

Molecular Mechanisms of Drug Abuse, Dependency and Craving

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Abstract

Drug abuse and dependence are major medical, social, and economic problems for the world. Whereas the means to reduce abuse are well known, drug dependency is a complex medical disease and current treatments attempt to reduce or prevent drug craving in dependent people as part of therapy. With the increased understanding of the neural mechanisms of drug dependence and the availability of several drugs that can treat craving in certain drug dependent populations it is important to summarize development of anti-craving therapeutics world-wide. The present paper briefly outlines the problems of drug abuse and dependence, key aspects of the drug dependence process, the nature and mechanisms of drug craving in dependent people, current drug dependence theories, and finally mechanisms of action of anti-craving agents. We conclude with suggestions about potentially useful leads for anti-craving therapy.

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Abbreviations: MOA: Mechanism of Action; DA: Dopamine; 5HT = Serotonin; NE = Norepinephrine; MSN = Medium Spiny Neurons

Introduction

How serious are drug abuse and drug dependence? Currently in the USA, alcohol abuse is associated with an overall cost of \$224 billion, tobacco abuse, \$295 billion and illicit drug abuse, \$193 billion^[1]. How many people are affected? As an example in the USA, among people ages 18 or older, the lifetime prevalence of alcohol use was 87%, while 25% of people reported binge drinking in the past month (in 2013)^[2,3]. Similarly, in the USA, 7% of people ages 18 and older (17 million adults) had an Alcohol Use Disorder (AUD)^[3].

Most people who become serious substance users (DSM-V; drug dependent in DSM-IV) initially are drug abusers. Many drug abusers never go on to develop drug dependence. The essential difference between drug abuse and drug dependence is that the latter is a medical disease characterized by a loss of control over drug use and drug seeking (DSM-IV, DSM-V^[4,5]).

The above suggests and the literature has demonstrated that clinically there are two sub-populations of people who use drugs: drug abusers and drug dependent people. Drug abuse is under voluntary control and can be reduced via coercion, education, reduced drug supply, punishment, and increased drug cost^[5]. In contrast drug dependence (severe drug use disorder) cannot be reduced by these means and is associated with loss of control over drug seeking and taking and a marked craving for the drug (to the exclusion of other thoughts and activities)^[6].

A large body of evidence now shows that drug dependence is much more likely to occur with drug exposure in at risk individuals - people with specific genetic deficits associated with impaired neural activity in the brain's pleasure pathway (dopaminergic projection from the ventral tegmental area of Tsai, VTA) and its projections to the limbic system (especially the nucleus accumbens, frontal and prefrontal cortices)^[4,7].

Nature and Mechanisms of Craving

Drug dependence develops as an "adaptive" process in which the firing of neural circuits associated with emotion generally and stimulus salience and reward more specifically is altered long-term^[7,8,9]. As such, drug dependence parallels other types of

Dursteler, et al.^[21] reviewed studies in which methylphenidate (MPH, a dopamine uptake inhibitor used in treating attention deficit hyperactivity disorder, ADHD) could be used as a cocaine substitute to reduce cocaine craving. To date, the results overall were disappointing when MPH was used in persons who did not also have a diagnosis of ADHD. One potential reason for the treatment failure is that MPH is an extremely effective blocker of DA uptake. On the other hand, what is needed for such “substitution” therapy is an agent that only weakly blocks the dopamine transporter (such as modafinil) or an agent that combines blockade of the DA transporter with other actions (such as blocking the norepinephrine and dopamine transporters by bupropion). Below we will provide evidence to substantiate this position.

O’Brien’s^[28] review was one of the early reports of the effectiveness of bupropion on alleviating the craving for nicotine. Islam and Rahman^[29] have discussed the role of bupropion as a part of the treatment of the craving for nicotine. Modafinil is an agent primarily used to reduce sleepiness in persons suffering from jet lag or narcolepsy. Its mechanisms of action include a modest direct stimulation of alpha-noradrenergic receptors and, significantly, a weak blockade of DA transport. Modafinil appears to reduce craving to cocaine. This is consistent with the view that an ideal agent for “substitution” therapy would have some ability to mimic the addictive drug but do so more weakly (have reduced pharmacological efficacy compared to the addictive agent). Essentially, an ideal therapeutic agent for craving would not allow the person to get “high” but would still be able to reduce craving by weakly mimicking the addictive agent’s actions.

George, et al.^[22] evaluated the roles of dopamine and Corticotropin Releasing Factor (CRF) in the neurochemical mechanism of craving. They postulated two types of brain activities. The within-system process is one in which the addictive agent elicits an opposing (“neutralizing”) reaction in the same system where the drug has its major action. The author’s between-system process is one in which the addictive drug recruits brain circuits beyond the one in which it has its primary effect. The authors postulated that repeated reduced dopaminergic activity coupled with enhanced activity in the CRF system (during drug withdrawal) is a critical part of the mechanism of dependence (we would say especially in development of NEED). In 2013 Koob^[17] suggested that compulsive drug seeking in alcoholism occurs via negative reinforcement (an action that reduces a negative emotional state, i.e., withdrawal). He argued that in addition to dopamine and CRF other modulators of the brain stress response including norepinephrine, dynorphin, and neuropeptide Y could play a role in the extended amygdala (a brain region linking emotion and memory) in mediating the drug seeking that attempts to reduce the reward deficit in the dependent brain.

Lee, et al.^[30] reviewed studies indicating some conflict between the results of human trials and tests of therapy in animal models of psycho-stimulant abuse. These authors highlighted a need for drug combination therapy used in a specific temporal sequence. Thus, a dopamine agonist (that would mimic some aspects of DA itself at one of DA’s receptors) would be given initially followed by a second agent (such as a serotonin or neurokinin-1 receptor antagonist) for normalizing behavior. Myers^[23] noted that amperozide (a serotonin-2 receptor antag-

onist that also releases dopamine) is able to attenuate alcohol craving in animal models. Similarly, Nava, et al.^[24] found that gamma-hydroxybutyrate^[1], naltrexone, or disulfiram were all equally able to reduce both craving for alcohol and biological markers of alcohol abuse in alcoholics. GHB inhibits dopamine release; naltrexone blocks opioid receptors and indirectly modulates DA neural activity in some brain regions; and disulfiram inhibits ethanol metabolism but may also reduce the metabolism of dopamine via MAO (Monoamine Oxidase).

