Curr Psychiatry Rep (2014) 16:489
DOI 10.1007/s11920-014-0489-1

SUBSTANCE USE AND RELATED DISORDERS (F LEVIN AND E DAKWAR, SECTION EDITORS)

Antagonist Models for Treating Persons With Substance use Disorders

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Published online: 3 September 2014

Abstract This paper provides an overview on the status of antagonist models for treating patients with substance use disorders. It begins with an overview describing the ambivalence about stopping or not stopping substance use and how antagonist approaches, combined with psychosocial treatment, are aimed to address it. It then goes on to review data on disulfiram and acamprosate treatment of alcohol dependence and naltrexone treatment of opioid and alcohol dependence. The superior results achieved by extended release formulations are emphasized. The mixed findings on naltrexone treatment for amphetamine dependence are presented and the chapter ends with a brief review of vaccine development for treatment of substance use disorders. Overall conclusions are that the strongest treatment effects are with extended release naltrexone with opioid dependence. Disulfiram treatment of alcohol dependence also has strong effects but is not widely used due to low levels of patient acceptance and concerns about its potential for serious adverse events. Less robust but clinically meaningful effects are seen with naltrexone or acamprosate treatment of alcohol dependence. Vaccines are a very interesting and promising new development but many challenges and hurdles must be overcome before they are ready for clinical use.

Keywords Antagonists · Treatment · Alcohol · Opioids · Amphetamines · Vaccines

This article is part of the *Topical Collection on Substance Use and Related Disorders*

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Introduction

Substance use disorders, unlike other medical problems, typically begin with voluntary exposure to one or more substances that cause relaxation, elevation of mood, temporary relief of stress and pain, or other rewarding effects. For many individuals, use is sporadic and relatively short-lived but for others, the rewarding effects are so powerful that use becomes more frequent, the ability to control it is diminished, and the user experiences one or more of the psychosocial and medical problems that are described in the Substance Use Disorders sections of DSM-IV and 5, and in many papers and reviews. At this point, the user often seeks treatment or is forced into it by relatives, friends, employers, law enforcement, or licensing boards. Inherent in this situation is ambivalence about continuing substance use due to its rewarding effects, or stopping use due to its adverse effects. This ambivalence repeatedly emerges in treatment when patients say they want to stop using one day, but go on to use the next day. Examples are patients on methadone or buprenorphine maintenance who reduce but do not stop opioid use; or when an opioid addicted patient completes a 5-7 day detoxification, agrees to receive a naltrexone implant that blocks opioid effects for 2-3 months, and then tries to remove it a week or two later.

Such ambivalence is rarely seen in other medical disorders and is a focus of constant attention by substance abuse treatment providers and self-help groups, particularly for persons whose use has become compulsive and is associated with tolerance and withdrawal. Antagonist models can be viewed as pharmacological approaches to treating this ambivalence because they diminish, block, or adversely interact with the reinforcing effects of the abused substance. In so doing, they can reduce cravings or other desires to use, and provide more time for the patient to shift the ambivalence away from substance use and toward healthy behaviors.

Psychosocial interventions such as counseling, psychotherapy, and self-help groups are recommended to be used with antagonist models because they have the potential to help the patient take advantage of the protection afforded by the antagonist and develop more healthy behaviors. The degree to which psychosocial interventions magnify the effects of antagonist treatment has not been explored but is worthy of study.

The following sections will briefly summarize current information on antagonist models for treating substance use disorders. The studies that provide this information were done using DSM-IV, DSM-IV-TR, or ICD-10 criteria thus the term "dependence" is often used in describing their results.

Antagonist Medications

Disulfiram for Alcohol use Disorders This medication was discovered in the 1920s and is an antagonist in the sense that it causes adverse effects when a person who is taking it is exposed to alcohol. It works by inhibiting the action of acetaldehyde dehydrogenase thus causing an increase in acetaldehyde, an intermediate metabolite of alcohol. The result is that the individual experiences dysphoria, flushing, tachycardia, shortness of breath, nausea, vomiting, headache, visual disturbances, confusion, and even fatal cardiovascular collapse. Danish researchers discovered these effects by accident in the late 1940s and the result was the development of Antabuse in 250 mg and 500 mg tablets that are prescribed for daily use to treat alcohol dependence. The effectiveness of disulfiram has been difficult to study due to low patient interest and high dropout rates, however one study found that supervised dosing resulted in an abstinence rate of over 50 % [1] while in another, adherence was only 20 % and there were no differences between the disulfiram and counseling groups [2]. Disulfiram implants have been developed and used in Russia to improve adherence but they have not been approved or widely used in the U.S.

