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Can Intranasal Oxytocin Reduce Craving In Automated Addictive Behaviours? A Systematic Review

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BH, CK, TD, YP and AB conceived and designed the review; BH conducted the systematic literature review, study selection and quality assessment; BH, AB and YP extracted the data; BH, AB and YP drafted the first version of the manuscript; BH, CK, TD, AB and YP revised the manuscript critically and gave final approval.

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Abstract

Existing pharmacotherapies for managing craving, a strong predictor of relapse to automated addictive behaviours, are limited in efficacy and characterised by increased health risks associated with their pharmacological profile. Preclinical studies have identified oxytocin as a promising pharmacotherapy with anti-craving properties for addictive behaviours. Here, we provide the first systematic review of 17 human studies (N=722; 30% female) investigating the efficacy of intranasal oxytocin to reduce craving or consumption in addictive behaviours. We identify intranasal oxytocin as a method that warrants further investigation regarding its capacity to decrease cue-induced, acute stress-induced or withdrawal-related craving and relapse related to alcohol, cannabis, opioids, cocaine, or nicotine, including a potential role as ad-hoc medication following exposure to drug-related cues. Future studies should investigate the role of factors such as treatment regimes and sample characteristics, including the role of the amygdala, which we propose as a distinct mechanism mediating oxytocin's anti-craving properties.

List of non-standardised abbreviations

B	Between Subject Design
BOLD	Blood-Oxygen-Level-Dependent
CG	Cingulate Gyrus
DB	Double-Blind
DSM	Diagnostic and Statistical Manual
F	Females
FG	Frontal Gyrus
HIPP	Hippocampus
HPA	hypothalamic-pituitary-adrenal
ICD	International Classification of Diseases
IFG	Inferior Frontal Gyrus
IPL	Inferior Parietal Lobule
IU	International Unit
L	Left
M	Males
MET	Motivational Enhancement Therapy
MGF	Middle Frontal Gyrus
LOC	Lateral Occipital Cortex
N/A	Not Applicable
NAc	Nucleus Accumbens
OG	Occipital Gyrus
OT	Oxytocin
PL	Placebo
PrCG	Paracingulate Gyrus
PCG	Precentral Gyrus
R	Right
RD	Randomised
SMA	Supplementary Motor Area
SFG	Superior Frontal Gyrus
STG	Superior Temporal Gyrus
VAS	Visual Analog Scale
W	Within Subjects Design

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Introduction

Craving is defined as a strong desire, sensation or urge to use a substance or perform an activity (American Psychiatric Association, 2013; World Health Organisation, 2018). It is an established multifaceted antecedent predictor of automated addictive behaviours such as drug seeking behaviour (Tiffany et al, 2012), or gambling disorder, internet gaming disorder, compulsive eating, exercise addiction, pornography addiction, and social network use disorder (Hormes, 2017). A systematic review of ninety-one studies observing participant behaviours in real-time prior to relapse found a positive concurrent and prospective relationship between craving and substance use in 92% of studies (Serre et al, 2015), highlighting craving as a key driver for relapse. In substance use disorders, relapse may trigger treatment drop out and accidental overdose (Eliason and Amodia, 2007), rendering it a major challenge in addiction management, with suboptimal treatment options. Given the etiological links between craving and relapse, the development of interventions that target craving are deemed to be critical for the management of drug addiction and associated harm to individuals and the wider society.

Though many different theoretical, cognitive, and phenomenological models of craving exist (Drummond, 2001), craving can be broadly categorized into cue-induced and withdrawal-related craving. Cue-induced craving can be triggered by environmental cues associated with substance use or other addictive behaviours (e.g. people, places, things), internal cues such as physical pain changing and emotional states, or by acute stressors (acute stress-induced). Cue-induced craving is central to the loop of continued drug use, it can be conscious or subliminal and may involve any of the sensory modalities (Jasinka et al, 2014). Withdrawal-related craving is the consequence of the continuous underlying stress induced by withdrawal from substances like nicotine, alcohol or opioids (Shalev et al 2002), where reinstatement of substance use is triggered in an attempt to relieve withdrawal symptoms (Mantsch et al, 2016). Many substance users describe drug seeking as feeling automatic and out of their control (Tiffany, 1990), which causes a significant challenge in relapse prevention. Relapse into drug seeking is partly dependent on one's perception of self-efficacy in applying coping behaviours (Hendershot et al, 2011), while arguably the development of pharmacotherapies that reduce craving could greatly assist in relapse prevention.

Currently, pharmacotherapies for managing craving only exist for a subset of addictive behaviours (e.g., opioid and alcohol use disorders), are limited in efficacy, and associated with increased health risks. For example, substitute medications such as the μ-receptor agonist methadone and the μ-receptor partial-agonist buprenorphine have been shown to have efficacy in reducing withdrawal-related craving at high doses in opioid use disorders (Clinical Guidelines on Drug Misuse and Dependence Update, 2017). However, these medications are unsuitable for the management of cue-induced craving. This is because the ad-hoc use of substitute opiates would result in inconsistent dosing levels and heighten the risk of accidental opioid overdose (Clinical Guidelines on Drug Misuse and Dependence Update, 2017). Naltrexone, an opioid receptor antagonist, has shown poor compliance rates when used as an anticraving medication in abstinent opioid users (Bart, 2012). Naltrexone is also used to reduce craving in alcohol use disorders (Volpicelli et al, 1992; O'Malley et al, 1996), but its use is problematic as it requires daily dosing of a medication with a high liver toxicity profile (Naltrexone, 2020) in a population with likely liver impairment. Another medication used to reduce craving in alcohol use disorders is acamprosate, which activates

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glutamate receptors (Weinstein et al, 2003), but has been found to be half as effective as naltrexone at preventing relapse, and suffers from poorer compliance than naltrexone across one year (Rubio et al, 2001). Therefore, the need for a novel, safe and efficacious pharmacotherapy which can be used on an ad-hoc basis to manage cue-induced craving is warranted. Given that the risks associated with the current anticraving medication are intrinsically associated with their pharmacological profile, a therapeutic agent with a distinct mechanism of action from those currently available is needed to aid craving management.

Distinct neurobiological mechanisms underlining stress and cue-induced craving have been proposed including alterations in cortico-striatal and prefrontal control circuitries (Pickens et al, 2011; Spagnolo et al, 2019) and changes in corticotropin-releasing factor, noradrenaline, dopamine, dynorphin and glutamate (Shalev et al, 2002; Pickens et al, 2011; Spagnolo et al, 2019). Nonetheless, hyperactivity of the amygdala has been consistently identified as a common mechanism underlining both cue and stress induced craving in several different types of addiction based on preclinical and clinical data (Shalev et al, 2002; Pickens et al, 2011; Spagnolo et al, 2019). MRI studies have revealed that drug-related cues induce hyperactivation of amygdala in different types of substance users (Mclernon et al, 2007; Wang et al, 2007; Buffalari and See, 2010; Seo, Sinha, 2014; Murphy et al, 2018), which is implicated in emotional, cognitive and behavioural responses related to seeking and using drugs (London et al, 2000; Wong et al, 2015). Amygdala hyperactivity is also implicated in cue reactivity for behavioural addictions such as gambling (Goudriaan et al, 2010), porn, video games and food (Olsen, 2011). Modern addictions such as social networking are also susceptible to cue induced craving (Niu et al, 2016) and have also been linked to amygdala hyperactivity (He et al, 2017). As such, evidence points towards amygdala hyperactivity as a common underlining craving mechanism driving automated addictive behaviours of a range of different types of addictions.

