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THEMED ISSUE REVIEW

# The role of glucagon-like peptide 1 (GLP-1) in addictive disorders

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Drug, alcohol and tobacco use disorders are a global burden affecting millions of people. Despite decades of research, treatment options are sparse or missing, and relapse rates are high. Glucagon-like peptide 1 (GLP-1) is released in the small intestine, promotes blood glucose homeostasis, slows gastric emptying and reduces appetite. GLP-1 receptor agonists approved for treating Type 2 diabetes mellitus and obesity have received attention as a potential anti-addiction treatment. Studies in rodents and non-human primates have demonstrated a reduction in intake of alcohol and drugs of abuse, and clinical trials have been initiated to investigate whether the preclinical findings can be translated to patients. This review will give an overview of current findings and discuss the possible mechanisms of action. We suggest that effects of GLP-1 in alcohol and substance use disorders is mediated centrally, at least partly through dopamine signalling, but precise mechanisms are still to be uncovered.

**LINKED ARTICLES:** This article is part of a themed issue on GLP1 receptor ligands (BJP 75th Anniversary). To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v179.4/issuetoc

**KEYWORDS**
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## 1 | INTRODUCTION

Worldwide, an estimated 35 million people suffer from substance use disorders (SUDs) (United Nations Publication, 2020) and 280 million people from alcohol use disorder (AUD) (World Health Organization [WHO], 2018). In 2015, a quarter of the global adult population (above 15 years of age) were current users of tobacco (WHO, 2019). AUD is associated with high mortality due to medical complications, injuries (Carvalho et al., 2019) and suicide (Borges et al., 2017). AUD has serious consequences not only for the individual suffering from this disease but also for the relatives (Connor et al., 2016) and society at large due to high healthcare and socio-economical costs (WHO, 2018). Harmful use of alcohol is globally estimated to account for over 5% of deaths, making it a leading cause of preventable deaths (WHO, 2018), and the treatment gap is wide when compared with other psychiatric disorders (Kohn et al., 2004).

Globally, an estimated 19 million people are users of cocaine (United Nations Publication, 2020), and about five million people suffer from cocaine use disorder (CUD) (Peacock et al., 2018). Deaths caused by cocaine overdose are rapidly increasing in recent years, now rivalling or exceeding opioid overdose deaths in some American populations (Kampman, 2019). When it comes to stimulants, an estimated 27 million

**Abbreviations:** AUD, alcohol use disorder; DAT, dopamine transporter; DPP-4, dipeptidyl peptidase-4; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; fMRI, functional MRI; GLP-1, glucagon-like peptide 1; NAc, nucleus accumbens; NTS, nucleus tractus solitarius; OUD, opioid use disorder; SPECT, single-photon emission CT; SUD, substance use disorder; VTA, ventral tegmental area.

  

people used amphetamines in 2018 (United Nations Publication, 2020). Amphetamines are associated with severe physical health consequences, psychiatric illness, aggressive behaviours, risky sexual behaviour and the risk of contracting blood-borne viruses after needle sharing (Lee et al., 2018). In 2018, an estimated 58 million people used opioids; this number includes those who misused pharmaceutical synthetic opioids (United Nations Publication, 2020). In 2016, more than 100,000 people died from opioid overdose, most likely from respiratory depression. The societal costs are high, due to harm to family cohesion, reduced employment and the cost of crimes (Strang et al., 2020).

Together with alcohol, tobacco use is one of the largest preventable causes of premature death, but still, six million people die due to tobacco-related diseases every year (The Tobacco Atlas, 2021). Despite the available treatment options, many smokers attempt to quit without medication or support, with a failure rate of 95–98% (Prochaska & Benowitz, 2016). There is also a high prevalence of co-use of two or more substances. This has consequences for the associated disease burden, treatment strategies and outcomes. Most (50 - 90%) people who use cocaine also consume alcohol simultaneously (Goldstein et al., 2009), and 80% of individuals who use cocaine or opioids are also smoking tobacco (Kalman et al., 2005). A review based on preclinical and clinical studies has shown that co-use of alcohol and nicotine potentiates craving and self-administration of both substances (McKee & Weinberger, 2013).

The mechanisms behind addictive disorders have been extensively reviewed by several authors and comprise drug-induced dysregulations of numerous neurocircuits and neurochemicals, such as dopamine, opioid peptides, corticotropin-releasing factor (CRF), dynorphin, glutamate and GABA, and also vulnerability factors such as genetics, initial drug exposure and social environment (Badiani et al., 2011; Berridge & Robinson, 2016; Koob & Volkow, 2016; Volkow, Michaelides, et al., 2019; Zorrilla & Koob, 2019). Attention has also been directed to the behavioural, cognitive and neurobiological heterogeneity of different SUDs, even though they are all classified diagnostically, without regard to drug class (Badiani et al., 2011).

There are several theories about the development of addiction, but among the most dominant is the idea that a process termed 'incentive sensitization' underlies the excessive 'wanting' triggered by reward cues in addicted individuals, without necessarily 'liking' the drug. 'Wanting' is believed to be generated in the dopaminergic mesolimbic system, projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), whereas 'liking' comes from tiny hedonic hotspots in the brain and is not dependent on dopamine release. As an individual becomes more addicted, 'wanting' will overshadow 'liking' and become independent of 'liking' (Berridge & Robinson, 2016). 'The dark side' theory of addiction contends that impulsivity, compulsivity and negative urgency are derived from stress experienced during withdrawal or 'negative affect stage', even several months into abstinence. The neurocircuitry identified involves several neuropeptides, including CRF (Zorrilla & Koob, 2019). Dopamine plays a prominent role in the immediate reinforcing/rewarding effects of drugs—'the dopamine theory', and dysregulation of the dopamine system is thought to contribute to the addicted state as a predisposing factor and/or a consequence of chronic substance use (Volkow, Michaelides, et al., 2019).

Pharmacological treatments against AUD, opioid use disorder (OUD) and tobacco use disorder are available (see Table 1) (European Monitoring Centre for Drugs and Drug Addiction, 2012; Kampman, 2019; Kranzler & Soyka, 2018; Lee et al., 2018; Prochaska & Benowitz, 2016; Wang et al., 2019). The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) do not approve any medications for the treatment of cocaine or stimulant use disorders. Even when pharmacotherapy is available, success rates for achieving long-term abstinence are modest, highlighting the urgent need for new, effective medications against SUD and AUD (Kampman, 2019; Lee et al., 2018; Lyon, 2017; National Institute on Drug Abuse [NIDA], 2020; Volkow, 2020; Volkow, Jones, et al., 2019).