Naltrexone for Opioid use Disorders Naltrexone was discovered in the 1970s and the FDA approved it for preventing relapse to opioid dependence in 1984 based on its pharmacological profile. It is a prototypical opioid antagonist because it binds tightly to μ-opioid receptors [3] and competitively blocks opioid effects for 24 hours when administered as a single daily oral dose of 50 mg; oral doses of 100–150 mg can block opioid effects for 48–72 hours [4]. In theory, it is an ideal treatment for opioid addiction but its effectiveness has been limited due to low patient interest and high dropout, probably because it produces no reinforcing effects and does not attenuate the protracted opioid abstinence syndrome that can persist for weeks after detoxification. It will precipitate withdrawal if used in the presence of opioid physiological dependence, thus patients must be detoxified before taking it. Detoxification is most successful if done on an inpatient unit over 5-7 days, but this resource is often financially or otherwise unavailable in the U.S. Interest and adherence have been much better in Russia where inpatient detoxification is widely available and agonist treatment is not allowed [5, 6], and in persons under significant legal pressure to stop opioid use [7].

While there is an extensive literature on naltrexone treatment spanning more than 35 years, work continues on how to improve adherence and identify individuals for whom it may be particularly helpful. One approach has been to combine it with family therapy and contingency management, which improved adherence somewhat [8], and contributed to positive findings from studies in Russia where patients' family members were recruited to supervise adherence [5, 6]. Another has been the development and approval of extended release formulations that block opioid effects for 30 days or longer after a single dose.

These include an implant that has been developed by Australian clinicians, can block opioids for several months, and has been widely used but is not approved by any regulatory agency [9]; an implant developed in Russia (Prodetoxon®) that blocks opioid effects for 2-3 months, was approved ("registered") in Russia in 2005, and was significantly more effective than oral naltrexone or detoxification and psychosocial treatment in a placebo controlled, randomized trial [10•]; an injectable formulation that blocked opioid effects for a month and was effective but is no longer available [11]; and extended-release injectable naltrexone (Vivitrol®) that was approved in the U.S. in 2006 for treating alcohol dependence (discussed below), and approved for preventing relapse to opioid dependence in 2010 on the basis of a placebo controlled trial that was conducted in Russia by Krupitsky et al. [12].

Criminal justice settings in the U.S. are beginning to show interest in extended release injectable naltrexone (Vivitrol®) because it is FDA approved and fits into their usual detoxification approach for opioid addicted offenders. An unpublished study that was recently completed showed that it improved outcomes of opioid addicted offenders on probation or parole [13]. Extended release formulations could be particularly helpful if given to detoxified, opioid addicted prisoners shortly before release from correctional facilies since they will prevent relapse in the first month after reentry when risks for relapse and overdose death are particularly high [14, 15], and thus provide a measure of "protected" time to engage in treatment and, hopefully, improve long term outcomes

Regarding adverse effects, concerns have been expressed that naltrexone increases depression, anxiety, and the risk for overdose death. However data from the studies of oral and extended release naltrexone in Russia, and emerging data from studies done in the U.S., have not supported these concerns. For example, the Russian studies have shown that

anxiety and depression actually decrease in patients that continued naltrexone treatment [5, 6, 10•], and followup data from the study comparing oral with implantable and placebo naltrexone provided no evidence that naltrexone increased the risk for overdose death [16]. Naltrexone appears to have no significant interactions with antiretroviral medications used to treat HIV disease, and patients that continue naltrexone treatment typically have marked decreases in HIV risk injecting behavior. The most common adverse event for the oral formulation has been nausea; for the extended release injectable formulation it has been irritation at the injection site that typically resolves in 1-3 days (see FDA package insert); and for the implant it has been local irritation or infection that resolved with treatment in 3-5 days [10•].

