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Future Med Chem. Author manuscript; available in PMC 2012 December 1.

Published in final edited form as:

Future Med Chem. 2012 February ; 4(2): 227–243. doi:10.4155/fmc.11.190.

Pharmacokinetic strategies for treatment of drug overdose and addiction

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Abstract

The pharmacokinetic treatment strategy targets the drug molecule itself, aiming to reduce drug concentration at the site of action, thereby minimizing any pharmacodynamic effect. This approach might be useful in the treatment of acute drug toxicity/overdose and in the long-term treatment of addiction. Phase IIa controlled clinical trials with anticocaine and antinicotine vaccines have shown good tolerability and some efficacy, but Phase IIb and III trials have been disappointing because of the failure to generate adequate antibody titers in most participants. Monoclonal antibodies against cocaine, methamphetamine and phencyclidine have shown promise in animal studies, as has enhancing cocaine metabolism with genetic variants of human butyrylcholinesterase, with a bacterial esterase, and with catalytic monoclonal antibodies. Pharmacokinetic treatments offer potential advantages in terms of patient adherence, absence of medication interactions and benefit for patients who cannot take standard medications.

Conventional pharmacological treatments for drug addiction aim to modulate or disrupt the effects of a drug at sites of action in the body. This treatment strategy (termed a ‘pharmacodynamic’ [PD] strategy) has not yielded broadly effective medications for many drugs of abuse. This failure may be due to several factors, including an incomplete understanding of the neuropharmacological mechanisms mediating the psychoactive actions of the abused drug (e.g., when a drug has multiple mechanisms of action) or lack of therapeutic compounds that have the appropriate safety and ‘pharmacokinetic’ (PK) properties for clinical use.

In view of these limitations, interest has been growing in a treatment strategy that targets the drug molecule itself (termed a PK strategy), aiming to keep the target drug below its minimally effective concentration at its sites of action. This effect might be useful in two clinical contexts. First, acutely reducing (free) drug concentration after drug intake might reduce or prevent consequences from acute drug toxicity or overdose (a clinical problem for all abused drugs except nicotine). Second, long-term prevention of effective concentrations at the site of action in the brain might keep the drug-addicted (dependent) patient from experiencing any reinforcing drug effects; either the positive reinforcement of the ‘high’ or the negative reinforcement of relief of withdrawal symptoms, or both. Over time, this might lead to extinction of drug-seeking and drug-taking behavior. It might also reduce the chance of relapse in abstinent patients by blocking the priming effect of a single drug dose (i.e., reducing the likelihood of a lapse becoming a relapse) [1]. In addition, long-term reduction

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Financial & competing interests disclosure

No writing assistance was utilized in the production of this manuscript.

The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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in peripheral concentrations of free drug could minimize peripherally mediated adverse effects of drug use, such as the cardiovascular toxicity of psychostimulants.

In both clinical contexts, a key factor in treatment success is the generation of sufficient PK capacity to substantially reduce free drug concentrations regardless of the total body burden of drug. The degree of reduction in free drug concentration that is needed will vary with the PD action of the drug. Binding of all drug molecules (i.e., zero free drug concentration or zero receptor occupancy) is not necessarily required to abolish PD effects. PK alterations, *per se*, may also be of therapeutic benefit. The rate of onset of psychoactive drug action is positively correlated with the reinforcing subjective effects of the drug (so-called rate hypothesis of psychoactive drug action) [2], suggesting that slowing the rate of drug entry into the brain or of receptor binding might be beneficial. For a few drugs, such as nicotine, slowing of drug clearance from the body might be beneficial, based on the observation that cigarette smokers who are slow nicotine metabolizers (on a genetic basis) smoke fewer cigarettes daily and may be more successful at smoking cessation than those who are faster metabolizers [3].

Two factors are key to the success of long-term addiction treatment:

- Sufficient PK capacity to prevent rapid drug distribution into the brain after intravenous (iv.) or smoked drug intake;
- Making it impractical for the patient to increase drug intake sufficiently to overcome the treatment effect.

The latter factor does not require that this be theoretically impossible, but merely that the amount of drug required be unlikely to be available and accessible to the patient. In this regard, the PK strategy can be considered analogous to the PD strategy of receptor blockade. Complete receptor blockade (0% receptor availability) is not necessarily required for successful treatment, as long as the degree of blockade is impractical for the patient to overcome with increased drug use.

The PK strategy has several theoretical advantages over the PD strategy [4]. First, no knowledge is needed of the mechanism of action of the drug. Second, because the treatment targets only the molecules of the abused drug (rather than the brain or other tissues of the body), it should have little or no PD actions, thus minimizing side effects. In addition, there should be little or no interactions with other medications, minimizing potential for adverse drug–drug interactions. This makes PK treatment especially attractive for patients who are taking other medications or who should avoid taking conventional medications (e.g., pregnant women and those with severe medical or psychiatric co-morbidity).

Conversely, the PK strategy has several theoretical disadvantages. First, its therapeutic specificity means that the patient may switch to another drug that is not affected by the treatment, either from the same pharmacological class (e.g., a patient abusing stimulants switching from cocaine to amphetamines) or a different pharmacological class. In patients abusing multiple drugs, reduction in use of the targeted drug may leave other drug use unchanged or increased in compensation. In principle, this could be addressed by developing antibodies that bind to more than one drug, or by administering a combination of different antidrug antibodies. Second, the treatment will not reduce drug craving or withdrawal symptoms, thus leaving the patient at continued risk for drug abuse. To the extent that peripheral drug binding rapidly reduced brain concentrations of free drug, the PK strategy might even precipitate or worsen a withdrawal syndrome. In theory, attempts to self-medicate craving or withdrawal by trying to overcome the treatment effect could result in increased drug use. Third, the PK strategy provides no intrinsic reinforcement of its own, unlike agonist treatments, such as methadone for opioid addiction. This may make it

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difficult to motivate patients for treatment, similar to the difficulties in motivating patients for opioid receptor antagonist treatment with naltrexone. Therefore, the PK strategy is best delivered in the context of psychosocial treatment that enhances motivation for treatment and addresses the underlying psychological and behavioral issues of addiction.

Implementation of the PK strategy

Two major PK treatment strategies are currently in active development: 'peripheral blocker' and increased drug metabolism (Box 1).

Peripheral blocker

This strategy aims to bind the drug of abuse with antidrug antibodies in the peripheral circulation, reducing the concentration of free (unbound) drug available to exert PD effects. The antibody–drug complexes are too large to cross the blood–brain barrier, thus keeping drug out of the brain. The bound drug is also unavailable to activate receptors in peripheral organs that mediate adverse physiological effects, such as the cardiovascular toxicity of psychostimulants. Molecules of abused drugs are too small to generate an active immune response themselves, so the drug molecule (hapten) must be made antigenic by coupling it to a larger carrier molecule (active immunity via antidrug vaccine). Generally, this is a protein or protein complex. Characteristics of the generated antibodies, such as their affinity and specificity of drug binding, are influenced by the structure of the hapten, constraints on its conformation, and the location and length of the hapten-carrier link [5–9]. Alternatively, antidrug antibodies created outside the body could be administered (passive immunity). Several characteristics of the antibody influence its efficacy.