## 2 | GLUCAGON-LIKE PEPTIDE 1

In the search for new treatments of AUD (Lyon, 2017), nicotine use disorder (Polosa & Benowitz, 2011) and SUD (Klein, 2016), the gut hormone glucagon-like peptide 1 (GLP-1) has received much attention (Eren-Yazicioglu et al., 2021; Fink-Jensen & Vilsbøll, 2016; Jerlhag, 2020; Reddy et al., 2014; Skibicka, 2013). Endogenous GLP-1 is produced by cleavage of the prohormone proglucagon in the intestinal endocrine L cells and is released in response to food intake. It is rapidly inactivated with a half-life of just 1–2 min by the enzyme, dipeptidyl peptidase 4 (DPP-4). GLP-1 receptors are present in many tissues throughout the body, and GLP-1 potentiates insulin secretion, inhibits glucagon secretion, slows gastric emptying

**TABLE 1** Current FDA- and EMA-approved pharmacological treatments for alcohol and substance use disorders

| SUD | FDA and EMA approved | Reference |
|---|---|---|
| Alcohol (AUD) | Disulfiram, acamprosate, naltrexone, nalmefene (only EMA-approved) | Kranzler & Soyka, 2018 |
| Cocaine (CUD) | No approved medications | Kampman, 2019 |
| Stimulants | No approved medications | Lee et al., 2018 |
| Opioids (OUD) | Opioid agonist therapy: methadone and buprenorphine, naltrexone, supervised injectable heroin (few countries) | Wang et al., 2019; European Monitoring Centre for Drugs and Drug Addiction, 2012 |
| Nicotine | Bupropion, varenicline<br>Nicotine replacement therapies: lozenges, patch, gum, spray, inhaler | Prochaska & Benowitz, 2016 |

Abbreviations: AUD, alcohol use disorder; CUD, cocaine use disorder; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; OUD, opioid use disorder; SUD, substance use disorder.

and reduces appetite (Holst, 2007). GLP-1 is also produced in the nucleus tractus solitarius (NTS) of the brain stem and is released as a neurotransmitter in several brain regions. GLP-1 receptors are expressed in brain regions believed to be involved in reward and addiction (Cork et al., 2015; Han et al., 1986; Jensen et al., 2018; Merchenthaler et al., 1999; Rinaman, 2010; Vrang & Grove, 2011). Studies in mice indicate that several GLP-1 receptor agonists can cross the blood–brain barrier at least to some extent when administered systemically (Gabery et al., 2020; Kastin et al., 2002; Salinas et al., 2018; Secher et al., 2014; Zhang et al., 2020). A recent clinical trial including patients with Parkinson's disease reported that systemically administered **exenatide**, a GLP-1 receptor agonist, in a licensed dose for the treatment of Type 2 diabetes, did cross the blood–brain barrier (Athauda et al., 2017). In contrast, another clinical study including patients with Type 2 diabetes treated with the GLP-1 receptor agonist **liraglutide** found limited transfer of liraglutide to the CSF (Christensen et al., 2015). Still, it remains to be determined if other available GLP-1 receptor agonists differ with respect to brain penetration in humans.

### 2.1 | Types of GLP-1 receptor agonists and safety

One attractive aspect of GLP-1 receptor agonists, as opposed to other neuropeptides examined in the context of addiction (such as **orexin**, **relaxin**, **ghrelin**, **NPY**, CART, dynorphin, neurotensin, **oxytocin** and **α-MSH**—for an overview, see 'The Role of Neuropeptides in Addiction and Disorders of Excessive Consumption', International Review of Neurobiology, Vol. 136, 2017, Edited by Todd E. Thiele), is that a number of these compounds are already used clinically, meaning that they could become available rapidly to AUD or SUD patients if the approach proves successful. The FDA and EMA have approved a number of GLP-1 receptor agonists, but in this review, we will focus on those compounds that have been investigated preclinically, that is, exenatide, liraglutide, **semaglutide** and **dulaglutide**. GLP-1 receptor agonists differ in pharmacokinetic and pharmacodynamic properties, with newer agonists developed to be much longer acting relative to the native GLP-1 peptide and the first synthetic GLP-1 receptor agonists. The ligands also differ in their ability to activate second messenger systems (biased agonism; see another chapter in this themed issue), and with respect to the degree of receptor internalization they stimulate, all of which may influence their effectiveness as possible AUD or SUD treatments.

Early observational studies (Chis & Fodor, 2017; Elashoff et al., 2011) reported an increased risk of pancreatitis or pancreatic cancer when patients were treated with GLP-1 receptor agonist. This might have hampered the incentive to investigate the potential effects of GLP-1 receptor agonists as a treatment against AUD, as patients are already at a higher risk for developing pancreatitis or pancreatic cancer (National Institute for Health and Care Excellence, 2011). However, a recent systematic review and meta-analysis including three high-quality long-term randomized clinical trials with 9347 patients with Type 2 diabetes allocated to GLP-1 receptor agonist treatment, found no significant association (Storgaard et al., 2017). Another meta-analysis confirmed this finding in data based on GLP-1 receptor agonist therapy and cardiovascular outcome, including 55,921 patients (Abd El Aziz et al., 2020), as well as studies comparing the risk of pancreatitis (Azoulay et al., 2016a) or pancreatic cancer (Azoulay et al., 2016b) between GLP-1 receptor agonists and other antidiabetic medications.

## 3 | ROLE OF GLP-1 IN ALCOHOL USE DISORDER

### 3.1 | Basic research, effects of GLP-1 receptor agonists

The effects of GLP-1 receptor activation on alcohol consumption in laboratory animals have been investigated more extensively compared with other substances of abuse. Several GLP-1 receptor agonists have been tested in male rats, mice and non-human primates. Most studies have focused on acute effects, but more recent investigations have also assessed the effects of subchronic or repeated dosing regimens (Marty et al., 2020; Thomsen, Barrett, et al., 2017). This is important, as AUD is a chronic, relapsing illness that typically requires long-term treatment, and acute effects do not always adequately predict the effectiveness of repeated or chronic dosing.

Systemic administration of the GLP-1 receptor agonist exenatide has been reported to decrease or abolishe the rewarding effects of systemically injected alcohol, measured by conditioned place preference. This was the case when treatment was administered during the conditioning phase and also during the expression phase (Egecioglu, Steensland, et al., 2013; Shirazi et al., 2013) or when injected directly into the NTS (Vallöf, Vestlund, et al., 2019) or into the shell region of the NAc (Vallöf, Kalafateli, et al., 2019). Similar results were reported for the GLP-1 receptor agonist liraglutide (Vallöf et al., 2016).

Systemically administered exenatide (Egecioglu, Steensland, et al., 2013; Shirazi et al., 2013; Sirohi et al., 2016) or the exenatide analogue AC3174 (Suchankova et al., 2015) and centrally administered exenatide into the VTA (Colvin et al., 2020; Shirazi et al., 2013), NTS (Vallöf, Vestlund, et al., 2019), NAc, dorsal hippocampus, lateral hypothalamus (Colvin et al., 2020), NAc shell (Colvin et al., 2020; Vallöf, Kalafateli, et al., 2019) and laterodorsal tegmental area (Vallöf, Kalafateli, et al., 2019) has been reported to significantly decrease alcohol intake in a two-bottle choice paradigm. Exenatide also decreases operant oral alcohol self-administration in rats when injected systemically (Egecioglu, Steensland, et al., 2013) or into the VTA (Dixon et al., 2020). However, all those treatment modalities also affect food consumption (Grill, 2020), and it is therefore not clear, if the effects of GLP-1 receptor agonists in these models can be distinguished from potential effects due to the caloric value of alcohol.

The effects of systemically injected exenatide were abolished in mice where GLP-1-receptors were ablated in the CNS, indicating that the effects on alcohol intake are most likely to be centrally rather than peripherally mediated (Sirohi et al., 2016).

