by subscale: thoughts/interfere (0.90), desire and control (0.84), and resistance (0.41) Test-retest reliability DDQ ICC by subscale: desire (0.83), negative reinforcement (0.82), control (0.74) and OCDUS ICC by subscale: thoughts/interfere (0.79), desire and control (0.72), and resistance (0.79)	Convergent validity (VAS, DDQ, OCDUS)
Hassani-Abharian 2016*	131 patients currently in methadone treatment	Persian	100%	DDQ: 1) desire and intention to use drugs 2) negative reinforcement 3) drug abuse control OCDUS: 1) desire and mental preoccupation with drugs 2) effects of desire for drug and drug-related thoughts on patient's work and life 3) motivation, emotion, and lack of control 4) resistance to drug use	Internal consistency DDQ Cronbach's alpha by subscale: desire and intention (0.89), negative reinforcement (0.79), and drug abuse control (0.40) and OCDUS* Cronbach's alpha by subscale: desire (0.81), effects on thoughts (0.02), motivation (0.72), and resistance (0.45)	Convergent validity (DDQ and OCDUS)
Heinz 2006	101 outpatients currently on agonist treatment	English	67%	HCCQ: 1) desire 2) lack of self-efficacy 3) relief 4) compulsivity	NR	Convergent validity (VAS and HCCQ) Predictive validity
Kiçikkarapınar 2018	176 patients that recently completed opioid detoxification	Turkish	96%	CBQ: 1) psychophysical reactions to craving 2) weakness to cope with craving Craw-Hero Inventory (Single factor)	Internal consistency CBQ Cronbach's alpha by subscale: reactions (0.93) and weakness to cope (0.88)	NA
Maremmani 2015 and 2016	114 participants not currently in treatment	Italian	80%	Craw-Hero Inventory (Single factor)	Internal consistency (Craw-Hero Inventory Cronbach's alpha = 0.97)	NA
Tsui 2014	147 patients currently in buprenorphine treatment	English	76%	PCS (Single factor)	Internal consistency (PCS Cronbach's alpha = 0.88)	Convergent validity (PCS and DDQ) Predictive validity
Yen 2016	314 patients currently in methadone treatment	Chinese	89%	DDQ: 1) thoughts about heroin and interference, 2) desire and control, 3) resistance to thoughts and intention	Internal consistency DDQ Cronbach's alpha across subscales: control (0.72), negative reinforcement (0.84), and desire and intention (0.88)	Convergent validity (VAS and OCDUS)

Note: Craving Beliefs Questionnaire (CBQ); Desires for Drug Questionnaire (DDQ); Heroin Craving Questionnaire (HCCQ); ICC, interclass correlation coefficient; NR, not reported (outcome was not assessed); Obsessive Compulsive Drug Use Scale (OCDUS); Penn Craving Scale (PCS); Visual Analogue Scale (VAS) (a statistic used to evaluate test-retest reliability). Asterisk (\*) indicates studies that recommended removing an item due to low internal consistency.

Crav-Hero Inventory and the PCS (Maremmanni et al., 2016, 2015; Tsui et al., 2014).

The categories represented across the assessments that determined multiple underlying factors (as determined by factor analysis) are listed in Table 8 and can be generally categorized into the following 3 underlying constructs:

- **Control** (i.e., will power, ability to cope with craving, degree of control over use, compulsivity, self-efficacy, resistance to drug use),
- **Negative reinforcement** (i.e., relief from negative states or feelings), and,
- **Thoughts/preoccupation with craving** (i.e., psychological reactions to craving, desire, intention to use, thoughts and interference, mental preoccupation with drugs, effects of desire for drug and drug-related thoughts on patient's work and life, resistance to thoughts and intention).

However, the above construct categories do not account for the Crav-Hero Inventory and PCS craving assessments, which were not reported to have factor analysis results consistent with underlying constructs (Table 8). Thus, it could be the case that there are other additional, unique factors associated with craving that are not represented by the above control-, negative reinforcement-, or thought-related constructs.