The most serious adverse effect reported from naltrexone treatment is hepatocellular injury, but it has almost always been associated with oral doses of 1400 to 2100 mg per week. These doses result in much greater exposure to naltrexone than the 380 mg from a monthly injection of extended release naltrexone or from an 1000 mg implant, that is inserted every 2-3 months. At oral doses below 600 mg/week, only relatively minor changes in liver tests have been reported and these have not been clearly attributed to naltrexone. For example, a study of actively drinking alcoholics who received once-monthly extended release injectable naltrexone found no evidence of liver toxicity. This study enrolled 624 patients and randomly assigned them to placebo (N=210), 380 mg (N=205), or 190 mg (N=210) of the extended release injectable product. There were no significant differences in ALT, AST, or bilirubin between study groups; the GGT in the 380 mg group was lower compared to placebo at weeks 4, 8, 12, and 20; and high (>3 times upper limit of normal) liver tests and hepatic-related adverse events were infrequent in all treatment groups. In a subset of patients who were drinking heavily throughout the study, or were obese or taking non-steroidal analgesics, there was no increase in frequency of hepatic-related adverse events in those receiving either dose [17]. No evidence of liver toxicity attributable to naltrexone has been seen in any of the Russian naltrexone studies.

Naltrexone for Alcohol use Disorders Though originally developed for treating opioid dependence, animal and human studies found that naltrexone reduced the rewarding effects of alcohol. These findings led to the studies by Volpicelli et al. [18] and O'Malley et al. [19] that found it reduced relapse to alcohol dependence and led to FDA approval for this indication in 2006.

One of the most interesting findings from these studies was that naltrexone did not result in abstinence, but it reduced the proportion of individuals that progressed to the full dependence syndrome when they drank after completing detoxification. Thus, naltrexone appeared to "dampen the fires" of addiction by somehow interfering with the usual, and typically rapid, progression from use to uncontrolled drinking that is characteristic of alcoholics and captured by the AA saying "One drink is too much and 1000 is not enough". This effect has been hypothesized to result from blocking alcohol induced endorphin effects on dopamine release and thereby attenuating the rewarding effects of alcohol, somewhat like turning down a rehostat reduces the strength of an electrical current. Perhaps due to this indirect mechanism of action, naltrexone's effect in preventing relapse to alcohol dependence is not as strong or consistent as seen in opioid dependence, but it is statistically and clinicallly significant and has been replicated in the majority of placebo-controlled studies.

Another opioid antagonist that has been studied for treatment of alcohol dependence is nalmefene. Mason et al. found that it is effective for preventing relapse to alcohol dependence [20, 21]. It is available as an oral formulation in the European Union (Selincro®) and blocks opioid effects for about 48 hours at dosages of 50–100 mg/day, and the EU has approved it for as needed use by alcohol dependent patients that have a high level of risk for resuming problematic drinking. For example, it might be helpful to someone who is in recovery but going to a social event where alcohol will be used. The most common side effects are nausea and dizzinges, similar to naltrexone.

Acamprosate for Alcohol use Disorders The FDA approved acamprosate for preventing relapse to alcohol dependence in 2004, however it had been available in Europe since 1989. It is marketed as Campral and structurally similar to gamma-aminobutyric acid (GABA) and thought to reduce or prevent alcohol consumption by reducing glutamate release that is associated with alcohol withdrawal as well as increasing GABA effects and reducing the sympathetic overstimulation that occurs in the course of alcohol dependence. Its most common side effect is diarrhea that appears to be dose-related.

The largest randomized trial comparing acamprosate to naltrexone, done by Anton et al. [22], found no evidence of efficacy, however a review by Maisel et al. [23••] of 64 randomized trials found that it was slightly more efficacious in promoting abstinence than naltrexone, and that naltrexone was slightly better at reducing heavy drinking and craving. A longer period of abstinence before treatment was associated with larger effects from both acamprosate and naltrexone, a finding that may explain the difference between the Anton et al. study, done in the U.S. where extended inpatient treatment is uncommon, and the acamprosate studies done in Europe, where it is more common. Extended release naltrexone most likely improves upon the outcomes of oral acamprosate or oral naltrexone for alcohol dependence treatment but studies making these comparisons have not been done.

