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Effects of buprenorphine on opioid craving in comparison to other medications for opioid use disorder: A systematic review of randomized controlled trials

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ABSTRACT

Background: Craving is a distressing symptom of opioid use disorder (OUD) that can be alleviated with medications for OUD (MOUD). Buprenorphine is an effective MOUD that may suppress craving; however, treatment discontinuation and resumed opioid use is common during the early phases of treatment. More information on the craving response through the high-risk period of initiating buprenorphine may provide meaningful information on how to better target craving, which in turn may enhance outcomes. This systematic review investigated buprenorphine doses and formulations on craving during the induction and maintenance phases of treatment, and for context also compared the craving response to other MOUD (i.e., methadone, extended-release naltrexone [XR-NTX]).

Methods: PubMed, PsycInfo, Embase, and Cochrane Central databases were searched for randomized trials of buprenorphine versus placebo, various buprenorphine formulations/doses, or other MOUD that included a measure of opioid craving.

Results: A total of 10 studies were selected for inclusion. Buprenorphine and buprenorphine/naloxone (BUP/NAL) were each associated with lower craving than placebo over time. Craving was greater among those prescribed lower versus higher buprenorphine doses. In comparison to other MOUD, buprenorphine or BUP/NAL was linked to greater craving than methadone in 3 of the 6 studies. BUP/NAL was associated with greater reported craving than XR-NTX.

Discussion: Craving is reduced over time with buprenorphine and BUP/NAL, although other MOUD may provide greater reductions in craving. Although there is currently considerable variability in the measurement of craving, it may be a valuable concept to address with individuals receiving MOUD, especially early in treatment.

1. Introduction

The opioid epidemic is a significant public health crisis associated with excess morbidity and mortality within the United States (Hickton & Leary, 2015). Opioid overdose deaths increased by 35% from 2020 to 2021, with over 75,000 opioid overdose deaths in 2021 (Centers for Disease Control and Prevention, 2021). The economic burden of opioid use disorder (OUD) and opioid-related overdose is approximately $1.02 trillion annually, largely due to opioid overdose fatalities and reductions in quality of life from OUD (Florence, Luo, & Rice, 2021). Thus, effective OUD treatments are critical to combat this costly and deadly epidemic (Blanco & Volkow, 2019; Sordo et al., 2017).

Food and Drug Administration (FDA)-approved medications for OUD (MOUD) are the recommended first-line OUD treatment, which include the full opioid agonist methadone, the partial agonist buprenorphine, and the extended-release injectable formulation of the antagonist naltrexone (XR-NTX). All three MOUD have demonstrated enhanced treatment engagement, survival rates, and psychosocial functioning

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(Ling, Nadipelli, Aldridge, et al., 2020; Substance Abuse and Mental Health Services Administration [SAMHSA], 2021; Thomas et al., 2014). Buprenorphine has several advantages over XR-NTX and methadone, and its prescribing has trended upwards in recent years (Olfson, Zhang, Schoenbaum, & King, 2020; Roehler, Guy, & Jones, 2020). First, unlike methadone, buprenorphine is not required to be dispensed through opioid treatment programs and can be prescribed in any clinical setting by prescribers with Drug Enforcement Agency certification (SAMHSA, 2021). Second, buprenorphine is combined with the antagonist naloxone to deter misuse of the medication (Center for Substance Abuse Treatment, 2004; SAMHSA, 2021). Third, as a partial opioid agonist, buprenorphine has a greater safety profile than full agonists such as methadone (Fairley et al., 2021; Thomas et al., 2014); therefore, buprenorphine may be a preferred MOUD for patients with multiple health comorbidities, as it has less side effects and drug-drug interactions than methadone (SAMHSA, 2021). Fourth, buprenorphine, which is available as a generic prescription and prescribed in public health clinics, may be more cost effective than XR-NTX, which is currently not available off patent in the U.S. (Jackson, Mandell, Johnson, Chatterjee, & Vanness, 2015).

A major concern with buprenorphine is the premature discontinuation and/or resumed opioid use in the initial weeks of initiation (Hser et al., 2016; Ling, Nadipelli, Solem, et al., 2020). In fact, nearly a quarter of patients initiating buprenorphine discontinue treatment within the first week, with up to 64% discontinuing services by 6 months (Stein et al., 2010; Timko, Schultz, Cucciare, Vittorio, & Garrison-Diehn, 2016). Therefore, it is crucial to identify and better understand modifiable factors that may impact early buprenorphine outcomes. Craving, the subjective desire or urge to use a drug (Drummond, 2001; Sayette et al., 2000), is one modifiable factor that may be important for exploration, given that stress enhances craving (MacLean, Armstrong, & Sofuoglu, 2019), and the initiation of buprenorphine may be a particularly challenging and stressful time for patients. In addition, craving is familiar to both practitioners and patients, appears to vary among patients with OUD, can be targeted in treatment, has been added to the substance use disorders section of DSM-5, and has been increasingly incorporated as an outcome measure in clinical trials (Association, 2013; Northrup et al., 2015; Skinner & Aubin, 2010; Tiffany, Friedman, Greenfield, Hasin, & Jackson, 2012). Although craving may decrease with higher doses of buprenorphine (Ahmadi, Jahromi, Ghahremani, & London, 2018), it is not completely eliminated (Fareed, Vayalapalli, Casarella, Amar, & Drexler, 2010) and may affect outcomes. The few studies that have examined the relationship between craving and subsequent opioid use during buprenorphine treatment have found no relationship (Dreifuss et al., 2013) or a positive association between craving and opioid use (Baxley, Weinstock, Lustman, & Garner, 2019; Messina & Worley, 2019; Tsui, Anderson, Strong, & Stein, 2014),

