Minding the brain: the role of pharmacotherapy in substance-use disorder treatment

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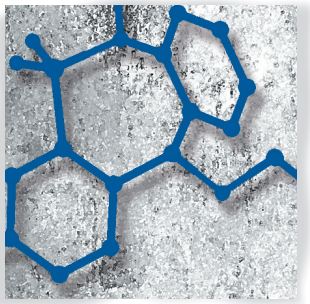

With its medicalization as a brain-based disease, addiction has come to be regarded as amenable to biomedical treatment approaches, most commonly pharmacotherapy. Various vulnerabilities are recognized to contribute to maladaptive substance use, and have been linked to diverse neurobiological alterations that may be targeted with pharmacotherapy: withdrawal, craving and cue reactivity, and aberrant reward processing are the most significant. Here, we summarize current thinking regarding pharmacotherapy for substance-use disorders, grouping medications by the type of vulnerability they propose to address and providing insight into their neurobiological mechanisms. We also examine the limitations of the brain-based disease model in addiction treatment, especially as these shortcomings pertain to the place of pharmacotherapy in recovery. We conclude by sketching a framework whereby medications might be integrated fruitfully with other interventions, such as behavioral, existential, or peer-based treatments, targeting aspects of addiction beyond neurobiological deficits.

© 2017, AICH – Servier Research Group *Dialogues Clin Neurosci*. 2017;19:289-297.

Keywords: *addiction; alcohol; cannabis; cocaine; nicotine; opioid; pharmacotherapy; treatment*

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Introduction

As with other psychiatric disorders, it was only when addiction was recognized as a disease that medications began to be considered for treating it. For most of its history, addiction was not considered a disease, much less a disability; it was, instead, a moral problem. In the *Nicomachean Ethics*, Aristotle argued that because an individual is responsible for the choice to drink—and the many decisions to drink subsequently—then he is also responsible for being intoxicated, as well as for any drinking-related encroachments on rational or responsible behavior (ie, poor decisions) that might emerge.[1] He therefore believed that we are morally accountable for our actions while addicted, as well as for the addiction itself, by virtue of the chain of free decisions leading to addiction. This view remained unchallenged for centuries and provided a foundation for handling addiction as primarily a breach of proper behavior, as with other matters of clear personal responsibility (such as breaking the law). Accordingly, until recently, Western societies have understood substance-use disorders as an infraction in moral conduct, be it sinfulness or criminality, and most properly dealt with by recourse to the pillory or pulpit.[2]

The 20th century saw a dramatic shift in our understanding of addiction and of other behavioral disorders, with many of these conditions coming under the purview of the medical disciplines. The reasons for

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this are varied and complex and include cultural and financial forces (the expansion of rational humanism, for example, and of the pharmaceutical industry) in addition to scientific developments. With its medicalization, addiction became the focus of efforts to identify treatments that might be incorporated into existing therapeutic contexts, such as faith-based healing programs and standard medical centers. At the same time, addiction was reified according to the "hard" tenets of neurobiology and was recast as a "brain-based" disturbance, whereby the behavior is rooted not in free choice or personal responsibility but chiefly in inherited or acquired neurobiological vulnerabilities.[3] This conceptualization has served many purposes, one of which being the establishment of addiction as a disease like any other and, therefore, free of any significant ethical dimension. Addiction has come to be construed, alongside other diseases in the lexicon of modern medicine, as an entirely material phenomenon traceable to biological disruptions, which in turn are amenable to assessment, in some cases precise quantification, and also, perhaps, focused medical interventions. The more fully that addiction approximates this concept of disease, and the more persuasively the argument can be made that problematic drug use resides in the physical workings of the brain, the less credence we give to the viewpoint that addiction is a moral or legal issue, and the less likely, it is hoped, that our society will lapse into punitive or judgmental approaches that may do more harm than good.[4] This emphasis on brain-based disruptions works to exonerate the addicted individual of intentional wrongdoing: it is the disturbed brain that acts, not the person, and so the person should be treated as sick, not as criminal.

