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(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF VIRGINIA PATENT FOUNDATION** [US/US]; 250 West Main Street, Suite 300, Charlottesville, Virginia 22902 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **JOHNSON, Bankole, A.** [GB/US]; 4098 Wood Lane, Keswick, Virginia 22947 (US). **TIOURIRINE, Nassima Ait-Daoud** [DZ/US]; 465 Foxdale Lane, Charlottesville, Virginia 22903 (US). **LYNCH, Wendy J.** [US/US]; 695 Victoria Court, Charlottesville, Virginia 22901 (US).

(74) Agent: **SPARKS, Rodney L.**; University of Virginia Patent Foundation, 250 West Main Street, Suite 300, Charlottesville, Virginia 22902 (US).

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(54) **Title:** MEDICATION COMBINATIONS FOR THE TREATMENT OF ALCOHOLISM AND DRUG ADDICTION

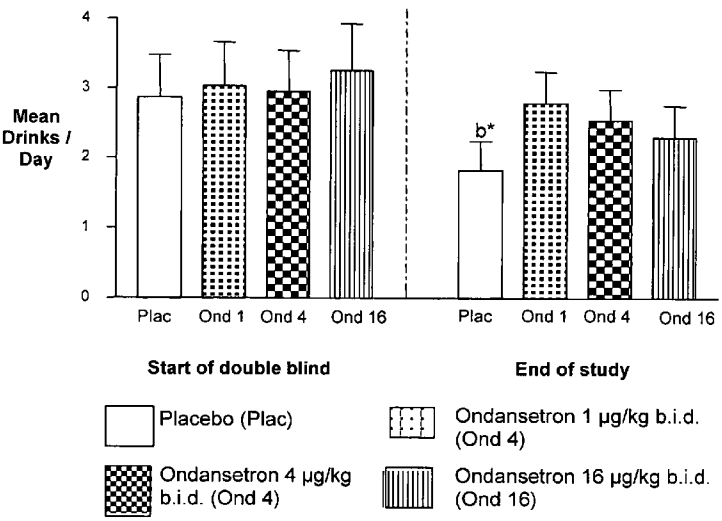

FIG. 1A

(57) **Abstract:** The present invention provides for the use of combinations of drugs to treat addictive disorders. More specifically, the present invention provides compositions and methods for treating disorders using combinations of drugs such as topiramate, ondansetron, and naltrexone.

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MEDICATION COMBINATIONS FOR THE TREATMENT OF ALCOHOLISM AND DRUG ADDICTION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is entitled to priority pursuant to 35 U.S.C. § 119(e) to U.S. provisional patent application no. 60/966,265, filed on August 27, 2007. The entire disclosure of the afore-mentioned patent application is incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made in part with United States Government support under National Institutes of Health Grant Nos. AA012964 and AA13074. The United States Government has certain rights in the invention.

FIELD OF THE INVENTION

The present invention relates generally to the use of combination therapies to treat addiction-related diseases and disorders and impulse control disorders, particularly alcohol-related diseases and disorders.

BACKGROUND

Neuroscientific advances have greatly increased the understanding of the pharmaco-behavioral effects of various neurotransmitter systems in the acquisition and maintenance of alcohol dependence. Medications that interact either directly or indirectly with neurotransmitters that modulate cortico-mesolimbic dopamine (CMDA) neurons have been central to most pharmacological strategies in the last decade (for reviews, see Wise and Bozarth, 1987, Psychol. Rev., 94:469-492; Hyman and Malenka, 2001, Nat. Rev. Neurosci., 2:695-703; Koob, 2003, Alcohol Clin. Exp. Res., 27:232-243); and Weiss and Porrino, 2002, J. Neurosci., 22:3332-3337). The addictive effects of most abused drugs and alcohol are mediated through increased dopaminergic activity in the cortico-mesolimbic system that originates in the ventral tegmental area, relays in the nucleus accumbens, and sends forward profuse connections to the cortex and other higher brain centers. Direct DA

antagonists have failed to demonstrate therapeutic efficacy consistently, possibly because the high degree of neuroadaptation that occurs with direct post-synaptic blockade mitigates against any long-standing therapeutic effect (Johnson and Ait-Daoud, 2002, Psychopharmacology, 149:327-344; Kreek et al., 2002, Nat. Rev. Drug Discov., 1:710-726.

Three major issues have promulgated scientific interest in the development of medicational adjuncts to psychosocial or behavioral therapy for the treatment of alcoholism. First, up to one-half of alcoholics relapse shortly after detoxification, psychosocial, or behavioral treatment. Second, advances in the neurosciences have implicated several target neurotransmitter systems such as those within the mesocorticolimbic pathway which mediate some of alcohol's rewarding effects associated with its abuse liability. Selective medications designed to oppose these neuronal systems may enhance the effectiveness of alcoholism treatments. Third, some alcoholics may possess biological abnormalities which predispose them to disease. These biologically-vulnerable alcoholics might benefit from specific adjunctive medication targeted towards correcting or ameliorating the underlying abnormalities. Because these abnormalities involve several neurotransmitters, combinations of medications targeting specific systems may yield better clinical outcomes than treatment of only one affected pathway would alone. Hence, obtaining optimal treatment matching combinations for various types of alcoholic remains an important research goal.

Alcohol abuse and dependence are widespread and it is estimated that 14 million American adults abused alcohol or were dependent on it in 1992 and that approximately 10% of Americans will be affected by alcohol dependence sometime during their lives. Alcohol dependence, characterized by the preoccupation with alcohol use, tolerance, and withdrawal, is a chronic disorder with genetic, psychosocial, and environmental factors influencing its development and manifestations. Studies have demonstrated the significance of opioids (i.e., beta-endorphin), dopamine (DA), serotonin (5-HT), γ-amino-butyric acid (GABA), and glutamate for the development and maintenance of alcohol dependence. To date, most pharmacotherapy trials have focused on single pharmacological agents. However, because of the failure to find consistent results with these drug therapies, investigating the efficacy of combining drugs that target multiple neurotransmitter systems or genes is perhaps more important to the development of future

pharmacotherapies for treatment of alcohol dependence and treatment of other addictive disorders and impulse control disorders.

Various medications and behavioral therapy have been used to treat alcohol dependence. The neuronal targets of alcohol include many neurotransmitter systems and the molecules participating in or regulating the systems, including GABA, glutamate, DA, opioids, and serotonin (for a review see Johnson, 2004, Expert Opin. Pharmacother., 5:9:1943-1955).

Despite the number of studies performed in this area, few drugs for alcohol dependence are approved in the U.S. The approved drugs are disulfiram, naltrexone, Vivitrex®/Vivitrol® (a long-acting depot formulation of naltrexone), and acamprosate. Disulfiram is an irreversible inhibitor of aldehyde dehydrogenase leading to increased levels of acetaldehyde, a toxic intermediate in alcohol metabolism. Patients who take disulfiram and drink alcohol experience an increased dilation of arterial and capillary tone producing hypotension, nausea, vomiting, flushing, headache and possibly in some, worse symptoms. Therefore, the concept behind the use of disulfiram is that the alcohol-dependent individual associates drinking with unpleasant adverse events and, as a result, avoids further alcohol consumption. Nevertheless, recent research shows that disulfiram has limited utility because compliance is low unless it is administered by a partner or spouse.

Naltrexone's principal site of action is at the μ opioid receptors in the mesolimbic pathway, putatively blocking the reinforcing effects of alcohol by decreasing DA release in the nucleus accumbens (NAc). Studies using naltrexone report that the opioid antagonist is more effective than placebo in reducing craving and heavy drinking, and increasing the percentage of non-drinking days, but does not necessarily enhance abstinence. Although these studies support the efficacy of naltrexone, others report limited utility for the drug only when individuals were highly compliant or even not at all.

Acamprosate, a structural analogue of GABA, was approved to promote abstinence in recently detoxified individuals. Although the exact mechanism of action is unknown, the drug is thought to restore glutamatergic-mediated inhibitory and excitatory neurotransmission in the NAc. Despite the important contributions these drugs make to alcohol treatment, abstinence or even reduced heavy drinking levels still remain elusive for many. This suggests the need for discovering medications providing more efficacious treatments.

Serotonin (5-HT) dysfunction probably contributes to the development of alcoholism. Serotonin's receptors contribute to alcohol use in animals, as alcohol increases basal levels of 5-HT affecting receptors. Of the seven distinct families of 5-HT receptors, three are known to contribute to alcohol dependence: 5-HT_{1A} receptors might be associated with alcohol consumption and the development of tolerance; 5-HT_2 receptors with reward; and 5-HT_3 receptors with the development of reinforcement. Based on such evidence, several serotonergic drugs have been examined, but with inconsistent results. Presently only sertraline and ondansetron (a serotonin-3 (5-HT_3) antagonist) appear to show any promise with certain subtypes of alcoholic patients and fluoxetine with depressed alcoholics (see Kenna, 2005, Drug Discovery Today: Therapeutic Strategies, 2:1:71-78 and Johnson, 2000, Alcohol. Clin. Exp. Res., 24:1597-1601).

The 5-HT_3 receptor is involved in the expression of alcohol's rewarding effects. Behavioral pharmacological studies show that many of alcohol's rewarding effects are mediated by interactions between DA and 5-HT receptors in the midbrain and cortex. 5-HT receptors are densely distributed in the terminals of mesocorticolimbic DA containing neurons, where they regulate DA release in these brain regions. These DA pathways, particularly those in the NAc, are critically involved in mediating the rewarding effects of abused substances including alcohol. Demonstration that 5-HT_3 receptor blockade reduces DA activity, and therefore the rewarding effects of abused drugs (including alcohol), comes from at least three different animal paradigms. 5-HT_3 receptor antagonists: 1) attenuate hyperlocomotion in the rat induced by DA or ethanol injection into the nucleus accumbens; 2) inhibit DiMe-C7 (a neurokinin)-induced hyperlocomotion, which is also attenuated by the DA antagonist, fluphenazine; and 3) decrease alcohol consumption in several animal models and across different species.

Despite reductions in drinking in lab studies with animals and in human drinking sessions in which subjects have been administered selective serotonin re-uptake inhibitors (SSRIs), most double-blind placebo-controlled studies using SSRIs have not reduced drinking or any other measures of alcohol dependency. Recent research however, suggests that because of the heterogeneity of the disease, perhaps subtypes of alcoholics respond differently to SSRIs.

Animal studies demonstrated that the 5-HT_3 receptor facilitates some of the biochemical and behavioral effects of alcohol through midbrain DA release. 5-HT_3

antagonists are consistently shown to suppress alcohol preference in animal studies, with recent evidence suggesting the 5-HT_{3A} receptor subunit requisite for 5-HT_3 antagonist-induced reductions in alcohol consumption.

Ondansetron, a 5-HT_3 receptor antagonist, has functionally opposite effects to SSRIs and blocks serotonin agonism at the 5-HT_3 receptor. Ondansetron can be effective for early-onset alcoholics (EOA) but not late-onset alcoholics (LOA), where age of onset of alcoholism (younger versus older than 25 years old) is the basis for subtyping alcoholics (Johnson, 2000, Alcohol. Clin. Exp. Res., 24:1597-1601). In a placebo-controlled trial, 271 participants were stratified into EOA and LOA subtypes by 1, 4, and 16 μg/kg twice-daily doses of ondansetron compared with placebo (Johnson, 2000, J. Am. Med. Assoc., 284:963-971). Patients with EOA who received ondansetron showed significant reductions in drinking (particularly those receiving 4 μg/kg twice daily) compared with LOA across all groups. In another study, it was shown that ondansetron treatment is more likely to be associated with improved drinking outcomes among EOA compared with LOA (Kranzler et al., (2003, Alcohol. Clin. Exp. Res., 27:1150-1155). Ondansetron continues to be examined for individuals with early-onset alcoholism.

The reasons for these differential effects are unknown; however, one hypothesis suggests that alcoholics with a biological predisposition have a dysregulation of serotonergic function primarily associated with serotonin transporter (SERT) function (Johnson, 2000, Alcohol. Clin. Exp. Res. 24:1597-1601). The polymorphic variation of the SERT (the 5′-HTTLPR) is hypothesized to be involved with the effectiveness of ondansetron and sertraline in EOA and LOA alcohol-dependent individuals, respectively. Given that epidemiologic studies demonstrate that alcohol dependence has an approximately 50–60% heritability, the prospect for positive outcomes to drug therapy at least partly dependent on genetic predisposition in some alcoholics is strong. Recent studies have, therefore, attempted to delineate the genetic components associated with alcohol dependence. These findings highlight the important role that 5-HT plays in alcohol consumption, although drug trials using serotonergics have had difficulty delineating responders from non-responders.

Animal studies suggest that fluctuating DA levels contribute to craving leading in turn to relapse in abstinent alcoholics. Reward associated with alcohol cues manipulating DA release by the mesolimbic pathway and positive symptoms of

schizophrenia seem to share similar dopaminergic dysfunction. Neuroleptics that regulate DA occupancy at DRD2, possibly causing an up-regulation of DRD2, might be associated with reduced positive symptoms of schizophrenia and reduced substance use.

Haloperidol, tiapride, olanzapine, and clozapine have all demonstrated various degrees of efficacy reducing craving and alcohol consumption or increasing abstinence. Although they are theoretically interesting drugs to study, the risks associated with the side effects of typical or atypical neuroleptics have outweighed the benefits for using DA antagonists as serious treatments for alcoholism.

Aripiprazole, an atypical neuroleptic, has few of the limiting side effects associated with these related medications. Aripiprazole is a partial dopamine agonist (PDA) with mixed $HT_{1A/2A}$ activity. As with other PDAs, aripiprazole has a high affinity to bind to DA receptors but with low intrinsic activity, subsequently acting as an antagonist or agonist under conditions of hyper- or hypodopaminergic availability, respectively. Additionally, as a mixed $HT_{1A/2A}$ receptor drug aripiprazole has been proposed as a medication that may reduce alcohol consumption.

Nevertheless, extensive research on such medications as direct dopamine blocking agents has not proven to be useful as clinical treatment for alcohol or drug use related disorders. This is probably because direct dopamine blocking agents produce rapid neuroadaptation in the brain, thereby reducing any early therapeutic gains. Furthermore, because of their propensity for adverse events, direct dopamine blocking agents are not taken reliably by patients; hence limiting their capacity to be effective as a treatment for alcohol or substance use, abuse, or dependence.

Midbrain and cortical DA pathways mediate alcohol's rewarding effects. Alcohol consumption increases GABA receptor activity which inhibits midbrain DA neurons and facilitates DA neurotransmission. Non-N-methyl-D-aspartate (NMDA) glutamate antagonists oppose GABA activity, thereby decreasing DA release. Topiramate (a GABA/glutamate modulator) and gabapentin are FDA-approved antiepileptics. Topiramate is thought to have multiple mechanisms of action, including enhanced GABA inhibition that results in decreased DA facilitation in the midbrain, antagonism of kainate to activate the kainite or AMPA type glutamate receptor subtypes, and inhibition of carbonic anhydrase Type II and IV isoenzymes (Johnson, 2004, Alcohol. Clin. Exp. Res., 28:1137-1144). Gabapentin reduces

glutamate and increases GABA neurotransmission in the brain. Theoretically therefore, the unique pharmacology of these medications is well suited to the treatment of alcohol dependence or withdrawal and could normalize the brain dysregulation seen during the early abstinence period.

In a double-blind placebo-controlled trial, 150 men and women were titrated up to a maximum of 300 mg of topiramate per day during a 12-week period (Johnson et al., 2003, Lancet, 361:1677-1685). Participants in the topiramate arm reported significantly fewer drinks per day, drinking days, and drinks per drinking day, significantly more days of abstinence, and significantly less craving than placebo. Because abstinence was not a goal at the start of the study, the medication might be more beneficial during the abstinence-initiation phase of treatment. Although gabapentin has seen increased use as an alternative to benzodiazepines in alcohol withdrawal syndrome, its use as a potential adjunct to naltrexone for promoting abstinence in alcoholism is also being investigated.

The basis for combining naltrexone and acamprosate lies in positive and negative reinforcement of alcohol dependence. Naltrexone can influence positive reinforcement of alcohol use affected by the β-endorphin opiate system, which modulates dopamine release. Negative reinforcement, which occurs when one drinks to reduce anxiety, or relieve withdrawal, might be helped by the abstinence reinforcing effects of acamprosate. Although each drug individually appears to provide modest yet significant effects on treatment and drinking outcomes, taking advantage of naltrexone's reduction in relapse rates and acamprosate's reduced drinking frequency and abstinence promotion was the basis for the COMBINE trial which combined both in addition to behavioral strategies for treating alcohol dependence.

Naltrexone has been administered with ondansetron in EOA. In an 8-week, double-blind, placebo-controlled trial, the combination was found to significantly reduce drinks per day and drinks per drinking day and to have a positive effect on the percentage of days abstinent compared with placebo (Ait-Daoud et al., 2001, Psychopharmacology, 154:23-27). The authors suggested that adding ondansetron to naltrexone can provide a synergistic action in the EOA patient subtype.

Both ondansetron and topiramate have proven to be efficacious in treating alcohol dependence in humans, presumably through their actions on cortico-mesolimbic dopamine (CMDA).

Various types of combination therapies have been used in an attempt to treat and prevent alcohol dependence and binge drinking. For example, Anton et al. (2006, J. Am. Med. Assoc., 295:2003-2017) combined pharmacotherapies (naltrexone and acamprosate) with behavioral therapy. However, current evidence for the usefulness of combination pharmacotherapy is lacking (Williams, 2005, Am. Fam. Physician, 72:9:1775-1780). Combination therapies are also being tested in an attempt to treat other addiction-related diseases and disorders.

There is a long-felt need in the art for compositions and methods useful for treating addiction-related diseases and disorders. The present application satisfies this need.

SUMMARY OF THE INVENTION

The present invention, in one aspect, differs from prior art in that it discloses combinations of multiple medications, preferably at least three different medications, which can be used in single combined formulations, or used singly, within specific dosing ranges to produce severe reduction or cessation of alcohol or drug taking. In one aspect, two or more medications are administered. In another aspect, three or more medications are administered. Further, the invention encompasses a unique dosing strategy to enable the combination to be provided safely and with a minimum of adverse events.

Nevertheless, it must be emphasized that this is a complex neuroadaptive brain system and the effects of neural changes can often be reversed with chronic medication administration. One important point about the present invention is that because most of the neuromodulation that is proposed occurs via ion channels — mainly glutaminergic and serotonergic — the capacity for neuronal neuroadaptation is reduced. Therefore, it would be reasonable to expect this combination to work uniquely well because the brain will not show rapid neuroadaptation following chronic medication administration.

It is proposed herein that a more promising approach than the use of direct dopamine antagonists will be the development of medications that are indirect modulators of cortico-mesolimbic DA function through effects at serotonergic, opiate, glutamate (GLU), or gamma-amino-butyric acid (GABA) receptors. To date, the most promising agent from this approach has been topiramate, a sulfamate-substituted fructopyranose derivative. Indeed, topiramate is a safe and efficacious

treatment for alcohol dependence. Yet, there remains a pharmacological opportunity to enhance topiramate's therapeutic response. Given that cortico-mesolimbic neurons have interactions with several neurotransmitter systems including opioids in critical brain reinforcement regions such as the nucleus accumbens (NAcc), and alcohol has multiple and varied effects at these same neurotransmitters, it is reasonable to propose that adding the opiate antagonist, naltrexone, to topiramate would act to modulate CMDA function contemporaneously and suppress alcohol reinforcement more reliably. Essentially, this combination of topiramate and naltrexone would lead to an added or synergistic therapeutic response in treating alcohol-dependent individuals. Further, it is proposed that because delivery of the topiramate and naltrexone combination would lead to CMDA neuromodulation in widespread areas of the brain — rostrally from the ventral tegmental area and through the orbito-frontal cortex — the neuropharmacological effects of the medication combination would be less susceptible to neuroadaptation, and therapeutic effects would be maintained with long-term and chronic dosing. Additionally, as described above, ondansetron's effects make it useful as a third drug for drug combination therapies encompassed by the present invention.

Further, because both topiramate and naltrexone have the ability to produce weight loss — probably through different mechanisms (naltrexone by peripheral effects on gut motility and satiety and topiramate through central or metabolic effects on glucose metabolism) — these effects also might add up or be synergistic to produce a therapeutic agent that could be used to treat obesity. Indeed, the attraction of this combination for the treatment of obesity would be that weight loss would be induced alongside a decrease in cravings or impulsivity (also mediated through CMDA neurons) to consume large amounts of food.

The present application discloses the combination of topiramate, ondansetron, and naltrexone for the treatment of addictive disorders and for associated impulsivity including obesity. The present invention encompasses formulating the combination of topiramate and naltrexone, as well as other drugs, in multiple formats to optimize the invention.

When compounds of the invention are to be administered at the same time, they can be administered in a formulation containing more than one compound of the invention.

The present invention encompasses an approach that combines drugs for the treatment or prevention of addictive disorders such as alcohol dependence. Because the reinforcing effects of most abused drugs are also mediated by CMDA neurons, the present invention provides combination therapy with drugs such as topiramate, ondansetron, and naltrexone as efficacious treatments for addictive disorders including (but not limited to) alcohol, eating, cocaine, methamphetamine, marihuana, tobacco abuse and addiction, and other addictive behaviors, including, but not limited to, gambling and sex. Based on the unexpected discoveries described herein, one of ordinary skill in the art will now appreciate that the compounds of the invention useful for combination drug therapy can in some instances be used singly instead of as part of a combination. Additionally, based on the present application, one of ordinary skill in the art will also appreciate that the compounds of the invention useful for combination drug therapy can in some instances be used in any combination. Until the present discovery of useful combination therapies as disclosed herein, one or ordinary skill in the art would not have had such an appreciation.

Notably, the exact medication combination(s) that may be useful is neither obvious nor is it likely to be the simple addition of any two or more compounds that might singly have an effect. As evidence for this, a case in point is that the combinations that so far have been tried and published in the scientific literature have not been demonstrated to be more effective than the single medication but also not even more effective than placebo. For instance, whilst a European study proposed that the combination of naltrexone and acamprosate would have an additive effect, this was not the finding of the study. While the results of that study suggested that the combination may be better than acamprosate, it did not show that the combination was significantly better than naltrexone alone (Kiefer et al., Arch Gen Psychiatry, 2003, 60:92-99). Furthermore, in a much larger sample study conducted recently in the US, the combination of naltrexone and acamprosate was no better than either medication alone or placebo (Anton et al., JAMA 2006, 295:2003-2017). Therefore, there is no reliable evidence that the combining naltrexone and acamprosate has additive effects on alcohol treatment. Furthermore, proposed combinations of other medications, potentially useful on their own, such as gabapentin and naltrexone and naltrexone and sertraline have all failed to show an improvement of effect over the single medication or placebo. Hence, finding the

right combination of medication that will be superior to either medication alone, or even placebo, is not obvious, has hitherto not been achieved reliably, and is not predictable from ordinary skill or knowledge of the art.

Regarding direct dopamine blocking agents, a more promising approach for their use than what has been tested previously, is hypothesized herein to encompass the use of neuromodulators of dopamine function (rather than direct dopamine blocking agents) as potential treatments for alcohol use, abuse, or dependence. Such medications should have reduced potential to induce rapid neuroadaptation and a favorable adverse-effect profile. Additionally, we propose that the right combination of such neuromodulators, not presently obvious given the state-of-the-art, may be even more beneficial by enhancing efficacy and reducing adverse events.

In one embodiment, the present invention provides compositions and methods for treating or preventing an alcohol-related disease or disorder comprising administering to a subject a therapeutically effective amount of at least two anti-alcohol agents or compounds, and optionally other therapeutic agents. Preferably, at least three anti-alcohol agents or compounds are used in the combination therapy. The present invention further encompasses the adjunctive use of psychosocial management techniques. In one aspect, the drug combination therapy is more effective alone than when combined with psychosocial management techniques. In another aspect, the drug combination therapy combined with psychosocial management techniques is more effective than drug combination therapy alone. In one aspect, the present invention provides methods for treating or preventing an alcohol-related disease or disorder in a subject comprising administering an effective amount of at least two compounds, or preferably at least three compounds, or analogs, homologs, derivatives, modifications, and pharmaceutically acceptable salts thereof, selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, norepinephrine antagonists, GABA agonists, GABA inhibitors, GABA receptor antagonists, GABA channel antagonists, glutamate agonists, glutamate antagonists, glutamine agonists, glutamine antagonists, anti-convulsant agents, NMDA-blocking agents, calcium channel antagonists, carbonic anhydrase inhibitors, neurokinins, small molecules, peptides, vitamins, co-factors, anti-orexin agents, regulators of cannabanoid receptor-1, and Corticosteroid Releasing Factor

antagonists. In one aspect, the neurokinin is NPY. The present invention further encompasses administering other small molecules and peptides.

In one embodiment, the alcohol-related disease or disorder being treated includes, but is not limited to, early-onset alcoholic, late-onset alcoholic, alcohol-induced psychotic disorder with delusions, alcohol abuse, excessive drinking, heavy drinking, problem drinking, alcohol intoxication, alcohol withdrawal, alcohol intoxication delirium, alcohol withdrawal delirium, alcohol-induced persisting dementia, alcohol-induced persisting amnestic disorder, alcohol dependence, alcohol-induced psychotic disorder with hallucinations, alcohol-induced mood disorder, alcohol-induced or associated bipolar disorder, alcohol-induced or associated posttraumatic stress disorder, alcohol-induced anxiety disorder, alcohol-induced sexual dysfunction, alcohol-induced sleep disorder, alcohol-induced or associated gambling disorder, alcohol-induced or associated sexual disorder, alcohol-related disorder not otherwise specified, alcohol intoxication, and alcohol withdrawal. In one aspect, the alcohol-related disease or disorder is early onset alcoholic. In another aspect, the alcohol-related disease or disorder is late onset alcoholic.

In one embodiment, the present invention provides compositions and methods for reducing the frequency of alcohol consumption compared with the frequency of alcohol consumption before the treatment. One of ordinary skill in the art will appreciate that the frequency can be compared with prior consumption by the subject or with consumption by a control subject not receiving the treatment. In one aspect, the type of alcohol consumption is heavy drinking. In another aspect, it is excessive drinking.

In one embodiment, the present invention provides compositions and methods for reducing the quantity of alcohol consumed in a subject compared with the amount of alcohol consumed before the treatment or compared with the alcohol consumption by a control subject not receiving the treatment.

One of ordinary skill in the art will appreciate that in some instances a subject being treated for and addictive disorder is not necessarily dependent. Such subjects include, for example, subjects who abuse alcohol, drink heavily, drink excessively, are problem drinkers, or are heavy drug users. The present invention provides compositions and methods for treating or preventing these behaviors in non-dependent subjects.

In one embodiment of the invention, the present invention provides compositions and methods for improving the physical or psychological sequelae associated with alcohol consumption compared with a control subject not receiving the treatment.

In one embodiment, the present invention provides compositions and methods for increasing the abstinence rate of a subject compared with a control subject not receiving the treatment.

In one embodiment, the present invention provides compositions and methods for reducing the average level of alcohol consumption in a subject compared with the level of alcohol consumption before the treatment or compared with the level of alcohol consumption by a control subject not receiving the treatment.

In one embodiment, the present invention provides compositions and methods for reducing alcohol consumption and for increasing abstinence compared with the alcohol consumption by the subject before treatment or with a control subject not receiving the treatment.

In one embodiment, the present invention provides compositions and methods for treating a subject with a predisposition to early-onset alcoholism.

In one embodiment, the present invention provides compositions and methods for treating a subject with a predisposition to late-onset alcoholism.

One of ordinary skill in the art will appreciate that there are multiple parameters or characteristics of alcohol consumption which may characterize a subject afflicted with an alcohol-related disease or disorder. It will also be appreciated that combination therapies may be effective in treating more than one parameter, and that there are multiple ways to analyze the effectiveness of treatment. The parameters analyzed when measuring alcohol consumption or frequency of alcohol consumption include, but are not limited to, heavy drinking days, number of heavy drinking days, average drinking days, number of drinks per day, days of abstinence, number of individuals not drinking heavily or abstinent over a given time period, and craving. Both subjective and objective measures can be used to analyze the effectiveness of treatment. For example, a subject can self-report according to guidelines and procedures established for such reporting. The procedures can be performed at various times before, during, and after treatment. Additionally, assays are available for measuring alcohol consumption. These assays

include breath alcohol meter readings, measuring serum CDT and GGT levels, and measuring 5-HTOL urine levels.

The present invention further provides adjunctive therapies to be used in conjunction with the combination drug therapies. The present invention further provides adjunctive therapy or treatment wherein the subject is also submitted to a psychosocial management program. Psychosocial management programs are known in the art and include, but are not limited to, Brief Behavioral Compliance Enhancement Treatment, Cognitive Behavioral Coping Skills Therapy, Motivational Enhancement Therapy, Twelve-Step Facilitation Therapy (Alcoholics Anonymous), Combined Behavioral Intervention, Medical Management, psychoanalysis, psychodynamic treatment, and Biopsychosocial, Report, Empathy, Needs, Advice, Direct Advice and Assessment. The present invention further encompasses the use of additional adjunct therapies and treatment, including hypnosis and acupuncture.

The present invention further provides for advice to be provided to subjects in conjunction with drug combination therapy. Advice constitutes a set of instructions pertaining to the potential consequences of excessive drinking, a calendar or other method for monitoring drinking, and instructions or suggestions about how to reduce or stop drinking. Any of these strategies either alone or in any combination, and no matter how brief or lengthy, can constitute advice. The advice can be provided in a format such as written, electronic, or interpersonal. In one embodiment, the drug combination therapy is more effective at treatment or prevention than merely administering a placebo and providing advice, administering no drugs and providing advice, or not administering drugs or providing advice. In one aspect, the combination drug therapy is more effective at treatment or prevention than drug therapy used in combination with a psychosocial management program.

In one embodiment, at least one of the compounds being administered is administered at least once a day. In one aspect, it is administered at least twice a day. In another embodiment, it is administered at least once a week. In yet another embodiment, it is administered at least once a month.

In one embodiment, at least one of the compounds is a serotonin receptor antagonist. In one aspect, the serotonin receptor is the serotonin-3 receptor. In one aspect, the compound is ondansetron.

In one embodiment, at least three different compounds are administered to the subject.

It will be appreciated by one of ordinary skill in the art that the multiple compounds, preferably three or more compounds, being administered do not necessarily have to be administered at the same time or in equal doses. In one aspect, the compounds being administered as part of the drug combination therapy are separately administered. In another aspect, a first compound is administered before a second or third compound is administered. In yet another aspect, a first compound and a second compound are administered nearly simultaneously, while a third compound is administered at a different time. In a further aspect, the first compound is administered subsequent to administration of a second compound or third compound.

The invention further provides pharmaceutical compositions comprising compounds of the invention. The pharmaceutical composition may comprise one or more compounds of the invention, and biologically active analogs, homologs, derivatives, modifications, and pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier. In one embodiment, the compounds are administered as a pharmaceutical composition.

The route of administration can vary depending on the type of compound being administered. In one aspect, the compounds are administered via routes such as oral, topical, rectal, intramuscular, intramucosal, intranasal, inhalation, ophthalmic, and intravenous.

The present invention further provides for administration of a compound of the invention as a controlled-release formulation.

In one embodiment, the present invention provides administering at least three compounds, wherein at least three of the compounds are topiramate, ondansetron, and naltrexone.

In one embodiment, the present invention provides compositions and methods for treating alcohol-related diseases and disorders using pharmaceutical compositions comprising effective amounts of topiramate, ondansetron, and naltrexone.

The dosage of the active compound(s) being administered will depend on the condition being treated, the particular compound, and other clinical factors such as age, sex, weight, and health of the subject being treated, the route of administration

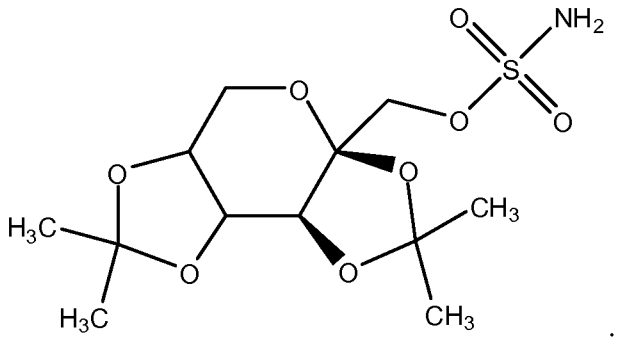
of the compound(s), and the type of composition being administered (tablet, gel cap, capsule, solution, suspension, inhaler, aerosol, elixir, lozenge, injection, patch, ointment, cream, etc.). It is to be understood that the present invention has application for both human and veterinary use.