To date, systematic reviews have explored craving in the context of MOUD, though the primary focus of these reviews has been on craving during methadone treatment (Fareed, Vayalapalli, Stout, et al., 2010), the impact of stress on craving and MOUD outcomes (MacLean et al., 2019), opioid craving assessment (Kleykamp et al., 2019), or a combination of FDA and non-FDA-approved MOUD (with the exception of methadone) on craving (Fareed, Vayalapalli, Casarella, et al., 2010). The current literature is lacking a review synthesizing buprenorphine's impact on craving during the early phases of treatment, as well as a comparison of buprenorphine to all other FDA-approved MOUD on the outcome of craving. Therefore, the present review had two exploratory aims: 1) to examine how the initiation and maintenance of buprenorphine impacts opioid craving, and 2) determine if buprenorphine is more or less effective than other FDA-approved MOUD in reducing opioid craving at the onset of treatment. Findings may provide meaningful information on how to better target craving, which in turn may enhance buprenorphine outcomes. Further, findings may assist prescribers in choosing the best MOUD for their patients who report significant craving.

2. Method

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009) were utilized to conduct and report findings of this systematic review.

2.1. Eligibility criteria

The inclusion criteria for the review were: 1) participants had a diagnosis of OUD; 2) participants completed self-reported opioid craving measures; 3) participants were prescribed any formulation of buprenorphine for OUD; 4) participants were induced on buprenorphine during the study (to capture the full trajectory of opioid craving beginning with the first dose or prior to the first dose); 5) randomized controlled designs that compared FDA-approved MOUD (i.e., buprenorphine formulations, XR-NTX, methadone). Given that detoxification is generally not recommended for the treatment of OUD (SAMHSA, 2021), we excluded studies that utilized buprenorphine or BUP/NAL for detoxification-only (e.g., high dose detoxification; Assadi, Hafezi, Mokri, Razzaghi, & Ghaeli, 2004). We chose to focus on randomized trials of buprenorphine or BUP/NAL since these experimental designs tend to reduce bias by balancing observed and unobserved differences between treatment groups; thus, any differences that emerge between groups can be attributed to the treatment (Hariton & Locascio, 2018).

2.2. Search strategy and selection process

In September of 2021, PubMed, PsychInfo, Embase, and Cochrane Central were searched (see **Appendix A**) and included variations of the following concepts: opioid use disorder, buprenorphine, randomized controlled trial, and craving. The search strategy was not restricted by date. Google scholar and references from relevant articles were manually searched and screened to capture all pertinent studies not identified in the database searches. Identified studies were uploaded to a systematic review software program, DistillerSR (DistillerSR, 2021), where duplicates were identified and manually removed. Next, study titles and abstracts were screened. If an article included more than one study or separately analyzed phases of treatment, each study or phase was considered separately for inclusion. The studies that appeared relevant were independently reviewed in full-text (by CB and JR), and any discrepancies on study inclusion were discussed until consensus was met.

2.3. Data extraction

Data was extracted using customized forms in DistillerSR to collect: authors, title of study, year of publication, study location, design, duration, intervention, sample size, sample characteristics, craving (including these pre-specified components: craving definition, timeframe, measurement, frequency of measure administration, craving differences between interventions), and percentage of buprenorphine or BUP/NAL treatment discontinuation at study completion. Considerable variability in the measurement of the type of opioid craving, timeframe, and measure precluded the conduct of a meta-analytic integration (Kleykamp et al., 2019).

2.4. Risk of bias assessment

The risk of bias assessment utilized was the Cochrane Risk of Bias Assessment (Higgins & Green, 2008), which evaluates the quality of RCTs and potential study biases. Data collected and assessed included the following: allocation sequence generation, allocation concealment, parameters related to blinding, loss of outcome data, selective outcome reporting, and other sources of bias. The extracted data and risk of bias assessments were conducted and reviewed independently (by CB and JR) for reliability purposes.