Intrinsic affinity for the drug – affinity should be high enough to substantially reduce the amount of free drug in circulation. Theoretical calculations suggest that an IgG antibody with an affinity of 20 μM at a concentration of 40 μg/ml would bind approximately two-thirds of circulating cocaine molecules [10].

Specificity of drug binding – the ideal antidrug antibody should not bind structurally similar endogenous compounds (e.g., neurotransmitters) so as to avoid interfering with normal physiological function. Similarly, the ideal antibody should not bind to treatment medications that might be administered concurrently. Even binding of inactive drug metabolites is disadvantageous because it occupies binding sites that become unavailable for active drug. However, binding of active metabolites might be either advantageous or disadvantageous, depending on their PD actions. For a drug such as methamphetamine, whose active metabolite, amphetamine, is also psychoactive and abused, binding to the active metabolite as well should be an advantage. For a drug such as nicotine, rat studies suggest that binding to its metabolite cotinine might be a disadvantage [6]. Cotinine binding to the nicotinic receptor results in neuronal dopamine release [11] and desensitization of the receptor [12], actions that potentially have therapeutic benefit.

Speed of drug binding – smoked and iv. injected drugs reach the brain in seconds and exert psychological and physiological effects within minutes. Antibody binding of drug should be extremely rapid to prevent brain entry. Studies of antibodies in model systems suggest that binding of small molecules occurs in seconds, making it plausible that antidrug antibodies would be effective *in vivo* [10].

Increased drug metabolism

This strategy aims to increase drug metabolism so that an effective concentration of drug is not reached and/or maintained at the site of action. Cocaine is currently the only drug for which this strategy is being actively pursued, using either catalytic monoclonal antibodies

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(mAbs) or cocaine-hydrolyzing enzymes. Both human and bacterial enzymes have been used, either in their natural state (wild-type) or genetically engineered with enhanced catalytic properties.

mAbs have been reported that catalyze the oxidative degradation of methamphetamine [13] and nicotine [14] *in vitro*. To the knowledge of the author, no *in vivo* work with these enzymes has been published.

Advantages and disadvantages of each strategy

Each PK treatment strategy has its own potential advantages and disadvantages (Table 1), which, in the absence of clinical studies (except for antidrug vaccines), must be considered theoretical at this time. Antidrug vaccines generate active immunity, so that antidrug antibodies persist for months after vaccination. This offers substantial patient adherence advantages over treatments that must be taken daily. A recent study with cocaine users found that more than three-quarters (77%) of those offered an escalating schedule of monetary incentives completed a long course of hepatitis B vaccination (seven injections over 6 months), compared with less than half (46%) of these receiving a fixed amount per visit [15]. However, even a complete course of vaccination generates a highly variable antibody response that takes weeks to months to fully develop, making it ineffective for treating acute drug overdose/toxicity and leaving addicted patients vulnerable in the interim. Another disadvantage is that vaccines may not be effective in patients with impaired immune systems, such as those with HIV infection.

Exogenous antibodies (passive immunity) or drug-metabolizing agents have several potential treatment advantages, including immediate onset of therapeutic effect, making them effective for treatment of acute drug overdose/toxicity, no requirement for an active immune response by the patient, and more precise control of the characteristics and dose of administered agent. A potential disadvantage of exogenous antibodies is likely shorter duration of action than active immunity, probably only hours to weeks, based on the known *in vivo* half-lives of other exogenous antibodies. Other potential disadvantages include the need for large doses (thus requiring large-scale, efficient manufacture to keep costs affordable) and possible antigenicity of the therapeutic agent (which might trigger unwanted immune reactions in patients).

The catalytic mechanism of a drug-metabolizing agent allows one molecule of therapeutic agent to inactivate (break down) multiple drug molecules. In contrast, each molecule of an antidrug monoclonal antibody (passive binding agent) can inactivate (bind) only one drug molecule per binding site. Thus, passive binding agents, unlike catalytic agents, in theory, might have to be administered in doses achieving mole equivalence between binding sites and drug molecules, potentially requiring very large doses of the therapeutic agent. However, this has not been the case in animal studies with mAbs against methamphetamine, nicotine and phencyclidine (PCP) [16,17]. Furthermore, additional drug intake might saturate the binding sites, resulting in no further therapeutic effect. A potential disadvantage of enhancing drug metabolism is the generation of drug metabolites that may themselves have undesirable pharmacological activity.

This pattern of advantages and disadvantages suggests that antidrug vaccines may be most useful for prevention or long-term treatment of drug addiction, while passive immunity or enzymatic approaches may be most useful for treatment of acute drug toxicity or overdose. A combination of treatments may be most effective in some circumstances. For example, initial 'bridge' treatment with an immediately active passive immunity or enzymatic agent might be useful until an antidrug vaccine generated sufficient active immunity to be protective. A recent rat study with nicotine supports this concept, finding that treatment with

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a nicotine-specific mAb after vaccination enhanced the protection afforded by an antinicotine vaccine against the behavioral effect of nicotine [18]. Combined treatment might also have an additive effect in reducing free drug concentrations, as shown recently for a combination of anticocaine antibodies and cocaine hydrolase [19].

Antidrug vaccines

Antidrug vaccines for nicotine (four) and cocaine (one) dependence have entered clinical development (Table 2). Vaccines for methamphetamine and opiates have been studied in animals, but none has yet been studied in humans.

Antinicotine vaccines

Nic002—This vaccine, formerly known as CYT002-NicQb, was developed by Cytos Biotechnology, Zurich, Switzerland, and is now licensed to Novartis. Nicotine is covalently bonded to virus-like particles formed from the protein coat of the Qb bacteriophage virus [20]. Each particle exposes approximately 585 nicotine molecules, making them highly antigenic.

In a Phase II, multisite controlled clinical trial, smokers received a monthly injection for 5 months of active vaccine (100 µg) with alum adjuvant (n = 229) or adjuvant alone (n = 112) [21]. All subjects received individual smoking cessation counseling for 3 months beginning one month after the first vaccination, which was the target quit date. The vaccine produced a 100% antibody response after the first injection and was generally well tolerated. In the intent-to-treat analysis, the vaccine significantly increased abstinence (point prevalence) over placebo at 2 months (47.2 vs 35.1%), but there was no significant difference in continuous abstinence between 2 and 6 months. However, in a subgroup analysis that excluded subjects who used nicotine replacement therapy, significantly more subjects in the top tercile of antibody levels (n = 53) had continuous abstinence than did placebo subjects (n = 80; 56.6 vs 31.3%, respectively), while subjects with lower antibody levels did not differ from placebo. The difference in continuous abstinence rates continued to 12 months (42 vs 21%, respectively).