For example, in one embodiment relating to oral administration to humans, a dosage of between approximately 0.1 and 300 mg/kg/day, or between approximately 0.5 and 50 mg/kg/day, or between approximately 1 and 10 mg/kg/day, is generally sufficient, but will vary depending on such things as the disorder being treated, the length of treatment, the age, sex, weight, and/or health of the subject, etc. The combinations of drugs can be administered in formulations that contain all drugs being used, or the drugs can be administered separately. In some cases, it is anticipated that multiple doses/times of administration will be required or useful. Additionally, for most treatment regimens, at least two compounds will be used. In one aspect, at least three compounds will be administered. The present invention further provides for varying the length of time of treatment.

Topiramate is disclosed herein as a drug useful in combination drug therapy. In one embodiment, topiramate is provided at a dosage ranging from about 15 mg/day to about 2500 mg/day. In one aspect, topiramate is administered at a dosage ranging from about 25 mg/day to about 1000 mg/day. In yet another aspect, topiramate is administered at a dosage ranging from about 50 mg/day to about 500 mg/day. In one aspect, topiramate is administered at a dosage of about 400 mg/day. In another aspect, topiramate is administered at a dosage of 400 mg/day. In a further aspect, topiramate is administered at a dosage of about 300 mg/day. In yet a further aspect, topiramate is administered at a dosage of about 275 mg/day. In one aspect, topiramate is administered at a dose of about 1 mg/day. In one aspect, up to about 300 mg/day is administered.

In one embodiment, topiramate is provided at a dose of about 1 mg/kg. In one aspect, topiramate is provided at a dose of about 10 mg/kg. In one aspect, topiramate is provided at a dose of about 100 mg/kg. In one embodiment, topiramate is administered at a dosage ranging from about 0.1 mg/kg/day to about 100 mg/kg/day.

Topiramate ($C_{12}H_{21}NO_8S$; IUPAC name: 2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate; CAS Registry No. 97240-79-4) has the following structure:



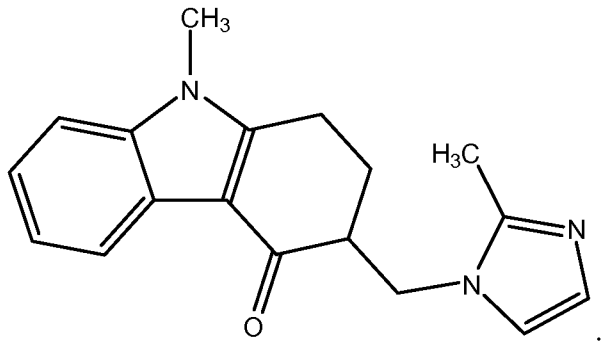
An important aspect of psychotropic drugs is to produce weight gain. These increases in weight gain can induce a range of metabolic problems including abnormal sugar, fat, and carbohydrate metabolism. Because topiramate can cause weight loss and improve endocrine function, it is proposed herein that topiramate may be used to ameliorate weight gain caused by other psychotropic drugs with which it is combined as well as alcohol and any other abused drugs.

An important adverse event of topiramate is cognitive impairment. In the general population, this is reported by 2.4% of individuals who take topiramate (Johnson & Johnson Pharmaceutical Research & Development. Investigator's Brochure: Topiramate (RWJ-17021-000), 10th ed.; December 2005). In the substance abuse field, the occurrence rate of cognitive impairment is about 18.7% (Johnson BA, Ait-Daoud N, Bowden CL et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 2003, 361:1677-1685). Topiramate-associated cognitive effects are due to its anti-glutaminergic properties. It is, therefore, not obvious that ondansetron, a serotonin-3 receptor antagonist, will alleviate these complaints of cognitive impairment. Ondansetron appears to have cholinergic effects, perhaps though interactions with the GABA system, that seem to ameliorate topiramate-associated cognitive impairment. Hence, it is to be expected that the rate of cognitive impairment reported by this triple combination would be less than that for topiramate on its own.

Ondansetron is disclosed herein as a drug useful in the combination drug therapy of the invention. The dosage and treatment regimen for administering ondansetron when it is being used as one compound of a combination therapy can be varied based on the other drug or drugs with which it is being administered, or based on other criteria such as the age, sex, health, and weight of the subject. The present

invention therefore provides for the use of ondansetron at varying doses such as about 0.01 μg/kg, about 0.1 μg/kg, about 1.0 μg/kg, about 5.0 μg/kg, about 10.0 μg/kg, about 0.1 mg/kg, about 1.0 mg/kg, about 5.0 mg/kg, and about 10.0 mg/kg. In another embodiment, ondansetron is administered at a dosage ranging from about 0.01 μg/kg to about 100 μg/kg per application. In one aspect, ondansetron is administered at a dosage ranging from about 0.1 μg/kg to about 10.0 μg/kg per application. In yet another aspect, ondansetron is administered at a dosage ranging from about 1.0 μg/kg to about 5.0 μg/kg per application. In a further aspect, ondansetron is administered at a dosage of about 4.0 μg/kg per application. In another aspect, ondansetron is administered at a dosage of about 3.0 μg/kg per application. In one aspect, ondansetron is administered at a dose of about 4 μg/kg twice daily (about 0.25 to 0.6 mg twice daily for body weights between about 50 kg and 150 kg).

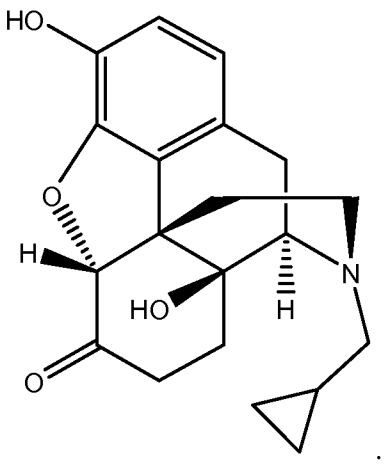
Ondansetron ($C_{18}H_{19}N_3O$; CAS Registry No. 99614-02-5; IUPAC name: 9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-1,2,3,9-tetrahydrocarbazol-4-one) has the following structure:



The present invention further provides for the use of other drugs such as naltrexone as part of the drug combination therapy disclosed herein. In one embodiment, naltrexone is administered at a dose of about 10 mg/day. In one aspect, naltrexone is administered at a dosage at a dosage of about 50 mg/day. In one aspect, naltrexone is administered at a dosage of about 100 mg/day. In one aspect, naltrexone is administered at a dosage ranging from about 1 mg to about 300

mg per application. In another aspect, naltrexone is administered at a dosage ranging from about 10 mg to about 50 mg per application. In a further aspect of the invention, naltrexone is administered at a dosage of about 25 mg per application. In one embodiment, naltrexone is administered at least once a month. In a further embodiment, naltrexone is administered once a month. In one embodiment, naltrexone is administered at least once a week. In another embodiment, naltrexone is administered at least once a day. In a further embodiment, naltrexone is administered at least twice a day. In one aspect, naltrexone is administered twice a day.

Naltrexone ($C_{20}H_{23}NO_4$; 17-(Cyclopropylmethyl)-4,5a-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride; CAS Registry No. 16590-41-3) has the following structure:



Naltrexone also has important adverse events — nausea and vomiting — that reduce compliance to it. Indeed, about 15% of individuals in alcohol trials are unable to tolerate a naltrexone dose of 50 mg/day. This has led to the development of depot formulations that release naltrexone slowly to reduce the incidence of nausea and vomiting. Nevertheless, these depot formulation(s) appear to have similar compliance rates to the oral form of the medication. Importantly, ondansetron reduces nausea and decreases vomiting by slowing gut motility. Therefore, a combination that adds ondansetron to naltrexone will diminish the nausea and vomiting caused by naltrexone. This is an important therapeutic advance because many more people will be able to tolerate the treatment due to increased compliance, and higher doses than the typically administered naltrexone dose of 50 mg/day can be given to improve the therapeutic response.

In one embodiment where at least three compounds are administered, topiramate, ondansetron, and naltrexone are administered. In one aspect, topiramate is administered at a dosage of as much as about 400 mg/day, ondansetron is administered at a dosage of about 1 to 10 μg/kg twice daily, and naltrexone is administered at a dosage of about 25 mg/application to about 150 mg/application. In a further aspect, topiramate is administered at a dosage of about 300 mg/day, ondansetron is administered at a dosage of about 4.0 μg/kg twice daily, and naltrexone is administered at a dosage of about 25-50 mg/application.

In one aspect, the treatment comprises combining ondansetron and naltrexone at full doses at the beginning of the treatment, followed by titrating topiramate administration up from 0 to about 300 mg/day over the first few weeks of the treatment, preferably for about 6 weeks. This titration procedure is used to avoid the development of important adverse events that would preclude further medication administration. For example, ondansetron can be administered at an approximate dose of 4 μg/kg twice daily (about 0.25 to 0.60 mg twice daily for body weights between 50 and 150 kg), and naltrexone at a dose of up to 100 mg/day. Then, topiramate administration would be titrated from 0 to about 300 mg/day over a period of about six weeks.

This varied administration schedule is based on the observations described herein where the combination of topiramate and ondansetron is additive but the addition of naltrexone completely blunts the response to alcohol reinforcement. This is an unexpected result, as the initial assumption for the experiments described herein was that the addition of naltrexone to topiramate and ondansetron would simply be additive. Instead, the triple combination produces a complete blunting of alcohol reinstatement in animals. Translated to humans, this triple combination encompasses producing a major suppression of the drive to relapse following a period of recovery from alcohol. Therefore, the invention further encompasses the ability to come close to abolishing the drive or propensity to drink excessively and should be of help to stop or severely reduce alcohol consumption by alcoholics who are still drinking when they start the medication. One of ordinary skill in the art will appreciate that the doses and scheduling of administration can be adjusted based on variables such as the age, sex, weight, overall health, and severity of the particular alcohol-related problem in the subject to be treated.

In one embodiment, the results of treating a subject with a combination of two or more compounds are additive compared with the effects of using any of the compounds alone. This does not mean that if three or more compounds are administered that the results will be additive as to the combination of all drugs, just two or more. In one aspect, the effects seen when using two or more compounds are greater than when using any of the compounds alone. In one embodiment, the results of treating a subject with a combination of two or more compounds are synergistic compared with the effects of using the compounds alone, at least with regard to two compounds.

In one embodiment, other compounds may be used in combination with topiramate and naltrexone, for example, ondansetron.

Additional compounds can be used to treat subjects of the invention. In addition to the combination treatment of at least two drugs, or at least three drugs, described above, the present invention further provides for the administration of at least one additional compound to treat or prevent diseases and disorders of the invention, including, but not limited to, disulfiram, acamprosate, sertraline, galanthamine, nalmefene, naloxone, desoxypeganine, benzodiazepines, neuroleptics, risperidone, rimonabant, trazodone, baclofen, regulators of cannabanoid receptor-1, regulators of orexin, and aripiprazole. In one aspect, an additional compound is used with the combination therapy drugs topiramate and ondansetron. One of ordinary skill in the art will appreciate that in some cases the combination therapy using these additional compounds will have additive effects and in some cases synergistic effects. Methods for testing these combinations and analyzing the results are known in the art.

In addition to the combination drug therapy described herein for treating or preventing addiction-related diseases and disorders such as alcohol-related diseases and disorders, additional types of compounds can be administered to treat further the addiction-related diseases and disorders or to treat other diseases and disorders. The additional types of compounds include, but are not limited to, adrenergics, adrenocortical steroids, adrenocortical suppressants, aldosterone antagonists, amino acids, analeptics, analgesics, anorectic compounds, anorexics, anti-anxiety agents, antidepressants, antihypertensives, anti-inflammatories, antinauseants, antineutropenics, antiobsessional agents, antiparkinsonians, antipsychotics, appetite suppressants, blood glucose regulators, carbonic anhydrase inhibitors, cardiotonics,

cardiovascular agents, choleretics, cholinergics, cholinergic agonists, cholinesterase deactivators, cognition adjuvants, cognition enhancers, hormones, memory adjuvants, mental performance enhancers, mood regulators, neuroleptics, neuroprotectives, psychotropics, relaxants, sedative-hypnotics, stimulants, thyroid hormones, thyroid inhibitors, thyromimetics, cerebral ischemia agents, vasoconstrictors, and vasodilators.

In one embodiment, the present invention provides methods and compositions useful for decreasing mesocorticolimbic dopamine activity.

In one embodiment, the present invention provides methods and compositions useful for regulating mesocorticolimbic dopamine activity.

In one embodiment, the present invention provides methods and compositions useful for inhibiting glutamate function.

In one embodiment, the present invention provides methods and compositions useful for facilitating γ-amino-butyric acid activity.

In one embodiment, the present invention provides methods and compositions useful for regulating γ-amino-butyric acid activity.

The present invention provides for multiple methods for delivering the compounds of the invention. The compounds may be provided, for example, as pharmaceutical compositions in multiple formats as well, including, but not limited to, tablets, capsules, pills, lozenges, syrups, ointments, creams, elixirs, suppositories, suspensions, inhalants, injections (including depot preparations), and liquids.

The present invention further encompasses biologically active analogs, homologs, derivatives, and modifications of the compounds of the invention. Methods for the preparation of such compounds are known in the art. In one aspect, the compounds are topiramate, naltrexone, and ondansetron.

The compositions and methods described herein for treating or preventing alcohol-related diseases and disorders are also useful for treating or preventing other addiction-related diseases and disorders and impulse control disorders. In one aspect, the compositions and methods elicit an indirect effect on CMDA neurons. Such effects may be elicited, for example, by regulating serotonergic, opiate, glutamate, or γ-amino-butyric acid receptors. In one aspect, the addictive diseases and disorders include eating disorders, impulse control disorders, nicotine-related disorders, methamphetamine-related disorders amphetamine-related disorders,

cannabis-related disorders, cocaine-related disorders, hallucinogen use disorders, inhalant-related disorders, benzodiazepine abuse or dependence related disorders, and opioid-related disorders.

The compositions and methods described herein are also useful for treating or preventing heavy drug use, including, but not limited to, cocaine, methamphetamine, other stimulants, phencyclidine, other hallucinogens, marijuana, sedatives, tranquilizers, hypnotics, and opiates. It will be appreciated by one of ordinary skill in the art that heavy use or abuse of a substance does not necessarily mean the subject is dependent on the substance.

The compositions and methods of the present invention are also useful as a multi-faceted combination therapy approach to treating and regulating weight loss, obesity, and weight gain. The invention provides not just single compounds, but instead acts on multiple points in the feeding and satiety pathway. Further, because some drugs such as topiramate, ondansetron, and naltrexone have the ability to produce weight loss, probably through different mechanisms (ondansetron by peripheral effects on gut motility and satiety, naltrexone by decreasing the impulse to binge, and topiramate through central or metabolic effects on glucose metabolism), these effects also might add up or be synergistic to produce a therapeutic agent that could be used to treat obesity or to aid in inducing weight loss in overweight individuals or in any case where it would be beneficial to lose weight. Indeed, the attraction of this combination for the treatment of obesity would be that weight loss would be induced alongside a decrease in cravings or impulsivity (also mediated through CMDA neurons) to consume large amounts of food.

Therefore, the combination therapy of the present invention for the treatment of addictive disorders and associated impulsivity, including obesity, is a new and useful therapy. Based on the data and descriptions provided herein, as well as what is known in the art, one of ordinary skill in the art will know how to combine and use drugs such as topiramate, ondansetron, and naltrexone in multiple formats to optimize the invention. These pharmacological formats include (but are not limited to) tablets, gel caps, capsules, chewable and orally absorbable materials (for example, sublingual tablets), elixirs, suspensions, inhalants, sprays, patches, ointments and balms, long-acting intramuscular injections (with FDA-approved polylactide capsules or nanotechnology), and intravenous, subcutaneous, intramucosal, or any other avenues for injection.

In one embodiment, the present invention provides compositions and methods for treating obesity or being overweight comprising administering to a subject in need thereof an effective amount of at least two compounds, or analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, anti-convulsant agents, and NMDA-blocking agents, thereby treating or preventing, optionally in combination with at least one additional therapeutically active compound.

In one embodiment of treating obesity, the additional therapeutically active compound is selected from the group consisting of antidiabetic agents, antihyperlipidemic agents, antiobesity agents, antihypertensive agents, and agents for the treatment of complications resulting from or associated with diabetes.

In one embodiment of treating obesity, the subject has a body mass index of about 30.0 or greater.

In one embodiment of treating being overweight, the subject has a body mass index of between 25.0 and 29.9.

In one aspect, a subject being treated for obesity is also subjected to a psychosocial management program.

In one aspect, a subject being treated for being overweight is also subjected to a psychosocial management program or provided with advice regarding the benefits of maintaining normal weight.

The compositions, combination therapies, and psychosocial management programs useful for treating alcohol-related diseases and disorders and obesity are also useful for regulating weight gain and weight loss. In one embodiment, the present invention provides compositions and methods useful for preventing or inhibiting weight gain. In another aspect, the present invention provides compositions and methods useful for stimulating weight loss. For example, the compositions and methods of the invention can be used to treat an overweight subject, such as one with a body mass index of about 25.0 to about 29.9. One of

ordinary skill in the art will appreciate that similar dosages and drugs can be used compared with preventing or reducing weight gain, but will also understand how to make useful modifications in the dosages of compounds administered and the regimens used. In one embodiment, the present invention provides treatments for regulating weight control using such drugs as topiramate, ondansetron, and naltrexone.

In one embodiment, the compositions and methods are also useful for suppressing appetite.

In one embodiment, the composition and methods are also useful for suppressing thoughts, urges, compulsions, or cravings for food.

In one embodiment, the compositions and methods of the present invention are also useful for treating or preventing an addiction-related disease or disorder other than alcohol-related diseases and disorders and weight control diseases and disorders. The method comprises administering an effective amount of at least three compounds of the invention, or analogs, derivatives, modifications, and pharmaceutically acceptable salts thereof. In one aspect, the compounds include, but are not limited to, serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, norepinephrine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, glutamine agonists, glutamine antagonists, anti-convulsant agents, N-methyl-D-aspartate-blocking agents, calcium channel antagonists, carbonic anhydrase inhibitors, neurokinins, and Corticosteroid Releasing Factor antagonists. In one aspect, the compounds are topiramate, ondansetron, and naltrexone.

In one embodiment, the addiction-related disease or disorder is drug use. In one embodiment, the present invention provides a method for treating or preventing heavy drug use. The method encompasses administering an effective amount of at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine

release inhibitors, dopamine antagonists, norepinephrine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, glutamine agonists, glutamine antagonists, anti-convulsant agents, N-methyl-D-aspartate-blocking agents, calcium channel antagonists, carbonic anhydrase inhibitors, neurokinins, small molecules, peptides, vitamins, co-factors, and Corticosteroid Releasing Factor antagonists.

In one aspect, the heavy drug use is selected from the group consisting of cocaine, methamphetamine, other stimulants, phencyclidine, other hallucinogens, marijuana, sedatives, tranquilizers, hypnotics, and opiates. In one aspect, the frequency of said heavy drug use is at least once a month. In another aspect, the heavy drug use is at least once a week. In one aspect, advice is provided to the subject. In one aspect, the advice is provided in a format selected from the group consisting of written, electronic, or interpersonal. In one aspect, the method is more effective at treating or preventing heavy drug use than administering a placebo and providing advice, administering no drugs and providing advice, or not administering drugs or providing advice. In one aspect, the method is more effective at treating or preventing heavy drug use than the method used in combination with a psychosocial management program.

The invention provides all possible combination and permutations for the use of such drugs to treat addictive diseases and disorders, either singly or in any combination. In one embodiment, the addictive disorders include, but are not limited to, eating disorders, impulse control disorders, gambling disorders, sexual disorders, nicotine-related disorders, amphetamine-related disorders, cannabis-related disorders, cocaine-related disorders, hallucinogen use disorders, inhalant-related disorders, benzodiazepine abuse- or dependence-related disorders, and opioid-related disorders. Food and eating disorders include, for example, binge eating. In one aspect, the combination pharmacotherapy is provided in conjunction with behavioral modification therapy or intervention.

One of ordinary skill in the art will appreciate that the compounds, combinations, dosages, and administration regimens described above for treating alcohol related disorders are also applicable to the treatment of the other addictive disorders described herein.

The invention further provides kits for administering the compounds of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1, comprising Figures 1A (Early Onset Alcoholics) and 1B (Late Onset Alcoholics), graphically illustrate the effects of ondansetron treatment. The data represent the mean (± SE) of drinking outcomes (mean drinks/day) during the double-blind response period for Early and Late Onset Alcoholics. The left panel of each figure represents the start of the double blind study and the right panel of each represents the end of the study. Open bars represent placebo; Small squares represent ondansetron at 1 μg/kg; Large squares represent ondansetron at 4 μg/kg; Vertical lines in the bar represent ondansetron at 16 μg/kg.

Figure 2, comprising Figures 2A (EOA) and 2B (LOA), graphically illustrates the effects of ondansetron on Carbohydrate Deficient Transferrin (CDT) ratio in Early and Late Onset Alcoholics. The ordinate represents Mean Log CDT Ration. Mean log CDT ratio = mean log CDT at a given visit (i.e., 4, 8, or 12)/mean log CDT at visit 0. ** = $p < 0.01$; * = $p < 0.05$. Open bars represent placebo; Small squares represent ondansetron at 1 μg/kg; Large squares represent ondansetron at 4 μg/kg; Vertical lines in the bar represent ondansetron at 16 μg/kg.

Figure 3 graphically illustrates the effects of Naltrexone on alcohol consumption in non-human primates (rhesus monkeys). Naltrexone was administered at 0.1 (○), 0.3 (●), 1.0 (□) or 3.0 (■) g/kg. The ordinate represents cumulative deliveries as percent change from baseline. The abscissa represents time in 10 minute blocks.

Figure 4, comprising Figures 4A (Drinks/Day) and 4B (Drinks/Drinking Day), graphically illustrates the effects of the combination of Ondansetron and Naltrexone (●) or placebo (○) on drinking outcomes in Early Onset Alcoholics in an eight week study. Baselines are indicated by arrow at time zero and the Start of the Double-Blind is indicated by an arrow at time point 1. The data are presented as mean (± SE).

Figure 5 graphically illustrates the effects of treatment with Ritanserin in conjunction with Cognitive Behavioral Therapy. The ordinate represents the mean number of drinks since the last visit and the abscissa indicates the time period of

assessment in the study (in weeks). Subjects were treated with 2.5 mg Ritanserin (●), 5.0 mg Ritanserin (✖), or received placebo (▲).

Figure 6 is a schematic representation of an experimental recruitment and design protocol for using alcohol dependent patients in a study.

Figure 7 graphically illustrates a representative example of a study time line comparing the number of enrolled subjects (cross-hatched bars) and the number of subjects completing (open bars) the study. The ordinate represents Study Years and the abscissa represents the number of subjects.

Figure 8 graphically illustrates the combined effect of topiramate and naltrexone on alcohol consumption in alcohol-preferring (P) rats. Rats received either vehicle, topiramate at 5 mg/kg, topiramate at 10 mg/kg, naltrexone at 1/mg/kg and topiramate at 5 mg/kg, naltrexone at 1/mg/kg and topiramate at 10 mg/kg, or naltrexone at 1 mg/kg. Each data point represents the mean (± SE) of 8 rats as a change from baseline.

Figure 9 schematically illustrates some of the brain pathways and their regulation related to addiction.

Figure 10, comprising 5 panels- Figs. 10A to 10E, graphically illustrates the combined effect of topiramate (10 mg/kg, IP), ondansetron (0.001 mg/kg, IP), and naltrexone (1 mg/kg, IP) on alcohol consumption in alcohol-preferring (P) rats. 10A- Topiramate alone; 10B- Ondansetron alone; 10C- Vehicle; 10D- Topiramate + Ondansetron; 10E- Topiramate + Ondansetron + Naltrexone. Data are plotted across seven consecutive sessions, which include a 3-day baseline period, the test session in which the ondansetron, topiramate, and naltrexone injection was administered, and the three sessions that followed the test session. Each data point represents a mean (± SE) of at least six rats. The ordinate represents ethanol intake in g/kg and the abscissa represents session number.

Figure 11 is a schematic model summarizing some of the interactive pathways in the brain involved in related to addiction and addictive behavior, as well as various receptors and neurotransmitters known to be involved.

DETAILED DESCRIPTION

Abbreviations, Generic Names, and Acronyms

5-HT- serotonin

5-HT_3- a subtype of serotonin receptor, the serotonin-3 receptor

5-HTOL- 5-hydroxytryptophol

ADE- alcohol deprivation effect

ASPD- antisocial personality disorder

BBCET- Brief Behavioral Compliance Enhancement Treatment

BED- binge eating disorder

b.i.d.- twice a day

BRENDA- Biopsychosocial, Report, Empathy, Needs, Direct advice, and Assessment

CBI- combined behavioral intervention

CBT- Cognitive Behavioral Coping Skills Therapy, also referred to as cognitive behavioral therapy

CDT- carbohydrate-deficient transferrin

CMDA- cortico-mesolimbic dopamine

DA- dopamine

DSM- Diagnostic and Statistical Manual of Mental Disorders

EOA- early-onset alcoholic(s)

GABA- γ-amino-butyric acid (also referred to as γ-amino butyric acid and γ-aminobutyric acid)

GGT- γ-glutamyl transferase

ICD- impulse control disorder

IP- intraperitoneal

LOA- late-onset alcoholic(s)

MET- Motivational Enhancement Therapy

MM- Medical Management

NAc- nucleus accumbens (also referred to as nACC)

Naltrexone- a μ opioid receptor antagonist

NMDA- N-methyl-D-aspartate

NOS- not otherwise specified

Ondansetron (Zofran®)- a serotonin receptor antagonist

P- alcohol-preferring rats

SSRI- selective serotonin re-uptake inhibitor

Topiramate (Topamax®)- an anticonvulsant

TSF- Twelve-Step Facilitation Therapy (e.g., Alcoholics Anonymous)

VTA- ventral tegmental area

Definitions

In describing and claiming the invention, the following terminology will be used in accordance with the definitions set forth below. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described herein. As used herein, each of the following terms has the meaning associated with it in this section. Specific and preferred values listed below for radicals, substituents, and ranges are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

As used herein, the articles "a" and "an" refer to one or to more than one, i.e., to at least one, of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "about," as used herein, means approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

"Addictive disorders" include, but are not limited to, eating disorders, obesity-related disorders, impulse control disorders, alcohol-related disorders, nicotine-related disorders, amphetamine-related disorders, methamphetamine-related disorders, cannabis-related disorders, cocaine-related disorders, gambling, sexual disorders, hallucinogen use disorders, inhalant-related disorders, benzodiazepine abuse or dependence related disorders, and opioid-related disorders.

One of ordinary skill in the art will appreciate that addictive disorders such as those related to alcohol or drugs, does mean that a subject is dependent unless specifically defined as such.

The term "additional therapeutically active compound", in the context of the present invention, refers to the use or administration of a compound for an additional therapeutic use other than just the particular disorder being treated. Such a

compound, for example, could include one being used to treat an unrelated disease or disorder, or a disease or disorder which may not be responsive to the primary treatment for the addictive disease or disorder being treated. Disease and disorders being treated by the additional therapeutically active agent include, for example, hypertension and diabetes.

As used herein, the term "aerosol" refers to suspension in the air. In particular, aerosol refers to the particlization or atomization of a formulation of the invention and its suspension in the air.

As used herein, the term "affected cell" refers to a cell of a subject afflicted with a disease or disorder, which affected cell has an altered phenotype compared with a subject not afflicted with a disease, condition, or disorder.

Cells or tissue are "affected" by a disease or disorder if the cells or tissue have an altered phenotype relative to the same cells or tissue in a subject not afflicted with a disease, condition, or disorder.

As used herein, an "agonist" is a composition of matter that, when administered to a mammal such as a human, enhances or extends a biological activity of interest. Such effect may be direct or indirect.

The term "alcohol abuser", as used herein, refers to a subject who meets DSM IV criteria for alcohol abuse (i.e., "repeated use despite recurrent adverse consequences") but is not dependent on alcohol.

"Alcohol-related disorders" as used herein refers to diseases and disorder related to alcohol consumption and include, but are not limited to, alcohol-induced psychotic disorder, with delusions; alcohol abuse; excessive drinking; heavy drinking; problem drinking; alcohol intoxication; alcohol withdrawal; alcohol intoxication delirium; alcohol withdrawal delirium; alcohol-induced persisting dementia; alcohol-induced persisting amnestic disorder; alcohol dependence; alcohol-induced psychotic disorder, with hallucinations; alcohol-induced mood disorder; alcohol-induced or associated bipolar disorder; alcohol-induced or associated post traumatic stress disorder; alcohol-induced anxiety disorder; alcohol-induced sexual dysfunction; alcohol-induced sleep disorder; and alcohol-related disorder not otherwise specified (NOS).

As used herein, "amino acids" are represented by the full name thereof, by the three letter code corresponding thereto, or by the one-letter code corresponding thereto, as indicated in the following table:

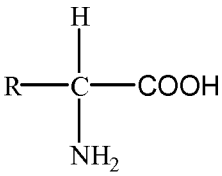
Full Name	Three-Letter Code	One-Letter Code
Aspartic Acid	Asp	D
Glutamic Acid	Glu	E
Lysine	Lys	K
Arginine	Arg	R
Histidine	His	H
Tyrosine	Tyr	Y
Cysteine	Cys	C
Asparagine	Asn	N
Glutamine	Gln	Q
Serine	Ser	S
Threonine	Thr	T
Glycine	Gly	G
Alanine	Ala	A
Valine	Val	V
Leucine	Leu	L
Isoleucine	Ile	I
Methionine	Met	M
Proline	Pro	P
Phenylalanine	Phe	F
Tryptophan	Trp	W

The expression "amino acid" as used herein is meant to include both natural and synthetic amino acids, and both D and L amino acids. "Standard amino acid" means any of the twenty standard L-amino acids commonly found in naturally occurring peptides. "Nonstandard amino acid residue" means any amino acid, other than the standard amino acids, regardless of whether it is prepared synthetically or derived from a natural source. As used herein, "synthetic amino acid" also encompasses chemically modified amino acids, including but not limited to salts, amino acid derivatives (such as amides), and substitutions. Amino acids contained within the peptides of the present invention, and particularly at the carboxy- or amino-terminus, can be modified by methylation, amidation, acetylation or substitution with other chemical groups which can change the peptide's circulating

half-life without adversely affecting their activity. Additionally, a disulfide linkage may be present or absent in the peptides of the invention.

The term "amino acid" is used interchangeably with "amino acid residue," and may refer to a free amino acid and to an amino acid residue of a peptide. It will be apparent from the context in which the term is used whether it refers to a free amino acid or a residue of a peptide.

Amino acids have the following general structure:



Amino acids may be classified into seven groups on the basis of the side chain R: (1) aliphatic side chains; (2) side chains containing a hydroxylic (OH) group; (3) side chains containing sulfur atoms; (4) side chains containing an acidic or amide group; (5) side chains containing a basic group; (6) side chains containing an aromatic ring; and (7) proline, an imino acid in which the side chain is fused to the amino group.

As used herein, the term "conservative amino acid substitution" is defined herein as exchanges within one of the following five groups:

I. Small aliphatic, nonpolar or slightly polar residues:
Ala, Ser, Thr, Pro, Gly;

II. Polar, negatively charged residues and their amides:
Asp, Asn, Glu, Gln;

III. Polar, positively charged residues:
His, Arg, Lys;

IV. Large, aliphatic, nonpolar residues:
Met Leu, Ile, Val, Cys

V. Large, aromatic residues:
Phe, Tyr, Trp

The nomenclature used to describe the peptide compounds of the present invention follows the conventional practice wherein the amino group is presented to the left and the carboxy group to the right of each amino acid residue. In the formulae representing selected specific embodiments of the present invention, the

amino- and carboxy-terminal groups, although not specifically shown, will be understood to be in the form they would assume at physiologic pH values, unless otherwise specified.

The term "basic" or "positively charged" amino acid, as used herein, refers to amino acids in which the R groups have a net positive charge at pH 7.0, and include, but are not limited to, the standard amino acids lysine, arginine, and histidine.