3. Results

3.1. Study selection

In total, 2099 records were identified through database searches and 1 from manual searches (see Fig. 1). Duplicates were removed resulting in a total of 1414 records subsequently screened by their title and abstract. Of the records screened, 1348 records were excluded primarily for reasons such as the studies did not involve OUD treatment, the prescription of buprenorphine, or a randomized study design comparing buprenorphine to other MOUD. Next, the remaining 66 full-text articles were reviewed and 10 met inclusion criteria (see Fig. 1 for PRISMA diagram; Moher, Liberati, Tetzlaff, Altman, & The, 2009).

3.2. Study characteristics

Individual characteristics of the 10 studies meeting inclusion criteria are presented in Table 1. Half of the studies ($n = 5$) were conducted in the United States. Studies are presented in ascending order of the duration of the study, ranging from 2 to 52 weeks. The overall sample included 2468 participants, with study sample sizes ranging from 19 to 736 participants. The mean age of the sample was 34.2 years, and 76.75% were male and 67.92% were White; 2 studies did not report race. One study investigated MOUD among people who inject buprenorphine (Otiashvili et al., 2013).

3.2.1. Interventions

The study designs were either double blind (n = 5) or open-label (n = 5) trials. Only one of the double-blind studies was placebo-controlled. Most of the studies ($n = 6$) compared buprenorphine or BUP/NAL to methadone. Two of the studies compared buprenorphine formulations (buprenorphine vs. BUP/NAL) or buprenorphine doses. Two studies examined BUP/NAL to XR-NTX. Regarding induction procedures, half of the studies required the participants to be in opioid withdrawal. Specifically, Law et al. (2017) required participants to abstain $\geq$ 12 h from heroin and $\geq$ 20 h from methadone, while Nava, Manzato, Leonardi, and Lucchini (2008) and Neumann, Blondell, Hoopsick, and Homish (2020) asked participants to abstain from opioids the day or midnight before their induction visit, respectively. Lee et al. (2018) required participants assigned to XR-NTX to abstain from opioids for 3 days and those assigned to BUP/NAL to abstain until withdrawal symptoms emerged. Similarly, Ling, Wesson, Charuvastra, and Klett (1996) had participants complete a withdrawal checklist and be evaluated by a physician prior to starting medication. One study required completion of inpatient detoxification prior to induction (Tanum & Solli, 2017). The remaining four studies did not describe the induction procedures (Fudala et al., 2003; Ling et al., 1998; Otiashvili et al., 2013; Petitjean et al., 2001).