An emerging body of evidence from pre-clinical studies has identified oxytocin as a novel pharmacotherapy for substance use disorders with potential anticraving properties (Bowen and Neumann, 2017; Zanos et al, 2018). Oxytocin is a hypothalamic neuropeptide involved in the regulation of a range of physiological processes and behavioural responses including the development (Miller and Caldwell, 2015) and regulation of social behaviour (Churchland and Winkielman, 2012; Johnson and Young, 2017), the modulation of pain processing (Poisbeau et al., 2018; Paloyelis et al., 2016b), feeding behaviour (Leslie et al, 2018) and neuroinflammation after brain ischemia (Karelina et al, 2011). The intranasal administration of oxytocin has been identified as a promising pharmacological intervention in humans to harness the central oxytocin system (Martins et al, 2020; Paloyelis et al, 2016a) and improve outcome in several conditions currently lacking efficacious treatments (e.g. autism spectrum disorder (Anagnostou et al, 2014), schizophrenia (Shilling and Feifel, 2016), migraine (Tzabazis et al, 2017), stroke (Karelina et al, 2011), obesity (Olszewski et al, 2017), Prader-Willi (Rice et al, 2018). Animal studies have shown that the intracerebroventricular injection of oxytocin can suppress the reinstatement of methamphetamine, opioid and cocaine-seeking behaviour in abstinent rodents, suggesting a potential anticraving property of the drug (Bowen and Neumann, 2017). Preclinical studies have identified several mechanisms of action of oxytocin that could explain its effect on drug seeking behaviour. These include the modulation of monoamine and glutamatergic systems, and the suppression

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of the HPA axis and amygdala hyperactivity (for extensive reviews of this topic see Bowen and Neumann (2017), Zanos et al (2018) and Leong et al (2018)).

Beyond its safe pharmacological profile, one of the attractive properties of intranasal oxytocin as a potential anti-craving pharmacotherapeutic agent is its distinct mechanism of action compared to currently available anti-craving pharmacotherapy. Although the mechanism underlining the potential anti-craving effect of oxytocin is not well understood, one possible mechanism involves the amygdala. Human neuroimaging studies have demonstrated that the suppression of activity in the amygdala is one of the most robust effects of intranasal oxytocin, both in the resting human brain (Martins et al, 2020) and regarding the response of the amygdala to social emotional cues (Spengler et al., 2017). Consistent with human findings, suppression of amygdala activity by oxytocin has been reported in animal studies (Campbell-Smith et al, 2015). As such, the fact that amygdala hyperactivity is a common craving mechanism driving automated addictive behaviours of a range of different types of addictions (as discussed above), makes oxytocin an attractive anti craving potential therapeutic based on its unique amygdala supressing properties.

Figure 1 illustrates the proposed mechanism underlining cue-induced craving and consumption in automated addictive behaviours triggered by drug-related cues. We propose that amygdala hyperactivity in response to cues seizes up flexibility to objectively assess the situational salience of the cue and decreases inhibitory control of attentional bias, thus contributing to automated addicted behaviours. Attentional bias is well documented in substance use disorders (Franken et al, 2000; Waters et al, 2012; Zamani et al, 2014; Zhang et al, 2018), can predict future drug use (Garland et al, 2014) and is associated with higher self-reported drug-related craving scores (Field et al, 2009). There is considerable evidence of a significant relationship between heightened amygdala activation and attentional bias towards drug-related cues in people who use substances (Hester and Luijten, 2014) which in turn may contribute to the mechanism controlling craving and consumption in other automated addictive behaviours. As such, we suggest that intranasal oxytocin administration following cue exposure would be able to exert anticraving effects by supressing amygdala hyperactivity and hence reinstate inhibitory control over attentional bias and executive control over situational salience (Figure 1). This would subsequently interrupt the loop of automated addictive behaviour. Future studies are warranted to test the validity of this proposed mechanism. Interestingly, contrary to the proposed hypothesis over the inhibitory effect of oxytocin on attentional bias to drug related cues in substance use disorders, oxytocin was found to increase vigilance to food images in bulimia nervosa and binge eating disorder which are characterised by recurrent, loss-of-control binge eating behaviour (Leslie et al., 2020).

Our study provides the first systematic review aiming to synthesize evidence from human studies investigating the efficacy of intranasal oxytocin as a pharmacotherapy to reduce craving in addictive behaviours, or its concomitant effects on the consumption of either licit or illicit substances, or on engagement in behavioural addictions. We will also propose a potential mechanism underlying the effect of intranasal oxytocin in reducing craving.

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Methods

Literature Search

We followed PRISMA guidelines (PRISMA, 2009) to identify peer-reviewed studies that investigated the effects of intranasal oxytocin, compared to placebo, on craving induced by a cue paradigm, an acute stressor, or withdrawal related stress in humans. The following electronic databases were searched, from inception until July 2020: PubMed (Medline), Embase, Web of Science, Psychinfo and Google Scholar. Google Scholar was included to improve the chance of returning documents outside of commercial publishers to reduce the risk of publication bias (Bramer et al, 2017). Google Scholar search reports were limited to the first 200 results within a topic search in line with recommendations for using Google Scholar as part of a systematic review (Haddaway et al, 2015). We used the following search terms (adapted according to the format required by each database): "oxytocin" AND (craving OR addictive behaviours OR pornography OR pathological gambling OR compulsive eating OR social networking sites OR internet addiction OR internet gaming).

Eligibility

We included studies meeting the following inclusion criteria: (a) peer-reviewed study, available in English; (b) used human adult volunteers; (c) compared the administration of intranasal oxytocin to placebo; (d) focused on substance use disorders, compulsive eating, gambling addiction, pornography addiction, social network use disorder and gaming addiction as defined by DSM-IV, DSM-V or ICD11 (American Psychiatric Association, 2013; World Health Organisation, 2018). Disorders recognised by DSM-IV or V within the context of the review include substance use disorders and gambling. Compulsive sexual behavioural disorders which include pornography and sex addiction, gaming addiction and social network use disorder are recognised by ICD11 but not by DSM5 currently. Compulsive eating disorders have been recognised by both ICD11 and DSM5, and we included Bulimia Nervosa or Binge Eating disorders, as binge eating has been conceptualised from a food addiction perspective (Treasure et al, 2018); (e) included one of the following measures of craving or consumption/engagement: validated self-report drug craving scale, oral fluid mouth swab drug screen and/or urine drug screen to provide objective measures of drug use, self-reported quantity and frequency of substance use. For food craving studies they were included if they used at least one of the following: validated self-report food craving scale, quantity of food or nutritive substance consumed. For gambling, porn, social network, gaming addictive behaviour studies, they were included if they measured at least one of the following: validated self-report craving scale, quantity of bets placed, quantity of pornographic material viewed, amount of time spent on social networking sites, time spent playing video games.

