

Pharmacological aspects

Therapeutic options and challenges for substances of abuse

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Addiction to substances continues to be a significant public health concern in the United States. The following review of current pharmacological treatments discusses a range of substances: nicotine, alcohol, cocaine, and opioids. The goal is to provide an overview of currently available and new pharmacological treatments for substance use disorders, while also addressing the pharmacotherapeutic challenges remaining. The significant advances in pharmacotherapy have had limited utilization, however. For example, naltrexone for alcoholism is infrequently prescribed, buprenorphine for opiates still has relatively few qualified prescribers, and stimulants have no Food and Drug Administration-approved pharmacotherapy. These pharmacotherapies are needed, with the rate of even the relatively uncommon abuse of opiates now rising sharply.

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The following review of current pharmacological treatments for nicotine, alcohol, cocaine, and opioid dependence addresses pharmacotherapies aimed at two stages of treatment: (i) acute withdrawal or the initial attainment of abstinence and (ii) chronic maintenance or prevention of relapse. Maintenance pharmacotherapies act as either blocking or substitution agents to attenuate protracted withdrawal symptoms. Detoxification is required prior to administration of a blocking agent, in order to prevent withdrawal from an abused agent. For example, naltrexone, a competitive opioid antagonist, completely blocks the subjective euphoria and production of physiological dependence of heroin use. Substitution agents will not precipitate withdrawal when given to drug-dependent patients, and instead act to reduce withdrawal symptoms and the desire for more drugs. Substitution agents may also produce cross-tolerance to other drugs from the same pharmacological class. Methadone is one example of an agent that is effective in reducing illicit opioid use by producing cross-tolerance to heroin. The need for these pharmacotherapies is highlighted by the sharp increase in the rate of even the relatively uncommon abuse of opiates; 12.4% of young adults abused prescription pain relievers in the past year.^{1,2}

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Nicotine

In 2005 approximately 20.9% of US adults were cigarette smokers.¹ New medications and counseling have helped many smokers quit, but the majority of those who try to quit are still unsuccessful.³⁻⁵ Pharmacotherapies range from nicotine replacement therapy to antidepressants for the relief of acute withdrawal symptoms and relapse prevention.

Nicotine replacement therapies

Nicotine replacement therapies (NRT) are designed to replace nicotine obtained through smoking in order to attenuate tobacco withdrawal symptoms and improve smoking cessation outcomes. There are currently five Food and Drug Administration (FDA)-approved NRT products, which include: the transdermal patch, gum, lozenge, inhaler, and nasal spray. These products are available over-the-counter or by prescription. They can be given alone or taken in conjunction with antidepressants like bupropion in order to alleviate acute withdrawal symptoms and sustain abstinence. A small dose of nicotine in these products allows the patient to reduce nicotine withdrawal symptoms after the patient has stopped smoking. Patients are often counseled to quit, provided options for treatment, and helped to establish a quit date. On the quit date the NRT is started and other forms of tobacco use are stopped.⁶ Choice of specific NRT typically depends on the patient's preference, the side-effect profile, and the route of administration.⁷

The nicotine transdermal patch is available in 16- or 24-hour delivery systems. Recommended duration of use is 6 to 12 weeks, with a tapering of the patch dose over that period. Patients usually start with a high-dose patch (21 or 22 mg); however, an intermediate-dose patch (11 or 14 mg) is available for those who smoke fewer than 15 cigarettes per day.⁵ Though patients usually develop tolerance to common side effects, they may experience insomnia, nausea, and vivid dreams. Skin irritation can also occur, and is usually alleviated with rotation of the patch placement site.⁸⁻¹¹ The nicotine patch can also be utilized in combination with other NRT, such as the gum, which increases its efficacy in treatment-resistant cases.¹²

Nicotine polacrilex gum and lozenges are available over-the-counter as aids in smoking cessation in 2 and 4 mg doses of nicotine. The 4-mg dose is recommended for heavy smokers (>25 cigarettes per day).^{8,13,14} The recom-

mended dosage of nicotine gum is to use one piece every 1 to 2 hours.⁶ The nicotine lozenge should be sucked on rather than chewed. The lozenge delivers about 25% more nicotine than the gum, since some nicotine is retained in the gum and the lozenge is dissolved completely.¹⁵ The dose can be tapered over 6 to 12 weeks by either decreasing the gum or lozenge dose from 4 mg to 2 mg or by increasing the time between doses,⁶ with peak concentrations of nicotine absorbed through the buccal mucosa achieved in 15 to 30 minutes.^{16,17} Nicotine absorption can be blunted with use of acidic beverages; therefore, coffee, juices, and soda should be avoided immediately before or during NRT use.¹⁸ Side effects of the gum may include jaw soreness or difficulty chewing.^{13,19} The lozenge offers an alternative to gum but also may elicit side effects such as nausea, heartburn, and mild throat or mouth irritation.^{13,19}