In contrast, Pierce, et al.^[25] noted that while effective therapies for reducing craving for alcohol, opioids and nicotine have emerged, promising medications to reduce craving for psycho-stimulants have not fared well in clinical trials. One possible reason for this, highlighted by Lee above^[30], is that a combination of agents (or agents given in a specific temporal sequence) may be needed to fully reverse the neural adaptations associated with craving, in order to manifest a beneficial effect. Thus, Rothman, et al.^[26] emphasized the value of dual dopamine / serotonin releasers as treatments for psycho-stimulant addiction. The efficacy of such an agent suggests that serotonin release may dampen the dopamine-mediated stimulant effects yielding a benefit on craving without getting the person “high”. Finally, Self^[27] summarized a large body of work on neurochemical adaptations that occur with chronic exposure to addictive drugs. He indicated that whereas dopamine triggers relapse by stimulating D2 DA receptors that inhibit cAMP, drugs that selectively activate D1 DA receptors (and enhance cAMP) prevent relapse and may be of benefit in reducing craving. Thus, the type of DA mimetic agent should be considered in anti-craving drug development.

Serotonergic (5HT) Agents: As indicated above, one of the roles played by 5HT within the limbic system is the modulation of dopamine activity (especially dopamine release). Ago, et al.^[31] looked at psycho-stimulant induced behavioral sensitization in mice and its modulation by serotonergic agents. Serotonergic receptor blockers tend to have actions at a large number of serotonin receptors because of the marked similarities in affinities across the receptor family. In the Ago study, the authors found that osmomezotan (selective serotonin-1A agonist), ritanserin (a serotonin-2A/2C antagonist)¹, and azasetron (serotonin-3 antagonist) inhibited the development and maintenance of sensitization to varying extents with the 5HT3 antagonist having the greatest clinical effects. Johnson^[32] likewise demonstrated that ondansetron (an antagonist of the 5HT3 receptor) was able to reduce craving significantly in a subpopulation of alcohol-dependent patients.

Hauser, et al.^[33] examined the most recently discovered member of the 5HT receptor family, the 5HT7 receptor, since links have been shown between alcoholism and variants of the 5HT7 receptor gene. Blockade of the 5HT7 receptor with SB269, 970 prevented amphetamine-induced inhibition of neural firing in the VTA (cited in (33)), but the neuroanatomical mechanism whereby this effect was achieved was unclear. Lanteri, et al.^[34] showed that chronic dosing with several different addictive drugs sensitized 5HT and noradrenergic (NE) neurons by disrupting the reciprocal inhibition between them.

¹Ritanserin also blocks 5-HT1D, 5-HT2B, 5-HT5A, 5-HT6, and 5-HT7 receptors.

Furthermore, these authors demonstrated that RS10, 222 (5HT_{2C} agonist) reversed the effects of the addictive drugs and the authors suggested that a 5HT/NE uncoupling is a common neurochemical consequence of repeated consumption of addictive agents. As discussed above, Lee, et al.^[30] showed that sequential administration of a dopaminergic drug followed by a second agent (such as a 5HT_{2A/2C} antagonist) that modified dopamine activity indirectly was beneficial in reducing psycho-stimulant induced sensitization. Also we noted above that Myers^[23] reported that amperozide (a serotonin-2 receptor antagonist that also releases dopamine) attenuates alcohol craving in animal models. Finally, we also indicated above that Rothman, et al.^[26] emphasized the potential value of dual dopamine / serotonin releasers as potential treatments for psycho-stimulant addiction due to a dampening effect of 5HT release on dopamine-mediated stimulant effects.

Noradrenergic Agents (NE): NE drugs are generally not as well recognized for their anti-craving potential as the DA and 5HT drugs discussed above. However, there is a substantial literature indicating a role for NE transmission in the induction of the addictive process and in the development and modulation of drug craving especially for nicotine. The effects of the dual action agent bupropion (that blocks both DA and NE transport) were discussed above^[28,29]. Interactions between 5HT and NE neurons were mentioned above in the work by Lanteri, et al.^[34] who showed that chronic dosing with several different addictive drugs sensitized 5HT and noradrenergic (NE) neurons by disrupting a reciprocal inhibitory link between them and that 5HT/NE uncoupling is a common neurochemical consequence of repeated consumption of addictive agents.

In 2014 Lin^[35] reported on the two general strategies for treating craving – substitution therapy and anti-craving medications. The review included a discussion of the role of bupropion in treating the craving for nicotine (strong effect) but also in treating craving for food in binge eating and obesity (which shows significant overlap in brain substrates and neurochemistry with the drug addictions). As discussed above, Nava, et al.^[24] found that 3 agents that directly or indirectly altered DA and / or NE, (GHB, naltrexone, or disulfiram) could both reduce ethanol craving and aid in maintaining abstinence (see also (35)). Sofuoglu and Sewell^[36] described the critical role of NE in mediating many effects of psycho-stimulants, including sensitization and the reinstatement of drug seeking (following extinction and a priming drug exposure). These authors noted that disulfiram appears to block NE synthesis as well as potentially inhibiting its metabolism. The same authors noted that lofexidine, an alpha-2 adrenergic direct agonist, reduced the craving induced by stress and drug cues in cocaine users. Upadhyaya, et al.^[37] provided a novel perspective on the role of NE in craving. They discussed the abuse potential of the drug atomoxetine (which selectively blocks NE uptake) but found that the literature does not support the idea that selective NE uptake inhibitors are addictive. Thus, a drug that that selectively blocks NE, but not DA, transport would probably not reduce craving either. Nevertheless a drug that reduces noradrenergic transmission, e.g. lofexidine (by stimulating pre-synaptic alpha-2 axon terminal autoreceptors), may be useful in treating craving.