Data extraction

The following data were extracted from all papers independently by reviewers BH, AB and YP: first author, year of publication, country of origin, addictive behaviour, severity of substance use disorder, craving type, study design, sample size, dose administered, post-dosing measurement interval (single dose), administration regime (repeat dose), outcome measures related to craving or consumption, statistically significant effects of intranasal oxytocin (compared to placebo) on each outcome measure. Any discrepancies were resolved through discussion. Information from included studies is presented in Table 1. A narrative

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summary of the included studies and reported significant results is provided. A meta-analysis was not possible due to substantial heterogeneity in study designs, addictive behaviours and outcome measures.

Risk of bias

One reviewer (BH) used the Cochrane Collaboration's risk of bias tool (Higgins et al, 2016) to conduct a quality assessment for methodological risk of bias. The following risk of bias criteria were applied for each study:

- Random sequence generation (selection bias). Methods used to generate allocation sequence recorded as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method not clearly stated); and high risk of bias (studies that included a biased randomisation procedure).
- Allocation concealment (selection bias). Methods used to conceal allocation to interventions from participants and/or researchers prior to assignment recorded as: low risk of bias (e.g. electronic or third party randomisation; consecutively numbered, sealed envelopes); unclear risk of bias (method not clearly stated) and high risk of bias (no randomisation, participants and/or researchers were aware whether they received placebo or oxytocin).
- Blinding of outcome assessment (detection bias). Methods used to blind researchers from knowledge of which intervention a participant received. Methods recorded as: low risk of bias (study had a clear statement that outcome assessors were unaware of treatment allocation); unclear risk of bias (study stated that outcome assessors were blind to treatment allocation but lacked a clear statement on how it was achieved); high risk of bias (study stated that outcome assessors were aware of treatment allocation).
- Incomplete outcome data (attrition bias). Incomplete data and incomplete explanation of incomplete data was recorded as: low risk (attrition fully reported and no differences between completers and non-completers); unclear risk of bias (attrition unclear or unclear differences between completers and non-completers); high risk of bias (attrition not reported or unaccounted for missing data).
- Selective reporting (reporting bias). Where all outcomes identified in methodology were reported within results this was recorded as low risk of bias; unclear risk of bias (outcomes reported descriptively without statistical analysis reporting); high risk of bias (missing outcome data).

Accepted Article

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Results

Study selection

The PRISMA chart can be found in Figure 2. We identified 516 records, and after duplicates were removed, 302 studies remained. Their titles and abstracts were screened by one reviewer (BH). We excluded 285 studies for not meeting one of more of the inclusion criteria (see Figure 2). We reviewed the full-text, and extracted data, from the remaining 17 publications (see Table 1).

Characteristics of included studies

We identified a total of 17 studies meeting our inclusion criteria, originating in countries across the world (see Table 1). Of these, 13 studies reported the effects of a single dose of intranasal oxytocin, compared to placebo, directly on outcome measures of craving or consumption for addictive behaviours related to alcohol (4 studies), cannabis (2 studies), cocaine (1 study), nicotine (4 studies), and opioids (2 studies). Most single-dose studies assessed only cue-induced or acute-stress induced craving (N=10; three of which assessed both cue-induced/acute stress-induced and withdrawal related craving), while 3 single-dose studies assessed both cue-induced craving and consumption. Four studies measured the effect of various regimes of repeated administration of intranasal oxytocin, compared to placebo, directly on withdrawal-related craving for alcohol (one study), cue-induced craving for heroin/cocaine (one study), baseline craving for food (one study), or cannabis consumption (one study).

Of the 13 studies that investigated the effects of a single dose of intranasal oxytocin administration on craving, most studies utilised study-specific visual analog scales (VAS) or validated craving measures (see Table 1). One study (Bach et al, 2019) did not report directly behavioural craving ratings, but the association between behavioural craving ratings during an fMRI cue-induction craving paradigm and connectivity between the blood oxygen level dependent (BOLD) response in specific brain regions. The studies varied substantially in the time they obtained measures of craving post dosing. Six single dose studies obtained single measures at intervals that ranged from 20 to 95 min post-dosing; while the remaining studies performed multiple assessments at intervals that varied from 0 – 360 minutes post-dosing.

All 3 studies that investigated the effects of a single dose of intranasal oxytocin on consumption also measured cue-induced craving. These studies measured consumption over intervals that ranged from 60 – 240 minutes post-dosing. Of the 3 repeated oxytocin administration studies that measured consumption, one used self-report diaries (Agabio et al, 2016), and one used self-report measures and a urine drug screen test (Stauffer et al, 2016). The remaining study examined the potential intranasal oxytocin, compared to placebo, to enhance the effects of a psychotherapeutic intervention on cannabis consumption (Sherman et al., 2017).

Frequency of administration and dose. Doses in the studies that investigated the effects of a single dose of intranasal oxytocin administration ranged from 20IU to 40IU. One study investigated two doses: 20IU and 40IU (Stauffer et al, 2019). Doses, daily frequency and duration of treatment varied substantially across the 3 repeated oxytocin administration studies, with daily doses ranging from 40IU – 96 IU.

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Adverse effects. Most studies (11 out of 17) did not mention adverse effects, one study mentioned that there were no adverse effects reported (Stauffer et al., 2016), while three studies reported no significant differences in reported adverse effects between the oxytocin and placebo groups (Agabio et al., 2016; Mitchell et al., 2016; Stauffer et al., 2019). One study reported one case of nasal irritation and one case of headache in the placebo group, and one case of irritability and unpleasant taste in the mouth in the oxytocin group (McRae-Clark et l., 2013), while another study reported that 7 out of the 11 cases of reported adverse effects were in the oxytocin group, with mild/moderate headache and light-headedness being the most common effects (McClure et al., 2019).

Summary of results

Table 2 summarises the main effects of intranasal oxytocin, compared to placebo, by addictive behaviour, regime of administration, and outcome measure.

Single dose oxytocin administration studies (craving): Overall, for studies that included measures of craving, we observed an equal number of significant decreases and negative results for craving ratings related to cannabis, nicotine, or opioids. Regarding craving ratings for alcohol, none of the three studies reported a main effect of treatment, but one study reported that intranasal oxytocin, compared to placebo, decreased cue-induced craving ratings for alcohol in those participants with high attachment anxiety, while it increased craving ratings in those participants with low attachment anxiety. An oxytocin induced (compared to placebo) increase in withdrawal-related craving for cocaine, and cue-induced ratings of excitement (but not urge to use, irritation or heart pounding) was also reported.

Repeated oxytocin administration studies (craving): For addictive behaviours related to food or cocaine/opioids, neither of the two studies investigating the effect of repeated intranasal oxytocin administration, compared to placebo, reported significant treatment effects regarding cue-induced craving. A single study reported though a significant decrease in withdrawal-related craving for alcohol following repeated treatment with intranasal oxytocin, compared to placebo. No studies examined the effects of the repeated administration of intranasal oxytocin on measures of craving for cannabis or nicotine.