The nicotine inhaler and nicotine nasal spray are available by prescription only and provide faster delivery of nicotine than gum or lozenge; 4 to 15 minutes for nasal spray, 15 minutes for the inhaler.²⁰ The spray is administered to each nostril every 1 to 2 hours with a range of 8 to 40 doses per day.²¹ The usual recommended dose is 1 mg per administration over 8 weeks. Gradual taper is recommended between weeks 9 and 14.²¹ Side effects of the nasal spray may include nasal and throat irritation, sneezing, coughing, and watery eyes.²²⁻²⁴ The nicotine inhaler administers nicotine via cartridges placed in cigarette-like plastic rods which produce a nicotine vapor (0.013 mg/puff) when inhaled.^{25,26} The nicotine is absorbed through the buccal mucosa and following inhalation. The recommended dose is 6 to 16 cartridges daily, with use for approximately 12 weeks.⁶ Each cartridge contains 10 mg of nicotine and delivers a maximum of 4 mg of nicotine, and provides approximately 20 minutes of active puffing. Peak plasma nicotine concentrations are typically achieved within 15 minutes.²⁰ Throat irritation or coughing can occur in up to 50% of inhaler users.^{26,27} Because of the rapid delivery of the spray and inhaler, there is some potential for abuse liability after quitting smoking, leading to continued use >6 months.²⁸⁻³¹

Patients who utilize nicotine replacement therapy improve their likelihood of quitting by 1.5 to 2 times.^{6,32} Long-term efficacy of NRT on smoking cessation may actually be modest, however (5% to 10% above placebo).³³ Most trials assess the effect of smoking reduction at 1 year or less, and the effect is attenuated by about 12% after 12 months due to relapse occurring after the first year.³³

Antidepressants

The observed relationship between nicotine dependence and mood disorders such as depression supports the use of antidepressant medications as effective pharmacotherapies for cigarette smoking cessation.³⁴ Sustained-release bupropion, an atypical antidepressant agent, has been the most commonly used medication for the pharmacotherapy of smoking cessation, improving quit rates in short- and long-term follow-up. Bupropion blockade of norepinephrine and dopamine uptake may attenuate nicotine withdrawal symptoms. In addition, bupropion also blocks the nicotinic acetylcholine receptor, thus offering a potential reduction in the reinforcing effects of nicotine.^{35,36} Patients start treatment at the recommended 150 mg/day 7 days prior to their target quit date, since steady-state plasma levels are achieved within 1 week of initiation. Dosing is then increased to 300 mg/day after 3 to 4 days.⁶ Bupropion can also be used in combination with NRT. Two large, multicenter clinical trials demonstrated the efficacy of bupropion for the treatment of nicotine dependence, and it is recommended as a first-line treatment for smoking cessation.²¹ Bupropion alone (30%), or in combination with the nicotine patch (35%), was demonstrated to be significantly more effective at 1-year follow-up than the nicotine patch alone (16%) or placebo (16%).³⁷ For patients with a history of depression, the bupropion dose is equivalent, allowing for the pharmacological treatment of both disorders simultaneously.⁶ Side effects of bupropion primarily consist of gastrointestinal symptoms, rash, headache, insomnia, and dry mouth.³⁸ As with other antidepressants, bupropion lowers seizure threshold, so it should not be used in patients with a history of seizure disorders.⁶ Second-line pharmacotherapies for smoking cessation include nortriptyline, clonidine, selegiline and, most recently, varenicline. Nortriptyline, like bupropion, is an antidepressant that shows promising effects for smoking cessation.^{39,40} It may also be useful in the treatment of depressed cigarette smokers; however, its efficacy does not appear to depend on comorbidity with a depressive disorder.⁶ Though shown to be efficacious, nortriptyline has significant side effects which limit its safety (eg, risk of toxicity in overdose amounts).⁶ Clonidine, an antihypertensive agent, is an α -2-adrenergic receptor agonist that decreases central sympathetic activity. It may be an effective treatment option for those who have failed other smoking cessation methods. Side effects from its

clinical use include sedation, dizziness, dry mouth, constipation, and orthostatic hypotension.⁴¹⁻⁴³ Other agents (eg selegiline and mecamylamine) have also been studied, but their efficacy for smoking cessation has not yet been established. For example selegiline, a monoamine oxidase-B (MAO-B) inhibitor for the treatment of Parkinson's disease may also be useful in reducing nicotine craving by decreasing dopamine metabolism.⁴⁴⁻⁴⁵

Partial agonist

Varenicline, an α 4 β 2 nicotinic acetylcholine receptor partial agonist, is an efficacious treatment for smoking cessation. Clinical trials indicate that this partial agonist can reduce craving and withdrawal symptoms following cessation or reduction of nicotine consumption. In addition its partial antagonism can also reduce smoking satisfaction through the occupation of the receptors and blocking the full agonist nicotine from binding.⁴⁶ Varenicline, administered 1 mg twice daily, has demonstrated superiority to placebo and bupropion.^{46,47} It is generally safe and well tolerated. Nausea and insomnia are commonly reported adverse reactions to varenicline.^{46,47}