Though this neurobiological model of addiction has been criticized as misguided, reductive, and insufficiently concerned with psychological or environmental factors,[4] it is widely regarded as one of our safeguards against the barbarous treatment inflicted on addicted individuals in less-enlightened times (the current war on drug users in the United States and other modern nations notwithstanding). This model also provides a framework for addressing addiction in a manner comparable to how other diseases are treated—that is, with medications or other interventions focused on remedying physical deficits. Any discussion of pharmacotherapies for addiction therefore necessitates an examination of this neurobiological conceptualization. We begin our review of existing and emerging pharmacotherapies with a summary of this medical model, particularly as it relates to the identification of neural targets for medication treatments. We then examine the different types of medications that have proven effective or that are under development, grouping them by the vulnerabilities and neural disruptions they propose to address. We conclude with some remarks on the successes and failures of a pharmacotherapy-centered approach to treating substance-use disorders.

Understanding the neurobiological correlates of addiction

Substance-use disorders are characterized chiefly by progressively uncontrollable drug use in the face of negative consequences. The course of disease, across a range of different substances, is invariably marked by a transition, in some cases precipitous and in others more insidious, toward substance use that is unregulated and destructive. This transition is more likely to occur with some drugs than with others, and for all drugs, it is the minority that initiates problematic use, with most individuals remaining casual, responsible users.[5,6] What leads some to transition to problematic use, whereas most others do not, is a crucial question in addiction research, and one that the medical paradigm aims to resolve by discovering the neural deficits that drive problematic use.

The advent of addiction involves the development of various vulnerabilities that work to intensify and complicate drug consumption and ultimately perpetuate a seemingly intractable pattern of problematic use. These vulnerabilities include tolerance to the substance, often coupled with compulsive use to override diminished subjective effects; withdrawal phenomena upon cessation of the drug; cravings (increased desire for the drug); attenuated motivation for nondrug rewards; stress sensitivity and heightened responsivity to drug-related cues; impulsivity and delay discounting, which refers to the reduced value placed on deferred reward; and tenuous motivation for changing destructive behavior. Importantly, these vulnerabilities are believed to represent brain-based adaptations to repeated drug consumption, even though some of them (most notably, impulsivity and stress sensitivity) might also precede the initiation of drug use altogether. Some individuals are more susceptible to developing these vulnerabili-

ties than are others due to genetic, psychiatric, or environmental factors[5]; and these are the individuals most likely to transition to problematic consumption characteristic of a substance-use disorder.

The neural changes associated with these deficits and neuroadaptations continue to be investigated and elucidated. The field has identified several brain-based changes that appear to be closely linked to key adaptations across different substances of abuse. Tolerance, for example, has been linked to a downregulation of certain receptors, such as the μ-opioid receptor in opioid users, due to chronic drug exposure,[7] and withdrawal is believed to represent a downtick in receptor signaling, given the decreased density of receptors, upon abrupt cessation of a drug.[8] Other receptor-based adaptations include changes in glutamate receptors, such as the *N*-methyl-D-aspartate receptor (NMDAR), and alterations in serotonergic and dopaminergic receptors; these disruptions have been implicated in a range of dependence-related adaptations according to functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies, including attenuated dopamine signaling at the nucleus accumbens and associated problems with the salience of natural rewards.[9-11] Other neural and regional alterations identified by fMRI and PET for different substance-use disorders include disruptions in prefrontal modulation of the mesolimbic system, alterations in the reward system, and changes in prefrontal activity.[10-12]

These different adaptations are believed to account for the vulnerabilities that constitute the core deficits of addiction, such as tolerance, withdrawal, craving, cue and stress sensitivity, and low motivation for changing drug use, but a key component of addiction remains difficult (and perhaps impossible) to locate in a neural or regional disruption: the decision to continue using drugs. Absent this decision to consume drugs, addiction would not exist, despite the presence of vulnerabilities predisposing to it. Indeed, we know that individuals will modulate their drug use in the presence of alternative reinforcers, altering the course of their addiction even though in other respects their deficits remain the same (ie, tolerance, craving).[13] We also know that the deficits themselves might be modulated by the intentions and perspectives of the individual; in a recent study, the activation of the brain in response to tobacco cues was altered when addicted individuals brought to mind the negative consequences of smoking, effectively dampening their cue reactivity by virtue of a deliberate shift in perspective.[14] These findings indicate that chronic neural disruptions (if not the acute effects of a drug) might be overridden by a willful subjective state, such as an intention, decision, or perspective, not directly attributable to preexisting brain-based alterations. It therefore appears that addiction, despite deficits predisposing toward it, is not inevitable. In other words, these vulnerabilities might increase the risk of addiction, but they are not sufficient to drive it. The person must ultimately *act,* in one way or another.