Novartis conducted a second Phase II, controlled clinical trial in 200 smokers (NCT00736047) [101]. An interim intent-to-treat analysis did not show a significant difference between vaccine and placebo groups in continuous abstinence from 8–12 weeks after the start of treatment, which the investigators attributed to insufficiently high antibody titers [102].

NicVAX®—This vaccine, developed by Nabi Biopharmaceuticals, Rockville, MD, USA, and now licensed to GlaxoSmithKline, uses 3´-aminomethyl-nicotine coupled to recombinant *Pseudomonas aeruginosa* exoprotein A (3´AmNicrEPA), administered with aluminum hydroxide adjuvant. In a Phase IIb multicenter, controlled clinical trial, 301 smokers received one of two vaccine doses (200 or 400 µg) or placebo four (at 0, 6, 12 and 24 weeks) or five times (at 0, 4, 8, 16 and 26 weeks) over 6 months (n = 50 or 51/group), with the target quit date 1 week after the second vaccination [22]. All subjects received five brief counseling sessions. The intent-to-treat analysis showed that only the 400-µg group receiving five vaccinations differed significantly from placebo in rates of continuous abstinence for 6 months (17.6 vs 6.0%, respectively) and 12 months (15.7 vs 6.0%, respectively). An analysis by serum antibody titer (area under the curve from 0–26 weeks) showed that the 30% of subjects with the highest titers (regardless of study group) differed significantly from placebo in 7-day point prevalence abstinence rates at 26 weeks (36.1 vs 16.0%, respectively) and 52 weeks (31.0 vs 12.0%, respectively) and continuous abstinence rates from 19–26 weeks (24.6 vs 12.0%, respectively) and 19–52 weeks (19.7 vs 10.0%,

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respectively). The group with lower antibody titers did not differ significantly from placebo on any variable. There was no evidence of a compensatory increase in smoking or increase in withdrawal symptoms.

Two large (1000 subjects each) multicenter, Phase III controlled clinical trials completed enrollment in July 2010 (NCT00836199) [101] and November 2010 (NCT01102114) [101,103]. Both trials used a vaccination schedule of six 400-μg doses over 6 months (0, 4, 8, 12, 16 and 26 weeks), with counseling aligned to a target quit date 14 weeks after the start of treatment. In a Phase II immunogenicity study conducted in 2008 [103], this schedule generated antibody titers at 14 weeks more than twice as high as those achieved with five vaccinations in the Phase IIb clinical trial [22]. A preliminary analysis of the first Phase III trial showed no significant difference between the vaccine and placebo groups in continuous abstinence rates between weeks 37–52 (~11% in both groups) [104].

TA–Nic—This vaccine (originally developed by Xenova, now owned by Celtic Pharma Management, LP, Hamilton, Bermuda) uses nicotine butyric acid covalently linked to a nontoxic subunit of recombinant cholera toxin B. Little clinical data are publicly available. In a Phase I/II controlled clinical trial, 60 subjects received six injections over 12 weeks of either active vaccine or placebo [23]. Peak antibody levels were reached at around 15 weeks. At 12 months, subjects receiving the higher vaccine doses (1000 or 250 μg) had a higher point prevalence of abstinence than subjects receiving placebo (38 and 19 vs 8%, respectively).

On 29 October 2007, the company announced that it had enrolled more than 520 subjects in a Phase IIb, multicenter, controlled clinical trial involving three treatment arms (two vaccine doses, one placebo), with the primary end point abstinence rate at 6 months [105]. Although no data are publically available, news reports indicate that the vaccine was no better than placebo, which the company attributed to manufacturing problems with the vaccine [106].

Niccine®—This vaccine, developed at the Karolinska Institute, Sweden, in conjunction with Independent Pharmaceutica AB, uses nicotine coupled to keyhole limpet hemocyanin [6]. The company announced in 2008 that it had completed enrollment for a Phase II controlled clinical trial to evaluate the vaccine for relapse prevention in smokers who had recently quit with the help of medication and counseling [24]. Although no data are publically available, news reports indicate that the vaccine was no better than placebo [106]. The company was liquidated in 2010 [107].

Preclinical studies—At least nine different antinicotine vaccines have been evaluated in animals, several of which have been shown to increase peripheral nicotine concentrations, reduce the ability of nicotine to enter the brain, and attenuate the response to a nicotine challenge [5,25]. An alternative approach is an anticotinine vaccine created by coupling 4-thio-cotinine to tetanus toxoid [26]. Cotinine is a major nicotine metabolite that may counteract nicotine's actions in the brain [11,12]. Thus, reducing brain cotinine levels could enhance the response to nicotine, resulting in decreased nicotine intake and improved response to nicotine replacement therapy.

Anticocaine vaccine

TA–CD—This vaccine (originally developed by Xenova, now owned by Celtic Pharma Management, LP, Hamilton, Bermuda) uses succinylnorcocaine coupled to a nontoxic subunit of recombinant cholera toxin B, administered with aluminum hydroxide adjuvant. In a Phase IIb, controlled clinical trial, 114 cocaine- and opioid-dependent (on methadone maintenance treatment) outpatients received 360 μg of vaccine (or placebo) at 0, 2, 4, 8 and

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12 weeks along with weekly individual cognitive–behavioral therapy, with follow-up for 8 weeks after the last injection [27]. All but one of the 55 subjects who received all five vaccinations made detectable anticocaine antibodies, with peak antibody titers at 8–16 weeks. The intent-to-treat analysis showed no significant difference between vaccine and placebo groups in overall proportion of cocaine-free urine samples. However, an analysis of weekly data showed that the proportion of cocaine-free urine samples increased more quickly in the vaccine group over the first 16 weeks, then became similar to the placebo group over the last 8 weeks, as antibody titers declined. The 38% of vaccinated subjects with the highest IgG antibody titers (≥43 µg/ml) had a significantly greater proportion of cocaine-free urine samples over weeks 9–16 than either the other 62% of vaccinated subjects or the placebo group. The two antibody groups did not differ significantly in proportion of opioid-free urine samples [28], suggesting that the vaccine exerted its effect specifically on cocaine use. A *post hoc* analysis found no gender difference in the cocaine treatment response [29].