Single dose oxytocin administration studies (consumption): We observed no significant decreases in measures of cue-induced or acute stress induced consumption of cannabis. One study reported no significant effect of oxytocin treatment on acute stress induced nicotine consumption, while another study reported that a single dose of intranasal oxytocin, compared to placebo, decreased the substance-induced nicotine consumption.

Repeated oxytocin administration studies (consumption): Three studies examined the effects of the repeated administration of intranasal oxytocin, compared to placebo, on consumption related to cocaine/opioids, cannabis (examining the potential enhancement of the effect of motivational enhancement therapy) and food; none of these studies reported a significant treatment effect. No studies examined the effects of the repeated administration of intranasal oxytocin on consumption in relation to alcohol or nicotine.

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Risk of bias

Random sequence generation. Sixteen out of the 17 studies were adjudged to be of low risk of bias. One study did not explicitly state whether randomization took place (Van Hedger et al, 2019).

Allocation concealment. Ten out of the 17 studies provided adequate descriptions of allocation concealment and were adjudged to have low risk of bias. Seven out of the 17 studies were unclear regarding the processes used to conceal allocation following randomisation (Bach et al, 2019; Flanagan et al, 2019; Lee et al, 2014; Miller et al, 2016; Reed et al, 2019; Sherman et al, 2017; Van Hedger et al, 2019).

Blinding of outcome assessment. Three studies were adjudged to have low risk of bias for blinding outcome assessors (Stauffer et al, 2019; Van Hedger et al, 2019; Woolley et al, 2016); the remaining fourteen studies were assessed as unclear.

Incomplete outcome data. Ten out of the 17 studies showed completeness of data collection. Three were listed as unclear risk of bias due to missing information on reported drop-outs (Moeini et al, 2019; Reed et al, 2019; Van Hedger et al, 2018); three were adjudged to be of high risk of attrition bias due to computer error losing data (Stauffer et al, 2016), lack of explanation for participants who were not retained (Bach et al, 2019) and missing outcome data (McClure et al, 2019).

Selective reporting. Fifteen studies reported data for all outcomes and were marked as low risk of bias. Two studies were adjudged to as unclear regarding reporting bias (McClure et al, 2019; Stauffer et al 2016). McClure et al (2019) provided complete data for participants who completed the study however 30 participants did not complete the study and no explanation was given for these. Stauffer et al (2016) only reported cocaine consumption and did not report heroin consumption.

Discussion

This the first systematic review aiming to synthesize evidence from 17 human studies investigating the efficacy of single dose or repeated intranasal oxytocin administration as a pharmacotherapy to reduce craving in addictive behaviours, or reduce the consumption of either alcohol, cannabis, cocaine, opioids, nicotine, or food. Five out of 15 studies that investigated the effects of intranasal oxytocin on self-report measures of craving reported a decrease in cue-induced craving, one study reported a decrease or increase depending on the participants' attachment style, one study reported an increase in craving, while the remaining eight studies found no effect. Regarding measures of consumption, only one out of six studies involving the administration of intranasal oxytocin reported a decrease in consumption, with the remaining five studies reporting no effect. The included studies were characterised by marked heterogeneity in terms of methodology, outcome measures, oxytocin dose and administration regime, sample characteristics, addiction severity, and some studies had notably small sample sizes, suggesting they did not have sufficient power to detect but the largest effect sizes, if an effect existed. Overall, the existing volume of work suggests that intranasal oxytocin may affect self-reported craving for alcohol, cannabis, cocaine, nicotine and opioids, but not food (in a sample with binge eating disorder), though no firm

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conclusions can be drawn at this stage. Our findings warrant further investigation of intranasal oxytocin as a method to decrease cue-induced, acute stress-induced, or withdrawal-related craving regarding addictive behaviours related to alcohol, cannabis, opioids, cocaine or nicotine.

Notably, the systematic analysis of all studies revealed a safe pharmacological profile for intranasal oxytocin in populations with addictive behaviours. Most studies (15 out of 17 studies) either did not report adverse effects, or reported that there were no significant differences in the profile of effects between the oxytocin and placebo conditions. The remaining two studies reported mild effects that were observed in either the placebo (6 cases) or oxytocin (8 cases) groups. In addition, no issues were reported with respect to the tolerability of oxytocin in this population which adds to its attractiveness as a potential anti-craving medication.

Future studies seeking to elucidate the potential of intranasal oxytocin as a pharmacotherapy to reduce craving, and potentially relapse, need to systematically investigate a number of factors related to treatment administration, study design and sample characteristics that are likely to impact efficacy. Below, we discuss evidence related to the potential impact of factors in each of these three categories.

First, studies need to carefully investigate the effects of method of administration (Martins et al., 2020), dose (Spengler et al., 2017), and frequency of repeated administrations (Kou et al., 2020), as all three factors have been associated with differences in behaviour and central target engagement (e.g. the amygdala). Human studies assessing a range of different doses of intranasal oxytocin on behavioural and neural outcomes have been scarce (Spengler et al, 2017; Quintana et al, 2018; Wynn et al, 2019; Lieberz et al, 2020) which is a serious limitation for the selection of the optimal dose which would exert maximal efficacy at a particular time point and brain region. With respect to craving, only one study (Stauffer et al, 2019) in this review compared two different doses (20IU and 40IU) of intranasal oxytocin on the reduction of cue-induced alcohol craving, reporting no significant effect of either dose of intranasal oxytocin versus placebo. The importance of establishing dose-response curves regarding the effects of intranasal oxytocin on craving and central target engagement is highlighted by recent evidence that the effects of intranasal oxytocin on social cognition in schizophrenia may follow a U-shaped dose response curve (Erdozain and Peñagarikano, 2020). Suboptimal treatment regimes are likely to result in inconsistent findings and missed opportunities to elucidate the role of intranasal oxytocin as a pharmacotherapy to reduce craving.

Second, future studies need to systematically consider the timing of inducing craving and obtaining measures of craving post-dosing. Most studies involving the administration of a single dose of intranasal oxytocin obtained ratings of craving either on a single or on multiple occasions over post-dosing intervals that ranged from a few minutes up to 360 minutes. The timing with respect to intranasal oxytocin administration has been mainly driven by historical precedence (e.g. Born et al., 2002), while recent evidence suggests that intranasal oxytocin may dampen activity in the amygdala as early as 15-32 minutes post-dosing (Martins et al., 2020). As suppression of amygdala hyperactivity is suggested to be one of the key mechanism by which oxytocin is thought to supress cue-induced craving, it is likely that the optimal effect of oxytocin on cue-induced craving is induced at a much earlier

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time point following oxytocin administration. It is also important to take into account the time course of feelings of craving post cue-induction. For example, with respect to optimal time of craving measurement following cue induction, studies have reported that the BOLD response in the amygdala following opioid-related cue-inducement peaks as early as 7 minutes and diminishes gradually over a period of 14 minutes (Murphy et al, 2018). Therefore, the assessment of the effect of intranasal oxytocin on cue-induced or acute stress-induced cravings must be carefully planned to take into account not only the pharmacodynamics of intranasal oxytocin but the time course of cue-induced feelings of craving. Sampling craving at suboptimal intervals is likely to result in inconsistent reports of efficacy across studies.