Effects of chronic or repeated GLP-1 receptor agonist administration are less consistent: In one study, the GLP-1 receptor agonists liraglutide and semaglutide potently decreased ethanol intake when given acutely, but when testing repeated administration, effects were transient, not lasting more than 48 h (Marty et al., 2020). Another study found modest or variable indications of development of tolerance after repeated liraglutide administration (Vallöf et al., 2016). However, once-weekly injections of the long-acting GLP-1 receptor agonist dulaglutide for 5 or 9 weeks decreased alcohol intake in male and female rats with no indication of tolerance (Vallöf et al., 2020). Also, subchronic administration of liraglutide reduced operant oral alcohol self-administration in rats (Vallöf et al., 2016). Finally, a model of relapse behaviour reported an attenuated binge-like increase in alcohol drinking, with protracted latency to the first drink and reduced drinking bouts, after subchronic treatment with exenatide (Thomsen, Dencker, et al., 2017).

The effects of GLP-1 receptor stimulation on alcohol intake have also been reported in non-human primates (Thomsen et al., 2018). The GLP-1 receptor agonists exenatide and liraglutide were tested in alcohol-preferring African vervet monkeys with long-term alcohol experience. In the exenatide experiment, exenatide or vehicle was administered for 5 weeks, and in the liraglutide experiment, liraglutide or vehicle was administered for 2 weeks, to obtain steady-state blood levels. In both studies, no alcohol was available under up-titration of the study-drug. Alcohol was then reintroduced for 2 weeks, and alcohol intake was recorded while the assigned GLP-1 receptor agonist treatment was continued. Both GLP-1 receptor agonists reduced alcohol consumption without emetic events (Thomsen et al., 2018).

To investigate the effect of endogenous GLP-1 on alcohol intake, GLP-1 release from the small intestines (as the precursor proglucagon) was stimulated using two different receptor agonists of the orphan receptor **GPR119**, **AR231453** and APD668. However, neither receptor agonist decreased alcohol intake (Marty et al., 2020). This might be due to rapid degradation or limited access to the brain of systemically released native GLP-1 and supports the contention that GLP-1 effects on alcohol consumption are centrally mediated. Another approach employed to increase levels of endogenous GLP-1 is the inhibition of DPP-4, an enzyme responsible for the degradation of GLP-1 and other peptides, by compounds such as **sitagliptin**. Still, this approach did not significantly affect alcohol intake (Marty et al., 2020). However, systemic administration of the GLP-1 receptor antagonist **exendin**-9 increased alcohol intake (Shirazi et al., 2013), supporting a role for endogenous GLP-1 in modulating alcohol consumption. DPP-4 degrades endogenous GLP-1 within minutes, and DPP-4 inhibitors are approved for treatment of Type 2 diabetes (Deacon, 2020) as an indirect way to stimulate GLP-1 receptors (Łupina et al., 2020). One study of ethanol withdrawal-induced anxiety in rats reports delayed withdrawal-induced anxiety after treatment with a DPP-4 inhibitor (Sharma et al., 2015a), but it is not clear what the neural mechanism behind this effect might be.

Regarding interactions between alcohol consumption and the endogenous GLP-1 system, elevated GLP-1 receptor expression in

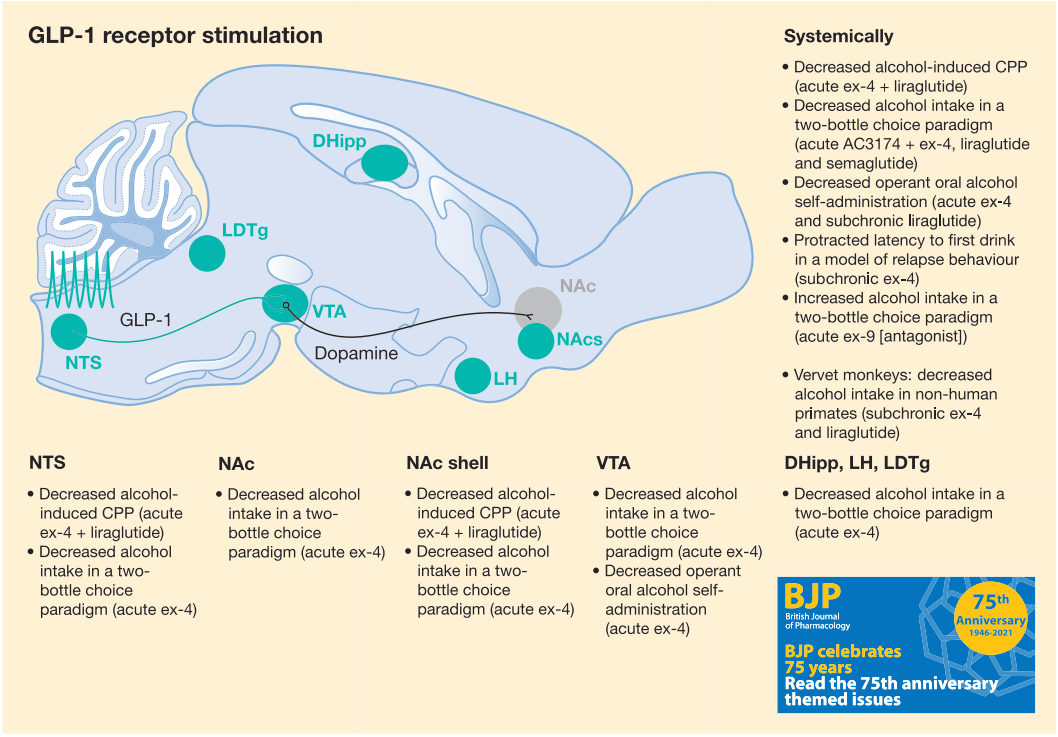


**FIGURE 1** Effects of glucagon-like peptide 1 (GLP-1) receptor stimulation on alcohol reward-related behaviours in preclinical models. CPP, conditioned place preference; DHipp, dorsal hippocampus; ex-4, exenatide; ex-9, exendin 9–39; LDTg, laterodorsal tegmental nucleus; LH, lateral hypothalamus; NAc, nucleus accumbens; NAcs, nucleus accumbens shell; NTS, nucleus tractus solitarius; VTA, ventral tegmental area

the NAc has been reported in high alcohol-consuming animals compared with low alcohol-consuming animals (Vallöf, Kalafateli, et al., 2019). No changes in GLP-1 receptor expression in the VTA, amygdala, hippocampus, prefrontal cortex or striatum were observed in the same study (Vallöf, Kalafateli, et al., 2019).

A notable omission from the published reports are those on the effects of GLP-1 receptor agonists on truly alcohol-dependent animals. In most of the studies described above, animals were exposed to modest quantities of alcohol in models focusing on the reinforcing aspects of alcohol consumption. AUD is characterized by continued drinking despite negative consequences, and studies addressing this aspect of AUD are lacking. Also, studies addressing the effects of GLP-1 receptor agonists on the long-term adaptations of the brain to high levels of alcohol consumption are needed (see Figure 1 for a summary).

## 3.2 | Clinical/human studies

The potential effects of GLP-1 receptor agonists in reducing alcohol intake in humans were first reported in a scientific meeting abstract from 2011, in a cross-sectional review among patients with Type 2 diabetes treated with liraglutide for 3 months (Kalra, 2011).