Cholinergic Agents: As presented above, Islam and Rahman^[29]

evaluated the effectiveness of treatments for nicotine craving. In addition to bupropion (DA and NE uptake inhibitor) they also evaluated varenicline, a nicotinic partial agonist (substitution therapy). The authors indicated that oral therapy with either agent had limitations. Similarly, O'Brien^[28], in studying the same two agents, reported limitations in their effectiveness in reducing nicotine craving.

GABAergic Agents: As the major inhibitory transmitter in the brain, GABA should play some role in the addictive process and craving. Furthermore, some of the addictive drugs, in particular ethanol, have important direct actions on GABA receptors. Fehr, et al.^[38] evaluated the effects of tiagabine (GABA uptake blocker) on the activation of the VTA pathway. The paradigm employed an intravenous challenge dose of ethanol in non-addicted people to determine if tiagabine attenuated the acute response to ethanol. This work hypothesized that stimulation of DA release in the limbic system by addictive agents could be reduced by augmenting GABA transmission. The author's results using PET imaging did not support the idea that potentiating GABA synaptic levels (via blocking GABA transport) could diminish the effects of ethanol challenge on brain activity. A caveat in this study of course is that addicted people and normal individuals likely have differences in brain function. Also, the study is important in highlighting the anti-craving potential of the large set of anti-seizure / mood stabilizing agents now available clinically (see below). Consistent with the importance of the role of GABA in reducing craving, baclofen is a GABA-B direct agonist with a modest ability to reduce craving for alcohol and nicotine^[35].

NMDA agents: Acamprostate was reported by Lin to have robust effects in reducing craving for ethanol, nicotine, opioids, and pathological gambling, with modest effects on amphetamine craving^[35]. Acamprostate is an NMDA receptor partial co-agonist (binding to the glycine co-agonist site that must be occupied for the NMDA receptor-gated channel to open). Jung and Namkoong^[39] emphasized that although acamprostate was effective, it worked well only in certain patients, suggesting a role for genotypic or phenotypic subtyping in the treatment of craving. Olive, et al.^[40] recognized that, as the brain's major excitatory transmitter, glutamate should logically play a role in the addictive process and craving. Furthermore, there is an extensive literature showing that addictive agents (including ethanol) alter glutamatergic function and that changes in brain glutamate activity modulate the VTA pathway^[7].

Like acamprostate, D-cycloserine^[2] acts as a co-agonist at the NMDA receptor glycine co-agonist site and facilitates the opening of the NMDA receptor channel^[40]. DCS may reduce the craving for cocaine and for nicotine. Memantine is an interesting agent with its primary clinical use being symptom reduction in patients with dementia. This drug is a non-competitive NMDA receptor antagonist that blocks active NMDA receptors thereby preventing NMDA channel function. Since the activation of NMDA receptors is essential for encoding memory, the key to the clinical effectiveness of memantine in Alzheimer's disease is its ability to target only those NMDA receptors that are active. In appropriate doses, memantine reduces excess stimulation of the receptors that would otherwise produce an "excitotoxic" destruction of neurons. Memantine may also block 5HT₃ and nicotinic cholinergic receptors. Together, these mechanisms allow

memantine to reduce craving to nicotine and heroin. However, the literature suggests that both glutamatergic agonists and antagonists are useful in treating craving, an unusual situation from a neuropharmacological perspective.

Also^[35] N-acetylcysteine (NAC) may modulate both glutamate and DA by mechanisms other than its ability to facilitate the body's antioxidant defense system. NAC appears able to somewhat reduce craving for cocaine (and for pathological gambling, a syndrome sharing much in common with the drug addictions in terms of changes in brain activity).

Opioid agents: Substitution therapy for opioids (initially heroin and now also prescription opioids) has been a mainstay of opioid addiction treatment for a generation. Initially, the direct opioid full agonist methadone was utilized^[41]. Methadone fully activates the same opioid receptors that are activated by heroin. More recently, the advantages of administering partial opioid agonists either alone (buprenorphine) or combined with an opioid antagonist (naloxone) that was inactive orally but active when the drug combination was diverted for smoking or injection were discovered.

Fishman, et al.^[42] described a woman dependent on opioids with co-morbid alcohol use disorder who was also depressed. While the case was complex and the patient's progress was uneven, she eventually responded well to buprenorphine–naloxone plus her antidepressant. Grimm, et al.^[43] evaluated the effects of the general opioid antagonist naloxone on sucrose craving in rats because of the relationship mentioned earlier between craving for drugs and for certain foods. Naloxone was somewhat effective in reducing the behavioral response for sucrose in protracted abstinence.

Koob^[17] argued forcefully that alcoholism is a chronic emotional distress syndrome consistent with the activation of brain stress systems discussed in many of Koob's reviews. Thus, involvement of the opioid system (including dynorphin) is expected. Consistent with this view, dynorphin (an endogenous opioid peptide that activates primarily kappa opioid receptors) levels are elevated after chronic dosing with psycho-stimulants or opioids^[17].

By blocking opioid (especially mu) receptors with drugs such as naltrexone, nalmefene and naloxone, clinicians may disrupt the addictive process and begin to reinstate more normal patterns of neural firing within the VTA pathways. As discussed above^[35], naltrexone is a competitive antagonist at mu and kappa opioid receptors. It is highly effective in preventing the euphoric effects of opioid agonists and can help improve abstinence. However, it is considered to be a second line agent (after methadone and buprenorphine) because of low patient adherence. This may be because naltrexone prevents endogenous opioids from activating opioid receptors whereas full or partial opioid agonists allow these receptors to be activated (by endorphins / enkephalins etc. as well as by the anti-craving drugs themselves) to at least some extent. For many drug dependent people, abstinence requires at least some activation of the relevant brain pathways rather than their complete inhibition! Nevertheless^[24,28] investigators found that naltrexone was one of several therapeutic agents able to reduce craving in alcoholics and normalize at least some biological markers of alcohol use disorder.