As used herein, an "analog" of a chemical compound is a compound that, by way of example, resembles another in structure but is not necessarily an isomer (e.g., 5-fluorouracil is an analog of thymine).

An "antagonist" is a composition of matter that when administered to a mammal such as a human, inhibits or impedes a biological activity attributable to the level or presence of an endogenous compound in the mammal. Such effect may be direct or indirect.

As used herein, the term "anti-alcohol agent" refers to any active drug, formulation, or method that exhibits activity to treat or prevent one or more symptom(s) of alcohol addiction, alcohol abuse, alcohol intoxication, and/or alcohol withdrawal, including drugs, formulations and methods that significantly reduce, limit, or prevent alcohol consumption in mammalian subjects.

The term "appetite suppression", as used herein, is a reduction, a decrease or, in cases of excessive food consumption, an amelioration in appetite. This suppression reduces the desire or craving for food. Appetite suppression can result in weight loss or weight control as desired.

The term "average drinking," as used herein, refers to the mean number of drinks consumed during a one week period. The term "average drinking" is used interchangeably herein with the term "average level of drinking."

A "compound," as used herein, refers to any type of substance or agent that is commonly considered a drug, or a candidate for use as a drug, as well as combinations and mixtures of the above.

A "control" subject is a subject having the same characteristics as a test subject, such as a similar type of dependence, etc. The control subject may, for example, be examined at precisely or nearly the same time the test subject is being treated or examined. The control subject may also, for example, be examined at a time distant from the time at which the test subject is examined, and the results of

the examination of the control subject may be recorded so that the recorded results may be compared with results obtained by examination of a test subject.

A "test" subject is a subject being treated.

As used herein, a "derivative" of a compound refers to a chemical compound that may be produced from another compound of similar structure in one or more steps, as in replacement of H by an alkyl, acyl, or amino group.

A "disease" is a state of health of a subject wherein the subject cannot maintain homeostasis, and wherein if the disease is not ameliorated then the subject's health continues to deteriorate. In contrast, a "disorder" in a subject is a state of health in which the subject is able to maintain homeostasis, but in which the subject's state of health is less favorable than it would be in the absence of the disorder. However, the definitions of "disease" and "disorder" as described above are not meant to supersede the definitions or common usage related to specific addictive diseases or disorders.

A disease, condition, or disorder is "alleviated" if the severity of a symptom of the disease or disorder, the frequency with which such a symptom is experienced by a patient, or both, are reduced.

As used herein, an "effective amount" means an amount sufficient to produce a selected effect, such as alleviating symptoms of a disease or disorder. In the context of administering compounds in the form of a combination, such as multiple compounds, the amount of each compound, when administered in combination with another compound(s), may be different from when that compound is administered alone. Thus, an effective amount of a combination of compounds refers collectively to the combination as a whole, although the actual amounts of each compound may vary. The term "more effective" means that the selected effect is alleviated to a greater extent by one treatment relative to the second treatment to which it is being compared.

The term "elixir," as used herein, refers in general to a clear, sweetened, alcohol-containing, usually hydroalcoholic liquid containing flavoring substances and sometimes active medicinal agents.

The term "excessive drinker," as used herein, refers to men who drink more than 21 alcohol units per week and women who consume more than 14 alcohol units per week. One standard drink is 0.5 oz of absolute alcohol, equivalent to 10 oz of

beer, 4 oz of wine, or 1 oz of 100-proof liquor. These individuals are not dependent on alcohol but may or may not meet DSM IV criteria for alcohol abuse.

As used herein, a "functional" molecule is a molecule in a form in which it exhibits a property or activity by which it is characterized. A functional enzyme, for example, is one that exhibits the characteristic catalytic activity by which the enzyme is characterized.

The term "heavy drinker," as used herein, refers to men who drink more than 14 alcohol units per week and women who consume more than 7 alcohol units per week. One standard drink is 0.5 oz of absolute alcohol, equivalent to 10 oz of beer, 4 oz of wine, or 1 oz of 100-proof liquor. These individuals are not dependent on alcohol but may or may not meet DSM IV criteria for alcohol abuse.

A "heavy drinking day," as used herein, refers to the consumption by a man or woman of more than about five or four standard drinks per drinking day, respectively.

The term "heavy drug use," as used herein, refers to the use of any drug of abuse, including, but not limited to, cocaine, methamphetamine, other stimulants, phencyclidine, other hallucinogens, marijuana, sedatives, tranquilizers, hypnotics, opiates at intervals or in quantities greater than the norm. The intervals of use include intervals such as at least once a month, at least once a week, and at least once a day. "Heavy drug use" is defined as testing "positive" for the use of that drug on at least 2 occasions in any given week with at least 2 days between testing occasions.

As used herein, the term "inhaler" refers both to devices for nasal and pulmonary administration of a drug, e.g., in solution, powder and the like. For example, the term "inhaler" is intended to encompass a propellant driven inhaler, such as is used to administer antihistamine for acute asthma attacks, and plastic spray bottles, such as are used to administer decongestants.

The term "inhibit," as used herein, refers to the ability of a compound or any agent to reduce or impede a described function, level, activity, synthesis, release, binding, etc., based on the context in which the term "inhibit" is used. Preferably, inhibition is by at least 10%, more preferably by at least 25%, even more preferably by at least 50%, and most preferably, the function is inhibited by at least 75%. The term "inhibit" is used interchangeably with "reduce" and "block."

The term "inhibit a complex," as used herein, refers to inhibiting the formation of a complex or interaction of two or more proteins, as well as inhibiting the function or activity of the complex. The term also encompasses disrupting a formed complex. However, the term does not imply that each and every one of these functions must be inhibited at the same time.

The term "inhibit a protein," as used herein, refers to any method or technique which inhibits protein synthesis, levels, activity, or function, as well as methods of inhibiting the induction or stimulation of synthesis, levels, activity, or function of the protein of interest. The term also refers to any metabolic or regulatory pathway which can regulate the synthesis, levels, activity, or function of the protein of interest. The term includes binding with other molecules and complex formation. Therefore, the term "protein inhibitor" refers to any agent or compound, the application of which results in the inhibition of protein function or protein pathway function. However, the term does not imply that each and every one of these functions must be inhibited at the same time.

As used herein, an "instructional material" includes a publication, a recording, a diagram, or any other medium of expression which can be used to communicate the usefulness of a compound of the invention in the kit for effecting alleviation of the various diseases or disorders recited herein. Optionally, or alternately, the instructional material may describe one or more methods of alleviating the diseases or disorders in a subject. The instructional material of the kit of the invention may, for example, be affixed to a container which contains the identified compound invention or be shipped together with a container which contains the identified compound. Alternatively, the instructional material may be shipped separately from the container with the intention that the instructional material and the compound be used cooperatively by the recipient.

As used herein, a "ligand" is a compound that specifically binds to a target compound or molecule. A ligand "specifically binds to" or "is specifically reactive with" a compound when the ligand functions in a binding reaction which is determinative of the presence of the compound in a sample of heterogeneous compounds.

A "receptor" is a compound or molecule that specifically binds to a ligand.

As used herein, the term "linkage" refers to a connection between two groups. The connection can be either covalent or non-covalent, including but not limited to ionic bonds, hydrogen bonding, and hydrophobic/hydrophilic interactions.

As used herein, the term "linker" refers to a molecule that joins two other molecules either covalently or noncovalently, e.g., through ionic or hydrogen bonds or van der Waals interactions.

The term "nasal administration" in all its grammatical forms refers to administration of at least one compound of the invention through the nasal mucous membrane to the bloodstream for systemic delivery of at least one compound of the invention. The advantages of nasal administration for delivery are that it does not require injection using a syringe and needle, it avoids necrosis that can accompany intramuscular administration of drugs, and trans-mucosal administration of a drug is highly amenable to self administration.

As used herein, the term "nucleic acid" encompasses RNA as well as single and double-stranded DNA and cDNA. Furthermore, the terms, "nucleic acid," "DNA," "RNA" and similar terms also include nucleic acid analogs, i.e. analogs having other than a phosphodiester backbone. For example, the so-called "peptide nucleic acids," which are known in the art and have peptide bonds instead of phosphodiester bonds in the backbone, are considered within the scope of the present invention. By "nucleic acid" is also meant any nucleic acid, whether composed of deoxyribonucleosides or ribonucleosides, and whether composed of phosphodiester linkages or modified linkages such as phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphoramidate, bridged phosphoramidate, bridged methylene phosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, bridged phosphorothioate or sulfone linkages, and combinations of such linkages. The term nucleic acid also specifically includes nucleic acids composed of bases other than the five biologically occurring bases (adenine, guanine, thymine, cytosine and uracil). Conventional notation is used herein to describe polynucleotide sequences: the left-hand end of a single-stranded polynucleotide sequence is the 5'-end; the left-hand direction of a double-stranded polynucleotide sequence is referred to as the 5'-direction. The direction of 5' to 3' addition of nucleotides to nascent RNA transcripts is referred to as the transcription direction. The DNA strand having the

same sequence as an mRNA is referred to as the "coding strand"; sequences on the DNA strand which are located 5' to a reference point on the DNA are referred to as "upstream sequences"; sequences on the DNA strand which are 3' to a reference point on the DNA are referred to as "downstream sequences."

Unless otherwise specified, a "nucleotide sequence encoding an amino acid sequence" includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. Nucleotide sequences that encode proteins and RNA may include introns.

"Obesity" is commonly referred to as a condition of increased body weight due to excessive fat. Drugs to treat obesity are generally divided into three groups: (1) those that decrease food intake, such as drugs that interfere with monoamine receptors, such as noradrenergic receptors, serotonin receptors, dopamine receptors, and histamine receptors; (2) those that increase metabolism; and (3) those that increase thermogenesis or decrease fat absorption by inhibiting pancreatic lipase (Bray, 2000, Nutrition, 16:953-960 and Leonhardt et al., 1999, Eur. J. Nutr., 38:1-13). Obesity has been defined in terms of body mass index (BMI). BMI is calculated as weight (kg)/[height (m)]^2, according to the guidelines of the U.S. Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO). Physical status: The use and interpretation of anthropometry. Geneva, Switzerland: World Health Organization 1995. WHO Technical Report Series), for adults over 20 years old, BMI falls into one of these categories: below 18.5 is considered underweight, 18.5-24.9 is considered normal, 25.0-29.9 is considered overweight, and 30.0 and above is considered obese.

The term "oligonucleotide" typically refers to short polynucleotides, generally no greater than about 50 nucleotides. It will be understood that when a nucleotide sequence is represented by a DNA sequence (i.e., A, T, G, C), this also includes an RNA sequence (i.e., A, U, G, C) in which "U" replaces "T."

The term "peptide" typically refers to short polypeptides.

"Polypeptide" refers to a polymer composed of amino acid residues, related naturally occurring structural variants, and synthetic non-naturally occurring analogs thereof linked via peptide bonds, related naturally occurring structural variants, and synthetic non-naturally occurring analogs thereof. Synthetic polypeptides can be synthesized, for example, using an automated polypeptide synthesizer.

The term "protein" typically refers to large polypeptides.

A "recombinant polypeptide" is one which is produced upon expression of a recombinant polynucleotide.

A peptide encompasses a sequence of 2 or more amino acids wherein the amino acids are naturally occurring or synthetic (non-naturally occurring) amino acids. Peptide mimetics include peptides having one or more of the following modifications:

1. peptides wherein one or more of the peptidyl --C(O)NR-- linkages (bonds) have been replaced by a non-peptidyl linkage such as a --CH2-carbamate linkage (--CH2OC(O)NR--), a phosphonate linkage, a -CH2-sulfonamide (-CH 2--S(O)2NR--) linkage, a urea (--NHC(O)NH--) linkage, a --CH2 -secondary amine linkage, or with an alkylated peptidyl linkage (--C(O)NR--) wherein R is C1-C4 alkyl;

2. peptides wherein the N-terminus is derivatized to a --NRR1 group, to a -- NRC(O)R group, to a --NRC(O)OR group, to a --NRS(O)2R group, to a --NHC(O)NHR group where R and R1 are hydrogen or C1-C4 alkyl with the proviso that R and R1 are not both hydrogen;

3. peptides wherein the C terminus is derivatized to --C(O)R2 where R2 is selected from the group consisting of C1-C4 alkoxy, and --NR3R4 where R3 and R4 are independently selected from the group consisting of hydrogen and C1-C4 alkyl.

The term "per application" as used herein refers to administration of a drug or compound to a subject.

As used herein, the term "pharmaceutically acceptable carrier" includes any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions such as an oil/water or water/oil emulsion, and various types of wetting agents. The term also encompasses any of the agents approved by a regulatory agency of the US Federal government or listed in the US Pharmacopeia for use in animals, including humans.

As used herein, the term "physiologically acceptable" ester or salt means an ester or salt form of the active ingredient which is compatible with any other ingredients of the pharmaceutical composition, and which is not deleterious to the subject to which the composition is to be administered.

The term "prevent", as used herein, means to stop something from happening, or taking advance measures against something possible or probable from

happening. In the context of medicine "prevention" generally refers to action taken to decrease the chance of getting a disease or condition.

The term "problem drinker," as used herein, encompasses individuals who drink excessively and who report that their alcohol consumption is causing them problems. Such problems include, for example, driving while intoxicated, problems at work caused by excessive drinking, and relationship problems caused by excessive drinking by the subject.

As used herein, "protecting group" with respect to a terminal amino group refers to a terminal amino group of a peptide, which terminal amino group is coupled with any of various amino-terminal protecting groups traditionally employed in peptide synthesis. Such protecting groups include, for example, acyl protecting groups such as formyl, acetyl, benzoyl, trifluoroacetyl, succinyl, and methoxysuccinyl; aromatic urethane protecting groups such as benzyloxycarbonyl; and aliphatic urethane protecting groups, for example, tert-butoxycarbonyl or adamantyloxycarbonyl. See Gross and Mienhofer, eds., *The Peptides*, vol. 3, pp. 3-88 (Academic Press, New York, 1981) for suitable protecting groups.

As used herein, "protecting group" with respect to a terminal carboxy group refers to a terminal carboxyl group of a peptide, which terminal carboxyl group is coupled with any of various carboxyl-terminal protecting groups. Such protecting groups include, for example, tert-butyl, benzyl, or other acceptable groups linked to the terminal carboxyl group through an ester or ether bond.

The term "psychosocial management program," as used herein, relates to the use of various types of counseling and management techniques used to supplement the combination pharmacotherapy treatment of addictive and alcohol-related diseases and disorders.

As used herein, the term "purified" and like terms relate to an enrichment of a molecule or compound relative to other components normally associated with the molecule or compound in a native environment. The term "purified" does not necessarily indicate that complete purity of the particular molecule has been achieved during the process. A "highly purified" compound as used herein refers to a compound that is greater than 90% pure.

"Reduce"- see "inhibit".

The term "regulate" refers to either stimulating or inhibiting a function or activity of interest.

A "sample," as used herein, refers to a biological sample from a subject, including, but not limited to, normal tissue samples, diseased tissue samples, biopsies, blood, saliva, feces, semen, tears, and urine. A sample can also be any other source of material obtained from a subject which contains cells, tissues, or fluid of interest.

By "small interfering RNAs (siRNAs)" is meant, inter alia, an isolated dsRNA molecule comprising both a sense and an anti-sense strand. In one aspect, it is greater than 10 nucleotides in length. siRNA also refers to a single transcript which has both the sense and complementary antisense sequences from the target gene, e.g., a hairpin. siRNA further includes any form of dsRNA (proteolytically cleaved products of larger dsRNA, partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA) as well as altered RNA that differs from naturally occurring RNA by the addition, deletion, substitution, and/or alteration of one or more nucleotides.

By the term "specifically binds," as used herein, is meant a molecule which recognizes and binds a specific molecule, but does not substantially recognize or bind other molecules in a sample, or it means binding between two or more molecules as in part of a cellular regulatory process, where said molecules do not substantially recognize or bind other molecules in a sample.

The term "standard," as used herein, refers to something used for comparison. For example, it can be a known standard agent or compound which is administered or added and used for comparing results when adding a test compound, or it can be a standard parameter or function which is measured to obtain a control value when measuring an effect of an agent or compound on a parameter or function. Standard can also refer to an "internal standard", such as an agent or compound which is added at known amounts to a sample and is useful in determining such things as purification or recovery rates when a sample is processed or subjected to purification or extraction procedures before a marker of interest is measured. Internal standards are often a purified marker of interest which has been labeled, such as with a radioactive isotope, allowing it to be distinguished from an endogenous marker.

A "subject" of diagnosis or treatment is a mammal, including a human.

The term "subject comprises a predisposition to the early onset of alcoholism," as used herein, refers to a subject who has, or is characterized by, a predisposition to the early onset of alcoholism.

The term "symptom," as used herein, refers to any morbid phenomenon or departure from the normal in structure, function, or sensation, experienced by the patient and indicative of disease. In contrast, a sign is objective evidence of disease. For example, a bloody nose is a sign. It is evident to the patient, doctor, nurse and other observers.

As used herein, the term "treating" may include prophylaxis of the specific disease, disorder, or condition, or alleviation of the symptoms associated with a specific disease, disorder or condition and/or preventing or eliminating said symptoms. A "prophylactic" treatment is a treatment administered to a subject who does not exhibit signs of a disease or exhibits only early signs of the disease for the purpose of decreasing the risk of developing pathology associated with the disease. "Treating" is used interchangeably with "treatment" herein.

A "therapeutic" treatment is a treatment administered to a subject who exhibits signs of pathology for the purpose of diminishing or eliminating those signs.

A "therapeutically effective amount" of a compound is that amount of compound which is sufficient to provide a beneficial effect to the subject to which the compound is administered.

Chemical Definitions

As used herein, the term "halogen" or "halo" includes bromo, chloro, fluoro, and iodo.

The term "haloalkyl" as used herein refers to an alkyl radical bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like.

The term "C_1-C_n alkyl" wherein n is an integer, as used herein, represents a branched or linear alkyl group having from one to the specified number of carbon atoms. Typically, C_1-C_6 alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl, and the like.

The term "C_2-C_n alkenyl" wherein n is an integer, as used herein, represents an olefinically unsaturated branched or linear group having from two to the specified

number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, 1-propenyl, 2-propenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl, and the like.

The term "C_2-C_n alkynyl" wherein n is an integer refers to an unsaturated branched or linear group having from two to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, and the like.

The term "C_3-C_n cycloalkyl" wherein n = 8, represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

As used herein, the term "optionally substituted" refers to from zero to four substituents, wherein the substituents are each independently selected. Each of the independently selected substituents may be the same or different than other substituents.

As used herein the term "aryl" refers to an optionally substituted mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, benzyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, and the like. "Optionally substituted aryl" includes aryl compounds having from zero to four substituents, and "substituted aryl" includes aryl compounds having one or more substituents. The term (C_5-C_8 alkyl)aryl refers to any aryl group which is attached to the parent moiety via the alkyl group.

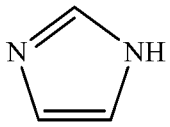
The term "heterocyclic group" refers to an optionally substituted mono- or bicyclic carbocyclic ring system containing from one to three heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, and nitrogen. As used herein the term "heteroaryl" refers to an optionally substituted mono- or bicyclic carbocyclic ring system having one or two aromatic rings containing from one to three heteroatoms and includes, but is not limited to, furyl, thienyl, pyridyl and the like.

The term "bicyclic" represents either an unsaturated or saturated stable 7- to 12-membered bridged or fused bicyclic carbon ring. The bicyclic ring may be attached at any carbon atom which affords a stable structure. The term includes, but is not limited to, naphthyl, dicyclohexyl, dicyclohexenyl, and the like.

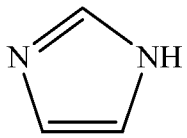
The compounds of the present invention contain one or more asymmetric centers in the molecule. In accordance with the present invention a structure that

does not designate the stereochemistry is to be understood as embracing all the various optical isomers, as well as racemic mixtures thereof.

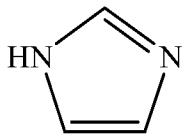
The compounds of the present invention may exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers. For example the following structure:



is understood to represent a mixture of the structures:



and



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The term "pharmaceutically-acceptable salt" refers to salts which retain the biological effectiveness and properties of the compounds of the present invention and which are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Embodiments

The present invention encompasses the use of combinations of drugs or compounds to treat addictive and compulsive diseases and disorders, particular alcohol-related diseases and disorders. The present invention further encompasses the use of adjunctive treatments and therapy such as psychosocial management regimes, hypnosis, and acupuncture.

In some embodiments, a first compound and a second compound are administered nearly simultaneously. In other embodiments, a first compound is administered prior to the second compound. In yet other embodiments, the first compound is administered subsequent to the second compound. If three or more compounds are administered, one of ordinary skill in the art will appreciate that the three or more compounds can be administered simultaneously or in varying order.

In certain embodiments disclosed herein, an individual is given a pharmaceutical composition comprising a combination of two or more compounds to treat or prevent an addiction-related disease or disorder or impulse control-related

disease or disorder. In some of these embodiments, each compound is a separate chemical entity. However, in other embodiments, the at least two compounds can be joined together by a chemical linkage, such as a covalent bond, so that the at least two different compounds form separate parts of the same molecule. In one aspect, the chemical linkage is selected such that after entry into the body, the linkage is broken, such as by enzymatic action, acid hydrolysis, base hydrolysis, or the like, and the two separate compounds are then formed.

Data from previous structure-activity relationship (SAR) studies within the art may be used as a guide to determine which compounds to use and the optimal position or positions on the molecules to attach the tether such that potency and selectivity of the compounds will remain high. The tether or linker moiety is chosen from among those of demonstrated utility for linking bioactive molecules together. Disclosed herein are representative compounds that can be attached together in different combinations to form heterobivalent therapeutic molecules.

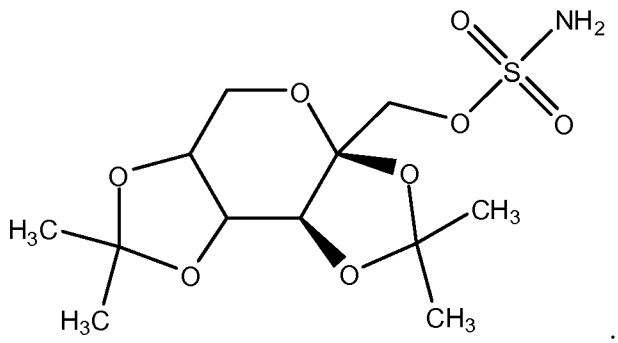
Examples of linkers reported in the scientific literature include methylene $(CH_2)_n$ linkers (Hussey et al., J. Am. Chem. Soc., 2003, 125:3692-3693; Tamiz et al., J. Med. Chem., 2001, 44:1615-1622), oligo ethyleneoxy $O(-CH_2CH_2O-)_n$ units used to link naltrexamine to other opioids, glycine oligomers of the formula $–NH-(COCH_2NH)_nCOCH_2CH_2CO--(NHCH_2CO)_nNH--$ used to link opioid antagonists and agonists together ((a) Portoghese et al., Life Sci., 1982, 31:1283-1286. (b) Portoghese et al., J. Med. Chem., 1986, 29:1855-1861), hydrophilic diamines used to link opioid peptides together (Stepinski et al., Internat. J. of Peptide & Protein Res., 1991, 38:588-92), rigid double stranded DNA spacers (Paar et al., J. Immunol., 2002, 169:856-864) and the biodegradable linker poly(L-lactic acid) (Klok et al., Macromolecules, 2002, 35:746-759). The attachment of the tether to a compound can result in the compound achieving a favorable binding orientation. The linker itself may or may not be biodegradable. The linker may take the form of a prodrug and be tunable for optimal release kinetics of the linked drugs. The linker may be either conformationally flexible throughout its entire length or else a segment of the tether may be designed to be conformationally restricted (Portoghese et al., J. Med. Chem., 1986, 29:1650-1653).

With respect to alcohol-related disorders, including but not limited to alcohol abuse and alcohol dependence, at least two compounds selected from the group consisting of topiramate, ondansetron, and naltrexone, and analogs, derivatives, and

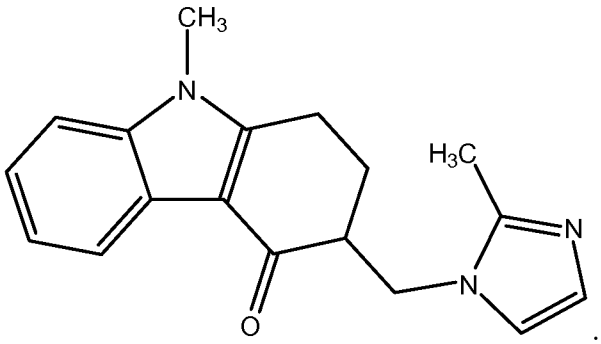
modifications thereof, and pharmaceutically acceptable salts thereof, can be used to decrease ethanol consumption associated with such alcohol-related disorders. In one aspect, topiramate and ondansetron are used. Accordingly, the present invention provides a method for treating or preventing alcohol-related disorders based on ethanol consumption, comprising administering to a subject in need of such treatment or prevention an effective amount of at least two compounds selected from the group consisting of topiramate, ondansetron, and naltrexone, and analogs, derivatives, and modifications thereof or a pharmaceutically acceptable salt thereof. In a further aspect, the combination pharmacotherapy treatment is used in conjunction with behavioral modification or therapy.

The present invention encompasses biologically active analogs, homologs, derivatives, and modifications of the compounds of the invention. Methods for the preparation of such compounds are known in the art. In one aspect, the compounds are topiramate, ondansetron, and naltrexone.

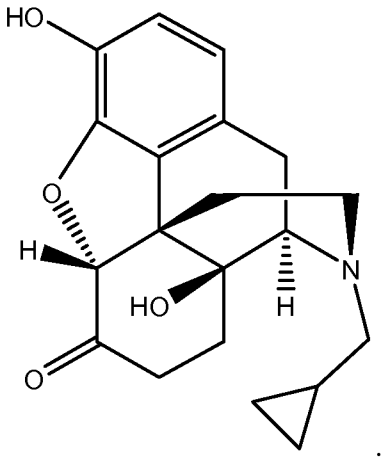
Topiramate ($C_{12}H_{21}NO_8S$; IUPAC name: 2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate; CAS Registry No. 97240-79-4) has the following structure:



Ondansetron ($C_{18}H_{19}N_3O$; CAS Registry No. 99614-02-5; IUPAC name: 9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-1,2,3,9-tetrahydrocarbazol-4-one) has the following structure:



Naltrexone ($C_{20}H_{23}NO_4$; 17-(Cyclopropylmethyl)-4,5a-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride; CAS Registry No. 16590-41-3) has the following structure:



The effectiveness of treatment or prevention of alcohol-related diseases and disorders can be detected and measured in several ways. For example, subjects can self-report according to guidelines and procedures set up for such reporting. Objective measures of alcohol consumption include the use of breath alcohol meter readings, measuring serum CDT levels, and measuring serum γ-glutamyl transferase (GGT) levels. Urinary 5-HTOL may also be measured and is an indicator of recent alcohol consumption. 5-HTOL is a minor metabolite of 5-HT. More than one of these types of assays may be performed to ensure accuracy. Other subjective and objective measures are also known. These measurements can be taken or performed at various times before, during, and after treatment.

The routes of administration, dosage amounts, and dosage forms described herein can be utilized for the administration of compounds of the invention or pharmaceutically acceptable salt thereof for the prevention or treatment of ethanol consumption. Suitable forms of the compounds for use in biologically active compositions and methods of the present invention include its pharmaceutically acceptable salts, polymorphs, solvates, hydrates, and prodrugs.

Administration of an effective amount of at least two compounds of the invention, or pharmaceutically acceptable salts thereof, whether alone or in combination with a secondary therapeutic agent, to a subject will detectably treat or prevent ethanol consumption in the subject. In exemplary embodiments, administration of at least two compounds of the invention, or pharmaceutically acceptable salts thereof, whether alone or in combination with additional therapeutic agents, will yield a reduction in ethanol consumption by at least about 10%, 20%, 30%, 50% or greater, up to about 75-90%, or about 95% or greater.

The present compositions can optionally comprise a suitable amount of a pharmaceutically acceptable vehicle so as to provide the form for proper administration to the patient.

The present compositions can also be administered to a subject in combination with behavioral therapy or interaction.

Included within the scope of this invention are the various individual anomers, diastereomers and enantiomers as well as mixtures thereof. In addition, the compounds of this invention also include any pharmaceutically acceptable salts, for example: alkali metal salts, such as sodium and potassium; ammonium salts; monoalkylammonium salts; dialkylammonium salts; trialkylammonium salts; tetraalkylammonium salts; and tromethamine salts. Hydrates and other solvates of the compounds are included within the scope of this invention.

Additional therapeutic agents administered as combination therapies to treat alcohol-related disorders can include traditional anti-alcohol agents and/or other agents. Useful anti-alcohol agents in combinatorial formulations and coordinate treatment methods of the invention include, but are not limited to: disulfiram (Litten et al., Expert Opin Emerg. Drugs 10(2):323-43, 2005); naltrexone (Volpicelli et al., Arch. Gen. Psychiatry 49:876-880,1992; O'Malley et al., Arch. Gen. Psychiatry 49(11):881-887, 1992); acamprosate (Campral®) (Swift, N. Engl. J. Med. 340(19):1482-1490, 1999); ondansetron (Pettinati et al., Alcohol Clin. Exp. Res.

24(7):1041-1049, 2000; Stoltenberg, Scott, Clinical & Experimental Research 27(12):1853-1859, 2003); sertraline (Zoloft®) (Pettinati et al., Alcohol Clin. Exp. Res. 24(7):1041-1049, 2000); tiapride (Shaw et al., Br. J. Psychiatry 150:164-8, 1987); gamma hydroxybutyrate (Alcover®) (Poldrugo F. and Addolorato G., Alcohol Alcoholism 34(1), 15-24, 1999); galanthamine (Novel pharmacotherapies and patents for alcohol abuse and alcoholism 1998-2001, Expert Opinion on Therapeutic Patents, Vol. 11, No. 10, pages 1497-1521 (2001); U.S. Pat. No. 5,932,238); nalmefene (Revex) (Drobes et al., Alcohol Clin Exp Res., 28(9):1362-70 (2004); naloxone (Julius, D., and Renault, P., eds., Narcotic Antagonists: Naltrexone Progress Report, NIDA Research Monograph Series, Number 9. DHEW Publication No. (ADM) 76-387, Bethesda, Md.: National Institute on Drug Abuse, 1976; Jenab and Inturrisi, Molecular Brain Research 27:95-102, 1994); desoxypeganine (Doetkotte et al., Alcoholism: Clinical & Experimental Research, International Society for Biomedical Research on Alcoholism 12th World Congress on Biomedical Alcohol Research, Sep. 29-Oct. 2, 2004, Heidelburg/Mannheim, Germany, 28(8) Supplement:25A, 2004); benzodiazepines (Ntais et al., Benzodiazepines for alcohol withdrawal, Cochrane Database Syst. Rev. (3):CD005063, 2005; Mueller T I et al., Alcohol Clin. Exp. Res. 29(8):1411-8, 2005); neuroleptics such as laevomepromazine (Neurocil®) and thioridazine (Melleril®); piracetam; clonidine; carbamazepine; clomethiazole (Distraneurin®); levetiracetam; quetiapine (Monnelly et al., J. Clin. Psychopharmacol. 24(5):532-5, 2004); risperidone; rimonabant; trazodone (Janiri et al., Alcohol 33(4):362-5, 1998); topiramate (Johnson B A et al., Lancet 361:1677-1685, 2003); aripiprazole (Beresford et al., J. Clin. Psychopharmacol. 25(4):363-6, 2005); and modafinil (Saletu et al., Prog. Neuropsychopharmacol. Biol. Psychiatry 14(2):195-214, 1990); amperozide, and modafinil.

The sulfamate derivatives of topiramate, or any of the other compounds of the invention and their derivatives, analogs or modifications thereof, may be used in conjunction with one or more other drug compounds and according to the methods of the present invention so long as the pharmaceutical agent has a use that is also effective in treating alcohol-related disorders. Those of ordinary skill in the art will be able to identify readily those pharmaceutical agents that have utility with the present invention. Those of ordinary skill in the art will recognize also numerous other compounds that fall within the categories and that are useful according to the

invention for treating alcohol-related disorders. In one aspect, the anti-alcohol compounds of the invention are used in combination with drugs useful for other conditions.