**3.4.5.1. Reliability.** Estimates of reliability were reported for a subset of the craving assessments and included Cronbach's  $\alpha$  (a measure of internal consistency) and intraclass correlation coefficient (ICC; a measure of test-retest reliability). Seven studies examined the internal consistency of 5 craving assessments and results revealed that Cronbach's  $\alpha$  values ranged from low to high across measures (moderate to high reliability is reflected by  $\alpha$  levels  $> 0.70$ ; Cortina, 1993): CBQ (0.81-0.93; Chang et al., 2011; Küçükkarapinar et al., 2018), Crav-Hero Inventory (0.97; Maremmanni et al., 2016, 2015), DDQ (0.40 – 0.88; Franken et al., 2002; Hassani-Abharian et al., 2016; Yen et al., 2016), OCDUS (0.41 – 0.91; Franken et al., 2002; Hassani-Abharian et al., 2016), and PCS (0.88; Tsui et al., 2014). Importantly, as represented in Table 8, alpha levels for some subscales of the DDQ and OCDUS were low, prompting researchers to suggest the removal of some items. Franken and colleagues (2002) recommended that item 7 be deleted from the DDQ due to a low alpha of 0.37 for the control subscale ("I would accept heroin now if it was offered") and item 10 be deleted from the 'resistance to thoughts and intention' subscale of the OCDUS due to an alpha of 0.41 ("If you were prevented from using heroin when you desired it, how anxious or upset would you become?"). In contrast, Hassani-Abharian and colleagues (2016) did not exclude any items from the DDQ after examination of alpha levels despite a low value for the control subscale (0.40), but did remove an item from the OCDUS after examination of the alpha levels (Item 4; How much distress or disturbance do these thoughts relate to heroin use?).

In addition, 2 studies examined the test-retest reliability of the CBQ, OCDUS, and DDQ for a subset of participants (46 of 445 respondents in an analysis of the CBQ, Chang et al., 2011; 18 of 102 respondents in an analysis of the DDQ and OCDUS, Franken et al., 2002). Results revealed that ICC values were representative of low to high internal consistency depending on the subscale (ICC  $> 0.75$  considered to be high; Cicchetti, 1994), as follows: 0.80 for the CBQ (values ranged from 0.51 – 0.76 for subscales of the CBQ, 0.74 - 0.83 for subscales of the DDQ, and 0.72 - 0.79 for subscales of the OCDUS).

**3.4.5.2. Validity.** Five studies examined the convergent validity of craving assessments, or the degree to which similar craving assessments correlated with each other (Franken et al., 2002; Hassani-Abharian et al., 2016; Heinz et al., 2006; Tsui et al., 2014; Yen et al., 2016) (Table 8). The majority of these studies examined the

DDQ relative to other assessments including the OCDUS (Franken et al., 2002; Hassani-Abharian et al., 2016), VAS (Franken et al., 2002; Yen et al., 2016), and PCS (Tsu et al., 2014). Of these studies, 1 reported that the DDQ significantly correlated with both the OCDUS and VAS, likewise the DDQ and VAS were significantly correlated with each other, suggesting overlap across all assessments ( $r$ s ranged from 0.23 to 0.76,  $P$ s  $< 0.05$ ) (Franken et al., 2002). Franken and colleagues (2002) did not address whether certain subscales of the OCDUS and DDQ might be more closely related than others as found in other studies (see below). Turkish versions of the DDQ and OCDUS were also significantly correlated across all subscales of the DDQ and 3 of 4 subscales of the OCDUS ( $r$ s = .20 to .67;  $P$ s  $< 0.05$ ) Hassani-Abharian et al., 2016. However, that study found that a 4<sup>th</sup> subscale of the OCDUS ('resistance to drug use,' a similar construct to what other researchers referred to as 'control') was not significantly related to the DDQ ( $r$ s  $\leq 0.09$ ,  $P$ s  $> 0.05$ ).

