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COMMENTARY

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New Medications for Substance Use Disorders: Challenges and Opportunities

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An increased understanding of the biological mechanisms underlying the process of addiction has led to unique molecular targets and strategies for pharmacotherapies against addiction. However, the successful translation of these discoveries will require: 1) a more active engagement of the pharmaceutical sector, 2) partnership with regulatory agencies to arrive at meaningful outcomes for medication approval and 3) a greater involvement of the healthcare system in the screening and treatment of substance use disorders.

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Substance use disorders (SUDs) profoundly affect nearly every aspect of our society. In 2004, the economic costs associated with SUDs were estimated to be $500 billion a year in the USA (ONDCP, 2004), and are likely increasing. Both the health and societal consequences of SUDs are devastating, exemplified by the more than 400 000 smoking-related deaths each year, and alcohol-related automobile fatalities, the principal cause of death in young adults. Moreover, SUDs are profoundly disruptive to social networks, thereby contributing to criminal behaviors, child neglect, and lost productivity. Nonetheless, investments in medications to treat SUDs have been modest, and as a result, there are few approved drugs available to treat SUDs (Table 1). This is not because of a lack of scientific advances. Indeed, the past 15 years have yielded significant advances in our understanding of the neurobiology of SUDs, with several of these advances ripe for translation. However, the very modest investment from the pharmaceutical sector in SUDs has limited the translation process to a greater extent than other neuropsychiatric disorders. Here we highlight significant advances and opportunities for medications development, as well as challenges that must be met in order to bring effective pharmacotherapies to our patients.

Research on SUDs has shed light on the mechanisms through which chronic drug abuse alters the central nervous system (including epigenetic, molecular, cellular, and circuit level effects), resulting in the profound behavioral disruption seen in SUDs. Of particular relevance for medication development is the identification of neurotransmitter receptors and transporters involved in the processes of drug reward and neuroplasticity. In principle, these receptor and transporter targets are among the most tractable for medications development. Table 1 identifies some of the molecular targets for which there is preclinical evidence, and in some instances, pilot clinical data supporting their promise as targets for SUD medications. Identification of circuits that are disrupted by repeated drug administration provide yet additional targets for medications development (Volkow *et al*, 2007).

In parallel, advances in vaccine technology have made it feasible to develop vaccines as potential treatments for SUDs (Orson *et al*, 2008). These vaccines rely on the immune system to produce antibodies that bind to a specific drug (eg, cocaine, nicotine) while it is still in the blood, thus altering its pharmacokinetic profile, with lower amounts of drug entering the central nervous system. An example is NicVAX, developed for smoking cessation and currently in Phase 3 clinical trials. Early results showed that smokers who achieved high antibody levels were three-times more likely to achieve sustained abstinence compared with placebo (Hatsukami *et al*, 2011). Even subjects unable to achieve abstinence reduced their smoking by more than 50%. Major challenges remain, such as increasing vaccine antigenicity so that a greater number of those vaccinated will produce antibody levels necessary for a therapeutic response. NIDA is funding research to explore new vaccine strategies, such as research on vaccines for various drug classes, and passive immunization (monoclonal antibodies) to treat SUDs.

Technological advances in drug delivery now permit a much better control of slow release formulations, resulting in unique opportunities to change the way SUDs are treated. An example is Vivitrol, an extended release naltrexone

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TABLE 1 Medications Currently Approved for the Treatment of SUD and Molecular Targets Being Investigated as Potential Targets for New Medications

Drug	Approved medication
Nicotine	*Nicotine replacement therapies (NRT), Bupropion, Varenicline*
Alcoholism	*Naltrexone, Acamprosate, Disulfiram*
Opiates	*Buprenorprhine, Methadone, Naltrexone, Naloxone*
Target	**Effects in animal models**
Glutamate	
AMPA	Antagonists inhibit relapse
NMDA	Partial agonists facilitate extinction (*d-cycloserine*)
mGluR2/3	Agonists inhibit relapse
mGluR5	Negative allosteric modulators inhibit drug intake and relapse
Cysteine–glutamate exchanger[a]	Upregulation prevents relapse and facilitates extinction (*N-acetylcysteine*)
GLT1	Upregulation prevents relapse (*ceftriaxone*)
GABA	Enhancers (*topiramate, GVG, baclofen*)
Dopamine	
DAT	Blockers interfere with drug intake (*stimulants, bupropion*)
D3R	Antagonists inhibit relapse (*buspirone*[b])
Serotonin	
5HT2A	Antagonists interfere with cue-induced relapse
5HT2C	Agonists decrease drug intake
Nicotine	
Alpha 5	Partial agonists may be beneficial in nicotine treatment
Beta 4	Partial agonist interferes with alcohol intake
Cannabinoids	
Anatgonists	Interfere with drug use
Agonists	Decrease withdrawal (*marinol*)
FAAH inhibitors	Prevents reinstatement
Opioids	
Antagonists/agonists	Interfere with drug intake (*buprenorphine*[a])
Kappa antagonists	Interfere with stress-induced relapse
Peptides	
Orexin antagonists	Interfere with drug conditioning
CRF antagonists	Interferes with stress-induced relapse