The other therapeutic agent can be an anti-nicotine agent. Useful anti-nicotine agents include, but are not limited to, clonidine and bupropion.

The other therapeutic agent can be an anti-opiate agent. Useful anti-opiate agents include, but are not limited to, methadone, clonidine, lofexidine, levomethadyl acetate HCl, naltrexone, and buprenorphine.

The other therapeutic agent can be an anti-cocaine agent. Useful anti-cocaine agents include, but are not limited to, desipramine, amantadine, fluoxidine, and buprenorphine.

The other therapeutic agent can be an appetite suppressant. Useful appetite suppressants include, but are not limited to, fenfluramine, phenylpropanolamine, and mazindol.

The other therapeutic agent can be an anti-lysergic acid diethylamide ("anti-LSD") agent. Useful anti-LSD agents include, but are not limited to, diazepam.

The other therapeutic agent can be an anti-phencyclidine ("anti-PCP") agent. Useful anti-PCP agents include, but are not limited to, haloperidol.

The other therapeutic agent can be an anti-Parkinson's-disease agent. Useful anti-Parkinson's-disease agents include, but are not limited to, dopamine precursors, such as levodopa, L-phenylalanine, and L-tyrosine; neuroprotective agents; dopamine agonists; dopamine reuptake inhibitors; anticholinergics such as amantadine and memantine; and 1,3,5-trisubstituted adamantanes, such as 1-amino-3,5-dimethyl-adamantane (U.S. Pat. No. 4,122,193 to Sherm et al.).

The other therapeutic agent can be an anti-depression agent. Useful anti-depression agents include, but are not limited to, amitriptyline, clomipramine, doxepine, imipramine, trimipramine, amoxapine, desipramine, maprotiline, nortriptyline, protripylinc, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, bupropion, nefazodone, trazodone, phenelzine, tranylcypromine, selegiline, clonidine, gabapentin, and 2-pyridinyl[7-(pyridine-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl]methanone compounds having at least one substituent on both the 2- and 4-pyridinyl rings. Useful classes of antidepressant agents include without limitation monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants, tetracyclic antidepressants, norepinephrine uptake

inhibitors, selective norepinephrine reuptake inhibitors, and serotonin and norepinephrine uptake inhibitors.

The other therapeutic agent can be an anxiolytic agent. Useful anxiolytic agents include, but are not limited to, benzodiazepines, such as alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam; non-benzodiazepine agents, such as buspirone; and tranquilizers, such as barbiturates.

The other therapeutic agent can be an antipsychotic drug. Useful antipsychotic drugs include, but are not limited to, phenothiazines, such as chlorpromazine, mesoridazine besylate, thioridazine, acetophenazine maleate, fluphenazine, perphenazine, and trifluoperazine; thioxanthenes, such as chlorprothixene, and thiothixene; and other heterocyclic compounds, such as clozapine, haloperidol, loxapine, molindonc, pimozide, and risperidone. Exemplary anti-psychotic drugs include chlorpromazine HCl, thioridazine HCl, fluphenazine HCl, thiothixene HCl, and molindone HCl.

The other therapeutic agent can be an anti-obesity drug. Useful anti-obesity drugs include, but are not limited, to beta-adrenergic receptor agonists, for example beta-3 receptor agonists such as, but not limited to, fenfluramine; dexfenfluramine; sibutramine; bupropion; fluoxetine; phentermine; amphetamine; methamphetamine; dextroamphetamine; benzphetamine; phendimetrazine; diethylpropion; mazindol; phenylpropanolamine; norepinephrine; serotonin reuptake inhibitors, such as sibutramine; and pancreatic lipase inhibitors, such as orlistat.

A list of types of drugs, and specific drugs within categories which are encompassed within the invention is provided below.

Adrenergic: Adrenalone; Amidephrine Mesylate; Apraclonidine Hydrochloride; Brimonidine Tartrate; Dapiprazole Hydrochloride; Deterenol Hydrochloride; Dipivefrin; Dopamine Hydrochloride; Ephedrine Sulfate; Epinephrine; Epinephrine Bitartrate; Epinephryl Borate; Esproquin Hydrochloride; Etafedrine Hydrochloride; Hydroxyamphetamine Hydrobromide; Levonordefrin; Mephentermine Sulfate; Metaraminol Bitartrate; Metizoline Hydrochloride; Naphazoline Hydrochloride; Norepinephrine Bitartrate; Oxidopamine; Oxymetazoline Hydrochloride; Phenylephrine Hydrochloride; Phenylpropanolamine Hydrochloride; Phenylpropanolamine Polistirex; Prenalterol Hydrochloride;

Propylhexedrine; Pseudoephedrine Hydrochloride; Tetrahydrozoline Hydrochloride; Tramazoline Hydrochloride; Xylometazoline Hydrochloride.

Adrenocortical steroid: Ciprocinonide; Desoxycorticosterone Acetate; Desoxycorticosterone Pivalate; Dexamethasone Acetate; Fludrocortisone Acetate; Flumoxonide; Hydrocortisone Hemisuccinate; Methylprednisolone Hemisuccinate; Naflocort; Procinonide; Timobesone Acetate; Tipredane.

Adrenocortical suppressant: Aminoglutethimide; Trilostane.

Alcohol deterrent: Disulfiram.

Aldosterone antagonist: Canrenoate Potassium; Canrenone; Dicirenone; Mexrenoate Potassium; Prorenoate Potassium; Spironolactone.

Amino acid: Alanine; Aspartic Acid; Cysteine Hydrochloride; Cystine; Histidine; Isoleucine; Leucine; Lysine; Lysine Acetate; Lysine Hydrochloride; Methionine; Phenylalanine; Proline; Serine; Threonine; Tryptophan; Tyrosine; Valine.

Analeptic: Modafinil.

Analgesic: Acetaminophen; Alfentanil Hydrochloride; Aminobenzoate Potassium; Aminobenzoate Sodium; Anidoxime; Anileridine; Anileridine Hydrochloride; Anilopam Hydrochloride; Anirolac; Antipyrine; Aspirin; Benoxaprofen; Benzydamine Hydrochloride; Bicifadine Hydrochloride; Brifentanil Hydrochloride; Bromadoline Maleate; Bromfenac Sodium; Buprenorphine Hydrochloride; Butacetin; Butixirate; Butorphanol; Butorphanol Tartrate; Carbamazepine; Carbaspirin Calcium; Carbiphene Hydrochloride; Carfentanil Citrate; Ciprefadol Succinate; Ciramadol; Ciramadol Hydrochloride; Clonixeril; Clonixin; Codeine; Codeine Phosphate; Codeine Sulfate; Conorphone Hydrochloride; Cyclazocine; Dexoxadrol Hydrochloride; Dexpemedolac; Dezocine; Diflunisal; Dihydrocodeine Bitartrate; Dimefadane; Dipyrone; Doxpicomine Hydrochloride; Drinidene; Enadoline Hydrochloride; Epirizole; Ergotamine Tartrate; Ethoxazene Hydrochloride; Etofenamate; Eugenol; Fenoprofen; Fenoprofen Calcium; Fentanyl Citrate; Floctafenine; Flufenisal; Flunixin; Flunixin Meglumine; Flupirtine Maleate; Fluproquazone; Fluradoline Hydrochloride; Flurbiprofen; Hydromorphone Hydrochloride; Ibufenac; Indoprofen; Ketazocine; Ketorfanol; Ketorolac Tromethamine; Letimide Hydrochloride; Levomethadyl Acetate; Levomethadyl Acetate Hydrochloride; Levonantradol Hydrochloride; Levorphanol Tartrate; Lofemizole Hydrochloride; Lofentanil Oxalate; Lorcinadol;

Lomoxicam; Magnesium Salicylate; Mefenamic Acid; Menabitan Hydrochloride; Meperidine Hydrochloride; Meptazinol Hydrochloride; Methadone Hydrochloride; Methadyl Acetate; Methopholine; Methotrimeprazine; Metkephamid Acetate; Mimbane Hydrochloride; Mirfentanil Hydrochloride; Molinazone; Morphine Sulfate; Moxazocine; Nabitan Hydrochloride; Nalbuphine Hydrochloride; Nalmexone Hydrochloride; Namoxyrate; Nantradol Hydrochloride; Naproxen; Naproxen Sodium; Naproxol; Nefopam Hydrochloride; Nexeridine Hydrochloride; Noracymethadol Hydrochloride; Ocfentanil Hydrochloride; Octazamide; Olvanil; Oxetorone Fumarate; Oxycodone; Oxycodone Hydrochloride; Oxycodone Terephthalate; Oxymorphone Hydrochloride; Pemedolac; Pentamorphone; Pentazocine; Pentazocine Hydrochloride; Pentazocine Lactate; Phenazopyridine Hydrochloride; Phenyramidol Hydrochloride; Picenadol Hydrochloride; Pinadoline; Pirfenidone; Piroxicam Olamine; Pravadoline Maleate; Prodilidine Hydrochloride; Profadol Hydrochloride; Propirarn Fumarate; Propoxyphene Hydrochloride; Propoxyphene Napsylate; Proxazole; Proxazole Citrate; Proxorphan Tartrate; Pyrroliphene Hydrochloride; Remifentanil Hydrochloride; Salcolex; Salethamide Maleate; Salicylamide; Salicylate Meglumine; Salsalate; Sodium Salicylate; Spiradoline Mesylate; Sufentanil; Sufentanil Citrate; Talmetacin; Talniflumate; Talosalate; Tazadolene Succinate; Tebufelone; Tetrydamine; Tifurac Sodium; Tilidine Hydrochloride; Tiopinac; Tonazocine Mesylate; Tramadol Hydrochloride; Trefentanil Hydrochloride; Trolamine; Veradoline Hydrochloride; Verilopam Hydrochloride; Volazocine; Xorphanol Mesylate; Xylazine Hydrochloride; Zenazocine Mesylate; Zomepirac Sodium; Zucapsaicin.

Anorectic compounds including dexfenfluramine.

Anorexic: Aminorex; Amphecloral; Chlorphentermine Hydrochloride; Clominorex; Clortennine Hydrochloride; Diethylpropion Hydrochloride; Fenfluramine Hydrochloride; Fenisorex; Fludorex; Fluminorex; Levamfetamine Succinate; Mazindol; Mefenorex Hydrochloride; Phenmetrazine Hydrochloride; Phentermine; Sibutramine Hydrochloride.

Anti-anxiety agent: Adatanserin Hydrochloride; Alpidem; Binospirone Mesylate; Bretazenil; Glemanserin; Ipsapirone Hydrochloride; Mirisetron Maleate; Ocinaplon; Ondansetron Hydrochloride; Panadiplon; Pancopride; Pazinaclone; Serazapine Hydrochloride; Tandospirone Citrate; Zalospirone Hydrochloride.

Anti-cannabis agent: Rimonabant and other useful drugs, including drugs regulating the cannabanoid receptors.

Antidepressant: Adatanserin Hydrochloride; Adinazolam; Adinazolam Mesylate; Alaproclate; Aletamine Hydrochloride; Amedalin Hydrochloride; Amitriptyline Hydrochloride; Amoxapine; Aptazapine Maleate; Azaloxan Fumarate; Azepindole; Azipramine Hydrochloride; Bipenarnol Hydrochloride; Bupropion Hydrochloride; Butacetin; Butriptyline Hydrochloride; Caroxazone; Cartazolate; Ciclazindol; Cidoxepin Hydrochloride; Cilobamine Mesylate; Clodazon Hydrochloride; Clomipramine Hydrochloride; Cotinine Fumarate; Cyclindole; Cypenamine Hydrochloride; Cyprolidol Hydrochloride; Cyproximide; Daledalin Tosylate; Dapoxetine Hydrochloride; Dazadrol Maleate; Dazepinil Hydrochloride; Desipramine Hydrochloride; Dexamisole; Deximafen; Dibenzepin Hydrochloride; Dioxadrol Hydrochloride; Dothiepin Hydrochloride; Doxepin Hydrochloride; Duloxetine Hydrochloride; Eclanamine Maleate; Encyprate; Etoperidone Hydrochloride; Fantridone Hydrochloride; Fehmetozole Hydrochloride; Fenmetramide; Fezolamine Fumarate; Fluotracen Hydrochloride; Fluoxetine; Fluoxetine Hydrochloride; Fluparoxan Hydrochloride; Gamfexine; Guanoxyfen Sulfate; Imafen Hydrochloride; Imiloxan Hydrochloride; Imipramine Hydrochloride; Indeloxazine Hydrochloride; Intriptyline Hydrochloride; Iprindole; Isocarboxazid; Ketipramine Fumarate; Lofepramine Hydrochloride; Lortalamine; Maprotiline; Maprotiline Hydrochloride; Melitracen Hydrochloride; Milacemide Hydrochloride; Minaprine Hydrochloride; Mirtazapine; Moclobemide; Modaline Sulfate; Napactadine Hydrochloride; Napamezole Hydrochloride; Nefazodone Hydrochloride; Nisoxetine; Nitrafudam Hydrochloride; Nomifensine Maleate; Nortriptyline Hydrochloride; Octriptyline Phosphate; Opipramol Hydrochloride; Oxaprotiline Hydrochloride; Oxypertine; Paroxetine; Phenelzine Sulfate; Pirandamine Hydrochloride; Pizotyline; Pridefine Hydrochloride; Prolintane Hydrochloride; Protriptyline Hydrochloride; Quipazine Maleate; Rolicyprine; Seproxetine Hydrochloride; Sertraline Hydrochloride; Sibutramine Hydrochloride; Sulpiride; Suritozole; Tametraline Hydrochloride; Tampramine Fumarate; Tandamine Hydrochloride; Thiazesim Hydrochloride; Thozalinone; Tomoxetine Hydrochloride; Trazodone Hydrochloride; Trebenzomine Hydrochloride; Trimipramine; Trimipramine Maleate; Venlafaxine Hydrochloride; Viloxazine Hydrochloride; Zimeldine Hydrochloride; Zometapine.

Antihypertensive: Aflyzosin Hydrochloride; Alipamide; Althiazide; Amiquinsin Hydrochloride; Amlodipine Besylate; Amlodipine Maleate; Anaritide Acetate; Atiprosin Maleate; Belfosdil; Bemitradine; Bendacalol Mesylate; Bendroflumethiazide; Benzthiazide; Betaxolol Hydrochloride; Bethanidine Sulfate; Bevantolol Hydrochloride; Biclodil Hydrochloride; Bisoprolol; Bisoprolol Fumarate; Bucindolol Hydrochloride; Bupicomide; Buthiazide: Candoxatril; Candoxatrilat; Captopril; Carvedilol; Ceronapril; Chlorothiazide Sodium; Cicletanine; Cilazapril; Clonidine; Clonidine Hydrochloride; Clopamide; Cyclopenthiazide; Cyclothiazide; Darodipine; Debrisoquin Sulfate; Delapril Hydrochloride; Diapamide; Diazoxide; Dilevalol Hydrochloride; Diltiazem Malate; Ditekiren; Doxazosin Mesylate; Ecadotril; Enalapril Maleate; Enalaprilat; Enalkiren; Endralazine Mesylate; Epithiazide; Eprosartan; Eprosartan Mesylate; Fenoldopam Mesylate; Flavodilol Maleate; Flordipine; Flosequinan; Fosinopril Sodium; Fosinoprilat; Guanabenz; Guanabenz Acetate; Guanacline Sulfate; Guanadrel Sulfate; Guancydine; Guanethidine Monosulfate; Guanethidine Sulfate; Guanfacine Hydrochloride; Guanisoquin Sulfate; Guanoclor Sulfate; Guanoctine Hydrochloride; Guanoxabenz; Guanoxan Sulfate; Guanoxyfen Sulfate; Hydralazine Hydrochloride; Hydralazine Polistirex; Hydroflumethiazide; Indacrinone; Indapamide; Indolaprif Hydrochloride; Indoramin; Indoramin Hydrochloride; Indorenate Hydrochloride; Lacidipine; Leniquinsin; Levcromakalim; Lisinopril; Lofexidine Hydrochloride; Losartan Potassium; Losulazine Hydrochloride; Mebutamate; Mecamylamine Hydrochloride; Medroxalol; Medroxalol Hydrochloride; Methalthiazide; Methyclothiazide; Methyldopa; Methyldopate Hydrochloride; Metipranolol; Metolazone; Metoprolol Fumarate; Metoprolol Succinate; Metyrosine; Minoxidil ; Monatepil Maleate; Muzolimine; Nebivolol; Nitrendipine; Ofornine; Pargyline Hydrochloride; Pazoxide; Pelanserin Hydrochloride; Perindopril Erbumine; Phenoxybenzamine Hydrochloride; Pinacidil; Pivopril; Polythiazide; Prazosin Hydrochloride; Primidolol; Prizidilol Hydrochloride; Quinapril Hydrochloride; Quinaprilat; Quinazosin Hydrochloride; Quinelorane Hydrochloride; Quinpirole Hydrochloride; Quinuclium Bromide; Ramipril; Rauwolfia Serpentina; Reserpine; Saprisartan Potassium; Saralasin Acetate; Sodium Nitroprusside; Sulfinalol Hydrochloride; Tasosartan; Teludipine Hydrochloride; Temocapril Hydrochloride; Terazosin Hydrochloride; Terlakiren; Tiamenidine; Tiamenidine Hydrochloride; Ticrynafen; Tinabinol; Tiodazosin; Tipentosin Hydrochloride; Trichlormethiazide;

Trimazosin Hydrochloride; Trimethaphan Camsylate; Trimoxamine Hydrochloride; Tripamide; Xipamide; Zankiren Hydrochloride; Zofenoprilat Arginine.

Anti-inflammatory: Alclofenac; Alclometasone Dipropionate; Algestone Acetonide; Alpha Amylase; Amcinafal; Amcinafide; Amfenac Sodium; Amiprilose Hydrochloride; Anakinra; Anirolac; Anitrazafen; Apazone; Balsalazide Disodium; Bendazac; Benoxaprofen; Benzydamine Hydrochloride; Bromelains; Broperamole; Budesonide; Carprofen; Cicloprofen; Cintazone; Cliprofen; Clobetasol Propionate; Clobetasone Butyrate; Clopirac; Cloticasone Propionate; Cormethasone Acetate; Cortodoxone; Deflazacort; Desonide; Desoximetasone; Dexamethasone Dipropionate; Diclofenac Potassium; Diclofenac Sodium; Diflorasone Diacetate; Diflumidone Sodium; Diflunisal; Difluprednate; Diftalone; Dimethyl Sulfoxide; Drocinonide; Endrysone; Enlimomab; Enolicam Sodium; Epirizole; Etodolac; Etofenamate; Felbinac; Fenamole; Fenbufen; Fenclofenac; Fenclorac; Fendosal; Fenpipalone; Fentiazac; Flazalone; Fluazacort; Flufenamic Acid; Flumizole; Flunisolide Acetate; Flunixin; Flunixin Meglumine; Fluocortin Butyl; Fluorometholone Acetate; Fluquazone; Flurbiprofen; Fluretofen; Fluticasone Propionate; Furaprofen; Furobufen; Halcinonide; Halobetasol Propionate; Halopredone Acetate; Ibufenac; Ibuprofen; Ibuprofen Aluminum; Ibuprofen Piconol; Ilonidap; Indomethacin; Indomethacin Sodium; Indoprofen; Indoxole; Intrazole; Isoflupredone Acetate; Isoxepac; Isoxicam; Ketoprofen; Lofemizole Hydrochloride; Lornoxicam; Loteprednol Etabonate; Meclofenamate Sodium; Meclofenamic Acid; Meclorisone Dibutyrate; Mefenamic Acid; Mesalamine; Meseclazone; Methylprednisolone Suleptanate; Momiflumate; Nabumetone; Naproxen; Naproxen Sodium; Naproxol; Nimazone; Olsalazine Sodium; Orgotein; Orpanoxin; Oxaprozin; Oxyphenbutazone; Paranyline Hydrochloride; Pentosan Polysulfate Sodium; Phenbutazone Sodium Glycerate; Pirfenidone; Piroxicam; Piroxicam Cinnamate; Piroxicam Olamine; Pirprofen; Prednazate; Prifelone; Prodolic Acid; Proquazone; Proxazole; Proxazole Citrate; Rimexolone; Romazarit; Salcolex; Salnacedin; Salsalate; Sanguinarium Chloride; Seclazone; Sermetacin; Sudoxicam; Sulindac; Suprofen; Talmetacin; Talniflumate; Talosalate; Tebufelone; Tenidap; Tenidap Sodium; Tenoxicam; Tesicam; Tesimide; Tetrydamine; Tiopinac; Tixocortol Pivalate; Tolmetin; Tolmetin Sodium; Triclonide; Triflumidate; Zidometacin; Zomepirac Sodium.

Antinauseant: Buclizine Hydrochloride; Cyclizine Lactate; Naboctate Hydrochloride.

Antineutropenic: Filgrastim; Lenograstim; Molgramostim; Regramostim; Sargramostim.

Antiobsessional agent: Fluvoxamine Maleate.

Antiparkinsonian: Benztropine Mesylate; Biperiden; Biperiden Hydrochloride; Biperiden Lactate; Carmantadine; Ciladopa Hydrochloride; Dopamantine; Ethopropazine Hydrochloride; Lazabemide; Levodopa; Lometraline Hydrochloride; Mofegiline Hydrochloride; Naxagolide Hydrochloride; Pareptide Sulfate; Procyclidine Hydrochloride; Quinetorane Hydrochloride; Ropinirole Hydrochloride; Selegiline Hydrochloride; Tolcapone; Trihexyphenidyl Hydrochloride. Antiperistaltic: Difenoximide Hydrochloride; Difenoxin; Diphenoxylate Hydrochloride; Fluperamide; Lidamidine Hydrochloride; Loperamide Hydrochloride; Malethamer; Nufenoxole; Paregoric.

Antipsychotic: Acetophenazine Maleate; Alentemol Hydrobromide; Alpertine; Azaperone; Batelapine Maleate; Benperidol; Benzindopyrine Hydrochloride; Brofbxine; Bromperidol; Bromperidol Decanoate; Butaclamol Hydrochloride; Butaperazine; Butaperazine Maleate; Carphenazine Maleate; Carvotroline Hydrochloride; Chlorpromazine; Chlorpromazine Hydrochloride; Chlorprothixene; Cinperene; Cintriamide; Clomacran Phosphate; Clopenthixol; Clopimozide; Clopipazan Mesylate; Cloroperone Hydrochloride; Clothiapine; Clothixamide Maleate; Clozapine; Cyclophenazine Hydrochloride; Droperidol; Etazolate Hydrochloride; Fenimide; Flucindole; Flumezapine; Fluphenazine Decanoate; Fluphenazine Enanthate; Fluphenazine Hydrochloride; Fluspiperone; Fluspirilene; Flutroline; Gevotroline Hydrochloride; Halopemide; Haloperidol; Haloperidol Decanoate; Iloperidone; Imidoline Hydrochloride; Lenperone; Mazapertine Succinate; Mesoridazine; Mesoridazine Besylate; Metiapine; Milenperone; Milipertine; Molindone Hydrochloride; Naranol Hydrochloride; Neflumozide Hydrochloride; Ocaperidone; Olanzapine; Oxiperomide; Penfluridol; Pentiapine Maleate; Perphenazine; Pimozide; Pinoxepin Hydrochloride; Pipamperone; Piperacetazine; Pipotiazine Palniitate; Piquindone Hydrochloride; Prochlorperazine Edisylate; Prochlorperazine Maleate; Promazine Hydrochloride; Remoxipride; Remoxipride Hydrochloride; Rimcazole Hydrochloride; Seperidol Hydrochloride; Sertindole; Setoperone; Spiperone; Thioridazine; Thioridazine

Hydrochloride; Thiothixene; Thiothixene Hydrochloride; Tioperidone Hydrochloride; Tiospirone Hydrochloride; Trifluoperazine Hydrochloride; Trifluperidol; Triflupromazine; Triflupromazine Hydrochloride; Ziprasidone Hydrochloride.

Appetite suppressant: Dexfenfluramine Hydrochloride; Phendimetrazine Tartrate; Phentermine Hydrochloride.

Blood glucose regulators: Human insulin; Glucagon; Tolazamide; Tolbutamide; Chloropropamide; Acetohexamide and Glipizide.

Carbonic anhydrase inhibitor: Acetazolamide; Acetazolamide Sodium, Dichlorphenamide; Dorzolamide Hydrochloride; Methazolamide; Sezolarmide Hydrochloride.

Cardiac depressant: Acecainide Hydrochloride; Acetylcholine Chloride; Actisomide; Adenosine; Amiodarone; Aprindine; Aprindine Hydrochloride; Artilide Fumarate; Azimilide Dihydrochloride; Bidisomide; Bucainide Maleate; Bucromarone; Butoprozine Hydrochloride; Capobenate Sodium; Capobenic Acid; Cifenline; Cifenline Succinate; Clofilium Phosphate; Disobutamide; Disopyramide; Disopyramide Phosphate; Dofetilide; Drobuline; Edifolone Acetate; Emilium Tosylate; Encainide Hydrochloride; Flecainide Acetate; Ibutilide Fumarate; Indecainide Hydrochloride; Ipazilide Fumarate; Lorajmine Hydrochloride; Lorcainide Hydrochloride; Meobentine Sulfate; Mexiletine Hydrochloride; Modecainide; Moricizine; Oxiramide; Pirmenol Hydrochloride; Pirolazamide; Pranolium Chloride; Procainamide Hydrochloride; Propafenone Hydrochloride; Pyrinoline; Quindonium Bromide; Quinidine Gluconate; Quinidine Sulfate; Recainam Hydrochloride; Recainam Tosylate; Risotilide Hydrochloride; Ropitoin Hydrochloride; Sematilide Hydrochloride; Suricainide Maleate; Tocainide; Tocainide Hydrochloride; Transcainide.

Cardiotonic: Actodigin; Amrinone; Bemoradan; Butopamine; Carbazeran; Carsatrin Succinate; Deslanoside; Digitalis; Digitoxin; Digoxin; Dobutamine; Dobutamine Hydrochloride; Dobutamine Lactobionate; Dobutamine Tartrate; Enoximone; Imazodan Hydrochloride; Indolidan; Isomazole Hydrochloride; Levdobutamine Lactobionate; Lixazinone Sulfate; Medorinone; Milrinone; Pelrinone Hydrochloride; Pimobendan; Piroximone; Prinoxodan; Proscillaridin; Quazinone; Tazolol Hydrochloride; Vesnarinone.

Cardiovascular agent: Dopexamine; Dopexamine Hydrochloride.

Choleretic: Dehydrocholic Acid; Fencibutirol; Hymecromone; Piprozolin; Sincalide; Tocamphyl.

Cholinergic: Aceclidine; Bethanechol Chloride; Carbachol; Demecarium Bromide; Dexpanthenol; Echothiophate Iodide; Isoflurophate; Methacholine Chloride; Neostigmine Bromide; Neostigmine Methylsulfate; Physostigmine; Physostigmine Salicylate; Physostigmine Sulfate; Pilocarpine; Pilocarpine Hydrochloride; Pilocarpine Nitrate; Pyridostigmine Bromide.

Cholinergic agonist: Xanomeline; Xanomeline Tartrate.

Cholinesterase Deactivator: Obidoxime Chloride; Pralidoxime Chloride; Pralidoxime Iodide; Pralidoxime Mesylate.

Coccidiostat: Arprinocid; Narasin; Semduramicin; Semduramicin Sodium.

Cognition adjuvant: Ergoloid Mesylates; Piracetam; Pramiracetam Hydrochloride; Pramiracetam Sulfate; Tacrine Hydrochloride.

Cognition enhancer: Besipirdine Hydrochloride; Linopirdine; Sibopirdine.

Hormone: Diethylstilbestrol; Progesterone; 17-hydroxy progesterone; Medroxyprogesterone; Norgestrel; Norethynodrel; Estradiol; Megestrol (Megace); Norethindrone; Levonorgestrel; Ethyndiol; Ethinyl estradiol; Mestranol; Estrone; Equilin; 17-alpha-dihydroequilin; equilenin; 17-alpha-dihydroequilenin; 17-alpha-estradiol; 17-beta-estradiol; Leuprolide (lupron); Glucagon; Testolactone; Clomiphene; Han memopausal gonadotropins; Human chorionic gonadotropin; Urofollitropin; Bromocriptine; Gonadorelin; Luteinizing hormone releasing hormone and analogs; Gonadotropins; Danazol; Testosterone; Dehydroepiandrosterone; Androstenedione; Dihydroestosterone; Relaxin; Oxytocin; Vasopressin; Folliculostatin; Follicle regulatory protein; Gonadoctrinins; Oocyte maturation inhibitor; Insulin growth factor; Follicle Stimulating Hormone; Luteinizing hormone; Tamoxifen.; Corticorelin Ovine Triftutate; Cosyntropin; Metogest; Pituitary, Posterior; Seractide Acetate; Somalapor; Somatrem; Somatropin; Somenopor; Somidobove.

Memory adjuvant: Dimoxamine Hydrochloride; Ribaminol.

Mental performance enhancer: Aniracetam.

Mood regulator: Fengabine.

Neuroleptic: Duoperone Fumarate; Risperidone.

Neuroprotective: Dizocilpine Maleate.

Psychotropic: Minaprine.

Relaxant: Adiphenine Hydrochloride; Alcuronium Chloride; Aminophylline; Azumolene Sodium; Baclofen; Benzoctamine Hydrochloride; Carisoprodol; Chlorphenesin Carbamate; Chlorzoxazone; Cinflumide; Cinnamedrine; Clodanolene; Cyclobenzaprine Hydrochloride; Dantrolene; Dantrolene Sodium; Fenalanide; Fenyripol Hydrochloride; Fetoxylate Hydrochloride; Flavoxate Hydrochloride; Fletazepam; Flumetramide;-Flurazepam Hydrochloride; Hexafluorenium Bromide; Isomylamine Hydrochloride; Lorbamate; Mebeverine Hydrochloride; Mesuprine Hydrochloride; Metaxalone; Methocarbamol; Methixene Hydrochloride; Nafomine Malate; Nelezaprine Maleate; Papaverine Hydrochloride; Pipoxolan Hydrochloride; Quinctolate; Ritodrine; Ritodrine Hydrochloride; Rolodine; Theophylline Sodium Glycinate; Thiphenamil Hydrochloride; Xilobam.

Sedative-hypnotic: Allobarbital; Alonimid; Alprazolam; Amobarbital Sodium; Bentazepam; Brotizolam; Butabarbital; Butabarbital Sodium; Butalbital; Capuride; Carbocloral; Chloral Betaine; Chloral Hydrate; Chlordiazepoxide Hydrochloride; Cloperidone Hydrochloride; Clorethate; Cyprazepam; Dexclamol Hydrochloride; Diazepam; Dichloralphenazone; Estazolam; Ethchlorvynol; Etomidate; Fenobam; Flunitrazepam; Fosazepam; Glutethimide; Halazepam; Lormetazepam; Mecloqualone; Meprobamate; Methaqualone; Midaflur; Paraldehyde; Pentobarbital; Pentobarbital Sodium; Perlapine; Prazepam; Quazepam; Reclazepam; Roletamide; Secobarbital; Secobarbital Sodium; Suproclone; Thalidomide; Tracazolate; Trepipam Maleate; Triazolam; Tricetamide; Triclofos Sodium; Trimetozine; Uldazepam; Zaleplon; Zolazepam Hydrochloride; Zolpidem Tartrate.

Serotonin antagonist: Altanserin Tartrate; Amesergide; Ketanserin; Ritanserin.

Serotonin inhibitor: Cinanserin Hydrochloride; Fenclonine; Fonazine Mesylate; Xylamidine Tosylate.

Serotonin receptor antagonist: Tropanserin Hydrochloride.

Stimulant: Amfonelic Acid; Amphetamine Sulfate; Ampyzine Sulfate; Arbutamine Hydrochloride; Azabon; Caffeine; Ceruletide; Ceruletide Diethylamine; Cisapride; Dazopride Fumarate; Dextroamphetamine; Dextroamphetamine Sulfate; Difluanine Hydrochloride; Dimefline Hydrochloride; Doxapram Hydrochloride; Etryptamine Acetate; Ethamivan; Fenethylline Hydrochloride; Flubanilate Hydrochloride; Flurothyl; Histamine Phosphate; Indriline Hydrochloride;

Mefexamide; Methamphetamine Hydrochlo ride; Methylphenidate Hydrochloride; Pemoline; Pyrovalerone Hydrochloride; Xamoterol; Xamoterol Fumarate. Synergist: Proadifen Hydrochloride.