Interestingly, two other studies found that a 'control' subscale of the DDQ did not correspond to other assessment tools. One study found that 2 of 3 subscales of a Chinese version of the DDQ correlated with a VAS assessment of craving ('thoughts' and 'resistance';  $r$ s 0.50 to 0.68;  $P$ s  $< 0.001$ ), but with a much less robust relationship for the 'control' subscale of the DDQ ( $r = -0.17$ ;  $P < 0.01$ ; Yen et al., 2016). The authors of this study hypothesized that the significant, but less robust relationship between the 'control' subscale and other subscales of this assessment could be due to cultural differences related to the concept of 'self-control' between the Chinese participants in this study and participants in other studies from different cultures/geographic regions (e.g., Dutch participants; Franken et al., 2002). However, a US-based study examining the relationship between an English version of the DDQ and the PCS once again found that 2 subscales of the DDQ subscales strongly correlated with the PCS ( $r$ s = 0.44 to 0.66;  $P$ s  $< 0.01$ ), but not a control subscale ( $r = 0.17$ ,  $P < 0.05$ ; Tsui et al., 2014).

An additional study examined the convergent validity of the brief and full versions of the HCQ along with 3 VAS craving assessments (Heinz et al., 2006). Findings revealed that the brief version of the HCQ was highly correlated with all 3 VASs ( $r$ s = 0.52 to 0.55,  $P$ s  $< 0.01$ ) and was also highly correlated with the full version of the HCQ ( $r = 0.57$ ;  $P < 0.01$ ). In contrast, the full version of the HCQ was not correlated with the VAS assessments prompting the authors to speculate this version of the HCQ might be a more comprehensive assessment of craving compared to the brief HCQ or a VAS (Heinz et al., 2006).

In addition to convergent validity, 2 studies examined the predictive validity of craving as reported on the HCQ, PCS, DDQ, and VAS assessments (Table 8; Heinz et al., 2006; Tsui et al., 2014). The first study, a 12-week agonist outpatient treatment trial that did not include a placebo control, found a counterintuitive relationship between craving and treatment outcomes. That is, greater opioid craving at baseline on the full version of the HCQ and on 2 VAS assessments (i.e., ratings of 'craving' and 'wanting') was associated with less opioid use during agonist treatment, as represented by an increase in negative opioid urines;  $r$ s = 0.26 to .031;  $P$ s  $< 0.01$ ; Heinz et al., 2006). In contrast, the same study found that the brief version of the HCQ (14-items) had no relationship with illicit opioid use. A separate study found that higher opioid craving at baseline, as assessed by the PCS and the 'desire/intention subscale' of the DDQ, predicted more opioid positive urines during 3 months of buprenorphine treatment (Tsui et al., 2014). A closer analysis of the PCS (the focus of the study) found that with each 1-point increase in scores (7-point scale) was associated with a significant increase in the likelihood of opioid use at the next assessment (OR = 1.27, 95% CI 1.08–1.49;  $P < 0.01$ ). Neither study examined treatment responsiveness, that is, whether different treatment groups differed significantly in craving outcomes.

### 3.5. Reviews of opioid craving in OUD treatment studies

Two systematic reviews that examined craving as a key outcome in

studies of OUD were included for review (Fareed et al., 2010, 2011). One review included 16 studies that assessed the effects of methadone on craving (Fareed et al., 2011), while the other review included 12 studies that assessed the effects of other, non-methadone pharmacological treatments on craving (e.g., buprenorphine, naltrexone, haloperidol) (Fareed et al., 2010). Both reviews were conducted by the same research team and the majority of publications included for review were observational designs examining craving in response to agonist treatment (e.g., methadone, buprenorphine) without a placebo control comparison. Both reviews catalogued the type of craving outcome assessments used across studies, and findings paralleled those of the present review with most studies utilizing VAS craving assessments, and a subset using multi-factor outcomes (e.g., HCQ, DDQ). An additional consideration is that these reviews typically treated craving as a single, unidimensional construct and did not address the varying underlying constructs that are connected to craving and its relationship with drug use behavior (e.g., control, negative reinforcement, thoughts/pre-occupation).