Currently, there is lack of clarity regarding the mechanisms mediating the effects of exogenous oxytocin on behaviour, and the mechanisms through which exogenous oxytocin may reach the brain, and this has been an area of intense research. Exogenous oxytocin in systemic circulation is metabolised quickly (~ 1-5 minutes half-life in plasma), while the half-life of oxytocin in the cerebrospinal fluid is about 19 minutes (Mens et al., 1983). When administered intranasally, oxytocin reaches systemic circulation (eg see Martins et al., 2020 for the pharmacokinetics of 40IU of intranasal oxytocin in blood plasma in men over 115 min post-dosing). It is thought that oxytocin, as a large hydrophilic neuropeptide, does not cross the blood brain barrier in sufficient amounts (Ermisch et al., 1985), though recent evidence has identified mechanisms of active transport from the blood to the brain (Yamamoto et al., 2019). Nonetheless, there is also evidence to suggest that intranasal oxytocin can directly reach the brain bypassing the blood brain barrier through nose-to-brain transportation (eg Martins et al., 2020). Once in the brain, the time course of the effects of oxytocin vary as a function of method of administration and point of entry, dosage, and target region (Martins et al., 2020). With respect to oxytocin's modulatory effect on the amygdala, recent studies have shown that intranasally administered oxytocin (40IU) can decrease resting blood perfusion in the amygdala from 15 – 32 minutes post-dosing, whereas effects on other brain regions can be observed several minutes later (e.g. 87-95 minutes post-dosing for the anterior cingulate cortex) (Martins et al, 2020). Other studies investigating the BOLD response to emotional faces in the amygdala have shown dose dependent effects peaking 45-70 minutes post-dosing (Sprengler et al, 2017). Taking these studies under consideration, the inconsistency among reports focusing on the efficacy of intranasal oxytocin on craving is not surprising, and it is clear the further research is required to elucidate the mechanisms and time-course of the effects of intranasal oxytocin for a range of behaviours and targeted brain regions.

Third, future studies need to also carefully consider sample characteristics as potential moderating factors. For example, while there were more male participants than female participants in the studies included in this review, gender was not examined as a moderating factor (possibly due to the small sample sizes). It is well-known that the effects of intranasal oxytocin on key brain structures (e.g. the amygdala), and its effects on anxiety, vary between men and women (Lieberz et al., 2020; Lynn et al 2014; Xu et al., 2017; Spengler et al., 2017; Steinman et al., 2016). Interestingly, given the impact of drugs or addictive behaviours on reward saliency (Volkow et al, 2010), sexual dimorphic effects of intranasal oxytocin have also been discussed in relation to amygdala function and salience processing (Gao et al, 2016). Additionally, one study showed that the effects of intranasal oxytocin, compared to placebo, on cue-induced craving for alcohol depended on the participants' attachment style, specifically attachment anxiety (Mitchell et al., 2016). Attachment style is a risk factor for alcoholism and alcohol may provide a coping mechanism for insecurely attached individuals

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(Buckner et al., 2008; McNally et al., 2013), while it is known that intranasal oxytocin has both anxiolytic properties (Neumann and Slattery, 2016; Yoon and Kim, 2020), plays a key role in separation related anxiety disorder (Schiele et al., 2020) and its effects can be moderated by attachment style (Bartz et al., 2011). Clearly, the role of relevant sample characteristics needs to be carefully considered in future, adequately powered studies.

Interestingly, the study investigating the effects of the repeated daily administration of intranasal oxytocin on baseline craving for food or number of binge-eating episodes over a period of 8 weeks in a sample with binge-eating disorder (Agabio et al., 2016) did not report significant effects. This is partly consistent with studies with healthy volunteers, where intranasal oxytocin, compared to placebo, is reported to be ineffective in modulating baseline, cue- or acute stress-induced craving for food, but contrasts the reported effect of intranasal oxytocin in decreasing both energy intake after overnight fasting (Spetter et al., 2018; Thienel et al., 2016), and reward related eating (Burmester et al., 2018; Burmester et al., 2019; Ott et al., 2013). The anorexigenic effects of oxytocin in humans are consistent with evidence from animal studies (Leslie et al., 2018). It is worth noting the study by Agabio et al. (2016) had a very small sample size (N=8-9 per treatment arm), which raises concerns regarding power. Additionally, it used a repeated administration regime, with a divided dose of 96IU delivered daily over 8 weeks. The optimal pattern and dosage of oxytocin administration in repeated administration regimes are currently unclear, with certain administration regimes resulting in no effects or even opposite effects than those expected (Kou et al., 2020). This is not surprising, given that the effects of oxytocin on central intracellular signalling pathways are complex and can vary as a function of the amount of oxytocin that is available extracellularly (Chini et al., 2017). Future studies need to clarify the mechanisms mediating the anorexigenic effects of oxytocin in humans (Maejima et al., 2018), including its potential role, if any, in regulating food craving and feeding in eating disorders.

A number of recent papers have reviewed preclinical evidence regarding the role of oxytocin in addiction, including craving and drug consumption. Preclinical studies have certain distinct advantages compared to human studies, such as the direct central administration of oxytocin (Lee and Weerts, 2016; Bowen and Neumann, 2017), or simpler cue-conditioning in a controlled environment which is not confounded by individual differences in cue association reactivity with multiple different outcomes and expectancies (Bartz et al, 2011). In vivo studies also offer the opportunity to refine the molecular mechanisms underlining the effect of oxytocin on addictive behaviour which is something not always possible in human studies. As such, Bowen and Neumann (2017) reviewed the effects of oxytocin on the neural substrates of addiction, Zanos et al (2018) reviewed the effects of oxytocin on opioid addiction, King et al (2020) reviewed the role of oxytocin in alcohol and drug abuse, and Baracz et al (2020) reviewed the effect of early life stress on the central oxytocin system and susceptibility for drug addiction. The evidence from these reviews concurred on the idea that oxytocin may play an important role in the treatment of addiction, and the need for translational studies in humans to investigate the role of intranasal oxytocin as a pharmacotherapy to reduce craving, at least in relation to alcohol, cannabis, cocaine, opioid, or food addiction.