It may be fanciful, therefore, to expect that pharmacotherapy alone, or any other brain-based treatment, will lead an individual to stop using drugs. Such interventions might work to address the vulnerabilities that predispose to the decision to use drugs; they may even improve the capacity for making free decisions by ameliorating encroachments on rational action, such as behavioral reactivity or the disproportionate overvaluation of drug-based over natural rewards. But the decision itself is not occurring in a specific brain-based alteration: it is happening at the level of the person. And for an intervention to be most effective, it will need to address the person, with all one's perspectives, intentions, and habits, as well as the environments and contexts in which one lives. We will return to this point later.

Withdrawal

Withdrawal emerges when an organism inured to a relatively stable level of certain reinforcing substances is suddenly deprived of them. The most effective way to address withdrawal, therefore, is to introduce an agent that has a similar effect on neural circuits, ie, an agonist, and to taper the agent in a slow and gradual manner that facilitates comfortable discontinuation.[15] This strategy has been applied to a range of substance-use disorders associated with withdrawal, including tobacco, alcohol, opioids, sedatives, and cannabis. Alcohol withdrawal, for example, is treated with benzodiazepines, which have a comparable effect on γ-aminobutyric acid (GABA)[16]; tobacco withdrawal is addressed with nicotine replacement[17]; and emerging research suggests that tetrahydrocannabinol (THC) analogs, such as dronabinol or nabilone, may be helpful at ameliorating withdrawal from cannabis.[18,19] Long-acting formulations, moreover, might be effective at promoting gradual dis-

continuation by virtue of protecting individuals from the emergence of precipitous withdrawal, which is commonly associated with agonists with shorter half-lives. Thus, for opioid withdrawal, the preferred medications for facilitating discontinuation are methadone and buprenorphine, both of which have long half-lives.[20]

Another strategy for addressing withdrawal is to address the specific symptoms that might be associated with the withdrawal syndrome. Sleep disturbances, restlessness, enervation, indigestion, and mood problems have all been the target of pharmacotherapy for withdrawal from a range of substances. Commonly used medicines include zolpidem, benzodiazepines, and stimulants.[21] The α_2 agonists, such as clonidine, lofexidine, and guanfacine, have shown promise in managing the restlessness and anxiety associated with both cannabis- and opioid-use disorders.[21,22] They are believed to work by dampening the noradrenergic surge characteristic of withdrawal states, which might lead to anxiety, restlessness, and agitation. Other medications are in development aimed at mollifying withdrawal through novel mechanisms, such as glutamatergic modulation and improved endocannabinoid signaling.[21,23]

Craving and cue reactivity

Craving is a complex phenomenon involving heightened desire for a drug, often coupled with difficulty in experiencing a cue without incurring a high level of drug wanting; repeated failures to resist the desire to use; and intolerable affective or physical states, such as dysphoria or indigestion, in the absence of drug use. Cue reactivity, which is an important component of craving, has been linked by fMRI studies to increased activity in the amygdala, ventral striatum, and prefrontal regions, suggesting altered processing in those structures.[23]

As with withdrawal, craving may be addressed with administration of an agonist. Agonist maintenance strategies, such as methadone maintenance treatment (MMT) for opioid-use disorders, are intended to both protect against withdrawal and to address any craving that might emerge.[20,24] Buprenorphine, a partial opioid agonist with high binding affinity for opioid receptors, is also used as a treatment for opioid-use disorders and has certain advantages over methadone.[25] It can be prescribed in an office-based setting without the need for the intensive clinical framework associated with MMT; its high avidity for opioid receptors displaces most other opioids, effectively diminishing the effects of coadministered illicit opioids; and its partial agonist effects renders respiratory depression and overdose less likely.[25,26] Researchers are currently investigating depot formulations of buprenorphine, such as probuphine, that do away with the need for daily dosing (though the peak available dose, an 8-mg daily equivalent, is insufficient for most patients), thereby protecting individuals from the risk of impulsively stopping treatment and lapsing on illicit opioids. Both methadone and buprenorphine have been associated with high retention and reductions in opioid use (eg, heroin, synthetic opioids, fentanyl) in numerous clinical trials, but other strategies have been investigated, such as morphine- and diacetylmorphine-based maintenance, for individuals unresponsive to more conventional agonist treatments.[20,24]