Overall, Fareed and colleagues (2010; 2011) noted that there was considerable variability across studies making it difficult to draw clear conclusions. For example, the review of methadone and craving reported that of the 16 studies included, 7 demonstrated a methadone-related reduction in craving, 8 found no effect of methadone on craving, and 1 study found that methadone actually increased craving (Curran et al., 1999; Fareed et al., 2011). In addition, 7 of the 28 studies reviewed by Fareed and colleagues (2010; 2011) examined whether craving was reduced in a placebo condition compared to an active treatment condition (a measure of treatment responsiveness; Dworkin et al., 2005). The type of treatments examined and research findings varied considerably across these studies. Five studies found that five different active treatment conditions (rapamycin, tetrodotoxin, memantine, buprenorphine, and hydromorphone) reduced craving compared to placebo (Comer and Sullivan, 2007; Fudala et al., 2003; Greenwald et al., 1999; Shi et al., 2009a,b). In addition, one study found that haloperidol had no effect on craving compared to placebo (Franken et al., 2004) and another found an increase in craving after methadone compared to placebo (Curran et al., 1999). None of these studies examined whether craving accounted for the relationship between a treatment intervention and other outcomes such as opioid use behavior (e.g., a mediation analysis; Baron and Kenny, 1986). In addition, none of the studies examined whether craving moderated, or influenced the effect of treatment on other study outcomes such as quality of life (craving as a moderator; Baron and Kenny, 1986; Dworkin and Edwards, 2017).

#### 4. Discussion

The present scoping review was designed to answer the following key questions related to the role of craving in OUD:

##### 4.1. What assessments of craving have been used in studies of OUD?

The VAS was the most common opioid craving assessment and was represented in 41 of the 85 studies included for review (most of these studies were either experimental or randomized-controlled studies). The VAS assessments were most often single-items that addressed 'immediate/present moment' craving with various prompts and response formats (Table 5). While single-item (unidimensional) assessments are considered time efficient and high in face validity, they have been criticized for not being reliable or capable of capturing multiple underlying constructs associated with craving (e.g., intensity, frequency, self-control; Franken et al., 2002; Heinz et al., 2006; McMillan and Gilmore-Thomas, 1996; Tiffany, 1997). For example, some researchers have argued that the validity and reliability of craving assessments can be increased by including multiple items rather than a single-item (Sayette et al., 2000; Shiffman et al., 2004). These drawbacks have

prompted the creation of several multi-factor assessments of opioid craving of which 12 were identified in the present review (Table 4). The most common multi-factor assessments identified in the present review were the Desires for Drug Questionnaire (DDQ, 12 studies), Heroin Craving Questionnaire (HCQ, 10 studies), and Obsessive-Compulsive Drug Use Scale (OCDUS, 10 studies). An additional type of craving assessment included those found in diary or EMA study designs. These assessments tended to include brief prompts suitable for use on mobile devices that asked participants to report their immediate/present moment craving. Lastly, 10 of the studies reviewed included craving assessments that were not labeled with a title and were only described with limited information making it difficult to categorize them into any of the above craving assessment categories (Table 7).

##### 4.2. Have assessments of opioid craving been evaluated for their psychometric properties (I.E., reliability and validity)?

The accurate measurement of any hypothetical construct, including opioid craving, requires that assessment tools meet specific psychometric standards including reliability, validity, and sensitivity to change (Haynes et al., 2018; Sayette et al., 2000; Smith and Combs, 2010; Tiffany et al., 2000). These psychometric standards help to ensure the accuracy of an instrument so that it can be trusted to inform clinical assessments and treatment decisions (Haynes et al., 2018). Therefore, the scientific and clinical value of the craving assessments identified in the present review is dependent on the degree to which such assessments have been evaluated for their ability to consistently measure (reliability) what they are intended to measure (validity). Relatedly, and a key motivator in preparing the present review, are FDA guidance recommendations that describe approaches for developing and qualifying drug development tools (FDA, 2009, 2010). These guidance documents emphasize key psychometric outcomes that should be evaluated when developing assessment tools such as those described in the present review (FDA, 2009; 2010; see also section 4.4).