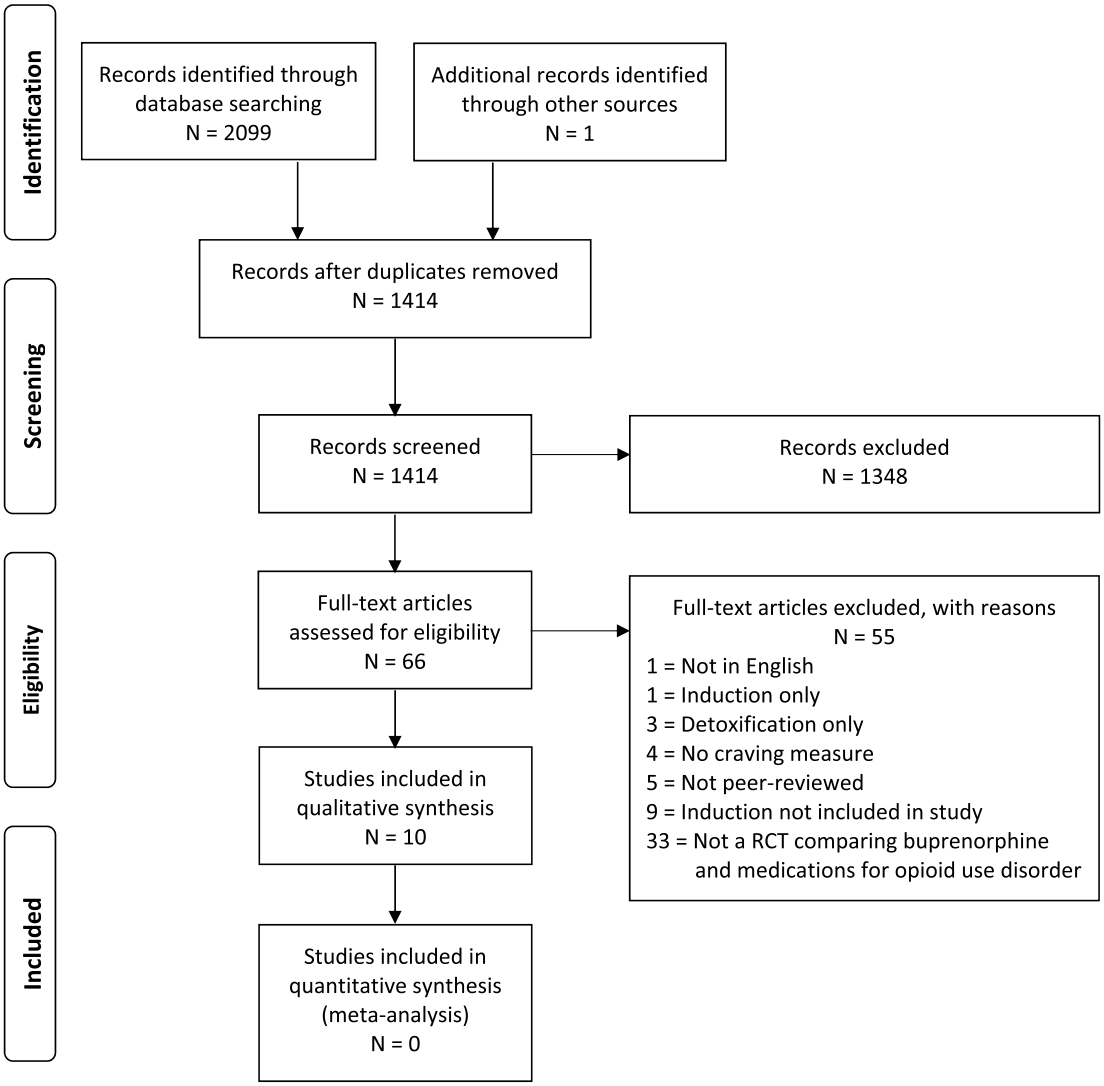

Fig. 1. PRISMA diagram.

Table 1
Randomized trials that investigated buprenorphine and opioid craving.

Study, Location	Duration (Weeks)	Sample Size (% Male, % White)	Design	Interventions	Treatment DC	Craving Definition, Time	Craving Measure	Craving Frequency of Assessment Administration	Craving Differences[a]
Law et al. (2017) (Phase 1) UK	2–6	BUP/NAL: 40 (77.5%, NR) MTD: 40 (65%, NR)	DB	BUP/NAL: sublingual tablet, 4 mg MTD: oral, 30 mg	BUP/NAL: 25% MTD: 25%	Opiate, last 24-hour	Opiate Craving Scale	NR	BUP/NAL > MTD
Fudala et al. (2003) (Study 1) USA	4	BUP: 105 (66.7%, 59.0%) BUP/NAL: 109 (62.4%, 59.6%) Placebo: 109 (65.1%, 64.2%)	DB, PC	BUP: sublingual tablet, 16 mg BUP/NAL: sublingual tablet, 16 mg Placebo	BUP: 3.8% BUP/NAL: 10.1% Placebo: 11%	Opiate, past 24-hour peak	VAS (0 = "no craving," 100 = "most intense craving I ever had")	Baseline, 1x/week	BUP < placebo BUP/NAL < placebo
Petitjean et al. (2001) Switzerland	6	BUP: 27 (81%, 67% Swiss) MTD: 31 (84%, 71% Swiss)	DB	BUP: sublingual tablet, 8–16 mg MTD: oral, 30–120 mg	BUP: 44.4% MTD: 9.7%	Heroin, past 7-day peak	VAS (0 = "no craving," 100 = "maximum craving ever experienced")	1x/week	BUP = MTD
Tanum and Solli (2017) Norway	12	BUP/NAL: 79 (68.4%, 88.6%) XR-NTX: 80 (76.3%, 90.0%)	OL	BUP/NAL: sublingual, 4–24 mg XR-NTX: injection, 380 mg/ every 28 days	BUP/NAL: 38% XR-NTX: 30%	Heroin, NR	VAS (0 = "none," 10 = "very strong")	Weeks 4, 8, and 12	BUP/NAL > XR-NTX
Ling et al. (1998) USA	16	BUP 1mg: 185 (NR, NR) BUP 4mg: 182 (NR, NR) BUP 8mg: 188 (NR, NR) BUP 16mg: 181 (NR, NR)	DB	BUP: sublingual, 1mg BUP: sublingual, 4mg BUP: sublingual, 8mg BUP: sublingual, 16mg	BUP 1mg: 60% BUP 4mg: 49% BUP 8mg: 48% BUP 16mg: 39%	Heroin, past 7-day peak	VAS (0 = "no craving for heroin," 100 = "the most intense craving ever experienced for heroin")	Baseline, weeks 4, 8, 12, and 16	BUP 1mg = BUP 4, 8, 16 mg BUP 4mg = BUP 8, 16 mg BUP 8mg = BUP 16 mg
Otiashvili et al. (2013) Republic of Georgia	20	BUP/NAL: 40 (97.5%, 100%) MTD: 40 (92.5%, 100%)	OL	BUP/NAL: sublingual, 4-16mg MTD: oral, 17-80mg	BUP/NAL: 12.5% MTD: 17.5%	Opioid, current	VAS (0 = "not at all," 100 = "very much")	Baseline, weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 20	BUP/NAL = MTD
Lee et al. (2018) USA	24	BUP/NAL: 287 (72%, 75%) XR-NTX: 283 (69%, 73%)	OL	BUP/NAL: sublingual film, 8-24mg XR-NTX: injection, 380mg/every 28 days	BUP/NAL: 57% XR-NTX: 53%	Opioid, NR	VAS (NR)	Baseline, 1x/week	BUP/NAL = XR-NTX