Cannabinoid Agents: While marijuana use is widespread in the USA, marijuana dependence is considered to be less of a problem than dependence on heroin, nicotine, ethanol, and psycho-stimulants. Whereas the lifetime prevalence was 46% for adults ages 26 and older, daily use in the past month for adults ages 26 and older was 6%^[44]. However, the role of the endogenous cannabinoid system in the abuse of or dependence on other agents may be significant. Gamaledin, et al.^[45] highlighted the role of the endogenous cannabinoid system in nicotine addiction. Rimonabant (SR141, 716) is a cannabinoid-1 (CB1) "inverse agonist / antagonist". An inverse agonist is able to activate receptors in their "resting" state while a pure antagonist would merely prevent the endogenous transmitter from activating that receptor. Such an agent may be useful in the treatment of nicotine and other addictions. Yang, et al.^[46] explored the potential role of the other major class of cannabinoid receptors (CB2). Both receptors are members of the GPCR (G protein coupled receptor) family; CB1 is primarily expressed in brain whereas CB2 resides primarily in peripheral tissues, especially those associated with immune system modulation. CB2 ligands may be of benefit as anti-craving drugs since they appear to be anti-convulsant (see below). As we have mentioned above and will discuss in detail in the final section of this paper, drugs that treat seizure disorders are able to do so because they restore the balance between excitatory and inhibitory activity in the brain, especially in the areas that constitute the epileptic focus. This action also leads naturally to the potential of these same drugs as mood stabilizers (for people with bipolar disorder) and also as anti-craving medications. Recent work has demonstrated that CB2 receptors are also present in brain, reinforcing their possible involvement in several CNS disorders.

CRF Agents: Koob and his collaborators have written extensively on the role of brain stress systems in the long-term, primarily negative, aspects of drug dependence and craving (NEED)^[17,22]. Thus the role of CRF and the extended amygdala in stress and the view of addictions such as alcoholism as reward deficit disorders have helped to draw the attention of investigators to peptides in general and to CRF in particular. Much of the work done to date has focused on small molecules that can pass the blood-brain barrier or direct microinjection of peptides into the brains of animals. However, the continuing development of novel drug delivery systems that can allow drugs to cross the blood brain barrier ("e-cigarette" vaporization devices, fusion protein systems, etc.) is likely to speed this research. Koob summarized pre-clinical work showing that administration of a CRF antagonist can reduce drug self-administration in animals made dependent on cocaine, opioids, ethanol and nicotine^[17].

Mood Stabilizers and Dopamine System Stabilizers

Over the last quarter century, it has been realized that successful treatment of epileptic seizures requires a reinstatement of the balance between brain excitation and brain inhibition and that any of a large variety of mechanisms can achieve this end (Table 1). In turn, investigators have similarly realized that the most effective treatment strategy for bipolar disorder (in which mood swings from depression to mania and back again) is to stabilize mood by using agents that can restore the balance between brain excitation and inhibition. Related to this is the idea that schizophrenia can be most effectively treated using novel

(atypical) antipsychotic agents that block serotonin-2A receptors fully and D2 DA receptors partially or that act as partial DA and perhaps serotonin agonists (Table 2).

Table 1: Anti-seizure drugs

GENERIC	MOA	TRADE
Sodium Channel Recovery		
Phenytoin	Slows Na ⁺ channel recovery	Dilantin
Carbamazepine	Slows Na ⁺ channel recovery	Tegretol
Carbamazepine XR	same as carbamazepine	Carbatrol-Xr, Tegretolxr
Eslicarbazepine		Aptiom
Lamotrigine	Slows Na ⁺ channel recovery	Lamictal
Topiramate	Slows Na ⁺ channel recovery	TOPAMAX, TrovendiXR, Qudexyxr
Fosphenytoin	Phenytoin prodrug Slows Na ⁺ channel recovery	Cerebryx
Oxcarbazepine	Slows Na ⁺ channel recovery	Trileptil
Lacosamide	Increases SLOW inactivation of volt-gated Na channels	Vimpat
Rufinamide	Slows Na ⁺ channel recovery	Banzel
Enhances GABA Activity		
Lorazepam	GABA allosteric modifier at BDZ site*	Ativan
Clonazepam	GABA allosteric modifier at BDZ site	Klonopin
Diazepam	GABA allosteric modifier at BDZ site	Valium
Clobazam	GABA allosteric modifier at BDZ site	Anxibloc
Phenobarbital	GABA allosteric modifier at BARB site**	Phenobarbitalone
Primidone	Metabolized to phenobarbital	Mysoline
Valproic acid	Stimulates synthesis & Inhibits metabolism of GABA	Depakene
Gabapentin	Increases GABA release; Negative modulation of VGCC	Neurotonin
Tiagabine	Blocks GABA reuptake; Negative modulation of VGCC	Gabatril
Pregabalin	Increase GABA transport; Negative modulation of VGCC	Lyrica
Gamma-vinyl-GABA, VIGABA-TRIN	Inhibits GABA metabolism by blocking GABA-T irreversibly	Sabril
Reduces Glutamate activity		
Felbamate	NMDA receptor BB at Glycine site	Felbatol
Propofol	NMDA receptor BB (& GA-BA-A SS)	Diprivan
PERAMPANEL	NON-COMPET AMPA Receptor BB	Fycompa
Calcium and Potassium channels		
Ethosuximide	Reduces T-type Ca ⁺⁺ currents	Zarontin
Zonisamide	BB Na ⁺ chan, BB T-type Ca ⁺⁺ chan, Increases GABA release	Zonegran
Ezogabine	Postasium channel modulator	Potiga
Somatic Vesicle Associated Protein		
Levetiracetam	Modulates SVA2	Keppra
Brivaracetam	Modulates SVA2	

ABBREVIATIONS

*BDZ is benzodiazepine; **BARB is barbiturate; SS = agonist; BB = blocker; SVA2 = synaptic vesicle associated protein #2
VGCC = voltage-gated calcium channels GTC = generalized tonic-clonic