Thyroid hormone: Levothyroxine Sodium; Liothyronine Sodium; Liotrix.

Thyroid inhibitor: Methimazole; Propyithiouracil.

Thyromimetic: Thyromedan Hydrochloride.

Cerebral ischemia agents: Dextrorphan Hydrochloride.

Vasoconstrictor: Angiotensin Amide; Felypressin; Methysergide; Methysergide Maleate.

Vasodilator: Alprostadil; Azaclorzine Hydrochloride; Bamethan Sulfate; Bepridil Hydrochloride; Buterizine; Cetiedil Citrate; Chromonar Hydrochloride; Clonitrate; Diltiazem Hydrochloride; Dipyridamole; Droprenilamine; Erythrityl Tetranitrate; Felodipine; Flunarizine Hydrochloride; Fostedil; Hexobendine; Inositol Niacinate; Iproxamine Hydrochloride; Isosorbide Dinitrate; Isosorbide Mononitrate; Isoxsuprine Hydrochloride; Lidoflazine; Mefenidil; Mefenidil Fumarate; Mibefradil Dihydrochloride; Mioflazine Hydrochloride; Mixidine; Nafronyl Oxalate; Nicardipine Hydrochloride; Nicergoline; Nicorandil; Nicotinyl Alcohol; Nifedipine; Nimodipine; Nisoldipine; Oxfenicine; Oxprenolol Hydrochloride; Pentaerythritol Tetranitrate; Pentoxifylline; Pentrinitrol; Perhexiline Maleate; Pindolol; Pirsidomine; Prenylamine; Propatyl Nitrate; Suloctidil; Terodiline Hydrochloride; Tipropidil Hydrochloride; Tolazoline Hydrochloride; Xanthinol Niacinate.

Assays and methods for testing compounds of the invention are described herein or are known in the art. For example, see Lippa et al., U.S. Pat. Pub. No. 2006/0173-64, published August 3, 2006.

The invention further encompasses treating and preventing obesity, i.e., for affecting weight loss and preventing weight gain. Obesity is a disorder characterized by the accumulation of excess fat in the body. Obesity has been recognized as one of the leading causes of disease and is emerging as a global problem. Increased instances of complications such as hypertension, non-insulin-dependent diabetes mellitus, arteriosclerosis, dyslipidemia, certain forms of cancer, sleep apnea, and osteoarthritis have been related to increased instances of obesity in the general population In one aspect, the invention encompasses administering to a subject in need thereof a combination therapy to induce weight loss. For example, subjects having a BMI of greater than about 25 (25.0-29.9 is considered overweight)

are identified for treatment. In one aspect, the individuals have a BMI of greater than 30 (30 and above is considered obese). In another aspect, a subject may be targeted for treatment to prevent weight gain. In one embodiment, an individual is instructed to take at least one compound of the invention at least once daily and at least a second compound of the invention at least once daily. The compound may be in the form of, for example, a tablet, a lozenge, a liquid, etc. In one aspect, a third compound is also taken daily. In one embodiment, compounds may be taken more than once daily. In another embodiment, compounds are taken less than once daily. The dosages can be determined based on what is known in the art or what is determined to be best for a subject of that age, sex, health, weight, etc. Compounds useful for treating obesity according to the methods of the invention, include, but are not limited to, topiramate, naltrexone, and ondansetron. See Weber (U.S. Pat. Pub. No. 20070275970) and McElroy (U.S. Pat. No. 6,323,236) for additional information and techniques for administering drugs useful for treating obesity, addictive disorders, and impulse control disorders, and for determining dosage schemes.

The subjects being treated to induce weight loss may be monitored for a period of months. In one aspect, it is recommended that the dosage be adjusted so that each individual loses weight at a rate of 10% of initial weight every 6 months. However, the rate of weigh loss for each individual may be adjusted by the treating physician based on the individual's particular needs.

If the initial dosage is not effective, then the dosage of one or more compounds of the combination therapy can be increased. If the initial dosage results in a more rapid weight loss than the above rate, the dosage of one or more of the at least two compounds can be reduced.

Pharmaceutically-acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted

cycloalkyl amines, disubstituted cycloalkyl amines, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amines, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group. Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like.

Psychosocial Intervention and Management

The drug combination treatments of the present invention can be further supplemented by providing to subjects a form of psychosocial intervention and/or management, such as Brief Behavioral Compliance Enhancement Treatment (BBCET). BBCET, a standardized, manual-guided, brief (i.e., delivered in about 15 minutes), psychosocial adherence enhancement procedure, emphasizes that

medication compliance is crucial to changing participants' drinking behavior (Johnson et al., Brief Behavioral Compliance Enhancement Treatment (BBCET) manual. In: Johnson BA, Ruiz P, Galanter M, eds. Handbook of clinical alcoholism treatment. Baltimore, MD: Lippincott Williams & Wilkins; 2003, 282-301). Brief interventions (Edwards et al., J. Stud. Alcohol. 1977, 38:1004-1031) such as BBCET, have been shown to benefit treatment of alcohol dependence. BBCET was modeled on the clinical management condition in the National Institute of Mental Health collaborative depression trial, which was used as an adjunct to the medication condition for that study (Fawcett et al. Psychopharmacol Bull. 1987, 23:309-324). BBCET has been used successfully as the psychosocial treatment platform in the single-site and multi-site efficacy trials of topiramate for treating alcohol dependence (Johnson et al., Lancet. 2003, 361:1677-1685; Johnson et al., JAMA, 2007, 298:1641-1651). It is delivered by trained clinicians, including nurse practitioners and other non-specialists. Uniformity and consistency of BBCET delivery are ensured by ongoing training and supervision. BBCET is copyrighted material (Johnson et al., Brief Behavioral Compliance Enhancement Treatment (BBCET) manual. In: Johnson BA, Ruiz P, Galanter M, eds. Handbook of clinical alcoholism treatment. Baltimore, MD: Lippincott Williams & Wilkins; 2003, 282-301).

The present invention further encompasses the use of psychosocial management regimens other than BBCET, including, but not limited to, Cognitive Behavioral Coping Skills Therapy (CBT) (Project MATCH Research Group. Matching Alcoholism Treatments to Client Heterogeneity: Project MATCH posttreatment drinking outcomes. J Stud Alcohol. 1997;58:7-29), Motivational Enhancement Therapy (MET) (Project MATCH Research Group. Matching Alcoholism Treatments to Client Heterogeneity: Project MATCH posttreatment drinking outcomes. J. Stud. Alcohol. 1997, 58:7-29), Twelve-Step Facilitation Therapy (TSF) (Project MATCH Research Group. Matching Alcoholism Treatments to Client Heterogeneity: Project MATCH posttreatment drinking outcomes. J. Stud. Alcohol. 1997, 58:7-29), Combined Behavioral Intervention (CBI), (Anton et al., JAMA, 2006, 295:2003-2017) Medical Management (MM) (Anton et al., JAMA, 2006, 295:2003-2017), or the Biopsychosocial, Report, Empathy, Needs, Direct advice, and Assessment (BRENDA) model (Garbutt et al., JAMA, 2005, 293:1617-1625). The present invention further encompasses the use of alternative

interventions such as hypnosis or acupuncture to assist in treating an addictive disease or disorder.

The psychosocial management programs can be used before, during, and after treating the subject with the combination drug therapy of the invention.

One of ordinary skill in the art will recognize that psychosocial management procedures, as well as alternative interventions such as hypnosis or acupuncture, can also be used in conjunction with combination drug therapy to treat addictive and impulse-related disorders other than alcohol-related diseases and disorders.

The present invention further encompasses the use of combination pharmacotherapy and behavioral (psychosocial) intervention or training to treat other addictive and/or impulse control disorders.

For example, binge eating disorder (BED) is characterized by discrete periods of binge eating during which large amounts of food are consumed in a discrete period of time and a sense of control over eating is absent. Persons with bulimia nervosa have been reported to have electroencephalographic abnormalities and to display reduced binge eating in response to the anti-epileptic drug phenytoin. In addition, in controlled trials in patients with epilepsy, topiramate was associated with suppression of appetite and weight loss unrelated to binge eating. Ondansetron has been shown to reduce binge eating.

BED is a subset of a larger classification of mental disorders broadly defined as Impulse Control Disorders (ICDs) characterized by harmful behaviors performed in response to irresistible impulses. It has been suggested that ICDs may be related to obsessive-compulsive disorder or similarly, maybe forms of obsessive-compulsive disorders. It has also been hypothesized that ICDs may be related to mood disorder or may be forms of affective spectrum disorder, a hypothesized family of disorders sharing at least one common physiologic abnormality with major depression. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the essential feature of an ICD is the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others. For most ICDs, the individual feels an increasing sense of tension or arousal before committing the act, and then experiences pleasure, gratification, or release at the time of committing the act. After the act is performed, there may or may not be regret or guilt. ICDs are listed in a residual category, the ICDs Not Elsewhere Classified, which includes intermittent explosive disorder (IED), kleptomania,

pathological gambling, pyromania, trichotillomania, and ICDs not otherwise specified (NOS). Examples of ICDs NOS are compulsive buying or shopping, repetitive self-mutilation, nonparaphilic sexual addictions, severe nail biting, compulsive skin picking, personality disorders with impulsive features, attention deficit/hyperactivity disorder, eating disorders characterized by binge eating, and substance use disorders.

Many drugs can cause physical and/or psychological addiction. Those most well known drugs include opiates, such as heroin, opium and morphine; sympathomimetics, including cocaine and amphetamines; sedative-hypnotics, including alcohol, benzodiazepines, and barbiturates; and nicotine, which has effects similar to opioids and sympathomimetics. Drug addiction is characterized by a craving or compulsion for taking the drug and an inability to limit its intake. Additionally, drug dependence is associated with drug tolerance, the loss of effect of the drug following repeated administration, and withdrawal, the appearance of physical and behavioral symptoms when the drug is not consumed. Sensitization occurs if repeated administration of a drug leads to an increased response to each dose. Tolerance, sensitization, and withdrawal are phenomena evidencing a change in the central nervous system resulting from continued use of the drug. This change motivates the addicted individual to continue consuming the drug despite serious social, legal, physical, and/or professional consequences.

Attention-deficit disorders include, but are not limited to, Attention-Deficit/Hyperactivity Disorder, Predominately Inattentive Type; Attention-Deficit/Hyperactivity Disorder, Predominately Hyperactivity-Impulsive Type; Attention-Deficit/Hyperactivity Disorder, Combined Type; Attention-Deficit/Hyperactivity Disorder not otherwise specified (NOS); Conduct Disorder; Oppositional Defiant Disorder; and Disruptive Behavior Disorder not otherwise specified (NOS).

Depressive disorders include, but are not limited to, Major Depressive Disorder, Recurrent; Dysthymic Disorder; Depressive Disorder not otherwise specified (NOS); and Major Depressive Disorder, Single Episode.

Parkinson's disease includes, but is not limited to, neuroleptic-induced parkinsonism.

Addictive disorders include, but are not limited to, eating disorders, impulse control disorders, alcohol-related disorders, nicotine-related disorders,

amphetamine-related disorders, cannabis-related disorders, cocaine-related disorders, gambling, sexual disorders, hallucinogen use disorders, inhalant-related disorders, and opioid-related disorders, all of which arc further subclassified as listed below.

Eating disorders include, but are not limited to, Bulimia Nervosa, Nonpurging Type; Bulimia Nervosa, Purging Type; and Eating Disorder not otherwise specified (NOS).

Impulse control disorders include, but are not limited to, Intermittent Explosive Disorder, Kleptomania, Pyromania, Pathological Gambling, Trichotillomania, and Impulse Control Disorder not otherwise specified (NOS).

Nicotine-related disorders include, but are not limited to, Nicotine Dependence, Nicotine Withdrawal, and Nicotine-Related Disorder not otherwise specified (NOS).

Amphetamine-related disorders include, but are not limited to, Amphetamine Dependence, Amphetamine Abuse, Amphetamine Intoxication, Amphetamine Withdrawal, Amphetamine Intoxication Delirium, Amphetamine-Induced Psychotic Disorder with delusions, Amphetamine-Induced Psychotic Disorders with hallucinations, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder, Amphetamine Related Disorder not otherwise specified (NOS), Amphetamine Intoxication, and Amphetamine Withdrawal.

Cannabis-related disorders include, but are not limited to, Cannabis Dependence; Cannabis Abuse; Cannabis Intoxication; Cannabis Intoxication Delirium; Cannabis-Induced Psychotic Disorder, with delusions; Cannabis-Induced Psychotic Disorder with hallucinations; Cannabis-Induced Anxiety Disorder; Cannabis-Related Disorder not otherwise specified (NOS); and Cannabis Intoxication.

Cocaine-related disorders include, but are not limited to, Cocaine Dependence, Cocaine Abuse, Cocaine Intoxication, Cocaine Withdrawal, Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder with delusions, Cocaine-Induced Psychotic Disorders with hallucinations, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder, Cocaine-Related Disorder not otherwise specified (NOS), Cocaine Intoxication, and Cocaine Withdrawal.

Hallucinogen-use disorders include, but are not limited to, Hallucinogen Dependence, Hallucinogen Abuse, Hallucinogen Intoxication, Hallucinogen Withdrawal, Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder with delusions, Hallucinogen-Induced Psychotic Disorder with hallucinations, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder, Hallucinogen-Induced Sexual Dysfunction, Hallucinogen-Induced Sleep Disorder, Hallucinogen Related Disorder not otherwise specified (NOS), Hallucinogen Intoxication, and Hallucinogen Persisting Perception Disorder (Flashbacks).

Inhalant-related disorders include, but are not limited to, Inhalant Dependence; Inhalant Abuse; Inhalant Intoxication; Inhalant Intoxication Delirium; Inhalant-Induced Psychotic Disorder, with delusions; Inhalant-Induced Psychotic Disorder with hallucinations; Inhalant-Induced Anxiety Disorder; Inhalant-Related Disorder not otherwise specified (NOS); and Inhalant Intoxication.

Opioid-related disorders include, but are not limited to, Opioid Dependence, Opioid Abuse, Opioid Intoxication, Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, with delusions, Opioid-Induced Psychotic Disorder with hallucinations, Opioid-Induced Anxiety Disorder, Opioid-Related Disorder not otherwise specified (NOS), Opioid Intoxication, and Opioid Withdrawal.

Tic disorders include, but are not limited to, Tourette's Disorder, Chronic Motor or Vocal Tic Disorder, Transient Tic Disorder, Tic Disorder not otherwise specified (NOS), Stuttering, Autistic Disorder, and Somatization Disorder.

The present invention further encompasses the treatment of at least two addictive diseases or disorders or impulse control disorders simultaneously. For example, the present invention provides for the simultaneous treatment of alcohol related disorders and weight control (see Examples).

The present invention also encompasses the use of the compounds and combination therapies of the invention in circumstances where mandatory treatment may be applicable. For example, a court may require that a subject be treated or take part in a treatment program using compounds or combination therapies of the invention as part of a mandated therapy related to alcohol abuse, excessive drinking, drug use, etc. More particularly, the invention encompasses forensic uses where a court would require a subject who has been convicted of driving under the influence

to be subjected to the methods of the invention as part of a condition of bail, probation, treatment, etc.

The invention also encompasses the use of pharmaceutical compositions comprising compounds of the invention to practice the methods of the invention, the compositions comprising at least one appropriate compound and a pharmaceutically-acceptable carrier.

Other methods useful for the practice of the invention can be found, for example, in U.S. Pat. Pub. No. 2006/0173064 (Lippa et al.), U.S. Pat. No. 6,323,236 (McElroy), U.S. Pat. Pub. No. 2007/0275970, PCT application PCT/US/2008/052628 (Johnson et al.) filed January 31, 2008, and PCT application PCT/US/2007/088100 (Johnson and Tiouririne), filed December 19, 2007.

In one embodiment, a composition of the invention may comprise one compound of the invention. In another embodiment, a composition of the invention may comprise more than one compound of the invention. In one embodiment, additional drugs or compounds useful for treating other disorders may be part of the composition. In one embodiment, a composition comprising only one compound of the invention may be administered at the same time as another composition comprising at least one other compound of the invention. In one embodiment, the different compositions may be administered at different times from one another. When a composition of the invention comprises only one compound of the invention, an additional composition comprising at least one additional compound must also be used.

The pharmaceutical compositions useful for practicing the invention may be, for example, administered to deliver a dose of between 1 ng/kg/day and 100 mg/kg/day.

Pharmaceutical compositions that are useful in the methods of the invention may be administered, for example, systemically in oral solid formulations, or as ophthalmic, suppository, aerosol, topical or other similar formulations. In addition to the appropriate compounds, such pharmaceutical compositions may contain pharmaceutically-acceptable carriers and other ingredients known to enhance and facilitate drug administration. Other possible formulations, such as nanoparticles, liposomes, resealed erythrocytes, and immunologically based systems may also be used to administer an appropriate compound, or an analog, modification, or derivative thereof according to the methods of the invention.

Compounds which are identified using any of the methods described herein may be formulated and administered to a subject for treatment of the diseases disclosed herein. One of ordinary skill in the art will recognize that these methods will be useful for other diseases, disorders, and conditions as well.

A "prodrug" refers to an agent that is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug, or may demonstrate increased palatability or be easier to formulate. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to provide the active moiety.

The invention encompasses the preparation and use of pharmaceutical compositions comprising a compound useful for treatment of the diseases disclosed herein as an active ingredient. Such a pharmaceutical composition may consist of the active ingredient alone, in a form suitable for administration to a subject, or the pharmaceutical composition may comprise the active ingredient and one or more pharmaceutically acceptable carriers, one or more additional ingredients, or some combination of these. The active ingredient may be present in the pharmaceutical composition in the form of a physiologically acceptable ester or salt, such as in combination with a physiologically acceptable cation or anion, as is well known in the art.

The formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with a carrier or one or more other accessory ingredients, and then, if necessary or desirable, shaping or packaging the product into a desired single- or multi-dose unit.

Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for ethical administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions of the invention is contemplated include, but are not limited to, humans and other primates, mammals including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, and dogs, and birds including commercially relevant birds such as chickens, ducks, geese, and turkeys.

One type of administration encompassed by the methods of the invention is parenteral administration, which includes, but is not limited to, administration of a pharmaceutical composition by injection of the composition, by application of the composition through a surgical incision, by application of the composition through a tissue-penetrating non-surgical wound, and the like. In particular, parenteral administration is contemplated to include, but is not limited to, subcutaneous, intraperitoneal, intramuscular, and intrasternal injection, and kidney dialytic infusion techniques

Pharmaceutical compositions that are useful in the methods of the invention may be prepared, packaged, or sold in formulations suitable for oral, rectal, vaginal, parenteral, topical, pulmonary, intranasal, inhalation, buccal, ophthalmic, intrathecal or another route of administration. Other contemplated formulations include projected nanoparticles, liposomal preparations, resealed erythrocytes containing the active ingredient, and immunologically-based formulations.

A pharmaceutical composition of the invention may be prepared, packaged, or sold in bulk, as a single unit dose, or as a plurality of single unit doses. As used herein, a "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject, or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

The relative amounts of the active ingredient, the pharmaceutically acceptable carrier, and any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

In addition to the active ingredient, a pharmaceutical composition of the invention may further comprise one or more additional pharmaceutically active agents. Particularly contemplated additional agents include anti-emetics and scavengers such as cyanide and cyanate scavengers.

Controlled- or sustained-release formulations of a pharmaceutical composition of the invention may be made using conventional technology.

A formulation of a pharmaceutical composition of the invention suitable for oral administration may be prepared, packaged, or sold in the form of a discrete solid dose unit including, but not limited to, a tablet, a hard or soft capsule, a cachet, a troche, or a lozenge, each containing a predetermined amount of the active ingredient. Other formulations suitable for oral administration include, but are not limited to, a powdered or granular formulation, an aqueous or oily suspension, an aqueous or oily solution, or an emulsion.

As used herein, an "oily" liquid is one which comprises a carbon-containing liquid molecule and which exhibits a less polar character than water.

A tablet comprising the active ingredient may, for example, be made by compressing or molding the active ingredient, optionally with one or more additional ingredients. Compressed tablets may be prepared by compressing, in a suitable device, the active ingredient in a free-flowing form such as a powder or granular preparation, optionally mixed with one or more of a binder, a lubricant, an excipient, a surface active agent, and a dispersing agent. Molded tablets may be made by molding, in a suitable device, a mixture of the active ingredient, a pharmaceutically acceptable carrier, and at least sufficient liquid to moisten the mixture. Pharmaceutically acceptable excipients used in the manufacture of tablets include, but are not limited to, inert diluents, granulating and disintegrating agents, binding agents, and lubricating agents. Known dispersing agents include, but are not limited to, potato starch and sodium starch glycollate. Known surface active agents include, but are not limited to, sodium lauryl sulphate. Known diluents include, but

are not limited to, calcium carbonate, sodium carbonate, lactose, microcrystalline cellulose, calcium phosphate, calcium hydrogen phosphate, and sodium phosphate. Known granulating and disintegrating agents include, but are not limited to, corn starch and alginic acid. Known binding agents include, but are not limited to, gelatin, acacia, pre-gelatinized maize starch, polyvinylpyrrolidone, and hydroxypropyl methylcellulose. Known lubricating agents include, but are not limited to, magnesium stearate, stearic acid, silica, and talc.

Tablets may be non-coated or may be coated using known methods to achieve delayed disintegration in the gastrointestinal tract of a subject, thereby providing sustained release and absorption of the active ingredient. By way of example, a material such as glyceryl monostearate or glyceryl distearate may be used to coat tablets. Further by way of example, tablets may be coated using methods described in U.S. Patents numbers 4,256,108; 4,160,452; and 4,265,874 to form osmotically-controlled release tablets. Tablets may further comprise a sweetening agent, a flavoring agent, a coloring agent, a preservative, or some combination of these in order to provide pharmaceutically elegant and palatable preparation.

Hard capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin. Such hard capsules comprise the active ingredient, and may further comprise additional ingredients including, for example, an inert solid diluent such as calcium carbonate, calcium phosphate, or kaolin.

Soft gelatin capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin. Such soft capsules comprise the active ingredient, which may be mixed with water or an oil medium such as peanut oil, liquid paraffin, or olive oil.

Lactulose can also be used as a freely erodible filler and is useful when the compounds of the invention are prepared in capsule form.

Liquid formulations of a pharmaceutical composition of the invention which are suitable for oral administration may be prepared, packaged, and sold either in liquid form or in the form of a dry product intended for reconstitution with water or another suitable vehicle prior to use.

Liquid suspensions may be prepared using conventional methods to achieve suspension of the active ingredient in an aqueous or oily vehicle. Aqueous vehicles

include, for example, water and isotonic saline. Oily vehicles include, for example, almond oil, oily esters, ethyl alcohol, vegetable oils such as arachis, olive, sesame, or coconut oil, fractionated vegetable oils, and mineral oils such as liquid paraffin. Liquid suspensions may further comprise one or more additional ingredients including, but not limited to, suspending agents, dispersing or wetting agents, emulsifying agents, demulcents, preservatives, buffers, salts, flavorings, coloring agents, and sweetening agents. Oily suspensions may further comprise a thickening agent. Known suspending agents include, but are not limited to, sorbitol syrup, hydrogenated edible fats, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia, and cellulose derivatives such as sodium carboxymethylcellulose, methylcellulose, and hydroxypropylmethylcellulose. Known dispersing or wetting agents include, but are not limited to, naturally occurring phosphatides such as lecithin, condensation products of an alkylene oxide with a fatty acid, with a long chain aliphatic alcohol, with a partial ester derived from a fatty acid and a hexitol, or with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene stearate, heptadecaethyleneoxycetanol, polyoxyethylene sorbitol monooleate, and polyoxyethylene sorbitan monooleate, respectively). Known emulsifying agents include, but are not limited to, lecithin and acacia. Known preservatives include, but are not limited to, methyl, ethyl, or n-propyl para hydroxybenzoates, ascorbic acid, and sorbic acid. Known sweetening agents include, for example, glycerol, propylene glycol, sorbitol, sucrose, and saccharin. Known thickening agents for oily suspensions include, for example, beeswax, hard paraffin, and cetyl alcohol.

In one aspect, a preparation in the form of a syrup or elixir or for administration in the form of drops may comprise active ingredients together with a sweetener, which is preferably calorie-free, and which may further include methylparaben or propylparaben as antiseptics, a flavoring and a suitable color.

Liquid solutions of the active ingredient in aqueous or oily solvents may be prepared in substantially the same manner as liquid suspensions, the primary difference being that the active ingredient is dissolved, rather than suspended in the solvent. Liquid solutions of the pharmaceutical composition of the invention may comprise each of the components described with regard to liquid suspensions, it being understood that suspending agents will not necessarily aid dissolution of the active ingredient in the solvent. Aqueous solvents include, for example, water and

isotonic saline. Oily solvents include, for example, almond oil, oily esters, ethyl alcohol, vegetable oils such as arachis, olive, sesame, or coconut oil, fractionated vegetable oils, and mineral oils such as liquid paraffin.

Powdered and granular formulations of a pharmaceutical preparation of the invention may be prepared using known methods. Such formulations may be administered directly to a subject, used, for example, to form tablets, to fill capsules, or to prepare an aqueous or oily suspension or solution by addition of an aqueous or oily vehicle thereto. Each of these formulations may further comprise one or more of a dispersing or wetting agent, a suspending agent, and a preservative. Additional excipients, such as fillers and sweetening, flavoring, or coloring agents, may also be included in these formulations.

A pharmaceutical composition of the invention may also be prepared, packaged, or sold in the form of oil in water emulsion or a water-in-oil emulsion. The oily phase may be a vegetable oil such as olive or arachis oil, a mineral oil such as liquid paraffin, or a combination of these. Such compositions may further comprise one or more emulsifying agents including naturally occurring gums such as gum acacia or gum tragacanth, naturally occurring phosphatides such as soybean or lecithin phosphatide, esters or partial esters derived from combinations of fatty acids and hexitol anhydrides such as sorbitan monooleate, and condensation products of such partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. These emulsions may also contain additional ingredients including, for example, sweetening or flavoring agents.

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for rectal administration. Such a composition may be in the form of, for example, a suppository, a retention enema preparation, and a solution for rectal or colonic irrigation.

Suppository formulations may be made by combining the active ingredient with a non irritating pharmaceutically acceptable excipient which is solid at ordinary room temperature (i.e. about 20°C) and which is liquid at the rectal temperature of the subject (i.e. about 37°C in a healthy human). Suitable pharmaceutically acceptable excipients include, but are not limited to, cocoa butter, polyethylene glycols, and various glycerides. Suppository formulations may further comprise various additional ingredients including, but not limited to, antioxidants and preservatives.

Retention enema preparations or solutions for rectal or colonic irrigation may be made by combining the active ingredient with a pharmaceutically acceptable liquid carrier. As is well known in the art, enema preparations may be administered using, and may be packaged within, a delivery device adapted to the rectal anatomy of the subject. Enema preparations may further comprise various additional ingredients including, but not limited to, antioxidants and preservatives.

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for vaginal administration. Such a composition may be in the form of, for example, a suppository, an impregnated or coated vaginally-insertable material such as a tampon, a douche preparation, or gel or cream or a solution for vaginal irrigation.

Methods for impregnating or coating a material with a chemical composition are known in the art, and include, but are not limited to methods of depositing or binding a chemical composition onto a surface, methods of incorporating a chemical composition into the structure of a material during the synthesis of the material (i.e. such as with a physiologically degradable material), and methods of absorbing an aqueous or oily solution or suspension into an absorbent material, with or without subsequent drying.

Douche preparations or solutions for vaginal irrigation may be made by combining the active ingredient with a pharmaceutically acceptable liquid carrier. As is well known in the art, douche preparations may be administered using, and may be packaged within, a delivery device adapted to the vaginal anatomy of the subject. Douche preparations may further comprise various additional ingredients including, but not limited to, antioxidants, antibiotics, antifungal agents, and preservatives.

As used herein, "parenteral administration" of a pharmaceutical composition includes any route of administration characterized by physical breaching of a tissue of a subject and administration of the pharmaceutical composition through the breach in the tissue. Parenteral administration thus includes, but is not limited to, administration of a pharmaceutical composition by injection of the composition, by application of the composition through a surgical incision, by application of the composition through a tissue-penetrating non-surgical wound, and the like. In particular, parenteral administration is contemplated to include, but is not limited to,

subcutaneous, intraperitoneal, intramuscular, and intrasternal injection, and kidney dialytic infusion techniques.

Formulations of a pharmaceutical composition suitable for parenteral administration comprise the active ingredient combined with a pharmaceutically acceptable carrier, such as sterile water or sterile isotonic saline. Such formulations may be prepared, packaged, or sold in a form suitable for bolus administration or for continuous administration. Injectable formulations may be prepared, packaged, or sold in unit dosage form, such as in ampules or in multi-dose containers containing a preservative. Formulations for parenteral administration include, but are not limited to, suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and implantable sustained-release or biodegradable formulations. Such formulations may further comprise one or more additional ingredients including, but not limited to, suspending, stabilizing, or dispersing agents. In one embodiment of a formulation for parenteral administration, the active ingredient is provided in dry (i.e., powder or granular) form for reconstitution with a suitable vehicle (e.g., sterile pyrogen free water) prior to parenteral administration of the reconstituted composition.

The pharmaceutical compositions may be prepared, packaged, or sold in the form of a sterile injectable aqueous or oily suspension or solution. This suspension or solution may be formulated according to the known art, and may comprise, in addition to the active ingredient, additional ingredients such as the dispersing agents, wetting agents, or suspending agents described herein. Such sterile injectable formulations may be prepared using a non-toxic parenterally acceptable diluent or solvent, such as water or 1,3-butane diol, for example. Other acceptable diluents and solvents include, but are not limited to, Ringer's solution, isotonic sodium chloride solution, and fixed oils such as synthetic mono- or di-glycerides. Other parentally-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form, in a liposomal preparation, or as a component of a biodegradable polymer systems. Compositions for sustained release or implantation may comprise pharmaceutically acceptable polymeric or hydrophobic materials such as an emulsion, an ion exchange resin, a sparingly soluble polymer, or a sparingly soluble salt.

Formulations suitable for topical administration include, but are not limited to, liquid or semi-liquid preparations such as liniments, lotions, oil in water or water

in oil emulsions such as creams, ointments or pastes, and solutions or suspensions. Topically-administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient may be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers, and preferably from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant may be directed to disperse the powder or using a self-propelling solvent/powder-dispensing container such as a device comprising the active ingredient dissolved or suspended in a low-boiling propellant in a sealed container. Preferably, such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. More preferably, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions preferably include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

Low boiling propellants generally include liquid propellants having a boiling point of below 65°F at atmospheric pressure. Generally, the propellant may constitute about 50% to about 99.9% (w/w) of the composition, and the active ingredient may constitute about 0.1% to about 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non-ionic or solid anionic surfactant or a solid diluent (preferably having a particle size of the same order as particles comprising the active ingredient).

Pharmaceutical compositions of the invention formulated for pulmonary delivery may also provide the active ingredient in the form of droplets of a solution or suspension. Such formulations may be prepared, packaged, or sold as aqueous or dilute alcoholic solutions or suspensions, optionally sterile, comprising the active

ingredient, and may conveniently be administered using any nebulization or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration preferably have an average diameter in the range from about 0.1 to about 200 nanometers.

The formulations described herein as being useful for pulmonary delivery are also useful for intranasal delivery of a pharmaceutical composition of the invention.

Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to about 500 micrometers. Such a formulation is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

Formulations suitable for nasal administration may, for example, comprise from about as little as about 0.1% (w/w) and as much as about 100% (w/w) of the active ingredient, and may further comprise one or more of the additional ingredients described herein.

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets or lozenges made using conventional methods, and may, for example, comprise about 0.1% to about 20% (w/w) active ingredient, the balance comprising an orally dissolvable or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations suitable for buccal administration may comprise a powder or an aerosolized or atomized solution or suspension comprising the active ingredient. Such powdered, aerosolized, or atomized formulations, when dispersed, preferably have an average particle or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1% to 1.0% (w/w) solution or suspension of the active ingredient in an aqueous or oily

liquid carrier. Such drops may further comprise buffering agents, salts, or one or more other of the additional ingredients described herein. Other opthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form or in a liposomal preparation.