(*continued on next page*)

Table 1 (*continued*)

Study, Location	Duration (Weeks)	Sample Size (% Male, % White)	Design	Interventions	Treatment DC	Craving Definition, Time	Craving Measure	Craving Frequency of Assessment Administration	Craving Differences[a]
Neumann et al. (2020) USA	24	BUP/NAL: 10 (NR, NR) MTD: 9 (NR, NR)	OL	BUP/NAL: sublingual, 8/2–16/4mg MTD: tablets, 30-60mg	BUP/NAL: 60% MTD: 33.3%	NR, current	VAS (NR)	Baseline, week 24	BUP/NAL = MTD
Ling et al. (1996) USA	52	BUP: 75 (72%, 19%) MTD 30mg: 75 (84%, 11%) MTD 80mg: 75 (83%, 13%)	DB	BUP: oral concentration, 8mg MTD: oral, 30mg MTD: oral, 80mg	BUP: 80% MTD 30mg: 81% MTD 80mg: 69%	Opioid, past 7-day peak	VAS (0 = "no craving," 100 = "maximum craving ever experienced")	1x/week	BUP, MTD 30mg > MTD 80mg
Nava et al. (2008) Italy	52	BUP: 110 (76%, unknown) MTD: 108 (80%, unknown)	OL	BUP: sublingual, 8, 16, 24, and 32mg MTD: oral, 80, 120, 160, and 200mg	BUP: 24.5% MTD: 19.4%	Heroin, past 24- hour peak	VAS (0 = "no craving for heroin," 10 = "most intense craving ever experienced for heroin")	Baseline, months 1, 3, 6, and 12	BUP 8, 16, 24mg > MTD 80, 120, 160mg

Note. DC = discontinuation; BUP = buprenorphine; BUP/NAL = buprenorphine/naloxone; DB = double blind; VAS = visual analogue scale; MTD = methadone; NR = not reported; PC = placebo-controlled; OL = open-label; XR-NTX = extended-release naltrexone.
[a] Craving differences reported at end of study; ">" = greater craving; "<" = less craving; "=" no differences.

3.2.2. Treatment discontinuation

Within the 10 studies, treatment discontinuation rates varied considerably between interventions, as did the study durations (see Table 1). Treatment discontinuation rates ranged from 3.8% to 80% for buprenorphine, 10.1% to 60% for BUP/NAL, 9.7% to 81% for methadone, and 30% to 53% for XR-NTX.

3.3. Differences in craving by treatment condition

3.3.1. Craving measurement

Nearly all of the studies measured self-reported craving with a visual analogue scale (VAS), with the exception of one study utilizing the Opiate Craving Scale. The VAS craving anchors varied considerably across studies. Most studies ($n = 7$) reported that their VAS ranged from 0 to 100 mm, 1–10 cm, or 0–100. Other studies utilized a 0–10 VAS (n = 1) or did not report their VAS range (n = 1). Additional information on the craving VAS anchors is in Table 1. Craving timeframe varied considerably across craving measures, ranging from current craving, past 24-hour peak craving, or past 7-day peak craving. Two studies did not specify participants' craving timeframe. There was also notable variation in the timing of craving assessments: three studies did not measure craving at baseline (pre-induction), and one study did not specify the frequency of administration of their craving measure.

3.3.2. Craving differences: buprenorphine formulations and dosages

Three studies compared buprenorphine formulations and/or doses (Fudala et al., 2003; Ling et al., 1998; Nava et al., 2008). The first study investigated buprenorphine (16 mg) and BUP/NAL (16 mg) compared to placebo (Fudala et al., 2003). There were no craving differences between groups at baseline. During the 4-week trial, patients in both buprenorphine and BUP/NAL reported significantly lower mean craving than the placebo group. Craving decreased at a similar rate in the buprenorphine and BUP/NAL groups, approximately a 34-point decrease in total on a 0–100 mm VAS.

Ling et al. (1998) compared four buprenorphine doses (1 mg, 4 mg, 8 mg, and 16 mg) over 16 weeks. Controlling for baseline craving, participants on 1 mg of buprenorphine reported greater mean craving at 4 weeks (versus 4 mg, 8 mg, and 16 mg), 8 weeks (versus 8 mg and 16 mg), and 12 weeks (versus 8 mg). There were no differences between groups at week 16. When analyses were restricted to only those who completed all 16 weeks, the 1 mg group reported greater mean craving than the 8 mg and 16 mg groups at 8 weeks only. Lastly, Nava et al. (2008) compared craving within fixed buprenorphine doses (i8, 16, 24, and 32 mg). At baseline, craving was similar between groups. After 3 months, mean craving was greater in the 8 mg buprenorphine dose than the 24 and 32 mg doses of buprenorphine. After 6 months, 8 mg of buprenorphine was associated with greater mean craving than 16 mg of buprenorphine.