Nicotine vaccine

Currently, three nicotine vaccines have completed phase I-II clinical trials; NicVAX, CYT002-NicOb, and TA-NIC. In a phase II clinical trial, 68 smokers were randomized to receive one of 3 doses of a nicotine conjugate vaccine, NicVax (50, 100, or 200 μ g) or placebo. The vaccine was shown to be safe and well tolerated. In addition, vaccine immunogenicity was dose-related ($P < 0.001$) with the highest rate of 30-day abstinence occurring with 200 μ g ($P < 0.02$).⁴⁸ The NicQb vaccine was also shown to elicit significant quantities of antinicotinic antibodies,⁴⁹ and a similar observation was made that subjects in the upper third of antibody responses had almost two times the quit rate of placebo (57% vs 31%). Subjects in the TA-NIC vaccine trial were immunized with 4 doses over the first 8 weeks and then given a booster dose at 32 weeks. All subjects were encouraged to quit smoking after 12 weeks of the trial, and at 12 months, the quit rate in the highest-dose group significantly exceeded the control group (38% vs 8%).⁵⁰ Based on these studies suggesting that high antibody titers correlate with smoking cessation, evaluation of nicotine conjugate vaccines are progressing and a phase IIb/III trial was recently announced for NicQb.⁵¹

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Alcohol

Alcohol dependence is a major cause of morbidity and mortality in the United States and throughout the world. Acute withdrawal from alcohol is a serious medical condition which can precipitate adrenergic activation, seizures, or delirium tremens, the last condition leading to 15% mortality when untreated.⁵² Many medications have been evaluated for the treatment of alcohol dependence in recent years, including those that interact with dopaminergic, serotonergic, opioid, glutamate, and γ -aminobutyric acid (GABA) systems.

Acute withdrawal

Benzodiazepine use is the standard approach to treating withdrawal symptoms such as irritability, autonomic hyperactivity, and seizures associated with alcohol detoxification. Benzodiazepines act at GABA-A receptors to stimulate GABA release and gradually detoxify the patient from alcohol, thus avoiding associated withdrawal symptoms.⁵³ The current standard approach to alcohol detoxification uses tapering dosages of benzodiazepines such as chlordiazepoxide, clonazepam, diazepam, oxazepam, or lorazepam.^{54,55}

Anticonvulsants, including carbamazepine and valproate, have also been studied for their efficacy in alcohol withdrawal treatment.⁶ Carbamazepine has been widely used in alcohol withdrawal. Carbamazepine has demonstrated its superiority to placebo in the speed of onset to relieve alcohol withdrawal symptoms such as tremor, sweating, palpitations, sleep disturbances, depression, anxiety, and anorexia.⁵⁶ Furthermore, studies have also demonstrated that higher success rates and reduction in withdrawal symptoms in patients treated with carbamazepine than with benzodiazepines.⁵⁷⁻⁵⁹

Relapse prevention and maintenance

Disulfiram, acamprosate, oral naltrexone, and extended-release injectable naltrexone have FDA approval for the treatment of alcohol dependence.

Disulfiram is the first agent to be approved for treatment of alcohol dependence and has been used for over 40 years. It acts as an alcohol-sensitizing agent, creating an aversion to alcohol. Disulfiram is an irreversible inhibitor of the enzymatic conversion of acetaldehyde to acetic acid. Accumulation of acetaldehyde results in the disul-

firm-alcohol reaction: hypotension, flushing, nausea, and vomiting.^{60,61} Patients must be motivated to remain abstinent and comply with prescribed dosing; usual dosage is 250 mg/day. However, some patients may receive optimal benefit from 125 to 500 mg/day.⁶ Additional unpleasant symptoms such as chest pain, seizures, hepatotoxicity, renal failure, and even death have been reported in severe cases.⁶² Controlled trials of disulfiram versus placebo have not demonstrated significant improvement over placebo,^{63,64} and meta-analyses have only shown slight improvement in drinking.⁶⁵ A large Veterans Cooperative Study with over 600 subjects found, however, that disulfiram may be effective in patients with no major comorbid psychiatric disorder and who were motivated for abstinence.⁶⁴ More recently, an evaluation of subjects with current depression on disulfiram reported lower craving over time than subjects with depression on naltrexone.⁶⁶ The utility of combining disulfiram with other therapeutic interventions has also been examined. In a trial of disulfiram and acamprosate, the number of abstinent days was greater when utilizing a combination of disulfiram and acamprosate than using either medication alone.⁶⁷

Naltrexone acts as an antagonist at the opioid receptors, which are known to mediate the rewarding effects of alcohol and thus thought to reduce desire or craving of alcohol. Studies have found that naltrexone is more effective than placebo in promoting abstinence, reducing heavy drinking days and decreasing relapse rates,⁶⁸⁻⁷⁰ particularly when it is combined with cognitive behavioral therapy.⁷¹⁻⁷³ Naltrexone has also shown greater efficacy when compared with acamprosate. In a randomized controlled trial comparing the efficacy of acamprosate and naltrexone in the treatment of alcohol dependence, significant increases in time to first relapse was seen in those receiving naltrexone in subjects with no depression and low dependency.⁷⁴ Furthermore, combined pharmacotherapy studies have also demonstrated that naltrexone administered with behavioral therapy can significantly reduce the risk of heavy drinking.⁷⁵ Naltrexone is prescribed as 50 mg oral administration, most commonly for 12 weeks, and can also be given as a long-acting depot formulation every 4 weeks. Acamprosate attenuates alcohol desire or craving by normalizing the dysregulation of N-methyl-D-aspartate (NMDA)-mediated glutaminergic excitation that occurs in alcohol withdrawal and early abstinence. Acamprosate, when given at 2 g administered three times daily, has increased abstinence by 50% in over 3000 patients across a dozen clinical trials.⁷⁶⁻⁷⁸ Side effects such as diarrhea are

generally well tolerated. A placebo-controlled trial enrolled 272 patients and treated patients for 48 weeks. Compared with placebo, acamprosate-treated alcohol-dependent patients had twice the rate of sustained abstinence at 48 weeks (43% vs 21%), and this difference from placebo was sustained at 96 weeks after starting the medication (37% vs 17%).⁷⁸ Thus, this appears to be a very effective approach to treating patients in order to maintain alcohol abstinence after detoxification.

