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Addiction Therapeutics: Obstacles and Opportunities

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Research over the past 2 decades has led to a fundamental understanding of the neurobiological bases of addiction (1). These insights have resulted in the identification of multiple targets (2), many already proven drugable, that could potentially revolutionize the treatment of substance use disorders (SUDs). Nonetheless, the goal of developing highly effective medications to treat SUDs remains largely unmet. Thus, there are no medications approved to treat either stimulant or cannabis use disorders, and the efficacy of available therapies for other SUDs (e.g., opiates, tobacco, alcohol) is far from ideal.

The dearth of innovative medications to treat SUDs has been attributed to a low level of interest by the pharmaceutical and biotechnology sectors, a problem exacerbated by the retrenchment in psychiatry research and development (3). However, both the number of potential targets (2) and the molecules that have either failed in other psychiatric indications or are now parked for strategic reasons make SUDs an attractive rescue indication. In this commentary, we will briefly summarize some of the principal obstacles to developing medications for SUDs (reviewed in [4]), as well as some recent developments, including the report by Mariani *et al.* (5), that offer new therapeutic opportunities.

Obstacles

Although there are multiple issues contributing to the paucity of effective medications for treating SUDs, the prospect of a low return on investment is most often cited as the primary driver responsible for a lack of enthusiasm by the pharmaceutical sector. The estimated costs associated with bringing a new chemical entity to market have recently been estimated to be as high as $4 billion to $11 billion (http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/). Given the risks and costs associated with bringing a new chemical entity to market, investor interest in SUDs has been limited by the generally held perception of a small market size. However, with multiple treatment options available (including methadone, Subutex, and Vivitrol), the annual sales of Suboxone (a formulation of sublingual naloxone and buprenorphine that discourages diversion) in excess of $1.2 billion belie the myth of a small market size. Estimates of the market size for a first in class medication to treat cocaine use disorders are even more compelling, based on a target treatment group in the United States of 1.6 million patients (4). Moreover, given the prospect for universal health care coverage and parity for mental health services, an effective treatment for cocaine dependence could result in even greater number of patients seeking

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treatment. Thus, the size of the SUD market should incent, not deter, investment, particularly for a first or best-in-class therapeutic.

The limited private sector investment in traditional drug development efforts for SUDs compels most investigators to rely on repurposed molecules and drug combinations as exemplified by the report by Mariani *et al.* (5). Repurposing is a more cost-effective strategy than a from-scratch approach but nonetheless requires multiple double-blind, placebo-controlled trials to demonstrate efficacy. Off-label prescribing remains an option, but Food and Drug Administration (FDA) approval (implementing the study by Mariani *et al.* [5] would require a change in current labeling for both medications) is important for reimbursement by payors as well as establishing treatment guidelines and is the most effective strategy for delivering a therapeutic to the targeted patient population. In the absence of patent protection, some form of market exclusivity or other economic incentives, it is unlikely that repurposing a generic molecule will result in dramatic changes in prescribing practices. This also pertains for drug combinations, which are often used in treating chronic diseases, and are now being evaluated for the treatment of SUDs (5).

Clinical trials in SUDs are unique among psychiatric disorders because treatment efficacy can be assessed using the abused substance as a biomarker. Thus, a drug-free urine (the biological matrix of choice, most often sampled two to three times per week during in-clinic visits) is viewed as prima facie evidence that a therapy either reduces or abolishes drug use. Mariani *et al.* (5) reported the combination of extended release amphetamine salts and topiramate was twice as effective as placebo (33.3% vs. 16.7%) in achieving any three consecutive weeks of cocaine abstinence during the 12-week trial. Although encouraging, these data fall short of the FDA view of an effective therapy, which is a period of abstinence that lasts through the end of treatment (6,7). Using alcoholism as an example, a trial design based on a 6-month period of abstinence seems “reasonable for other trials of treatments of other addictive disorders as well” (6). A prolonged period of abstinence is a very high bar, and perhaps unrealistic for a medication, even when combined with psychotherapy (7). Thus, regardless of market size projections, the perception of a high regulatory bar can act to dampen enthusiasm for investment in SUDs.