Naltrexone Studies and FDA Approval Decisions An interesting and important result of the naltrexone alcohol studies was

that the FDA moved away from its traditional standard of abstinence as a necessary condition for approval of an addiction treatment medication and accepted reduction in days of heavy use and total amount consumed as grounds for approval. This decision appears to have been made because data showed that reductions in alcohol use are associated with health benefits. It is important because it has implications for future FDA decisions about medications for other substance use disorders that may have health benefits associated with reduced use, but not necessarily abstinence.

Naltrexone for Amphetamine Dependence Jayaram-Lindstrom and colleagues in Sweden conducted a series of animal and human studies showing that naltrexone reduces amphetamine use [24–26]. These studies led to a randomized 12-week trial comparing 50 mg oral naltrexone/day with placebo that found significantly less amphetamine use in the naltrexone than the placebo group [27]. A study by Tiihonen et al. [28] of individuals that were dually addicted to opioids and amphetamines found that it reduced amphetamine use, however it was unclear if this effect was due to a specific effect on amphetamine use or mostly due to a redution in opioids that were used in combination with amphetamine. An attempt to replicate the Swedish results in Iceland using extended release injectable naltrexone with individuals having a primary diagnosis of amphetamine dependence did not find a naltrexone effect, however the Icelandic patients received much more intensive psychosocial treatment than the Swedish patients, which may account for the differences between the two studies. The Iceland results were presented at the 2013 meeting of the College on Problems of Drug Dependence and are being prepared for submission to a journal [29].

Vaccines

Work is currently underway to develop vaccines for amphetamine, cocaine, opioid, and nicotine use disorders. These drugs are too small to elicit strong immune responses so one approach to vaccine development is to conjugate them with a large immunogenic protein such as inactivated tetanus or cholera toxin, both of which have been successful with other vaccines, and combine them with adjuvants that magnify the strength and duration of their effects. This process can produce antibodies that slow or prevent the drug from crossing the blood-brain barrier and having its effects, but there are many hurdles to overcome to achieve a clinically meaningful product [30•].

Nicotine vaccines are the only ones that have been commercially developed but larger scale clinical trials failed to meet the sustained abstinence criterion and development appears to have been put on hold pending further development [31]. Though work on opioid vaccines has been underway for a longer period of time, it appears to have stalled due to challenges associated with developing a vaccine that is effective against the many opioids that are being abused, and the presence of effecive pharmacotherapies for opioid dependence.

The result has been that most current work is focused on amphetamine and cocaine vaccines since neither drug has an effective pharmacotherapy. The cocaine work is farthest along as seen in a phase II trial that involved five injections with 115 subjects where about a third had antibody levels sufficient to block cocaine doses for 3 months after the last vaccination. No safety concerns occurred and this work has progressed to a phase IIb, placebo-controlled trial involving 300 treatment-seeking cocaine dependent individuals that are scheduled to receive five vaccinations [30•]. Studies involving development of monoclonal antibodies, or an enzyme that involves gene transfer and increases cocaine metabolism are underway, but they are at a very early phase of development [32•].

Conclusions

The antagonist model includes medications that discourage use by causing adverse effects (disulfiram); medications that directly block the pharmacological effects of the abused substance (naltrexone for opioid dependence); that indirectly block or attenuate the affects of the substance (naltrexone, nalmafene, and acamprosate for alcohol dependence); or that prevent drug effects by blocking its passage into the brain barrier or speeding up its metabolism (vaccines).

Among these models, extended release naltrexone for opioid dependence has had the strongest effects, at least in the short-term. The degree to which patients will continue this treatment and achieve longer term benefits is likely to become clearer over the next several years. However even in the absence of long term effects, short periods of antagonist treatment have the potential to prevent overdose deaths among opioid addicts in the very high risk periods following release from correctional facilities or completing a short-term detoxification program.

Disulfiram works very well for alcohol dependence when patients take it, but use has been limited due to patient acceptance and concern about serious adverse events that can occur with exposure to alcohol. Naltrexone and acamprosate have clinically meaningful but less robust effects on preventing relapse to alcohol dependence, but are relatively free of serious adverse events and thus appear to be more acceptable to clinicians and patients than disulfiram. Extended release naltrexone likely produces better outcomes for alcohol dependence than oral naltrexone or oral acamprosate, but studies of these comparisons have not been done. Vaccines have great

potential but are in an early stage of development with many challenges and hurdles to overcome.

Compliance with Ethics Guidelines

Conflict of Interest George E. Woody declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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