METHODS FOR THE TREATMENT OF SUBSTANCE ABUSE AND DEPENDENCE

CROSS-REFERENCE TO RELATED APPLICATIONS

The present invention relies on, for priority, United States Provisional Patent Application Number 60/669,033, entitled "Improved Method for the Treatment of Substance Abuse", filed on April 7, 2005, United States Provisional Patent Application Number 60/728,979 entitled "Methods for the Treatment of Substance Abuse and Dependence", filed on October 21, 2005, and United States Provisional Patent Application Number 60/729,013 entitled "Methods for Treating Anxiety-Related Diseases", filed on October 21, 2005.

FIELD OF THE INVENTION

The present invention relates to methods of and compositions for treating and relieving symptoms and disease associated with indications caused by a physiological drive to alleviate a sensation of anxiety. More specifically, the present invention relates to methods of and compositions for treating and relieving symptoms associated with substance abuse and withdrawal. The present invention relates to methods of and compositions for treating addiction to antidepressants, opiates, nicotine or marijuana.

The present invention is also relates to a methodology for diagnosing a person in an altered $GABA_A$ receptor state. In particular, the methodology is directed toward determining the relative receptivity of a patient to the treatment methodologies of the present invention by qualitatively or quantitatively measuring progesterone levels in a patient, or, more preferably, the allopregnanolone levels within a patient's brain.

The present invention also relates to a treatment methodology that, in a first stage, improves a patient's physiological receptivity to treatment. In particular, the methodology is directed toward preventing the up-regulation of endogenous neuroactive steroids or actively down-regulating the production of endogenous neuroactive steroids to avoid cross-tolerance effects between exogenous and endogenous substances.

The present invention also relates to a treatment methodology that, in a second stage, employs methods of and compositions for modulating the expression of certain $GABA_A$ receptor subunits, thus treating the withdrawal symptoms associated with psychological and physiological addiction and dependence in a comprehensive treatment plan. The present invention also relates to optionally employing conventional treatment programs in

combination with the methods of and compositions of the present invention in a comprehensive treatment plan.

More specifically, the present invention relates to methods of, devices for, and treatment protocols for using pharmaceutical compositions from a class of compounds that directly or indirectly modulates $GABA_A$ by modulating the expression of the $GABA_A$ receptor α_4 subunit.

The present invention also relates to a class of compounds, and methods of identifying such compounds, that modulates the expression of certain $GABA_A$ receptor subunits. More specifically, the compound of choice is one that a) acts as a partial agonist of $GABA_A$; b) inhibits the upregulation of the $GABA_A$ receptor α_4 subunit and/or increases the relative ratio of the $GABA_A$ receptor α_1 subunit to the $GABA_A$ receptor α_4 subunit; and c) does not cause the upregulation of the $GABA_A$ receptor α_4 subunit and/or does not cause the decrease of the relative ratio of the $GABA_A$ receptor α_1 subunit to the $GABA_A$ receptor α_4 subunit once the composition is no longer present in the patient's system.

BACKGROUND OF THE INVENTION

Substance addiction and abuse is a multi-factorial neurological disease. Over time, repeated exposure to various substances, both endogenous and exogenous, causes modification of the neurotransmission circuits and adaptations in post-receptor signaling cascades. There are several effects of this neuronal modification. Among them, there is a reduction in the ability of natural rewards to activate the reward pathways leading to depressed motivation and mood and an increased compulsion to compensate for the physiological change.

While the common perception underlying addiction is that of a "reward circuit", pleasure may not necessarily be a strong enough impetus to drive people towards their addictions. Rather, addictive behavior arises from an intense desire to manage and/or avoid the anxiety that arises when someone is experiencing withdrawal.

Traditional treatments for substance dependency, such as benzodiazepine abuse, have been based upon cognitive-behavioral therapy or drug therapy, or a combination thereof. Conventional methods of treatment fail, however, in that they do not address the physiochemical changes that occur with addiction and dependence. Thus, conventional treatments for controlling withdrawal symptoms and cravings for addictive substances have had limited success and often have undesirable side effects.

What is therefore needed are improved methods of, compositions for, and treatment protocols for preventing psychological addiction to, and physiological dependence upon addictive substances.

What is also needed is an improved treatment methodology for controlling cravings and withdrawal symptoms caused by substance abuse.

What is also needed is an improved methodology and protocol for treating substance abuse, which results in reduced patient dropout rates.

SUMMARY OF THE INVENTION

According to its major aspects and broadly stated, the present invention is directed towards methods of, and compositions for, preparing a patient for treatment and modulating the expression of certain $GABA_A$ receptor subunits. The present invention therefore treats withdrawal symptoms associated with psychological addiction and physiological dependence upon various exogenous and endogenous substances in the context of a comprehensive treatment plan of behavioral and/or pharmacological treatment.

The multiple phase treatment methodology of the present invention employs one or more compounds to reset physiochemical changes in a patient that is experiencing withdrawal from addictive and/or dependency-inducing substances, including but not limited to opioids and derivatives, nicotine, benzodiazepines, caffeine, cannabis, or anti-depressant drugs.

The present invention relates to methods of and compositions for treating and relieving symptoms and disease associated with indications caused by a physiological drive to alleviate a sensation of anxiety. More specifically, the present invention relates to methods of and compositions for treating and relieving symptoms associated with substance abuse and withdrawal. In one embodiment, a patient is treated with a composition from a class of compounds that directly or indirectly modulates $GABA_A$ by modulating the expression of the $GABA_A$ receptor α_4 subunit.

The present invention also provides methods that, in a first stage, improve an individual's physiological receptivity to treatment. In particular, the methodology is directed toward preventing the up-regulation of endogenous neuroactive steroids or actively down-regulating the production of endogenous neuroactive steroids to avoid cross-tolerance.

The present invention also provides methods that, in a second stage, employs methods of, and compositions for, modulating the expression of certain $GABA_A$ receptor subunits, thus treating the withdrawal symptoms associated with psychological and physiological addiction and dependence in a comprehensive treatment plan. The present invention also

relates to optionally employing conventional treatment programs in combination with the methods of and compositions of the present invention in a comprehensive treatment plan.

Methods are also provided for treating anti-depressant addiction by administering a compound from a class of compounds that selectively modulates $GABA_A$ receptor expression. In one embodiment, the method includes the steps of assessing a patient for treatment compatibility; preparing a patient for treatment; and administering a compound from the class of compounds that selectively modulates $GABA_A$ receptor expression to a patient.

Methods are also provided for treating opiate addiction comprising the step of administering a compound from a class of compounds that selectively modulates $GABA_A$ receptor expression. In one embodiment, the method includes the steps of assessing a patient for treatment compatibility; preparing a patient for treatment; and administering a compound from the class of compounds that selectively modulates $GABA_A$ receptor expression to a patient.

Methods are also provided for treating nicotine addiction where the method includes the steps of assessing a patient for treatment compatibility; preparing a patient for treatment; and administering a compound from the class of compounds that selectively modulates $GABA_A$ receptor expression to a patient.

Methods are also provided for treating marijuana addiction where the method includes the steps of assessing a patient for treatment compatibility; preparing a patient for treatment; and administering a compound from the class of compounds that selectively modulates $GABA_A$ receptor expression to the patient.

The present invention also provides a class of compounds, and methods of identifying such compounds, that modulates the expression of certain $GABA_A$ receptor subunits. More specifically, the compound of choice is one that a) acts as a partial agonist of $GABA_A$; b) inhibits the upregulation of the $GABA_A$ receptor α_4 subunit and/or increases the relative ratio of the $GABA_A$ receptor α_1 subunit to the $GABA_A$ receptor α_4 subunit; and c) does not cause the upregulation of the $GABA_A$ receptor α_4 subunit and/or does not cause the decrease of the relative ratio of the $GABA_A$ receptor α_1 subunit to the $GABA_A$ receptor α_4 subunit once the composition is no longer present in the patient's system.

It is therefore an object of the invention to provide methods and compositions for inhibiting the formation of neurosteriods.

It is another object of the invention to provide methods and compositions for modulating chloride channels such as $GABA_A$ receptors.

It is another object of the invention to provide methods and compositions for treating symptoms of stimulant substance abuse.

It is another object of the invention to provide methods and compositions for treating addiction to antidepressants, opiates, nicotine or marijuana.

Another object of the invention is to provide for the use of a $GABA_A$ receptor modulator in the preparation of a medicament to treat addiction to antidepressants, opiates, nicotine or marijuana.

Another object of the invention is to provide for the use of a neurosteroid production inhibitor in the preparation of a medicament to treat addiction to antidepressants, opiates, nicotine or marijuana.

These and other objects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiments and claims and the drawings provided.

BRIEF DESCRIPTION OF THE DRAWINGS

The Detailed Description should be considered in light of the drawings, as briefly described below:

Figure 1 illustrates the spectrum between inhibition and substantially or completely reduced inhibition via the direct and/or indirect allosteric modulation of $GABA_A$;

Figure 2 illustrates the internal thought filtering mechanism in a person's brain;

Figure 3a is a first schematic presentation of a plurality of $GABA_A$ receptor subunits;

Figure 3b is a second schematic presentation of a plurality of $GABA_A$ receptor subunits;

Figure 3c is an illustration of the insensitivity of the modulated $GABA_A$ receptor to benzodiazepines. Note the $\alpha 1$ subunit: $\alpha 1\beta 2\gamma 2$-containing $GABA_A$ receptors are the most common GABA receptors in the brain.

Figure 4 is a chemical diagram of the blockade of the conversion of progesterone to allopregnanolone via inhibitors of neurosteroid production.

DETAILED DESCRIPTION OF THE INVENTION

I. INTRODUCTION

Drug addiction is a disorder characterized by compulsive drug intake, loss of control over intake, and impairment in social and occupational function. Allostatic changes in

reward function lead to excessive drug intake, providing a framework with which to identify the neurobiologic mechanisms involved in the development of drug addiction. Neuropharmacologic studies have provided evidence for the dysregulation of specific neurochemical mechanisms in brain reward and stress circuits that result in negative reinforcement or essentially, decreased efficacy of brain reward pathways, further resulting in addiction. The allostatic model integrates molecular, cellular and circuitry neuroadaptations in brain motivational systems produced by chronic drug ingestion with genetic vulnerability. Both positive and negative changes in mood are strongly correlated with allostasis in substance dependence. In addition, it has been shown that substance abuse leads to prolonged alterations in neurophysiological responses to corticotrophin-releasing factor (CRF) and neuropeptide Y (NPY), peptides known to influence stress responses.

Substance abuse, however, may be more accurately characterized as disease further characterized by an individual's need to avoid adverse effects. In a typical dependence and subsequent withdrawal situation, repeated exposure to drugs causes neurological dysfunction which sets in motion a cascade of changes by which motivation and drive (via the anterior cingulate), reward (via the nucleus accumbens and ventral tegmental area), and memory and learning functions (via the amygdala and hippocampus) are modified, resulting in the loss of cortical inhibitory influence (orbitofrontal cortex, where control is located). This loss of inhibitory control contributes to craving and irrational behavior to obtain and consume drug regardless of consequences, despite the fact that, in many cases, the reward center is decreasingly responsive.

The GABAergic system, responsible for most inhibitory control, typically begins with the $GABA_A$ receptor and glutamate receptors in allostatic equilibrium. Allostatic equilibrium refers to the normal complement of receptors on the cell membrane in a normal individual not experiencing dependency, tolerance, or withdrawal. Intake of a particular substance leads to feeling of reward and reduced anxiety in a subject. The "substance" is defined as any substance that will relieve anxiety. Long-term use and subsequent withdrawal from a substance, however, causes GABA dysregulation mediated through $GABA_A$ receptors, causing the glutamate and $GABA_A$ receptors to lose their relative allostatic equilibrium, further resulting in modified levels of inhibition.

Thus, when the $GABA_A$ receptor is dysregulated, the clinical manifestation of this dysregulation is initially anxiety. In addition, the anxiety is often accompanied by compulsive behavior. Certain compulsive behaviors, such as but not limited to drug abuse, gambling, compulsive sexual activity, and compulsive video game playing, can lead to

increased euphoria, neurosteroid production and brain simulation. Subsequent discontinuation of these activities can result in withdrawal syndrome that manifests itself through heightened anxiety and $GABA_A$ regulator dysregulation.

In a non-dependent subject, the most common $GABA_A$ receptor in the brain is the $\alpha_1\beta_2\gamma_2$ receptor, which is a benzodiazepine sensitive receptor. The α_1 subunit is an important binding site for benzodiazepines. During a person's withdrawal from an addictive substance, the amount of α_1 subunits decreases relative to the amount of α_4 subunits. Withdrawal from the substance often causes symptoms of depression, anxiety, impulsivity, and dysphoria, as GABA uptake is decreased due to the reduced number of $GABA_A$ receptor α_1 subunits relative to $GABA_A$ receptor α_4 subunits. Benzodiazepines do not bind favorably to the α_4 subunit, and, therefore, the $\alpha_4\beta_2\gamma_2$ receptor is considered a benzodiazepine insensitive receptor. People who have a high amount of α_4 receptor subunits relative to α_1 receptor subunits can be considered to be in a "withdrawal state". The present invention is thus directed towards restoring an individual to a non-withdrawal state, or a "normal" receptor balance, from a "withdrawal state".

The present invention is also directed towards methods of and compositions for treating and relieving symptoms and disease associated with indications caused by a physiological drive to alleviate a sensation of anxiety. The present invention is also directed towards methods of and compositions for treating and relieving symptoms associated with substance abuse and withdrawal.

The present invention is further directed towards a class of compounds, and methods of identifying such compounds, that modulates the expression of certain $GABA_A$ receptor subunits. More specifically, the compound of choice is one that a) acts a partial agonist of $GABA_A$; b) inhibits the up-regulation of the $GABA_A$ receptor α_4 subunit and/or increases the relative ratio of the $GABA_A$ receptor α_1 subunit to the $GABA_A$ receptor α_4 subunit; and c) does not cause the up-regulation of the $GABA_A$ receptor α_4 subunit and/or does not cause the decrease of the relative ratio of the $GABA_A$ receptor α_1 subunit to the $GABA_A$ receptor α_4 subunit once the composition is no longer present in the patient's system.

The present invention is also directed towards a methodology for diagnosing a person in an altered $GABA_A$ receptor state. In particular, the methodology is directed toward determining the relative receptivity of a patient to the treatment methodologies of the present invention by measuring progesterone levels in a patient, or, more preferably, the allopregnanolone levels within a patient's brain.