Topiramate, an anticonvulsant medication, has been shown to improve the drinking outcomes of alcohol-dependent individuals vs placebo, but only in a single study thus far, by Johnson et al.⁷⁹ In this topiramate study the patients were actively drinking when started on medication, rather than being first detoxified from alcohol and being abstinent. The outcome was remarkable, with an increase from no days abstinent at baseline to 44% of days abstinent by week 12, compared with 18% of days abstinent for the placebo group. In cases of dual dependency on opiates and alcohol, topiramate may be useful at a low dose in buprenorphine or methadone maintained, alcohol-abusing patients who do not need medical detoxification for alcohol.

Serotonergic agents, including buspirone (a serotonin [5HT]-1A agonist),⁸⁰ selective serotonin uptake inhibitors (SSRIs), and the 5-HT₃ antagonist ondansetron⁸¹ have been studied more extensively as treatments for alcohol dependence. Fluoxetine or citalopram, two SSRIs, have been effective in reducing alcohol consumption in some studies, though results have been inconsistent.⁸²⁻⁸⁹ Results may be inconsistent due to heterogeneity in study populations. For example, Kranzler et al suggested that SSRIs may be more effective in heavy drinkers or those with a family history of alcoholism, as well as those with a comorbid major depressive disorder.

Cocaine

Cocaine addiction affected approximately 2.4 million people in the United States in 2005.² Behavioral interventions are helpful in treating cocaine addiction, but currently there are no approved medications to treat this disorder despite over 60 medications having been investigated.

Dopaminergic agents

Directly acting dopaminergic agents such as bromocriptine and pergolide have had limited efficacy, but indirect

mechanisms for increasing dopamine seem to be a promising approach.^{90,91} Disulfiram indirectly increases dopamine by inhibiting dopamine- β -hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine. In outpatient clinical trials, disulfiram (250 mg/day) has been successful in reducing cocaine use with few associated adverse events,^{92,93} with sustained results in reduction of cocaine and alcohol use at 1-year follow-up. Findings have been replicated.⁹² Disulfiram may be an effective medication for reduction in cocaine use; however, it may not be suitable for treatment in all populations.^{92,94,95} Nich et al reported that men responded to disulfiram in reduction of cocaine use, whereas women did not.⁹⁶ Further studies are needed to determine the optimum dose and duration of treatment with this agent, as well as to assess the efficacy of disulfiram related to gender and comorbid conditions such as alcohol use or opioid dependence.

Selegiline, a monoamine oxidase (MAO)-B inhibitor, blocks the catabolic enzyme that breaks down dopamine resulting in greater synaptic levels of dopamine. This medication also exhibits amphetamine-like effects and can enhance dopamine release and block dopamine reuptake.⁹⁷ A laboratory study of cocaine users showed that short-term treatment with selegiline did not alter physiological or subjective effects of cocaine.⁹⁸ In another study however, cerebral metabolic effects of cocaine and attenuated the cocaine "high" were altered by selegiline.⁹⁹

Antidepressants

Antidepressants are another class of medications also used to treat cocaine dependence. Chronic stimulant use causes presynaptic upregulation, and antidepressants are thought to contribute the opposite effect by downregulating synaptic catecholamine receptors.¹⁰⁰ Although antidepressants have a relatively benign side-effect profile, good patient compliance rates, and lack of abuse liability, only desipramine, a tricyclic antidepressant, has shown some efficacy in selected populations of cocaine abusers.^{6,100} Though a meta-analysis of placebo-controlled studies showed that desipramine produced greater cocaine abstinence than placebo,¹⁰¹ other studies failed to report positive findings with desipramine.^{6,102} Secondary analyses of studies with imipramine, desipramine, and bupropion have suggested that depressed cocaine abusers are more likely to show significant reductions in cocaine abuse than nondepressed cocaine abusers.¹⁰³⁻¹⁰⁵

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Furthermore, additional work with desipramine has suggested its efficacy in opioid-dependent patients, particularly in combination with contingency management therapies.^{106,107} Early studies suggested some efficacy for fluoxetine and bupropion, but this has not been confirmed in controlled trials.^{6,108}

GABA agonists

GABA agonists show promise in treatment for cocaine, following initial studies. Baclofen, for example has shown greater reduction in cocaine use compared with placebo and may be more efficacious among individuals with greater cocaine use.¹⁰⁹

