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Magic Bullets and Arrows: Biologic Approaches to Treat Substance Use Disorders

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As for other psychiatric disorders, pharmacological approaches to treating substance use disorders (SUDs) have traditionally focused on small molecules. This approach has not yielded highly effective medications. Perhaps the most glaring example is the absence of medications approved to treat stimulant (e.g. cocaine and methamphetamine) abuse, with no approvals on either the short- or mid-term horizon. Moreover, medication options to treat other SUDs, when available, are far from ideal. Using nicotine addiction as an example, the rate of sustained (1 year) abstinence in individuals treated with available smoking cessation medications (nicotine replacement therapies, bupropion, and varenicline) is below 20%. This special issue for *CNS & Neurological Disorders-Drug Targets* is devoted to biological approaches to treating SUDs. The approaches described here include a bioengineered esterase capable of rapidly inactivating cocaine as well as immunization strategies directed against methamphetamine, nicotine, cocaine, and heroin. The principle underlying these biological approaches is pharmacokinetic - preventing or slowing the entry of abused substance into the central nervous system. While not comprehensive, this collection of reviews provides the reader with insights about the feasibility and potential of biological approaches to treating SUDs.

In this volume, Stephen Brimijoin overviews the development of a genetically engineered cocaine hydrolase as a means of “intercepting” cocaine before it reaches the CNS. As for both vaccines and monoclonal antibodies, this enzyme is highly specific, and will only reduce the entrance of cocaine (but not other stimulants or abused drugs) into the CNS. This article also highlights the potential for viral gene transfer as a novel strategy for relapse prevention. Shen and Kosten review the concept of immunotherapy for drug abuse, and describe a cocaine vaccine made by conjugating a cocaine containing hapten to inactivated cholera toxin B that is currently being tested in the clinic. Koob and coworkers describe preclinical studies using an anti-cocaine vaccine developed by coupling a cocaine analog to a disrupted adenovirus. The approach is based on studies demonstrating that adenovirus capsid proteins are highly immunogenic in humans, and if preclinical results can be successfully translated, would result in circulating levels of high-affinity, high-titer antibodies against cocaine. The contribution by Fahim *et al.* describes the development of a nicotine vaccine. While the initial proof of concept study [1] provided a significant efficacy signal, this vaccine failed to achieve its primary endpoint in Phase III clinical trials (NABI Pharmaceutical press release, www.nabi.com). The contribution by Stowe, *et al.* describes the challenges in developing a vaccine against heroin, which has several psychoactive metabolites. While the preceding chapters on vaccines rely on the ability of the immune

system to raise antibodies targeted at the abused substance, the article by Owens *et al.* describes the development of monoclonal antibodies, a passive immunization technique, for the treatment of methamphetamine abuse.

There are both advantages and disadvantages to these biological approaches. Perhaps the most compelling reason to develop biologics is the promise of a long-lived protective effect, which requires the patient to make “one good decision” to receive a biologic, compared to one (or multiple) good daily decisions to remain compliant with a traditional medication. The specificity of an effective vaccine developed against (e.g.) heroin should dramatically reduce the use of this opiate, but would neither preclude an individual from receiving maintenance therapy nor prevent the patient from abusing a structurally unrelated opiate. The ability of a patient to circumvent the therapy by taking drugs other than the one targeted by the biologic (e.g., an effective heroin vaccine would not preclude abuse of cocaine) is a limitation of these approaches. However, this is also an issue for current medications, exemplified by a heroin abuser using cocaine despite receiving methadone maintenance therapy. Given the high incidence of polysubstance abuse, even a highly effective biologic will require parallel interventions (including behavioral therapy) to modify lifestyles in order to either remove or mitigate precipitants of relapse. Immunization therapies currently in clinical trials can take weeks or months before antibody titers reach pharmacologically relevant levels [1, 2]. This “therapeutic lag”, taken together with the need for multiple immunizations and high patient expectations of a cure, could be problematic for the ultimate commercial success of such a product. Nonetheless, given the limited success of traditional pharmacological approaches to treating SUDs coupled with the rapid technological advances described in these reviews, biological approaches represent appealing alternatives that, when coupled with behavioral therapy, have the potential to dramatically change the practice of addiction medicine.

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