The present invention is also directed towards a treatment methodology that, in a first stage, improves a patient's physiological receptivity to treatment. In particular, the methodology is directed toward preventing the up-regulation of endogenous neuroactive steroids or actively down-regulating the production of endogenous neuroactive steroids to avoid cross-tolerance.

The present invention is also directed towards a treatment methodology that, in a second stage, employs methods of and compositions for modulating the expression of certain $GABA_A$ receptor subunits in combination with conventional treatment programs, thus treating the withdrawal symptoms associated with psychological and physiological addiction and dependence in a comprehensive treatment plan.

More specifically, the present invention is directed towards methods of, devices for, and treatment protocols for using pharmaceutical compositions from a class of compounds that directly or indirectly modulates $GABA_A$ by modulating the expression of the $GABA_A$ receptor α_4 subunit.

The present invention is further directed towards methods of, devices for, and treatment protocols for treating substance abuse, dependence, and tolerance.

II. THE GABAergic SYSTEM

a. GAMMA-AMINOBUTYRIC ACID (GABA)

GABA is a neurotransmitter that acts at inhibitory synapses in the brain and spinal cord. The GABA system is found, among other places, in the hippocampus, an area of the brain associated with memory formation. Glutamic acid, or glutamate, is important in brain function, as an excitatory neurotransmitter and as a precursor for the synthesis of GABA in GABAergic neurons. Glutamate activates both ionotropic and metabotropic glutamate receptors, described in further detail below. GABA signals interfere with registration and consolidation stages of memory formation.

b. GABA RECEPTOR TYPES

The GABA receptors are a group of receptors with GABA as their endogenous ligand. Several classes of GABA receptors are known, including ionotropic receptors, which are ion channels themselves, and metabotropic receptors, which are G-protein coupled receptors that open ion channels via intermediaries. Glutamate and GABA mediate their actions by the activation of their receptors.

The ionotropic GABA receptors ($GABA_A$ receptors) are based on the presence of eight subunit families consisting of 21 subunits (α_{1-6}, β_{1-4}, γ_{1-4}, δ, ε, π, θ, ρ_{1-3}) and display an

extraordinarily structural heterogeneity. $GABA_A$ receptors are composed of five circularly arranged, homologous subunits and are important sites of drug action. Most often, the $GABA_A$ receptor isomers comprise two α subunits, two β subunits and one γ subunit. The metabotropic GABA receptors ($GABA_B$ receptors) consist of two subunits: $GABA_{B1}$ and $GABA_{B2}$. Physiological responses following activation of $GABA_B$ receptors require the co-assembly of $GABA_{B1}$ and $GABA_{B2}$. $GABA_C$ receptors also exist natively.

c. $GABA_A$ RECEPTOR SUBUNITS

The $GABA_A$ receptor system is implicated in a number of central nervous system disorders, making $GABA_A$ receptor ligands potential therapeutic agents. $GABA_A$ receptors are ligand-gated ion channels that belong to the same super family of receptors as glycine, nicotinic cholinergic, and serotonin $5HT_3$ receptors. Enhanced function of several $GABA_A$ receptors accounts for the major actions of benzodiazepines, described in greater detail below. In addition, a number of compounds have exhibited functional selectivity for $GABA_A$ receptors.

The $GABA_A$ receptor complex is a pentameric receptor protein structure formed by co-assembly of subunits from seven different classes. Five subunits are situated in a circular array surrounding a central chloride-permeable pore. It has been suggested that the mechanism for ligand-induced channel opening in nicotinic acetylcholine receptors involves rotations of the subunits in the ligand binding domain. Assuming that $GABA_A$ receptors utilize a similar mechanism for channel opening, since $GABA_A$ receptors belong to the same super family as the nicotinic acetylcholine receptors, large substituents may interfere with the channel opening (steric hindrance) resulting in antagonistic effects of certain compounds. In addition, the activation of GABA receptors will influence several other systems, ultimately resulting in a general acute modification of the overall function of the central nervous system.

The particular combination of subunits yields receptors with different pharmacological and physiological properties, however, the $GABA_A$ receptor composition is not immutable. Withdrawal from anxiolytic benzodiazepines, which produce their effects by facilitating $GABA_A$ receptor mediated inhibition, yields an increase in the steady state mRNA levels of α_4 and β_1 subunit mRNA in both the cortex and hippocampus. It should be noted that the δ subunit is often associated with $GABA_A$ receptor subtypes containing the α_4 subunit.

GABA and $GABA_A$ receptors are involved in disease states such as seizures, depression, anxiety and sleep disorders. GABA and some of the other indirectly or directly acting $GABA_A$ receptor agonists (GABA-mimetics), including allopregnanolone and

tetrahydrodeoxycorticosterone respectively, bind specifically to a recognition site located at the interface between an α and a β subunit. The classical benzodiazepines, however, such as diazepam and flunitrazepam, bind to an allosteric site located at the interface between an α and a γ subunit.

More specifically, GABA binds to the cleft between α and β subunits, an action which gates open the chloride channel to allow for the influx of chloride ions into the cell. This typically hyperpolarizes the cell, having an inhibitory action on neuronal activity, by making the membrane potential of the cell more negative, and consequentially, increases the depolarization threshold to generate an action potential.

Most depressant and sedative drugs such as the benzodiazepine tranquilizers, barbiturates, anesthetics and alcohol are believed have a modulatory effect on the $GABA_A$ receptor at unique sites where they can enhance the actions of GABA in accumulating negatively charged chloride ions into the cell, inducing sedative or anesthetic effects.

The conformational restriction of various parts of the molecule of GABA and biosteric replacements of the functional groups of the amino acid leads to a broad spectrum of specific $GABA_A$ agonists. Some of these molecules have played a key role in the understanding of the pharmacology of the $GABA_A$ receptor family.

The absence or presence of a particular α subunit isoform in the $GABA_A$ receptors confers selectivity for certain drugs. Different α subunits also mediate distinct pharmacological actions of benzodiazepines, including sedative-hypnotic and anxiolytic effects. Long-term administration of benzodiazepines results in the development of tolerance to some of the effects of these drugs, thus reducing their clinical efficacy. While the molecular basis for these dependencies remains unclear, tolerance and dependence appear to be related to the pharmacodynamics of benzodiazepines.

Long-term administration of benzodiazepines modifies the expression of genes that encode various $GABA_A$ subunits. These changes in gene expression alter the sensitivity of $GABA_A$ receptors to their pharmacological modulators and thereby underlie the development of tolerance to or dependence on these drugs. The subunit composition of $GABA_A$ receptor determines their affinity for benzodiazepine receptor ligands as well as the efficacy of these ligands. For example, classical benzodiazepine agonists (e.g. diazepam), imidazopyridines, imidazoquinolones and pyrazolopyrimidines show no affinity for or efficacy at $GABA_A$ receptors that contain α_4 or α_6 subunits.

The subunit composition of native $GABA_A$ receptors plays an important role in defining their physiological and pharmacological function. It is possible to characterize the

physiological, pharmacological, and pathological roles of $GABA_A$ receptors by understanding the mechanisms by which the subunit composition of $GABA_A$ receptors is regulated. Thus, the expression of specific $GABA_A$ receptor subunit genes may be affected by various physiological and pharmacological modulators, including but not limited to, pharmacological agents, endogenous neurosteroids, and food.

For example, long-term exposure to and subsequent withdrawal of benzodiazepines, zalpelon, zolpidem, or neurosteroids result in selective changes in the expression of specific $GABA_A$ receptor mRNA, including an increase of the α_4 subunit mRNA, and polypeptide subunits and in $GABA_A$ receptor function in cultured cells. Withdrawal from diazepam or imidazenil was associated with both a reduced ability of diazepam to potentiate GABA action and the ability of flumazenil to potentiate GABA action. Chronic benzodiazepine treatment and subsequent withdrawal lead to a change in the receptor subunit composition, and these new synthesized receptors are less responsive to benzodiazepines. The up-regulation of the α_4 subunit, however, may be necessarily coupled with the down-regulation of other subunits for the development of benzodiazepine dependence.

Withdrawal of zalpelon or zolpidem, like that of diazepam, induced a marked increase in the amount of α_4 subunit mRNA. These effects of zalpelon and zolpidem on $GABA_A$ receptor gene expression are consistent with the reduced tolerance liability of these drugs, compared with that of diazepam, as well as with their ability to induce both physical dependence and withdrawal syndrome.

Ethanol withdrawal-induced increases in the amounts of α_4 subunit mRNA and protein are associated with reduced sensitivity of $GABA_A$ receptors to GABA and benzodiazepines. The effects of alcohol are similar to those of drugs that enhance the function of $GABA_A$ receptors, which gate the Cl- currents that mediate most inhibitory neurotransmission in the brain, as described above. Acutely high doses of alcohol potentiate GABA-gated currents at both native and recombinant $GABA_A$ receptors, and chronically alter $GABA_A$ receptor expression. Ethanol elicits its central effects through modulation of neurotransmission mediated by various receptors, especially that mediated by $GABA_A$ receptors. It has been shown that long-term ethanol administration also affects the subunit composition and, consequently, the functional properties of native $GABA_A$ receptors. The pharmacological profile of ethanol is similar to that of benzodiazepine and also results in the development of cross-tolerance and dependence.

Exposure to diazepam at the time of ethanol withdrawal antagonizes the withdrawal-induced increase in the abundance of the α_4 subunit mRNA. The replacement of ethanol with

diazepam also blocked the ethanol withdrawal-induced impairment in cellular metabolism. Cells exposed to GHB at the time of ethanol withdrawal results in an inhibition in the increase in the abundance of the α_4 subunit mRNA.

The modulatory action of flumazenil in cells that are exposed to ethanol is similar to that measured in cells not exposed to ethanol. In contrast, however, in ethanol withdrawn cells, 3 μM flumazenil potentiates the GABA evoked Cl- current consistent with the ethanol withdrawal-induced up-regulation of the α_4 subunit in these cells. The substitution of 10 μM diazepam or 100 mM GHB for ethanol negated the positive modulation of 3 μM flumazenil induced by ethanol withdrawal.

The presence of the α_4 subunit in recombinant $GABA_A$ receptors is associated with a reduced sensitivity to classical benzodiazepine agonists and to zolpidem as well as with a distinct pattern of regulation (positive rather than no allosteric modulation) by flumazenil.

In general, chronic treatment with agonists that act at different sites of the $GABA_A$ receptor results in changes in the biochemical and functional properties of the receptor that are accompanied by changes in the abundance of specific receptor subunit mRNAs. In addition, chronic treatment with substances that modulate $GABA_A$ function via a neurosteroid pathway results in changes in the biochemical and functional properties of the receptor that are accompanied by changes in the abundance of specific receptor subunit mRNAs. The observation that the ethanol withdrawal-induced increase in the expression of the α_4 subunit gene in cultured cerebellar granule cells is prevented by diazepam is consistent with the fact that benzodiazepine treatments are effective in treating alcohol withdrawal symptoms in humans. Thus, a rapid and marked increase in the abundance of the α_4 subunit induced by ethanol withdrawal might therefore contribute to the development of diazepam-sensitive withdrawal symptoms in humans.

III. GABA AND NEUROSTEROIDS

Characterizations of the role of $GABA_A$ receptors require an understanding of the mechanisms by which subunit composition is regulated. The long-term administration of sedative-hypnotic, anxiolytic, or anticonvulsant drugs can affect expression of $GABA_A$ receptor subunit genes as well as the drug sensitivity and function of these receptors, suggesting that the mechanisms responsible for such changes might also underlie the physiological modulation of $GABA_A$ receptors by endogenous compounds such as neurosteroids.

The neuroactive steroids 3α-hydroxy-5α-pregnan-20-one (allopregnanolone) and 3α,21-dihydroxy-5α-pregnan-20-one (allotetradihydrodeoxycorticosterone, or THDOC) induce anxiolytic, sedative, hypnotic, and anticonvulsant effects similar to benzodiazepines and other anxiolytic drugs. The concentrations of these neurosteroids are increased in the brain of humans both in response to treatment with anxiogenic, antidepressant or antipsychotic drugs as well as physiological or pathological conditions (such as depression, stress, the luteal phase of the menstrual cycle, and pregnancy) that affect mood and emotional state. Additional studies implicate endogenous allopregnanolone as a physiological regulator of both basal and stress-induced dopamine release in the rat brain.

Steroid metabolites react with the GABA receptor complex to alter brain excitability. Several of these steroids accumulate in the brain after local synthesis or after metabolism of adrenal steroids. Neurosteroids are synthesized in the peripheral and central nervous system, from cholesterol or steroidal precursors imported from peripheral sources. Both progesterone and estrogen alter excitability of neurons of the central nervous system. For example, estrogen reduces inhibition at the $GABA_A$ receptor, enhances excitation at the glutamate receptor, and increases the number of excitatory neuronal synapses. In contrast, progesterone enhances GABA-mediated inhibition, increases GABA synthesis, and increases the number of $GABA_A$ receptors. In particular, progesterone and its metabolites have been demonstrated to have profound effects on brain excitability. The levels of progesterone and its metabolites vary with the phases of the menstrual cycle, decreasing prior to the onset of menses. Progesterone is readily converted to allopregnanolone (3α-OH-5α-pregnan-20-one or 3α,5α-THP) in human brains. Allopregnanolone-induced $GABA_A$ receptor dysregulation has been closely linked to major anxiety-related diseases, thus linking anxiety to allopregnanolone "withdrawal".

Neurosteroids rapidly alter neuronal excitability thorough interaction with neurotransmitter-gated ion channels. Allopregnanolone is a positive potent modulator of the $GABA_A$ receptor and enhances the action which gates open the chloride channel to allow influx of chloride ions into the cell. This typically hyperpolarizes the cell, having an inhibitory action on neuronal activity, and thus allopregnanolone acts as a sedative or anxiolytic agent and decreases anxiety.

$GABA_A$-modulatory allopregnanolone, as described above, is also responsible for producing anxiogenic withdrawal symptoms. The withdrawal profile shown therein is similar to that reported for other $GABA_A$-modulatory drugs such as the benzodiazepines, barbiturates, and ethanol. Thus, the actions of neuroactive steroids on traditional transmitter

receptor in the brain lead to alterations in the $GABA_A$ receptor subunit composition that result in changes in the intrinsic channel properties of the receptor and behavioral excitability. Changes are also associated with significant increases in both the mRNA and protein for the α_4 subunit of the $GABA_A$ receptor in the hippocampus. It has also been demonstrated that chronic administration of progesterone inhibits the upregulation of the α_4 subunit of the $GABA_A$ receptor and/or suppresses receptor activity.

