

Future advances in addiction treatment

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Abstract

In the next decade, we should witness a number of treatment advances for opioids, stimulants, and cannabis derivatives. For opioids, this will include long acting, i.e., one month to one year, injectable or implants of the antagonist naltrexone, injectable or implants of the partial agonist buprenorphine, and innovative detoxification methods using buprenorphine. In addition, there should be much wider office based prescribing of buprenorphine for maintenance as financial, stigma, and numerical prescribing barriers are overcome.

Possible new developments for cocaine dependence include vaccines that provide either active or passive immunization; agonists that could decrease craving without producing euphoria; blocking agents that do not block normal pleasures; and CRF (corticotrophin releasing factor) antagonists which could decrease both craving and relapse. In the short term, medications currently marketed for other indications that show promise for cocaine include modafinil, tiagabine, topiramate, and disulfiram.

Until recently, there has been little effort toward developing medications to treat marijuana abuse/dependence. Potential medications now being considered include the agonist dronabinol, rimonabant, an antagonist and inverse agonist, and Sativex, an aerosol combining THC and cannabidiol, a non-psychoactive cannabis ingredient. Behavioral interventions will continue to be necessary, not just to increase the likelihood that patients will take effective medications but also to assist them in improving their interpersonal, educational, and vocational skills so as to develop positive rather than just negative reasons for wanting to stop drug use.

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While the past few decades have witnessed some useful additions to the treatment of addiction, the marked increase in basic science knowledge involving intracellular changes, brain imaging studies, and genetic analysis hold out the promise of more rapid advances over the next decades. It is important, however, to keep in mind that it is hard enough to predict the past let alone the future. We can probably be sure though that unless some good fairy appears and says, 'Everything bad for you is now good for you,' there will continue to be major substance-related problems. Individuals who use various drugs of abuse in a variety of self-destructive patterns, harmful not only to themselves but also to their families and the society around them, will remain a significant concern.

A useful place to begin is to look at predictions about the next 5 years regarding what we will be treating in 2010. Cocaine abuse has remained endemic during the past decade with numbers remaining more or less stable and no

treatment breakthroughs. My prediction for 2010 is that generational forgetting about cocaine will yield a new cohort of cocaine snorters, especially among the affluent, which could lead to an upward trend again. We have already begun to see this happening among late teens and young adults and it appears that this may very well continue.

Unfortunately, dependence on heroin continues to rise. From one-half million in the 1980s to approximately 750,000 in the 1990s, the numbers now appear to have markedly increased to about 1 million. The continued rise is fueled by the increased purity and decreased price of heroin. In New York, for example, which traditionally had heroin purity of only 10–20%, heroin purity is now between 50 and 80% and the source of supply has shifted from Southeast and Southwest Asia to South America, especially Colombia. My prediction for 2010 is that, because of the price and purity factors, as well as the increased popularity of prescription opioids, dependence will have risen to well over 1 million and not yet peaked.

Indeed, the major growth story in the decade of the 1990s was less the rise in heroin than the rise in prescription opioid