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Limitations

Apart from the factors discussed above, a number of further limitations should be acknowledged. First, there were considerable individual differences across participants and studies. For example, participants within studies differed considerably in terms of severity of drug or alcohol dependence. Future studies need to consider the possibility that the effects on craving may vary as a function of addiction severity. Second, the use of more than one drug concurrently is common among substance users, who use differing drugs to differing levels ranging from habitual to dependent use (European Monitoring Centre for Drugs and Drug Addiction, 2020). Therefore, it is not clear to what extent other drugs had or were currently being used by participants, to what degree and the impact of these on craving and consumption. Future studies should routinely perform urine drug screening to confirm self-report of abstinence from other drugs. Third, participants receiving substitute opiates were not adequately described. High dose methadone for instance is well known to supress withdrawal-related craving (Clinical Guidelines on Drug Misuse and Dependence Update, 2017) and as such could mediate any reduction in withdrawal-related craving caused by intranasal oxytocin administration. Fourth, the effect of intranasal oxytocin versus placebo on cue-induced or withdrawal-related craving in alcohol or opioid dependent populations cannot be assumed to be the same as the effect on craving of daily nicotine or cannabis smokers due to the differing levels in reinforcement of each substance. Interestingly, one of the confounding factors which appears to limit the efficacy of intranasal oxytocin in reducing craving is their motivation status with regards to seeking treatment for their substance use. McClure et al (2019) and Lee et al (2019) recruited participants specifically who were non-treatment seeking for their substance use and none of these studies found intranasal oxytocin was able to reduce craving or consumption. Not all studies stated the treatment seeking status of participants which prohibited further analysis but we propose that this is included in subsequent studies as it may influence the results. Failure to take into account variability in participant characteristics increases the likelihood of inconsistent or null results and limits our ability to draw any firm conclusions. Fifth, differing measures of craving were used across the studies reviewed here, adding to variability. Sixth, whilst consumption was measured together with craving in many studies, some studies were restricted to only craving. As consumption may occur independently of craving, the potential effect of intranasal oxytocin to reduce substance use independent of changes in craving may have been missed. Finally, maybe the biggest limitation of the studies discussed in this review is the limited sample sizes. This is indeed acknowledged to be a limitation of intranasal oxytocin studies in the field as a whole as recent evaluation of intranasal oxytocin meta-analyses has found that designs are typically statistically underpowered to either detect or reject a wide range of effect sizes (Quintana, 2020). Larger, appropriately powered double blind, placebo-controlled human interventional studies assessing intranasal oxytocin efficacy to reduce craving and consumption across all automated addictive behaviours are warranted.

Conclusions

Craving is an established predictor of automated addictive behaviours but current pharmacotherapies with anticraving properties have limited efficacy or are unsuitable to use due to poor compliance and aspects of their pharmacological profile such as side effects and risk of overdose when used for cue-induced craving. Overall, our findings, consistent with preclinical evidence, indicate that the investigation of intranasal oxytocin as a method to

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decrease cue-induced, acute stress-induced or withdrawal-related craving regarding addictive behaviours related to alcohol, cannabis, opioids, cocaine, or nicotine warrants further attention. Combined with an excellent tolerability and safety profile, the distinct effect of intranasal oxytocin on amygdala activity is unique amongst existing anticraving pharmacotherapies. This effect compliments its attractiveness as a potential ad-hoc medication to be administered following exposure to drug-related cues, as an asthmatic would use an asthma inhaler during an attack, to ultimately prevent relapse. Future studies should systematically investigate the role of a range of factors that might affect efficacy (e.g. treatment regimes and sample characteristics), and elucidate the neurobiological mechanisms underlying the effects of intranasal oxytocin on cue and withdrawal-related craving in adequately powered randomised controlled trials.

Data Availability Statement

Data sharing not applicable – no new data generated.

Accepted Article

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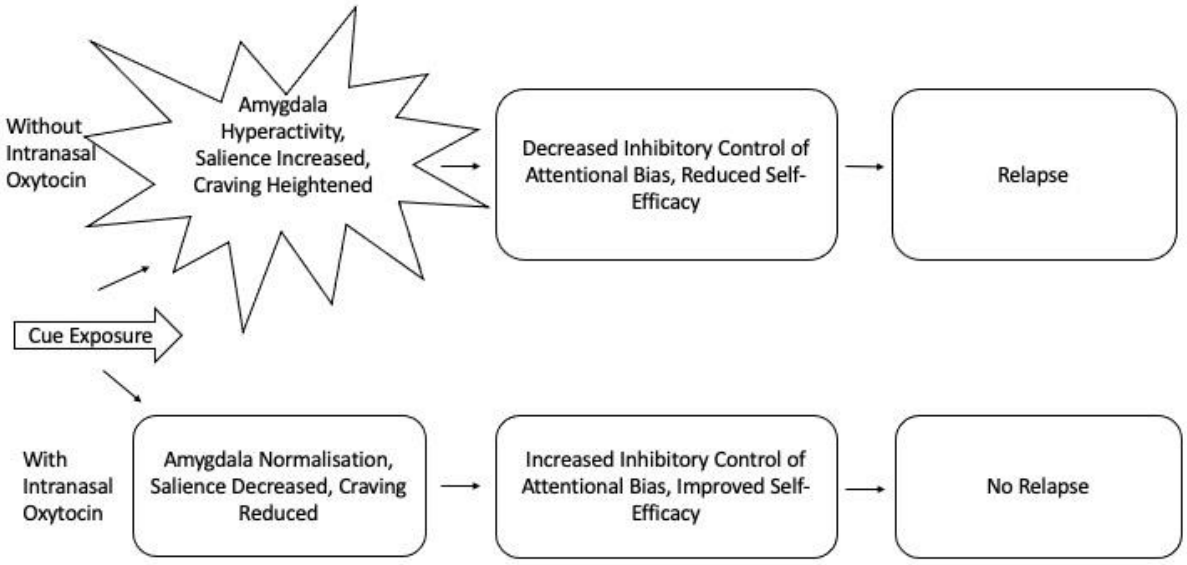

Figure 1: Proposed model of mechanism for cue induced opioid craving. (Top) Under standard conditions, following exposure to drug related cues the amygdala becomes hyperactive, craving is heightened and the salience of cues is increased. Self-control of attentional bias is decreased and this leads to relapse. (Bottom) Following the administration of intranasal oxytocin, the amygdala response to drug-related cues is normalised, the salience of cues is decreased, self-control of attentional-bias is increased and relapse is avoided.