Thus, the endogenous neurosteroid allopregnanolone exhibits withdrawal properties, similar to GABA-modulators such as tranquilizers and alcohol, as described above, increasing anxiety susceptibility following abrupt discontinuation after chronic administration. The increase in neuronal excitability has been attributed to upregulation of the $GABA_A$ α_4 subunit. Thus, the $\alpha_4\beta_2\gamma$ is preferentially expressed following hormone withdrawal. Blockade of the α_4 gene transcript prevents withdrawal properties.

The increase in expression of the $GABA_A$ receptor α_4 subunit relative to the $GABA_A$ receptor α_1 subunit can thus be attributed to many factors. These include, but are not limited to 1) compositions, both endogenous and exogenous, which, upon withdrawal, increase the $GABA_A$ receptor α_4 subunit relative to the $GABA_A$ receptor α_1 subunit; and 2) compositions, both exogenous or endogenous that result in the increase of expression of the $GABA_A$ receptor α_4 subunit or the decrease of expression of the $GABA_A$ receptor α_1 subunit.

Certain substances, both endogenous and exogenous, can cause modifications in the allostatic control of $GABA_A$, directly or indirectly, via an endogenous neurosteroid pathway. Most substances that cross the blood-brain barrier in sufficient quantity can stimulate a neuroprotective, neurosteroid response. In general, the more neuroexcitatory the substance, the more neurosteroid response is achieved. With the up-regulation of neurosteroids, $GABA_A$ receptor activity is enhanced, causing a constant state of activation which, over time, may cause neurosteroid tolerance. Therefore, once the neuroexcitatory substance is no longer present, the brain's neurosteroid levels will decrease to natural levels, causing the individual to go through a state of "withdrawal" from the neurosteroid.

In the course of this "withdrawal", certain $GABA_A$ receptor subunits may be expressed, or suppressed, in a manner that causes the person's brain to be susceptible to greater feelings of anxiety. In particular, his brain's $GABA_A$ receptor α_1 subunits decrease in relative amounts to $GABA_A$ receptor α_4 subunits. As a result of neurosteroid "withdrawal" and the subsequent up-regulation of α_4 subunits relative to α_1 subunits, the GABA receptor is no longer effectively modulated by GABA, and, therefore, results in the person experiencing a greater sense of anxiety.

In one embodiment, an individual's lowered degree of inhibitory control over his thoughts is caused by the modification of the receptivity of the synaptic $GABA_A$ receptors to the neurotransmitter GABA in the individual's brain. For example, substance abuse diminishes GABA receptivity; thus, the exogenous substance or "drug" modulates the $GABA_A$ receptor. When the user ceases consumption of the exogenous substance, due to changes in the $GABA_A$ receptor composition upon withdrawal (i.e. increased relative amount of $GABA_A$ receptor α_4 subunits compared to $GABA_A$ receptor α_1 subunits), the receptor is not effectively modulated by GABA, thus causing anxiety.

Figure 1 illustrates the spectrum between inhibition and disinhibition via the direct and/or indirect allosteric modulation of $GABA_A$. Spectrum 100 further depicts the range between inhibition 105 and disinhibition 110. An increase in an exogenous or endogenous substance that directly or indirectly enhances the function of GABA or the $GABA_A$ receptor 115 can result in an increase in GABA agonism and thus an increase in inhibition, anxiolysis, amnesia, and sedation, and even a comatose state.

However, as mentioned in greater detail above, stress, drug use, and even behavior activates these adaptive responses and disrupts homeostasis - the brain's internal balance. Upon withdrawal of both endogenous and exogenous substances, there is a marked increase in the α_4 subunit 120 of relative to the α_1 subunit 125 of the $GABA_A$ receptor 115, as shown in spe0ctrum 150. The increase of the α_4 subunit 120 of the $GABA_A$ receptor 115 causes the receptor to become insensitive to benzodiazepines and other compositions that act upon and/or enhance the function of GABA and the $GABA_A$ receptor. Therefore, when the systems involved in allostasis do not self-regulate (i.e. do not shut off when not needed or do not activate when needed), the brain experiences a compensatory drive to address this inactive or constantly active state, often exhibited in the form of anxiety or cravings.

IV. ANXIETY AND INHIBITION

Anxiety may be defined in a plurality of ways, including a vague unpleasant emotion that is experienced in anticipation of some, often ill-defined misfortune, a complex combination of the feeling of fear, apprehension and worry often accompanied by physical sensations such as palpitations, chest pain and/or shortness of breath, a feeling of apprehension, fear, nervousness, or dread accompanied by restlessness or tension, and/or a debilitating condition of fear, which interferes with normal life functions. Anxiety is evaluated clinically using diagnostic inventories such as the Hamilton Anxiety Rating Scale (Guy, William, "048 HAMA Hamilton Anxiety Scale," ECDEU Assessment Manual, U.S.

Department of Health and Human Services, Public Health Service – Alcohol, Drug Abuse, and Mental Health Administration, Rev. 1976, pp. 194-198) or the Beck Anxiety Inventory (Encephale. 1994 Jan-Feb; 20(1): 47-55), which are herein incorporated by reference.

In one embodiment, anxiety comprises a physiological state in which an individual has a lowered degree of inhibitory control over his thoughts, as described above with respect to Figure 1. Such lowered degree of inhibitory control may be caused by the turning off, inhibition, or otherwise down-modulation of an internal thought filtering mechanism in the person's brain. Referring to Figure 2, the internal thought filtering mechanism 200 comprises certain centers within a person's prefrontal cortex 205, including the orbitofrontal cortex 210, which is considered responsible for exerting control, and the anterior cingulate 215, which is considered responsible for motivation and drive impulses. These brain centers are substantially affected by certain physiological inputs, such as a reward circuit that comprises the nucleus accumbens 220 and ventral tegmental 225 areas of the brain.

When normally regulated, the orbitofrontal cortex 210 can exert control over a person's thoughts and avoid having an individual feel "overwhelmed" by vague, unpleasant emotions and feelings of fear, apprehension and worry. If $GABA_A$ receptor functionality is somehow impaired, however, GABA dysregulation occurs and can result in an impaired ability of the orbitofrontal cortex 210 to exert control over a person's thoughts and, therefore, a lowered degree of inhibitory control.

Consequently, the individual becomes compulsively driven to "address" this anxiety by making sure he obtains whatever substance, or engage in whatever activity, his brain believes it needs in order to eliminate the feelings of anxiety, e.g. regain inhibitory control over his thoughts. Therefore, it is the physiological drive to address feelings of anxiety that causes an individual to consciously engage in behavior which could be classified as self-destructive, such as substance abuse.

In the absence of a solution to address anxiety, a person is in a constant stress response state which, both psychologically and physiologically, directs the person to search for and obtain a solution to the anxiety. Many indications are implicated as being caused by the physiological drive to address feelings of anxiety. As discussed below, certain indications are caused by the psychological addiction and physiological dependence upon various substances, both exogenous and endogenous.

Exogenous substances, such as opioids, benzodiazepines, cannabis, caffeine, nicotine, and other drugs, directly or indirectly affect $GABA_A$ receptor functionality and, when those exogenous substances are withheld from an individual, cause the expression of the $GABA_A$

receptor α_4 subunit (hereinafter generally referred to as the α_4 subunit) to increase relative to the expression of the α_1 subunit.

In particular, during use, such substances may directly or indirectly stimulate $GABA_A$ via a neurosteroid mediated pathway. When those substances are later withheld, the amount of α_4 subunits relative to α_1 subunits increases. This ratio change is often temporary and is subject to reversal. However, a distinct pathophysiology emerges when it becomes non-reversing, namely when α_4 subunits no longer down-regulate relative to α_1 subunits. As described above, when such pathophysiology gets established, the $GABA_A$ receptor therefore becomes less sensitive to benzodiazepines and effectively, modulation by the neurotransmitter GABA, and is less capable of exerting inhibitory control over an individual's thoughts and behavior.

In one embodiment, it is possible to calculate a GABA-active steroid score ("GS Score") for nearly all substances. For every substance that crosses the blood brain barrier, or is active on the central nervous system, there is a minimum threshold level needed of that particular substance to effectively raise levels of GABA-active steroids. Thus, the GS Score correlates direct agonism of $GABA_A$ and the indirect modulation of $GABA_A$ via a neurosteroid mediated pathway, such as, but not limited to allopregnanolone. For example, but not limited to such example, cocaine has a lower GS Score than aspartame, since cocaine is more potent and it takes a lower threshold dose of cocaine to raise levels of GABA-active steroids. The GS Score is a methodology for measuring and assigning a numeric value to the relative addictive properties of substances.

Referring to Figure 3a, a benzodiazepine sensitive $GABA_A$ receptor 300a is shown. The $GABA_A$ receptor comprises a plurality of subunits, including two β_2 subunits 305a, a γ_2 subunit 310a, and two α_1 subunits 315a. By affecting the functionality and expression of receptor subunit mRNAs, certain endogenous and exogenous substances cause the expression of the $GABA_A$ receptor α_4 subunit to increase relative to the expression of the α_1 subunit. Referring to Figure 3b, the modified $GABA_A$ receptor 300b comprises a plurality of subunits, including two β_2 subunits 305b, a γ_2 subunit 310b, and two α_4 subunits 315b. As shown in Figure 3c, the $GABA_A$ receptor therefore becomes less sensitive to benzodiazepines and effectively, modulation by the neurotransmitter GABA, and is less capable of exerting inhibitory control over an individual's thoughts and behavior.

Endogenous substances may also have similar effects. Specifically, GABA-modulatory steroids, such as progesterone and deoxycorticosterone (DOC) and their metabolites allopregnanolone and tetrahydrodeoxycorticosterone respectively, affect $GABA_A$

receptor functionality and thus, when progesterone or DOC is decreased or "withdrawn" in an individual, cause the expression of the $GABA_A$ receptor α_4 subunit to increase relative to the expression of the α_1 subunit.

In addition, an increase in the level of endogenous neurosteroid is associated with tolerance. Thus, engaging in activities that increase neurosteroid production is an often temporary solution, because as described above, a distinct pathophysiology emerges and when it becomes non-reversing, namely when α_4 subunits no longer down-regulate relative to α_1 subunits. This loss of inhibitory control impairs an individual's ability to act on cravings and thus contributes to irrational behavior to engage in activities regardless of consequences.

Many systems within the body are subject to inhibitory control via GABAergic neurons located in the brain. In the event that an endogenous system is subject to inhibitory feedback by GABA, then the dysregulation of $GABA_A$ receptors can result in reduced inhibition or disinhibition of that particular system. Thus, it can be determined whether a primary system is dysregulated, and thus disinhibited, often noted because a patient exhibits a particular indication or disease state, and more specifically, a disease state where higher levels of an endogenous marker are present. For example, but not limited to such example, abnormal cholesterol levels are indicative of dysregulation of a primary system. If, however, a primary system is not dysregulated, then it can be determined whether an inhibitory system is disinhibited or dysregulated, and whether that inhibitory system is restored in the presence of endogenous neurosteroids, such as allopregnanolone and progesterone.

For example, but not limited to such example, prolactin inhibits dopamine, and thus when a patient presents with lower levels of dopamine, it is suggested that prolactin is not being subjected to inhibitory feedback, resulting in increased levels of prolactin. Increased levels of prolactin may be, at least in part, due to $GABA_A$ receptor dysregulation, and thus disinhibition.

V. COMPOSITIONS USED IN THE NOVEL TREATMENT METHODOLOGIES OF THE PRESENT INVENTION

The compositions described herein, and the compounds identified through the screening methodologies described herein, are intended to be used as drugs in the treatment methodologies described below. As used in this description, the term drug is used to refer to prescription or non-prescription pharmaceutical compositions and/or medications that include an active ingredient and, optionally, non-active, buffering, or stabilizing ingredients, including pharmaceutically acceptable carriers or excipients suitable for the form of

administration of said pharmaceutical compositions. It should be appreciated that the administration of the drug may be achieved through any appropriate route of administration, for example, orally, inhaled, anally, sublingual, bucally, transdermally, nasally, implant, or parenterally, for which it will be formulated using the appropriate excipients for the form of administration.

Table 1 is attached hereto and offers an exemplary listing of pharmacological compounds in the classes of compounds described herein. It should be noted however, that Table 1 is not an exhaustive list of all of the compositions that can be used with the present invention and that the present invention is not limited to the use of such compounds.

a. COMPOUNDS THAT INHIBIT NEUROSTEROID PRODUCTION

In one embodiment, the present invention is directed towards a method of using a compound from a class of compounds that inhibit neurosteroid production ("Inhibitors of Neurosteroid Production"). In one embodiment, the compound is one that inhibits the conversion of progesterone to its metabolite allopregnanolone. In another embodiment, the compound is one that inhibits the conversion of progesterone metabolite 5α-dihydroprogesterone into allopregnanolone.

As shown in Figure 4, progesterone is first converted to 5α-dihydroprogesterone via an enzyme called 5α-reductase. 5α-dihydroprogesterone is then converted to 5α,3α-pregnanolone (allopregnanolone) via the 3α-hydroxysteroid oxidoreductase enzyme.

Reference will now be made to specific classes of inhibitors of neurosteroid production for use in the present invention. While the classes and inhibitors of neurosteroid production are described generally herein, it should be understood to those of ordinary skill in the art that any number of inhibitors of neurosteroid production that prevent the conversion of progesterone into its metabolite allopregnanolone can be used in the present invention and that the list is not exhaustive.

In one embodiment, an individual is administered a therapeutically effective amount of a 5-alpha-reductase inhibitor which blocks the conversion of progesterone into allopregnanolone. One exemplary 5-alpha-reductase inhibitor is finasteride or analogs or derivatives thereof. Preferably, the 5α-reductase inhibitor is capable of acting as a Type I inhibitor, a Type II inhibitor, or a combination thereof, and inhibits the 5α-reductase enzyme from converting progesterone to 5α-dihydroprogesterone and thus from creating progesterone metabolite allopregnanolone.

There are currently accepted dosing regimens for 5-alpha-reductase inhibitors. The present invention contemplates operating within the maximum limits of currently accepted

dosing regimens in order to maximally decrease the production of allopregnanolone and make the individual most receptive to treatment.

In one embodiment, an individual is administered a therapeutically effective amount of a 3-alpha-hyrodxysteroid oxidoreductase inhibitor which blocks the conversion of progesterone metabolite 5α-dihydroprogesterone into allopregnanolone. One exemplary 3-alpha-hyrodxysteroid oxidoreductase is indomethacin or analogs or derivatives thereof. There are currently accepted dosing regimens for 3-alpha-hyrodxysteroid oxidoreductase inhibitors. The present invention contemplates operating within the maximum limits of currently accepted dosing regimens in order to effectively decrease the production of allopregnanolone and make the individual most receptive to treatment.