Two clinical trials have investigated the effects of GLP-1 receptor agonists on alcohol intake in 'heavy drinkers' or patients diagnosed with AUD (Table 2). The first study—performed by our group—is a randomized, double-blinded, placebo-controlled clinical trial investigating reduction in heavy drinking days after treatment with exenatide once weekly for 26 weeks in patients diagnosed with AUD. A subgroup of the patients had functional MRI (fMRI) and single-photon emission CT (SPECT) scans performed at baseline and after 26 weeks of treatment, to investigate potential neurobiological changes (the clinical study has been completed, and the manuscript is in preparation, ClinicalTrials.gov identifier NCT03232112) (Antonsen et al., 2018). The second trial is a double-blind, randomized, placebo-controlled, crossover study design investigating the acute effects of exenatide on alcohol intake in heavy drinkers (ClinicalTrials.gov identifier NCT03645408; recruitment is ongoing [April 2021]).

In terms of GLP-1-related mechanisms that might affect vulnerability to or development of AUD, a genetic study composed of four human genetic association studies has shown that the GLP-1 receptor 168Ser allele is associated with increased alcohol self-administration and a higher fMRI blood-oxygen-level-dependent (BOLD) response in the globus pallidus when receiving rewarding feedback in the monetary incentive delay task. This suggests a more dysfunctional reward system, which might contribute to a higher vulnerability to AUD (Suchankova et al., 2015). A clinical trial investigating the effects of alcohol given intravenously or intragastrically reports no changes in plasma GLP-1 concentrations in healthy male volunteers (Lanng et al., 2019). This is supported by other studies in healthy volunteers, consuming alcohol before an oral glucose test (Svartberg et al., 1998), after an overnight fast

**TABLE 2** Unpublished or ongoing clinical trials of GLP-1-based therapies for addictive disorders

| SUD | Study name | Drug | Administration | Estimated patient enrolment | Primary outcome(s) | Expected end date | NCT identifier |
|---|---|---|---|---|---|---|---|
| Alcohol | EXALT | Exenatide | s.c., 2 mg, once weekly | 127 | Reduction in heavy drinking days in patients with AUD, after 26 weeks of treatment | October 2020 | NCT03232112 |
| Alcohol | | Exenatide | s.c. single injection, 5 μg | 36 | Alcohol consumption for 4 h in heavy drinkers, alcohol craving for 4 h in heavy drinkers | December 2021 | NCT03645408 |
| Alcohol/nicotine | GHADD | Exenatide | i.v. dose 0.06 pmol·kg$^{-1}$·min$^{-1}$ | 95 | Functional MRI measure of brain activation during cigarette, alcohol and food picture evaluation task. | August 2020 | NCT02690987 |
| Nicotine | DAL | Liraglutide | s.c., 3.0 mg, once daily | 40/80? | 7-day point prevalence smoking abstinence at 12 weeks, 7-day point prevalence smoking abstinence at 26 weeks | May 2021 | NCT03712098 |
| Nicotine | SKIP | Dulaglutide | s.c., 1.5 mg, once weekly | 256 | Point prevalence abstinence rate at Week 12 | March 2021 | NCT03204396 |
| Opioids | | Liraglutide | s.c., 3.0 mg, once daily | 40 | Change in self-reported cue-elicited drug craving, change in ambient drug craving over time | December 2021 | NCT04199728 |

Abbreviations: AUD, alcohol use disorder; GLP-1, glucagon-like peptide 1; NCT, National Clinical Trial; SUD, substance use disorder.

(Calissendorff et al., 2012) or after consumption of red wine (Abraham et al., 2016). However, in patients with Type 2 diabetes, who consumed alcohol and a fat-rich meal, postprandial GLP-1 levels were decreased (Dalgaard et al., 2004). It is thus unclear whether the latter result can be attributed to alcohol ingestion, as opposed to other nutrients.

Detoxified patients with AUD have been reported to have a lower serum DPP-4 concentration than healthy controls, and it is hypothesized that this diminished activity, may be involved in the neuroendocrine pathophysiology of alcohol dependence (Maes et al., 1999).

## 4 | ROLE OF GLP-1 IN SUBSTANCE USE DISORDER

### 4.1 | Cocaine: Basic and clinical research

Modulation of the addiction-related effects of cocaine by GLP-1 receptor agonists is also well documented (Hernandez & Schmidt, 2019). Systemic exenatide administration has been reported to suppress both the acquisition and the expression of **cocaine**-conditioned place preference in mice (Egecioglu, Engel, & Jerlhag, 2013a; Graham et al., 2013). Two studies examined the acute effects of exenatide on intravenous cocaine self-administration and this is considered the 'gold standard' approach for studying the effects of injectable drugs including cocaine. Both systemically administered in mice and centrally administered exenatide into the VTA in rats decreased cocaine self-administration (Schmidt et al., 2016; Sørensen et al., 2015). Exenatide injected systemically or into the NAc, VTA or laterodorsal tegmental nucleus suppressed operant responding during reinstatement paradigms thought to reflect cocaine seeking; that is, reinstatement of lever pressing was induced by cocaine injections or cues previously associated with cocaine reinforcement (Hernandez et al., 2018, 2019, 2020).

Acute exenatide has been reported to inhibit cocaine-stimulated locomotor hyperactivity and decrease or abolish cocaine-induced dopamine release in the NAc and lateral septum in mice (Egecioglu, Engel, & Jerlhag, 2013a; Reddy et al., 2016; Sørensen et al., 2015). This effect appears to be centrally mediated, as exenatide administered into the lateral ventricles of the brain similarly suppressed cocaine-evoked dopamine signalling in the NAc (Fortin & Roitman, 2017). Mice lacking GLP-1 receptors showed exaggerated locomotor and conditioned place preference responses to cocaine (Harasta et al., 2015). The effects were reversed by viral vector-mediated expression of GLP-1 receptors in the lateral septum, indicating a crucial role of this structure in GLP-1 modulation of cocaine effects (Harasta et al., 2015).

Self-administration of cocaine, and expectancy of cocaine injections, increased endogenous GLP-1 in rats (You et al., 2019). In contrast, a human study reported decreased GLP-1 levels 1 h after intravenous cocaine injection in experienced cocaine users (Bouhlal et al., 2017). These findings were replicated in a recent study with 13 non-treatment-seeking patients with CUD (Angarita et al., 2021). However, the latter study could not demonstrate an effect of acute pretreatment with exenatide on cocaine self-administration or cocaine-induced subjective effects. Although these early findings in human subjects are somewhat surprising, as pointed out by the authors, they do not preclude the possibility that different doses, ligands, dosing regimens (e.g., subchronic) could modulate cocaine-taking behaviour in patients with CUD (Angarita et al., 2021).

In summary, preclinical studies show promising effects of GLP-1 receptor agonists against cocaine intake, but little information is yet available regarding possible effects of cocaine use on the GLP-1 system or GLP-1 as a predisposing factor to developing CUD.

### 4.2 | Amphetamine: Basic and clinical research

Fewer studies have examined the effects of GLP-1 receptor activation on central stimulant effects, all of them using **D-amphetamine**. Two studies investigated the acute effects of systemically injected exenatide on the expression of amphetamine-conditioned place preference in mice. Both studies reported attenuated amphetamine-conditioned place preference (Egecioglu, Engel, & Jerlhag, 2013a; Sirohi et al., 2016). The psychomotor stimulant effects of amphetamine were also reduced by exenatide or liraglutide administration, measured by locomotor activity in rats and mice, respectively (Chaves Filho et al., 2020; Erreger et al., 2012). Moreover, liraglutide inhibited the deleterious effects of amphetamine on cognitive performance in some assays (Chaves Filho et al., 2020). DPP-4 inhibitors reduced amphetamine-induced hyperactivity in rats receiving an acute dose of D-amphetamine (Lautar et al., 2005).

