

Buprenorphine for Dual Dependency: Cocaine, Alcohol and Opiates

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Summary

Dual-drug dependency is common in Europe and America and represents a complex management and treatment challenge. Most heroin addicts abuse stimulants or alcohol in addition to opiates. Cocaine pharmacotherapy remains a challenge, but there has been some success with Buprenorphine, Disulfiram, Modafinil and GABA agonists. A promising cocaine vaccine is also under development. Triple-dependency with alcohol or benzodiazepines is also common and can lead to serious dependence requiring detoxification. In addition to regular monitoring following alcohol detoxification, relapse prevention pharmacotherapy is essential. The following review will briefly describe concurrent-drug abuse with cocaine and opiates as well as describe current pharmacotherapies for multi-drug dependence. In addition, we will briefly discuss the implications for combining behavioral therapies with medications to improve treatment efficacy.

Key Words: Dual Dependency - Cocaine - Alcohol - Opiates

Dual-drug dependency is very common throughout Europe and America. Most heroin addicts abuse other drugs besides opiates. Stimulant abuse is common and increasing in European countries with up to 40% of heroin addicts also abusing cocaine and less commonly amphetamine. Alcohol and benzodiazepines are also commonly abused and can lead to serious dependence requiring detoxification. Benzodiazepines are covered separately and the focus of this review will include alcohol pharmacotherapy as well as stimulants. Cannabis abuse is minimally addressed in most opiate treatment programs, and there are no established pharmacotherapies for cannabis at this time.

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Alcohol Abuse and Dependence

The management challenge of dual-drug dependency is complex and often can involve triple dependency on alcohol as well as opiates and stimulants. For alcohol dependent patients detoxification may be required, and that treatment has been well reviewed elsewhere^[9]. Prevention of relapse to alcohol abuse after detoxification is the greater challenge and requires regular monitoring by urine drug and breath alcohol levels. Another possible monitoring approach for alcohol uses blood carbohydrate deficient transferrin to assess abstinence^[11]. This assay can be used as infrequently as every other week and provide adequate monitoring.

In addition to monitoring for return to alcohol use, relapse prevention pharmacotherapy should be considered. Relapse prevention pharmacotherapy for alcohol includes Acamprosate, Topiramate, and Disulfiram (with monitored ingestion). The other important pharmacotherapy for alcoholism - opiate antagonists such as Naltrexone (and nalmefene) are contra-indicated, since they may precipitate opiate withdrawal. Acamprosate (N-acetylhomotaurine) involves dosing with 2 mg total, given three times daily. The side effects primarily include diarrhea, but it is generally well tolerated. Acamprosate has increased abstinence by 50% in over 3,000 patients across a dozen clinical trials^[2, 15, 17, 21, 22]. An illustrative trial enrolled 272 patients and treated them for 48 weeks^[19]. Compared to placebo the 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%). Thus, this appears to be a very effective approach to treating patients who are both opiate and alcohol dependent after detoxification from alcohol in order to maintain alcohol abstinence. Similar success has been described with topiramate vs. placebo, but only in a single study so far^[6]. In that topiramate study the patients were actively drinking when started on medication rather than being first detoxified from alcohol and being abstinent. The outcome again was remarkable with an increase from no days abstinent at baseline to 44% of days abstinent by week 12 compared to 18% of days abstinent for the placebo group. Thus, a treatment strategy can be to start on topiramate at a low dose for buprenorphine maintained, alcohol abusing patients who do not need medical detoxification for alcohol. Each week then steadily increase the topiramate dose for up to 8 weeks in order to attain a week of abstinence. If and when abstinence is attained, discontinue the topiramate gradually over several weeks while you start the patient on acamprosate or disulfiram. The choice will depend on your patient's preference and need for either an anti-craving medication (acamprosate) or an aversive agent (disulfiram).

Cocaine Abuse

The prevalence of cocaine abuse across Europe appears to be growing, which is a particular problem for estimating the current need for treatment capacity since the most recent data are from 2001, and these data indicate substantial variability across Europe. In 2001 the United Kingdom reported that 35% of its population had ever used an illicit drug, and about 5%, or 15% of these illicit drug abusers, reported cocaine use. Italy and Germany each had rates of about 20% for any illicit drug use and about 3%, or again 15% of these illicit drug abusers, had used cocaine. Finally, Spain, like the United Kingdom, reported about 5% abuse rates for cocaine, but no statistics on overall illicit drug use. This cocaine abuse is usually combined with heroin, and only 15% of

cocaine use and 10% of crack cocaine use is primary cocaine use. As an example, England has a large overlap in severe heroin and crack cocaine addicts with almost 50% of heroin addicts also abusing cocaine. There are 120,000 heroin and cocaine users and only 22,000 cocaine users who do not use heroin in England.