Bitran et al (1995) have demonstrated that treatment with a 5-alpha-reductase inhibitor prevents the conversion of progesterone to allopregnanolone and eliminates the anxiolytic activity of progesterone. In addition, it has been suggested that the anxiogenic withdrawal properties of allopregnanolone can be prevented by previous administration of a 3α-hydroxysteroid oxidoreductase blocker such as indomethacin.

i. 5α-REDUCTASE INHIBITORS

The 5α-reductase inhibitors are a group of drugs with anti-androgenic activity that effectively decrease the amount of the 5α-reductase enzyme and thus inhibit neurosteroid production.

1. FINASTERIDE

Finasteride is a synthetic 4-azasteroid compound, and is a 5alpha-reductase inhibitor. Finasteride is 4-azaandrost-1-ene-17-carboxamide,*N*-(1,1-dimethylethyl)-3-oxo-,(5α,17β)-. The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55.

Finasteride is a competitive and specific 5α-reductase inhibitor. Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects.

Progesterone is metabolically converted to the $GABA_A$ receptor-potentiating neuroactive steroid allopregnanolone by 5α-reductase isoenzymes followed by 3α-hydroxysteroid oxidoreduction. Finasteride acts as a competitive 5α-reductase inhibitor and thus blocks the production of allopregnanolone from progesterone.

In one embodiment, finasteride is delivered using at least one oral tablet with a total daily dose of less than 10 mg, preferably less than 5 mg. It should be appreciated that, to the extent approved by regulatory authorities, finasteride can also be delivered in gel capsules or via injection or infusion. Finasteride should not be used by women of childbearing age.

Finasteride's side effects include breast enlargement and tenderness, skin rash, swelling of lips, abdominal pain, back pain, decreased libido, decreased volume of ejaculate, diarrhea, dizziness, headache, impotence, and testicular pain.

2. DUTASTERIDE

Dutasteride is a synthetic 4-azasteroid compound that is a selective inhibitor of both the Type I and Type II isoforms of the steroid 5α-reductase, an intracellular enzyme. Dutasteride is chemically designated as (5α,17β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula of dutasteride is $C_{27}H_{30}F_6N_2O_2$, representing a molecular weight of 528.5.

As a competitive Type I and Type II 5α-reductase inhibitor, dutasteride inhibits the conversion of progesterone to allopregnanolone. Dutasteride does not bind to the human androgen receptor.

In one embodiment, dutasteride is delivered using at least one capsule with a total daily dose of less than 10 mg, preferably less than 0.5 mg. It should be appreciated that, to the extent approved by regulatory authorities, dutasteride can also be delivered in tablets or via injection or infusion. Dutasteride should not be used by women of childbearing age. Dutasteride's side effects include cough, difficulty swallowing, dizziness, fast heartbeat, hives or welts, itching skin, puffiness or swelling of the eyelids or around the eyes, face, lips, or tongue, redness of skin, shortness of breath, skin rash, swelling of face, fingers, feet, and/or lower legs, tightness in chest, unusual tiredness or weakness, wheezing, abnormal ejaculation, decreased interest in sexual intercourse, decreased sexual performance or desire, impotence, inability to have or keep an erection, loss in sexual ability, desire, drive, or performance, or swelling of the breasts or breast soreness.

3. Other 5α-REDUCTASE INHIBITORS

The present invention also encompasses the use of other 5-alpha reductase inhibitors, including a) 4-aza-4-methyl-5 alpha-pregnane-3,20-dione (AMPD), which inhibits pituitary progesterone 5-alpha reduction, b) cyproterone acetate, and c) spironolactone, which is a diuretic that blocks two pathways to the production of androgens, or male hormones, one of which is the inhibition of 5α-reductase.

The present invention also encompasses the use of organic sources of 5-alpha reductase inhibition, including organic sources such as saw palmetto. Saw palmetto (*Serenoa repens*) is a natural source of a 5α-reductase inhibitor. Some studies suggest that it may be

comparable to finasteride if taken for six months. Saw Palmetto is advantageous because it is 1) substantially free of side effects and 2) cost effective.

ii. Other Inhibitors of Neurosteroid Production

The present invention further includes the use of 3α-hydroxysteroid oxidoreductase blockers. Gallo and Smith (1993) suggest that the anxiogenic withdrawal property of progesterone could be prevented by previous administration of a 3α-hydroxysteroid oxidoreductase blocker. In one embodiment, indomethacin is used. Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) that reduces fever, pain and inflammation. It is similar to ibuprofen and naproxen. Indomethacin is effective in reducing the production of prostaglandins.

It should be appreciated that any composition that can be used to inhibit neurosteroid production can be used in the present invention. In one embodiment, compounds are preferably screened to determine whether they can be used in the treatment methodologies of the present invention.

Specifically, an appropriate cellular model is used to model the inhibition of neurosteroid production. The efficacy of the composition is measured by measuring the relative levels of progesterone and allopregnanolone in a model prior to the administration of the composition and after the administration of the composition. In cases where the relative levels of progesterone and allopregnanolone decrease after administration, the composition may be suitable as an inhibitor to neurosteroid production.

b. COMPOUNDS THAT MODULATE THE EXPRESSION OF CERTAIN $GABA_A$ RECEPTOR SUBUNITS

Molecular biology studies have revealed a high degree of structural heterogeneity of the $GABA_A$ receptors. Development of subtype selective or specific compounds is of key importance for the understanding of the physiological and pathological roles of different GABA receptor subtypes and may lead to valuable therapeutic agents. It has been shown that functional selectivity is obtainable for a number of $GABA_A$ agonists.

Characterizations of the role of $GABA_A$ receptors require an understanding of the mechanisms by which subunit composition is regulated. The long-term administration of sedative-hypnotic, anxiolytic, or anticonvulsant drugs can affect expression of $GABA_A$ receptor subunit genes as well as the drug sensitivity and function of these receptors, suggesting that the mechanisms responsible for such changes might also underlie the

physiological modulation of $GABA_A$ receptors by endogenous compounds such as neurosteroids.

The level of efficacy of a partial agonist/antagonist depends upon the disease or dependence in question. Thus, by measuring the level of efficacy or activity of a partial agonist/antagonist at a receptor site, it is possible to determine what the disease state is and determine what conformational changes have occurred in the $GABA_A$ receptor subunits. Based upon this information, certain compositions can be classified according to the changes they cause in $GABA_A$ subunits. In addition, since the GABA binding site in the $GABA_A$ receptor is located at the interface between α and β subunits, the $GABA_A$ antagonists can bind to and stabilize a distinct inactive receptor conformation.

The present invention is thus directed towards a class of compounds that modulates the expression of certain $GABA_A$ receptor subunits. More specifically, the compound is one that serves as an agonist at the $GABA_A$ receptor, and more specifically, at either the α_4 subunit or α_6 subunit, and is capable of positively potentiating GABA current.

Still more specifically, the compound of choice is one that a) acts a partial agonist of $GABA_A$; b) inhibits the up-regulation of the α_4 subunit and/or increases the amount of the α_1 subunit relative to the amount of the α_4 subunit; and c) does not cause the up-regulation of the α_4 subunit and/or does not cause the amount of the α_4 subunit to increase relative to the amount of the α_1 subunit once the compound is no longer present in the patient's system.

The changes in expression of the $GABA_A$ receptor α_4 subunit relative to the $GABA_A$ receptor α_1 subunit can be attributed to many factors. These include, but are not limited to 1) compositions, both endogenous and exogenous, that transform the $GABA_A$ receptor α_4 subunit relative to the $GABA_A$ receptor α_1 subunit and vice versa; 2) compositions that result in the decrease of expression of the $GABA_A$ receptor α_4 subunit or the increase of expression of the $GABA_A$ receptor α_1 subunit; and 3) compositions that do not modify existing subunit levels, but rather prevent the upregulation of $GABA_A$ receptor α_4 subunit.

Thus, the compound of choice is one that effectuates an increase in the expression of the $GABA_A$ receptor α_1 subunit relative to the expression of the α_4 subunit. This increase in expression of the α_1 subunit may be effectuated by one or more of the following: a) upregulating the expression of α_1 subunits; b) downregulating the expression of α_4 subunits; c) masking α_4 subunits; or d) preventing the upregulation of the α_4 subunit.

The focus is thus on using a compound from the class of compounds that modulates the expression of certain $GABA_A$ receptor subunits, and more specifically, moves the relative

balance of the α_4 subunit to the α_1 subunit closer to a normal state from an abnormal, allostatic state.

i. Flumazenil

In one embodiment, the present invention relates to the use of a therapeutically effective quantity of a drug, and more specifically, one that modulates the expression of $GABA_A$ subunits, such as, but not limited to, flumazenil, in a methodology for treatment of substance abuse. In one embodiment, the compound may comprise certain imidazobenzodiazepines and derivatives of ethyl 8-fluoro-5, 6-dihydro-5-methyl-6-oxo-4H-imidazo-[1,5-a][1,4] benzodiazepine-3-carboxylate, including various substitutions of the carboxylate functional group, such as carboxylic acids, esters, acyl chlorides, acid anhydrides, amides, nitriles, alkyls, alkanes, cycloalkanes, alkenes, alcohols, aldehydes, ketones, benzenes, phenyls, and salts thereof. In another embodiment, the compound comprises flumazenil or carboxylic acids, esters, acyl chlorides, acid anhydrides, amides, nitriles, alkyls, alkanes, cycloalkanes, alkenes, alcohols, aldehydes, ketones, benzenes, phenyls, and salts thereof.

Flumazenil acts a partial agonist of $GABA_A$, inhibits the upregulation of the α_4 subunit and/or increases the amount of the α_1 subunit relative to the amount of the α_4 subunit, and does not cause the upregulation of the α_4 subunit and/or does not cause the amount of the α_4 subunit to increase relative to the amount of the α_1 subunit once the compound is no longer present in the patient's system.

ii. Miltirone

In another embodiment, the compound may comprise miltirone, as described in Mostallino et al., "Inhibition by miltirone of up-regulation of $GABA_A$ receptor α_4 subunit mRNA by ethanol withdrawal in hippocampal neurons", European Journal of Pharmacology, 494 (2004) 83-90.

iii. Flavonoids

In another embodiment, the compound may comprise certain flavonoids that act as a partial agonist of $GABA_A$, inhibit the upregulation of the α_4 subunit and/or increase the amount of the α_1 subunit relative to the amount of the α_4 subunit, and does not cause the upregulation of the α_4 subunit and/or does not cause the amount of the α_4 subunit to increase relative to the amount of the α_1 subunit once the compound is no longer present in the patient's system.

It should be appreciated that any composition that can function as described above, can be used in the present invention. In one embodiment, compounds are preferably screened to determine whether they can be used in the treatment methodologies of the present invention. In one embodiment, experiments are conducted to determine whether it functions as a partial agonist of $GABA_A$, inhibits the upregulation of the α_4 subunit, and does not cause the upregulation of the α_4 subunit once the compound is no longer present in the patient's system. While one of ordinary skill in the art can devise such experiments, an exemplary embodiment of such an experiment is provided in Mostallino et al., "Inhibition by miltirone of up-regulation of $GABA_A$ receptor α_4 subunit mRNA by ethanol withdrawal in hippocampal neurons", European Journal of Pharmacology, 494 (2004) 83-90.

VI. NOVEL TREATMENT METHODOLOGIES

The present invention is directed towards a comprehensive treatment protocol that employs methods of, and compositions for, preparing a patient for treatment and modulating the expression of certain $GABA_A$ receptor subunits. The present invention therefore treats withdrawal symptoms associated with psychological addiction and physiological dependence upon various exogenous and endogenous substances in the context of a comprehensive treatment plan of behavioral and/or pharmacological treatment.

The multiple phase treatment methodology of the present invention employs one or more compounds to reset physiochemical changes in a patient that is experiencing withdrawal from addictive and/or dependency-inducing substances, including but not limited to opioids and derivatives, nicotine, benzodiazepines, caffeine, cannabis, or anti-depressant drugs. Effective treatment of such indications requires addressing the maladaptive behaviors underlying addiction and physiological dependence upon various exogenous substances, namely the increased expression of the $GABA_A$ receptor α_4 subunit relative to the α_1 subunit.

The treatment methodology of the present invention thus incorporates 1) determining if a person is in a receptive state for treatment and/or causing a person to be in a receptive state for treatment and 2) treating a person using appropriate drugs in a comprehensive treatment protocol that includes pre-drug assessment including optional detoxification, treatment, and aftercare. The term "receptive state", as used herein, refers to a physiological state in which the patient is withdrawn from both endogenous and exogenous substances.

As used in this description, the term "substance abuse" is used to refer to the various physical and psychological states that manifest an individual's impaired control over substance use, continued substance use despite adverse consequences, compulsive substance

use, and/or drug cravings. The term is intended to include psychological dependence, physical dependence, tolerance, a maladaptive pattern of substance use, preoccupation with substance use, and/or the presence of withdrawal symptoms upon cessation of use. Notwithstanding the above, the terms "addiction" and "dependency" are used interchangeably throughout this text. While it is traditionally understood that addiction and dependency relate to illegal or narcotic substances, it should be understood here that the treatment protocol of the present invention may also be used to treat other drug addictions, withdrawal reaction from prescribed medication, and other types of compulsive behaviors relating to food, sex, or gambling.

As used in this description, the term "substance" refers to a composition to which a person may exhibit withdrawal symptoms from abrupt cessation of intake or production of the composition, and includes, but is not limited to, opiates, nicotine, benzodiazepines, caffeine, cannabis, and anti-depressants.

As used in this description, the term patient refers to a male or female human being of any race, national origin, age, physiological make-up, genetic make-up, disease predisposition, height, or weight, and having any disease state, symptom or illness.

It should further be appreciated that the methods and processes of the present invention can be implemented in a computer system having a data repository to receive and store patient data, a memory to store the protocol steps that comprise the methods and processes of the present invention, a processor to evaluate patient data in relation to said protocol steps, a network interface to communicate via a network with other computing devices and a display to deliver information to users. In one embodiment, specific protocol steps are stored in said memory and compared against patient data, including behavioral, psychological or physiological profiles, to determine which protocol steps should be applied. Results of the comparison are communicated to a user via a network and other computing devices or display. The methodologies of the present invention are therefore accessed, tailored, and communicated as a software program operating on any hardware platform.

