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Narcotic antagonists in drug dependence: pilot study showing enhancement of compliance with SYN-10, amino-acid precursors and enkephalinase inhibition therapy

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Summary We decided to test the hypothesis that possibly by combining a narcotic antagonist and amino-acid therapy consisting of an enkephalinase inhibitor (D-phenylalanine) and neurotransmitter precursors (L-amino- acids) to promote neuronal dopamine release might enhance compliance in methadone patients rapidly detoxified with the narcotic antagonist Trexan® (Dupont, Delaware). In this regard, Thanos et al. [J. Neurochem. 78 (2001) 1094] and associates found increases in the dopamine D2 receptors (DRD2) via adenoviral vector delivery of the DRD2 gene into the nucleus accumbens, significantly reduced both ethanol preference (43%) and alcohol intake (64%) of ethanol preferring rats, which recovered as the DRD2, returned to baseline levels. This DRD2 overexpression similarly produced significant reductions in ethanol non-preferring rats, in both alcohol preference (16%) and alcohol intake (75%). This work further suggests that high levels of DRD2 may be protective against alcohol abuse [JAMA 263 (1990) 2055; Arch, Gen. Psychiatr. 48 (1991) 648]. The DRD2 A1 allele has also been shown to associate with heroin addicts in a number of studies. In addition, other dopaminergic receptor gene polymorphisms have also associated with opioid dependence. For example, Kotler et al. [Mol. Phychiatr. 3 (1997) 251] showed that the 7 repeat allele of the DRD4 receptor is significantly overpresented in the opioid-dependent cohort and confers a relative risk of 2.46. This has been confirmed by Li et al. [Mol. Psychiatry 2 (1997) 413] for both the 5 and 7 repeat alleles in Han Chinese case control sample of heroin addicts. Similarly Duaux et al. [Mol. Psychiatry 3 (1998) 333] in French Heroin addicts, found a significant

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association with homozygotes alleles of the DRD3-Bal 1. A study from NIAAA, provided evidence which strongly suggests that DRD2 is a susceptibility gene for substance abusers across multiple populations (2003). Moreover, there are a number of studies utilizing amino-acid and enkephalinase inhibition therapy showing reduction of alcohol, opiate, cocaine and sugar craving behavior in human trials (see Table 1). Over the last decade, a new rapid method to detoxify either methadone or heroin addicts utilizing Trexan® sparked interest in many treatment centers throughout the United States, Canada, as well as many countries on a worldwide basis. In using the combination of Trexan® and amino-acids, results were dramatic in terms of significantly enhancing compliance to continue taking Trexan®. The average number of days of compliance calculated on 1000 patients, without amino-acid therapy, using this rapid detoxification method is only 37 days. In contrast, the 12 subjects tested, receiving both the Trexan® and amino-acid therapy was relapse-free or reported taking the combination for an average of 262 days ($p < 0.0001$). Thus coupling amino-acid therapy and enkephalinase inhibition while blocking the δ-receptors with a pure narcotic antagonist may be quite promising as a novel method to induce rapid detox in chronic methadone patients. This may also have important ramifications in the treatment of both opiate and alcohol-dependent individuals, especially as a relapse prevention tool. It may also be interesting too further test this hypothesis with the sublingual combination of the partial opiate mu receptor agonist buprenorphrine.

Introduction

The purpose of this paper is to review the clinical efficacy of using narcotic antagonism in the treatment of opiate and alcohol dependence. While there is a plethora of evidence for opiate dependence the research on alcohol dependence is more sparse. However, the method called rapid detoxification that relies upon the use of narcotic antagonism both oral and intravenous may be enhanced by amino-acid precursor and enkephalinase inhibition. Thus this paper serves two purposes: (1) a brief review of the literature; (2) pilot clinical evidence showing the synergy between narcotic antagonism and amino-acid and enkephalinase therapy.

Alcohol

It is important to begin by reminding ourselves that we do not fully understand the major effects of alcohol on the brain. There are no easily identified, highly specific "alcohol receptors" [1]. In addition, alcohol exerts an impact on almost all brain chemicals, making it difficult to determine which, if any, are key to the intoxicating or subsequent craving phenomena associated with this drug [2]. To make matters even more complicated, the initial administration of alcohol has different effects on brain chemicals than are seen after repeated administration of this drug, and all these effects are likely to be different at different doses.