To the best of our knowledge, no clinical trials have or are currently investigating GLP-1 receptor activation as a treatment of central stimulant use disorder in humans.

### 4.3 | Opioids: Basic and clinical research

Two larger preclinical studies have reported on the effects of exenatide on opioid-related behaviours in rodents. The first study was performed in male mice and reported that **morphine**-conditioned place preference, intravenous self-administration of the short-acting synthetic opioid **remifentanil**, morphine-stimulated locomotor activity and somatic symptoms of morphine withdrawal (measured as jumps) were not affected by exenatide treatment (Bornebusch et al., 2019). Neither did exenatide significantly affect the analgesic effects of morphine in a hotplate assay (including male and female mice) (Bornebusch et al., 2019). Reinforcing effects of remifentanil (self-administration assay) were comparable or increased in mice lacking GLP-1 receptors in the CNS, compared with wild-type controls (Bornebusch et al., 2019).

The second study investigated the behavioural and neurochemical effects of exenatide and **oxycodone** in rats. In discordance with the previous study, it was reported that exenatide injected systemically or

centrally into the NAc shell region decreased oxycodone self-administration, as well as responding in a reinstatement paradigm (Zhang et al., 2020). However, in agreement with the previous study, exenatide did not significantly affect the analgesic effects of oxycodone using a tail immersion test (Zhang et al., 2020). To identify the central mechanisms of action, a group of rats was injected systemically with fluorescently labelled exenatide, which was shown to cross the blood–brain barrier and bind putative GLP-1 receptors expressed on **dopamine $D_1$** and **$D_2$ receptor**s, expressing GABAergic medium spiny neurons in the NAc shell (Zhang et al., 2020). The discrepant results in the self-administration paradigm may indicate species differences between rats and mice. Indeed, another rat study reported that exenatide reduced responding for cues previously associated with **heroin** injections in a reinstatement procedure of operant behaviour (Douton et al., 2021). Treatment with the selective DPP-4 inhibitor **linagliptin** was also reported to reduce morphine-conditioned place preference and facilitate extinction of the morphine preference in rats (Łupina et al., 2020).

One randomized, double-blinded clinical trial (ClinicalTrials.gov identifier NCT04199728) is currently investigating the effects of the GLP-1 receptor agonist liraglutide, 3.0 mg daily for 30 days, on craving in patients diagnosed with OUD (Table 2).

### 4.4 | Nicotine: Basic and clinical research

Two rodent nicotine studies have been reported. The first study reported attenuation of nicotine-induced locomotor hyperactivity and sensitization, nicotine-conditioned place preference and nicotine-induced accumbal dopamine release (measured by microdialysis) after acute systemic exenatide administration (Egecioglu, Engel, & Jerlhag, 2013b). The second study found that systemic exenatide or the DPP-4 inhibitor sitagliptin decreased intravenous nicotine self-administration in mice and that GLP-1 receptor knockout mice, that is, mice lacking GLP-1 receptors, self-administered more nicotine than the wild-type controls (Tuesta et al., 2017). The study further reports that exenatide injected into the interpeduncular nucleus decreased nicotine self-administration and prevented nicotine from modulating intracranial self-stimulation threshold in rats (Tuesta et al., 2017). Chemogenetic activation of GLP-1 neurons in NTS similarly decreased nicotine intake. This is consistent with a central site of action for GLP-1 regulation of motivational properties of nicotine. The authors (Tuesta et al., 2017) suggest that endogenous GLP-1 released from the NTS decreases nicotine intake by activating the medial habenula interpeduncular nucleus circuit.

According to ClinicalTrials.gov, three human clinical trials are investigating the potential effects of a GLP-1 receptor agonist against tobacco use disorder (Table 2), and one randomized clinical pilot trial has investigated the effects of exenatide, 2.0 mg once weekly, in combination with transdermal nicotine replacement therapy on smoking cessation. They have reported that exenatide increased smoking abstinence and reduced craving (Yammine et al., 2021). Two other clinical trials investigating subcutaneous liraglutide, 3.0 mg daily (ClinicalTrials.gov identifier NCT03712098), and subcutaneous dulaglutide, 1.5 mg once weekly (ClinicalTrials.gov identifier NCT03204396), are still recruiting. In addition to the randomized clinical trials, one fMRI study is investigating whether intravenous exenatide reduces cue reactivity when patients are presented with visual stimuli of alcohol and tobacco (ClinicalTrials.gov identifier NCT02690987).

### 4.5 | Influence of GLP-1 receptor agonists on dopamine regulation

Dopamine plays a prominent role in the immediate reinforcing/rewarding effects of drugs, and dysregulation of the dopamine system is thought to contribute (as a predisposing factor and/or a consequence of chronic substance use) to the addicted state (Volkow, Michaelides, et al., 2019). Dopaminergic neurons emerging from the VTA project to the NAc, amygdala, hippocampus and prefrontal cortex, and dopamine neurons emerging from substantia nigra (SN) project to the dorsal striatum (Volkow et al., 2017). Disinhibition/stimulation of dopaminergic VTA neurons is known to play a critical role in the reinforcing effects of alcohol, nicotine and opioids (Volkow et al., 2017). Cocaine inhibits dopamine reuptake by blocking the dopamine transporter (DAT), increasing or prolonging synaptic dopamine levels (Volkow et al., 2002). Other central stimulants can increase synaptic dopamine levels by several modes of action, for example, blockade of dopamine reuptake, 'reverse' DAT function and dopamine release (Lee et al., 2018). Radiotracer imaging studies in patients with AUD (Volkow et al., 1996), cocaine users (Volkow et al., 1993) and **methamphetamine** users (Volkow et al., 2001) have reported of decreased postsynaptic dopamine receptor availability, which is suggested as one of the explanations for lower dopamine function in this group of patients (Nutt et al., 2015). Another mechanism explaining the abnormal radiotracer imaging results could be a blunted dopamine response, compensating for other neurotransmitter deficits, that is, glutamate or GABA (Volkow et al., 2011). Several preclinical studies have tried to elucidate how GLP-1 systems modulate dopamine signalling. Microdialysis or fast-scan cyclic voltammetry studies have repeatedly reported that GLP-1 receptor agonists acutely decrease accumbal dopamine efflux induced by substances of abuse. However, information from chronic dosing studies is lacking. Systemically injected liraglutide (Vallöf et al., 2016) and exenatide (Egecioglu, Steensland, et al., 2013) attenuate alcohol-induced accumbal dopamine release, and exenatide injection into the NTS also attenuates this response as well (Vallöf, Vestlund, et al., 2019). Exenatide can similarly suppress cocaine-induced increases in accumbal and lateral septal dopamine levels (Fortin & Roitman, 2017; Reddy et al., 2016; Sørensen et al., 2015) and amphetamine- and nicotine-induced accumbal dopamine levels in rats (Egecioglu, Engel, & Jerlhag, 2013a, 2013b). GLP-1 receptor agonists do not seem to suppress baseline accumbal dopamine, as opposed to the modulation of stimulated levels, and modulation may differ between NAc shell and core regions (Egecioglu, Engel, & Jerlhag, 2013a; Fortin & Roitman, 2017).