The exemplary treatment methodology of the present invention comprises pre-treatment, co-treatment, and post-treatment phases further comprising various components of an exemplary methodology.

As described herein, reference will be made to specific components of the individual phases of the treatment methodology. It should be noted, however, that the individual components comprising each phase of the methodology – pre-treatment, co-treatment, and post-treatment – are interchangeable and may be performed variably, and should be

determined on a per-patient basis. Thus, any reference to administering the individual components of the phases of methodology in a particular order is exemplary and it should be understood to one of ordinary skill in the art that the administration of methodology may vary depending on the assessed needs of the patient. Furthermore, while the invention will be described in conjunction with specific embodiments, it is not intended to limit the invention to one embodiment. In addition, many combinations of the methodology components described above are possible; thus, the invention is not limited to such examples as provided.

The treatment protocols will first be generally described and then specific examples of the treatment protocols will be provided thereafter.

a. PRE-TREATMENT/PATIENT ASSESSMENT PHASE

Prior to admittance into the treatment program of the present invention, each patient should undergo a pre-treatment analysis. The pre-treatment analysis may be used to determine whether a patient is a candidate for the treatment methodology of the present invention. In addition, the pre-treatment process may be administered to prepare a patient for admittance into the treatment methodology of the present invention. The pre-treatment phase typically includes, but is not limited to a medical history and physical examination, a psychological and behavioral assessment, a determination of required medications, and detoxification if needed to render the patient in a state receptive to treatment.

The treatment methodology for substance abuse has multiple phases and components that, in combination, provide a comprehensive and integrated neurological, physiological, and psychosocial approach for the substance-dependent patient. Each component has been selected to address specific effects of chronic substance use and the corresponding symptoms of withdrawal, with the objective of restoring a balance in neurological circuits. The methodology does not address the specific physical injury often associated with substance dependence. It is, therefore, essential that each patient be assessed and the appropriate treatments be instituted to address physical injury, with due consideration for the potential interaction of any medicaments used for this treatment with those used for the dependency treatment.

While the present methodology can be applied to any patient, it is preferred that the patient be equal to or greater than eighteen years old.

i. Complete Physical Examination

Before starting the treatment, the patient undergoes a medical history, physical examination and laboratory assessment, including but not limited to a complete blood count, a biochemical profile [for example, creatinine, glucose, urea, cholesterol (HDL and LDL),

triglycerides, alkaline phosphatase, LDH (lactic dehydrogenase) and total proteins], hepatic function tests [GOT, GPT, GGT, bilirubin), electrocardiogram and, if appropriate, pregnancy test and x-ray examinations. Exclusion criteria are applied to ensure no other acute or uncompensated illness exists within the patient and to ensure that the patient does not require, or is currently not taking, a drug that is contraindicated with the $GABA_A$ receptor modulating compound being used.

ii. Diagnosis of Substance Abuse, Dependence, and Tolerance

It is preferred that the patient meet at least a portion of recognized criteria for dependence on a particular substance, such the DSM-IV criteria. The DSM-IV criteria is known to those of ordinary skill in the art and can be described as a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by any of the following, occurring at any time in the same 12-month period:

- Tolerance, as defined by either of the following:
  - A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
  - Markedly diminished effect with continued use of the same amount of the substance.
- FULL WITHDRAWAL, as manifested by either of the following:
  - The characteristic withdrawal syndrome for the substance.
  - The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
  - Physiological Determination (as described in greater detail below)
- The substance is often taken in larger amounts or over a longer period than was intended (loss of control).
- There is a persistent desire or unsuccessful efforts to cut down or control substance use (loss of control).
- A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects (preoccupation).
- Important social, occupational, or recreational activities are given up or reduced because of substance use (continuation despite adverse consequences).
- The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (adverse consequences).

It should further be noted that certain exclusion criteria should be applied to the screening of patients. The exclusion criteria may be tailored to an outpatient or inpatient treatment scenario. For example, it is preferred not to treat a patient on an inpatient basis for substance abuse or dependence where the patient has current medical or psychiatric problems that, per the screening physician, require immediate professional evaluation and treatment, has current medical or psychiatric problems that, per the screening physician, render the client unable to work successfully with the methodology or with the staff administering the treatment, has current benzodiazepine and other sedative-hypnotic-anxiolytic use (urine toxicology must be negative) or is taking anti-psychotic medication(s).

b. PREPARING A PATIENT FOR TREATMENT WITH THE PROTOCOL OF THE PRESENT INVENTION ("RECEPTIVE STATE FOR TREATMENT")

It should be noted, however, that the individual components comprising the preparation phase of the methodology are interchangeable and may be performed variably, and should be adapted to the patient. Thus, any reference to administering the individual components of the preparation phase of the methodology in a particular order is exemplary and it should be understood to one of ordinary skill in the art that the administration of methodology may vary depending on the assessed needs of the patient. In addition, many combinations of the methodology components described above are possible; thus, the invention is not limited to such examples as provided.

i. PLACING A PATIENT IN A STATE OF WITHDRAWAL

As used herein, the term "withdrawal" refers to a physiological state in which an individual has begun to have adverse psychological and/or physiological effects from not having a bioavailable amount of particular substance or from having a decreasing bioavailable amount of a particular substance. More specifically, withdrawal can be attributed to an increase in the $GABA_A$ receptor α_4 subunit expression relative to the $GABA_A$ receptor α_1 subunit.

The treatment methodologies of the present invention include a first step of placing a patient in a state of withdrawal. In one embodiment, a person is placed in a receptive state for treatment by actively inhibiting the upregulation of endogenous neurosteroids and/or causing the downregulation of endogenous neurosteroids. The upregulation of neurosteroids could be caused by a number of external factors, including the ingestion or administration of

certain substances, such as caffeine or nicotine, or psychological stress. The present invention therefore includes the step of avoiding all such activities that could result in the upregulation of an individual's neurosteroid level.

In another embodiment, a person is placed in a receptive state for treatment by actively causing the downregulation of endogenous neurosteroids, such as allopregnanolone, through the administration of inhibitors of neurosteroid production that block the production of endogenous neurosteroids and/or their metabolites. The present invention also includes the inhibition of the modulatory effects of neurosteroids on $GABA_A$. By doing so, one accelerates the exposure or upregulation of α_4 subunits relative to α_1 subunits and ensures that a substantial number of α_4 subunits are exposed and available to enhance the efficacy of subsequent treatment steps.

In one embodiment, to place the patient in a state receptive to treatment, the patient is induced into a state of withdrawal from the substance upon which the patient is addicted or dependent. The withdrawal state can be initiated by withholding the substance or by a process of sequentially decreasing daily dosing of an agonist or partial agonist medication with similar pharmacological properties (e.g. methadone of buprenorphine for heroin dependence).

For example, but not limited to such example, in the case of opiate substance abuse or dependence, the opiate user is administered an opiate agonist that preferably has a longer half-life and is less potent than the drug to which the patient has an addiction. Appropriate methodologies for titrating a person down from an addictive substance are discussed in greater detail below with respect to exemplary treatment protocols. Administration of certain compositions serves to flush the user's system and places the user in a physiological state capable of effectively receiving an administration of a drug for the purpose of alleviating cravings and other withdrawal symptoms.

Once a patient is no longer taking the addictive substance or has titrated his dependence down to sufficiently low levels, the present invention further includes the step of actively causing the downregulation of endogenous neurosteroids, such as allopregnanolone, through the administration of agents that block the production of endogenous neurosteroids and/or their metabolites. The present invention also includes the inhibition of the modulatory effects of neurosteroids on $GABA_A$. By doing so, one accelerates the exposure or upregulation of α_4 subunits relative to α_1 subunits and ensures that a substantial number of undesirable subunits are exposed and available for enhanced pharmacotherapeutic efficacy.

Particular methods for baselining endogenous neurosteroid production to a consistent level in the pre-treatment portion of the protocol are discussed below, but the treatment protocol is not limited to such methods. For the methods listed below, the present invention contemplates operating in a dosing range of established safety and efficacy in order to maximally decrease the production of progesterone and make the individual most receptive to treatment.

1. Avoid Stress-Inducing Activities

In one embodiment, the present invention includes the step of avoiding all such activities that could result in the upregulation of an individual's neurosteroid level and the step of actively causing the downregulation of endogenous neurosteroids, such as allopregnanolone. It should be noted that stress-inducing activities depend upon the patient and the patient's general condition. Thus, individual recommendations may be made by the treating physician.

2. Avoid Neurosteroid Production Enhancing Activities

The patient is advised to not engage in activities, or ingest any substances, that could likely increase neurosteroid production. Such activities include sex, stressful activities, fighting, or intense arguing. Such substances include chocolate, illegal drugs, prescription drugs, or over the counter medicines.

Although not preferred because these compositions may serve to increase neurosteroid production, in certain cases, it may be necessary to administer a composition to reduce stress.

In one embodiment, the stress-reducing composition is gabapentin. Gabapentin is an anxiolytic and anticonvulsant medication typically prescribed to patients suffering from epilepsy (effectively lowers brain glutamate concentrations) and has also been used in the treatment of anxiety disorders such as social anxiety disorder and obsessive-compulsive disorder. Prior to administering gabapentin to a patient, it is essential to assess the patient for interactions and contraindications. Gabapentin is to be used in adjunctive therapy in the treatment of epilepsy seizures (partial) and for the management of postherpetic neuralgia. Gabapentin is not appreciably metabolized and is excreted unchanged with an elimination half-life of 5-7 hours. Possible side effects from the use of gabapentin are dizziness, somnolence, other symptoms/signs of CNS depression, nausea, ataxia, tremor, and peripheral edema. In persons with epilepsy, abrupt discontinuation may increase seizure frequency. No clinically significant drug interactions have been reported in the literature.

In another embodiment, the stress-reducing composition is a H1 histamine receptor agonist, such as, but not limited to hydroxyzine. Hydroxyzine is indicated for treatment of generalized anxiety disorder symptoms and for use in the management of withdrawal from substance dependence during both the initial phase of inpatient treatment and post-discharge care (as necessary). It also has anti-emetic and skeletal muscle relaxation benefits and can be used as a sedative. This sedative effect can be useful for treating the sleep-disordered breathing and increased periodic leg movements that contribute to the insomnia often seen in patients recovering from alcohol dependency. This helps address on-going insomnia which, for some patients is significantly associated with subsequent alcoholic relapse.

Hydroxyzine is rapidly absorbed and yields effects within 15-30 minutes after oral administration. In addition, hydroxyzine aids the substance withdrawal process through anxiolytic, anti-nausea, relaxant, and various other properties. It should be noted that the effects of other sedating or tranquilizing agents may be synergistically enhanced with the administration of hydroxyzine. Exemplary trade names of these drugs include Atarax and Vistaril.

3. Avoid Heightened Progesterone Levels In Patient

In an optional embodiment, it is possible to minimize endogenous neurosteroid production by timing the treatment in a manner that avoids heightened progesterone cycles.

In women, progesterone levels are low during the pre-ovulatory phase of the menstrual cycle, rise after ovulation, and are elevated during the luteal phase. Specifically, progesterone levels tend to be <2 ng/ml prior to ovulation, and >5 ng/ml after ovulation. If pregnancy occurs, progesterone levels are maintained at luteal levels initially. With the onset of the luteal-placental shift in support of the pregnancy, progesterone levels start to rise further and may reach 100-200 ng/ml at term. After delivery of the placenta and during lactation, progesterone levels are low.

For example, but not limited to such example, since progesterone levels are highest during the luteal phase of the menstrual cycle, it is preferred not to treat a woman during this time window. Conversely, it is preferred to treat a woman during the pre-ovulatory phase of the menstrual cycle, when progesterone levels are low.

Progesterone levels are low in children, men, and postmenopausal women.

4. Actively Modulate a Woman's Progesterone Levels

In another embodiment, a woman's progesterone is actively modulated by the administration of prescription hormones, such as, but not limited to, contraception with progesterone, that keeps the woman on a constant progesterone level. Such contraception includes progestin implants and levonorgestrel implants. Administration of these compositions will effectively make a woman's progesterone levels constant.

Upon withdrawal of these contraception compositions, the woman's hormone level will decrease, thereby "unmasking" its α_4 receptor subunits and placing a woman in a state most receptive to treatment.

The present invention advantageously uses the time gap between when administered progesterone leaves the system and when endogenous progesterone production resumes. In one embodiment, this minimal progesterone point window is preferably when the treatment protocol of the present invention should begin.

In one embodiment, progesterone can be delivered orally, sublingually, via vaginal suppositories, via injection, topically, transdermally, or by implant. The rate of absorption of progesterone is highly dependent upon the administration route. Irrespective of the type used, progesterone, progestin, or other progesterone-like compounds should be administered in sufficient amounts to attain a heightened level of progesterone and then terminated in sufficient time to allow for the progesterone levels to decrease prior to treatment.

It should again be noted that Table 1 offers an exemplary listing of pharmacological compounds in the classes of compounds described herein. Several examples of contraception and recommended dosing parameters are also listed in Table 1 .

5. Actively Modulate a Male's or Female's Progesterone Levels

As mentioned above, various neurosteroid inhibitors prevent the conversion of progesterone into allopregnanolone. In an endogenous case, allopregnanolone is responsible for the modulation of the $GABA_A$ receptors. By compensating for the effects of the withdrawn substance, endogenous neurosteroids, when elevated, "mask" $GABA_A$ receptors and prevent flumazenil from being able to "re-set" those receptors. The administration of these drugs can effectively drive down endogenous neurosteroid levels.

In one embodiment, the compound is a 5α-reductase inhibitor. Preferably, the 5α-reductase inhibitor is capable of acting as a Type I inhibitor, a Type II inhibitor or a combination thereof and inhibits the 5α-reductase enzyme from converting progesterone to 5α-dihydroprogesterone and thus from creating progesterone metabolite allopregnanolone. In another embodiment, the compound is a 3α-hydroxysteroid oxidoreductase inhibitor, which

prevents the 3α-hydroxysteroid oxidoreductase enzyme from converting 5α-dihydroprogesterone into 5α,3α-pregnanolone (allopregnanolone).

While the class of compounds that inhibit neurosteroid production has been described in detail above, an exemplary list of compounds is described in detail in Table 1. It should be noted, however, that the present invention is not limited to such compounds and any compounds that effectively inhibit endogenous neurosteroid production, and in particular, the conversion of progesterone to its metabolite allopregnanolone, can be used with the present invention.

ii. INDUSTRY-STANDARD TREATMENT APPROACHES

In one embodiment, the patient is subjected to standard and/or industry-accepted treatment protocols. Several exemplary treatment protocols are detailed in the sections below. It should be noted, however, that the treatment protocols outlined herein are exemplary and any number of treatment protocols may be used with the present invention provided that they are not contraindicated with the use of a compound from the class of compounds that permanently increases the relative expression of the α_1 $GABA_A$ subunit relative to the α_4 $GABA_A$ subunit.