Tiagabine, a GABA reuptake inhibitor, has also reduced the reinforcing effects of cocaine by attenuating cocaine-induced dopamine release. In a clinical trial investigating the efficacy of tiagabine for cocaine use in opioid-dependent patients maintained on methadone, tiagabine dose-dependently attenuated cocaine use as measured with self-reports and urine drug screening.^{110,111} In a 10-week double-blind, placebo controlled trial of treatment seeking, cocaine-dependent, methadone-treated subjects, clinical efficacy of gabapentin was compared with tiagabine for reduction of cocaine use. Tiagabine significantly reduced cocaine-taking behavior compared with placebo or gabapentin-treated subjects.¹¹¹

Topiramate, another GABA-enhancing medication with a primary therapeutic indication for epilepsy, has yielded promising results for cocaine dependence as well. In a 14-week, double-blind, placebo-controlled outpatient study, subjects assigned to topiramate had more negative urine cocaine results than placebo.¹¹² Results suggest potential efficacy for GABAergic treatments for cocaine dependence, but outcomes must be replicated in additional, larger clinical trials.

Most recently, vigabatrin has shown efficacy in clinical studies for cocaine abusers, and placebo-controlled multisite studies are under way examining it for cocaine dependence.¹¹³

Other treatment agents and approaches

In addition to the dopaminergic agents and antidepressants, a number of miscellaneous agents, including amantadine, carbamazepine, and buprenorphine, have been examined for cocaine pharmacotherapy. Carbamazepine failed to show therapeutic effects in three controlled

studies after an initial enthusiasm.^{85,114,115} Buprenorphine also has had more negative than positive findings supporting its efficacy in treating cocaine-abusing opiate addicts.¹¹⁶⁻¹¹⁹ Studies of another agent, amantadine, have reported mixed results.¹²⁰⁻¹²³ In a trial of cocaine-dependent men treated for 10 days with amantadine 100 mg twice daily, urine toxicology screens were more likely to be free of cocaine among men taking amantadine at the 2-week and 1-month follow-up visits.¹²⁰ Amantadine 100 mg administered three times daily, however, was no more effective than placebo in reducing cocaine use.¹²² Amantadine also effectively reduced cocaine use among subjects with severe cocaine withdrawal symptoms at the start of treatment.¹²³ Though results of clinical trials do not appear to support amantadine as a treatment for cocaine dependence, further controlled studies are needed to determine if amantadine is efficacious in cocaine users with high withdrawal severity.

Modafinil, a medication used to treat narcolepsy, is a generally well-tolerated with low abuse potential, therefore it is frequently used for off-label indications such as attention deficit hyperactivity disorder (ADHD), depression, and cocaine dependence and withdrawal.^{124,125} The mechanism of action blunts cocaine euphoria under controlled conditions, acting as a glutamate-enhancing agent.^{124,126} Reduction in impulse responding has been seen among healthy volunteers as well as in patients with ADHD.^{127,128} In the first double-blind, placebo-controlled trial in 62 cocaine-dependent patients, modafinil reduced cocaine use to a greater extent than placebo. Modafinil patients provided significantly more cocaine-free urine samples compared with placebos, and were more likely to achieve a protracted period of cocaine abstinence.¹²⁶

Cocaine vaccine

Studies evaluating the efficacy of vaccination in cocaine addicts have shown reduction in some cocaine effects. A cocaine vaccine evaluated in clinical trials has used cholera toxin B subunit as a carrier protein linked to norcocaine at the methyl ester group as an immunogen.¹²⁹ In phase I and early phase II trials of immunogenicity, safety, and efficacy, no serious adverse effects had been found and the vaccine showed a reduction in cocaine effects during human laboratory cocaine administration studies and cocaine use in outpatient studies.¹²⁹⁻¹³² In a Phase I safety and immunogenicity trial, the vaccine induced cocaine-specific IgG cocaine antibodies, both

time- and dose-dependently. The vaccine was tolerated with no serious adverse effects during 12 months of follow-up.¹²⁹ In a Phase IIa, 14-week trial of 18 cocaine-dependent subjects in early recovery, conjugated cocaine vaccine was well tolerated at two dose levels (400 µg and 2000 µg). Cocaine-specific antibodies persisted for at least 6 months.¹³⁰ Furthermore, subjects who received the higher dose of vaccine had significantly higher mean antibody titer response and were more likely to maintain cocaine-free urines than the lower-dose group.¹³¹ Results demonstrated that a cocaine-specific vaccine can elicit a sufficient immunologic response that reduces cocaine usage and attenuates the self-reported psychological effects of cocaine during use. Since it is possible to override the effects by the vaccine by increasing the amount of cocaine usage, the vaccine is primarily for use in cocaine users who are motivated to quit.