A pharmaceutical composition of the invention may be prepared, packaged, or sold in a formulation suitable for intramucosal administration. The present invention provides for intramucosal administration of compounds to allow passage or absorption of the compounds across mucosa. Such type of administration is useful for absorption orally (gingival, sublingual, buccal, etc.), rectally, vaginally, pulmonary, nasally, etc.

In some aspects, sublingual administration has an advantage for active ingredients which in some cases, when given orally, are subject to a substantial first pass metabolism and enzymatic degradation through the liver, resulting in rapid metabolization and a loss of therapeutic activity related to the activity of the liver enzymes that convert the molecule into inactive metabolites, or the activity of which is decreased because of this bioconversion.

In some cases, a sublingual route of administration is capable of producing a rapid onset of action due to the considerable permeability and vascularization of the buccal mucosa. Moreover, sublingual administration can also allow the administration of active ingredients which are not normally absorbed at the level of the stomach mucosa or digestive mucosa after oral administration, or alternatively which are partially or completely degraded in acidic medium after ingestion of, for example, a tablet.

Sublingual tablet preparation techniques known from the prior art are usually prepared by direct compression of a mixture of powders comprising the active ingredient and excipients for compression, such as diluents, binders, disintegrating agents and adjuvants. In an alternative method of preparation, the active ingredient and the compression excipients can be dry- or wet-granulated beforehand. In one aspect, the active ingredient is distributed throughout the mass of the tablet. WO 00/16750 describes a tablet for sublingual use that disintegrates rapidly and comprises an ordered mixture in which the active ingredient is in the form of microparticles which adhere to the surface of water-soluble particles that are substantially greater in size, constituting a support for the active microparticles, the composition also comprising a mucoadhesive agent. WO 00/57858 describes a

tablet for sublingual use, comprising an active ingredient combined with an effervescent system intended to promote absorption, and also a pH-modifier.

The compounds of the invention can be prepared in a formulation or pharmaceutical composition appropriate for administration that allows or enhances absorption across mucosa. Mucosal absorption enhancers include, but are not limited to, a bile salt, fatty acid, surfactant, or alcohol. In specific embodiments, the permeation enhancer can be sodium cholate, sodium dodecyl sulphate, sodium deoxycholate, taurodeoxycholate, sodium glycocholate, dimethylsulfoxide or ethanol. In a further embodiment, a compound of the invention can be formulated with a mucosal penetration enhancer to facilitate delivery of the compound. The formulation can also be prepared with pH optimized for solubility, drug stability, and absorption through mucosa such as nasal mucosa, oral mucosa, vaginal mucosa, respiratory, and intestinal mucosa.

To further enhance mucosal delivery of pharmaceutical agents within the invention, formulations comprising the active agent may also contain a hydrophilic low molecular weight compound as a base or excipient. Such hydrophilic low molecular weight compounds provide a passage medium through which a water-soluble active agent, such as a physiologically active peptide or protein, may diffuse through the base to the body surface where the active agent is absorbed. The hydrophilic low molecular weight compound optionally absorbs moisture from the mucosa or the administration atmosphere and dissolves the water-soluble active peptide. The molecular weight of the hydrophilic low molecular weight compound is generally not more than 10000 and preferably not more than 3000. Exemplary hydrophilic low molecular weight compounds include polyol compounds, such as oligo-, di- and monosaccharides such as sucrose, mannitol, lactose, L-arabinose, D-erythrose, D-ribose, D-xylose, D-mannose, D-galactose, lactulose, cellobiose, gentibiose, glycerin, and polyethylene glycol. Other examples of hydrophilic low molecular weight compounds useful as carriers within the invention include N-methylpyrrolidone, and alcohols (e.g., oligovinyl alcohol, ethanol, ethylene glycol, propylene glycol, etc.). These hydrophilic low molecular weight compounds can be used alone or in combination with one another or with other active or inactive components of the intranasal formulation.

When a controlled-release pharmaceutical preparation of the present invention further contains a hydrophilic base, many options are available for

inclusion. Hydrophilic polymers such as a polyethylene glycol and polyvinyl pyrrolidone, sugar alcohols such as D-sorbitol and xylitol, saccharides such as sucrose, maltose, lactulose, D-fructose, dextran, and glucose, surfactants such as polyoxyethylene-hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, and polyoxyethylene sorbitan higher fatty acid esters, salts such as sodium chloride and magnesium chloride, organic acids such as citric acid and tartaric acid, amino acids such as glycine, beta-alanine, and lysine hydrochloride, and aminosaccharides such as meglumine are given as examples of the hydrophilic base. Polyethylene glycol, sucrose, and polyvinyl pyrrolidone are preferred and polyethylene glycol are further preferred. One or a combination of two or more hydrophilic bases can be used in the present invention.

The present invention contemplates pulmonary, nasal, or oral administration through an inhaler. In one embodiment, delivery from an inhaler can be a metered dose.

An inhaler is a device for patient self-administration of at least one compound of the invention comprising a spray inhaler (e.g., a nasal, oral, or pulmonary spray inhaler) containing an aerosol spray formulation of at least one compound of the invention and a pharmaceutically acceptable dispersant. In one aspect, the device is metered to disperse an amount of the aerosol formulation by forming a spray that contains a dose of at least one compound of the invention effective to treat a disease or disorder encompassed by the invention. The dispersant may be a surfactant, such as, but not limited to, polyoxyethylene fatty acid esters, polyoxyethylene fatty acid alcohols, and polyoxyethylene sorbitan fatty acid esters. Phospholipid-based surfactants also may be used.

In other embodiments, the aerosol formulation is provided as a dry powder aerosol formulation in which a compound of the invention is present as a finely divided powder. The dry powder formulation can further comprise a bulking agent, such as, but not limited to, lactose, sorbitol, sucrose, and mannitol.

In another specific embodiment, the aerosol formulation is a liquid aerosol formulation further comprising a pharmaceutically acceptable diluent, such as, but not limited to, sterile water, saline, buffered saline and dextrose solution.

In further embodiments, the aerosol formulation further comprises at least one additional compound of the invention in a concentration such that the metered amount of the aerosol formulation dispersed by the device contains a dose of the

additional compound in a metered amount that is effective to ameliorate the symptoms of disease or disorder disclosed herein when used in combination with at least a first or second compound of the invention.

Thus, the invention provides a self administration method for outpatient treatment of an addiction related disease or disorder such as an alcohol-related disease or disorder. Such administration may be used in a hospital, in a medical office, or outside a hospital or medical office by non-medical personnel for self administration.

Compounds of the invention will be prepared in a formulation or pharmaceutical composition appropriate for nasal administration. In a further embodiment, the compounds of the invention can be formulated with a mucosal penetration enhancer to facilitate delivery of the drug. The formulation can also be prepared with pH optimized for solubility, drug stability, absorption through nasal mucosa, and other considerations.

Capsules, blisters, and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the pharmaceutical compositions provided herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as l-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions provided herein for inhaled/intranasal administration may further comprise a suitable flavor, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium.

For administration by inhalation, the compounds for use according to the methods of the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the drugs and a suitable powder base such as lactose or starch.

As used herein, "additional ingredients" include, but are not limited to, one or more of the following: excipients; surface active agents; dispersing agents; inert

diluents; granulating and disintegrating agents; binding agents; lubricating agents; sweetening agents; flavoring agents; coloring agents; preservatives; physiologically degradable compositions such as gelatin; aqueous vehicles and solvents; oily vehicles and solvents; suspending agents; dispersing or wetting agents; emulsifying agents, demulcents; buffers; salts; thickening agents; fillers; emulsifying agents; antioxidants; antibiotics; antifungal agents; stabilizing agents; and pharmaceutically acceptable polymeric or hydrophobic materials. Other "additional ingredients" which may be included in the pharmaceutical compositions of the invention are known in the art and described, for example in Genaro, ed., 1985, Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, which is incorporated herein by reference.

Typically, dosages of the compounds of the invention which may be administered to an animal, preferably a human, range in amount from about 1.0 μg to about 100 g per kilogram of body weight of the animal. The precise dosage administered will vary depending upon any number of factors, including but not limited to, the type of animal and type of disease state being treated, the age of the animal and the route of administration. Preferably, the dosage of the compound will vary from about 1 mg to about 10 g per kilogram of body weight of the animal. More preferably, the dosage will vary from about 10 mg to about 1 g per kilogram of body weight of the animal.

The compounds may be administered to a subject as frequently as several times daily, or it may be administered less frequently, such as once a day, once a week, once every two weeks, once a month, or even less frequently, such as once every several months or even once a year or less. The frequency of the dose will be readily apparent to the skilled artisan and will depend upon any number of factors, such as, but not limited to, the type and severity of the disease being treated, the type and age of the animal, etc.

The invention also includes a kit comprising the compounds of the invention and an instructional material that describes administration of the compounds. In another embodiment, this kit comprises a (preferably sterile) solvent suitable for dissolving or suspending the composition of the invention prior to administering the compound to the mammal.

As used herein, an "instructional material" includes a publication, a recording, a diagram, or any other medium of expression that can be used to

communicate the usefulness of the compounds of the invention in the kit for effecting alleviation of the various diseases or disorders recited herein. Optionally, or alternately, the instructional material may describe one or more methods of alleviating the diseases or disorders. The instructional material of the kit of the invention may, for example, be affixed to a container that contains a compound of the invention or be shipped together with a container that contains the compounds. Alternatively, the instructional material may be shipped separately from the container with the intention that the instructional material and the compound be used cooperatively by the recipient.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. The following working examples, therefore, specifically point out the preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

Examples

A series of background drug combination studies are provided herein. Examples 1 and 2 are examples of using various combinations of two different drugs at a time, and serve as preludes to the topiramate, ondansetron, and naltrexone combination studies disclosed in Example 3.

Example 1

The studies described herein demonstrate, inter alia: a) ondansetron's effectiveness in the treatment of EOA and LOA; b) that EOA differs from LOA in serotonergic function; c) that age of onset discriminates between subtypes of alcoholic; d) naltrexone's effects on alcohol drinking in non-human primates; e) naltrexone's effects on drinking in humans; f) that the combination of ondansetron and naltrexone is clinically safe and effective in the treatment of EOA; and g) evidence of our expertise with Cognitive Behavioral Therapy as a psychosocial platform for testing the effectiveness of putative therapeutic medications.

a) <u>Ondansetron is effective at improving the drinking outcomes of EOA but not LOA</u>

It was hypothesized herein that the drinking outcomes of EOA, compared with LOA, would be more improved by the selective serotonin antagonist,

ondansetron. EOA differ from LOA by having greater serotonergic abnormality, an earlier age of onset, and antisocial behaviors. Thus, EOA may be especially responsive to treatment with a selective serotonergic agent.

The design was as follows: 321 alcoholics (EOA = 161; LOA = 160; mean age 40.6 years; 70.5% male, and 78.6% white) received one lead in week of single-blind placebo followed by 11 weeks of double-blind outpatient treatment using a 2 x 4 factorial design which examined age of onset (EOA vs. LOA) and medication dose (placebo, or ondansetron 1, 4, or 16 μg/kg b.i.d) combined with weekly standardized group Cognitive Behavioral Therapy. Efficacy measures were: 1) Self reported drinking (Drinks/Day, Drinks/Drinking Day, Percent Days Abstinent, and Total Days Abstinent/study week), and 2) plasma Carbohydrate Deficient Transferrin level (CDT).

The results were that at endpoint, EOA who received ondansetron (1 or 4 μg/kg b.i.d), compared with those on placebo had fewer Drinks/Day (1.89 or 1.56 vs. 3.30; $p < 0.05$) and Drinks/Drinking Day (4.75 or 4.28 vs. 6.90; $p < 0.05$). Ondansetron 4 μg/kg b.i.d was superior to placebo at increasing Percent Days Abstinent (70.10 vs. 50.20; $p < 0.05$) and Total Days Abstinent/study week (6.74 vs. 5.92; $p < 0.05$). Among EOA, there was a reduction in the mean log CDT ratio between endpoint and enrollment for those on ondansetron (1 and 4 μg/kg b.i.d) but not placebo (-0.17 and 0.19 vs. +0.11; $p < 0.05$). Drinking outcomes in LOA were not improved substantially by ondansetron. As an illustration, the figures below shows the Mean ± SE Drinks/Day and the Mean ± SE log plasma by treatment condition, respectively.

In summary, we concluded that ondansetron (particularly the 4 μg/kg b.i.d dose) is an effective treatment for EOA, presumably by ameliorating underlying serotonergic abnormality. (see Figures 1-7).

b) <u>EOA may have a greater predisposition to 5-HT abnormality than LOA</u>

This study was conducted based upon the hypothesis that the younger an alcoholic's age of onset the more likely he/she is to develop behavioral problems associated with 5-HT dysfunction such as impulsivity and a broad range of antisocial behaviors – just the type of individual likely to have EOA.
We studied the relationship between plasma TRYP/LNAA ratio in 58 (Males = 42) treatment-seeking alcoholics. Subjects had a mean: a) chronological age of 41.5

(SD 8.3) years; b) age of onset 24.2 (SD 9.7) years, and c) an average duration of illness of 17.3 (SD 8.9) years. Briefly, age of onset was significantly and positively correlated with plasma TRYP/LNAA ratio (0.292; $p < 0.05$); this is consistent with an association between earlier onset of alcoholism and reduced tryptophan availability. Additionally, plasma TRYP/LNAA ratio was positively correlated with legal problems (0.313; $p < 0.05$) on the Addiction Severity Index and self-directedness (0.287; $p < 0.05$) on the Temperament and Character Inventory (TCI). However, plasma TRYP/LNAA ratio was negatively correlated with harm avoidance on (0.351; $p < 0.05$) on the TCI and vigor (-0.260; $p < 0.05$) on the Profile of Mood States. Further, alcoholics with an additional diagnosis of antisocial personality disorder (ASPD) had comparatively lower plasma TRYP/LNAA ratios than those without ASPD (mean 0.019 ± 0.0067 vs. 0.018 0. ± 007; $p < 0.05$ respectively). These results were consistent with those of others which have found an association between low 5-HT function and an early age of alcoholism onset and related antisocial behaviors.

c) Age of onset discriminates between subtypes of alcoholic

In a cohort (N = 253) of the alcoholics enrolled into our effectiveness study of ondansetron for the treatment of alcoholism, we studied baseline differences between the three groups using a comprehensive set of psychopathological variables. These analyses were conducted using two different models. First, we examined the impact of specifying different ages of onset for the subtyping - that is, by comparing EOA and LOA depending upon whether the cut-off age for the distinction was ≤ 20 or ≤ 25 years. Second, we examined age of onset as a continuous variable by inclusion of a Middle Onset Group (MOA) – i.e., EOA ≤ 20 years; MOA = 20 – 25 years, and LOA > 25 years.

First, there were no important differences in psychopathological profile based on different cut-off onset ages for EOA (i.e., ≤ 20 or ≤ 25 years) or LOA (i.e., >20 or > 25 years). Second, using the ≤ 25 years or > 25 years cut-off criteria for onset age, EOA compared with LOA did have significantly ($p < 0.05$) higher: a) Visual Analogue Scores for the craving measures of: "thinking about the next time I will use alcohol" (21.8 ± 2.7 vs. 17.6 ± 2.4); "I want to buy alcohol" (35.2 ± 3.1 vs. 26.3 ± 2.8) , "I have the urge or desire to use alcohol" (24.3 ± 3.2 vs. 16.4 ± 2.3), and "if offered I can refuse alcohol (30.3 ± 3.5 vs. 20.9 ± 2.6); b) hostility scores on

the "resentment" (3.2 ± 0.2 vs. 2.4 ± 0.2), "assault" (4.2 ± 0.3 vs. 3.3 ± 0.3), "suspicion" (3.5 ± 0.3 vs. 2.6 ± 0.2), and "addictive propensity" (27.7 ± 0.5 vs. 25.3 ± 0.5) subscales of the Buss-Durkee ; c) reduction in childhood problem behaviors " (34.9 ± 1.1 vs. 38.6 ± 0.9); d) male family history (8.5 ± 0.8 vs. 5.3 ± 0.5) on the Comprehensive Drinker Profile (123); e) "depression-dejection" (21.5 ± 1.6 vs. 14.8 ± 1.2), "anger-hostility" (11.7 ± 1.0 vs. 6.6 ± 0.6), "fatigue-inertia" (10.0 ± 0.7 vs. 6.3 ± 0.5) and "confusion-bewilderment" (9.3 ± 0.5 vs. 6.6 ± 0.4) on the Profile of Mood States, and e) there were more EOA than LOA with antisocial personality disorder (ASPD) (18.9% vs. 6.4%). These results show that EOA differ from LOA on psychopathological characteristics associated with craving, hostility, family history, impulse-control, and antisocial behaviors.

d) Naltrexone's effects on alcohol drinking in non-human primates

Studies in non-human primates show that naltrexone is associated with dose-dependent reductions in alcohol drinking. From the figure opposite, it can be seen that increasing doses of naltrexone (g/kg) produced dose-dependent decreases in alcohol consumption (8% w/v) in three non food deprived rhesus monkeys under a fixed ratio schedule of reinforcement. During these 3 hour sessions, both water and alcohol were concurrently available. These results support clinical evidence of naltrexone as a treatment medication for alcoholism. However, the time-course data also show that naltrexone's non specific pharmacological effects play an important role in its ability to reduce drinking behavior (see Figure 3).

e) Naltrexone's effects on alcohol consumption in humans

In an open-label study, we evaluated the efficacy of naltrexone, an opioid antagonist, in the treatment of alcohol dependence. Since up to 92% of alcoholics are also co-dependent on nicotine, our cohort included dually dependent individuals. Naltrexone was chosen due to evidence which suggests utility in the treatment of alcoholism, and some evidence that opioid-DA interaction may mediate the reinforcing effects of nicotine. From a local newspaper advertisement, we enrolled 10 subjects (6 males and 4 females; aged 40 ± 2.56 years) into the study. All patients met DSM III-R criteria for both alcohol and nicotine dependence. Patients were instructed that the goal of treatment was abstinence by the end of the study. Patients received naltrexone (50 mg/day) in unmarked capsules with a riboflavin tracer for an 8 week period. Weekly attendance included combined coping skills

therapy for alcohol and nicotine dependence, nursing visits, and completion of rating scales. The results showed that there was a significant decrease in alcohol consumption (3.29 ± 2.16 drinks/day vs. 2.16 ± 1.88 drinks/day; $p < 0.05$), and a noticeable reduction in smoking (21.10 ± 5.57 cigarettes/day vs. 15.93 ± 3.09 cigarette/day). Objective biochemical measures of alcohol consumption and nicotine (urine cotinine from 33% to 54%), and craving showed a similar trend. No patient reported clinically significant nicotine withdrawal symptoms. Drop-out rate at 30% was similar to that observed in medication trials for alcoholism. This study supports the clinical evidence that naltrexone is a useful adjunct to Cognitive Behavioral Therapy for the treatment of alcoholism. Naltrexone's effects on cigarette smoking appears small but may warrant further exploration.

f) Safety and effectiveness of combining ondansetron and naltrexone in treating EOA

In an 8-week double-blind clinical trial, we tested the safety and effectiveness of ondansetron (4 μg/kg) + naltrexone (50 mg/day) vs. placebo for the treatment of alcoholism. We enrolled 20 DSM-IV diagnosed EOA (Males = 15, females = 5; mean age = 38.0 ± 1.78 years; Ethnicity - Caucasian = 12, Hispanics = 8). Ten of these subjects received the medication combination and the rest (N = 10) got placebo in addition to weekly sessions of manual-driven Cognitive Behavioral Therapy. All subjects were 'currently drinking' at enrollment. Only one subject with constipation and who received the medication combination reported any side-effect attributable to the study medication which was rated above 'minimal'. Minimal nausea and fatigue vs. constipation were reported by two vs. three subjects, respectively who received the medication combination. Comparatively, minimal headaches and constipation were reported in four and two subjects on placebo, respectively. No side-effect persisted between weekly study visits, or required medical intervention. No subject withdrew from the study due to side-effects. From these data, there was no clinical difference in the side-effect profile between the treatment groups. This would suggest that the side-effect profile of ondansetron + naltrexone is benign and unlikely to be significantly different from placebo.

While the small subject numbers in this study do not permit meaningful percentage comparisons with the much larger sample size study (Total N = 865; 295 received the reference condition and 570 naltrexone) of Croop and Colleagues, it is

notable that they reported a 15% rate of subject withdrawal due to naltrexone induced nausea. In our own study of ondansetron's effectiveness (N = 321; 88 of whom received the 4 μg/kg dose) (see C.a. above), no side-effect was reported more often than placebo, and nausea was not reported. Therefore, it is reasonable to expect that ondansetron will reduce naltrexone's propensity to induce nausea, thereby enhancing compliance.

Preliminary analyses of the data showed that at endpoint, those who received ondansetron + naltrexone vs. placebo had fewer: 1) Drinks/Day (adjusted mean 0.99 ± 0.60 vs. 3.68± 0.63; F1, 16 = 9.35, p = 0.008); 2) Drinks/Drinking Day (3.14 ± 0.87 vs. 6.76 ± 0.71; F1, 13 = 10.45, p = 0.007) (see fig. 3. below). There was a trend towards an improvement in Percent Days Abstinent among those receiving the medication combination vs. placebo from enrollment to endpoint (adjusted mean 72.06 ± 8.64 vs. 48.24 ± 9.12; F1, 16 = 3.53, p = 0.08). There were no significant differences in baseline drinking between the treatment groups. These data are striking given the small cohort, and the effect sizes for the Drinks/Day and Drinks/Drinking Day results were large – 1.4 and 1.7, respectively based on covariate adjustment and log transformation. Drop-out rate was about 25%.

In summary, these results provide strong evidence that the combination of ondansetron and naltrexone is safe and effective for the treatment of EOA. Further, this finding supports the hypothesis that the combination of ondansetron and naltrexone would provide added and possibly even synergistic therapeutic benefit given that the typical effect sizes for these medications alone are in the 0.2 – 0.5 range.

g) Additional recent clinical trial experience using Cognitive Behavioral Therapy

The applicants have considerable experience with the use of Cognitive Behavioral Therapy as the psychosocial foundation for assessing the efficacy of putative therapeutic compounds. As an example, provided below are the results from our center participating in a large multi center clinical trial. Dr. Johnson was the lead author in the publication that resulted from this multi center study (see Figure 5).

Ritanserin, a 5-HT2 antagonist, has been shown to reduce alcohol preference and consumption in rats, presumably via its interaction with midbrain dopamine

fibers. In this study, we examined the efficacy of ritanserin on alcohol consumption in a 12-week, outpatient, placebo-controlled clinical trial. This study overlapped in time and recruitment effort with the ondansetron study described above. Therefore, our research group has the expertise to conduct multiple treatment studies simultaneously. Fifty-four patients from our center who met DSM III-R criteria for alcoholism participated and were randomized to receive placebo, 2.5 mg, or 5 mg of ritanserin. All patients received standardized manual driven Cognitive Behavioral Therapy for alcoholism. Cognitive Behavioral Therapy was conducted by counselors with extensive experience with behavioral treatments, and over 500 therapy hours were logged. These groups did not differ in age, sex distribution, or severity of alcoholism. Fig. 3 shows that there was no significant difference on alcohol consumption between the three groups and no treatment effect using a repeated measures analysis of variance ($F=2.81$; $df=2,17$, $p=0.088$). There was no within time effect nor group interaction. Similarly, there was no difference in craving between the treatment groups. These results show that at these doses, ritanserin had no clinically significant effect on alcohol consumption or craving. These results are consistent with those of other researchers in this multi-center trial.

A typical experimental design chart is provided in Figure 6. In some cases telephone screening procedures are used. For example, in one trial the ratio of telephone screens to enrollment was approximately 4:1 (see Figure 7). Our telephone screening procedures are highly effective at identifying eligible subjects for our studies. Most subjects are excluded from the study at the telephone screening stage. Of those who appear to meet eligibility criteria on the telephone screen and who show up for the intake interview, less than 30% of these are excluded from enrollment. The most common reasons for exclusion at intake are abnormal laboratory tests, and/or other significant health problems.

Figure 7 is a representative example of enrollment and projected completion rates adjusting for start up and wind-down periods of about 8 weeks. The telephone screening procedures are highly effective at identifying eligible subjects for our studies. Most subjects are excluded from the study at the telephone screening stage. Of those who appear to meet eligibility criteria on the telephone screen and who show up for the intake interview, less than 30% of these are excluded from enrollment. The most common reasons for exclusion at intake are abnormal laboratory tests, and/or other significant health problems.

Example 2

Examination of the Combined Administration of Topiramate and Naltrexone as a Potential Treatment for Alcohol Dependence Using Animal Models

Figure 8 demonstrates the combined effect of topiramate (5 and 10 mg/kg, intraperitoneally) and naltrexone (1 mg/kg, intraperitoneally) on alcohol consumption in alcohol-preferring (P) rats. While topiramate alone only modestly decreased alcohol consumption (at the 10-mg/kg dose although this effect is not yet significant), when combined with a dose of naltrexone that did not affect alcohol consumption on its own, significant decreases from baseline were observed on alcohol consumption at both topiramate doses (see Figure 8). No significant differences were observed following vehicle injection. Data are plotted as change from baseline consumption, and each data point represents a mean (± SE) of 8 rats.

Model for Neural Control

The neural control mechanisms described herein are presented schematically in Figure 9.

Example 3

Examination of the combined administration of ondansetron, topiramate, and naltrexone as a potential treatment for alcohol dependence using animal models

The effects of ondansetron, topiramate, and naltrexone, medications shown to be efficacious in treating alcohol-dependent humans, on measures of alcohol dependence were determined in animal models in order to determine whether these medications may produce additive effects when combined. The experiments examined their ability to modulate total consumption under a 24-hour-access two-bottle choice procedure wherein rats had unlimited access to alcohol solutions (10%) and water. Figure 10 demonstrates the combined effect of topiramate (10 mg/kg, intraperitoneally), ondansetron (0.001 mg/kg, intraperitoneally), and naltrexone (1 mg/kg, intraperitoneally) on alcohol consumption in alcohol-preferring rats. While topiramate alone produced modest decreases in alcohol consumption (Fig. 10A; e.g., 12% ± 8% decrease from baseline), when combined with naltrexone and a dose of ondansetron that did not affect alcohol consumption on its own (Fig. 10B), robust

and persistent decreases from baseline were observed on alcohol consumption as measured under a two-bottle 24-hour consumption procedure (Fig. 10D- topiramate + ondansetron; Fig. 10E- topiramate + ondansetron + naltrexone, e.g., 28% ± 5% decrease from baseline). Data are plotted across 7 consecutive sessions, which include a 3-day baseline period, the test session in which the compound(s) were administered, and the 3 sessions that followed the test session. Each data point represents a mean (± SE) of at least 6 rats. The data suggest an additive beneficial effect of the topiramate/ondansetron/naltrexone combination as compared with each of the drugs alone.

The addictive effects of most abused drugs and alcohol are mediated through increased dopaminergic activity in the cortico-mesolimbic system that originates in the ventral tegmental area, relays in the nucleus accumbens, and sends forward profuse connections to the cortex and other higher brain centers. Figure 11 schematically illustrates that the opioid, glutamate, and serotonergic systems are all modulators of cortico-mesolimbic dopamine function.

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated by reference herein in their entirety.

Headings are included herein for reference and to aid in locating certain sections. These headings are not intended to limit the scope of the concepts described therein under, and these concepts may have applicability in other sections throughout the entire specification.

The previous description of the disclosed embodiments is provided to enable any person skilled in the art to make or use the present invention. Various modifications to these embodiments will be readily apparent to those skilled in the art, and the generic principles defined herein may be applied to other embodiments without departing from the spirit or scope of the invention. Accordingly, the present invention is not intended to be limited to the embodiments shown herein but is to be accorded the widest scope consistent with the principles and novel features disclosed herein.

CLAIMS

What is claimed is:

1. A method for treating or preventing an addictive disease or disorder in a subject in need thereof, said method comprising administering to said subject an effective amount of at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, wherein said at least three compounds are selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, norepinephrine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, glutamine agonists, glutamine antagonists, anti-convulsant agents, N-methyl-D-aspartate-blocking agents, calcium channel antagonists, carbonic anhydrase inhibitors, neurokinins, small molecules, peptides, vitamins, co-factors, and Corticosteroid Releasing Factor antagonists, and optionally administering at least one additional therapeutically active compound, thereby treating or preventing an addictive disease or disorder in a subject.

2. The method of claim 1, wherein said subject is a human.

3. The method of claim 2, wherein said addictive disease or disorder is selected from the group consisting of alcohol-related diseases and disorders, obesity-related diseases and disorders, eating disorders, impulse control disorders, nicotine-related disorders, amphetamine-related disorders, methamphetamine-related disorders, cannabis-related disorders, cocaine-related disorders, hallucinogen use disorders, inhalant-related disorders, benzodiazepine abuse or dependence related disorders, and opioid-related disorders.

4. The method of claim 3, wherein said addictive disease or disorder is an alcohol-related disease or disorder.

5. The method of claim 4, wherein said alcohol-related disease or disorder is selected from the group consisting of early onset alcoholic, late onset alcoholic, alcohol-induced psychotic disorder with delusions, alcohol abuse, heavy drinking, excessive drinking, alcohol intoxication, alcohol withdrawal, alcohol intoxication delirium, alcohol withdrawal delirium, alcohol-induced persisting dementia, alcohol-induced persisting amnestic disorder, alcohol dependence, alcohol-induced psychotic disorder with hallucinations, alcohol-induced mood disorder, alcohol-induced or associated bipolar disorder, alcohol-induced or associated post traumatic stress disorder, alcohol-induced anxiety disorder, alcohol-induced sexual dysfunction, alcohol-induced sleep disorder, alcohol-induced or associated gambling disorder, alcohol-induced or associated sexual disorder, alcohol-related disorder not otherwise specified, alcohol intoxication, and alcohol withdrawal.

6. The method of claim 5, wherein said treatment reduces the frequency of alcohol consumption compared with the frequency before said treatment or compared with a control subject not receiving said treatment.

7. The method of claim 6, wherein said alcohol consumption comprises heavy drinking or excessive drinking.

8. The method of claim 5, wherein said treatment reduces the quantity of alcohol consumed compared with the amount of alcohol consumed before said treatment or compared with a control subject not receiving said treatment.

9. The method of claim 8, wherein said alcohol consumption comprises heavy drinking or excessive drinking.

10. The method of claim 5, wherein said treatment improves the physical or psychological sequelae associated with alcohol consumption compared with a control subject not receiving said treatment.

11. The method of claim 5, wherein said treatment increases the abstinence rate of said subject compared with a control subject not receiving said treatment.

12. The method of claim 5, wherein said treatment reduces the average level of alcohol consumption compared with the level before said treatment or compared with a control subject not receiving said treatment.

13. The method of claim 3, wherein said treatment reduces alcohol consumption and increases abstinence compared with the alcohol consumption and abstinence before said treatment or compared with a control subject not receiving said treatment.

14. The method of claim 5, wherein said subject comprises a predisposition to early-onset alcoholism or late-onset alcoholism.

15. The method of claim 5, further wherein said subject is submitted to a psychosocial management program.

16. The method of claim 15, wherein said psychosocial management program is selected from the group consisting of Brief Behavioral Compliance Enhancement Treatment, Cognitive Behavioral Coping Skills Therapy, Motivational Enhancement Therapy, Twelve-Step Facilitation Therapy, Combined Behavioral Intervention, Medical Management, psychoanalysis, psychodynamic treatment, and Biopsychosocial, Report, Empathy, Needs, Direct Advice and Assessment.

17. The method of claim 1, wherein said subject is further subjected to hypnosis or acupuncture.

18. The method of claim 1, wherein at least one of said at least three compounds is administered at least once a week.

19. The method of claim 18, wherein at least one of said at least three compounds is administered at least once a day.

20. The method of claim 1, wherein at least one of said at least three compounds is a serotonin receptor antagonist.

21. The method of claim 20, wherein said serotonin receptor is the serotonin-3 receptor.

22. The method of claim 1, wherein three compounds are administered to said subject.

23. The method of claim 1, wherein said at least three compounds are separately administered.

24. The method of claim 23, wherein a first compound of said at least three compounds is administered before a second compound of said at least three compounds is administered.

25. The method of claim 1, wherein a first compound, a second compound, and a third compound of said at least three compounds are administered nearly simultaneously.