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abuse and dependence. During this decade there was a growing consensus in both lay and professional circles about the need for better treatment of pain. Concern over possible legal harassment and the fear of addicting patients, had led many US physicians for the past 80 years to be very cautious about prescribing opioids. This has been true not just for chronic, non-malignant pain, but even for acute and chronic malignant pain. The pendulum appears to have swung during the last decade of the 20th century to providing more pain relief, fueled by reports in professional journals about inadequate pain treatment and its effects on stress and healing, as well as law suits against physicians for inadequate prescribing of pain relief. Not surprisingly, as prescriptions increased for these opioid drugs, their availability on the illicit market also increased via doctor shoppers, 'script doctors,' pharmacy and home thefts, and the Internet. This led to the number of individuals abusing them also rising. Emergency room data (DAWN - Drug Abuse Warning Network) between 1990 and 2000 showed that mentions for prescription opioids doubled and this rise has continued in the new decade. Likewise, there has been a marked increase in such use among adolescents as measured by the *Monitoring the Future* study of high school students and the *National Household Survey*. The major prescription opioids of concern in this decade have been hydrocodone, fentanyl, and the long-acting form of oxycodone known as OxyContin, nicknamed *Hillbilly Heroin*. Its use spread especially in rural America, ranging from rural Maine down to West Virginia, following the Appalachian Mountain chain. In these areas where heroin historically has been scarce, prescription opioid abuse has been present for a substantial period of time, and its use accelerated during the decade. Street users quickly learned that the 12-hour formulation of OxyContin could be readily defeated by crushing and the active drug in large amounts could then be taken orally, or dissolved and snorted or injected. OxyContin, for example, sells for \$1/mg on the street with diversion coming not only from the sources noted above but as well from legitimate patients selling all or part of their doses, and diversion at the wholesale level. The search has continued for diversion-resistant ('tamper-proof') formulations that would help prevent such abuse but to date, there has been no satisfactory mechanical solution. It is not uncommon, in areas where there are high levels of diversion, to have pharmacies with signs in their windows saying, 'We do not stock OxyContin.' My prediction for 2010 is that prescription opioid abuse will have continued to rise rapidly, fueled both by new agents and continued public concern about adequate pain relief. While the new agents will probably be more difficult to divert than OxyContin, the ingenuity of street users and street chemists has defeated mechanical fixes for decades and no immediate solution is on the horizon. Continued search for development of better diversion-resistant formulations is important but needs to be combined with improved prevention and treatment as well as better rapid-warning risk management programs that can

alert manufacturers, doctors, and regulatory agencies to emerging trends. Quick fixes will probably need to be left to addicts while scientists, regulators, and funders press ahead with gradual progress on a number of fronts.

Methamphetamine for most of the past decade was a West Coast problem that gradually progressed to the Mid-West and somewhat slower to the East. The progression appears to be speeding up and New York City, which had been relatively free of methamphetamine, is now experiencing the drug as part of the Club Drug scene and in the gay community. This is leading, among others, problems, to a public health concern over increased unprotected sex and rises in HIV/AIDS. If the experience of other cities is any guide, there may be a more rapid increase over the next years in methamphetamine abuse in northeastern cities.

Marijuana use over the past few years has shown some slight decline. Its use among high school seniors is about 1/3 less than the peak year of 1980, but almost double what it was in 1992, the low point of the past 30 years. Over the coming decade, it is possible that marijuana use/abuse/dependence will rise led in part by the medical marijuana referenda, which convey that marijuana is not only safe but also beneficial, and the difficulty many parents have in dealing with the issue. The increased potency and knowledge about marijuana withdrawal and dependence, has already begun to lead marijuana users to seek treatment in greater numbers. As treatment methods and availability continue to improve, these numbers should rise even more.

Finally, at this time, it appears there is no widespread new epidemic on the immediate horizon. One might anticipate, based on the past few decades, a spotty flare-up of miscellaneous agents, just as Ecstasy sharply increased during the late 1990s before declining. Over-the-counter agents, such as dextromethorphan, will become more commonly abused as the Internet increases the rapidity of diffusion and access to new substances of abuse. The public reaction to all of the above may be diminished from what it has been in the past as there is an increasing disconnect between drugs and violence, and the government's lack of concentration on the issue decreases overall interest in the drug problem. One consequence of this diminished interest will be the marginalization and weakening of the Office of National Drug Control Policy, which has been decreasing in visibility over the past few years already.

1. Current status of pharmacotherapy

1.1. Introduction

Rational therapy for cocaine from neuroscience research has not yet produced a viable agent. In spite of numerous efforts over the past 20 years, and over 40 medications being tried, there is at present no generally effective

medication for cocaine dependence. There are, however, as will be noted later, a number of medications that appear promising. Useful medications for heroin dependence do exist. They are all, however, at least 20–30 years old, even though some have only recently been approved for the treatment of opioid dependence. Generally they were first developed for non-drug abuse indications such as pain and then became used for treatment of heroin withdrawal or dependence. There is also no generally effective medication for either methamphetamine or marijuana dependence. Future research will need to focus on medications that help with cessation, especially in the case of the stimulants and marijuana, and agents that prevent reinstatement for all of the drugs of abuse. One problem in the research to date, except for heroin treatment, has been a lack of adequate differentiation between agents to produce cessation and those to prevent relapse or reinstatement. Additional problems hampering research efforts include the hostility of many in abstinence-based and 12-Step Programs to the use of medication to treat addiction and the indifference of the large pharmaceutical companies to invest resources in this research.