There are other issues that have limited private sector investment (4), including the negative association of linking a company’s name with the use of illegal substances. A fragmented advocacy, sending mixed, often contradictory and polarizing messages (“… why substitute one addiction for another…”) can also intimidate potential investors. Nonetheless, the commercial success of a medication like Suboxone, which entered an arguably crowded space, may serve as an impetus for investment, especially in SUDs with no currently approved medications.

Opportunities

Despite the many challenges associated with developing medications to treat SUDs, there are currently multiple, exciting opportunities. Thus, there is now a bumper crop of potential drug candidates to treat SUDs that have either failed in other psychiatric indications or parked for strategic reasons. The prospects for partnering or monetizing these assets are low

in the current environment, and a National Institutes of Health-funded proof-of-concept trial presents an opportunity to refresh molecules, with the treatment of SUDs as an attractive rescue indication. Moreover, within the past few months, two drugs have been approved with the potential for treating SUDs. Lorcaserin (Belviq), a 5-hydroxytryptamine-2c agonist, was approved for the treatment of obesity. 5-Hydroxytryptamine-2c agonists are active in preclinical models against multiple drugs of abuse (including nicotine, cocaine, and methamphetamine); clinical studies with lorcaserin will determine whether it is useful for promoting abstinence and preventing relapse (4). A combination of phentermine and topiramate (Qsymia) was also approved for the treatment of obesity, which, viewed in the context of the study by Mariani *et al.* (5), suggests that Qsymia could be used to further explore the hypothesis that an amphetamine-like molecule combined with topiramate can modify cocaine intake. As a combined medication, compliance is likely to be higher and the risk of diversion lower compared with the two medications. Moreover, if a signal is obtained with Qsymia, the sponsor may be have an incentive to support the clinical program necessary for FDA approval as well as support its distribution and promotion.

Biological approaches, including active and passive immunization strategies as well as genetically engineered enzymes, also present exciting treatment approaches for SUDs. Their principle is simple: minimizing the entry of abused substance into the brain. There has been one successful proof-of-concept study with a nicotine vaccine (8); the cohort of smokers that produced the highest levels of antinicotine antibodies had a significantly higher rate of sustained (8 weeks) end-of-trial abstinence compared with placebo (24.6% vs. 12%,$p = .024$).Although this vaccine subsequently failed to achieve its primary end point in phase III trials (www.nabi.com), there are multiple efforts to engineer nicotine vaccines capable of producing higher antibody titers, with one vaccine currently in clinical development (www.selectabio.com). A unique approach to treat cocaine dependence is the genetic modification of butyrlcholinesterase, the enzyme that catalyzes the degradation of cocaine (9). Reported maximal velocity values for modified butyrlcholinesterases are greater than 1000-fold higher than the wild-type enzyme (9). Teva Pharmaceutical recently disclosed that it is pursuing clinical studies with a genetically engineered butyrylcholinesterase to treat cocaine dependence. There are also multiple projects underway to develop vaccines and monoclonal antibodies to treat cocaine, methamphetamine, and heroin dependence (4). Perhaps the most compelling reason to foster biological approaches is the potential for a long-lived protective effect that requires one good decision by the patient, in contrast to the one (or more) daily decisions to remain medication compliant using traditional approaches. The highly specific nature of a biological agent, such as a vaccine directed against heroin, could dramatically reduce the use of that molecule but would not preclude abuse of a structurally unrelated opiate. Given the problem of polydrug abuse, circumventing a highly specific therapy is not only a limitation of biological approaches but also occurs with current therapies, exemplified by patients using cocaine while under methadone therapy (10).

Despite the formidable obstacles to developing effective therapies to treat SUDs, there are now unprecedented opportunities on both the short- and mid-term horizons for translating the many promising approaches identified by basic research into therapies for SUDs.

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