In a complementary Phase II human laboratory study, ten nontreatment-seeking cocaine-dependent men received a vaccine dose (82 or 360 µg) at 1, 3, 5 and 9 weeks [30]. Cocaine-specific IgG antibody titers peaked at 13 weeks, had declined substantially at 26 weeks, and were negligible or undetected at 1 year. Subjects received a laboratory challenge of smoked cocaine (0, 25 or 50 mg) before the first vaccination and weekly thereafter for 13 weeks. At week 13, the five subjects with the highest antibody titers showed a 55–81% attenuation in the peak positive subjective effects of cocaine (compared with week 3 challenge), which was apparent within 4 min of cocaine smoking. They also showed a greater cocaine-induced tachycardia but no significant difference in blood pressure response or cocaine craving. The five subjects with lower antibody titers showed no change in their response to cocaine challenge. Across all ten subjects, there was no significant association between antibody titers and plasma concentrations of free or bound cocaine, or any evidence during the outpatient periods of a compensatory increase in cocaine use to try to overcome the vaccine effects.

Four subjects had brain PET imaging with C11-cocaine at baseline and after vaccination at week 13 [31]. Mean occupancy of biogenic amine presynaptic transporters by cocaine was 59% (range 37–71%) at baseline and 48% (range 25–70%) at week 13. One subject showed increased occupancy over the interval.

Preclinical studies

A novel anticocaine vaccine (dAd5GNC) was created by coupling a cocaine analogue (GNC) to capsid proteins of a noninfectious adenovirus [32]. A three-dose vaccination regimen (4 µg at 0, 3 and 6 weeks) generated increasing IgG antibody titers in mice over 13 weeks. Vaccinated mice had 41% lower brain cocaine concentrations than control mice and fivefold higher serum cocaine concentrations. Vaccinated mice also showed a significantly reduced locomotor response to iv. cocaine challenge.

Vaccine safety

The antinicotine and anticocaine vaccines discussed above have been well tolerated, with relatively low drop-out rates due to adverse events. The commonest adverse events were transient (1–3 days) local reactions at the injection site, such as pain, tenderness, edema, rash, erythema and itching, in up to 90% of subjects [21,22,27]. Up to two-thirds of subjects had transient, mild flu-like symptoms (headache, nausea, malaise, fever), almost always resolving within 24 h. Only two reported serious adverse events in Phase II clinical trials have been considered related to vaccination. One subject in the Nic002 trial developed flu-like symptoms associated with chest pain but had no evidence of heart disease and was well

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at the 6-month follow-up [21]. One subject in the NicVAX trial vaccine had an allergic anaphylactic reaction that resolved immediately with medication [22].

We are not aware of any published human studies on the reproductive safety of antidrug vaccines. One study of an antinicotine vaccine in rats found no effect on reproductive outcome of four vaccinations over 9 weeks, ending at least 1 week before conception [33]. This vaccination regimen generated a robust antibody response resulting in significantly reduced nicotine transfer into maternal and fetal brain and some transfer of antibody into fetal serum and brain.

Other antidrug vaccines

At least four research groups have studied anti-methamphetamine vaccines in rodents [8,34–36]. One vaccine also cross-reacts with the methamphetamine metabolite amphetamine [8]. This might be clinically advantageous because amphetamine is itself psychoactive and abused. Two vaccines altered the behavioral response to an acute methamphetamine challenge [35,36].

At least four research groups have developed antiopioid vaccines in rodents, including three vaccines against heroin/morphine [37–39] and one vaccine against oxycodone [40]. One vaccine reduced the reinstatement of previously extinguished heroin self-administration [37] and another reduced morphine-induced analgesia and acquisition of conditioned place preference (a measure of reinforcement) [38].

Route of administration

Conventional vaccines require intramuscular administration, which may raise two barriers to their use in drug abuse treatment. First, some patients may object to injection with a needle, reducing treatment acceptance. Second, intramuscular administration in the USA requires a licensed clinician (physician, nurse, pharmacist). Many drug-abuse treatment programs have limited availability of such staff because of financial or other constraints. A noninjection route of administration for an antidrug vaccine may overcome these barriers.

Two approaches to noninjection vaccine administration have been developed preclinically [4], but have not advanced to human studies. Nabi Biopharmaceuticals collaborated with Aktiv-Dry (Boulder, CO USA) to reformulate its NicVAX® antinicotine vaccine into particles 1–3 µm in diameter that form a stable, dry powder suitable for inhalation [108]. Lyfjathroun Biopharmaceuticals (Reykjavik, Iceland) developed a mucosal adjuvant (RhinoVax®) that allows effective intranasal vaccine administration [41]. When used in conjunction with an anticocaine vaccine (cocaine conjugated to keyhole limpet hemocyanin), two doses of intranasal vaccine generated specific anticocaine antibodies in mice, albeit at a fivefold lower serum level than after subcutaneous vaccination. Both vaccination routes comparably inhibited cocaine distribution into the brain after intranasal or intraperitoneal cocaine administration.

Clinical considerations

Phase II clinical trials of antidrug vaccines for treatment of nicotine and cocaine addiction have established proof-of-concept (POC) for efficacy and tolerability, using analyses based on achieved antidrug antibody titers. However, these studies fall short of conclusively establishing clinical effectiveness in a real-world setting. The first Phase III trial of an antinicotine vaccine and Phase IIb trials of antinicotine and anticocaine vaccines all failed to meet their prespecified intent-to-treat efficacy end points. This was largely due to substantial heterogeneity in vaccine response, with a majority of patients in all trials failing to generate sufficient titers of antidrug antibody. Increasing the number of vaccinations enhances the

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antibody response, but increases cost and reduces the treatment adherence advantage of vaccination over standard oral medications taken daily. Further work to improve vaccine immunogenicity and adjuvant effects is required to address this issue.

The existing vaccine trials have limited external validity as subjects were carefully screened to exclude those with other current substance dependence (except nicotine) or major psychiatric or medical comorbidity, including immunocompromised conditions, such as HIV infection. Thus, the effectiveness of the vaccine strategy in more typical addiction patients remains to be established.

Passive antidrug immunity

The goal of the passive immunity strategy, like that of the active immunity (vaccine) strategy, is to administer an agent that will bind enough drug molecules to keep drug levels below their minimally effective concentration in the brain. This strategy would also reduce peripheral concentrations of free drug, thereby potentially reducing some peripherally mediated adverse effects, such as cardiovascular toxicity. Current work uses mAbs (usually generated in mice). mAbs are homogenous, can be engineered and selected for high affinity and specificity, and can be chimerically humanized to minimize antigenicity [42]. No antidrug mAb has yet been studied in humans, but high-affinity mAbs against cocaine, PCP, methamphetamine and nicotine are in active preclinical development. Haptens have been designed to generate mAbs with high affinity for a group of structurally related drugs, for example, amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (ecstasy) [43,44], thus addressing the potential drawback of high drug target specificity.