1.2. Opioid dependence

As far as opioid-dependence is concerned, it is my belief that in the near future we will see a number of important developments. These will include a long acting, i.e., one month to one year, injectable or implant of the antagonist naltrexone and widespread, office-based prescribing of the newly approved buprenorphine/naloxone combination. This should help reach more of the 80% of heroin addicts not currently in treatment. If office-based prescribing of buprenorphine is successful, including minimal diversion, it might be possible to then see more widespread office-based prescribing of methadone for stabilized patients. The difference is that office-based prescribing of methadone will tend to be only for already stabilized patients while with buprenorphine, one will see many patients beginning on buprenorphine in doctors' offices. In addition to the long-acting naltrexone implants, one should expect within the next few years' studies of a long-acting buprenorphine implant, using a mechanism similar to that of the contraceptive drug Norplant. Regarding opioid detoxification, a number of studies to date suggest that the risks of the rapid opioid detoxification under anesthesia are greater than the benefits. In spite of this, such programs continue to proliferate, often charging sums as high as \$15,000 or more. There have been over two-dozen deaths from this procedure worldwide, often from pulmonary edema, usually occurring within the first 48 hours. Many patients who have experienced the procedure continue to have moderate to severe withdrawal symptoms for weeks afterwards and long-term efficacy does not seem substantial. No objective study has shown that there is any higher degree of success remaining abstinent after six months than with conventional

detoxification procedures. It appears more likely, therefore, that a method of rapid detoxification using buprenorphine without anesthesia but aided by the alpha-adrenergic agonist lofexidine, will become more popular. Lofexidine appears to have less problems with hypotension than the related anti-hypertensive agent, clonidine. It is currently available in England and studies are underway for approval in the United States for treatment of opioid withdrawal.

Human laboratory studies by our group of an injectable naltrexone depot in volunteer subjects has shown that blockade of the effects of heroin can be achieved for up to one month after injection. Similar positive findings were noted in an outpatient clinical trial of treatment-seeking opioid addicts. There are a number of such medications under development and it is expected that one of them will come to market in the next 1–2 years. Initially, however, the company is seeking FDA approval for alcoholism rather than for opioid addiction but it could be readily used off-label once approved. Buprenorphine, a partial opioid agonist, is a Schedule III agent, which has been approved for office based prescribing under the terms of the 2000 Drug Abuse Treatment Act. The prescribing physician has to have taken an 8-hour course and received a waiver from the Department of Health and Human Services. By the end of 2004, over 6000 physicians had been trained and approximately 4000 had applied for and received waivers. The total number of physicians who prescribed buprenorphine at least once is not clear, with differing figures being given by the Center for Substance Abuse Treatment of HHS and by the company. One often-quoted number has been 1, 800 prescribers. Buprenorphine is available in two sublingual forms: Subutex, buprenorphine alone, and Suboxone, a 4:1 combination of buprenorphine and the narcotic antagonist naloxone. Taken sublingual, little naloxone is absorbed but if the tablet is dissolved and injected, a substantial amount, as much as 100 times more, is available. By the end of the third quarter of 2004, over 90, 000 prescriptions for sublingual buprenorphine had been written. The relative slowness in the uptake of buprenorphine appears due to a number of factors described below.

The first and often the major factor is financial. While Medicaid and many private insurers cover the medication, the working poor may not be able to afford it. It costs approximately \$350/month for the average dose of 16 mg/day of Suboxone. Many patients with insurance are reluctant to use it for fear of their employer finding out. Reimbursement for the physician prescriber or for ancillary support is usually inadequate. A second factor is concern by many primary care physicians and their staff that they are not equipped to deal with addicts in their office. A third issue that needs to be kept in mind is that the availability of buprenorphine for office-based prescribing is a reversal of 80 years of regulation that discouraged physicians from treating addiction, by threatening them with loss of license and possibly prison for what was deemed inappropriate or illegal prescribing. This fear of DEA or state regulatory