Despite these complexities, there are at least three theories about how a drug that affects opiates might have an important impact in the treatment of alcoholism.

First, alcohol, at least indirectly, does affect the brain's natural opiate-like or endorphin system [3]. So, even if the impact is modest, it makes sense that any drug that alters the functioning of the natural brain opiates could alter the effects that alcohol exerts on the brain itself. There are data to indicate that one brain opiate substance; leucine-enkephalin in animals and β-endorphin in humans is decreased in amount in the presence of alcohol [4,5]. It is theorized that this could be the result of an inhibition of the production of this opiate by alcohol itself [6]. Similarly, another study documented that if opioid peptides are administered to an animal before alcohol is given, that animal is less likely to consume alcohol [7]. Consistent with these observations is an early study showing that animals with prior intake of alcohol are more likely to maintain their abstinence when given morphine [8]. These studies, along with the ill-advised turn of the century practice of administering morphine to alcoholics to attempt to maintain abstinence from alcohol, are consistent with some level of interaction between alcohol and the opiate systems.

A second area of support for the potential interaction between alcohol and the opiate systems occurs through studies of stress. Acute stresses do increase the level of the body's natural opiates. At least theoretically, if stress (either from the environment or from heavy drinking) occurs regularly enough, it is possible that the body becomes used to having higher levels of opiates. Thus, when stress levels decrease (either in the environment or through abstinence) the body might crave the higher levels of endogenous opiates to which it has become accustomed. This discomfort might cause symptoms that make it more likely that the

individual will then go back to his or her usual drug of abuse, in this instance alcohol. Consistent with this hypothesis is the observation that animals placed in a high-stress situation are likely to increase their selection of alcoholic beverages, but also that this alcohol-seeking behavior can be blocked by fairly modest doses of analoxone [9,10].

The third, and perhaps the most attractive, of the theories focuses on the hypothesized brain reward system. A number of investigators feel that most pleasurable experiences, including the acute effects of most drugs, are mediated through the actions of the brain chemical dopamine, especially in a part of the brain called the *nucleus accumbens*. This area is part of a complex of the brain called the *meso-limbic* system. Thus, it is possible that the pleasurable effects of alcohol occur, at least in part, through mechanisms that are similar to those that contribute to the pleasurable effects of opiates. If this is true, then a drug that blocks some of the effects of opiates could have a beneficial effect by decreasing the rewarding effects of alcohol, and this elimination of the expected reinforcements might even decrease craving [11–13].

However, just because a theory makes sense does not mean that it is correct. Nonetheless, there are good reasons to consider whether an opiate antagonist drug might have some beneficial effects in the treatment of alcohol dependence. After 12 years of struggle for approval, the US FDA approved the use of naltrexone/Trexan® for opioid detoxification, then in the mid-90s, the same drug was approved for the treatment of alcoholism under the name Rivera®.

Clinical trials for alcoholism

Thus, in this brief review, we focus on the few double-blind trials available. Volpicelli et al. [14] reported on a 12-weeks trial of 50 mg of naltrexone per day in 34 alcohol-dependent outpatient men, comparing results with 36 men treated with placebo. All individuals received the usual treatment for alcohol rehabilitation, and everyone was evaluated weekly. By the end of the 12 weeks, 23% of naltrexone treated patients had relapsed into excessive frequent drinking, compared to 54% of the patients on placebo. These data indicate naltrexone may have been especially helpful for patients who had "slipped" and begun to drink; almost half of them were likely to return to abstinence if they were on naltrexone, while the same is true for only 5% of those treated with placebo. The authors suggested it is possible the naltrexone blocked part of the high or reinforcing effect of alcohol, making it easier for people who had initially returned to drinking do not go on to escalating doses of alcohol. At the same time, the study also reported a possible decrease in craving for alcohol with this narcotic antagonist.

Also, O'Malley et al. [15] reported on 97 alcoholic men and women, 46 of who received 50 mg per day of naltrexone and the remainder placebo over 12 weeks. While the project was complex and other questions were being tested, those on naltrexone demonstrated improved rates of abstinence and lower rates of alcohol intake and problems if they had returned to drinking.

