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Drug discovery for the treatment of substance use disorders: novel targets, repurposing, and the need for new paradigms

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Drug addiction treatment medications available nowadays are limited in both efficacy and number.The increased understanding of drug addiction circuitries leads the scientific community to look for better molecules and targets for detoxification and relapse prevention.This review focus on known targets (e.g., metabotropic glutamate receptor 5 and $GABA_B$ receptor) and on novel potential treatment acting on oxytocin system, which interacts with diverse neurotransmitters, has proved successful in both preclinical and clinical studies on ethanol, cocaine and methamphetamine.A crucial issue is the identification of new investigational paradigms, which may help to predict treatment efficacy and improve effectiveness.

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Introduction

In the last few years a large body of scientific evidence investigated the neurobiological mechanisms underlying the effects of substances of abuse and the development of drug addiction. Moreover, it is now possible to identify stages of transition from recreational to sustained substance use based on individual genetic predisposition and drug-induced adaptation, up to the loss of control and fulfilment of diagnostic criteria for intervention.

The identification of key neurotransmitters, neurochemical pathways and specific receptors offers a unique opportunity for the identification of novel and safer targets for pharmacological treatment, in particular for the main approved therapeutic target of relapse prevention.

In spite of these tremendous advancement in the neuroscience of substance use disorders, the number of approved drugs for the treatment of drug addiction is still scarce. The efficacy of the current treatments is limited, relapse rates being extremely high within the first year of treatment, and it may be only modestly enhanced by the combination with psychosocial interventions.

This decoupling between research and clinical achievement make these chronic, relapsing brain disorders result in an enormous unmet medical need [1], and remain a big health and socioeconomic problem in many countries worldwide.

Research and Development are however still active. We will review the targets under study and status and progress in R&D pipeline for pharmacotherapies for drug addiction. We will also show three paradigmatic case studies of drug development based on three different target validation approaches based respectively on, (i) novel discovery (oxytocin), (ii) continuing research (mGluR5), and (iii) repurposing ($GABA_B$).

Targets for drug addiction treatment

Studies that correlated drugs of abuse-related behaviours (drug-taking, drug-seeking, impulsivity, withdrawal signs, among others) to neuronal pathways and neurochemical changes showed the involvement of different neurotransmitters such as dopamine (DA), glutamate, GABA, serotonin, endogenous opioids, corticotropin-releasing factors and several others. Others have been identified and recently proposed (see below).

However little translation took place from bench to bedside (for a critical appraisal see Badiani *et al.*, 2017 [2•]). In fact, the approved medication for treatment of substance use disorders (Table 1) are mostly based on a full or partial direct interaction at the receptor bound by the drug of abuse, with only bupropion and acamprosate showing an effect on neural pathways of addiction.

There is a return of interest for an old benzodiazepine, fenobam, and promising new directions have been created with the discovery of nociceptine (N/OFQ peptide)

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Table 1

Pharmacotherapies for treatment and detoxification of drug addiction. U.S. Food and Drug Administration (FDA)-approved drugs.

Pharmacotherapy	Clinical indication	Mechanism of action
Disulfiram	Prevention of relapse to alcohol use	Ethanol metabolism inhibition
Methadone	Opioid substitution therapy	Full opioid receptors agonism
Nicotine replacement therapies	Tobacco smoking substitution therapy	Full nicotinic receptors agonism
Naltrexone	Drinking reduction and prevention of relapse	Opioid receptors antagonism
Bupropion	Anti-craving drug. Relapse prevention in ex-smokers	Dopamine and noradrenaline re-uptake blocker Nicotinic receptors antagonism
Buprenorphine	Opioid detoxification therapy	Partial opioid receptors agonism
Acamprosate	Relapse prevention in ex-alcoholics	Partial glutamate receptors agonism
Nalmefene	Drinking reduction	Partial opioid receptors agonism
Varenicline	Relapse prevention in ex-smokers	Partial nicotinic receptors agonism

receptor ligands [3]. Interestingly, we also assist at repurposing as anti-abuse medications of the spasmolytic baclofen [4], the atypical antidepressant mirtazapine [5] and several antiepileptics.

The pipeline of drug discovery for the treatment of substance use disorders is mainly dominated by therapies of nicotine and alcohol addiction. Nevertheless, there are also several promising candidates in development targeting a range of other indications including opioid and cocaine addiction. Antagonists of N/OFQ peptide receptor, α6β2-nicotinic acetylcholine receptor (α6β2-nAChR) and orexin receptor (OXR) are some of the most interesting opportunities.

- The N/OFQ peptide has been shown to regulate the activity of mesolimbic dopaminergic neurons, glutamate, and opioid systems. The genetic deletion of its receptor or the inhibition with antagonists confers rat resilience to the development of ethanol addiction [6].
- The α6β2-nAChR containing both the α6 and β2 subunits are selectively distributed in the dopaminergic mesostriatal pathway (and retina, optic nerve and its visual afferents [7]). Recent papers have reported the functional role of these receptors in mediating the effects of systemic nicotine in dopamine release, locomotion and reinforcement. This suggests that selective α6β2-nAChRs antagonists could be promising drugs to affect nicotine addictive properties [8].
- Orexin peptides A and B (also called hypocretin 1 and 2) are produced by a small number of neurons within the hypothalamus [9,10]. Orexins activate two G-protein coupled receptors (OX1R and OX2R) which are distributed throughout the Central Nervous System (CNS). Originally, orexins and OXRs were identified as playing a key role in feeding behaviour. However, this role on appetite behaviour has been expanded including a range of reward-related behaviour from substance abuse and addiction [11]. Recently, James *et al.* (2017) [12] proposed the hypothesis that orexin peptides are preferentially engaged by situations of high motivational relevance; those happening during physiological necessity states, exposure to threats or reward opportunities. Based on James *et al.* (2017)'s evidence, orexin neurons are relevant to regulating motivated responding to drugs of abuse. The dual OX1–OX2R antagonist suvorexant has been approved by FDA for the treatment of insomnia. Being the compound well tolerated it could be tested in clinical trials in addicted subjects shedding some light on the role of OXRs in substance use disorders.

Case studies

Oxytocin: potential new mechanistic approach

Oxytocin (OT) is a nine-aminoacid polypeptide hypothalamic hormone acting through specific receptors located both in the central and peripheral nervous system. An important area of research for OT is learning and memory. OT has a long term inhibitory effect during acquisition, retention, consolidation and retrieval [13•], possibly modifying hippocampal and related limbic mechanisms. Substance use disorders have been hypothesized as a form of neural adaptation to repeated drug exposure and, therefore, as a form of learning [14]. It has been proposed that aspect of tolerance to opioids and ethanol can be considered a form of learning [15] and the sensitization to the behavioural effect of psychostimulant was found to be dependent on associative environmental factors [16]. In a small clinical trial the potential of OT as a treatment for alcohol use disorder was evaluated. Participants had a significantly fewer withdrawal symptoms and required less symptom triggered lorazepam for withdrawal symptom compared to placebo [17]. Cocaine-dependent inpatients anger and cue-induced craving were absent in the OT treatment [18•]. Preclinical studies supported the positive effect of OT in reducing chronic tolerance to the analgesic effect of opioids [19], cocaine-induced locomotor hyperactivity and stereotyped behaviour [20], cocaine self-administration and methamphetamine reward effect in the CPP model [21]. The positive effects of OT may possibly originate from its interaction with multiple neurotransmitters such as dopamine, with the Hypothalamic–Pituitary–Adrenal axis and Corticotropin-Releasing Factor stress systems. Investigation is necessary with OT receptor non-peptide agonists of longer half-life than OT

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