authorities will be slow to dissipate. A fourth consideration is concern because of the potential difficulty of the induction process. The patient must be in withdrawal before beginning buprenorphine; otherwise buprenorphine is likely to precipitate opioid withdrawal by displacing other opioids from the receptor. Physicians not familiar with treatment of addiction may be reluctant to try this initially in their office. To remedy this may require an increased use of induction centers that would start patients on buprenorphine and then transfer them to other physicians for on-going maintenance. A final problem with the acceptance of buprenorphine is fall out from negative attitudes toward methadone maintenance. Unfortunately methadone, although shown by numerous studies to be an effective and at times life-saving treatment for heroin addiction, is often disliked by patients, their families, their neighbors, and by physicians and the general public as well. How much of this is due to moral opposition to the use of agonist therapy versus problems due to the decrease in ancillary services over the past 35 years in methadone programs is not clear. As government funding for methadone has gradually declined, and programs have increasingly become private for-profit rather than not-for-profit, services other than the methadone itself have been drastically cut. Overall, 60% of methadone maintenance programs are now private, for-profit and in California the number is as high as 90%. These decreased services have led to programs 'silting up' with unemployed, poorly educated addicts who too often continue with polysubstance abuse and illegal activities

In the long term, medication development for opioid dependence will likely be based on principles of modulating brain systems that have been altered by chronic opioid abuse. For example, opioid addicts have long-term, perhaps even permanent dysregulation of their stress systems. This alteration results in exaggerated stress responses that may lead to relapse back to illicit drug use.

1.3. Cocaine dependence

In regard to the treatment of cocaine dependence, it appears that in the near future there will be a number of new developments that could markedly enhance the success of our treatments. These include vaccines that provide either active or passive immunization; agonists that could decrease craving without producing euphoria; blocking agents that do not block normal pleasures; and corticotrophin releasing factor (CRF) antagonists delivered via some type of pump. CRF modulates stress and an effective antagonist could decrease both craving and relapse. Until the above agents are available, there are a number of medications currently marketed that show promise for treating cocaine dependence in clinical trials, although none have yielded the kind of definitive evidence needed. These agents include modafinil, a mild stimulant used to treat narcolepsy; anti-epileptic agents such as tiagabine and topiramate; and the

drug disulfiram, better known as Antabuse. This latter has traditionally been used to treat alcoholism based on the very unpleasant reaction produced by the interaction between it and alcohol. However, disulfiram has another action that may be more relevant to cocaine use, namely it inhibits dopamine beta-hydroxylase resulting in increased dopamine and decreased synthesis of norepinephrine. Disulfiram may diminish cocaine craving or alter the cocaine high because of this effect on dopamine.

In the longer term, I expect there will be agents to both enhance cessation and decrease the likelihood of relapse. Reinstatement blocker candidates include: for drug-priming induced reinstatement, D1 agonists and AMPA antagonists; for cue-induced reinstatement, D1 antagonists and NMDA receptor antagonists; and for stress-induced reinstatement, the CRF antagonist mentioned earlier, and alpha-2 noradrenergic agonists.

1.4. Marijuana dependence

Because of the longtime belief that marijuana did not produce withdrawal or physical dependence, there has been little effort toward developing medications to treat marijuana abuse/dependence. Research over the past 5 years, however, has shown that there indeed is both withdrawal and physical dependence and this, along with the higher potency of marijuana, has been associated with more individuals coming in for treatment of marijuana abuse/dependence. Current estimates are that approximately 150,000 individuals/year seek treatment for marijuana as their primary drug of abuse. Medications that have not been successful have included bupropion, tried because of its success in treating nicotine dependence, and divalproex. Both appeared to worsen withdrawal symptoms. Nefazadone, perhaps because of its sedating effect, did appear to reduce irritability but not craving. The most promising medication to date has been dronabinol (Marinol), the Schedule III synthetic tetrahydrocannabinol. In both human laboratory studies and pilot trials, this agent has appeared to be promising and, in my clinical experience, I have found that it can be useful in helping individuals stop using marijuana. What has been required so far has been relatively high doses, between 30 and 50/mg day, for at least 2–3 weeks. This usually eventuates in the individual stopping using via the smoking route especially during the week, although some use during weekends is not uncommon. Following these weeks of stabilization on Marinol, a slow taper is begun. During this time the clinician may observe the emergence of symptoms that the patient may have been trying to self-medicate with the marijuana. This might require prescribing of an anti-depressant, an agent to treat ADHD, or a mood stabilizer. Such prescribing should be delayed for 7–10 days to ensure the symptoms are not simply due to withdrawal. A potential new agent is a medication called Sativex, an aerosol combining THC and cannabidiol, a non-psychoactive cannabis constituent. It is currently