Table 2: Antipsychotic Drugs

GENERIC	MOA	TRADE
First generation antipsychotics [FGA]		
chlorpromazine [LOW potency]	BB D2, mACh, alpha1	THORAZINE
haloperidol [HIGH potency] [2D6,3A3/3A4]	BB mostly D2 DA receptors	HALDOL
perphenazine [MEDIUM potency] [2D6]	D2 BB	TRILAFON
loxapine [MEDIUM potency]	BB D2 DA, alpha1, mACh & 5HT	LOXATANE
fluphenazine [HIGH potency]	5HT2A, D2, alpha1, Histamine 1 BB	PROLIXIN
Second generation antipsychotics [SGA]		
clozapine [1A2]	BB 5HT2A as well as D2 DA receptors, mACh HIST1 BB	CLOZARIL Versacloz
risperidone [2D6]	5HT2A, D2, alpha1 BB	RISPERDAL
paliperidone [9-hydroxyrisperidone] [2D6, 3A4 IN VITRO]	5HT2A, D2, alpha1 BB	INVEGA, depot is SUSTENNA
olanzapine [1A2]	5HT2A, D2, mACh, Hist1, alpha1 BB	ZYPREXA
quetiapine [3A3/3A4]	5HT2A, D2, alpha1, Hist1 BB	SEROQUEL
ziprasidone [3A3/3A4]	5HT2A, D2, alpha1 BB, 5HT1A part ag	GEODON
iloperidone [2D6, 3A4]	5HT2A, D2, alpha1 BB	FANAPT
asenapine [1A2]	5HT2A, D2, alpha1, Histamine 1 BB	SAPHRIS
lurasidone [3A4]	5HT2A BB, D2 BB, 5HT1A PA	LATUDA
	SS = agonist; BB = blocker; part ag = partial agonist	
DA SYSTEM STABILIZERS		
arapiprazole [3AE/3A4]	D2 part ag, 5HT1A part ag.	ABILIFY
arapiprazoleXR		Abilify Maintena
brexipiprazole [3A4, 2D6]	D2 & 5HT1A part ag. + antag at 5HT2A, alphaR, 5HT2B, 5HT7, & muscR	REXULTI

It now appears almost axiomatic that mood-stabilizing drugs might have potential value as anti-craving agents. However, this idea was a long-time coming^[4]. Initially, the leap was understanding that drugs used to restore a balance in brain activity between net excitation and net inhibition were of potential value in the treatment of epilepsy and a variety of drug mechanisms of action were identified in that context. Subsequently, the concept of restoring a balance between excitation and inhibition was extended to the treatment of manic episodes in bipolar patients and many antiepileptic agents have subsequently been found to be of value in treating this disorder as well. Finally, investigators realized that restoration of a balance in brain activity induced by

such mood stabilizers could apply to the treatment of craving.

As noted above, topiramate is an anti-seizure agent and mood stabilizer (like tiagabine) that blunts alcohol craving. Its pharmacology is somewhat complex, including classic inhibition of the recovery of voltage-gated sodium channels (necessary for calcium influx and transmitter release) plus enhancing GABA activity at GABA-A receptors and blocking glutamate activity at AMPA / Kainate glutamate receptors. Olive reviewed a number of agents including the mood stabilizers gabapentin, lamotrigine, and topiramate^[40]. Lamotrigine, gabapentin, and to some extent topiramate all block voltage-gated sodium and calcium channels. All three agents can reduce the craving for ethanol with some data suggesting that topiramate is superior to the “gold standard” naltrexone (see above). Lamotrigine also produces a beneficial reduction in craving for cocaine and for inhalants.

As with treatment of bipolar patients, treatment of psychosis has progressed from the simplistic use of drugs that blocked D2 DA receptors (reducing the positive but not the negative and cognitive symptoms of schizophrenia) to the use of atypical antipsychotic agents. Such agents exhibit a variety of MOA including blockade of 5HT_{2A} receptors or acting as partial agonists at D2 DA receptors (see below). Not surprisingly, from the perspective of hindsight, many of the atypical “antipsychotic drugs” are of value as mood stabilizers and should be also considered as potential anti-craving agents.

Drugs that are partial D2 DA agonists have fairly recently found a place as atypical antipsychotics and subsequently as mood stabilizers. These drugs, including aripiprazole and brexpiprazole, are now called dopamine system stabilizers and fulfill the criteria that seem to be necessary for reducing craving as follows. We will use the example of how these drugs work in treating the symptoms of schizophrenia to illustrate the point. Schizophrenia is a disorder in which the primary deficit is an underactive frontal / prefrontal cortex. Thus, a person suffering from schizophrenia may exhibit negative and cognitive symptoms due to the direct effects of the disease on the frontal / prefrontal cortex and benefit from treatments that enhance DA in these brain areas. Simultaneously, the schizophrenic person may exhibit positive symptoms due to the release of subcortical areas from inhibition with the associated enhanced release of DA. These symptoms would benefit from a net reduction in DA stimulation of its receptors. DA system stabilizing agents such as aripiprazole fulfill both needs. Such drugs substitute for DA in the frontal and prefrontal cortex where it is deficient but displace DA within subcortical brain regions where it is in excess.

Similarly, a drug-dependent person has a net increase in activation of brain DA within the limbic system due to the direct or indirect actions of the addictive drug with acute exposure (LIKE) and during the early phases of the addictive process (WANT). If the DA is severely reduced, as during drug withdrawal and perhaps in the later phases of the addictive process (NEED), then craving ensues. However, if the person is given aripiprazole, the net stimulation of DA receptors is normalized – cortical deficits reduced and subcortical excesses masked.