26. The method of claim 1, wherein a first compound of said at least three compounds is administered subsequent to administration of a second or third compound of said at least three compounds.

27. The method of claim 1, wherein said at least three compounds are administered as a pharmaceutical composition.

28. The method of claim 1, wherein said at least three compounds are administered via a route selected from the group consisting of oral, topical, rectal, intramuscular, intramucosal, and intravenous.

29. The method of claim 28, wherein said at least three compounds are administered via an oral route.

30. A pharmaceutical composition comprising at least three compounds of claim 1, or biologically active analogs, homologs, derivatives, modifications, or pharmaceutically-acceptable salts thereof, and a pharmaceutically acceptable carrier.

31. The pharmaceutical composition of claim 30, said composition comprising effective amounts of topiramate, ondansetron, and naltrexone, and biologically active analogs, homologs, derivatives, modifications, or pharmaceutically-acceptable salts thereof.

32. The method of claim 1, wherein at least one of said at least three compounds is administered as a controlled-release formulation.

33. The method of claim 1, wherein three of said at least three compounds are topiramate, naltrexone, and ondansetron, or biologically active analogs, homologs, derivatives, modifications, or pharmaceutically-acceptable salts thereof.

34. The method of claim 33, wherein three compounds, or biologically active analogs, homologs, derivatives, modifications, or pharmaceutically-acceptable salts thereof, are administered.

35. The method of claim 33, wherein at least one additional therapeutically active compound is administered.

36. The method of claim 33, wherein topiramate is administered at a dosage ranging from about 15 mg/day to about 2500 mg/day.

37. The method of claim 36, wherein topiramate is administered at a dosage ranging from about 25 mg/day to about 1000 mg/day.

38. The method of claim 37, wherein topiramate is administered at a dosage ranging from about 50 mg/day to about 500 mg/day.

39. The method of claim 38, wherein topiramate is administered at a dosage of about 300 mg/day or about 275 mg/day.

40. The method of claim 33, wherein topiramate is administered at a dosage ranging from about 0.1 mg/kg/day to about 100 mg/kg/day.

41. The method of claim 36, wherein topiramate is administered at a dose of bout 300 mg/day.

42. The method of claim 33, wherein topiramate is administered at least once a week.

43. The method of claim 42, wherein topiramate is administered at least once a day.

44. The method of claim 33, wherein naltrexone is administered at a dosage ranging from about 1.0 mg per application to about 100 mg per application.

45. The method of claim 44, wherein naltrexone is administered at a dosage ranging from about 10 mg per application to about 50 mg per application.

46. The method of claim 45, wherein naltrexone is administered at a dosage of about 25 mg per application.

47. The method of claim 33, wherein naltrexone is administered at least once a week.

48. The method of claim 47, wherein naltrexone is administered at least once a day.

49. The method of claim 48, wherein naltrexone is administered at least twice a day.

50. The method of claim 49, wherein naltrexone is administered twice a day.

51. The method of claim 33, wherein ondansetron is administered at a dosage ranging from about 0.01 μg/kg per application to about 100 μg/kg per application.

52. The method of claim 51, wherein ondansetron is administered at a dosage ranging from about 0.1 μg/kg per application to about 10.0 μg/kg per application.

53. The method of claim 52, wherein ondansetron is administered at a dosage ranging from about 1.0 μg/kg per application to about 5.0 μg/kg per application.

54. The method of claim 53, wherein ondansetron is administered at a dosage of about 4.0 μg/kg per application or about 3.0 μg/kg per application.

55. The method of claim 33, wherein ondansetron is administered at least once a week.

56. The method of claim 33, wherein ondansetron is administered at least once a day.

57. The method of claim 56, wherein ondansetron is administered once a day.

58. The method of claim 33, wherein topiramate is administered at a dosage of about 300 mg/day, ondansetron is administered at a dosage of about 4.0 μg/kg per application, and naltrexone is administered at a dosage of about 25 mg per application.

59. The method of claim 34, wherein topiramate is administered at a dosage of about 300 mg/day, ondansetron is administered at a dosage of about 4.0 μg/kg per application, and naltrexone is administered at a dosage of about 25 mg per application.

60. The method of claim 1, further wherein advice is provided to said subject.

61. The method of claim 60, further wherein said advice is provided in a format selected from the group consisting of written, electronic, or interpersonal.

62. The method of claim 61, wherein said method is more effective at treating or preventing an addictive disease or disorder than a method selected from the group

consisting of administering a placebo and providing advice, administering no drugs and providing advice, and not administering drugs or providing advice.

63. The method of claim 1, wherein said method is more effective in alleviating said addictive disease or disorder than said method used in combination with a psychosocial management program.

64. The method of claim 5, wherein said alcohol-related disease or disorder is alcohol abuse.

65. The method of claim 2, further wherein at least one compound administered to said subject is selected from the group consisting of disulfiram, acamprosate, sertraline, galanthamine, nalmefene, naloxone, desoxypeganine, benzodiazepines, neuroleptics, risperidone, rimonabant, trazodone, and aripiprazole.

66. The method of claim 33, further wherein at least one compound administered to said subject is selected from the group consisting of disulfiram, acamprosate, sertraline, galanthamine, nalmefene, naloxone, desoxypeganine, benzodiazepines, neuroleptics, risperidone, rimonabant, trazodone, and aripiprazole.

67. The method of claim 1, further wherein said subject is administered at least one compound selected from the group consisting of adrenergics, adrenocortical steroids, adrenocortical suppressants, aldosterone antagonists, amino acids, analeptics, analgesics, anorectic compounds, anorexics, anti-anxiety agents, antidepressants, antihypertensives, anti-inflammatories, antinauseants, antineutropenics, antiobsessional agents, antiparkinsonians, antipsychotics, appetite suppressants, blood glucose regulators, carbonic anhydrase inhibitors, cardiotonics, cardiovascular agents, choleretics, cholinergics, cholinergic agonists, cholinesterase deactivators, cognition adjuvants, cognition enhancers, hormones, memory adjuvants, mental performance enhancers, mood regulators, neuroleptics, neuroprotectives, psychotropics, relaxants, sedative-hypnotics, stimulants, thyroid hormones, thyroid inhibitors, thyromimetics, cerebral ischemia agents, vasoconstrictors, and vasodilators.

68. The method of claim 1, wherein the effect of said at least three compounds is additive.

69. The method of claim 1, wherein the effect of said at least three compounds is synergistic.

70. The method of claim 1, wherein said treatment decreases mesocorticolimbic dopamine activity.

71. The method of claim 1, wherein said treatment inhibits glutamate function.

72. The method of claim 1, wherein said treatment facilitates γ-amino-butyric acid activity.

73. A method of treating obesity in a subject in need thereof, said method comprising administering to said subject an effective amount of at least three compounds, or biologically active analogs, homologs, derivatives, modifications, or pharmaceutically acceptable salts thereof, wherein said at least one compound is selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, anti-convulsant agents, and NMDA-blocking agents, thereby treating or preventing, and optionally administering at least one additional therapeutically active compound, thereby treating obesity.

74. The method of claim 73, wherein three of said at least three compounds are topiramate, naltrexone, and ondansetron, or biologically active analogs, homologs, derivatives, modifications, or pharmaceutically-acceptable salts thereof.

75. The method of claim 73, wherein said at least one additional therapeutically active compound is selected from the group consisting of antidiabetic agents,

antihyperlipidemic agents, antiobesity agents, antihypertensive agents, and agents for the treatment of complications resulting from or associated with diabetes.

76. The method of claim 73, wherein said subject has a body mass index of about 30.0 or greater.

77. A method of preventing or inhibiting a subject from gaining weight or becoming overweight comprising administering to said subject an effective amount of at least three compounds, or biologically active analogs, homologs, derivatives, modifications, and pharmaceutically acceptable salts thereof, selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, anti-convulsant agents, and N-methyl-D-aspartate-blocking agents, thereby treating or preventing, and optionally administering at least one additional therapeutically active compound, thereby preventing or inhibiting a subject from gaining weight or becoming overweight.

78. The method of claim 77, wherein three of said at least three compounds are topiramate, naltrexone, and ondansetron, or biologically active analogs, homologs, derivatives, modifications, or pharmaceutically-acceptable salts thereof.

79. The method of claim 77, wherein said at least one additional therapeutically active compound is selected from the group consisting of antidiabetic agents, antihyperlipidemic agents, antiobesity agents, antihypertensive agents, and agents for the treatment of complications resulting from or associated with diabetes.

80. A method of inducing weight loss in a subject in need thereof comprising administering to said subject an effective amount of at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, selected from the group consisting of serotonergic agents,

serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, anti-convulsant agents, and N-methyl-D-aspartate-blocking agents, and optionally administering at least one additional therapeutically active compound, thereby inducing weight loss in a subject in need thereof.

81. The method of claim 80, wherein three of said at least three compounds are topiramate, naltrexone, and ondansetron, or biologically active analogs, homologs, derivatives, modifications, or pharmaceutically-acceptable salts thereof.

82. The method of claim 80, wherein said at least one additional therapeutically active compound is selected from the group consisting of antidiabetic agents, antihyperlipidemic agents, antiobesity agents, antihypertensive agents, and agents for the treatment of complications resulting from or associated with diabetes.

83. The method of claim 80, wherein said subject has a body mass index of about 25.0 to about 29.9.

84. The method of claim 80, further wherein said subject is submitted to a psychosocial management program.

85. The method of claim 84, wherein said psychosocial management program is selected from the group consisting of Brief Behavioral Compliance Enhancement Treatment, Cognitive Behavioral Coping Skills Therapy, Motivational Enhancement Therapy, Twelve-Step Facilitation Therapy, Combined Behavioral Intervention, Medical Management, psychoanalysis, psychodynamic treatment, and Biopsychosocial, Report, Empathy, Needs, Direct Advice, and Assessment.

86. The method of claim 80, wherein said subject is further subjected to hypnosis or acupuncture.

87. The method of claim 80, wherein at least one of said at least three compounds is administered at least once a week.

88. The method of claim 87, wherein at least one of said at least three compounds is administered at least once a day.

89. The method of claim 80, wherein at least one of said at least three compounds is a serotonin receptor antagonist.

90. The method of claim 89, wherein said serotonin receptor is the serotonin-3 receptor.

91. The method of claim 80, wherein at least three compounds are administered to said subject.

92. The method of claim 80, wherein said at least three compounds are separately administered.

93. The method of claim 92, wherein a first compound of said at least three compounds is administered before a second or third compound of said at least three compounds is administered.

94. The method of claim 80, wherein a first compound, a second compound, and a third compound of said at least three compounds are administered nearly simultaneously.

95. The method of claim 80, wherein a first compound of said at least three compounds is administered subsequent to administration of a second or third compound of said at least three compounds.

96. The method of claim 80, wherein said at least three compounds are administered as a pharmaceutical composition.

97. The method of claim 80, wherein said at least three compounds are administered via a route selected from the group consisting of oral, topical, rectal, intramuscular, intramucosal, intranasal, inhalation, ophthalmic, and intravenous.

98. The method of claim 97, wherein said at least three compounds are administered via an oral route.

99. A pharmaceutical composition comprising at least three compounds of claim 80, or biologically active analogs, homologs, derivatives, modifications, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

100. The pharmaceutical composition of claim 99, said composition comprising effective amounts of topiramate, ondansetron and naltrexone, or biologically active analogs, homologs, derivatives, modifications, and pharmaceutically acceptable salts thereof.

101. The method of claim 80, wherein at least one of said at least three compounds is administered as a controlled-release formulation.

102. The method of claim 81, wherein three compounds, or biologically active analogs, homologs, derivatives, and modifications thereof, are administered.

103. The method of claim 81, wherein topiramate is administered at a dosage ranging from about 15 mg/day to about 2500 mg/day.

104. The method of claim 103, wherein topiramate is administered at a dosage ranging from about 25 mg/day to about 1000 mg/day.

105. The method of claim 104, wherein topiramate is administered at a dosage ranging from about 50 mg/day to about 500 mg/day.

106. The method of claim 105, wherein topiramate is administered at a dosage of about 300 mg/day or about 275 mg/day.

107. The method of claim 81, wherein topiramate is administered at a dosage ranging from about 0.1 mg/kg/day to about 100 mg/kg/day.

108. The method of claim 81, wherein topiramate is administered at least once a week.

109. The method of claim 108, wherein topiramate is administered at least once a day.

110. The method of claim 81, wherein ondansetron is administered at a dosage ranging from about 0.01 μg/kg per application to about 100 μg/kg per application.

111. The method of claim 110, wherein ondansetron is administered at a dosage ranging from about 0.1 μg/kg per application to about 10.0 μg/kg per application.

112. The method of claim 111, wherein ondansetron is administered at a dosage ranging from about 1.0 μg/kg per application to about 5.0 μg/kg per application.

113. The method of claim 112, wherein ondansetron is administered at a dosage of about 4.0 μg/kg per application or about 3.0 μg/kg per application.

114. The method of claim 81, wherein ondansetron is administered at least once a week.

115. The method of claim 81, wherein ondansetron is administered at least once a day.

116. The method of claim 115, wherein ondansetron is administered once a day.

117. The method of claim 81, wherein naltrexone is administered at a dosage ranging from about 1.0 mg per application to about 100.0 mg per application.

118. The method of claim 117, wherein naltrexone is administered at a dosage ranging from about 10.0 mg per application to about 50.0 mg per application.

119. The method of claim 118, wherein naltrexone is administered at a dosage of about 25 mg per application.

120. The method of claim 81, wherein naltrexone is administered at least once a week.

121. The method of claim 81, wherein naltrexone is administered at least once a day.

122. The method of claim 121, wherein naltrexone is administered once a day.

123. The method of claim 81, wherein topiramate is administered at a dosage of about 300 mg/day, ondansetron is administered at a dosage of about 4.0 μg/kg per application, and naltrexone is administered at a dosage of about 25 mg per application.

124. A method of regulating appetite in a subject in need thereof comprising administering to said subject an effective amount of at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, wherein said compounds are selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, anti-convulsant agents, and N-methyl-D-aspartate-blocking agents, thereby treating or preventing, optionally in combination with at least one additional therapeutically active compound, and optionally administering at least one additional therapeutically active compound.

125. The method of claim 124, wherein said at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, are topiramate, ondansetron, and naltrexone.

126. A method for treating or preventing alcohol abuse in a subject in need thereof, said method comprising administering to said subject an effective amount of at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, norepinephrine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, glutamine agonists, glutamine antagonists, anti-convulsant agents, N-methyl-D-aspartate-blocking agents, calcium channel antagonists, carbonic anhydrase inhibitors, neurokinins, small molecules, peptides, vitamins, co-factors, and Corticosteroid Releasing Factor antagonists, thereby treating or preventing alcohol abuse in a subject.

127. The method of claim 126, wherein said at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, are topiramate, ondansetron, and naltrexone.

128. A method for treating or preventing heavy drinking in a subject in need thereof, said method comprising administering to said subject an effective amount of at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, norepinephrine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, glutamine agonists, glutamine antagonists, anti-convulsant agents, N-

methyl-D-aspartate-blocking agents, calcium channel antagonists, carbonic anhydrase inhibitors, neurokinins, small molecules, peptides, vitamins, co-factors, and Corticosteroid Releasing Factor antagonists, thereby treating or preventing heavy drinking in a subject.

129. The method of claim 128, wherein said at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, are topiramate, ondansetron, and naltrexone.

130. A method for treating or preventing excessive drinking in a subject in need thereof, said method comprising administering to said subject an effective amount of at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, norepinephrine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, glutamine agonists, glutamine antagonists, anti-convulsant agents, N-methyl-D-aspartate-blocking agents, calcium channel antagonists, carbonic anhydrase inhibitors, neurokinins, small molecules, peptides, vitamins, co-factors, and Corticosteroid Releasing Factor antagonists, thereby treating or preventing excessive drinking in a subject.

131. The method of claim 130, wherein said at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, are topiramate, ondansetron, and naltrexone.

132. A method for treating or preventing problem drinking in a subject in need thereof, said method comprising administering to said subject an effective amount of at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors,

serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, norepinephrine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, glutamine agonists, glutamine antagonists, anti-convulsant agents, N-methyl-D-aspartate-blocking agents, calcium channel antagonists, carbonic anhydrase inhibitors, neurokinins, small molecules, peptides, vitamins, co-factors, and Corticosteroid Releasing Factor antagonists, thereby treating or preventing problem drinking in a subject.

133. The method of claim 132, wherein said at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, are topiramate, ondansetron, and naltrexone.

134. A method for treating or preventing heavy drug use in a subject in need thereof, said method comprising administering to said subject an effective amount of at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, selected from the group consisting of serotonergic agents, serotonin antagonists, selective serotonin re-uptake inhibitors, serotonin receptor antagonists, opioid antagonists, dopaminergic agents, dopamine release inhibitors, dopamine antagonists, norepinephrine antagonists, γ-amino-butyric acid agonists, γ-amino-butyric acid inhibitors, γ-amino-butyric acid receptor antagonists, γ-amino-butyric acid channel antagonists, glutamate agonists, glutamate antagonists, glutamine agonists, glutamine antagonists, anti-convulsant agents, N-methyl-D-aspartate-blocking agents, calcium channel antagonists, carbonic anhydrase inhibitors, neurokinins, small molecules, peptides, vitamins, co-factors, and Corticosteroid Releasing Factor antagonists, thereby treating or preventing heavy drug use in a subject.

135. The method of claim 134, wherein said heavy drug use is selected from the group consisting of cocaine, methamphetamine, other stimulants, phencyclidine, other hallucinogens, marijuana, sedatives, tranquilizers, hypnotics, and opiates.

136. The method of claim 134, wherein the frequency of said heavy drug use is at least once a month.

137. The method of claim 134, wherein the frequency of said heavy drug use is at least once a week.

138. The method of claim 134, further wherein advice is provided to said subject.

139. The method of claim 138, further wherein said advice is provided in a format selected from the group consisting of written, electronic, or interpersonal.

140. The method of claim 139, wherein said method is more effective at treating or preventing said heavy drug use than a method selected from the group consisting of administering a placebo and providing advice, administering no drugs and providing advice, and not administering drugs or providing advice.

141. The method of claim 140, wherein said at least three compounds, or biologically active analogs, derivatives, modifications, or pharmaceutically acceptable salts thereof, are topiramate, ondansetron, and naltrexone.

142. A kit for administering compounds of the invention, said kit comprising a pharmaceutical composition comprising at least three compounds of the invention and optionally a pharmaceutically-acceptable carrier, an applicator, and an instructional material for the use thereof.

143. A kit for treating an addictive disease or disorder of the invention, said kit comprising a pharmaceutical composition comprising at least three compounds of the invention and optionally a pharmaceutically-acceptable carrier, an applicator, and an instructional material for the use thereof.

144. The kit of claim 143, said kit comprising topiramate, ondansetron, and naltrexone.

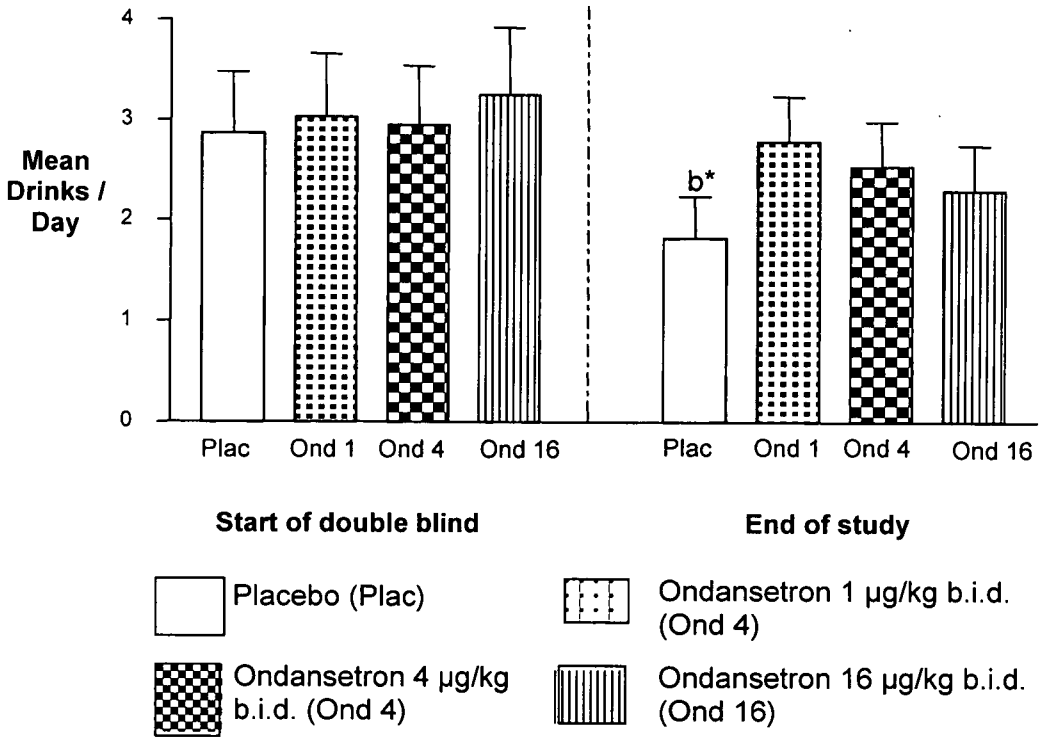

Mean Drinks / Day
4
3
2
1
0
b*
Plac
Ond 1
Ond 4
Ond 16
Plac
Ond 1
Ond 4
Ond 16
Start of double blind
End of study
Placebo (Plac)
Ondansetron 1 µg/kg b.i.d. (Ond 4)
Ondansetron 4 µg/kg b.i.d. (Ond 4)
Ondansetron 16 µg/kg b.i.d. (Ond 16)

FIG. 1A

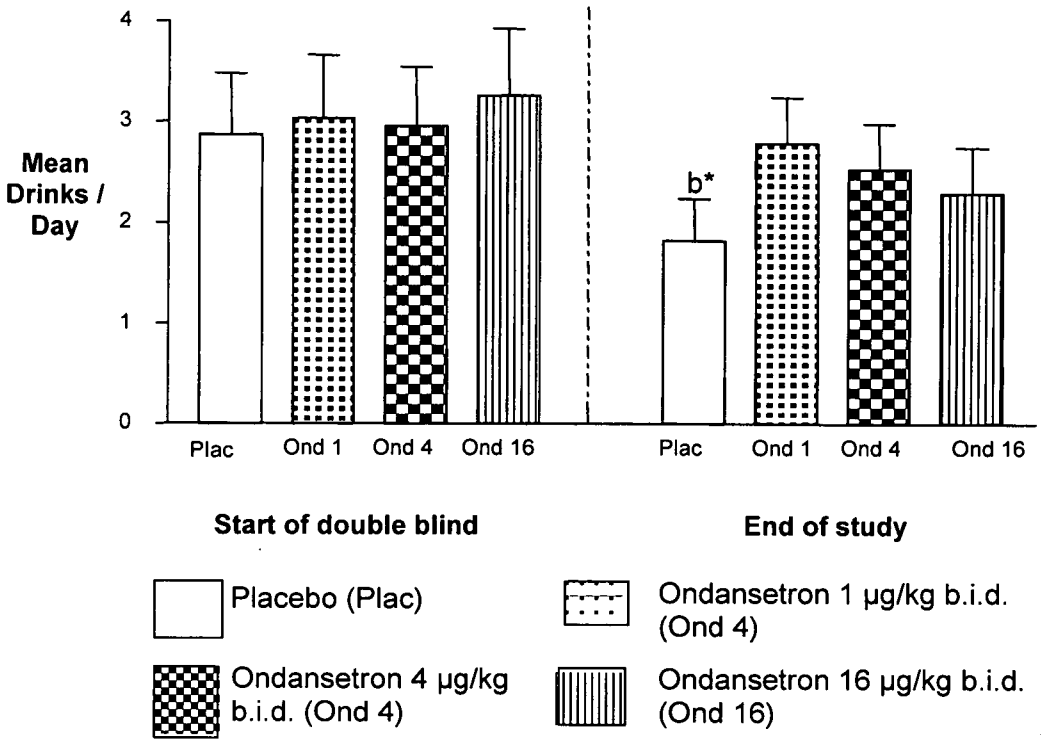

Mean Drinks / Day
4
3
2
1
0
b*
Plac
Ond 1
Ond 4
Ond 16
Plac
Ond 1
Ond 4
Ond 16
Start of double blind
End of study
Placebo (Plac)
Ondansetron 1 µg/kg b.i.d. (Ond 4)
Ondansetron 4 µg/kg b.i.d. (Ond 4)
Ondansetron 16 µg/kg b.i.d. (Ond 16)

FIG. 1B

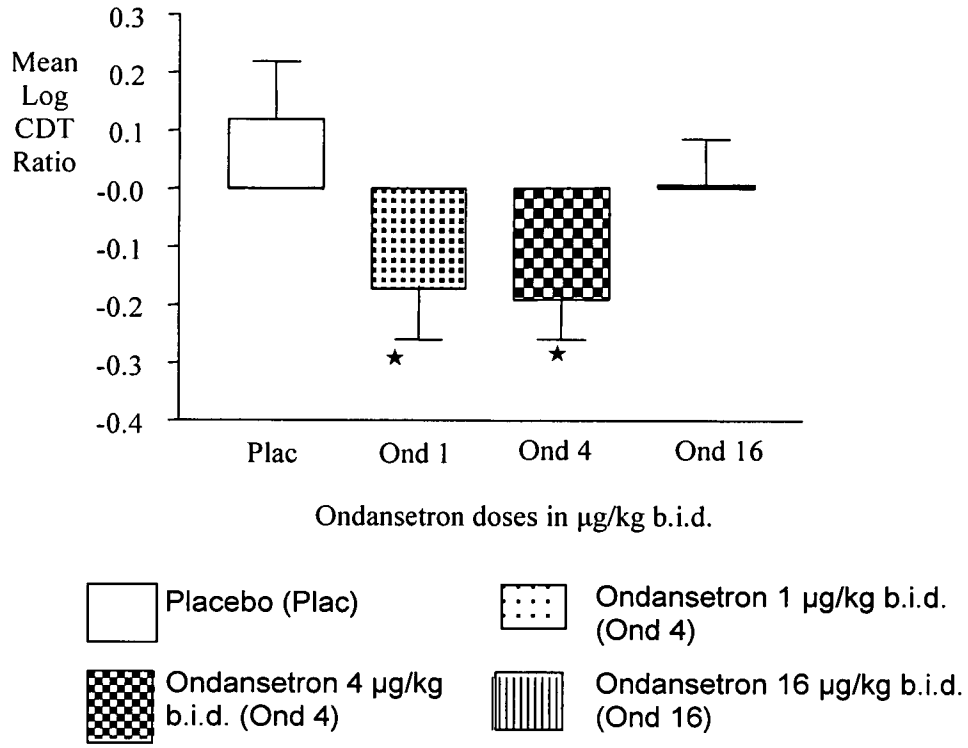

Mean Log CDT Ratio
0.3
0.2
0.1
-0.0
-0.1
-0.2
-0.3
-0.4
Plac
Ond 1
Ond 4
Ond 16
Ondansetron doses in µg/kg b.i.d.
Placebo (Plac)
Ondansetron 1 µg/kg b.i.d. (Ond 4)
Ondansetron 4 µg/kg b.i.d. (Ond 4)
Ondansetron 16 µg/kg b.i.d. (Ond 16)

FIG. 2A

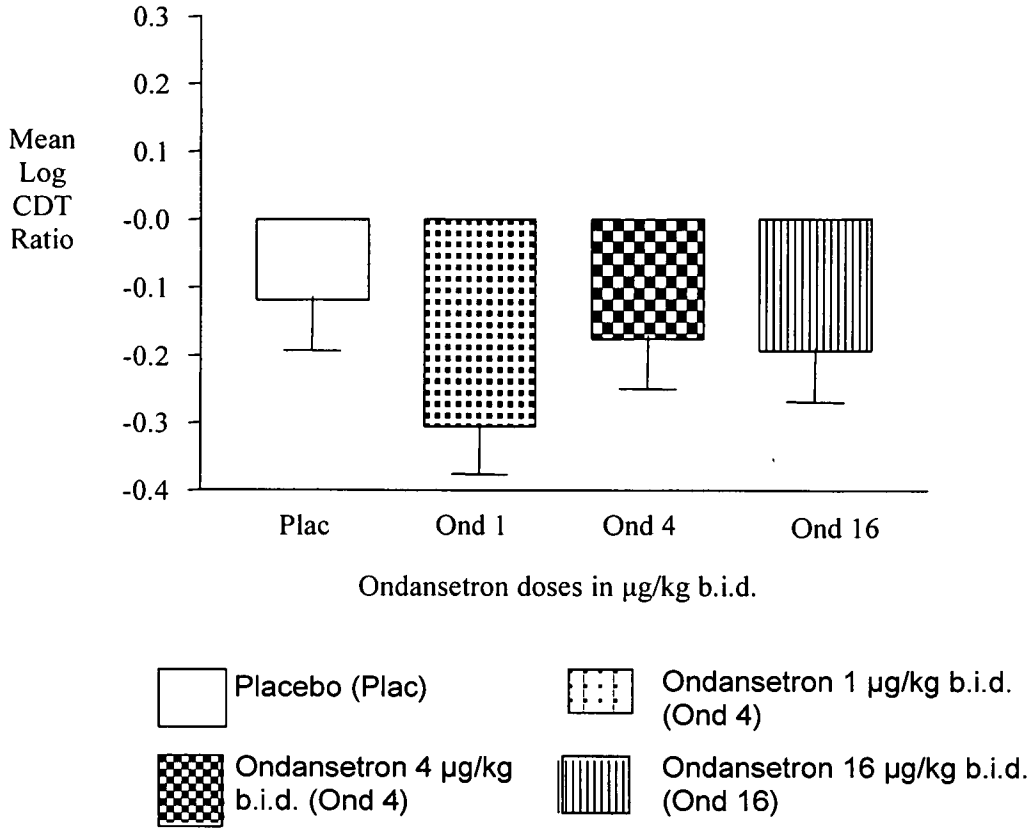

Mean Log CDT Ratio
0.3
0.2
0.1
-0.0
-0.1
-0.2
-0.3
-0.4
Plac
Ond 1
Ond 4
Ond 16
Ondansetron doses in µg/kg b.i.d.
Placebo (Plac)
Ondansetron 1 µg/kg b.i.d. (Ond 4)
Ondansetron 4 µg/kg b.i.d. (Ond 4)
Ondansetron 16 µg/kg b.i.d. (Ond 16)

FIG. 2B

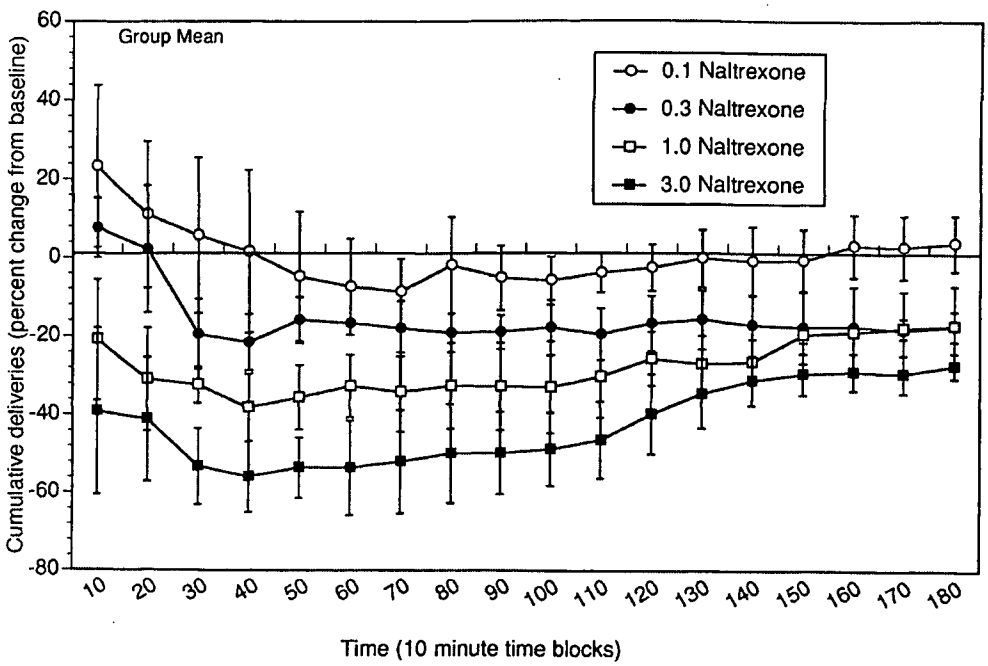

Group Mean
0.1 Naltrexone
0.3 Naltrexone
1.0 Naltrexone
3.0 Naltrexone
Cumulative deliveries (percent change from baseline)
60
40
20
0
-20
-40
-60
-80
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
Time (10 minute time blocks)