3.3.3. Craving differences: buprenorphine vs. extended-release naltrexone

Two studies were identified that compared BUP/NAL to XR-NTX (Lee et al., 2018; Tanum & Solli, 2017). Tanum and Solli (2017) reported that participants prescribed BUP/NAL (4–24 mg; $M_{daily\ dose}$ = 11.2 mg) experienced more craving on average than those prescribed XR-NTX (380 mg) at 4, 8, and 12 weeks; however, craving remained stable across time and analyses were not conducted to determine whether groups significantly differed in craving at baseline. Lee et al. (2018) compared BUP/NAL (8–24 mg; $Mdn_{daily\ dose}$ = 16 mg/day) and XR-NTX (380 mg). Craving was assessed weekly for 24 weeks, and mean opioid craving rapidly decreased from baseline in both groups (i.e., approximately 35–40-point decreases in craving on a 0–100 VAS at week 1). Over the course of 24 weeks, those in the BUP/NAL group reported significantly more craving at week 7 than those in the XR-NTX group, but by week 24 there were no group differences.

3.3.4. Craving differences: buprenorphine vs. methadone

Six studies compared buprenorphine or BUP/NAL to methadone. Three studies comparing buprenorphine or BUP/NAL to methadone

with fixed (prespecified) doses found buprenorphine or BUP/NAL to be associated with greater craving than methadone (see Fig. 2; Law et al., 2017; Ling et al., 1996; Nava et al., 2008). In one study, buprenorphine (8 mg) was compared to two methadone doses (30 mg and 80 mg; Ling et al., 1996). Craving was greater in the buprenorphine (8 mg) and low methadone (30 mg) dose groups in comparison to the high methadone (80 mg) dose group over 26 and 52 weeks. The buprenorphine and low methadone (30 mg) groups did not significantly differ on craving. Similarly, another study examining BUP/NAL (4 mg) to methadone (30 mg) in patients with less severe OUD found that mean craving was greater in the BUP/NAL group (Law et al., 2017). When higher doses of buprenorphine (8, 16, 24, and 32 mg) and methadone (80, 120, 160, and 200 mg) were compared, buprenorphine was associated with greater heroin craving than methadone on average, except at the highest doses of buprenorphine (32 mg) and methadone (200 mg; Nava et al., 2008).

Three other studies compared buprenorphine or BUP/NAL to methadone (Neumann et al., 2020; Otiashvili et al., 2013; Petitjean et al., 2001) in which participants received a range of buprenorphine dosages. These studies did not detect differences in craving between medications. Specifically, Petitjean et al. (2001) did not find differences in mean heroin craving between buprenorphine (8–16 mg; $M_{daily\ dose}$ = 10.5 mg) and methadone (30–120 mg; $M_{daily\ dose}$ = 69.8 mg); craving in both groups decreased approximately 25 points on a 0–100 mm VAS over the course of 6 weeks among study completers (i.e., 15/27 participants in buprenorphine and 28/31 participants in methadone). Likewise, Neumann et al. (2020) did not find differences between BUP/NAL (8/2–16/4mg; $M_{daily\ dose}$ = not reported) and methadone (30–60 mg; $M_{daily\ dose}$ = not reported) in mean craving; both groups reported fewer cravings (i.e., 91.8% reduction) at 6 months versus baseline. Lastly, Otiashvili et al. (2013) indicated that there were no differences in craving between BUP/NAL (4–16 mg; $M_{daily\ dose}$ = 8.5 mg) and methadone (17–80 mg; $M_{daily\ dose}$ = 39 mg) over 20 weeks, and that craving on average decreased for both groups.

3.3.5. Risk of bias assessments

Based on the Cochrane Risk of Bias Assessment (Higgins & Green, 2008), the studies included in this review ranged from low-to-high in their risk of bias (see Table 2). Allocation concealment fully ranged in bias across the studies. Regarding incomplete craving outcome data, all studies were rated as "unclear" in their risk for bias. Given that each study had participants discontinue at various timepoints, it is unknown whether the craving outcome data was missing due to participants with high levels of craving discontinuing the study prematurely or if craving data was missing for other reasons. It is also unknown how the authors specifically treated missing craving data within the studies. In terms of selective outcome reporting, the studies rated as "high risk" did not report all statistics (e.g., mean craving scores), did not report craving data separately by group, and/or lacked a baseline craving assessment. One study only reported craving findings for study completers (Petitjean et al., 2001). Another study was rated "high risk" as participants were able to switch medications during the study; the small sample size (N = 19) may have also impacted the ability of the analyses to detect group effects (Neumann et al., 2020). Finally, a study was rated as "unclear" for other sources of bias, as the study sample were individuals who injected buprenorphine and it is unknown if study findings would generalize to those who do not inject buprenorphine (Otiashvili et al., 2013).