Other Types of Agents

In a 2013 review, Koob^[17] noted that the brain stress systems mediated by CRF in the extended amygdala and the Hypothalamic-Pituitary-Adrenal (HPA) axis are dysregulated by all

of the major drugs with addictive potential. As a group, the addictive drugs elevate adrenocorticotrophic hormone (ACTH) and corticosterone systemically and CRF in the extended amygdala during their withdrawal after chronic dosing. One must be careful not to link withdrawal effects per se with craving since, while the processes may overlap, they also have distinct components^[7]. As mentioned above^[30] neurokinin-1 (NK-1) antagonists can reverse both the behavioral and neurochemical changes induced by psycho-stimulants in animals, particularly if the antagonist is given at a critical time following administration of a DA agonist (combination therapy). Very interestingly, Mahler, et al.^[47] discussed the role of certain hypothalamic peptides called orexins. These peptides known as orexin-A and orexin-B play a role in sleep/wakefulness and the drug suvorexant is available as a competitive antagonist of orexin A/B at both Ox1 and Ox2 receptors. The authors suggested that orexins may be involved in drug seeking that is triggered by external stimuli (including cues, contexts or stressors).

Potential Leads for Anti-Craving Agents

In this section we will highlight several productive strategies for development of improved treatment of drug craving. Overall, these approaches will either tend to stabilize the addictive process at its current level (substitution therapy) or reverse the process towards normal brain function (“reversal therapy”).

Substitution Therapy: Maintaining the addictive process at its current level for a given patient is a strategy that has worked extremely well for many years for people dependent on heroin. Methadone and subsequently buprenorphine (with or without naloxone) have allowed opioid-dependent people to function effectively without needing their “fix”. A key aspect of this therapy has been the use of an oral medication that activates the same receptors as the intravenous or smoked heroin (or oral prescription opioid agonist) mimicking the effects of the addictive drug in the brain. This allows sufficient receptor stimulation to prevent craving but it is hypothesized that the addictive process remains at its current level since the oral route of drug dosing (longer latency of drug onset) does not engage neural plasticity mechanisms to the same extent as those routes of administration (intravenous or inhalational) that lead to rapid increases (and decreases) in brain drug levels.

Buprenorphine, a partial agonist, activates opioid receptors at a lower pharmacological efficacy than that of full agonists such as heroin or methadone. This means that some receptor activation takes place but less than what occurs after heroin or methadone. The medication’s relative intrinsic efficacy must be sufficient high to prevent craving but ideally sufficiently low that the person does not get “high”. In addition, if a dependent individual attempts to increase the dose, buprenorphine then competes with heroin for the opioid receptors², greatly reducing the addictive liability of the drug.

Similarly, substitution therapy to reduce nicotine craving using nicotine patches, nicotine gum, nicotine e-cigarettes etc. has been an effective development in this field. In treating nicotine craving it is important to note that many dependent people do need additional medications. These may include bupropion that potentiates both DA and NE via blocking their uptake into the nerve ending or the direct partial nicotinic agonist

varenicline. Furthermore, nicotine from a cigarette passes the blood-brain barrier more rapidly than does intravenously administered nicotine. For that reason e-cigarettes appear to be a good substitution for cigarette smoking as well as an effective harm reduction strategy.

Substitution therapy has not really been attempted systematically for ethanol. Benzodiazepines only partially substitute and barbiturates are problematic. Similarly, substitution therapy has been quite disappointing for stimulants such as cocaine and the amphetamines. To reduce craving for stimulants, several direct or indirect DA agonists have been tried. These include direct D2 DA agonists, such as the anti-Parkinson's disease agent bromocriptine, that produces significant nausea and amazingly has itself been abused by stimulant-dependent persons! In fact, most agents used in an attempt to reduce stimulant craving appear to be drugs of abuse themselves. Exceptions may include bupropion and modafinil (as discussed above). As a dual action drug that potentiates both DA and NE, bupropion may have less abuse liability because of the added increase in synaptic NE levels which may somewhat dampen some of the effects of DA. In contrast, methylphenidate (MPD) is a powerful inhibitor of the uptake of DA into the nerve ending used in children with ADHD to boost DA levels. Thus, MPD should be effective in reducing the craving for both cocaine and methamphetamine since it blocks the DA transporter and enhances synaptic cleft levels of DA, thereby mimicking the net effects of cocaine (transport blockade) and amphetamine (exchange diffusion, leading to enhanced DA release). Furthermore, MPD is a safe and highly effective treatment for ADHD in both children and adults. However, the fact that MPD shares a mechanism of action with cocaine is problematic in stimulant-dependent persons because it may induce a craving for itself! Thus, MPD has not worked well in clinical practice as an anti-craving agent.

There are two key factors that operate here.

- First, an effective anti-craving drug for substitution therapy should mimic the agent of abuse at its target protein (receptor or transporter) but it should not do that job too well. Thus, partial direct agonists of a receptor or weak inhibitors of neurotransmitter transport would appear to be the most useful agents. A promising avenue for anti-craving drug development in this niche would be a weaker DA releaser (more like ephedrine than methamphetamine) with a relatively greater effect on DA than on norepinephrine, a moderately rapid onset and a fairly long half-life. Those requirements are met with the transport blockers modafinil and perhaps bupropion.
- Second, the drug's route of administration needs to allow effective brain concentrations to be reached in a reasonable amount of time (but not too quickly) to avoid further acceleration of the addictive process. Therefore, it will be important to look at the pharmacokinetics of methadone, buprenorphine, nicotine (in its various delivery forms), and modafinil to glean information about the kinetics of these agents.

Reversal Therapy: Substitution therapy has value in that it can stabilize the dependent person at his / her current level of addic-

²Heroin is diacetyl-morphine. This structural modification allows heroin to cross the blood brain barrier into brain much more effectively than is the case for morphine. However, once inside the brain, the heroin is de-acetylated back into morphine, which is the active component that binds to and activates opioid receptors.

tion and allow them to function in society. However, substitution therapy often does not allow the person to stop using drugs altogether and, thus, does not affect a "cure". Ideally, medications would not just reduce craving per se, but also reverse the addictive process, leading to an actual normalization of the person's brain functions – a true reversal of drug dependence.