Dulaglutide treatment for 9 weeks decreased dopamine tissue levels in the amygdala and striatum of rats, relative to vehicle (Vallöf et al., 2020).

The mechanisms by which GLP-1 receptor stimulation modulates dopamine function are less clear. Experiments in mice indicate that stimulation of GLP-1 receptors in the VTA weakens the synaptic strength of VTA–NAc projections (Wang et al., 2015), but relatively few VTA neurons express GLP-1 receptors (Cork et al., 2015; Harasta et al., 2015). Experiments in rats indicate that GLP-1 receptor stimulation in the VTA could increase dopaminergic neuron activity via a presynaptic mechanism of action (Mietlicki-Baase et al., 2013). One study focused on the lateral septum in mice, an area previously associated with reward (Harasta et al., 2015; Luo et al., 2011; Olds & Milner, 1954), and reported that GLP-1 receptor stimulation might dampen addiction-related effects by increasing the expression of DAT on the neuronal cell surface, thereby reducing free dopamine levels in the synapses (Reddy et al., 2016). These findings are supported by another study in rats investigating the effect of GLP-1 receptor activation on DAT up-regulation in striatal brain slices as well as in vivo by use of striatal microdialysis (Jensen et al., 2020). However, other studies reported unaffected DAT after exenatide treatment in rats (Fortin & Roitman, 2017), or mice (Jensen et al., 2020), or by genetic ablation of GLP-1 receptors, that is, knockout mice (Jensen et al., 2020).

To the best of our knowledge, only a single human study has investigated the acute effects of GLP-1 receptor activation on DAT availability as the primary endpoint. Ten healthy volunteers with no previous history of drug or alcohol abuse received intravenous infusions of the GLP-1 receptor agonist exenatide, while being in a SPECT scanner. The results showed no acute changes in DAT availability (Jensen et al., 2020). This is in line with findings from another clinical trial, investigating the effects of exenatide once weekly in patients with Parkinson's disease, where an effect on off-medication motor scores was reported, but no significant effect on DAT availability after 48 weeks of treatment (Athauda et al., 2017). Thus, it has been proposed that the GLP-1 receptor agonist-induced up-regulation of DAT availability might be species dependent, with no DAT–GLP-1 interaction in humans (Jensen et al., 2020).

## 5 | POSSIBLE MECHANISMS OF ACTION

Despite the preclinical research discussed above and a small number of clinical trials, it is still unclear how GLP-1 receptor stimulation modulates the effects of drugs of abuse and alcohol. At a behavioural level, the focus of most research has been on the rewarding/reinforcing effects. Currently, the FDA-approved medications to treat AUD, that is, **disulfiram**, **naltrexone** and **acamprosate**, reduce drinking through three different mechanisms of action: (i) unpleasant effects when consuming alcohol, (ii) reduced rewarding/reinforcing effects of alcohol and (iii) reduced negative state when abstinent. In the published reports, it has largely been assumed that GLP-1 receptor agonists reduce alcohol intake by decreased rewarding/reinforcing effects of alcohol, and the possibility that GLP-1 receptor stimulation might decrease alcohol intake through additional mechanisms has not been published. Similarly, studies on cocaine and amphetamine have focused on rewarding/reinforcing effects. An alternative mechanism (not mutually exclusive with reward modulation) is suggested by a study on nicotine, namely, that GLP-1 receptor stimulation may promote satiety and avoidance of aversive effects of the drug, in this case nicotine, via a habenula-dependent mechanism (Tuesta et al., 2017). Another study suggested that cocaine produces a GLP-1-dependent negative feedback loop through activation of stress circuits including **corticosterone**, limiting cocaine intake (Schmidt et al., 2016), which could also be interpreted as a form of GLP-1-potentiated cocaine 'satiety'. Mechanisms involving some form of satiation would be consistent with the known effects of GLP-1 system stimulation on the regulation of nutrient intake. However, several studies have reported that GLP-1 receptor stimulation can suppress drug-conditioned behaviours, in both classical conditioning (CPP procedures) and operant conditioning (drug seeking using reinstatement procedures), that is, tests during which the drug is unavailable (Douton et al., 2021; Egecioglu, Steensland, et al., 2013; Egecioglu, Engel, & Jerlhag, 2013a, 2013b; Graham et al., 2013; Harasta et al., 2015; Hernandez et al., 2018, 2019, 2020; Shirazi et al., 2013; Sirohi et al., 2016; Vallöf et al., 2016; Vallöf, Kalafateli, et al., 2019; Vallöf, Vestlund, et al., 2019). This would suggest that GLP-1 receptor stimulation also modulates mechanisms underlying drug and alcohol 'seeking' or 'wanting', and not only intake and satiation.

### 5.1 | GLP-1 and the stress system

One of the possible mechanisms proposed to suppress cocaine self-administration involves modulation of stress systems (Schmidt et al., 2016). The CRF neurons of the hypothalamus express GLP-1 receptors, and GLP-1 receptor stimulation has been shown to enhance CRF signalling (Kinzig et al., 2003; Larsen et al., 1997; Liu et al., 2017). This was also examined in the lateral septum, and in contrast to the findings in hypothalamus, blockade of the GLP-1 receptors with a GLP-1 antagonist did not reduce stress-induced corticosterone release (Terrill et al., 2018). GLP-1 receptor knockout mice also exhibited increased corticosterone responses to stress (MacLusky et al., 2000), suggesting a more complex relationship between GLP-1 and the stress systems. A large literature suggests that activation of stress systems contributes to the addictive effects of various drugs of abuse, in the withdrawal and 'negative affect' stages of addiction (Koob, 2008; Koob & Volkow, 2016). Thus, chronic use of alcohol, central stimulants, nicotine and opioids have all been shown to increase CRF levels, and CRF antagonists reduce drug seeking (Mantsch et al., 2016; Park et al., 2015). GLP-1 receptor agonists prevented 'relapse' to binge-like alcohol drinking after deprivation and attenuated alcohol withdrawal-induced anxiety-like behaviour (Sharma et al., 2015b; Thomsen, Dencker, et al., 2017; Vallöf et al., 2016). Taken together, although stress system activation may curb cocaine-taking behaviour by acting similarly to cocaine

(Schmidt et al., 2016), GLP-1 receptor-mediated activation of CRF signalling more generally might be expected to facilitate relapse to drug or alcohol intake.