Other more recent studies include both positive and negative reports but the consensus favors the limited use of narcotic antagonism in the treatment of alcoholism [16]. There are over 5000 papers on the subject since the first work of Blum and associates [17] and others in the early 70s, showing the anti-alcohol effect of naloxone in mice and rats (reduction of sleep-time, delay in withdrawal reactions, reduced ethanol intake, and reduction of ethanol-induced dependence).

Positive reports in humans include a number studies that are concerned with abstinence, tolerance, craving behavior in both young and older alcohol-dependent patients [14,15,18–23]. The most up to date and complete reviews of the subject is by Herz from the Department of Neuropharmacology at the Max-Planck Institute for Psychiatry in Germany [24], from Blum and Braverman [16], and from Gonzalez et al. [31].

Opiates

The use of heroin continues to increase and is estimated that 8 million people in the world (0.14%) abuse opiates. The region with the highest annual prevalence (2%) are South East and South West Asia and based on the National Household Survey, the annual prevalence of heroin use in the United States is 0.3% with a rising trend of heroin use in the last 2 years [24].

New pharmacological treatments for heroin addiction include drugs that reduce withdrawal symptoms and agents that are given during the maintenance phase of treatment. A variety of different types of pharmacological agents (opioid agonists, opioid antagonists and α_2-adrenoreceptor agonists) have been extensively studied.

Clinical trials for opiates

In a review and meta-analysis of randomized controlled studies evaluating the use of naltrexone as a

maintenance agent, Kurchmayer et al. [25] found a tendency in favor of naltrexone but concluded that there is not sufficient evidence to evaluate the efficacy of naltrexone treatment for opioid dependence. Shufman et al. [26] in a double-blind, controlled design evaluated the efficacy of naltrexone in reducing opioid positive urine tests during a 12-week trial and found naltrexone to be superior to placebo. Similarly, in a multi-center, randomized controlled trial, Hollister [27], examined 170 opiate-dependent patients at a 9 months follow-up, and found that the group treated with naltrexone had more opiate – free urine tests and reduced attrition rates. Finally, Hulse and Basso [28] evaluated treatment outcome at 6 months for 100 heroin-dependent patients maintained on naltrexone and found that complete abstinence was not characteristic of many of those patients continuing on naltrexone, in spite of its complete blocking of heroin reinforcement. Thus, periodic heroin use during naltrexone maintenance may occur but this periodic use did not prevent successful outcomes for those maintained on naltrexone.

In more recent years, the partial opiate μ-receptor agonist, buprenorphine has been used as opioid substitution therapy for opiate dependence in France since 1996 [29]. It is awaiting approval in the United States as a sublingual combination tablet with naloxone [30].

Additionally, clonidine and lofexidine are α_2-receptor agonists and are the most commonly used non-opiate drugs for detoxification from opiates in the US and the UK, respectively. Activation of the presynaptic α_2 results in the inhibition of the sympathetic outflow associated with the opiate withdrawal syndrome [31].

Rapid detox

The Against Medical Advice (AMA) rate (the rate at which patients or addicts leave treatment before treatment goals are reached) among hardcore addicts even today approaches 90%. The basic concept of a relatively new approach called "rapid detoxification method" is to provide the patient with a pure narcotic antagonist to block the opiate-induced euphoriant effects. Using this approach results in a significantly high recidivism rate due to non-compliance [16]. Once again we believe the non-compliance issue is due to the fact that while the narcotic antagonist blocks the opiate or alcohol-induced euphoria [13,22], the drug has little effect on craving behavior. To reiterate, Kirchmayer et al. [25] performed a recent systematic review on the efficacy of naltrexone maintenance treatment in opioid dependence and concluded that from the available clinical trials performed up until 2002, there is insufficient evidence to justify the use of naltrexone in the maintenance treatment of opioid addicts.