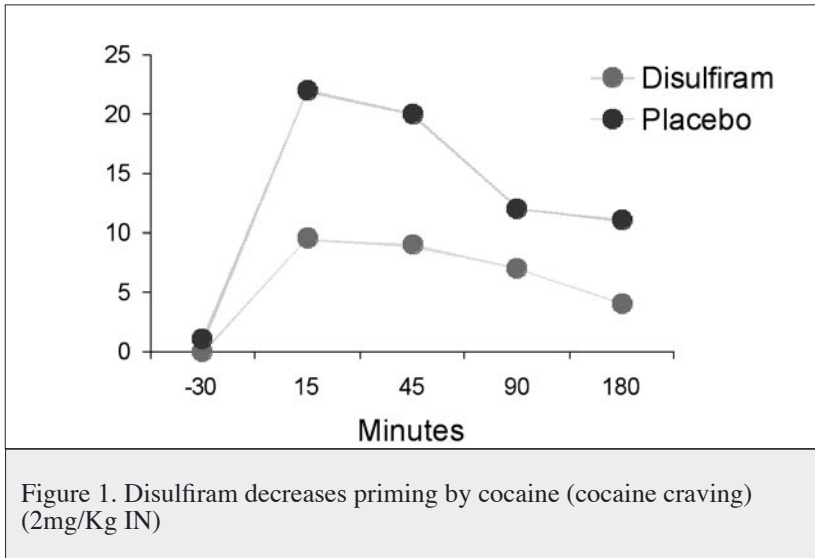
Cocaine pharmacotherapy is a continuing challenge, but we are evolving treatments including Buprenorphine, Disulfiram, Modafinil and GABA agonists^[11]. We are also developing a cocaine vaccine^[12]. Buprenorphine has shown a dose dependent reduction in cocaine abuse with less cocaine use associated with higher doses (e.g. 4 mg vs 16 mg daily)^[16,20]. Thus, the first approach to a patient who is abusing cocaine while taking buprenorphine should be to increase the buprenorphine dose to at least 16 mg daily.

Disulfiram is a complex medication that appears to act on the catecholamine system to increase dopamine and decrease norepinephrine production. Disulfiram decreases cocaine craving and cocaine-induced priming, as shown in several human laboratory studies where cocaine has been administered with placebo and active disulfiram. At a cocaine dose of 2 mg/kg intranasally, disulfiram reduced cocaine induced craving (or priming) by more than 50% for peak craving and area under the curve of craving over time^[13, 14] as shown in Figure 1. Disulfiram also increased cocaine-free urines in outpatient, placebo controlled clinical trials, and in over 600 outpatients treated across seven studies the disulfiram group had a statistically significant 35% higher rate of cocaine-free urines ($P < 0.01$ in meta-analysis).

Two other promising agents have very different pharmacological actions. Modafinil has shown a significantly increased rate of cocaine-free urines, with rates of 45% for modafinil compared to 20% rates for placebo^[3]. Several GABA enhancing agents also are being examined such as tiagabine, gabapentin and recently vigabatrin. While gabapentin has not shown efficacy, both tiagabine and vigabatrin look promising. In a recent clinical trial tiagabine increased cocaine free urines by 80% from baseline, while placebo increased only 20% from baseline^[5]. Thus, several medications from different classes of pharmacological actions are showing promise for cocaine.

In order to enhance the efficacy of pharmacotherapy, contingency management designs have proven very effective. The Contingency Management (CM) condition can be to reinforce attendance at treatment sessions, compliance with taking medications and of course, reduction in cocaine abuse. For reducing cocaine use patients are given payment for drug-free urinary toxicology (UTOX) results that are taken at least twice weekly (preferable three times weekly in order to capture all cocaine abuse). For consecutive cocaine-free urines there is an escalating reinforcement schedule. For example, an initial payment of \$3 per clean UTOX result will be increased by \$1 for each consecutive clean UTOX result to a maximum of \$15 per result. Positive or missed UTOX results are penalized by resetting the amount earned for clean UTOX results back to \$3.

In a study of bupropion plus contingency management (CM), the proportion of cocaine urines by week steadily decreased for the patients who got CM plus bupropion, while those who got bupropion alone or contingency management (CM) alone or neither bupropion nor CM showed no reduction in cocaine urine results during this 24 week clinical trial^[18]. The effect of bupropion on decreasing cocaine urines was easily seen within the patients who also got CM. For both groups, the proportion of cocaine positive urines started at 70% at week 1 then dropped to 35% from weeks 12 to 24 for the bupropion plus CM group, while for the placebo plus CM group the



cocaine urines remained between 55% and 60% throughout the 24 weeks. The conclusions are that the contingency management plus bupropion condition made a significant improvement in the proportion of cocaine-positive UTOX results during the first 13 weeks and that these gains were maintained across the 6 month period of study.

Finally, we are developing an anti-cocaine vaccine. This vaccine shows antibody production in animals, and these vaccine generated antibodies bind injected cocaine. This vaccine and the antibodies it produced have decreased cocaine self-administration in rodents [4, 7, 8]. This vaccine also produces substantial amounts of antibodies after 3 to 5 vaccinations [10, 12]. As these antibodies accumulate they become effective in patients within 6 to 8 weeks of initial vaccination, and act to keep cocaine out of the brain. Cocaine antibody levels rise as dosing is repeated, even more than antibody levels increase with increasing vaccine dose. For example, peak antibody levels increased more with five vaccinations at 82 μg (410 ug cumulative dose) than four vaccinations at 82 μg (328 ug cumulative dose) (320 vs 200 antibody units). Furthermore, antibody levels increased with four doses at 82 ug (328 ug cumulative dose) to twice the levels attained with three vaccinations at an almost ten times higher dose of 709 μg (2,127 ug cumulative dose) (100 vs 200 antibody units). These higher vaccine doses and more repeated dosing are not only associated with higher antibody levels, but also with less relapse to cocaine use. The percent of patients relapsing in a high vs low dosage group was 30% vs 75% for any cocaine use and no relapse vs 30% relapse for heavy cocaine use.

Summary

In summary, heroin addicts are commonly dually dependent on alcohol and cocaine most commonly. Alcohol pharmacotherapies include acamprosate, topiramate, and disulfiram with observed

ingestion needed for disulfiram. The promise of stimulant pharmacotherapies include disulfiram, modafinil and tiagabine or similar GABA enhancing agents, which may be enhanced in opiate dependent patients by using relatively high doses of buprenorphine (e.g. 16 mg daily). Combining contingency management with medications is highly effective for enhancing the efficacy of cocaine therapy. Sustained treatments such as the cocaine vaccine offer great promise to prevent relapse.

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