The essential feature of the effective anti-craving medications acamprosate and naltrexone (as well as those used off-label, including ondansetron, topiramate, nalmefene, and valproic acid)^[48] is that

- They seem to target some portion of the "addictive pathway" that may be common to a variety of addictive drugs and
- They may reverse some of the maladaptive processes associated with the "encoding" of addiction.

This opens an entire avenue of potential treatment options based on a current detailed knowledge of the brain substrates of addiction^[7,4] along with knowledge of what drug mechanisms of action are effective in stabilization of brain activity (restoring the balance between excitation and inhibition). As an example, only three drugs are actually approved to reduce ethanol consumption in people with severe alcohol-use disorder (aka alcoholics). These are acamprosate and naltrexone, both acting to reduce craving, and disulfiram, acting to reduce consumption because of the toxic effects that drinking produces in its presence. As discussed in an earlier section, acamprosate and naltrexone have very different mechanisms of action. Acamprosate acts as an NMDA (glutamate) receptor partial co-agonist. Thus, it is an effective modulator of maximal NMDA receptor activity while still providing some degree of tonic stimulation. Naltrexone is a competitive antagonist at opioid receptors, in particular the mu receptor but can modulate DA activity indirectly. Thus, at a molecular level the two drugs couldn't be more different. However, each agent appears able to reduce the net imbalance in firing within the VTA positive reinforcement pathway towards a more normal value. That may be the key! A summary of the agents discussed thus far is given in Table 3.

Components of the "final common pathway" for the addictive process: To recap what was presented in the section on neural mechanisms of craving, the VTA pleasure pathway and its terminal areas within n. accumbens, frontal and prefrontal cortices, plus the extended amygdala seem to represent the minimal neural substrate for the complete addictive process (from LIKE through WANT to NEED)^[4,5,7-9,20,49]. Each brain area represents a potential target for anti-craving drug therapy depending on the relative expression of the receptors most altered during the process of dependence development. The work of Lee, et al.^[30] discussed above is important to recall for two reasons. First, it highlights the potential importance of combination medication therapy (see below). Second, it recognizes that a specific temporal protocol for therapeutic drug administration may be essential to achieve the anti-craving effect. Below we will discuss this issue further in the context of judicious combinations of medication with non-drug therapies.

Table 3: Anti-Craving Drugs

TRANSMITTER SYSTEM	THERAPEUTIC DRUG	ADDICTIVE DRUG	MOA – EFFECT ON CRAVING	REFERENCE
DOPAMINE [DA]	METHYLPHENIDATE	COCAINE	DAT BLOCKER –NOT HELPFUL	[1]
	BUPROPION	NICOTINE	DAT/NET BLOCKER – HELPFUL	[2,3]
	GAMMA-HYDROXYBU-TYRATE	ETHANOL	BLOCKS DA RELEASE – HELPFUL	[4]
	NALOXONE	ETHANOL	OPIOID ANTAGONIST – HELPFUL	[4]
	MODAFINIL	COCAINE	WEAK DAT BLOCKER – HELPFUL	[5]
SEROTONERGIC [5HT]	5HT ANTAGONISTS – OSMEMOZOTAN, RITANSERIN, AZASETRON	STIMULANTS	BLOCKS VARIOUS 5HT RECEPTORS ESP 5HT2 – HELPFUL IN RODENTS	[6]
	ONDANSETRON	ETHANOL	5HT3 RECEPTOR BLOCKER- VERY HELPFUL IN SUBSET OF ALCOHOLICS	[7]
	AMPEROZIDE	ETHANOL	5HT2 ANTAGONIST – HELPFUL IN RODENTS	[8]
NOREPINEPHRINE [NE]	LOFEXIDINE	COCAINE	ALPHA2 AGONIST – HELPFUL	[9]
ACETYLCHOLINE [ACH]	VARENICLINE	NICOTINE	NICOTINIC PARTIAL AGONIST – HELPFUL	[2]
GABA	TIAGABINE	ETHANOL	GABA UPTAKE BLOCKER – NOT HELPFUL IN NON-ALCOHOLICS	[10]
	BACLOFEN	ETHANOL & NICOTINE	GABA-B RECEPTOR DIRECT AGONIST – HELPFUL	[11]
SODIUM CHANNELS	TOPIRAMATE	ETHANOL	BLOCKS VOLTAGE-GATED SODIUM CHANNELS – HELPFUL	[5]
	LAMOTRIGINE	ETHANOL	BLOCKS VOLTAGE-GATED SODIUM CHANNELS – HELPFUL	[5]
NMDA GLUTAMATE	ACAMPROSATE	ETHANOL, NICOTINE, OPIOIDS	NMDA RECEPTOR PARTIAL CO-AGONIST – HELPFUL	[11,12,5]
	D-CYCLOSERINE	COCAINE & NICOTINE	NMDA RECEPTOR CO-AGONIST – HELPFUL	[5]
	MEMANTINE	NICOTINE & HEROIN	NMDA RECEPTOR NON-COMPETITIVE ANTAGONIST – HELPFUL	[5]
	N-ACETYLCYSTEINE	COCAINE	ELEVATES EXTRACELLULAR GLUTAMATE LEVELS – SLIGHT EFFECT	[5]
OPIOID	METHADONE	HEROIN	OPIOID FULL AGONIST – HELPFUL	[13]
	BUPRENORPHINE	HEROIN	OPIOID PARTIAL AGONIST – HELPFUL	[14]
	NALOXONE, NALTREXONE	HEROIN & ETHANOL	OPIOID ANTAGONISTS – HELPFUL	[15,4,3]
CANNABINOID AGENTS	RIMONABANT	NICOTINE	CANNABINOID-1 RECEPTOR INVERSE AGONIST – HELPFUL IN RODENTS REMOVED FROM MARKET FOR PEOPLE	[16]
OREXIN	SUVOREXANT	POSSIBLE MULTIPLE DRUGS	OREXIN A/B RECEPTOR ANTAGONIST – NOT YET TESTED	[17]

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Combination Therapy for Reducing Craving: The overall modest ability of drugs to control craving should give us pause while the successes using substitution or reversal therapy should give us hope that medications are indeed a powerful portion of the toolkit for treating drug dependent people. We are just now in an era where it is feasible to consider two-drug combination therapy as a means for providing a societal benefit by reducing craving more effectively than current single agent treatments, while doing so in a greater proportion of those suffering from severe drug-use disorders.