Varenicline is a partial nicotinic-receptor agonist that is among the most effective pharmacotherapies for nicotine dependence and is believed to work principally by reducing cravings through agonist effects.[27] Other agonist maintenance strategies that have been explored are stimulants for cocaine-use disorder[28] and THC analogs for cannabis-use disorder.[18,19] Stimulants and cocaine have comparable effects on monoamine neurotransmitters, such as dopamine and norepinephrine. Both in laboratory and clinical research settings, stimulants (including amphetamine and methamphetamine) have been associated with reductions in craving and drug-seeking behavior in cocaine-dependent individuals.[28-30] Methamphetamine may also be helpful in promoting abstinence in a treatment-seeking cocaine-dependent sample engaged in behavioral treatment.[30] Dronabinol and nabilone have shown promise in a laboratory model of relapse at reducing cannabis-seeking behavior,[18,19] but the former did not separate from placebo in a randomized controlled trial and the latter has yet to be tested clinically.[31]

Other pharmacotherapy approaches to craving aim to target other neurotransmitter systems that may be involved in various facets of drug seeking, such as cue reactivity, stress sensitivity, and the heightened salience of drug reward. These include the glutamatergic, monoaminergic, and opioid systems. Bupropion is a dopamine and norepinephrine-reuptake inhibitor that has shown efficacy in reducing craving and promoting abstinence in nicotine dependence,[32] though it has not shown efficacy for other substance-use disorders.[33] Topiramate is a partial glutamate antagonist that may work to reduce

craving both among cocaine- and alcohol-dependent populations.[34,35] Other glutamatergic agents that may work to address craving, as well as associated vulnerabilities with cue sensitivity, include acamprosate for alcohol-dependent individuals[36]; gabapentin for alcohol- and cannabis-use disorders[37,38]; D-cycloserine, a partial NMDAR agonist, for tobacco or cocaine[39,40]; and memantine, a low-affinity NMDAR antagonist that has shown preclinical promise in reducing cue reactivity.[41] Naltrexone, an opioid-receptor antagonist that may work to inhibit the reinforcing effects of drugs of abuse, reduces craving in alcohol-dependent individuals,[42] as well as in opioid-dependent individuals.[43] Naltrexone additionally works to block the effects of opioids, which may serve to diminish craving in opioid users by eliminating the possibility of drug use and perhaps decoupling the conditioned association between a craving and its satisfaction. This behavioral mechanism is not unique to naltrexone; disulfiram works to inhibit the metabolism of alcohol, leading to a noxious buildup of aldehyde compounds whenever alcohol is consumed. Like naltrexone in opioid-dependent individuals, disulfiram precludes individuals from receiving the intended effect of the substance, but it also threatens a hurtful outcome. This disruption between the desire and the outcome to which it normally tends may have the additional effect of dampening the desire to drink; it may also work to change the orientation to alcohol cues, promote extinction learning (whereby a learned association is displaced), and reduce reactivity.

Recent research with subanesthetic infusions of ketamine, an NMDAR antagonist with potent downstream effects on neurogenesis and prefrontal modulation,[44] opens up a new avenue of research. A single infusion of ketamine has demonstrated effects on craving and on the choice to use cocaine for at least 28 hours after infusion.[45,46] Like other antidepressants, including serotonergic agents, ketamine may have effects on impulsivity and behavioral reactivity,[46,47] which may also work to address craving. Although the exact mechanisms of ketamine remain unclear, they are probably comparable to the effects postulated to account for its antidepressant benefits given the broad overlap in pathophysiology between substance-use disorders and stress-related disorders[46]; these mechanisms include the normalization of glutamate homeostasis in prefrontal regions, the reversal of synaptic pruning between prefrontal and mesolimbic regions, and sustained attenuations in resting-state (default mode network: DMN) hyperconnectivity, which has been linked to ruminations, obsessions, and overvalued ideation (eg, craving).[44,48] Preclinical research has long suggested a therapeutic role for the promotion of neural plasticity; in rodents, a direct infusion of brain-derived neurotrophic factor (BDNF) into the prefrontal circuits modulating the nucleus accumbens works to disrupt cocaine seeking.[49]

Aberrant reward processing

It has been observed in PET studies, across different substance-use disorders, that severity and prognosis are linked to stimulant-induced dopamine release at the nucleus accumbens, with blunted response correlating with a worse outcome.[50,51] This finding has provided a basis for understanding the disruptions in reward salience that represent a crucial deficit in substance-use disorders: low motivation for nondrug rewards superseded by a disproportionate emphasis on drug-based reward. This phenomenon is comparable to craving, but with an added level of complexity. It is not simply that the drug has high reward salience, heightening desire for it; other endeavors and rewards come to pale in comparison.