Unfortunately, only 6 of the 15 opioid craving assessments identified in the present review were psychometrically evaluated for their subscale components/factor structure, reliability, and/or validity (i.e., CBQ, Crav-Hero Inventory, DDQ, HCQ, OCDUS, and PCS; Table 8). Inspection of the factor analysis loadings across these assessments yielded three underlying constructs associated with opioid craving: (1) control (e.g., will power, compulsivity), (2) negative reinforcement (e.g., relief from negative states or feelings), and, (3) thoughts/pre-occupation (e.g., intrusive thoughts about drug use). However, the degree to which these hypothesized constructs fully capture the experience of opioid craving is not clear given that only 6 of the 85 studies included for review contributed to these findings. In addition, the ability to draw inferences across studies is limited if the assessments used to evaluate opioid craving vary in the underlying constructs that they examine, as well as in the language and cultures for which these questionnaires were tested (e.g., Yen et al., 2016).

Additional psychometric outcomes that were included in a subset of studies included internal consistency (as measured by Cronbach's alpha) and test-retest reliability (consistency over time; as measured by ICC). Findings were limited for these outcomes with low internal consistency found for some subscales of the DDQ and OCDUS (see Section 2.4.5). In addition, test-retest reliability analyses were limited to only two studies, were conducted on only a small subset of the overall sample, and were low in some cases (e.g., CBQ compulsive behavior subscale ICC = 0.51; Chang et al., 2011). However, some studies reported that subscales of the DDQ and OCDUS had low reliability and the deletion of particular items/questions improved these reliability estimates (Table 8).

Similarly, convergent validity (or the relationship between similar assessments of craving) was high across most craving outcomes, with a few exceptions. For example, the 'control' subscale of the DDQ and the full version of the HCQ did not correlate strongly with other craving

assessments in some of the studies (Heinz et al., 2006; Yen et al., 2016; Tsui et al., 2014). The lack of overlap between assessments suggests that craving is a multi-faceted concept that single-item assessments might not be equipped to fully capture (Heinz et al., 2006). Lastly, 2 of the psychometric studies included for review attempted to evaluate craving as a predictor of opioid positive urines (i.e., predictive validity; Heinz et al., 2006; Tsui et al., 2014). Findings were inconsistent across studies with 1 yielding the counterintuitive finding that higher craving at baseline predicted less illicit opioid use (Heinz et al., 2006), whereas a separate study found lower craving at baseline predicted less use of opioids (Tsui et al., 2014). It is possible that findings differed across studies due to the various craving assessments that were included for evaluation (DDQ, HCQ, PCS).

#### 4.3. What are the research gaps/limitations related to currently available assessments of craving and OUD?

The main limitations associated with the opioid craving assessments identified in the present review relate to variability across studies in terms of the type of assessments and underlying constructs examined, as well as the limited number of assessments that had been critically evaluated for their psychometric properties. That is, numerous craving assessments were identified across studies ( $n = 15$ ) and they varied considerably in their structure (number of items and response formats), content (type of opioid assessed, language, factor structure), making it difficult to infer commonalities across study findings, and types of underlying craving factors examined, as noted by existing systematic reviews (Fareed et al., 2010, 2011). One practical reason for the varying types of opioid craving assessments may be that each study and clinical setting has unique demands that necessitate the use of differing outcomes (Hawker et al., 2011; Heinz et al., 2006; Pavlick et al., 2009). For example, brief assessments that require minimal time for completion, such as a VAS, might be best suited for naturalistic studies or cue-reactivity studies that require efficient, real-time reports of craving. Conversely, the assessment of craving in longer-term studies that involve clinical interventions might be a better setting for longer, multi-factor assessments that require more time for completion. These practical considerations are discussed in greater detail below.