[a]Note that some of the approved medications may be beneficia for other addictions, and research is ongoing, for example, to assess the utility of buprenorphine+naloxone for the treatment of cocaine addiction. In italics are available medications that have either been approved for treatment of SUDs, or that are approved for other indications, but have affinity for the target of interest.
[b]Buspirone also binds with high affinity to D4 and 5HT1A receptors. These actions may contribute to the effects observed in animals, including the ability to potently suppress cocaine self-administration in primates.

initially approved for the treatment of alcoholism, and recently approved for preventing relapse to opiates. (Gastfriend, 2011) In a recent report, patients receiving Vivitrol had a median 90% rate of abstinence during the trial, craving was decreased by 50%, and treatment retention increased by 75%. As this medication is administered only once a month, it could help those who do not have access to methadone or buprenorphine. It also provides an alternative treatment for individuals ready to leave replacement therapy programs, as well as in settings (prisons, jails) or countries (eg, Russia), where replacement therapies are not permitted.

Clinical trials have also started to identify unique opportunities for combining medications for SUD treatment—a strategy effective in other therapeutic areas, such as HIV and cancer. Combinations of medications have already shown promise for treating cocaine addiction (buprenorphine + naltrexone) and smoking cessation (varenicline + bupropion) for which the combinations appear to improve the rate of abstinence, as compared with either drug alone. As there is opportunity for combining already approved medications, this approach may enable a more rapid path to registration than developing new chemical entities.

A major challenge in medications development is the high cost associated with bringing a medication to market, estimated at up to $2 billion over the 10–15 + years typically required for development of a new chemical entity. These costs have traditionally been assumed by pharmaceutical companies (Paul *et al*, 2010). However, for the most part, SUDs have not been high priority targets for the pharmaceutical industry. Even for smoking cessation, which offers a huge potential market, investments are negligible compared with the costs associated with developing medications to treat the consequences of smoking. For example, between 1987 and 2008, industry supported only 46 medication trials for smoking cessation, whereas sponsoring 544 treatment trials for lung cancer, a disease for which smoking contributes to at least 80% of cases. Perhaps the major factor for this lack of involvement in SUDs is economic, a perception that the patient population is small, generally lacks health insurance, and the ability to pay for medication. However, annual sales of Suboxone (sublingual buprenorphine/naloxone) in excess of $750 million indicate otherwise. There is also the perception of a stigma associated with treating a condition brought about by consumption of substances that are, by definition, illegal (eg, heroin, marijuana). These issues were identified 15 years ago by the Institute of Medicine (NAS, 1995), who, recognizing the scientific opportunities and the urgent need for medications to treat SUDs, made recommendations on how to incentivize the pharmaceutical industry. These recommendations, including lengthening the duration of drug patents, have not been implemented. Moreover, the recent announcements to abandon development of psychotherapeutics (GSK, Astra-Zeneca and Cephalon) will shrink the pool of potential compounds that could also have beneficial effects for SUDs.

Regulatory requirements can also impede the development of SUD medications. For example, the current FDA

position is that abstinence represents the only clearly beneficial outcome for individuals using substances illegally (eg, cocaine, marijuana). This may preclude identification and development of medications that dampen a binge or interfere with craving, but not completely eliminate use. NIDA is promoting research to determine if decreases in either the frequency or amount of substance use provide significant and quantifiable benefits (eg, health, economic, social) to patients. There is a clear parallel of such outcomes, with the ability of naltrexone and acamprosate to reduce the number of heavy drinking days in alcoholics, without necessarily inducing abstinence.

Finally, SUDs have been marginalized by the healthcare community, thereby limiting screening and treatment. Moreover, many SUD treatment programs either lack the infrastructure to prescribe (or dispense) medications or are ideologically opposed to medications. This problem is compounded by the failure of most individuals with an SUD to recognize the need for treatment, which further reduces the access to potentially beneficial medications.

The science underlying SUDs is rapidly evolving. However, its translation into new therapeutics will require public health and policy interventions to both incentivize the pharmaceutical sector to develop appropriate therapies and to promote the involvement of the healthcare system in the treatment of SUDs.

DISCLOSURE

Nora D Volkow has no conflicts to report. During the past 3 years, Phil Skolnick has received compensation either as an employee, consultant, or has provided other services to the following entities: DOV Pharmaceutical, Inc., Xintria Pharmaceutical Corp., Sunovion Pharmaceuticals, Inc., New York University-Langone Medical Center, University of Mississippi Medical Center, and John Wiley and Sons.

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