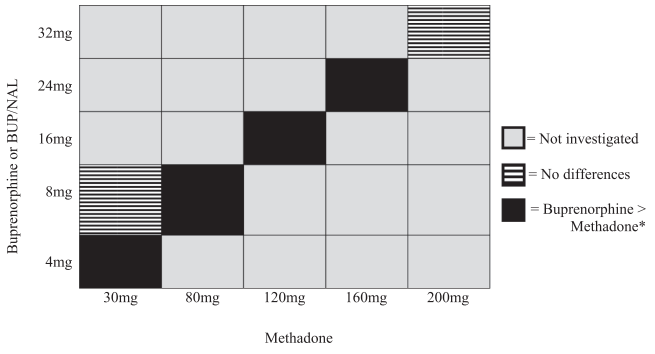

Fig. 2. Craving differences between fixed buprenorphine and methadone doses. Note. BUP/NAL = buprenorphine/naloxone. *Buprenorphine group(s) experienced greater craving than the methadone group(s).

4. Discussion

This systematic review is, to our knowledge, the first to explore self-reported opioid craving during buprenorphine induction and maintenance in comparison to other FDA-approved MOUD. Regarding how the initiation and maintenance of buprenorphine impacts opioid craving, buprenorphine and BUP/NAL were associated with reductions in opioid craving over time, with buprenorphine and BUP/NAL appearing to be superior to placebo in reducing craving. Second, opioid craving did not appear to differ between buprenorphine and BUP/NAL formulations. Third, higher doses of buprenorphine were related to greater reductions in craving versus lower doses. Specifically, buprenorphine doses of 8 mg and 16 mg are associated with greater reductions in craving by two months (vs. 1 mg of BP; Ling et al., 1998), and buprenorphine doses of 24 mg and 32 mg are linked to greater decreases in craving by three months (vs. 8 mg of BP; Nava et al., 2008), suggesting that patients reporting high levels of craving may benefit from high doses of the medication. Taken together, the current review provides further support for buprenorphine's effectiveness in reducing opioid craving.

We were also interested in whether buprenorphine is more or less effective than other FDA-approved MOUD in reducing opioid craving. When BUP/NAL was compared to XR-NTX, BUP/NAL demonstrated greater craving over time, though differences disappeared by 6 months. Half of the studies comparing buprenorphine or BUP/NAL to methadone found buprenorphine and BUP/NAL were associated with greater self-reported craving over time. Among these studies, buprenorphine and BUP/NAL fixed doses were sufficiently compared to methadone fixed doses in terms of their categorization of "low" (2–6 mg buprenorphine, ≤40 mg methadone), "moderate" (7–15 mg buprenorphine, 40–85 mg methadone), or "high" (≥16 mg buprenorphine, ≥85 mg methadone; Mattick, Breen, Kimber, & Davoli, 2014). Specifically, one study compared low doses of BUP/NAL (4 mg) and methadone (30 mg; Law et al., 2017), another compared moderate doses of buprenorphine (8 mg) and methadone (80 mg; Ling et al., 1996), and the third compared moderate and high doses of buprenorphine (8 mg, 16 mg, 24 mg) and methadone (80 mg, 120 mg, 160 mg; Nava et al., 2008). Although methadone may have more immediate reductions in craving, the overall findings suggest buprenorphine and BUP/NAL are effective in reducing opioid craving, especially at higher doses.

The remaining studies comparing buprenorphine or BUP/NAL to methadone did not find craving differences over time; both groups reported decreases in craving at a similar rate. Interestingly, these studies utilized flexible doses. For example, Petitjean and colleagues (2001) investigated 8–16 mg of buprenorphine (moderate-to-high doses) to 30–120 mg of methadone (low-to-high doses). It is possible that the wide range of dosages did not allow for an adequate comparison between medications. Although methadone should also be considered a first-line medication for decreasing craving (given its potential superiority in producing greater reductions in craving than buprenorphine; Law et al., 2017; Ling et al., 1996; Nava et al., 2008) the determination of which medication to prescribe should be individualized and informed by the medication's safety profile, side effects, and risk for adverse events, in conjunction with the patient's substance use, medical, and psychiatric symptoms (Substance Abuse and Mental Health Services Administration [SAMHSA], 2021). Given that buprenorphine has a more favorable safety profile than methadone (SAMHSA, 2021), it may have a slightly better or equivocal advantage to reducing craving if the patient cannot

Table 2

Risk of bias assessments

	Sequence Generation	Allocation Concealment	Blinding (Participants and Personnel)	Blinding (Outcome Assessors)	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
Fudala et al. (2003)							
Law et al. (2017)							
Lee et al. (2018)							
Ling et al. (1998)							
Ling et al. (1996)							
Nava et al. (2008)							
Neumann et al. (2020)							
Otiashvili et al. (2013)							
Petitjean et al. (2001)							
Tanum et al. (2017)							

Legend: Risk of bias

Low	
Unclear	
High	

tolerate the side effects based on pre-existing conditions. Further study is required before drawing firm conclusions on the most effective MOUD for craving.