Given that this deficit involves reduced dopamine signaling, a promising strategy is to improve dopamine firing or synaptic dopamine levels. A variety of agents have been tested to explore this strategy, including stimulants, such as amphetamine and modafinil; medications aimed at improving presynaptic and synaptic dopamine levels, such as Parkinson medications; and medications that impede the metabolism of dopamine, such as nepicistat and disulfiram. In clinical research settings, they may be coupled with contingency management (CM), a behavioral treatment aimed at promoting abstinence by rewarding it with vouchers or incentives, with the expectation that the hypothesized improvements in reward salience will lead to better engagement with contingency-based behavioral modification. In cocaine users, stimulants have shown efficacy in facilitating CM,[30] but other dopaminergic agents have not led to clinical benefits in the clinical research conducted thus far.

Antidepressants also work to normalize reward salience by targeting other neurotransmitters, such as serotonin, that have been associated with hedonic capacity and motivation. Serotonin-specific reuptake

inhibitors (SSRIs), when coupled with CM in clinical research, have shown promise at promoting abstinence in cocaine users.[52,53] Though their potential utility for treatment of substance-use disorders has been conceptualized in terms of reducing negative affective states associated with chronic drug or alcohol use,[54] they may also work to restore reward processing in addicted individuals.

Neuroimaging studies with fMRI in individuals with diverse substance-use disorders, as well as with addiction-like behavior oriented around natural rewards, have identified hyperactivation of the amygdala and striatum in response to problematic reward-related stimuli (eg, drugs).[11,12,55] Some pharmacotherapies aim to restore healthy reward processing by modulating these regions; glutamate neurotransmission, in particular, represents an important target of pharmacotherapy given its role in communication between prefrontal and mesolimbic structures, such as the nucleus accumbens and amygdala. For example, downregulation of the cysteine-glutamate exchanger in the nucleus accumbens is a dependence-related adaptation that has been linked to drug reinstatement. *N*-acetylcysteine (NAC), a naturally occurring prodrug of the amino acid cysteine, is believed to correct this deficit by upregulating the cysteine-glutamate exchanger. In a preliminary controlled trial comparing 1200 mg of NAC with placebo in conjunction with CM, it was found that the NAC group led to a significantly greater proportion of cannabis-negative urine tests,[56] though this failed to replicate in a larger trial. Interestingly, a trial of NAC with doses up to 2400 mg, in the absence of CM, demonstrated no effect on cocaine dependence, with comparable abstinence rates between the placebo and NAC groups.[57] These data suggest that NAC may be most effective if paired with a CM platform.

Recent research suggests that ketamine and related glutamatergic agents may work to correct aberrant reward processing by normalizing prefrontal modulations of striatal regions. In rodents, a single infusion was shown to mitigate distress related to withdrawal by exerting downstream effects on dopamine neurotransmission at the nucleus accumbens[58]; and in humans, a single infusion improved motivation to quit cocaine in non–treatment-seeking cocaine-dependent adults.[45] Further, in a controlled laboratory model of cocaine self-administration designed to detect shifts in the relative salience of cocaine now vs money later, ketamine led to a significant reduction in cocaine choices more than 24 hours after infusion, suggesting that, alongside craving, ketamine targets the disproportionate valuation of immediate drug over delayed nondrug rewards.[46] The clinical significance of these effects continues to be explored; meanwhile, these findings signal new directions in medication development for substance-use disorders more generally, given the broad overlap in the pathophysiology of neuroadaptations to different drugs.