Many of the conventional protocols described herein are adapted by the National Guideline Clearinghouse. The National Guideline Clearinghouse™ (NGC) is a comprehensive database of evidence-based clinical practice guidelines and related documents. NGC is an initiative of the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. NGC was originally created by AHRQ in partnership with the Americal Medical Association and the American Association of Health Plans (now America's Health Insurance Plans [AHIP]). The NGC mission is to provide physicians, nurses, and other health professionals, health care providers, health plans, integrated delivery systems, purchasers and others an accessible mechanism for obtaining objective, detailed information on clinical practice guidelines and to further their dissemination, implementation and use.

In addition, some clinical practice guidelines were adapted from the United States Department of Health and Human Services Substance Abuse and Mental Health Services Administration. More specifically, protocols were adapted from the National Clearinghouse for Alcohol and Drug Information.

Certain clinical practice guidelines were also adapted from the Expert Consensus Guidelines are being used throughout the country by clinicians, policy-makers,

administrators, case managers, mental health educators, patient advocates, and clinical and health services researchers.

The use of industry-accepted treatment protocols is optional.

c. ADMINISTRATION OF A COMPOUND FROM THE CLASS OF COMPOUNDS THAT MODULATES THE EXPRESSION OF CERTAIN $GABA_A$ RECEPTOR SUBUNITS

Whether used independently of, or part of, any other treatment approach, the present invention requires a patient to be administered a compound from the class of compounds that modulates the expression of certain $GABA_A$ receptor subunits, as described above. In one embodiment, the compound serves as an agonist at the $GABA_A$ receptor, and more specifically, at either the α_4 subunit or α_6 subunit, and is capable of positively potentiating GABA current.

It should be noted, however, that the present invention is not limited to such compounds and any compounds that effectively increase the expression of the α_1 $GABA_A$ subunit relative to the α_4 $GABA_A$ subunit, in a non-transitory manner, can be used with the present invention.

The present invention is directed towards, in one embodiment, the use of a compound that modulates the expression of certain $GABA_A$ receptor subunits, such as flumazenil, in multiple doses for a predetermined time period as part of the treatment methodology. When administered in accordance with the present invention, a therapeutically effective amount of the drug is maintained in the patient, thereby significantly reducing the upregulation of allopregnanolone. The methodology of the present invention also provides for the administration of a compound that modulates the expression of certain $GABA_A$ receptor subunits, such as flumazenil, without significant side effects.

Thus, in one embodiment, a method is provided for the treatment of substance abuse that includes the administration to a patient in need of said treatment of a therapeutically effective quantity of flumazenil in multiple doses during predetermined time periods/intervals, until a therapeutically effective quantity of flumazenil to treat substance abuse has been reached, as measured by quantitative and/or qualitative assessments of, for example, a patient's blood pressure, heart rate, feelings of cravings, and feelings of anxiety. Thus, it is possible to administer flumazenil in variable doses to obtain the desired therapeutic response, reducing the risk of secondary effects in the patient (as a result of reducing the quantity of drug administered per dose applied).

In another embodiment, a method is provided for the treatment of substance abuse that includes the administration to a patient in need of said treatment of a therapeutically effective quantity of flumazenil, usually between 0.5 mg/day and 20 mg/day, between 0.5 mg/day and 15 mg/day, specifically between 1.0 and 3.0 mg/day, and more specifically between 1.5 and 2.5 mg/day, of flumazenil, broken down into multiple doses of flumazenil between 0.1 and 0.3 mg and intended for administration during predetermined time periods or intervals, until said therapeutically effective quantity of flumazenil to treat substance abuse has been reached. In one embodiment, the predetermined time period is in the range of 1 and 15 minutes and the "per dose" quantity of flumazenil is between 0.1 and 0.3 mg.

One of ordinary skill in the art would appreciate that the individual doses can range in amount, and the time interval between the individual doses can range in amount, provided that the total dose delivered is in the range of 1.0 mg/day and 3.0 mg/day and the individual doses are delivered at relatively consistent time intervals. Therefore, the time period intervals can range from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 minutes or fractions thereof. Doses delivered at each time period, separated by the time intervals, can be between 0.1 and 0.3 mg, or fractions thereof, keeping in mind the total drug delivered is preferably less than 3.0 mg/day. The present invention therefore provides for the delivery of multiple, sequential doses, delivered at substantially consistent time intervals.

Conventional uses of flumazenil comprise either singular doses or much larger doses over shorter periods of time and are directed toward reversing sedative effects of anesthesia, conscious sedation, or benzodiazepine overdose. Further, Romazicon, a brand name for flumazenil marketed by Roche, is expressly indicated to complicate the management of withdrawal syndromes for alcohol, barbiturates and cross-tolerant sedatives and was shown to have an adverse effect on the nervous system, causing increased agitation and anxiety. For a single dose to address anesthesia and conscious sedation, it is conventionally recommended to use a dose of 0.2 mg to 1 mg of Romazicon with a subsequent dose in no less than 20 minutes. For repeat treatment, 1 mg doses may be delivered over five minutes up to 3 mg doses over 15 minutes. In benzodiazepine overdose situations, a larger dose may be administered over short periods of time, such as 3 mg doses administered within 6 minutes. One of ordinary skill in the art would appreciate that such conventional uses of flumazenil are not directed toward the treatment of substance abuse.

In addition, the administration method of the present invention provides a better use of flumazenil to treat the symptoms of substance abuse withdrawal and to reduce the

unnecessary consumption of said drug, thereby increasing convenience and the quality of life of the patient and reducing cost, to treat substance abuse in a very short period of time.

The method for the treatment of substance abuse provided by this invention is applicable to any patient who, when the treatment is to begin, has no medical illnesses that would make treatment with a compound that modulates the expression of certain $GABA_A$ receptor subunits, such as flumazenil hazardous or is taking medication contraindicated with a compound that modulates the expression of certain $GABA_A$ receptor subunits.

In general, the method of treatment of substance abuse provided by this invention begins with a complete medical and psychological examination, as described in detail above. Before, during, and after administration of flumazenil, the symptoms of substance abuse withdrawal, heart rate, and blood pressure are monitored.

In one embodiment, a compound that modulates the expression of certain $GABA_A$ receptor subunits, such as flumazenil, is administered until qualitative and quantitative parameters indicative of substance abuse are lowered to acceptable ranges.

In one embodiment, a compound that modulates the expression of certain $GABA_A$ receptor subunits, such as flumazenil, is administered at the latter of a) when the patient starts to feel anxious (this is when receptors are "unmasked" as progesterone is substantially no longer converted to allopregnanolone) or b) when it is safe to administer based upon prior drugs given to the patient.

In one embodiment, a compound that modulates the expression of certain $GABA_A$ receptor subunits, such as flumazenil, is administered at any rate, provided that the rate is not detrimental to the patient, as determined by patient self-report of symptoms, or physiological parameters such as heart rate, heart rhythm, or blood pressure.

d. ADDITIONAL TREATMENT OPTIONS

In some cases, in may be necessary to use, either during or post-treatment, the following optional components of the treatment protocol. The following optional components are exemplary and are dependent upon a variety of factors, including but not limited to responsiveness of the patient to treatment and if there is an indication of a sustained increase in 5-alpha reductase activity.

i. 5-ALPHA REDUCTASE INHIBITOR

It may be necessary to continually treat a patient with a 5-alpha reductase inhibitor if there is an indication of a sustained increase in 5-alpha reductase activity. 5-alpha-reductase inhibitors have been described in detail above and will not be repeated herein.

ii. PROLACTIN

In some cases, it may be necessary to treat a patient to resolve increased production of prolactin, due to an increase of estrogen levels caused by a decline in progesterone feedback. A sustained increase in the levels of prolactin leads to impairment of dopamine functionality, characterized by a higher stimulus threshold for dopamine release. Exemplary drugs include dopamine agonists, such as bromocriptine and prescription amphetamines, such as Ritalin and Adderal.

e. POST-TREATMENT PHASE OF PROTOCOL

After a patient successfully completes the treatment phase of the methodology of the present invention, each patient will be prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. The components of the post-treatment phase of the methodology of the present invention are described in greater detail below.

Before discharge from the hospital, one or more of the following compositions or drugs may be prescribed: gabapentin and fluoxetine hydrochloride. Preferably, the compositions or drugs can be administered in oral form to enable greater patient compliance and convenience. It should be appreciated that, to the extent any of drugs described herein are not available in the jurisdiction in which this invention is being practiced equivalent functioning drugs may be used.

Psychotherapy/behavioral therapy and counseling may be critical for the success of substance-dependency treatment when using pharmacological adjuncts. Thus, the methodology also provides for a maintenance program that includes medications and incentives for the patient to continue with their recovery process through continuing care programs. Due to the complexity of substance dependence, patients benefit most from a combination of pharmacologic and behavioral interventions.

As part of the treatment program, patients may optionally be instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months].

Likewise, a semi-structured follow-up of cognitive behavior therapy is optionally implemented. Individual and family psychotherapy is focused on a plurality of interventions, including cognitive restructuring, work therapy, prevention of relapse, and stress reduction, aimed at rehabilitating the social, family, work, personal and leisure life of the patient.

Depending upon the results of the initial examination, a universal or patient-specific diet plan may optionally be administered in conjunction with the methodology. Depending upon the results of the initial examination, a universal or patient-specific exercise programs may optionally be administered in conjunction with the methodology.

The following examples will serve to further illustrate the present invention without, at the same time, however, constituting any limitation thereof. On the contrary, it is to be clearly understood that resort may be had to various embodiments, modifications and equivalents thereof which, after reading the description herein, may suggest themselves to those skilled in the art without departing from the spirit of the invention.

VII. EXAMPLE 1: PROTOCOL FOR THE TREATMENT OF OPIOID ABUSE

"Opioid" is a term used for the class of drugs with opium-like and/or morphine-like pharmacological action. An opioid is any agent that binds to opioid receptors, which are mainly found in the central nervous system and gastrointestinal tract. There are many types of opioids, including endogenous opioids produced in the body (endorphins, dynorphins, enkephalins); opium alkaloids found in the opium plant (morphine, codeine, thebaine); semi-synthetic opioid derivatives (heroin, oxycodone, hydrocodone, dihydrocodeine, hydromorphine, oxymorphone, nicomorphine); and wholly synthetic opioid derivatives (phenylheptylamines, phenylpiperidines, diphenylpropylamine derivatives, benzomorphan derivatives, oripavine derivatives, morphinan derivatives, loperimide, diphenoxylate). As used herein, the term "opiates" shall refer to any compound that binds to opioid receptors, including natural opium alkaloids, semi-synthetic opioids derived therefrom, and synthetic opioids that have a similar physiochemistry to natural opiates and generally metabolize to morphine. In a clinical setting, opioids are used as analgesics and for relieving chronic and/or severe pain and other disease symptoms. Some opioids, however, are abused or used illegally for their euphoria-inducing properties when administered intravenously or when smoked.

The present example incorporates the teachings of the general treatment methodology described above. The components of the pre-treatment phase of the methodology of the present invention have been described in greater detail above and will not be repeated herein.

a. PRE-TREATMENT/PATIENT ASSESSMENT PHASE

As described above, prior to admittance into the treatment program of the present invention, each patient should undergo a pre-treatment analysis. The pre-treatment analysis may be used to determine whether a patient is an optimal candidate for the treatment

methodology of the present invention. In addition, the pre-treatment process may be administered to prepare a patient for admittance into the treatment methodology of the present invention.

b. PREPARING A PATIENT FOR TREATMENT WITH THE PROTOCOL OF THE PRESENT INVENTION

i. Placing a Patient in A State of Withdrawal

A patient may be placed in a state of withdrawal by actively inhibiting the upregulation of endogenous neurosteroids and/or causing the downregulation of endogenous neurosteroids. As previously described, this treatment step may be achieved by a) avoiding stress-inducing activities, b) avoiding neurosteroid production enhancing activities, c) avoiding heightened progesterone levels in a patient, d) actively modulating a woman's progesterone levels, or e) actively modulating a male's or female's progesterone levels through the administration of a neurosteroid inhibitor.

ii. Additional Pre-Treatments

Even if a patient is placed in a state of withdrawal, the patient may optionally be subjected to other pre-treatment protocols for the substance of addiction. An exemplary protocol is described below, and thus, it should be noted that the use of such protocol is exemplary and the invention is not limited to such protocol.

1. Optional Opiate Agonist Administration

The following treatment protocol is adapted from the Center for Substance Abuse Treatment, *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs.* Treatment Improvement Protocol (TIP) Series 43. DHHS Publication No. (SMA) 05-4048. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005, which is herein incorporated by reference. A few details of the protocol are described below, however, it should be understood by one of ordinary skill in the art that the Treatment Improvement Protocol referenced above should be consulted for details. Treatment Improvement Protocols (TIPs) are best-practice guidelines for the treatment of substance abuse disorders, provided as a service of SAMHSA's Center for Substance Abuse Treatment (CSAT).

In an optional first step, the opiate user is administered an opiate agonist that preferably has a longer half-life and is less potent than the drug to which the patient has an addiction. Preferably, the medicament is an opiate agonist, such as, but not limited to buprenorphine or methadone, and creates a dependency in the patient on a substance that is less addictive and self-titrating. In a preferred embodiment, the substance is titrated down to

slowly wean the patient off of its effects. Substitution to complete withdrawal, however, is very difficult and some patients have emergence of opiate withdrawal symptoms that may result in relapse to illicit opiate use. Thus, in the optional first step, the opiate agonist is decreased to the minimum dose that the patient can tolerate without relapse.

a. Methadone

Methadone [chemical name 6-(dimethylamino)-4,4-diphenyl-3-heptanone] is a synthetic opioid analgesic with low addiction potential. It is chemically unlike morphine or heroin, but acts on the opioid receptors and produces many of the same effects. It is typically administered orally or intravenously. Methadone is longer lasting than morphine-based drugs and has a typical half-life of 24 hours or more, permitting administration only once a day in opioid detoxification and maintenance treatment programs. A patient is typically slowly weaned off of methadone.