Opiates

Chronic illicit opiate use affects over 900 000 people in the US and an estimated 13 million people abused opiate drugs worldwide in 1999-2001, according to the World Health Organization.¹³³ More recently, prescription opiate abuse has become widespread with an estimated 4 million additional opiate abusers.² Opiate dependence is a chronic and relapsing medical disorder with a well-documented neurobiological basis, and that necessitates the use of long-term pharmacologic and behavioral intervention. Following acute withdrawal, individuals can be maintained on methadone, buprenorphine, or naltrexone. Although these highly effective pharmacotherapies for opioid dependence are available, only about 20% of illicit opioid users are enrolled in treatment programs.¹³⁴ Until recently, licensed opiate treatment facilities were the only providers of opioid maintenance therapy using methadone. Recent legislation changes and availability of sublingual Suboxone (buprenorphine plus naloxone) now enable general practitioners to offer opiate agonist treatment to as many as 100 patients through their offices.¹³⁵

Opioid agonists

Methadone is a µ-opioid agonist that directly stimulates the opiate receptor and acts as a replacement to the abused drug. Through development of cross-tolerance at doses of 100 mg or more per day, methadone blocks heroin effects as well as other opioids.¹³⁶ Morphine-like

effects evident in humans and include euphoria, drowsiness, analgesia, and nausea. Since its introduction in the 1960s it has been the gold standard for opioid maintenance treatment.¹³⁷ Initial clinical trials testing methadone for efficacy in the treatment of opioid dependence have found it to be safe and effective,¹³⁸⁻¹⁴⁰ particularly if combined with monitoring and behavioral interventions. Daily doses administered in methadone maintenance programs range from 30 to 100 mg, typically starting at lower levels (15 to 20 mg/day) with subsequent daily increases based on the patient tolerance.¹⁴⁰ Outpatient studies examining higher versus lower doses of methadone indicate greater reduction in opioid use with higher doses of methadone.^{141,142} Furthermore, doses over 100 mg/day may be indicated in patients with persistent heroin abuse or with comorbid conditions such as HIV infection, since some concomitant medications for AIDS increase metabolism of methadone.^{143,144} Tapering doses of methadone can be used in ambulatory detoxification, but the protracted withdrawal syndrome associated with methadone cessation contributes to a high rate of recidivism to opiate abuse.^{145,146} Methadone is therefore most often used in maintenance therapy and not for acute withdrawal or detoxification.

Partial agonists act like agonists, but do not stimulate the receptor to the same degree. In combining both a blocking and substitution approach, buprenorphine, a partial agonist at the µ-opioid receptor, suppresses withdrawal symptoms and produces some subjective reinforcing properties at low doses. Initial clinical trials of buprenorphine demonstrated efficacy in the outpatient setting. At 8 mg, the sublingual buprenorphine (in liquid formulation) treatment group demonstrated better study retention and decreased opiate use than active placebo or 1mg buprenorphine.^{147,148} At higher doses buprenorphine acts as an antagonist, and blocks the reinforcing properties of the agonist, resulting in lowered risk of abuse liability and potential for abuse of the drug.¹⁴⁹ Buprenorphine is available alone or in a 4:1 combination sublingual tablet with naloxone (Suboxone).¹⁵⁰ A multicenter, randomized, placebo-controlled clinical trial comparing buprenorphine tablet, Suboxone tablet, and placebo in opiate-dependent patients found that both buprenorphine alone and Suboxone reduced opiate use in the first month of the study compared with placebo.¹⁵¹ Suboxone also appears to decrease the potential for abuse or diversion compared with methadone.¹⁵² Injection of Suboxone could also precipitate opioid withdrawal.

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Drug	Medication	Dose	Mechanism of action	Special considerations	References
Nicotine	Transdermal patch*	11-22 mg 16- or 24-h delivery 6- to 12-week duration w/ taper	Nicotine replacement therapy (NRT)	Available over-the-counter (OTC)	5,8-12
	Polacrilex gum*	2 or 4 mg 1 pc/1-2 h 6- to 12-week duration w/ taper	NRT	OTC Avoid acidic beverages	6,8,14
	Lozenge*	2 or 4 mg 6 to 12 week duration w/ taper	NRT	OTC Do not chew, avoid acidic beverages	6,8,13
	Inhaler*	1 mg/admin Each nostril Q 1-2 h 8-40 doses/day 8 weeks w/ taper wks 9-14	NRT	Rapid delivery of nicotine, therefore some potential for abuse liability	20,21
	Nasal spray*	0.013 mg nicotine/ puff 10 mg nicotine/ cartridge for 20 min of puffing 6-16 cartridges/day 12 weeks	NRT	Rapid delivery of nicotine, therefore some potential for abuse liability	25,26
	Bupropion*	150 mg/day (7 d prior to quit date) 300 mg/day after 3-4 days	Antidepressant	2nd line: recommended to start prior to quit date; can be used in conjunction with NRT	21,37
	Nortryptylene	25 mg TID-QID	Antidepressant	2nd line; toxicity in overdose amounts	39,40
	Clonidine	0.1-0.3 mg/24-h ES patch 0.1-1.3 mg tablet	Antihypertensive	2nd line	41-43
	Selegiline	5 mg BID cap 6-12 mg/24-h patch	Antihypertensive; MAO-B inhibitor	2nd line	44-45
	Varenicline*	Titrate: 0.5 mg daily to 1 mg BID	Partial agonist		46
	NicVAX	**	Nicotine vaccine	Phase II clinical trials	48
	CYT002-NicOb	**	Nicotine vaccine	Phase IIb/III trial planned	49,51
	TA-NIC	**	Nicotine vaccine	Phase II	50
Alcohol	Chlordiazepoxide*	50-100 mg IM/IV (may repeat in 2-4 h)	Benzodiazepine	Acute withdrawal	54-55
	Clonazepam*	0.25 mg bid (max 4 mg/day)	Benzodiazepine	Acute withdrawal	54-55
	Diazepam*	10 mg IM/IV, then 5-10 mg in 3-4 h prn	Benzodiazepine	Acute withdrawal	54-55
	Oxazepam*	15-30 mg TID-QID	Benzodiazepine	Acute withdrawal	54-55
	Lorazepam*	0.05 mg/kg IM 2 mg or 0.044 mg/kg IV2-3 mg BID tab	Benzodiazepine	Acute withdrawal	54-55

Table I. Pharmacotherapeutic options for substances of abuse.