Experiential effects may also play a role in the benefits of ketamine. An analysis showed that mystical-type effects, comparable to what is reported during "conversion" experiences, may have a mediating role in the effect of ketamine on motivation to quit cocaine.[59] These mystical-type effects are similar to those produced by serotonergic hallucinogens, such as psilocybin, which have also shown promise for improving quality of life across a range of disorders, including alcohol- and tobacco-use disorders.[59] This finding is congruent with the hypothesis, first articulated by William James, that nonordinary experiences may have transformative potential and might motivate enduring changes in perspectives, values, and decision making.[60]

Toward an integrative approach to pharmacotherapy

It is clear that the pursuit of understanding of the biological correlates of addiction, and to propose medications to address them, has been fruitful. The medications currently approved and available for the treatment of addiction—buprenorphine, naltrexone, topiramate, varenicline, bupropion, clonidine, and methadone, among others—would not have been possible if it were not for the disease model. This model, and the neurobiological model in particular, has also been critical in the development of promising, innovative pharmacotherapies, such as modulators of diverse neural systems, including the glutamatergic, opioid, and endocannabinoid systems; and it has provided the foundation for investigations, much of it still preliminary, toward identifying biomarkers that serve to individualize the choice of pharmacotherapy, to more generally serve as mediators and moderators of treatment response, and to ascertain early quantifiable correlates of sustained recovery.[23] Finally, the neurobiological model has informed efforts to identify, and effectively address, psychiatric comorbid disorders—such as depression, attention-deficit hyper-

activity disorder, and anxiety—that may exacerbate or predispose to problematic substance use.

It remains important, however, to be mindful of what is most relevant to problematic substance use in humans: decisions and actions. Although the decision surrounding drug use might seem unavoidable to the addicted individual—given the intolerability of withdrawal or craving and the lack of motivation to pursue other rewards—it is far from inevitable. As we have seen, there are aspects of decision making, including intention, perspective, and the availability of alternative reinforcers, that serve to mitigate the neurobiological impairments associated with craving and cue reactivity, that play an important role in recovery, and that may not lend themselves so cleanly to pharmacological manipulation. These aspects of decision making and behavior have been more properly the provenance of behavioral treatments, including CM, motivational enhancement therapy, and cognitive behavioral therapy, which work to mobilize motivation, improve maladaptive cognitive processes, and modify behavior. However, decision making may also be shaped by social factors, such as public perceptions of certain substances and legal or occupational ramifications of unregulated drug use. It is clear that medications have a role to play in addressing the vulnerabilities that predispose to the choice to use, such as craving or impaired reward salience, but it is imperative that attention also be given to the decision-making process itself and to the person making the decision.

For medications to be most effective, therefore, it is important to concurrently address this crucial vulnerability—the decision to use drugs, despite clear and unavoidable negative consequences. This can only mean an engagement with the behavioral, experiential, and social factors that constitute the background against which these decisions and actions occur. The 12-step model, as in Alcoholics Anonymous (AA), provides an example of a treatment framework that operates at many levels, incorporating into its program elements of social rehabilitation, peer support, and psychospiritual interventions. Though AA and addiction psychiatry have had a historically uneasy relationship, and although the retention rates of AA are low and hovering at around 10% 1 year after treatment entry,[61] AA represents an early attempt at approaching the addicted individual in a comprehensive way—as a subjective and meaning-driven, but also socially embedded person—and provides guidance on what kinds of therapeutic milieus might be helpful at optimizing decision making

Withdrawal	
Methadone, buprenorphine, α_2-agonists (clonidine), auxiliary symptom–driven medications (ie, loperamide, benzodiazepines, ibuprofen), dronabinol (?)	Opioid-use disorder
Nicotine-replacement therapies	Nicotine-use disorder
Dronabinol, nabilone, α_2-agonists	Cannabis-use disorder
Benzodiazepines, barbiturates	Alcohol- and other sedative-use disorders
Craving and cue reactivity	
Methadone, buprenorphine (as maintenance treatment), naltrexone (as antagonist treatment)	Opioid-use disorder
Topiramate, acamprosate, gabapentin (?), naltrexone	Alcohol-use disorder
Nicotine-replacement therapy, varenicline, bupropion	Nicotine-use disorder
Topiramate (?), stimulant medications (amphetamine) (?), mirtazapine (?), ketamine (?)	Cocaine-use disorder
Dronabinol, nabilone, gabapentin (?)	Cannabis-use disorder
Aberrant reward processing	
N-acetylcysteine (?)	Cannabis-use disorder
Amphetamine (?), dopaminergic agents (?), disulfiram (?), ketamine (?), SSRIs (?)	Cocaine-use disorder
Naltrexone	Alcohol-use disorder