While tolerance, dependence and withdrawal symptoms may develop, they develop much slower and are less acutely severe than those of morphine and heroin. Closely related to methadone, a synthetic compound levo-alphacetylmethadol (LAMM) has a 48-72 hour duration of action and can be administered less frequently. Both LAAM and methadone are controlled substances and can only be used on an inpatient basis.

b. Buprenorphine

Buprenorphine [chemical name (2S)-2-[(-)-(5R,6R,7R,14S)-9a-cyclopropylmethyl-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]-3,3-dimethylbutan-2-ol] is a partial opioid agonist at μ-opioid receptors on GABA neurons and also an opioid antagonist. Buprenorphine is a thebaine derivative, and its analgesic effect is due to the agonism of the μ-opioid receptor. It is also a κ antagonist. Naloxone can partially revert the effects of buprenorphine. It has a long effect of about 48 hours, due to its slow dissociation from the opioid receptors. Buprenorphine is administered as hydrochloride as either intramuscular or intravenous injection or as sublingual tablets. It is not administered orally, due to high first-pass metabolism. Unlike methadone, buprenorphine can be used on an outpatient basis, as it is not a controlled substance.

2. Optional Opiate Antagonist Administration

Once the patient has stabilized at a dose level that is as low as possible, but not low enough to trigger cravings and withdrawal, an opioid antagonist is optionally administered, such as naloxone, naltrexone, or nalmefene. Opiate antagonist administration, serves to flush opioids from the user's system and places the user in a physiological state capable of effectively receiving an administration of compound from the class of compounds that

modulates $GABA_A$ receptor expression for the purpose of alleviating cravings and other withdrawal symptoms.

a. Naloxone

Naloxone [chemical name 17-allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one] is a drug used to counter the effects of overdosing on opioids such as heroin and morphine. It is a thebaine derivative and has an extremely high affinity for μ- opioid receptors. Naloxone is a μ- opioid receptor competitive agonist, and its rapid blocking of these receptors often leads to rapid onset of withdrawal symptoms. As a competitive agonist, naloxone displaces a substantial portion of receptor-bound opioid molecules, thus resulting in a reversal of effects of opioid overdose. Naloxone also has antagonist action, though with a lower affinity, at κ- and δ-opioid receptors. Naloxone is usually injected intravenously for fast action, showing signs of reversal of respiratory depression and reversal of coma within 30 seconds. It is a short-duration pharmaceutical, with a half-life of approximately 60-100 minutes. Its effects last about 45 minutes.

b. Naltrexone

Naltrexone [chemical name 17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one] is structurally similar to naloxone but has a slightly increased affinity for κ-opioid receptors over naloxone, can be administered orally, and has a longer duration of action. In addition, naltrexone can be administered in a sustained-release form via an injection. It is an opioid receptor antagonist used in the management of alcohol dependence and opioid dependence. Naltrexone, and its active metabolite 6-β-naltrexol are competitive antagonists at μ- and κ-opioid receptors, and to a lesser extent δ-opioid receptors. Because it reversibly blocks or attenuates the effects of opioids, naltrexone is used in the management of opioid dependence. Naltrexone is typically used for rapid detoxification procedures. It has a longer duration that naloxone, with a single oral dose being able to block injected heroine effects for 48 hours.

c. Nalmefene

Nalmefene [chemical name 17-(cyclopropylmethyl)-4,5α-epoxy-6-methylenemorphinan-3,14-diol, hydrochloride salt], an opioid antagonist, is the 6-methylene analogue of naltrexone. It is used to prevent or reverse the effects of opioids and has no opioid agonist activity.

c. ADMINISTRATION OF A COMPOUND FROM THE CLASS OF COMPOUNDS THAT MODULATES $GABA_A$ RECEPTOR EXPRESSION

Once the pre-treatment protocol has been adhered to and completed, a patient is administered a compound from the class of compounds that modulates $GABA_A$ receptor expression, such as flumazenil, as described above in the general treatment methodology.

d. ADDITIONAL TREATMENT OPTIONS

Once the treatment protocol has been administered, additional treatment options may be administered, as described above in the general treatment methodology.

e. POST-TREATMENT PHASE OF PROTOCOL

Once the treatment protocol has been administered, a post-treatment protocol is administered, as described above in the general treatment methodology.

f. HYPOTHETICAL TREATMENT EXAMPLE 1

Male, 45 years old, has been using heroin for 8 years and, under DSM IV criteria, after undergoing pre-treatment assessment, has been diagnosed as being addicted to heroin.

Patient Preparation: Four weeks prior to scheduled treatment, he is initiated on a scheduled finasteride administration of 5 mg per day. Three days prior to scheduled treatment, the finasteride administration is terminated and the patient is instructed to not engage in any stress-inducing activities or ingest any substances that would likely increase neurosteroid production.

Day 1 of Treatment: Male patient is administered flumazenil, via infusion, at an amount less than 15 mg/day. The patient's heart rate and blood pressure are monitored, along with the patient's own qualitative assessment of his health, including, but not limited to, subjective feelings of anxiety. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Male patient is administered flumazenil, via infusion, at a rate of at least 2.5 mg/day.

Day 3 of Treatment: Male patient is evaluated to determine if a third day of treatment is necessary. If he continues to report feelings of anxiety or cravings, he is again administered flumazenil, via infusion, at a rate of at least 2.5 mg/day.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Male patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety

return, he is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

g. HYPOTHETICAL TREATMENT EXAMPLE 2

Male, 45 years old, has been using heroin for 8 years and, under DSM IV criteria, after undergoing pre-treatment assessment, has been diagnosed as being addicted to heroin.

Patient Preparation: One week prior to scheduled treatment, male patient is subjected to a conventional protocol for the treatment of opiate addiction, such as described above. In one embodiment, male patient is administered opiate agonist buprenorphine in an amount therapeutically effective to begin titrating the substance down in the patient. There is no pre-determined time period for administering buprenorphine to the patient. When the patient is titrated to sufficiently low levels, the treatment protocol of the present invention is started. In one embodiment, a sufficiently low level of buprenorphine is 3 mg.

Day 1 of Treatment: Male patient's buprenorphine dosage is reduced by .25 mg, and thus male patient is administered 2.75 mg of buprenorphine. In addition, male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Male patient's buprenorphine dosage is again reduced by .25 mg, and thus male patient is administered 2.50 mg of buprenorphine. Male patient is administered flumazenil, via infusion, at a rate of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 3 of Treatment: Male patient's buprenorphine dosage is again reduced by .25 mg, and thus male patient is administered 2.25 mg of buprenorphine. Male patient is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Maintenance Phase Until Next Treatment: If needed, male patient is advised that he may take buprenorphine in the amount of no more that 2.25 mg/day until the next treatment.

Day 21 of Treatment: Male patient's buprenorphine dosage is reduced by half, and thus male patient is administered 1.125 mg of buprenorphine. In addition, male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 22 of Treatment: Male patient's buprenorphine dosage is again reduced by half, and thus male patient is administered 0.50 mg of buprenorphine. In addition, male patient is

administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 23 of Treatment: Male patient is instructed to stop taking all medications, including buprenorphine.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Male patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, he is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

h. HYPOTHETICAL TREATMENT EXAMPLE 3

Male, 45 years old, has been using heroin for 8 years and, under DSM IV criteria, after undergoing pre-treatment assessment, has been diagnosed as being addicted to heroin.

Patient Preparation: One week prior to scheduled treatment, male patient is subjected to a conventional protocol for the treatment of opiate addiction, such as described above. In one embodiment, male patient is administered opiate agonist buprenorphine in an amount therapeutically effective to begin titrating the substance down in the patient. There is no pre-determined time period for administering buprenorphine to the patient. When the patient is titrated to sufficiently low levels, the treatment protocol of the present invention is started. In one embodiment, a sufficiently low level of buprenorphine is 4 mg.

Day 1 of Treatment: Male patient's buprenorphine dosage is reduced by 1 mg, and thus male patient is administered 3 mg of buprenorphine. In addition, male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Male patient's buprenorphine dosage is again reduced by 1 mg, and thus male patient is administered 2 mg of buprenorphine. Male patient is administered flumazenil, via infusion, at a rate of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 3 of Treatment: Male patient's buprenorphine dosage is again reduced by 1 mg, and thus male patient is administered 1 mg of buprenorphine. Male patient is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Day 4 of Treatment: Male patient is instructed to stop taking all medications, including buprenorphine.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Male patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, he is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

i. HYPOTHETICAL TREATMENT EXAMPLE 4

Male, 45 years old, has been using heroin for 8 years and, under DSM IV criteria, after undergoing pre-treatment assessment, has been diagnosed as being addicted to heroin.

Patient Preparation: Male patient is administered buprenorphine in the lowest possible dose that patient can tolerate with substantially minimal or no withdrawal symptoms, thus creating a dependency in the patient on a substance that is less addictive and self-titrating. For example, but not limited to such example, male patient is "addicted" to an amount of heroin equivalent of 15 mg of buprenorphine.

Day 1 of Treatment: On Day 1 of treatment, patient is administered 14 mg of buprenorphine. In addition, male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Male patient's buprenorphine dosage is reduced by 1 mg, and thus male patient is administered 13 mg of buprenorphine. Male patient is administered flumazenil, via infusion, at a rate of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Days 3-14 of Treatment: Male patient's buprenorphine dosage is reduced by 1 mg/day. In addition, male patient is again administered flumazenil, each day, via infusion, at a rate of at least 1.0 mg/day.

Day 15 of Treatment: Male patient is instructed to stop taking all medications, including buprenorphine.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Male patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, he is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

VIII. EXAMPLE 2: PROTOCOL FOR THE TREATMENT OF BENZODIAZEPINE ABUSE

Benzodiazepines are often used for short-term relief of severe, disabling anxiety or insomnia. Long-term use can be problematic due to the development of tolerance and dependency. As described in detail above, they act on the GABA receptor $GABA_A$, the activation of which dampens higher neuronal activity. Benzodiazepine use can result in a variety of side effects, including, but not limited to drowsiness, ataxia, confusion, vertigo, and impaired judgment. In addition, benzodiazepines induce physical dependence and are potentially addictive. An abrupt discontinuation of substance use may result in convulsions, confusion, psychosis, or effects similar to delirium tremens. Onset of withdrawal syndrome may be delayed and is characterized by insomnia, anxiety, tremor, perspiration, loss of appetite, and delusions. Typical treatments for benzodiazepine abuse have been based on cognitive-behavioral therapy, weaning a patient off of the drug, and, in some cases, administering a benzodiazepine antagonist to counteract the drug's effects. These methods, however, fail in that they do not address the underlying physiochemical changes that occur with addiction.

a. PRE-TREATMENT/PATIENT ASSESSMENT PHASE

As described above, prior to admittance into the treatment program of the present invention, each patient should undergo a pre-treatment analysis. The pre-treatment analysis may be used to determine whether a patient is an optimal candidate for the treatment methodology of the present invention. In addition, the pre-treatment process may be administered to prepare a patient for admittance into the treatment methodology of the present invention.

b. PREPARING A PATIENT FOR TREATMENT WITH THE PROTOCOL OF THE PRESENT INVENTION

i. Placing a Patient in A State of Withdrawal

A patient may be placed in a state of withdrawal by actively inhibiting the upregulation of endogenous neurosteroids and/or causing the downregulation of endogenous neurosteroids. As previously described, this treatment step may be achieved by a) avoiding stress-inducing activities, b) avoiding neurosteroid production enhancing activities, c) avoiding heightened progesterone levels in a patient, d) actively modulating a woman's progesterone levels, or e) actively modulating a male's or female's progesterone levels through the administration of a neurosteroid inhibitor.

ii. Additional Pre-Treatments

In one pre-treatment approach, a patient is gradually withdrawn through a gradual reduction of the dose. In one embodiment, a patient is initiated on an administration of diazepam (Valium), 15 to 25 mg four times daily. Sufficient diazepam is administered to suppress signs of increased withdrawal (e.g., increased pulse, increased blood pressure, or increased perspiration). Once a diazepam dose is reached which suppresses signs of withdrawal, administration may continue for 2 additional days and then may be decreased by 10% per day. When the diazepam dose approaches 10% of the initial dose, the remaining dose is reduced slowly over 3 to 4 days and then discontinued. In this approach, benzodiazepine detoxification is accomplished in approximately 14 days prior to the administration of a compound from the class of compounds that selectively modulates $GABA_A$ expression. It should be appreciated, however, that longer detoxification may be required.

c. ADMINISTRATION OF A COMPOUND FROM THE CLASS OF COMPOUNDS THAT MODULATES $GABA_A$ RECEPTOR EXPRESSION

Once the pre-treatment protocol has been adhered to and completed, a patient is administered a compound from the class of compounds that modulates $GABA_A$ receptor expression, such as flumazenil, as described above in the general treatment methodology.

d. ADDITIONAL TREATMENT OPTIONS

Once the treatment protocol has been administered, additional treatment options, as described above in the general treatment methodology, may be administered.

e. POST-TREATMENT PHASE OF PROTOCOL

Once the treatment protocol has been administered, a post-treatment protocol is administered, as described above in the general treatment methodology.

f. HYPOTHETICAL TREATMENT EXAMPLE 1

Male, 25 years old, has been using alprazolam for 5 years and, under DSM IV criteria, after undergoing pre-treatment assessment, has been diagnosed as being addicted to alprazolam.

Patient Preparation: Four weeks prior to scheduled treatment, he is initiated on a scheduled finasteride administration of 5 mg per day. Three days prior to scheduled treatment, the finasteride administration is terminated and the patient is instructed to not engage in any stress-inducing activities or ingest any substances that would likely increase neurosteroid production.

Day 1 of Treatment: Male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Male patient is administered flumazenil, via infusion, at a rate of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 3 of Treatment: Male patient is evaluated to determine if a third day of treatment is necessary. If he continues to report feelings of anxiety or cravings, he is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Male patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, he is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

g. HYPOTHETICAL TREATMENT EXAMPLE 2

Male, 35 years old, has been using alprazolam for 5 years and, under DSM-IV criteria, after undergoing pre-treatment assessment, has been diagnosed as being addicted to alprazolam.

Patient Preparation: Four weeks prior to scheduled treatment, he is initiated on a scheduled finasteride administration of 5 mg per day. Three days prior to scheduled treatment, the finasteride administration is terminated and the patient is instructed to not engage in any stress-inducing activities or ingest any substances that would likely increase neurosteroid production.