Drug	Medication	Dose	Mechanism of action	Special considerations	References
	Carbamazepine	200 mg BID (Max 1200 mg/day)	Anticonvulsant; antiepileptic	Acute withdrawal, widely used	56-59
	Valproate	15 mg/kg/day (Max. 60 mg/kg/day)	Anticonvulsant	Acute withdrawal	6
	Disulfiram*	250 mg/day (125 to 500 mg/day)	Alcohol-sensitizing agent - inhibits enzymatic conversion of acetylaldehyde to acetic acid	Relapse prevention and maintenance; subject should be motivated to quit	60,61
	Naltrexone*	50 mg oral admin 12 weeks Extended release Q 4 wks	Opioid receptor antagonist	Relapse prevention and maintenance; mediates rewarding effects of alcohol	68-70
	Acamprosate*	2 g/3 x day (usual dose: 666 mg TID)	Normalizes the dysregulation of NMDA-mediated glutamnergic excitation	Relapse prevention and maintenance	76,77
	Topiramate	25 mg BID (titrate weekly to 400 mg/day)	Antiepileptic; GABA agonist	Relapse prevention and maintenance	78
	Buspirone	7.5 mg BID (titrate to 20-30 mg/day)	Serotonin (5-HT)-1A agonist	Relapse prevention and maintenance	80
	Fluoxetine	6-25 mg/day 90 mg/week	Selective serotonin uptake inhibitor (SSRI)	Relapse prevention and maintenance	82,85,87
	Citalopram	20 – 40 mg/day	SSRI	Relapse prevention and maintenance	83,84,86,88
	Ondansetron	2 mg/mL, 32 mg/50 mL injection 4 mg/5 mL solution 4 – 24 mg tab	5-HT ₃ antagonist; prevention of nausea/vomiting	Relapse prevention and maintenance	81
Cocaine	Disulfiram (Antabuse)	250 mg/day	Nonspecific enzyme inhibitor including aldehyde dehydrogenase and dopamine beta hydroxylase	Good efficacy data in nonalcoholics, relatively contraindicated in alcohol dependence with cocaine	92,93
	Selegiline	5 mg BID cap 6-12 mg/24 h patch	Antihypertensive; MAO-B inhibitor		97-99
	Desipramine	100-200 mg/day (max 300 mg/day)	Antidepressant		6,100,101
	Baclofen	40-80 mg/day	GABA agonist	Additive CNS effects w/ alcohol	109
	Tiagabine	4 mg/day (may increase to max 56 mg/day)	Anti-seizure; GABA agonist	Additive CNS depression w/ alcohol	110,111
	Topiramate	25 mg bid (titrate weekly to 400 mg/day)	Antiepileptic/antiseizure; GABA agonist	Potentiates CNS depression w/ alcohol; withdraw gradually	112
	Vigabatrin	**	GABA agonist		113
	Carbamazepine	200 mg BID (Max 1200 mg/day)	Anticonvulsant; Antiepileptic	Inconsistent results from clinical trials	114,115
	Buprenorphine	8 mg sublingual (liquid) 1 mg tablet 4:1 combination sublingual tablet w/ naloxone (Suboxone)	Partial agonist at mu-opioid receptor	Inconsistent results from clinical trials; low abuse potential	116,119

Table I. continued

Pharmacological aspects

Opioid antagonists

Naltrexone is an opioid antagonist that binds to receptors, but instead of activating the receptors, it blocks them, effectively removing the opiate user's ability to get high.^{153,154} Human laboratory studies of naltrexone have demonstrated the efficacy of naltrexone in blocking the effects of acute opioid use in human volunteers who have been withdrawn from opioids.^{154,155} In clinical trials, high attrition rates and unblinding by study patients who guess their treatment regimen have limited the utility of naltrexone maintenance treatment trials,^{156,157} though a subgroup analysis in a large controlled trial indicated potential efficacy in highly motivated patients and in those already in drug-free counseling.¹⁵⁷ Naltrexone has relatively few side effects, but liver function should be monitored as per labeling guidelines. Its depot formulation is particularly useful to address its main problem of poor adherence to the daily oral therapy, but the relative expense of depot compared with oral naltrexone can be a deterrent to potential widespread utilization. Patients must also be opiate free for 7 to 10 days prior to initiation in order to prevent severe withdrawal reactions. If naltrexone is intended for use as treatment of acute with-

drawal symptoms, use of clonidine in combination with naltrexone reduces the severity of acute opioid withdrawal during detoxification.