FIG. 3

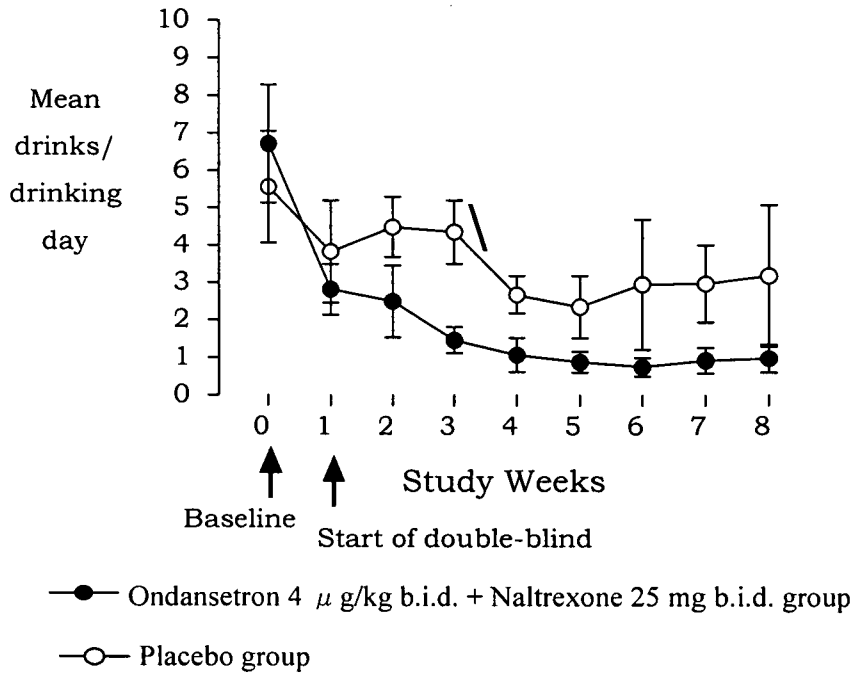

Mean drinks/ drinking day
10
9
8
7
6
5
4
3
2
1
0
0 1 2 3 4 5 6 7 8
Study Weeks
Baseline
Start of double-blind
Ondansetron 4 μ g/kg b.i.d. + Naltrexone 25 mg b.i.d. group
Placebo group

FIG. 4A

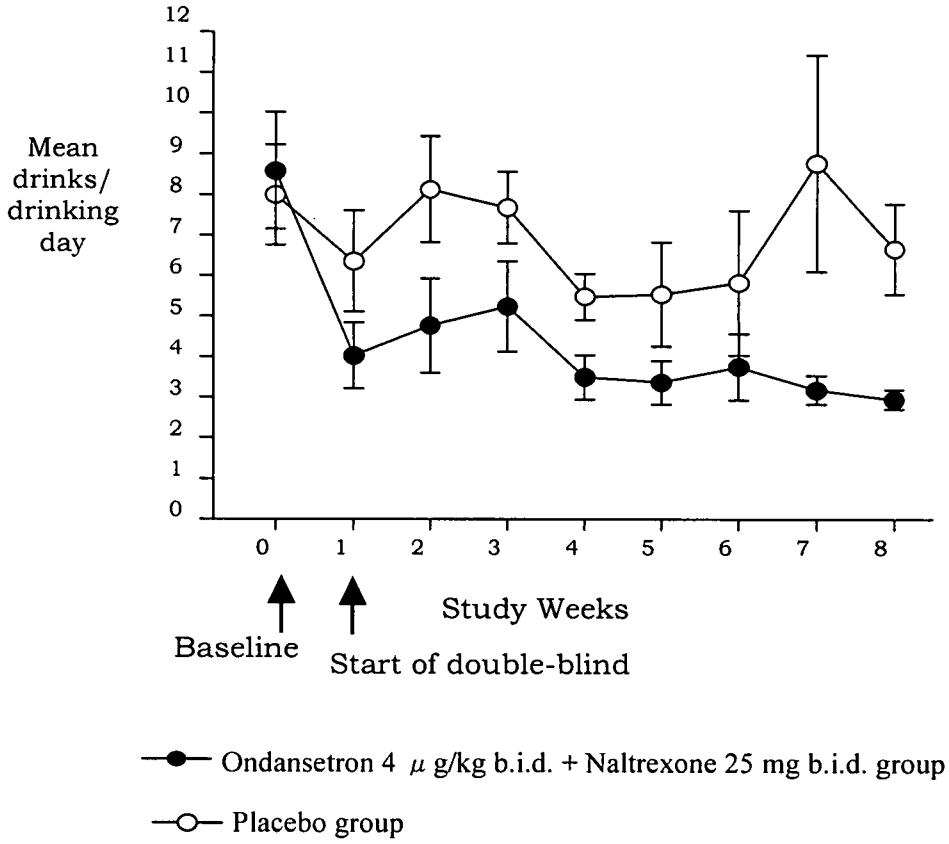

Mean drinks/ drinking day
12
11
10
9
8
7
6
5
4
3
2
1
0
0
1
2
3
4
5
6
7
8
Study Weeks
Baseline
Start of double-blind
Ondansetron 4 μ g/kg b.i.d. + Naltrexone 25 mg b.i.d. group
Placebo group

FIG. 4B

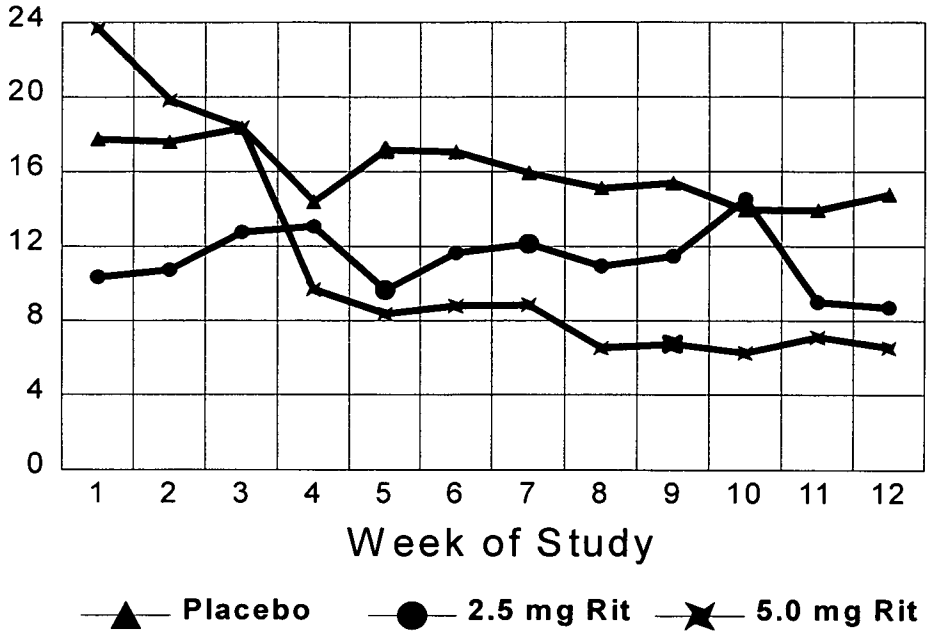

24
20
16
12
8
4
0
1 2 3 4 5 6 7 8 9 10 11 12
Week of Study
Placebo
2.5 mg Rit
5.0 mg Rit

FIG. 5

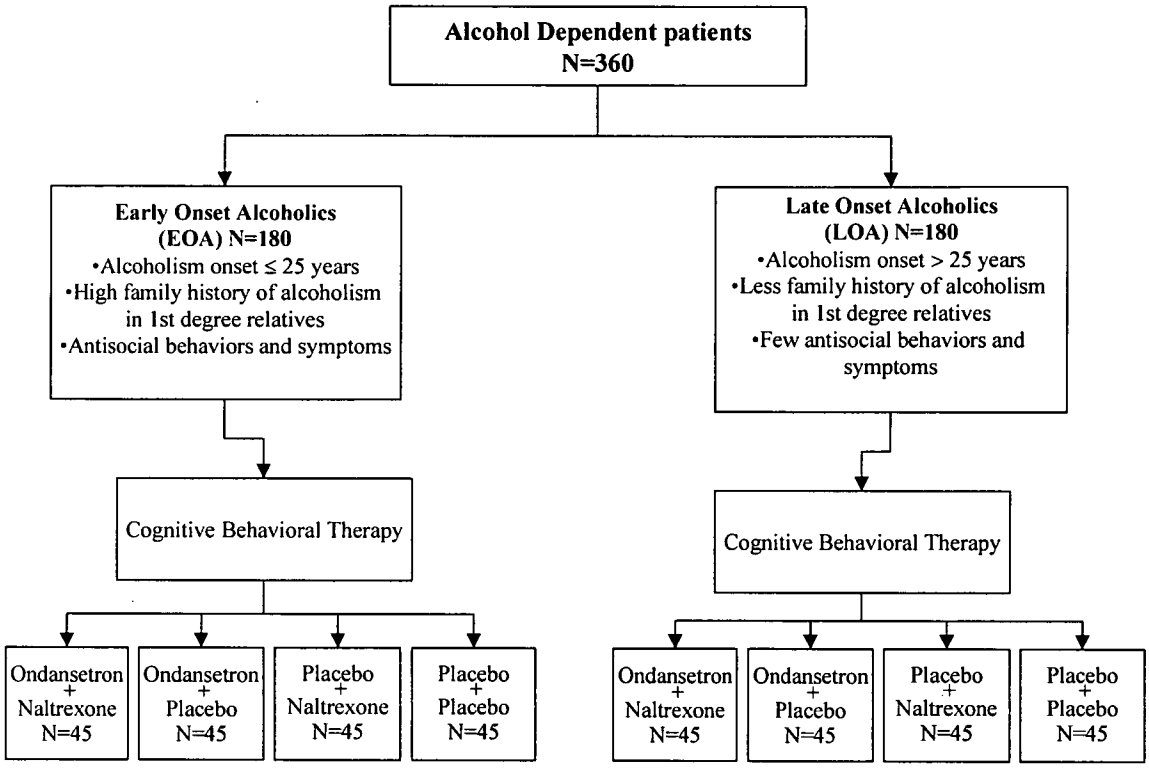

Alcohol Dependent patients
N=360
Early Onset Alcoholics
(EOA) N=180
•Alcoholism onset ≤ 25 years
•High family history of alcoholism in 1st degree relatives
•Antisocial behaviors and symptoms
Late Onset Alcoholics
(LOA) N=180
•Alcoholism onset > 25 years
•Less family history of alcoholism in 1st degree relatives
•Few antisocial behaviors and symptoms
Cognitive Behavioral Therapy
Cognitive Behavioral Therapy
Ondansetron + Naltrexone N=45
Ondansetron + Placebo N=45
Placebo + Naltrexone N=45
Placebo + Placebo N=45
Ondansetron + Naltrexone N=45
Ondansetron + Placebo N=45
Placebo + Naltrexone N=45
Placebo + Placebo N=45

FIG. 6

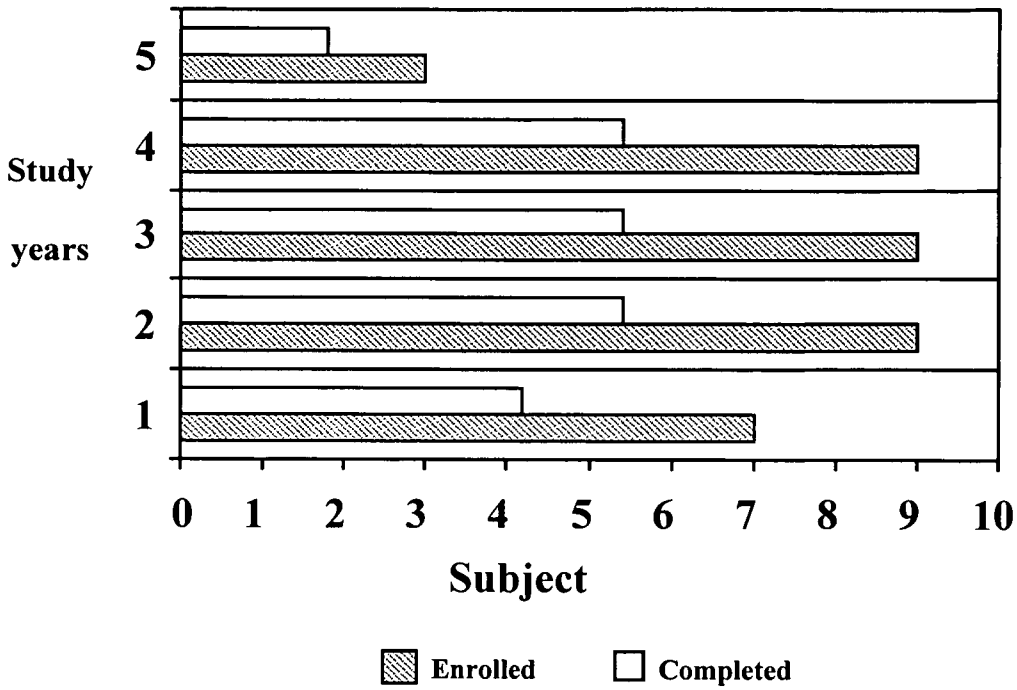

Study years
5
4
3
2
1
0 1 2 3 4 5 6 7 8 9 10
Subject
Enrolled
Completed

FIG. 7

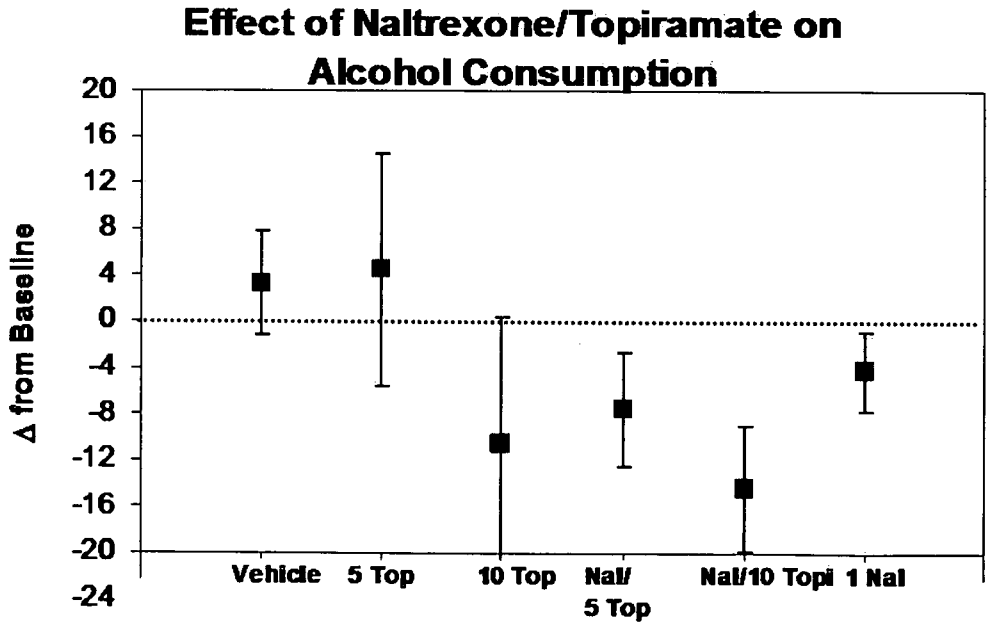

Effect of Naltrexone/Topiramate on Alcohol Consumption
Δ from Baseline
20
16
12
8
4
0
-4
-8
-12
-16
-20
-24
Vehicle
5 Top
10 Top
Nal/ 5 Top
Nal/10 Topi
1 Nal

FIG. 8

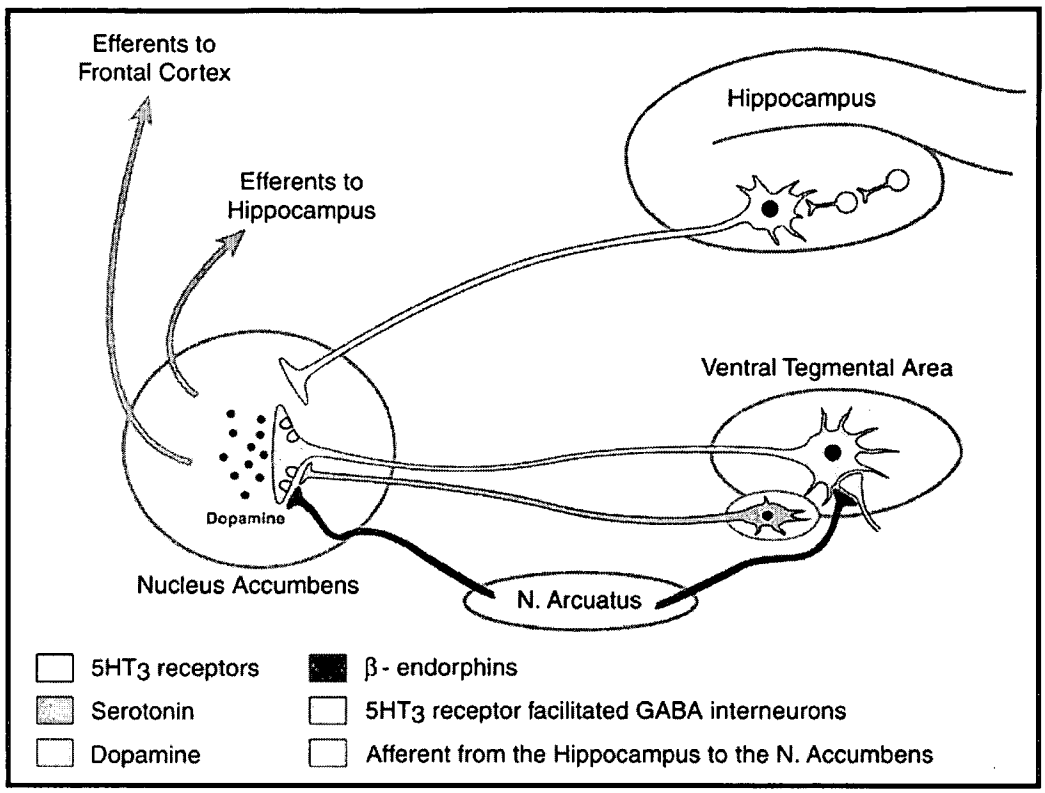

Efferents to
Frontal Cortex
Hippocampus
Efferents to
Hippocampus
Ventral Tegmental Area
Dopamine
Nucleus Accumbens
N. Arcuatus
5HT3 receptors
β - endorphins
Serotonin
5HT3 receptor facilitated GABA interneurons
Dopamine
Afferent from the Hippocampus to the N. Accumbens

FIG. 9

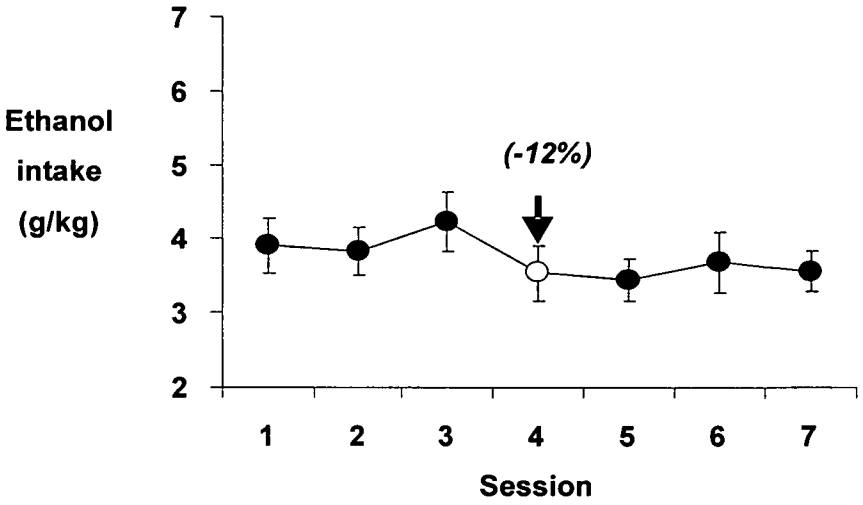


FIG. 10A

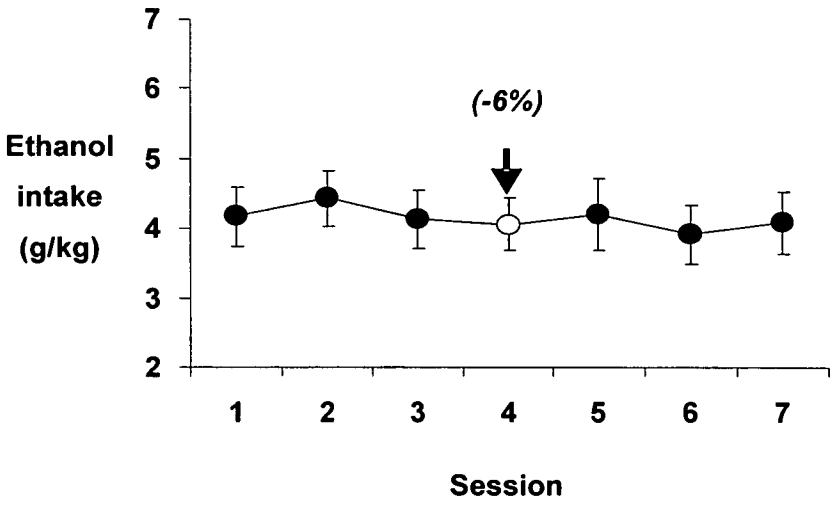


FIG. 10B

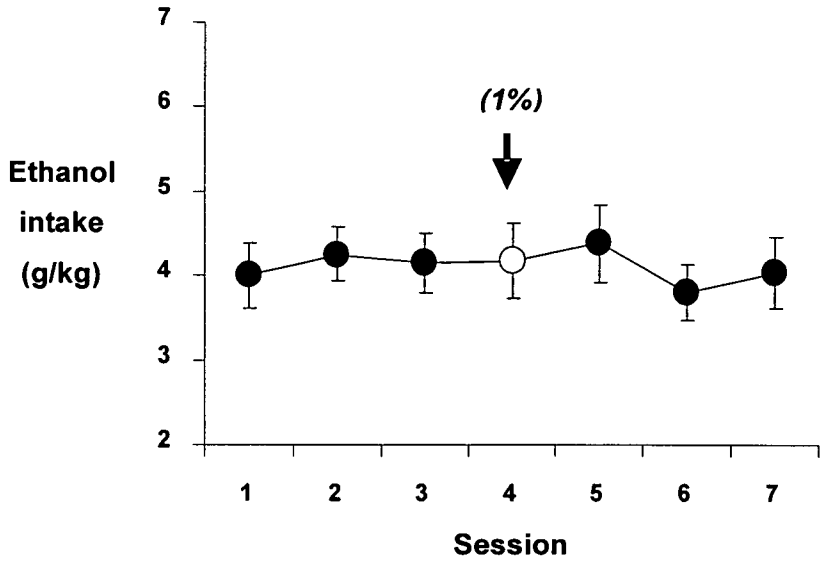


FIG. 10C

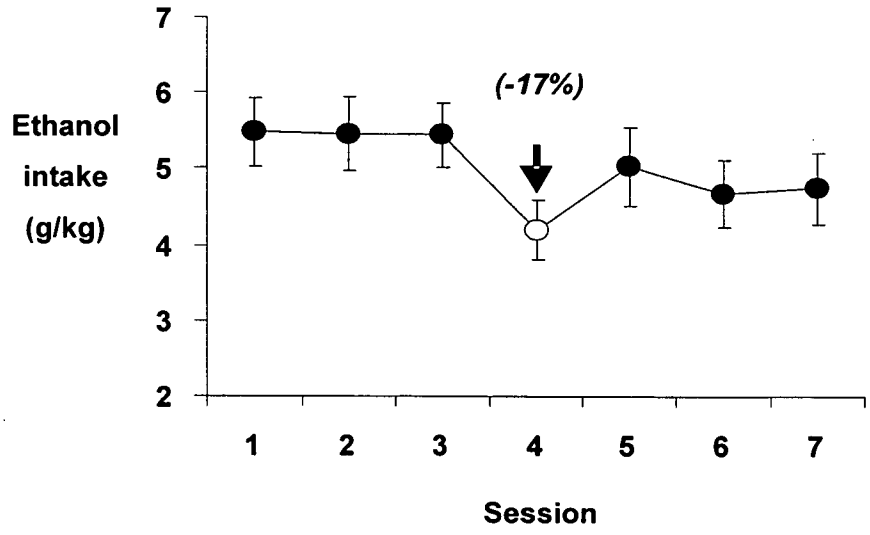


FIG. 10D

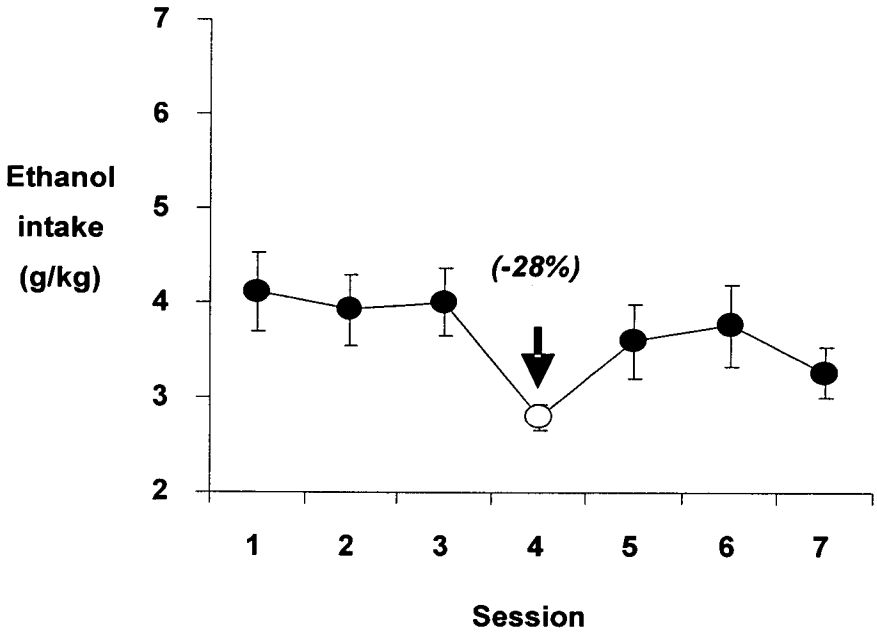


FIG. 10E

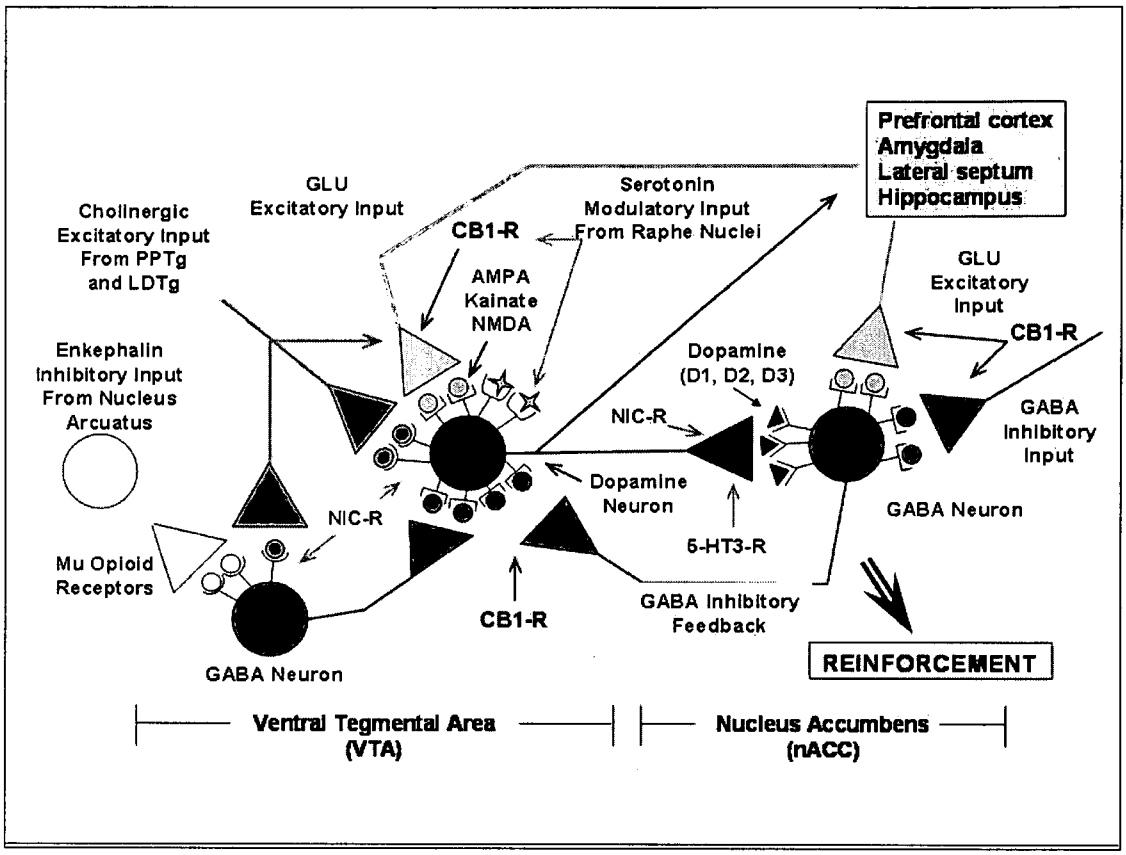

Prefrontal cortex
Amygdala
Lateral septum
Hippocampus
GLU
Excitatory Input
Serotonin
Modulatory Input
From Raphe Nuclei
Cholinergic
Excitatory Input
From PPTg
and LDTg
CB1-R
AMPA
Kainate
NMDA
GLU
Excitatory
Input
CB1-R
Enkephalin
Inhibitory Input
From Nucleus
Arcuatus
Dopamine
(D1, D2, D3)
NIC-R
GABA
Inhibitory
Input
Dopamine
Neuron
GABA Neuron
NIC-R
5-HT3-R
Mu Opioid
Receptors
CB1-R
GABA Inhibitory
Feedback
REINFORCEMENT
GABA Neuron
Ventral Tegmental Area
(VTA)
Nucleus Accumbens
(nACC)

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/64232

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/00 (2008.04)
USPC - 514/21
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/21 (see search terms below)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/811; 514/812; 514/813; 424/570 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: treat, disease, alcohol-related, ondansetron, combination, naltrexone, early onset, synergistically, topiramate, alcohol dependence, alcohol abuse, alcohol intoxication, alcohol withdrawal, composition, vehicle, oral, kit. INTERNET search - Google - same

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOHNSON et al., Combining Ondansetron and Naltrexone Effectively Treats Biologically Predisposed Alcoholics: From Hypotheses to Preliminary Clinical Evidence, Alcoholism: Clinical & Experimental Research, Vol. 24, Issue 5, pp 737-742, Published Online: 11 April 2006, Abstract only.	1-144
Y	WO 2007/039123 A2 (DAWSON et al.) 12 April 2007 (12.04.2007), pg 1, ln 21-24; pg 2, ln 4-6, 28-31; pg 4, ln 1-6; pg 8, ln 1 - pg 9, ln 22; pg 9, ln 38-41; pg 13, ln 6-9, 16-26; pg 20, ln 39 - pg 21, ln 6; pg 21, ln 8-19; pg 21, ln 41 - pg 22, ln 26.	1-144
Y	ANTON et al., Structured Psychosocial Interventions Focused on Adherence Combined with Naltrexone Make Drinking Relapse Less Likely, Annals of Internal Medicine, Vol 134, No 5, pp 388-389, 06 March 2001, pp 388-389.	15-16 and 84-85
Y	MONER, Acupuncture and Addiction Treatment, Journal of Addictive Diseases, Vol. 15, No. 3, pp 79-100, 1996, Abstract only.	17 and 86

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
07 August 2008 (07.08.2008)

Date of mailing of the international search report
15 AUG 2008

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer:
Lee W. Young
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)