being tested in England for treatment of some of the symptoms of multiple sclerosis. Agents to prevent reinstatement that have been tried include naltrexone, which appeared to increase intoxicating effects, and divalproex, which did not show effectiveness. The most promising agent here may be the CB-1 inverse agonist, Rimonabant, which is currently being tested for treatment of obesity and nicotine dependence. The diversity of interactions between the cannabinoid and the dopamine systems suggests that it may also be useful in treating cocaine withdrawal. Rimonabant (SR 141678) is both an inverse agonist (producing effects opposite to the agonist) and an antagonist (e.g., if given to THC-dependent rats, it produces immediate and severe withdrawal similar to what one sees if naloxone is given to opioid-dependent rats.)

2. Future prospects for pharmacotherapy development

For the next decade, it appears that the main source of new addiction treatment medications will probably be agents developed for better-funded and less-stigmatized indications such as depression and epilepsy. At the same time, new compounds will be screened and developed with specific brain mechanisms in mind. One of the techniques that may speed up this development is rapid screening of candidate compounds, which is more likely to occur if major pharmaceutical companies get involved. Up to now, they have been reluctant to do so because they perceive that the market is limited, the condition being treated is stigmatized, use of medications is discouraged by the 12-Step movement, and the main buyer may be the government which would markedly limit potential profit. Thus, involvement of the large pharmaceutical companies is unlikely to happen without special government financial incentives such as allowing a 6–12 month patent extension on a medication of the company's choice if they come up with a successful compound to treat cocaine. It is more likely that smaller up-start biotech companies will see potential profits and get involved. A variety of new methods could also help speed up screening but large-scale screening may remain problematic without demonstration of proof of concept.

Another development in the short term will be innovative delivery systems. This could involve all orifices, including better use of aerosols, new transdermal preparations, not just

a patch but superficial high speed injections as with vaccines, implantable pumps as currently happens in some cases of diabetes, and super long-acting implants. The Australians have developed a naltrexone implant that can last for 6-12 months and a buprenorphine implant that lasts up to 6 months is about to be tested by an American company.

In the longer term, that is 1–2 decades, it is reasonable to expect there will be blockers of existing drugs of abuse including both passive and active vaccines; receptor antagonists and transporter competitors; and reparative agents which could reverse some toxic effects of drugs on the brain, healing the intracellular changes related to addiction and craving. Gene therapy will become more likely - for example, delta fos B could be the long lasting 'molecular switch' that alters gene control after prolonged cocaine use. If so, questions might arise as to whether such brain changes can be altered without altering other necessary learning. A tantalizing question is why, in humans, is this 'molecular switch,' which is associated with compulsive use, less likely to occur when drugs are used for medicinal purposes such as treatment of pain as opposed to producing euphoria. It is also reasonable to expect more subtle agonists which will mimic some agonist effects but with minimal abuse liability and toxicity.

3. Conclusion

It does not appear unduly optimistic to expect that agents will emerge, both in the short and the long term that will markedly improve our treatment of addiction. It is important to realize, however, that no matter how good the medication; it will remain crucial that it be used in the context of appropriate psychosocial and behavioral interventions. A blocker that lasts for 6 months may have limited usefulness if the patient does not return for a second dose. Thus behavioral interventions will continue to be necessary, not just to increase the likelihood that these patients will take effective medications but also to assist them in improving their interpersonal, educational, and vocational skills so as to develop positive rather than just negative reasons for wanting to stop drug use. Such use, after all, can produce very desirable mood changes that are especially attractive in the absence of competing reinforcers.