A second limitation, noted previously, was the small number of studies that systematically evaluated the psychometric properties of craving outcomes including reliability, validity, and sensitivity to change. Most often, the craving assessments that were included in psychometric studies were evaluated for only a subset of such outcomes. In addition, the process for developing many of the craving assessments included for review was most often not reported including whether patient input was used when designing their format and content (a key step for ensuring content validity of an outcome assessment; FDA, 2009; 2010). Instead, many of the assessments reviewed evolved from those that had originally been developed for other substance use populations and had gone through several iterations before being applied to individuals diagnosed with OUD (e.g., DDQ, OCS, HCQ; Franken et al., 2002; Tiffany et al., 1993; Weiss et al., 1997). An additional consideration is that most of the studies included for review focused on heroin use in males who were currently in treatment (Table 8). Thus, the patient populations and treatment contexts in which many of the assessments were tested was narrow and not necessarily generalizable to all patients diagnosed with OUD (e.g., prescription opioid use; McHugh et al., 2014a, b; McHugh et al., 2016). It is possible that the psychometric properties of craving assessments could vary depending on these contextual factors and should be accounted for in future research.

#### 4.4. Are there any existing reliable and valid assessments of craving that can be recommended for use in studies of OUD and its treatment?

As stated above, only a limited number of the opioid craving

assessments in the present review had been evaluated for key psychometric properties including reliability, validity, and sensitivity to change. Some of those assessments, such as the DDQ, HCQ, and OCDUS, have the potential to meet rigorous psychometric standards such as those proposed by the FDA in guidelines for clinical outcome assessment (COA) qualification and patient reported outcome development (FDA, 2009; 2010). In combination, these FDA guidance documents detail the process for developing a reliable and valid outcome assessment tool with an emphasis on gaining patient feedback through qualitative research studies to establish content validity. Importantly, if an opioid craving assessment were approved through this FDA outcome qualification process, then the assessment tool could be made publicly available and used to facilitate treatment innovation across various stages of drug development (e.g., laboratory-based, cue-reactivity studies, randomized-controlled trials, surveillance studies).

However, a 'one-size-fits-all' opioid craving assessment is likely not useful across all research and treatment settings, as has been noted elsewhere (e.g., Tiffany et al., 2000). Thus, it may be necessary to consider the development of multiple opioid craving assessment tools that address these differences. For example, clinicians seeking to tailor OUD treatments early in a patient's recovery might find that single-item assessments that address present moment craving are most efficient for quickly collecting patient information in constrained clinical settings. In contrast, a patient who has been in recovery for an extended amount of time might be better served by a craving assessment that reviews more general craving across a range of situations. For these reasons it is challenging to recommend a 'gold-standard' assessment tool to researchers or clinicians that should be used consistently across studies. Researchers currently engaging or planning to engage in research examining craving and OUD should consider including both a brief craving assessment, such as a single-item VAS, as well as a multi-factor assessment that has been evaluated in some capacity for its reliability and validity (e.g., DDQ, HCQ, OCDUS). The choice of one particular multi-factor assessment tool over another, at this stage in craving assessment development, is likely best informed by the goals of the study and study-specific factors including time demands and whether the assessment tool measures present moment craving or general craving over time.

#### 4.5. Limitations of present review

The present scoping review was designed to give a general overview of craving assessments that have been used in the published literature examining OUD. As a consequence, the review does not critically evaluate whether craving can function as a clinically meaningful predictor of treatment outcome or how such a relationship might be influenced by patient-specific variables (motivation to stop drug use, mood, or personality) or environmental variables (stress- or drug-related cues). Similarly, this review did not critically examine how subjective reports of craving might relate to more indirect, nonverbal measures of craving including behavioral (e.g., multiple choice procedure), psychophysiological (e.g., heart rate, startle response), cognitive (e.g., attentional bias), cue-reactivity, and neuroimaging assessment tools (Badger et al., 2007; Field et al., 2009; Huhn et al., 2018; MacKillop et al., 2010; Skinner and Aubin, 2010). While these nonverbal assessment tools provide valuable information related to drug use behavior and can be modeled in animal studies (Rosenberg, 2009; Wilson and Sayette, 2014), they have also been criticized for their lack of specificity and connection to patient-reports of craving (Ooteman et al., 2006; Gawronski et al., 2007).