- Combinations of acamprosate plus naltrexone do not appear to be more effective in reducing alcohol craving than either agent given alone. However, combining acamprosate or naltrexone with novel agents should be explored.
- In particular, for the treatment-resistant craving for stimulants, a combination of an agent that has a relevant mechanism of action (long-acting weak DA uptake blocker or partial DA direct agonist) with acamprosate or naltrexone may be of benefit.
- Similarly, neither acamprosate nor naltrexone is in any sense a mood stabilizer. However, a combination of one of these drugs with one of the mood stabilizers shown to be effective in bipolar patients could produce a net additive effect in restoring brain/behavioral balance.
- Also, the role of DA in virtually all drug dependencies should not be forgotten. Direct DA agonists that are currently available, unfortunately, are very selective for the D2 DA receptor. Therefore we suggest that DA releasers with an ephedrine-like potency or agents with a marked selectivity but weak activity for the DA transporter (such as modafinil) be considered. Such agents should have a fairly long duration of action and would constitute step one in a two-step temporal therapy with acamprosate, naltrexone or a mood stabilizer. Patient compliance would be enhanced by formulating the drug combination as a rapidly released dopaminergic agent with a more slowly released second agent.
- Finally, the effectiveness of a combination of an antidepressant agents plus a drug that modulates glutamate or GABA function should also be considered.
- Perhaps even the combination of a mood stabilizer with an antidepressant (comprising the historical method for treating both mania and depression in bipolar subjects) could be evaluated³.

³The problem with using both a mood stabilizer and an anti-depressant in bipolar patients turned out to be that mania was not treated more effectively and patients tended to shift from depression straight into mania.

Drug Plus Non-Drug Therapies

Clearly non-drug (aka, talk) therapies have been the mainstay for treating virtually all types of addiction for decades. Beginning with Alcoholics Anonymous, different groups matching each type of dependency now exist. These do tend to be moderately successful, especially if all persons in the group suffer from similar addictions. Since learning changes brain activity, these therapies will always have a place along with the necessarily less targeted drug treatment options.

Recently, specific non-drug therapies have been developed that focus on the learned aspects of the addictive process and specifically on the factors that can initiate and maintain craving. It is well known that extinction trials, placing a person in an environment in which stimuli that are associated with drug use are not rewarded with drug, do not generalize to the “real world” (the person’s living environment), although the procedures do seem to work well in restricted laboratory settings. In contrast, the neuroscience literature reminds us that memories are volatile and can be modified every time that they are recalled under the correct circumstances^[50,51].

Thus, a single dose of methamphetamine in the rat can reinstate a previously extinguished conditioned place preference for methamphetamine reward and that “reminder” (priming) dose effect can be blocked by the antibiotic ceftriaxone (Abulseoud, et al.)^[52]. This suggests the possibility that the craving reinstatement by a secondary reinforcer in a drug-free person could be blocked by a therapeutic drug. Furthermore, Xue, et al.^[50] reported that in heroin dependent people, the retrieval of memories associated with drug use 10-minutes prior to an otherwise standard extinction session reduced cue-associated heroin craving up to 6-months later^[53]. Very recently, Degoulet, et al.^[51] suggested that long-term potentiation (LTP, the major neural mechanism for memory encoding) may contribute to the increased salience of drug-associated cues during relapse. These authors noted that the antihypertensive agent isradipine (an antagonist of L-type calcium channels) suppressed the acquisition of contextual memory for cues in rats (in a conditioned place preference, CPP, paradigm in which animals spend a greater proportion of time in the environment associated with reward). Thus, judicious use of insights from learning theory coupled with timed administration of appropriate medication combinations could be a new route to reducing craving in severe drug-use disorders of many types.

Conclusions

In this manuscript we have attempted to identify the underlying physiology of the motivational construct in drug addiction research known as the LIKE-WANT-NEED continuum. In sum, we see LIKE to represent a transient elevation in dopamine release in the nucleus accumbens that is rapidly reversed through the action of several negative feedback loops. In contrast WANT is a long acting elevation in dopamine release, most often manifest as a result of agents (e.g. amphetamine, cocaine, nicotine) that act directly on the dopamine terminal. The result is behavioral sensitization. We hypothesize that NEED is a condition in which dopamine receptors (and perhaps the dopamine transporter) are down-regulated due to excessive dopamine release, resulting in compulsive foraging for more drug to compensate for the reduced sensitivity of the dopamine receptors. But even when the foraging is successful, additional dopamine

release causes further receptor down-regulation, resulting in the “vicious cycle” of drug addiction.

Drug-craving occurs in the WANT condition and continues in the NEED state. In fact, even if the addict is abstinent for years, craving can still occur, often as a result of exposure to environmental stimuli (secondary reinforcers) previously associated with drug use. In all likelihood, craving results from an un-extinguished conditioned response to such stimuli. Behavioral approaches to craving reduction, including secondary reinforcer extinction trials, have been tried, but results to date have not been encouraging. A more promising approach may require a prior reminder trial of drug effects to increase the salience of secondary reinforcers (opening a re-consolidation window), followed by extinction training. Alternatively, it may prove possible to block neurochemically the recall of the drug memory induced by exposure to the secondary reinforcer.

Finally, we discuss the clinical efficacy of a variety of pharmacological agents (dopaminergic, serotonergic, noradrenergic, cholinergic, GABAergic, glutamatergic etc.) in both substitution therapy and in reducing drug craving (reversal therapy). New leads for both substitution and reversal therapy are also considered, as well as the prospects for anti-craving/anti-addiction drug combination therapy.

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