## 5.2 | Ingestive regulatory effects

Because the GLP-1 systems regulate food and fluid intake, and GLP-1 receptor agonists can decrease food consumption at doses comparable with those that decrease alcohol intake, non-specific effects may contribute to the observed decrease in alcohol drinking (Dickson et al., 2012; Tang-Christensen et al., 1996). These effects may relate to nausea or general malaise, to the regulation of nutrient intake and consummatory behaviours, or both. However, the fact that exenatide also reduced intravenous self-administration of alcohol (Sørensen et al., 2016) and GLP-1 receptor agonists reduced rewarding effects of alcohol injections as measured by place conditioning (Egecioglu, Steensland, et al., 2013; Shirazi et al., 2013; Vallöf et al., 2016) indicates that GLP-1 receptor stimulation modulates the rewarding and reinforcing effects of alcohol independently of its effects on oral consummatory behaviour. Rodents lack the ability of vomiting when nauseated, but nausea and malaise can be measured indirectly by pica, which is the consumption of the non-nutritive substance, kaolin clay (Kanoski et al., 2012). Twelve days of treatment with exenatide has been reported to increase pica, but the pica response following treatment with liraglutide was more transient (Kanoski et al., 2012). However, GLP-1 receptor activation with exenatide in the VTA, NAc core and NAc shell (Alhadeff et al., 2012) and in the NTS (Richard et al., 2015) have been reported not to produce a pica response. In non-human primates treated with the GLP-1 receptor agonists exenatide or liraglutide, no signs of nausea, that is, vomiting and/or reduced food intake, were registered (Thomsen et al., 2018). In humans, a recent systematic analysis of reported gastrointestinal side effects during treatment with GLP-1 receptor agonists, including 32 clinical trials and 10,367 patients, reports that the level of nausea and vomiting depends on several factors: (i) the higher the dose, the higher the frequency of nausea, (ii) other medication and (iii) long-acting GLP-1 receptor agonists compared with more short-acting GLP-1 receptor agonists, were associated with less nausea (Bettge et al., 2017). Although it is possible that some of the effect of GLP-1 receptor stimulation on alcohol drinking relates to consummatory behaviour and/or caloric intake from alcohol, this does not necessarily make the approach less useful in clinical practice. AUD sufferers are a heterogeneous group encompassing patients with malnutrition and low body weight, and patients with co-morbid metabolic syndrome (Jeynes & Gibson, 2017; Vancampfort et al., 2016). Clinical observations from patients treated with GLP-1 receptor agonists for Type 2 diabetes suggest that GLP-1 receptor agonists may reduce body weight more in subjects with higher baseline body mass index (Niswender et al., 2013), so, in future clinical trials, it may be useful to evaluate the effects of GLP-1 receptor agonists on alcohol intake in more specific subgroups of AUD patients, for example, in AUD patients with co-morbid obesity.

## 5.3 | Central versus peripheral effects

At a neurocircuit level, some effort has been devoted to identify neuron populations or brain regions that mediate decreases in alcohol intake in rats and mice. Evidence from genetically engineered mice lacking GLP-1 receptors in specific tissues, infusion of GLP-1 receptor agonists directly into the brain, and optogenetic or chemogenetic stimulation of neuron populations all indicate that central rather than peripheral mechanisms underlie the ability of GLP-1 receptor agonists to reduce intake of drugs and alcohol (Abtahi et al., 2018; Colvin et al., 2020; Dixon et al., 2020; Harasta et al., 2015; Hernandez et al., 2018, 2019, 2020; Schmidt et al., 2016; Shirazi et al., 2013; Sirohi et al., 2016; Tuesta et al., 2017; Vallöf, Kalafateli, et al., 2019; Vallöf, Vestlund, et al., 2019). It is also reported that GLP-1-producing NTS neurons project directly to the VTA and NAc (core and shell) (Alhadeff et al., 2012) and that GLP-1 receptor activation of the NTS alters expression of dopamine-related genes in the VTA (Richard et al., 2015) However, the growing number of brain regions that have shown a positive effect upon GLP-1 agonist infusion does not immediately suggest a clear and defined circuit-level mechanism. Instead, GLP-1 receptors seem to modulate brain circuits involved in reward and addiction at multiple levels. Effects in the classic mesolimbic reward pathway such as the VTA and NAc, which express GLP-1 receptors at moderate levels, are perhaps not surprising. A straightforward explanation for effects in the NTS could be that stimulation of GLP-1 autoreceptors in the NTS would be expected to reduce release of GLP-1 to other brain regions, removing a tonic inhibitory modulation on reward/consummatory functions. Such an inhibitory effect of endogenous GLP-1 is consistent with the reduction reported of GLP-1 receptor antagonists on drug and alcohol intake (Shirazi et al., 2013). At a synaptic or molecular level, basic electrophysiology studies and studies using food suggest that both presynaptic and postsynaptic mechanisms are likely to be involved in the effects of GLP-1 receptor agonists on reward pathways (Liu & Pang, 2016; Mietlicki-Baase et al., 2014, 2013; Wang et al., 2015) even though there are few such mechanistic studies for drugs of abuse and alcohol.

## 5.4 | GLP-1 receptor heterogeneity

It has also become clear that GLP-1 receptors in the brain are heterogeneous and can exert both inhibitory effects, as in the CA3 of hippocampus and lateral septum, and stimulatory effects, as in the CA1 of hippocampus and hypothalamic nuclei, at the cellular level (Liu & Pang, 2016). Thus, it may be appropriate to think of different functional subtypes of GLP-1 receptors, likely brought about by GLP-1 receptor ligands showing different signalling bias for different second messenger pathways, whose expression may vary by tissue (Fletcher et al., 2016; Zhang et al., 2015). Indeed, different GLP-1 receptor agonists display tissue-specific pharmacology (Pabreja et al., 2014). Based on rodent studies, GLP-1 receptor agonists also vary with respect to brain availability and how discrete or extensive brain regions show GLP-1 receptor binding after systemic GLP-1 receptor agonist

administration (Gabery et al., 2020; Salinas et al., 2018; Secher et al., 2014). GLP-1 receptors show desensitization and internalization after chronic GLP-1 receptor agonist treatment, which vary between different agonists and between different tissues or cell type (Fletcher et al., 2016; Roed et al., 2014). All those differences might explain differential adaptations (tolerance or no tolerance) depending on the agonist and dosing regimen.

## 5.5 | Gender differences

Almost all preclinical studies reported included only male animals. However, a recent investigation used female rats and reported that exenatide microinfused into the NAc shell region, decreased alcohol intake in a two-bottle choice system (Abtahi et al., 2018). Water intake was decreased, and alcohol preference, although not reported, may not have been decreased based on the relative effect sizes for water and alcohol intake. Because only female animals were tested, it is difficult to conclude any possible sex differences (Abtahi et al., 2018). Dulaglutide treatment was tested in both male and female rats and was found to reduce alcohol intake more in male rats than in female rats (Vallöf et al., 2020). Another study used both male and female mice to investigate the effects of GLP-1 receptor agonists on nicotine self-administration, but analyses of the sex variable were not reported, and data were only shown as sexes combined (Tuesta et al., 2017). Sex differences in the effects of GLP-1 receptor agonists have been reported for other endpoints, such as modulation of feeding behaviours in rats (López-Ferreras et al., 2018; Richard et al., 2016). In humans, the genetic association of the GLP-1 receptor allele with risk of AUD was most robust in men (Suchankova et al., 2015), suggesting a sex difference in sensitivity to GLP-1 receptor modulation of alcohol effects. Higher GLP-1 response after an oral glucose test in healthy women than in men has been reported. However, this difference was abolished when glucose tolerance was worsening (Faerch et al., 2015). A smaller study, including 14 healthy volunteers, reported that GLP-1 infusion changed taste preference in women significantly compared with men (Baretić et al., 2019). Another study reported higher GLP-1 plasma levels in premenopausal women compared with postmenopausal women, but this might be due to different microbiota compositions (Santos-Marcos et al., 2018). Clearly, it will be important to include both male and female subjects in future studies.