We decided to test the hypothesis that possibly by combining a narcotic antagonist and amino-acid therapy consisting of an enkephalinase inhibitor (D-phenylalanine) and neurotransmitter precursors (L-amino-acids) to promote neuronal dopamine release might enhance compliance in methadone patients rapidly detoxified with the narcotic antagonist Trexan®. In this regard, Thanos et al. [32] found increases in the dopamine D2 receptors (DRD2) via adenoviral vector delivery of the DRD2 gene into the nucleus accumbens, significantly reduced both ethanol preference (43%) and alcohol intake (64%) of ethanol preferring rats, which recovered as the DRD2, returned to baseline levels. This DRD2 overexpression similarly produced significant reductions in ethanol non-preferring rats, in both alcohol preference (16%) and alcohol intake (75%). This work further suggests that high levels of DRD2 may be protective against alcohol abuse [33,34]. The DRD2 A1 allele has also been shown to associate with heroin addicts in a number of studies [35]. In addition, other dopaminergic receptor gene polymorphisms have also associated with opioid dependence. For example, Kotler et al. [36] showed that the 7 repeat allele of the DRD4 receptor is significantly overpresented in the opioid-dependent cohort and confers a relative risk if 2.46. This has been confirmed by Li et al. [37] for both the 5 and 7 repeat alleles in Han Chinese case control sample of heroin addicts. Similarly Duaux et al. [38] in French Heroin addicts, found a significant association with homozygotes alleles of the DRD3-Bal 1. Moreover, there are a number of studies utilizing amino-acid and enkephalinase inhibition therapy showing reduction of alcohol, opiate, cocaine and sugar craving behavior in human trials (see Table 1). Over the last decade, a new rapid method to detoxify either methadone or heroin addicts utilizing Trexan® (Dupont, Delaware) sparked interest in many treatment centers throughout the United States, Canada, as well as many countries on a worldwide basis.

Hypothesis

In terms of negative reports, we believe a reason for non-compliance resides in the very nature of the pharmacological and physiological basis of the

Table 1 Summary of completed clinical studies with neutraceutical supplementation a literature review

Drug abused or dysfunction	Supplement used	No. of PTS	No. of days	Study type	Significant results	Reference
Alcohol	SAAVE	22	28	TO IP	100% Decrease in BUD scores. Detoxification measures: reduction in benzodiazepine requirement; reduction in withdrawal tremors after 72 h; reduction in depression	Blum, K, Trachtenberg, MC, Ramsey, J. Improvement of inpatient treatment of the alcoholic as a function of neuronutrient restoration: a pilot study. Int. J. Addiction 1988;23:991–8. Blum, Tractenberg. Neurogenic deficits caused by alcoholism: restoration by SAAVE, a neuronutrient intervention adjunct. J. Psychoactive Drugs 1988;20:297
Alcohol plus poly-drugs	SAAVE	62	21	DBPC IP	Reduction in psychosocial stress reaction as measured by SCL, reduced BESS score; improved physical score; six fold decrease in likelihood of leaving AMA after 5 days	Blum, et al. Enkephalinase inhibition and precursor amino acid loading improves inpatient treatment of alcoholics and poly-drug abusers: a double blind placebo controlled study of the neuronutrient intervention adjunct SAAVE. Alcohol 1989;5:481
Cocaine	Tropamine	54	30	TO IP	Drug hunger significantly reduced in patients taking SAAVE as compared to controls; 4.2% AMA rate for patients on Tropamine vs. 28% for patients on SAAVE and 37% for controls	Blum, et al. Reduction of both drug hunger and withdrawal against advice rate of cocaine abusers in a 30 day inpatient treatment program by the neuronutrient tropamine. Curr. Ther. Res. 1988;43:1204
Alcohol and cocaine	SAAVE and tropamine	60	379	TO OP	At end of 1 year over 50% of the alcoholic DUI offenders not using SAAVE dropped out of the program while less than 15% of those using SAAVE dropped out. For the cocaine abusers over 90% of the non-tropamine group dropped out, but less than 25% of the tropamine group dropped out	Brown, et al. Neurodynamics of relapse prevention: a neuronutrient approach to outpatient DUI offenders. J. Psychoactive Drugs 1990;22:173
Over-eating	PCAL-103	27	90	TO OP	The PCAL-103 group lost an average of 27 pounds in 90 days compared with an average loss of 10 pounds for the control group. Only 18.2% of the PCAL-103 patient group relapsed compared to 82% of the patients in the control group	Blum, et al. Neuronutrient effects on weight loss on carbohydrate bingeing in an outpatient bariatrics setting. Curr. Ther. Res. 1990;48:217