Animal studies with methamphetamine, nicotine and PCP show that equimolar concentrations of antibody and drug or an antibody dose equivalent to the total body burden of drug are not required for effectiveness [16,17]. This is also the case for some other antimedication antibodies used clinically, suggesting that a one-to-one correspondence between antibody-binding sites and drug molecules may not be necessary for efficacy. All that may be necessary is maintenance of a negative concentration gradient between brain and circulation so that drug is constantly being pulled out of brain tissue. These findings suggest that drug antibody treatment might be clinically effective, at least in the acute toxicity or overdose situation, at antibody doses that are well tolerated and affordable and that increasing drug intake would not overwhelm the protection afforded by antibodies.

Duration of action *in vivo* is influenced by the size and structure of the antibody administered [42]. A complete IgG antibody molecule (~150,000 Da) has an elimination half-life in human blood of approximately 3 weeks [45]. The antigen-binding fragment (Fab) (~50,000 daltons) and single-chain Fab (variable regions of both light and heavy antibody chains fused into one protein; scFv) (~27,000 Da) have half-lives of less than a day because of rapid clearance by renal glomerular filtration. The shorter distribution half-life and more rapid renal clearance of mAb fragments may be an advantage for treatment of acute drug toxicity as it promotes rapid renal excretion of the drug [17].

Promising murine anticocaine mAbs include 2E2 [46] and GNC92H2 [17]. 2E2, which has high affinity (K_D = 4 nM) for cocaine and its active metabolites norcocaine (generated by oxidative metabolism) and cocaethylene (formed from cocaine and ethanol), significantly reduces for at least 1 week the cocaine-primed reinstatement of previously extinguished cocaine self-administration in rats (an animal model of relapse) [46]. GNC92H2, which also has high affinity for cocaine (K_D = 2 nM), reduces cocaine self-administration in rats and protects mice from the acute toxicity of high-dose iv. cocaine (seizures and death), both as pretreatment or when given 3 min after the cocaine [17].

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High-affinity (K_D = ~10 nM) antimethamphetamine mAbs, such as mAb4G9 and mAb6H4, reduce methamphetamine self-administration in rats and protect against acute toxicity, whether given before or up to 30 min after methamphetamine administration [16,47]. These mAbs are being developed by InterveXion Therapeutics (Little Rock, AR, USA), with plans for Phase I human trials [109].

The high-affinity (K_D = 1.3 nM) antiPCP antibody mAB6B5, also being developed by InterveXion Therapeutics, decreases brain PCP concentrations and protects against the locomotor and toxic effects of PCP [16]. The protective effect may last up to 2 weeks after a single mAb injection and occurs with an mAb dose as low as one-hundredth the molar equivalent of the total body PCP burden.

A moderate affinity (K_D = ~200 nM) mAb generated against flunitrazepam protects mice from the sedation and impaired memory consolidation produced by a f lunitrazepam challenge [48].

Route of administration

All animal studies with free antidrug antibodies involved iv. administration. An alternative approach is the use of antibody-containing particles that can reach the brain after peripheral administration. This has been accomplished by expressing the anticocaine mAb GNC92H2 on the protein coat of filamentous bacteriophage viruses [49]. When administered intranasally to rats, these viruses penetrate into the brain and significantly reduce the locomotor and stereotyped behavioral responses to intraperitoneal cocaine for up to 4 days. Whether this route of administration has better efficacy than iv. administration remains unknown.

Clinical considerations

POC studies in rodents suggest that passive binding of drug molecules with mAb could be an effective treatment strategy for acute cocaine, methamphetamine or PCP overdose and toxicity. Therapeutic amelioration of toxic effects begins immediately after administration of the mAb. Duration of action may not be a substantial limitation, given that PCP mAb exerts effects for up to 2 weeks after a single injection in rodents [16].

A major unresolved question regarding clinical utility is the interval between drug ingestion and treatment administration. In the clinical context, patients do not usually present for treatment immediately after ingesting drug. Post-treatment studies in rodents only evaluated intervals up to 30 min after methamphetamine administration, which is not comparable to the treatment intervals likely in a clinical setting. In addition, there is not a close correlation between cocaine concentrations and behavioral or toxic effects in humans [50], so that the clinical benefits of rapid reductions in free cocaine concentrations are uncertain. Further research is needed in primates and, eventually, in humans, to address these questions.

A practical issue for clinical use of antidrug mAbs is cost-effective, large-scale production to Good Manufacturing Practice standards. In some clinical settings, doses of several grams may be needed for clinical effectiveness. mAbs for preclinical research are produced by expression in mammalian cells grown in cell culture, a method more efficient at producing full-length mAb than Fab or scFv [42]. scFv is easier to express than the multichain full-length antibody or Fab and hence may be more cost-effective for large-scale production [51]. Production by expression in bacteria, yeast and plant is currently being explored.

Another practical issue is the immunogenicity of mouse mAb in humans, with the potential for evoking clinically significant immune reactions. This can be addressed by converting the mAb to less immunogenic forms, as is done for other mAbs currently used in clinical

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medicine [45]. Genetic engineering methods allow replacement of mouse protein sequences with the corresponding human sequence. Chimeric mAb are only one-third mouse protein because the constant domains of the light and heavy chains are replaced with human protein sequences. Humanized mAb are 90–95% human protein because only the complementarity determining regions retain mouse protein sequences. Fully humanized mAb retain no mouse protein sequences and have little or no immunogenicity.

Increased drug metabolism

Current research focuses on increased metabolism of cocaine, which is readily hydrolyzed at the benzoyl moiety into inactive metabolites (ecgonine methyl ester and benzoic acid). Therefore, the theoretical issue of catalytic treatment producing pharmacologically active compounds does not arise with cocaine. Increased cocaine metabolism has been achieved by two approaches: drug-metabolizing enzymes and catalytic mAb. Both approaches allow the use of recombinant genetic techniques to engineer agents with optimized catalytic properties.

Drug-metabolizing enzymes

Several types of naturally occurring esterases metabolize cocaine. These include butyrylcholinesterase (BChE) (EC 3.1.1.8, previously known as pseudocholinesterase or serum cholinesterase), a cocaine esterase from the bacterium *Rhodococcus* strain MB1 (EC 3.1.1.84), and the intestinal variant (hiCE-2) of human carboxylesterase (EC 3.1.1.1) [52]. The author is not aware of any published development work with the latter enzyme.

BChE—Initial research efforts focused on BChE, a major cocaine-metabolizing enzyme in primates that is widely distributed in the body [4]. Mice genetically engineered to be BChE deficient show enhanced cocaine toxicity [53], suggesting the importance of BChE in metabolizing cocaine. Case reports of more than two dozen patients successfully treated with partially purified human BChE (derived from blood) to relieve toxicity from neuromuscular blocking agents such as succinylcholine and mivacurium (which are also hydrolyzed by BChE) suggested that administration of exogenous BChE would not raise safety issues, such as stimulation of an antienzyme immune response (reviewed by Gorelick [54]). No clinically significant adverse events were observed.