Behavioral therapy

Behavioral therapies constitute an extremely important component of substance abuse treatment by helping to retain patients in treatment and improvement in abstinence.¹⁵⁸ These therapies form the platform for any pharmacotherapy in order to engage the patient and facilitate more long-term changes including prevention of relapse.^{159,160} Contingency management (CM) deserves special mention because it has been successful to initiate abstinence and prevent relapse with many drugs of abuse, particularly for managing cocaine- and amphetamine-abusing individuals,¹⁶¹⁻¹⁶⁵ regardless of psychiatric severity.¹⁶⁶ Improvement in study retention, as well as associated abstinence outcomes in substance abusers, has been found in randomized clinical trials of cocaine users^{163,166} and in cocaine and methadone-maintained cocaine abusers.¹⁶³ CM has also been successful in studies of alcohol-abusing subjects, as well as those with polysubstance dependence or abuse.^{71,72,75,167} Community-based

Drug	Medication	Dose	Mechanism of action	Special considerations	References
	Amantadine	200 mg/day	Dopamine & NMDA agonist	Inconsistent results from clinical trials; potential use in severe withdrawal	120-123
	Modafinil	200 mg/day	Wakefulness-promoting agent	Low abuse potential; often used for many off-label indications	124,125
	TA-CD	**	Cocaine vaccine	Phase II trials; must be motivated to quit	129-131
Opiates	Methadone*	30 – 100 mg/daily (initial doses 15 to 20 mg/day) >100 mg/day in persistent heroin abuse or comorbid conditions	mu-opioid agonist	Gold standard for opioid maintenance treatment	136-144
	Buprenorphine*	8 mg sublingual (liquid) 1 mg tablet 4:1 combination sublingual tablet w/ naloxone (Suboxone)	Partial agonist at mu-opioid receptor & kappa antagonist	Injection of suboxone could precipitate opiate withdrawal	147-152
	Naltrexone	50 mg oral admin* Depot: extended release	Nonspecific opioid antagonist	Few side effects but monitor liver function; must be opiate free for 7 to 10 days prior to initiation	154-157

Table I. continued

efforts using CM have also been successful in improving retention and associated abstinence outcomes.¹⁶⁵ There is however, a significantly higher cost associated with the incentives group versus usual care group,¹⁶⁸ and therefore the utility of CM in real-world settings should be further evaluated based on cost-effectiveness.

Cognitive behavior therapy (CBT) is also an efficacious intervention for the treatment of substance abuse. In a pilot study CBT was examined in conjunction with pharmacotherapy to evaluate length of treatment, drug-free urinalyses, and reduction of alcohol and cocaine craving. Though CBT-treated subjects remained in treatment longer than subjects who received both disulfiram/CBT or naltrexone/CBT, the combination treatment groups achieved significantly greater reductions in cocaine positive urinalyses.¹⁶⁹ Where CM may be useful in engaging

substance users and attaining abstinence more quickly, CBT has better long-term treatment retention and is comparable to CM in helping patients ultimately achieve abstinence.¹⁷⁰

Conclusion

Substantial progress has been made in the development of pharmacotherapeutic options for substance use disorders. *Table I* summarizes the current therapeutic options for the substances of abuse mentioned in this review. Taken alone, in combination with other medications, or in conjunction with behavioral therapies, effective treatment options are available in the areas of nicotine, alcohol, cocaine, and opioid abuse. Preliminary studies on new medications and vaccines are promising for the future. □

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Alternativas terapéuticas y desafíos frente a las sustancias de abuso

La adicción a sustancias sigue siendo un importante tema de salud pública en los Estados Unidos. La siguiente revisión acerca de los tratamientos farmacológicos actuales incluye diversas sustancias: nicotina, alcohol, cocaína y opioides. El objetivo es entregar una panorámica de los actuales tratamientos disponibles y de las nuevas terapias farmacológicas para los trastornos por el uso de sustancias, consignando además el resto de los desafíos farmacoterapéuticos. A pesar de los significativos avances en la farmacoterapia, ésta ha tenido una utilización limitada. Por ejemplo, la naltrexona se prescribe infrecuentemente para el alcoholismo, la buprenorfina para los opioides todavía tiene relativamente pocos prescriptores calificados, y los estimulantes no tienen una farmacoterapia aprobada por la Food and Drug Administration. Estas farmacoterapias son necesarias, considerando que el porcentaje de abuso de opiáceos que ha sido relativamente constante ahora está creciendo marcadamente.

Défis et choix thérapeutiques en cas de dépendance à une substance

La dépendance à une substance reste encore un problème de santé publique préoccupant aux États-Unis. Cet article sur les traitements pharmacologiques actuels passe en revue une série de substances : la nicotine, l'alcool, la cocaïne et les opiacés. Il a pour but de donner une vue d'ensemble des nouveaux traitements pharmacologiques actuellement disponibles pour traiter les troubles liés à l'utilisation d'une substance, tout en abordant les autres options thérapeutiques pharmacologiques. Les progrès importants en pharmacothérapie ont cependant été peu utilisés. Ainsi, la naltrexone (pour l'alcoolisme) est rarement prescrite, la buprénorphine (pour les opiacés) seulement par quelques médecins qualifiés et les stimulants n'ont pas été approuvés par la Food and Drug Administration. Ces traitements sont nécessaires, car la dépendance aux opiacés, même si elle est relativement rare, augmente maintenant nettement.

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