Over-eating	PCAL-103	247	730	PCOT OP	After 2 years, craving and binge eating were reduced one-third in group of patients on PCAL-103 as compared to the control patients. PCAL-103 group regained 14.7% of their lost weight compared with 41.7% weight regained in control patients	Blum, K, Cull, JG, Chen, JHT, Garcia-Swan, S, Holder, JM, Wood, R, et al. Clinical evidence for effectiveness of PhenCal™ in maintaining weight loss in an open-label, controlled, 2-year study. Curr. Ther. Res. 1997;58:745–63
Over-eating	Chromium picolinate (CrP) and L-carnitine	40	112	RDBPC OP	21% increase ($p < 0.001$) in resting metabolic rate (RMR), no change in lean body mass (LBM), RMR:LBM increased 25% ($p < 0.001$). Body fat decreased approximately 1.5 lbs/wk and reduction in serum cholesterol while increasing RMR with no loss of LBM	Kaats, FR, et al. The short-term therapeutic efficacy of treating obesity with a plan of improved nutrition and moderate caloric restriction. Curr. Ther. Res. 1992;51:261
Over-eating	Chromium picolinate	32	180	DBPC OP	After 6 months CrP group had increase of lean body mass and avoided non-fat related weight loss. Difference between groups was significant at $p < 0.0001$	Bahadori, B, Habersack, S, Schneider, H, Wascher, TC, Topiak, H. Treatment with chromium-picolinate improves lean body mass in patients following weight reduction. Federation Am. Soc. Exp. Biol. 1995
Over-eating	Chromium picolinate	154	72	RDBPC OP	200 and 400 mcg of CrP brought about significant changes in Body Composition Indices compared with placebo	Kaats, GR, Blum, K, Fisher, JA, Adelman, JA. Effects of chromium picolinate supplementation on body composition: a randomized, double masked, placebo-controlled study. Curr. Ther. Res. 1996;57:747–56
Over-eating	Chromium picolinate	122	90	RDBPC OP	After controlling for differences in caloric expenditures and caloric intake as compared with placebo group, 400 mcg CrP group lost significantly more weight ($p < 0.001$) and body fat ($p = 0.004$), had a greater reduction in percent body fat ($p < 0.001$) significantly improved Body Composition Index ($p = 0.004$)	Kaats, GR, Blum, K, Pullin, D, Keith, SC, Wood R. A randomized, double-masked, placebo-controlled study of the effects of chromium picolinate supplementation on body composition: a replication of a previous study. Curr. Ther. Res. 1998;59:379–88
Over-eating	Chromium picolinate	122	90	RDBPC OP	Measures of change in fat weight, change in body weight, percent change in weight, and body weight change in kgms all were significant in A_2/A_2 group and non-significant in the A_1/A_2 and A_1/A_1 carriers	Blum K, Kaats G, Eisenberg A, Sherman M, Davis K, Comings DE, et al. Chromium picolinate induces changes in body composition as a function of the *Taq1* dopamine D_2 receptor A_2 alleles. J. Am. College Nutr. [submitted]

Table 1 *(continued)*

Drug abused or dysfunction	Supplement used	No. of PTS	No. of days	Study type	Significant results	Reference
Over-eating	Chromium nicotinate and chromium picolinate comparison	43	63	ROTPC OP	CrP supplementation resulted in significant weight gain, while exercise training combined with CrN supplementation resulted in significant weight loss and lowered insulin response to an oral glucose load. Concluded high levels of CrP supplementation are contraindicated for weight loss in young, obese women. Moreover, results suggest that exercise training combined with CrN may be more beneficial than exercise training alone for modification of certain CAD and NIDDM risk factors	Grant KE, Chandler RM, Castle AL, Ivy JL. Chromium and exercise training: effect on obese women. J. Am. College Sports Med. 1997;29(8):992–8
Healthy volunteers	Tropagen	15	30	DBPC OP	Non-drug-using subjects with Tropagen performed better on computer memory and performance tests as measured with P300 wave evoked potential. Changes in P300 wave evoked potential result in better focusing in ADHD patients	Defrance, JJ, Hymel, C, Trachtenberg, MC, et al. Enhancement of attention processing by Kantrol in healthy humans. A pilot study. Clin. Electroencephalogr. 1997;28:68–75