Although there does appear to be a link between craving and buprenorphine use, there was significant variability in the definition of opioid craving and its measurement across studies. Craving was primarily identified as "opioid craving" or "heroin craving". Previous work suggests that the type of opioid (prescription opioids vs. heroin) may moderate the craving response (McHugh, Fulciniti, Mashhoon, & Weiss, 2016), and therefore studies that broadly utilize the term "opioid" to assess craving may not capture important differences (Goodyear & Haass-Koffler, 2020). Nearly all studies included in this review utilized a self-report VAS to measure craving, though anchors ranged from "current craving" to "past 7-day peak craving". While these one-item measures have the advantage of being quickly administered and scored, memory bias may emerge when a craving rating requires recall (e.g., "past 7-day peak craving"). It is possible that these various definitions of craving (tonic or "long term" craving vs. phasic or "in-the-moment" craving) may have different antecedents and consequences (Goodyear & Haass-Koffler, 2020). For example, transdiagnostic (e.g., chronic pain; Ren, Shi, Epstein, Wang, & Lu, 2009) or individual factors (e.g., sex; Back et al., 2011) may impact tonic craving, while environmental characteristics (e.g., drug and paraphernalia cues; McHugh et al., 2016) may trigger phasic craving (Goodyear & Haass-Koffler, 2020). These various definitions of craving may even differentially impact resumed opioid use or treatment discontinuation. There are also potential issues with the VAS's psychometric properties (inability to measure internal reliability from single-item measures) and its inability to capture the multidimensional (cognitive, emotional, behavioral, and physiological) nature of craving (Rosenberg, 2009; Sayette et al., 2000; Tiffany, 1992). It is unknown whether similar results would be found if studies had utilized measures not reliant on self-report, such as self-administration, psychophysiological responding, neurobiological responding, and cognitive processing (Sayette et al., 2000). Future work should consider the inclusion of these measures in randomized trials to capture the full construct of craving during buprenorphine initiation and maintenance, which may differentially impact treatment outcomes.

The relationship between craving and treatment discontinuation or return to opioid use remains unstudied in the context of randomized trials. It is possible that patients with pronounced craving discontinued

treatment prematurely, potentially skewing the craving data over time. There also appears to be a differential impact of buprenorphine doses on craving, despite variations in craving measurement across studies. Future research should address methodological issues (i.e., assess craving at baseline and throughout the trial) to facilitate a more detailed analysis of whether craving impacts treatment outcomes, and if so, the possible mechanisms. Another direction includes further comparisons of buprenorphine formulations (film vs. tablet) on craving, given that some of the studies did not specify the buprenorphine formulation in their work and these different formulations have not fully been explored in relation to outcomes (Ling et al., 1998; Neumann et al., 2020).

The findings of this review should be interpreted within the context of the study limitations. First, this review only included peer reviewed, published literature; thus, findings from non-peer reviewed or unpublished work may be missing. Second, there may have been a study which met our search criteria that was not detected by our database queries or ancestry searches (examining references in included and considered studies). Third, White men and younger individuals dominated the samples, and therefore findings may not generalize to older populations, women, and racial and ethnic minority groups. Fourth, the high rates of treatment discontinuation may have impacted the study findings. Fifth, many of the trials had a "high risk of bias" for allocation concealment, which may have led to bias in measurement of craving or opioid use. Sixth, all studies were rated as "unclear" risk of bias for incomplete outcome data for craving, as it is unknown if participants who experienced high levels of craving may have been more likely to discontinue the studies prematurely or if this data was missing for other reasons. Finally, the majority of studies included in this review were rated as "high risk of bias" for selective outcome reporting for craving, as many statistics were missing from the results.

In sum, findings from the present review indicate that buprenorphine is linked to reductions in opioid craving over time. Various definitions and measurements of craving hindered the understanding of the impact of craving on buprenorphine induction and maintenance. Thus, more research is needed to elucidate the precise impact of buprenorphine and other MOUD on opioid craving, the impact of craving on MOUD and treatment outcomes, and also inform interventions designed to address OUD.

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Catherine Baxley: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Visualization. **Brian Borsari:** Conceptualization, Methodology, Resources, Writing – original draft. **Jill V. Reavis:** Validation, Methodology. **Jennifer K. Manuel:** Writing – original draft. **Ellen Herbst:** Writing – original draft. **William Becker:** Writing – original draft. **David Pennington:** Writing – original draft. **Steven L. Batki:** Writing – original draft. **Karen Seal:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addbeh.2022.107589.

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