An additional consideration is the relationship between opioid craving and craving for other substances. As noted in the Introduction, the first formal attempt to define and measure craving was organized by the WHO in 1954 with a focus on alcohol use (WHO, 1955). Since that time, there has been a considerable amount of research examining craving and substance use, which has led to the development of at least

9 alcohol, 5 cocaine, 4 cigarette/nicotine, and 2 marijuana craving assessment questionnaires (Ray et al., 2013; Rosenberg, 2009). Additionally, assessments of craving have been developed outside the field of drug abuse for topics such as eating behavior and obesity (Potenza and Grilo, 2014; Rodríguez-Martín and Meule, 2015) and generic craving assessments have been developed for use across a range of behaviors (e.g., The Craving Experience Questionnaire; May et al., 2014). Overall, research suggests that craving can differ depending on the type of drug or behavior being examined, thereby supporting continued use of drug-specific craving assessments such as those highlighted in the present review (Serre et al., 2018; Carter and Tiffany, 1999; Fatsas et al., 2015; Heinz et al., 2006; Mezinis et al., 1998).

A last limitation of the present review is the possibility that relevant studies might have been excluded because they did not meet inclusion criteria, such as having a sample size below the cutoff of 20 participants (Curran et al., 1999; Greenwald, 2002, 2005; Sideroff et al., 1978; Wolpe, 1965; Wolpe et al., 1980). However, as reflected in Table 1, the craving assessment tools used in the studies excluded due to small sample size overlapped with those identified in the present review. Thus, it is unlikely that the present review failed to identify common craving assessment tools in the existing literature.

#### 4.6. Conclusions and recommendations

This scoping review identified a large body of work that has examined craving as a key outcome of interest in studies of OUD. However, as noted, the assessments included in these studies have not been rigorously evaluated for their psychometric properties making it difficult to determine if they could be reliable and valid outcome assessment tools in studies of OUD and its treatment. Importantly, the results of this review suggest a disconnect between initiatives to develop novel OUD treatments with craving as a clinical target, such as those proposed by the FDA in recent public comments, and the availability of psychometrically sound craving outcome assessment that can guide such research (Food and Drug Administration, 2018b).

However, despite these shortcomings, the subjective experience of craving continues to be a prominent and common clinical phenomenon for many individuals diagnosed with OUD (Food and Drug Administration, 2018a). For this reason, we suggest that there is a critical need to develop and establish a psychometrically sound assessment(s) of opioid craving that can be incorporated into various types of OUD research studies including acute, laboratory studies and longer term, placebo-controlled treatment studies. Furthermore, we recommend that the development of such an assessment be guided by direct input from patients in order to establish content validity and align with FDA guidance related to patient-reported outcomes and clinical outcome assessment (COA) qualification (Food and Drug Administration, 2009, 2010). These opioid craving assessment tools could not only function as primary endpoints in treatment trials but could also function as mediator or moderator variables in predicting the effects of treatment on other primary endpoints including opioid use behavior or retention in treatment. Efforts to refine and/or develop a psychometrically sound opioid craving assessment tool would be a valuable contribution to the field of substance use treatment, as it would aid in the potential development of novel OUD treatment interventions, could help to better elucidate the biologic underpinnings of compelled drug use, and support ongoing efforts to address the devastating consequences of the opioid crisis.

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#### Contributors

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#### Declaration of Competing Interest

Betha A. Kleykamp, PhD, was previously employed by the healthcare consulting firm, Pinney Associates from 2014 to 2018. During her employment, she provided consulting advices to pharmaceutical companies, the e-cigarette company NJOY, and the tobacco company, RAI Services Company on non-combustible tobacco products including e-cigarettes. All work associated with this manuscript was completed after she joined the University of Rochester School of Medicine/ACTTION and thus is unaffiliated with Pinney Associates.

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Marta De Santis, PhD, Ivan D. Montoya, MPH, MD, Tanya Ramey, MD, Robert Walsh, BS, are employees of NIDA and have no disclosures to declare.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugalcdep.2019.107639>.

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