Abbreviations used: BUD, building up to drink; AMA, withdrawal against medical advice; OP, outpatient; MMPI, Minnesota multi-phasic personality inventory; DB, double-blind; IP, inpatient; SCL, skin conductance level; BESS, behavioral, emotional, social, spiritual; DBPC, double-blind Placebo-controlled; DUI, driving under the influence; R, randomized; TO, open trial.

use of narcotic antagonism in treating either opiates or alcohol dependence. Craving behavior is distinct from euphoria and different set of mechanisms are involved. Blocking of euphoria represents the occupancy of a narcotic antagonist, naltrexaone, on δ-opiate receptors. In order to ensure the reduction of craving behavior, however, substances should be employed that either occupy dopamine D2 receptors or cause the preferential pre-synaptic release of dopamine causing reduction of alcohol and opiate craving behavior. We believe based on our own work and others that the preferred therapy should consist of a combination of narcotic antagonists, narcotic agonists and amino-acid precursor and enkephalinase inhibition therapy.

Methods

Subjects

We tested our combined therapeutic approach at the J.T. Payte MD, PA Clinic, San Antonio, TX, with 1012 hardcore addicts who had abused euphoriants up to 30 years. Entry into the study included both male and female patients who were considered hardcore addicts as diagnosed using the DSM-IV criteria for heroin/opiate dependence. There were 700 males and 300 females in the 1000 patients in the non-experimental group and 9 males and 3 females in the experimental group. The age range was from 40–70 years of age with an average age of 49 years of age. Each patient signed a consent form and the project received IRB approval from the San Antonio Methadone Clinic and from PATH Medical Foundation IRB which approved future research in this area. (registration #IRB00002334).

Rapid detox methodology

Each patient ($n = 1000$) was pre-evaluated by first receiving an injection of 0.4–0.8 mg of Narcan and their withdrawal was assessed. If they passed this first test, they were administered an oral dose of 12.5 mg of Trexan® and again evaluated for withdrawal symptoms over a ninety minute period. If the patient passed this test, they were given 50 mg Trexan®. The 1000 patients received the 50 mg of Trexan® daily until the patient relapsed.

Amino-acid therapy

For this study 12 patients were selected, those selected received along with Trexan® a combination of amino-acids consisting of D,L-phenylalanine, L-tryptophan, L-tyrosine, L-glutamine, chromium picolinate and pyridoxal-5-phosphate (formerly SAAVE™ manufactured by Natural Alternatives, San Marcos, California) developed under US Patent Nos. 5189064, 4761429 and now governed by US Patent No. 6132724). The present research code name and number is Syn 10. The number of days without a relapse or self-report of refusal to take either the Trexan® alone or in combination with the amino-acid formula was counted. Each patient (with some degree of failure) was evaluated on a daily basis either via phone or in a face-to-face contact.

Statistics

A simple student *t*-test was used to determine statistical differences between the group with only Trexan® compared to the group also taking the amino-acid supplement. We utilized Satterthwaite's correction for unequal variances.

Results

The results were dramatic in terms of significantly enhancing compliance to continue taking Trexan®. The average number of days of compliance that the J.T. Payte Clinic of San Antonio, Texas, calculated on 1000 of their patients, without amino-acid therapy, using this rapid detoxification method is only 37 ± 7.7 SE days. In contrast, the 12 subjects tested, receiving both the Trexan® and amino-acid therapy was relapse-free or reported taking the combination for an average of $262 + 16.4$ SE days ($p < 0.0001$ @ 95% confidence) (see Fig. 1).

Comment

Based on this research we suggest that the addition of the anti-craving formula significantly reduced the craving for opiates (possibly alcohol) and, therefore, seems to be important in assisting those hardcore opiate addicts in preventing relapse – especially in conjunction with the narcotic antagonist Trexan®.