Animal studies showed that BChE administration substantially increased cocaine metabolism and reduced brain cocaine concentrations, while BChE pretreatment or short-term post-treatment significantly reduced the acute behavioral, cardiovascular and toxic effects of a cocaine challenge [4]. However, (−)cocaine, the naturally occurring active enantiomer, is not a preferred substrate for BChE, with a catalytic efficiency (k_{cat}/K_m) of only $0.9–1.25 \times 10^6$ M^{-1} min^{-1} [55,56]. This limited efficiency, with resulting high dose requirements, and limited availability of the natural (wild-type) enzyme, stimulated development of improved versions of BChE through genetic engineering.

Site-directed mutagenesis based on molecular modeling of BChE-cocaine transition state complexes created BChE variants (cocaine hydrolases) that hydrolyze (−)cocaine at least three orders of magnitude more efficiently than the wild-type enzyme (Table 3) [56].

One of the first quadruple mutants, AME359 (Phe227Ala/Ser287Gly/Ala328Trp/Tyr332Met), was developed by Applied Molecular Evolution (San Diego, CA; acquired by Eli Lilly in 2004) [4]. iv. pretreatment with this cocaine hydrolase prevented the lethal effects of a cocaine challenge in rats. An improved quadruple BChE mutant (Ala199Ser/Ser287Gly/Ala328Trp/Tyr332Gly) fused at its C terminus with human serum albumin to improve stability and extend plasma half-life was developed by CoGenesys, Inc. (Rockville,

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MD, USA) [57]. This construct (albu–CocH, known as TV-1380 since Teva Pharmaceuticals acquired CoGenesys in 2008) retains the high catalytic efficiency of the free enzyme (Table 3). In rats, pretreatment with TV-1380 reduces cocaine self-administration and cocaine-primed reinstatement of previously extinguished cocaine self-administration and prevents cocaine-induced (but not amphetamine-induced) seizures for up to 12 h [57,58]. Post-treatment with TV-1380 stopped cocaine-induced seizures within 1 min and raised cocaine's ED_{50} almost tenfold [57]. In cynomolgus monkeys, pretreatment with TV-1380 attenuates the physiological effects of a cocaine challenge (1 mg/kg iv.) given 3 h later and tends to shorten the time for parameters to return to baseline [59]. In squirrel monkeys, pretreatment with TV-1380 (5 mg/kg), which has a 56.6-h half-life, reduces plasma levels of parent cocaine and increases levels of the cocaine metabolite ecgonine methyl ester for up to 72 h after a cocaine challenge (1 mg/kg iv.) [60]. The same pretreatment significantly reduced self-administration of iv. cocaine for over 24 h, attenuated the priming effect of cocaine (0.1 or 0.3 mg/kg) in reinstating previously extinguished cocaine self-administration and attenuated the discriminative stimulus effects of cocaine.

Bacterial cocaine esterase—A highly active cocaine esterase (Table 3) is produced by *Rhodococcus* bacteria that grow in the rhizosphere soil of *Erythroxylum coca*, the cocaine-producing plant [61]. Pretreatment with this bacterial cocaine esterase protects mice against toxicity and death from lethal cocaine doses [62,63]. Longer pretreatment intervals were associated with declining protection, as expected from the short half-life of enzyme activity in plasma (10–13 min). Treatment 1 min after cocaine administration prevents the development of cardiovascular or neurologic toxicity, while treatment 1 min after the start of cocaine-induced seizures prevents death and restores cardiovascular function [63,64]. This protective action is retained after two prior enzyme exposures (at weekly intervals) but diminishes after three and four prior exposures [62]. Serum antienzyme antibody titers increase 100-fold over this period, suggesting that the enzyme is immunogenic [62].

A disadvantage of this enzyme is its short half-life in plasma (due to thermal instability), rapid degradation by serum proteases, and immunogenicity resulting in antienzyme antibodies. The first issue has been addressed by development of thermostable mutants with half-lives up to 10 h that have similar catalytic properties (Table 3) [61,65]. Pretreatment with a thermostable double mutant (Thr172Arg/Gly173Glu) protects rats for up to 3–4 h from cocaine-induced seizures and death, and reduces cocaine self-administration during 60-min test sessions [66]. Treatment of rhesus monkeys with the same mutant enzyme 10 min after cocaine challenge (1–3 mg/kg iv.) reduces plasma cocaine concentrations below detectable levels within 5–8 min [67] and reduces elevated blood pressure and heart rate to baseline levels within 5–10 and 20–40 min, respectively [68]. The monkeys show highly varied immune responses to the enzyme, with some having only tenfold increases in antienzyme antibody titers after four exposures, and others having 100-fold increases after three exposures [67,68]. The protective action of the enzyme was not influenced by the level of antibody titers.

All three stability issues are addressed by PEGylation of the esterase (i.e., conjugation with strands of polyethylene glycol polymer), which improves thermostability, protects against protease digestion and inhibits binding of anti-enzyme antibodies to the PEGylated enzyme [69]. Pretreatment with PEGylated enzyme protected mice against the lethal effects of a cocaine challenge at least as well as did unPEGylated enzyme.

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Catalytic antibodies

Catalytic antibodies were developed to avoid a potential limitation of conventional anticocaine antibodies, *viz.*, possible saturation of their binding sites by increasing cocaine doses. They bind noncovalently to a transition-state analogue of cocaine, which catalyzes hydrolysis of the cocaine molecule [70]. This frees the antibody to bind and hydrolyze another cocaine molecule. Catalytic antibodies are generated by immunizing animals with transition-state analogues of cocaine benzoyl ester hydrolysis.

A variety of anticocaine catalytic antibodies have been generated [70,71], with catalytic properties less favorable than those of BChE mutants or bacterial cocaine esterase. However, pretreatment with one of the most efficient, mAb 15A10, dose-dependently protects rodents against the increased blood pressure, seizures, and death produced by a cocaine challenge and significantly shifts the dose–response curve for iv. cocaine self-administration downward and to the right [14]. The duration of the protective effect is less than 10 days.

Route of administration

All human cases of BChE treatment and almost all animal studies of cocaine-metabolizing enzymes or catalytic antibodies involved iv. administration. Encapsulation of mAb 15A10 in poly(lactic-glycolic) acid microspheres results in detectable blood Abs in mice up to 10 days after subcutaneous injection [14] and may be a strategy for prolonging duration of action.

Clinical considerations

POC studies in rodents suggest that increased drug metabolism might be an effective treatment strategy for acute cocaine, methamphetamine or PCP overdose and toxicity. Therapeutic amelioration of toxicity begins immediately after administration of the enzyme or catalytic antibody. Short duration of action should not be a significant disadvantage because repeated administration is practical in the healthcare settings (e.g., emergency department), where such patients are likely to be seen, and is successfully used with short-acting opiate receptor antagonist (naloxone) treatment of opiate overdose. Rodent studies with cocaine and PCP indicate that effective doses do not have to be equimolar with the total body burden of drug, thus probably obviating the need for impractically massive doses of enzyme or antibody.