Table I. Established and emerging pharmacotherapies for withdrawal, craving and cue reactivity, and aberrant reward processing. ?, treatments for which evidence is still preclinical or preliminary; SSRI, serotonin-specific reuptake inhibitor

and facilitating behavioral modification. In a landmark study that also underscored the importance of therapeutic setting, McClellan and colleagues showed that methadone was most effective when paired with a comprehensive treatment framework, setting the stage for the MMT model in the years to come.[62] Even the consciousness-altering medicines that have shown promise for decision making via psychological effects, such as psilocybin and ketamine, have involved administration in more or less therapeutic contexts, whether it be an experiential, "psychedelic" psychotherapy, as with psilocybin, or a framework involving mindfulness training, as with ketamine. Alongside such behavioral, psychospiritual, and peer-based treatments, social programs also have an important role to play in recovery by engaging addicted individuals in rational decision making. An example of this are legal programs that provide additional support, incentives, and treatment for individuals who became involved with the criminal justice system but who are motivated to stop using drugs and to reduce any drug-related legal consequences.

We presently have an opportunity to synthesize the different perspectives that have been brought to addiction over the past century—psychospiritual, behavioral, social, and neurobiological—so as to more effectively address this devastating disorder and more wisely understand the place of pharmacotherapy in its treatment. In the past 20 years alone, we have gained a great deal in our biological explorations of addiction and its treatments. The challenge now is to endeavor to successfully integrate these discoveries pertaining primarily to the addicted *brain* with treatments and frameworks aimed at addicted *individuals*, who, even while addicted, continue to experience, evaluate, and purposefully act. ❑

Acknowledgments/Conflict of Interest: The authors have no conflicts of interest to report.

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Preocupación por el cerebro: el papel de la farmacoterapia en el tratamiento del trastorno por uso de sustancias

La medicalización de la adicción como una enfermedad de base cerebral, ha llegado a ser considerada como una condición sensible a un abordaje terapéutico biomédico, en especial con farmacoterapia. Se han reconocido diversas vulnerabilidades que contribuyen a la mala adaptación al uso de sustancias, las cuales se han vinculado con diversas alteraciones neurobiológicas y con blancos farmacológicos; las más importantes son la abstinencia, el craving y la reactividad a señales, junto con el procesamiento aberrante de la recompensa. En este artículo se resume el pensamiento actual relacionado con la farmacoterapia para los trastornos por uso de sustancias, se agrupan los medicamentos de acuerdo con el tipo de vulnerabilidad a la que ellos están dirigidos y se proporciona una visión acerca de sus mecanismos neurobiológicos. También se examinan las limitaciones del modelo de enfermedad cerebral en el tratamiento de las adicciones, especialmente porque estas alteraciones se relacionan con el papel que tiene la farmacoterapia en la recuperación. Para concluir se propone un esquema en que los medicamentos se pueden integrar de manera fructífera con otras intervenciones como los tratamientos conductuales, existenciales o basados en pares, focalizando aspectos de la adicción más allá de las alteraciones neurobiológicas.

Le rôle de la pharmacothérapie dans le traitement des troubles liés à l'utilisation de substances

Médicalisée comme une maladie cérébrale, l'addiction est maintenant considérée comme étant susceptible de répondre à des traitements biomédicaux, le plus souvent de la pharmacothérapie. Des vulnérabilités diverses, responsables de l'utilisation inadaptée de substances, sont liées à différentes altérations neurobiologiques et représentent des cibles pharmacologiques dont les plus significatives sont le sevrage, l'état de manque, la réactivité aux indices environnementaux et un fonctionnement anormal du circuit de la récompense. Nous résumons ici les concepts actuels sur la pharmacothérapie des troubles liés à l'utilisation de substances en regroupant les médicaments par type de vulnérabilité traitée et en donnant un aperçu de leurs mécanismes neurobiologiques. Nous analysons aussi les limites du modèle de maladie cérébrale dans le traitement des addictions, surtout lorsque ces failles concernent la place de la pharmacothérapie dans la guérison. Nous concluons en esquissant un cadre selon lequel les médicaments pourraient trouver leur place avec succès aux côtés d'autres traitements comme les traitements comportementaux, existentiels ou collégiaux et qui ciblent des aspects de l'addiction au-delà des déficits neurobiologiques.