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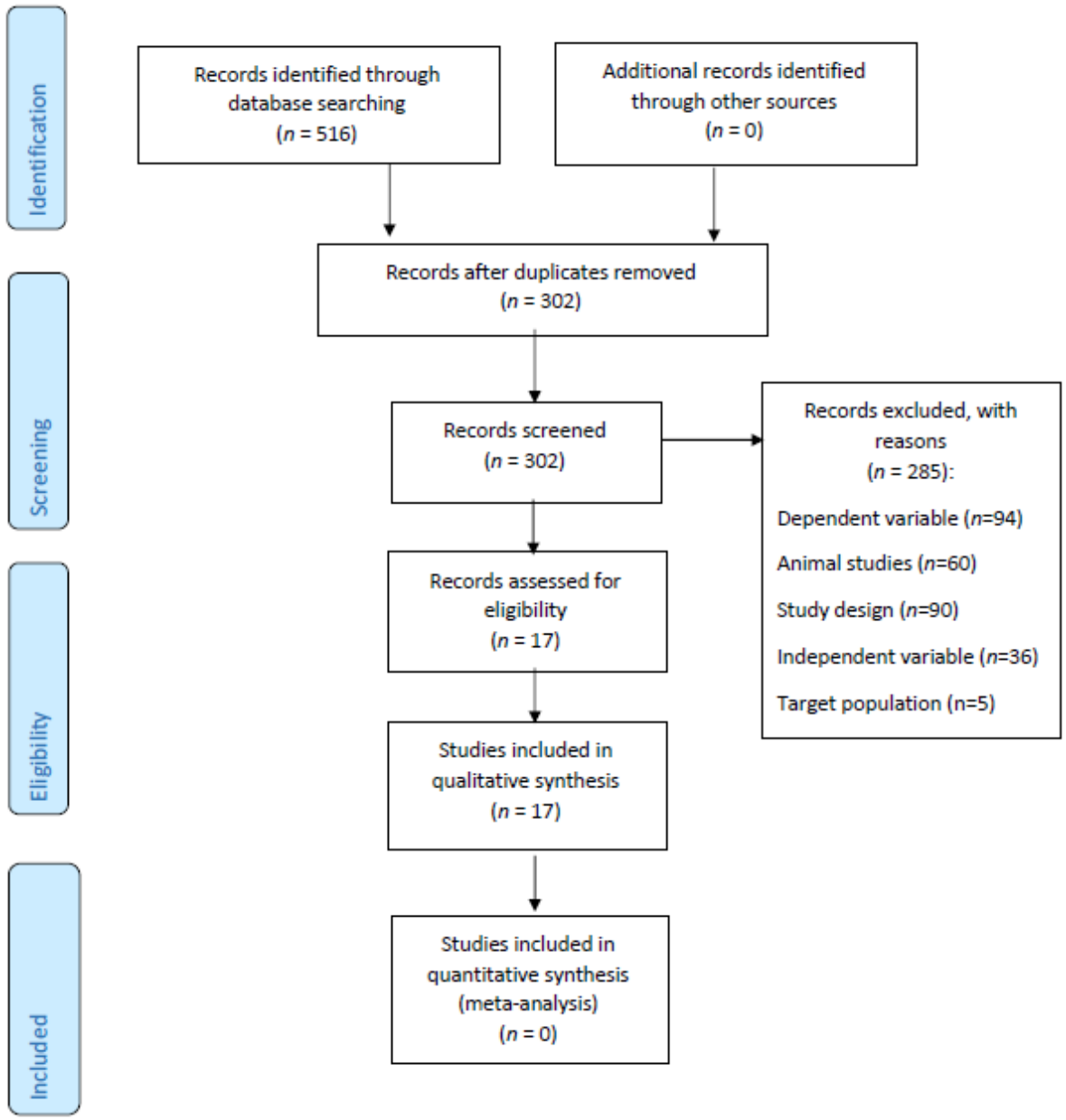

Figure 2: PRISMA diagram of search strategy

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Table 1. Data extracted from the 17 studies meeting our inclusion criteria.

Study		Addictive Substance/Behaviour		Study Design			Intranasal Oxytocin Administration				Effects of Oxytocin vs Placebo	
First author & Date	Country of Origin	Substance/Behaviour	Diagnosis/Severity	Craving Type Measured	Design	Sample Size	Dose	Post Dosing Measurement Interval (Single Dose)	Administration Regime (Repeat Dose)	Outcome Measures	Craving ratings/ BOLD response	Consumption
Single dose oxytocin administration												
Bach et al, 2019 (same sample as Hansson et al 2017)	Germany	Alcohol	No diagosis of SUD - social drinkers (including moderate/ heavy social drinking; minimum alcohol consumption ≥ 1	Cue-induced	RD, DB, W	13m	24IU	60 mins (onset of fMRI cue-induced craving paradigm)	N/A	fMRI BOLD connectivity response to cue-induced reactivity paradigm (OT vs. PL)	↓ (R NAc-R Cuneus; L Thalamus-R LOC) ↑ (R PrCG-R PCG)	N/A

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			standard drink, defined as 12g alcohol, on at least 2 days per week)							Correlations between mean subjective alcohol cue-induced craving and OT vs. PL fMRI BOLD connectivity response	with R NAc-R Cuneus: ↑ with Thalamus-LOC: - with PrCG-PCG: -	N/A
Flanagan et al, 2019	USA	Alcohol	Alcohol Use Disorder (DSM V) and PTSD (at least 5	Acute stress-induced (Trier Social	RD, DB, B	OT=32 m PL=35m	40IU	60-120 mins (0-60 min post-stress	N/A	study-specific subjective rating scale for craving (VAS)	–	N/A

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	days abstinent, by self report)	Stress Task)		inductio n)

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Mitchell et al, 2016	USA	Alcohol	Alcohol Abuse (DSM IV - non physically dependent)	Cue-induced	RD, DB, W	32 (13f)	40IU	30 -90 mins	N/A	Alcohol Urge Questionnaire	- (main effect of OT); ↓ if high attachment anxiety; ↑ if low attachment anxiety	N/A

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Stauffer et al, 2019	USA	Alcohol	Alcohol Use Disorder (DSM V) and PTSD	Cue-induced	RD, DB, W	47m patients 36m controls	20IU, 40IU	75 mins (after water cue exposure) 85 mins (after alcohol cue exposure)	N/A	Single VAS ("How much are you currently craving alcohol?")	–	N/A
McRae-Clark et al, 2013	USA	Cannabis	Marijuana Dependence (DSM-IV)	Acute stress-induced (Trier Social Stress Task)	RD, DB, B	OT=8 (1f) PL=8 (3f)	40IU	60-120 mins (pre-stressor, 0-, 5-, 35-, and 60-minutes post-stress induction)	N/A	Marijuana Craving Questionnaire (total score)	- (pre-stressor) ↓ (at 0- and 5- mins post-stressor) - (at 35- and 60-mins post-stressor)	N/A

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Reed et al, 2019	USA	Cannabis	smoking between 2-18 cannabis cigarettes per week but not meet moderate to severe DSM-V criteria for Cannibus Use Disorder	Acute stress-induced (Trier Social Stress Task) vs no-stress task	RD, W	63 (32f)	40IU	30-360 mins	N/A	Cannabis self-administration 60-240 min post dosing (0-180 mins post-stressor	N/A	–
										Drug craving (VAS) 30 min post-dosing (pre-stressor); 240min - 360min post-dosing (180min - 300min post-stressor)	–	N/A

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Lee et al, 2014	USA	Cocaine (abstinent)	Cocaine dependence (DSM-IV-TR)	Withdrawal-related	RD, DB, W	23 (1f)	24IU	45mins	N/A	Urge to use VAS (baseline)	↑	N/A
				Cue-Induced						Cue-induced urge to use plus 5 arousal related questions (all VAS, controlling for baseline)	↑ (excitement) - (urge/irritation, heart poundi ng)	N/A
McClure et al, 2019	USA	Nicotine	Smoke an average of 5 cigarettes/ day for at least 6 months (abstained for 12 hours before laboratory session)	Acute stress-induced (Trier Social Stress Task)	RD, B	OT = 72 (45f); PL = 72 (46f)	40IU	75 and 95 mins (two assessments)	N/A	4 Item Craving Questionnaire (before dosing, 30/60/80/100, 120, 125, 150, 180 post dosing) (TSST 40-60 min post-dosing))	–	N/A