As with passive drug binding (mAbs), a major unresolved question is the interval between drug ingestion and treatment administration. Most cocaine-associated deaths occur within 2 h of ingestion [72], so there may be a narrow window of opportunity for clinical application of enhanced cocaine metabolism. Post-treatment studies in animals have only evaluated intervals up to 10 min after cocaine administration, which is not comparable to the treatment intervals likely in a clinical setting. In addition, there is not a close correlation between cocaine concentrations and behavioral or toxic effects in humans [50], so that the clinical benefits of rapid reductions in cocaine concentrations are uncertain. Further research is needed in primates and, eventually, in humans to address these questions.

A practical issue for clinical use of metabolism-enhancing agents is cost-effective, large-scale production to Good Manufacturing Practice standards. Large-scale purification of BChE from human plasma is possible [73]; the limiting factor is the amount of donated plasma available. An alternative may be insertion of the enzyme gene into another organism designed for high-volume expression of the protein. This has been demonstrated on a model basis in plants (e.g., tomato, tobacco), silk worm larvae [74], and goat mammary gland (with secretion into milk) [75].

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The potential efficacy of chronic administration of drug-metabolizing enzymes or catalytic antibodies as treatment for addiction has not yet been evaluated in animal models. Rodent studies show that cocaine self-administration and cocaine-primed reinstatement of previously extinguished reinstatement can be reduced acutely, but it remains undetermined whether the reinforcing action of the drug can be reduced for a sufficient duration with this strategy to allow long-term extinction of drug-seeking and drug-taking behavior in humans. Also unknown is whether a human addict could overcome the enzyme effect by taking increased amounts of drug.

One unresolved practical issue with this treatment strategy is the relatively short duration of action of currently available enzymes (up to 10 h), which would require frequent administration to human patients. One approach to overcoming this problem is administration of the gene coding for the desired enzyme (rather than the enzyme itself), hopefully resulting in long-term production of the enzyme. Several studies in rodents have shown that injection of the gene for a human BChE mutant, using a harmless adenovirus as vector, can increase cocaine hydrolysis in plasma for up to 6 months, with associated decreases in the behavioral response to a cocaine challenge [76–78].

Another practical issue is possible immunogenicity of the enzyme itself, with generation of anti-enzyme antibodies leading to immune reactions and loss of efficacy. Recent studies in monkeys raise caution in this regard, with measurable levels of anti-enzyme antibodies appearing after two to three administrations of bacterial cocaine esterase [67,68]. Minimization of immunogenicity might be an advantage of human BChE over bacterial cocaine esterase.

Catalytic treatments aimed at cocaine raise a particular issue of specificity, in addition to those of affinity and speed of activity. Cocaine and the endogenous neurotransmitter acetylcholine (AChE) have structural similarities (cationic nitrogen and a reactive ester link) that might make it difficult to achieve high catalytic specificity [79]. In fact, BChE, a major cocaine-metabolizing enzyme in humans, has better catalytic efficiency for AChE than it does for cocaine [55]. Several anticocaine catalytic antibodies [79], bacterial cocaine esterase [79], BChE mutants [56] and TV-1380 [57] also hydrolyze AChE *in vitro*, although with much lower catalytic efficiency than for cocaine. The clinical significance of this issue remains unclear. Anticholinergic toxicity has not been reported in patients receiving partially purified human BChE to treat toxicity from organophosphate pesticides or neuromuscular blocking agents [4], but relevant signs and symptoms may have been masked or overlooked because of the urgent clinical situation. Obvious anticholinergic toxicity has not been reported in animal (almost exclusively rodent) studies to date, but probably was not systematically evaluated.

Ethical issues

Several ethical issues have been raised concerning use of an antidrug vaccine or antibody [80]. Patients would have detectable levels of antidrug antibody in their blood for prolonged periods, identifying them as being in treatment for addiction. This potential compromise of confidentiality risks serious adverse legal, employment, economic, and insurance consequences for patients. Should PK treatment be used for primary prevention in individuals at high risk for addiction (e.g., adolescents with drug use) who may not be in a position to make a completely voluntary decision? What about enforced treatment in the criminal justice, child welfare or employment settings? These issues must be addressed as PK treatments are developed and before they achieve widespread clinical use.

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Future perspective

High-affinity, drug-specific mAbs and high-efficiency drug-metabolizing enzymes (especially for cocaine) may eventually have a role in the short-term treatment of acute drug toxicity and overdose. However, comprehensive animal toxicology studies have not been completed and no human Phase I trials conducted, so that regulatory approval for Phase II clinical trials is likely at least 5 years away. None of these agents has yet advanced beyond preclinical development and only a handful of published studies have been conducted in nonhuman primates. Important developmental hurdles that remain to be overcome include demonstrating efficacy with post-drug administration intervals of up to several hours (to mirror the more clinically realistic situation), producing more humanized versions that do not themselves evoke an immune reaction and developing cost-effective methods for large-scale production. These agents may also be useful for the longer term treatment of drug addiction, if versions with effective half-lives of weeks or longer can be developed.

Antidrug vaccines are unlikely to enter routine clinical practice within the next 5 years, based on the disappointing intent-to-treat findings in the initial Phase IIb and III nicotine and cocaine vaccine trials. Short-term prospects depend heavily on the outcomes of several recently completed or currently ongoing controlled clinical trials, including the second large Phase III clinical trial (completed November 2010 [NCT01102114] [101] and an ongoing Phase IIb clinical trial (combined with varenicline [NCT00995033])[101] of the NicVAX® vaccine; a Phase II clinical trial with the Nic002 vaccine that started in December 2010 (NCT01280968) [101]; and the ongoing Phase IIb multicenter clinical trial of the TA–CD anticocaine vaccine (NCT00969878) [101], scheduled for completion in December 2013.

Longer term prospects may depend on adequate funding to support development of vaccines, adjuvants, and vaccination schedules that improve on the low proportion of subjects with high antibody titers generated by current vaccines. Several approaches to enhance the immunogenicity of vaccines are worth exploring, including conformationally constrained haptens and variations in the position and length of the hapten–carrier protein link.

Even after regulatory approval, PK treatments will face significant barriers to widespread use. Most drug addiction treatment in the USA is delivered in public or publicly funded treatment programs, which are chronically underfunded and often not medically staffed (except for methadone maintenance clinics). Thus, the high cost (up to several thousand dollars per mAb dose based on costs of mAbs used clinically in other areas of medicine [42]) and need for medical staff to administer injections and monitor for side effects may discourage the use of PK treatments. The mainstreaming of addiction treatment into primary care medicine and elimination of health insurance discrimination against coverage of addiction treatment would help resolve this issue. Individual patient objections to PK treatment may derive from concerns over inability to self-medicate drug craving or withdrawal, possible effects on the outcome of drug testing, and potential breach of confidentiality from detection of antidrug antibodies or enzymes in the blood. One advantage for PK treatments may be greater acceptance by patients and treatment staff who oppose addiction treatment medication. This opposition is based largely on belief that most such medications are potentially addictive because they are psychoactive. PK treatments may be more readily accepted because they target the drug molecules, not the brain, and do not themselves exert any psychoactive effects.