There is even very recent molecular genetic evidence, which supports Blum's original concept of common mechanisms between alcohol and opiates [39]. [3H] Naloxone binding was measured in frontal gray cortex, *caudate nucleus*, *amygdala*, *hippocampus* and *cerebella cortex* in human alcoholic and non-alcoholic subjects. Binding was found to be

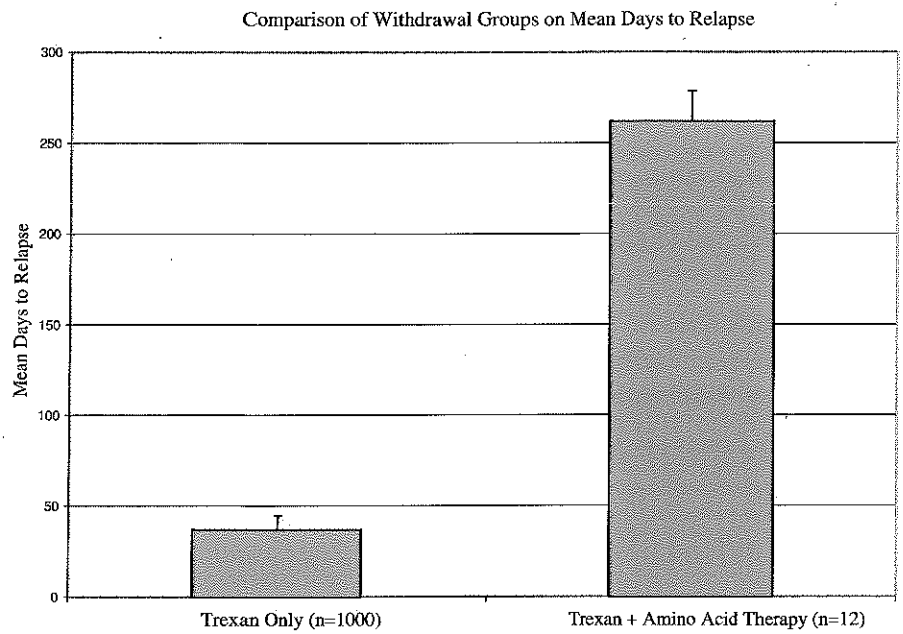

Figure 1 Comparison of withdrawal groups on mean days to relapse.

higher in alcoholics than in non-alcoholics for all of the brain regions examined. When subjects were grouped by the presence or absence of the DRD2A1 allele, [3H] naloxone binding was lower in all brain regions examined of subjects with the A1 allele than in those without this allele, with a significant difference in the caudate nucleus. According to Ritchie and Noble [40], these findings suggest one of the consequences of chronic alcohol exposure in humans is an enhancement of the brain opioid receptor system. However, the decreased [3H] naloxone binding with the A1 allele may be a compensatory response to their decreased dopaminergic modulation of opiate receptor activity. Moreover, Lawford et al. [35] studied 95 Caucasian opioid-dependent patients for over a one-year period in an outpatient methadone treatment program and found significant associations with heroin use and methadone treatment. There was a more than four fold higher frequency of the A1 allele in the poor treatment group compared with the successful treatment outcome group ($p = 0.00002$). Furthermore, the average use of heroin during the year prior to study entry was more than twice as great in patients with the A1 allele compared to those with the A2 allele ($p = 0.003$). The results indicate that DRD2 variants are predictors of heroin use and subsequent methadone treatment outcome. Other studies support the association of polymorphisms of the DRD2 gene (promoter −141 Delta C) and heroin use [41]. Finally, Dockstader et al. [41], found that opiate-naïve D2 receptor knockout mice demonstrated acquisition of morphine-conditioned place preference but failed to acquire place preference when conditioned in the deprived state. The authors suggest that D2 receptor function is critical in mediating the motivational effects of opiates only when the animal is in an opiate-dependent and withdrawn motivational state.

Thus coupling amino-acid therapy and enkephalinase inhibition while blocking the *delta*-receptors with a pure narcotic antagonist may be quite promising as a novel method to induce rapid detox in chronic methadone patients. This may also have important ramifications in the treatment of both opiate and alcohol-dependent individuals, especially as a relapse prevention tool. In further support for the genetic commonality of alcohol and heroin dependence, the National Institute on Alcohol Abuse and Alcoholism recently reported data that strongly suggests that DRD2 is a susceptibility gene for substance abuses across multiple populations. Specifically, a haplotype block of 25.8 kb region was highly associated with alcohol dependence and heroin addiction [42]. It may also be interesting too further test this hypothesis with the sublingual combination of the partial opiate mu receptor agonist buprenorphrine [43].

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