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											latency to smoke (resistance task) & ad-libitum smoking (120-180 min post-dosing)	N/A	-
Miller et al, 2016	USA	Nicotine	Daily smokers (abstained for 12 hours before laboratory session)	Withdrawal-related	RD, DB, W	17 (6f)	20IU	baseline and for 60 min (multiple assessments)	N/A	Short Tobacco Craving Questionnaire & Brief Questionnaire of Smoking Urges	-	N/A
				Cue-induced (30 min after top up)			top-up: 20IU (75 min after first dose)	120-210 min from first dose (multiple assessments)	N/A	(as above)	↓	N/A

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Van Hedger et al, 2018	USA	Nicotine	Daily smokers (abstained for 12 hours before laboratory session)	Withdrawal-related	RD, B & W	PL-PL=16 (7f) OT-PL=16 (7f) PL-OT=16 (7f)	40IU	baseline, 20 min post-dosing	N/A	Short Tobacco Craving Questionnaire at baseline (withdrawal-related)	–	N/A
				Acute stress-induced (Trier Social Stress Task)				60m (immediately after TSST)		Short Tobacco Craving Questionnaire following Trier Social Stress Test	–	N/A
Van Hedger et al 2019	USA	Nicotine	Daily smokers (abstained for 18 hours before laboratory session)	Withdrawal-related	DB, W	35 (17f)	40IU	baseline, 30m, 120-180 min (every 20 min)	N/A	Short Tobacco Craving Questionnaire & Brief Questionnaire of Smoking Urges	↓ (desire to smoke)	N/A
				Withdrawal-related				30m		Demand for cigarettes	-	N/A

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				Substance-induced				60-120 min		Desire to smoke	↓ (after first smoking opportunity)	N/A
								60-120 min		number of cigarettes smoked	N/A	↓
Moeini et al, 2019	Iran	Opioids	Heroin dependence (DSM-IV) (Abstinent for 6-9 days)	Cue-induced	RD, DB, B	OT=29 m PL=29m	40IU	45 mins	N/A	Desire for Drug Questionnaire (60 min post-dosing)	↓	N/A
										VAS (60 min post-dosing)	↓	N/A

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Woolley et al, 2016	USA	Opioids	Heroin use (on substitute opiates and abstinent from all illicit drugs for 2 weeks prior to study enrollment)	Cue-induced	RD, DB, W	33m	40IU	45 min	N/A	Craving & Urge to use (VAS) (before drug , directly before cue exposure, directly after cue exposure, 3 min following cue exposure, and again at the end of the study (135 min post-dosing)).	–	N/A
Repeated oxytocin administration												
Pedersen et al, 2013	USA	Alcohol	Alcohol dependent inpatients (average consumption of 8-30	Withdrawal-related	RD, DB, B	OT=7 (1f) PL=4 (1f)	24IU, twice daily (48IU per day)	N/A	At 09:00 and 17:00 for 3 consecutive days	Penn Alcohol Craving Scale shortly after morning	-	N/A

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							standard drinks per day for at least 2 weeks prior to enrollment in the study) with history of severe withdrawal symptoms who undergo medical detoxification using symptom-driven administration of lorazepam
							dose only on days 2 and 3

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										Alcohol Craving Visual Analog Scale shortly after morning dose only on days 2 and 3	↓ (day 2) - (day 3)	N/A
Sherman et al, 2017	USA	Cannabis	Cannabis-dependent adults (DSM-IV)	-	RD, B	OT=8 (3f) PL=8 (3f)	40IU plus motivational enhancement therapy (MET)	OT administered 30 before first 2 out of 3 MET sessions in weeks 1, 2 and 4		Timeline Follow-Back test during study period	N/A	-

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Stauffer et al, 2016	USA	Cocaine, Opioids	Opioid use disorder (receiving methadone) and concurrent Cocaine use disorder (DSM-IV)	Cue-induced	RD, DB, B	OT=11 (5f) PL=11 (6f)	40IU, twice daily (80IU per day)	N/A	2 weeks, doses 8-10hrs apart	Self-reported drug use during treatment period	N/A	–
										Urine sample measurement of benzoylecgonine(primary cocaine metabolite)	N/A	–
										Cue-induced craving (VAS) for heroin/cocaine (before cue, after 1 min of drug	-	N/A

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										cue video, after 3 min of neutral video), at day 1 (baseline), Day 15 (after 2 weeks of treatment), and Day 21 (after washout week)		
Agabio et al, 2016	Italy	Food	Binge eating disorder (DSM V); BMI>=30 (no current bulimia or anorexia)	Baseline craving	RD, DB, B	OT=8(7f) PL=9f	24IU, four times daily (96IU per day)	N/A	8 weeks (20mins prior to three meals and sleep)	Number of binge eating episodes (weeks 1, 4, 8 and once post treatment end)	N/A	–
										Food craving (VAS; weeks 1, 4, 8 and once post treatment end)	–	N/A

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Notes: B = between subject design; CG: Cingulate gyrus; DB = double blind; M = males; F = females; FG: frontal gyrus; hipp = hippocampus; IFG=inferior frontal gyrus; IPL = inferior parietal lobule; IU = international units; L = left; MET = Motivational enhancement therapy; MGF=Middle frontal gyrus; N/A = not applicable; LOC: Lateral occipital cortex; NAc = Nucleus Accumbens; OG=occipital gyrus; OT = oxytocin; PL = placebo; PrCG = paracingulate gyrus; PCG = precentral gyrus; RD = randomised; R = right; SMA=supplementary motor area; SFG: Superior frontal gyrus; STG: superior temporal gyrus; W = within subject design; VAS = visual analog scale;* = not stated; Statistically significance defined as P=<0.05; − = no effect for intranasal versus placebo; ↓ = intranasal oxytocin versus placebo reduced craving or consumption; ↑ = intranasal oxytocin versus placebo increased craving or consumption.

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Table 2. Summary effects of intranasal oxytocin, compared to placebo, on outcome measures of craving and consumption

Addictive behaviour		**Behavioural craving ratings***	**Consumption**
	N	Outcomes	Outcomes
Alcohol			
Single dose	**3 (4)****	X / (↓↑)*** / X	
Repeated dose	**1**	↓	
Cannabis			
Single dose	**2**	↓ / X	X
Repeated dose	**1**		X
Cocaine			
Single dose	**1**	↑	
Repeated dose (cocaine/opioids)	**1**	X	X
Nicotine			
Single dose	**4**	↓ / ↓ / X / X	↓ / X
Repeated dose	**0**		
Opioids			
Single dose	**2**	↓ / X	
Repeated dose	**0**		
Food			
Single dose	**0**		
Repeated dose	**1**	X	X
Total	**16 (17)***		

Notes: X = no effect; ↓ = decrease; ↑ = increase; N = number.

* Includes ratings in response to cue-induced, acute stress induced or withdrawal related craving. ** One study does not report directly behavioural craving ratings, but the association between behavioural craving ratings during an fMRI cue-induction craving paradigm and connectivity between the blood oxygen level dependent (BOLD) response in specific brain regions. *** No main effect; effect depended on attachment anxiety (increased rating if low attachment anxiety, decreased rating if high attachment anxiety).

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