Given the continued medical and societal burden of drug addiction and the absence of other broadly effective anti-addiction medications, development of the PK treatment strategy should continue. This will, hopefully, result, perhaps in a decade, in the following clinical

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scenarios: acute drug toxicity and overdose is successfully treated by iv. administration of a drug-specific mAb or drug-metabolizing enzyme, long-term addiction treatment includes a course of antidrug vaccination to complement psychosocial therapy. The initial few months of treatment, while awaiting development of adequate antibody titers, are bridged by administration of a longer-acting, perhaps PEGylated, agent or genetic transfer of the agent using a harmless viral vector.

Box 1. Pharmacokinetic strategies for the treatment of drug addiction

Peripheral blockers

- Active immunity (antidrug vaccine)
- Passive immunity (monoclonal antibody)

Increased drug metabolism

- Enzymes
  - Human butyrylcholinesterase: genetically improved
  - Bacterial cocaine esterase: genetically improved
- Catalytic monoclonal antibody

Combination treatment

- Peripheral blocker plus increased drug metabolism

Modes of administration

- Peripheral injection
- Gene transduction with a viral vector

Executive summary

Targets for pharmacokinetic treatment

- Acute drug toxicity/overdose (e.g., emergency department).
- Chronic addiction.
- Target drugs: nicotine, cocaine, methamphetamine and phencyclidine.

Peripheral blockers

- Create drug–antibody complexes too large to cross blood–brain barrier. Achieve with:
  - Active immunization (antidrug vaccine);
  - Passive immunization (antidrug monoclonal antibody).
- Antinicotine and anticocaine vaccines have shown promise in Phase IIa clinical trials:
  - Two-thirds of patients do not develop adequate antibody titers;
  - High antibody titers are associated with decreased drug use;
  - Vaccines are well tolerated.
- Antinicotine vaccines have been less successful in Phase III clinical trial.

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- Antidrug monoclonal antibodies protect against acute drug toxicity in animal studies.

Increased drug metabolism

- Protect against acute cocaine toxicity in animal studies with enzymes (both wild-type and genetically enhanced):
  - Human butyrylcholinesterase (derived from blood);
  - Bacterial cocaine esterase.
- Catalytic efficiency improved by site-directed mutagenesis.
- Duration of action increased by:
  - Mutagenesis;
  - PEGylation;
  - Transfection with enzyme gene using viral vectors.
- Catalytic antibody acts as enzyme to increase drug breakdown.

Issues needing further research

- Measures for achieving consistently high antibody titers in all individuals after vaccination:
  - Improved haptens, hapten–carrier coupling;
  - Improved adjuvants;
  - Determining optimum vaccination schedule.
- Determining the optimum concurrent treatments to accompany vaccination.
- Evaluating post-treatment (i.e., 'rescue') efficacy of antidrug antibodies and enzymes when administered after drug intake.

Key Term

Monoclonal antibody: Antibodies that are all specific for the same antigen because they are made by identical immune cells that are clones of the same parent cell.

Catalytic efficiency: Ratio of k_{cat} (rate at which an enzyme–substrate complex splits into enzyme plus product) to K_M (Michaelis constant; the amount of substrate needed for the enzyme to achieve half its maximum rate of reaction).

Catalytic antibody: Antibody that catalyzes the splitting of the molecule (antigen) to which it binds, thereby destroying the molecule and freeing the binding site for occupancy by another molecule.

Acknowledgments

D Gorelick is supported by the Intramural Research Program, US NIH, National Institute on Drug Abuse.

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▪▪ of considerable interest

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Table 1

Key characteristics of pharmacokinetic treatments for drug addiction.

Characteristic	Peripheral blocker (antibody)		Increased drug metabolism	
	Active immunity	Passive immunity	Enzyme	Catalytic antibody
Onset of action	Weeks to months	Immediate	Immediate	Immediate
Duration of action	Months	Days	Days	Days
Specificity of action	Very high	Very high	High	Very high
Control over treatment agent	Low	High	High	High
Possibility of saturating binding sites	Medium	Medium	Low	Low
Likely clinical use	Addiction	Toxicity/overdose	Toxicity/overdose	Toxicity/overdose

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Table 2

Antidrug vaccines that have entered clinical development.

Vaccine	Target drug	Hapten	Carrier protein	Clinical trial phase completed	Clinical trial phase active	Company
TA–CD	Cocaine	Succinyl-norcocaine	Cholera toxin B subunit	II	III	Celtic Pharma Management, LP
Nic002	Nicotine	Nicotine	Qb bacteriophage virus protein coat	II	II	Cytos/Novartis
NicVAX®	Nicotine	3'-aminomethyl-nicotine	*Pseudomonas aeruginosa* exoprotein A	II	III	Nabi/GlaxoSmithKline
TA–Nic	Nicotine	Nicotine butyric acid	Cholera toxin B subunit	II	Development suspended	Celtic Pharma Management, LP
Niccine®	Nicotine	Nicotine	Keyhole limpet hemocyanin	II	Development suspended	Independent Pharmaceutica, AB

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Table 3

Kinetic characteristics of cocaine-metabolizing enzymes with (−)cocaine as substrate.

Enzyme	Catalytic rate constant, k_{cat} (min^{-1})	Michaelis constant, K_m (μM)	Catalytic efficiency (k_{cat}/K_m)	Improvement over wild-type BChE
BChE wild-type	3	4	1.25	
BChE double mutant†	154	18	8.7	~sevenfold
BChE quadruple mutant (AME 359)‡	620	20	31	~25-fold
BChE sextuple mutant§	4430	3.5	1300	~1000-fold
TV-1380¶	2700	2.1	1300	~1000-fold
Bacterial cocaine esterase – wild-type	2323	21	110	~90-fold
Bacterial cocaine esterase – thermostable double mutant#	2247	24	95	~75-fold

†Ala328Trp/Tyr332Ala.

‡Phe227Ala/Ser287Gly/Ala328Trp/Tyr332Met.

§Ala199Ser/Phe227Ala/Ser287Gly/Ala328Trp/Tyr332Gly/Glu441Asp.

¶BChE quadruple mutant (Ala199Ser/Ser287Gly/Ala328Trp/Tyr332Gly) fused with human serum albumin.

#Thr172Arg/Gly173Glu.

BChE: Butyrylcholinesterase.
Data from [55,56,61].