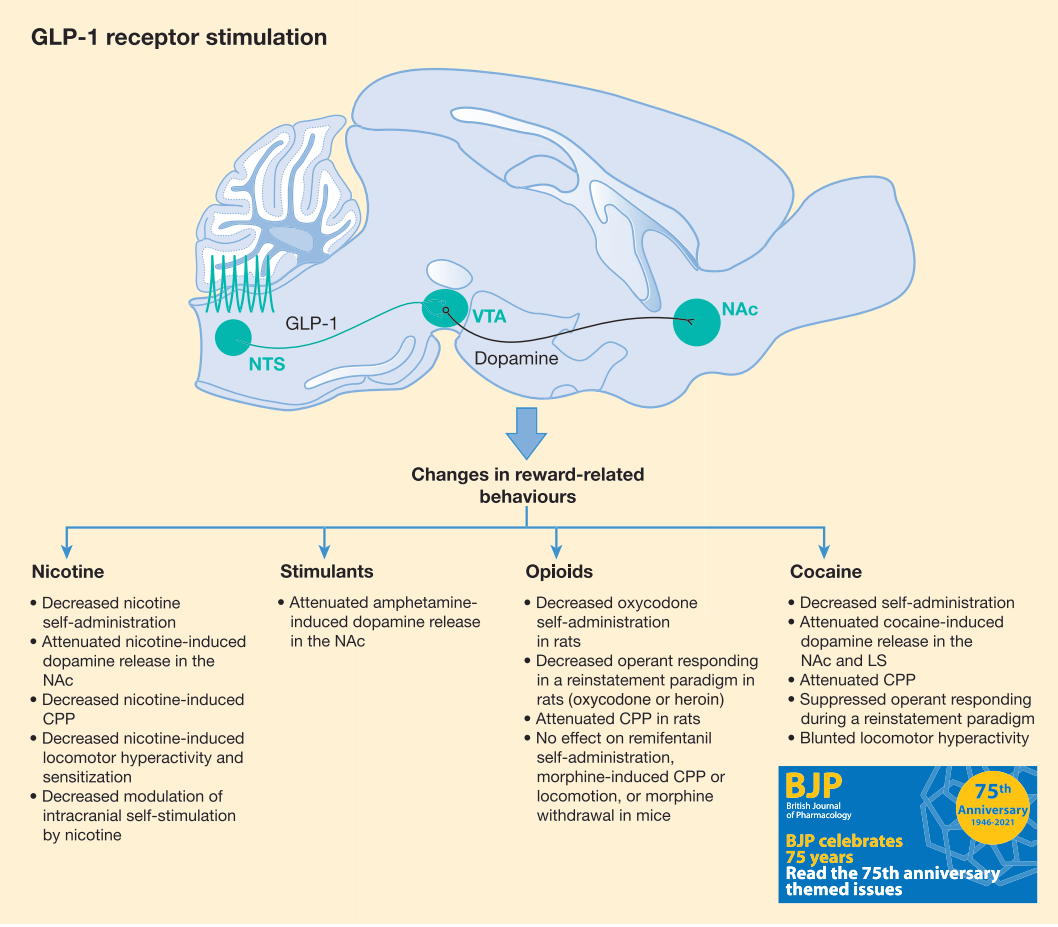


**FIGURE 2** Effects of glucagon-like peptide 1 (GLP-1) receptor stimulation in various substance reward-related behaviours in preclinical models. CPP, conditioned place preference; LS, lateral septum; NAc, nucleus accumbens; NTS, nucleus tractus solitarius; VTA, ventral tegmental area

## 6 | SUMMARY AND FUTURE PERSPECTIVE

The global burden of SUD, tobacco use disorder and AUD is increasing. Not only the individual suffering from these disorders is affected but also the families and society at large. Many patients are co-using several substances, drastically increasing the risks associated with each substance alone. Pharmacological treatment options are sparse (AUD, OUD and tobacco use disorder), if not non-existing (CUD and central stimulant use disorder). However, emerging evidence from basic research has pointed to GLP-1 receptors as a possible target for developing new pharmacological treatment options. In addition to the GLP-1 produced in the small intestines after food intake, GLP-1 is also produced in the NTS of the brain and is released as a neurotransmitter in several brain regions. GLP-1 receptors are expressed in regions previously identified as important players in the neurobiology of addiction, and importantly, GLP-1 receptor agonists seem to cross the blood–brain barrier. Overall, preclinical research has identified potent reductions in substance use and attenuation of drug-seeking behaviour with several different GLP-1 receptor agonists, especially regarding alcohol (alcohol, see Figure 1; nicotine, stimulants, opioids and cocaine, see Figure 2). A human genetic association study has reported on a GLP-1 receptor variant associated with increased alcohol self-administration and changes in brain response in reward-related areas, as revealed by fMRI brain imaging. It is also suggested that individuals suffering from obesity and individuals suffering from addiction have overlapping brain dysregulations, and the anti-obesity effects of GLP-1 receptor agonists support the potential usefulness of GLP-1 receptor agonists for the treatment of SUD and AUD. The possibility that rewarding effects (of alcohol at least) may relate to consummatory behaviour does not necessarily make the approach less useful in clinical practice. The precise mechanisms of GLP-1 receptor agonists' actions on addiction-related endpoints have yet to be established, but the effects seem to be mediated centrally, at least in part through modification of dopamine signalling. No clear and well-defined circuit-level mechanism has been identified yet, instead GLP-1 seems to modulate brain circuits at multiple levels, and the relevant mechanisms of action may well be species dependent. It is important to note that the present data pointing towards a beneficial effect of GLP-1 receptor agonists have not yet been translated into humans, except for (i) a pilot trial indicating positive effects of the GLP-1 receptor agonist exenatide, on nicotine abstinence and craving, and (ii) a minor study reporting no effect of acute low dose exenatide on cocaine self-administration. Although a few human studies have been initiated, further data have not yet been published (see Table 2).

Newer systematic reviews and meta-analyses including long-term randomized clinical trials in patients with Type 2 diabetes have found no association between GLP-1 receptor agonist treatment and pancreatitis or pancreatic cancer, which is critically important if treatment with GLP-1 receptor agonists should be contemplated in this vulnerable group of high-risk patients with AUD or SUD. With the approval of an oral GLP-1 receptor agonist, better adherence to treatment might be hoped for in the future, but only new clinical trials will show if treatment with oral GLP-1 receptor agonists is as effective as that with injected treatments. Many questions still need to be answered: Is there a gender difference in treatment response, as most preclinical trials have been performed on male animals only; is there a genetic variability in GLP-1 receptors, production or degradation that contributes measurably to AUD or SUD pathogenesis, widely or in subpopulations; which agonist(s) are best suited to target AUD and SUD, also in consideration of potential side effects, the latter may not be a 'one size fits all' both regarding the various addictive substances and regarding individual patient characteristics. Summing up, the stage is set for further basic research and for large-scale clinical trials to go ahead and bring to fruition the promising results from preliminary clinical studies and basic research.

### 6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY (http://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Christopoulos, et al., 2019; Alexander, Fabbro, et al., 2019; Alexander, Kelly, et al., 2019).

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### CONFLICT OF INTEREST

A.F.-J. has received an unrestricted research grant from Novo Nordisk A/S to investigate the effects of GLP-1 receptor stimulation on metabolic disturbances and weight gain in antipsychotic-treated patients with schizophrenia. There is no other possible conflicts of interest, for the remaining authors.

### DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article because no new data were created or analysed in this study.

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