At least two weeks prior to treatment, patient then undergoes a treatment-induced benzodiazepine withdrawal process. In a preferred approach, to prevent seizures and other problems, benzodiazepine withdrawal is accomplished by gradual reduction of the dose. The patient is withdrawn using diazepam, 15 to 25 mg four times daily. The patient is administered sufficient additional diazepam to suppress signs of increased withdrawal (e.g., increased pulse, increased blood pressure, or increased perspiration). Once a diazepam dose is reached which suppresses signs of withdrawal, the diazepam administration is continued for 2 days and then is decreased by 10% per day. When the diazepam dose approaches 10%, the dose is reduced slowly over 3 to 4 days and then discontinued.

Day 1 of Treatment: Male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Male patient is administered flumazenil, via infusion, at a rate of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 3 of Treatment: Male patient is evaluated to determine if a third day of treatment is necessary. If he continues to report feelings of anxiety or cravings, he is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Male patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, he is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

IX. EXAMPLE 3: PROTOCOL FOR THE TREATMENT OF NICOTINE ABUSE

Nicotine is a naturally occurring liquid alkaloid with strong stimulating effects. Nicotine readily diffuses through the skin, lungs, or mucous membranes and travels into blood vessels, the brain, and the rest of a person's body. When inhaled, within 10 to 15 seconds, a person achieves the stimulatory effects of nicotine. The half-life of nicotine is about 60 minutes. Nicotine changes brain and body functions and initially results in a rapid

release of adrenaline, thereby causing a rapid heartbeat, increased blood pressure, and rapid, shallow breathing.

Nicotine is a drug that induces both anxiolytic and anxiogenic effects, similar to those triggered by stressful events, contributing to emotion and reward. Through its interaction with nicotinic acetylcholine receptors in the brain, which are located predominantly on pre-synaptic terminals, nicotine modulates the release of many neurotransmitters, including serotonin, dopamine, noradrenaline, and GABA. Nicotine may directly or indirectly act on the GABA receptor $GABA_A$, the activation of which dampens higher neuronal activity. Nicotine activates the mesolimbic dopamine system, which is critical for the reinforcing properties of the drug. Like heroin, cocaine, and alcohol, it is suggested that nicotine induces both a sense of well-being and physical dependence and reduces stress-related anxiety in humans.

In addition, nicotine was demonstrated to increase the cerebrocortical concentrations of allopregnanolone and its precursors. Given that allopregnanolone enhances $GABA_A$ receptor function and plays an important role in the regulation of anxiety and mood disorders, the transient increase in the brain concentration of this endogenous neurosteroid triggered by nicotine may represent a homeostatic mechanism to reduce or counteract the neuronal excitability and anxiogenic-like action elicited by nicotine.

Given that allopregnanolone is among the most potent positive modulators of $GABA_A$ receptors, which contribute to inhibitory regulation of mesocortical and mesolimbic dopaminergic neurons, the nicotine-induced increase in the brain content of these hormones may facilitate the inhibition of these dopaminergic pathways induced by GABA.

Long-term use can be problematic due to the development of tolerance and dependency. An abrupt discontinuation of substance use may result in convulsions, confusion, psychosis, or effects similar to delirium tremens. Onset of withdrawal syndrome may be delayed and is characterized by insomnia, anxiety, tremor, perspiration, and loss of appetite. Typical treatments for nicotine abuse have been based on cognitive-behavioral therapy and weaning a patient off of the drug. These methods, however, fail in that they do not address the physiochemical changes that occur with addiction.

a. PRE-TREATMENT/PATIENT ASSESSMENT PHASE

As described above, prior to admittance into the treatment program of the present invention, each patient should undergo a pre-treatment analysis. The pre-treatment analysis may be used to determine whether a patient is an optimal candidate for the treatment methodology of the present invention. In addition, the pre-treatment process may be

administered to prepare a patient for admittance into the treatment methodology of the present invention.

b. PREPARING A PATIENT FOR TREATMENT WITH THE PROTOCOL OF THE PRESENT INVENTION

i. Placing a Patient in A State of Withdrawal

A patient may be placed in a state of withdrawal by actively inhibiting the upregulation of endogenous neurosteroids and/or causing the downregulation of endogenous neurosteroids. As previously described, this treatment step may be achieved by a) avoiding stress-inducing activities, b) avoiding neurosteroid production enhancing activities, c) avoiding heightened progesterone levels in a patient, d) actively modulating a woman's progesterone levels, or e) actively modulating a male's or female's progesterone levels through the administration of a neurosteroid inhibitor.

ii. Other Pre-Treatment Approaches

The following clinical guidelines are adapted from guidelines published by the United States Department of Health and Human Services, and more specifically, the Substance Abuse and Mental Health Services Administration (hereinafter, SAMHSA), in *Treating Tobacco Use and Dependence*, which is incorporated by reference. See Fiore MC, Bailey WC, Cohen SJ, et al. Treating Tobacco Use and Dependence. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. June 2000.

In one embodiment, a patient engages in counseling and behavioral therapies, including, but not limited to, the provision of practical counseling (problem solving/skills training); the provision of social support as part of treatment (intra-treatment social support); and assistance in securing social support outside of treatment (extra-treatment social support). In another embodiment, a patient is prescribed a pharmacotherapy that is known for increasing long-term smoking abstinence rates: Bupropion SR, Nicotine gum, Nicotine inhaler, Nicotine nasal spray, Nicotine patch, Clonidine, and/or Nortriptyline.

It should be appreciated that, regardless of the particular pre-treatment therapy adopted, the patient should cease such pharmacotherapies at least one week prior to the administration of a compound from the class of compounds that modulates $GABA_A$ expression.

c. ADMINISTRATION OF A COMPOUND FROM THE CLASS OF COMPOUNDS THAT MODULATES $GABA_A$ RECEPTOR EXPRESSION

Once the pre-treatment protocol has been adhered to and completed, a patient is administered a compound from the class of compounds that modulates $GABA_A$ receptor expression, such as flumazenil, as described above in the general treatment methodology.

d. ADDITIONAL TREATMENT OPTIONS

Once the treatment protocol has been administered, additional treatment options, as described above in the general treatment methodology, may be administered.

e. POST-TREATMENT PHASE OF PROTOCOL

Once the treatment protocol has been administered, a post-treatment protocol is administered, as described above in the general treatment methodology.

f. HYPOTHETICAL TREATMENT EXAMPLE 1

Female, 30 years old, has been using nicotine for 11 years and, is admittedly addicted to nicotine. She has been taking oral contraceptives for at least five years.

Patient Preparation: Treatment is scheduled during a time period in which progesterone is not administered (for example, in a 21 day pill pack, treatment is scheduled beginning with the first placebo day). If this is not possible, female patient is instructed to withhold contraceptive use for one week prior to scheduled treatment. Three days prior to scheduled treatment, the patient is instructed to not engage in any stress-inducing activities or ingest any substances that would likely increase neurosteroid production (including oral contraceptives).

Day 1 of Treatment: Female patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Female patient is evaluated to determine if a second day of treatment is necessary. If she continues to report feelings of anxiety or cravings, she is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Day 3 of Treatment: Female patient is evaluated to determine if a third day of treatment is necessary. If she continues to report feelings of anxiety or cravings, she is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Female patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety

return, she is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

g. HYPOTHETICAL TREATMENT EXAMPLE 2

Female, 30 years old, has been using nicotine for 11 years and, is admittedly addicted to nicotine.

Patient Preparation: Six weeks prior to scheduled treatment, female patient is administered oral contraceptives. One week prior to scheduled treatment, the administration of oral contraceptives is terminated. Two weeks prior to treatment, female patient ceases any use of nicotine and is prescribed a nicotine patch for withdrawal symptoms. The benzodiazepine is given for up to four days at a dose of 5 mg tds. Three days prior to scheduled treatment, the patient is instructed to not engage in any stress-inducing activities or ingest any substances that would likely increase neurosteroid production (including oral contraceptives).

Day 1 of Treatment: Female patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Female patient is evaluated to determine if a second day of treatment is necessary. If she continues to report feelings of anxiety or cravings, she is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Day 3 of Treatment: Female patient is evaluated to determine if a third day of treatment is necessary. If she continues to report feelings of anxiety or cravings, she is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Female patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, she is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

X. EXAMPLE 4: PROTOCOL FOR THE TREATMENT OF CANNABIS (THC) ABUSE

Cannabis, or marijuana, is a plant containing THC (delta-9-tetrahydrocannabinol), a psychoactive chemical. When smoked, THC readily diffuses into an individual's lungs and, consequently, into his bloodstream. THC changes brain and body functions and initially results in a feeling of haziness and light-headedness and deleterious effect on short-term memory, coordination, learning, and problem-solving.

Long-term use can be problematic due to the development of tolerance and dependency. THC may directly or indirectly act on the GABA receptor $GABA_A$, the activation of which dampens higher neuronal activity. THC use can result in a variety of side effects, including, but not limited to learning and memory problems, distorted perception, anxiety, paranoia, and panic attacks. In addition, THC induces physical dependence and is addictive. Although not medically dangerous, withdrawal symptoms include anxiety, irritability, perspiration, sleep disturbances, moodiness, and anorexia. Less common withdrawal symptoms include tremors, nausea and vomiting, occasional diarrhea, and excessive salivation.

Typical treatments for THC abuse have been based on cognitive-behavioral therapy and weaning a patient off of the drug. These methods, however, fail in that they do not address the physiochemical changes that occur with addiction.

a. PRE-TREATMENT/PATIENT ASSESSMENT PHASE

As described above, prior to admittance into the treatment program of the present invention, each patient should undergo a pre-treatment analysis. The pre-treatment analysis may be used to determine whether a patient is an optimal candidate for the treatment methodology of the present invention. In addition, the pre-treatment process may be administered to prepare a patient for admittance into the treatment methodology of the present invention.

b. PREPARING A PATIENT FOR TREATMENT WITH THE PROTOCOL OF THE PRESENT INVENTION

i. Placing a Patient in A State of Withdrawal

A patient may be placed in a state of withdrawal by actively inhibiting the upregulation of endogenous neurosteroids and/or causing the downregulation of endogenous neurosteroids. As previously described, this treatment step may be achieved by a) avoiding stress-inducing activities, b) avoiding neurosteroid production enhancing activities, c) avoiding heightened progesterone levels in a patient, d) actively modulating a woman's progesterone levels, or e) actively modulating a male's or female's progesterone levels through the administration of a neurosteroid inhibitor.

ii. Other Pre-Treatment Approaches

The following protocol is adapted from "Cannabis Dependence and Treatment", GP Drug & Alcohol Supplement No. 10 (June 1998). In one embodiment, a patient has been diagnosed with cannabis dependence because at least one of the following has been true for one month or longer a) cannabis is often taken in larger amounts or over a longer period than the person intended, b) there is a persistent desire or one or more unsuccessful efforts to cut down or control cannabis use, c) a great deal of time is spent in activities necessary to get cannabis, e.g. theft, taking cannabis, or recovering from its effects, d) frequent intoxication or withdrawal symptoms occur when expected to fulfill major role obligations at work, school, or home, or when cannabis is physically hazardous, e) there are important social occupational or recreational activities given up or reduced because of cannabis use, f) cannabis use was continued despite knowledge of having a persistent or recurrent social psychological or physical problem that is caused or exacerbated by the use of cannabis, and g) there is a marked tolerance

In one embodiment, a patient is prescribed a pre-treatment therapy based upon a) what the patient wants; b) the severity of the patient's cannabis-related problems; c) the safety of the patient, i.e. the risk of suicide or harm to others from psychotic or depressive symptoms; and d) whether the patient is ready to quit. In one embodiment, the pre-treatment therapy comprises prescribing medicine to address symptoms of agitation, sleep disturbance, restlessness, and irritability. In one embodiment, the medicine prescribed is a benzodiazepine (such as diazepam), which may be given for up to four days at a dose of 5 mg tds. Benzodiazepines should not be continued beyond four days in these patients.

It should be appreciated that, regardless of the particular medicine prescribed adopted, the patient should cease all such pharmacotherapies at least one week prior to the administration of a compound from the class of compounds that modulates $GABA_A$ receptor expression.

c. ADMINISTRATION OF A COMPOUND FROM THE CLASS OF COMPOUNDS THAT MODULATES $GABA_A$ RECEPTOR EXPRESSION

Once the pre-treatment protocol has been adhered to and completed, a patient is administered a compound from the class of compounds that modulates $GABA_A$ receptor expression, such as flumazenil, as described above in the general treatment methodology.

d. ADDITIONAL TREATMENT OPTIONS

Once the treatment protocol has been administered, additional treatment options, as described above in the general treatment methodology, may be administered.

e. POST-TREATMENT PHASE OF PROTOCOL

Once the treatment protocol has been administered, a post-treatment protocol is administered, as described above in the general treatment methodology.

f. HYPOTHETICAL TREATMENT EXAMPLE 1

Female, 30 years old, has been using cannabis for 9 years and, under DSM-III-R criteria, has been diagnosed as being addicted to cannabis. She has been taking oral contraceptives for at least five years.

Patient Preparation: One week prior to scheduled treatment, female patient withholds oral contraceptive administration. Three days prior to scheduled treatment, the patient is instructed to not engage in any stress-inducing activities or ingest any substances that would likely increase neurosteroid production (including oral contraceptives).

Day 1 of Treatment: Female patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Female patient is evaluated to determine if a second day of treatment is necessary. If she continues to report feelings of anxiety or cravings, she is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Day 3 of Treatment: Female patient is evaluated to determine if a third day of treatment is necessary. If she continues to report feelings of anxiety or cravings, she is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Female patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, she is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

g. HYPOTHETICAL TREATMENT EXAMPLE 2

Female, 30 years old, has been using cannabis for 9 years and, under DSM-III-R criteria, has been diagnosed as being addicted to cannabis.

Patient Preparation: Six weeks prior to scheduled treatment, female patient is administered oral contraceptives. One week prior to scheduled treatment, the administration of oral

contraceptives is terminated. Two weeks prior to treatment, female patient ceases any use of cannabis and is prescribed a benzodiazepine for cannabis withdrawal symptoms. The benzodiazepine is given for up to four days at a dose of 5 mg tds. Three days prior to scheduled treatment, the patient is instructed to not engage in any stress-inducing activities or ingest any substances that would likely increase neurosteroid production (including oral contraceptives).

Day 1 of Treatment: Female patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Female patient is evaluated to determine if a second day of treatment is necessary. If she continues to report feelings of anxiety or cravings, she is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Day 3 of Treatment: Female patient is evaluated to determine if a third day of treatment is necessary. If she continues to report feelings of anxiety or cravings, she is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Female patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, she is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

XI. EXAMPLE 5: PROTOCOL FOR THE TREATMENT OF CAFFEINE ABUSE

Caffeine, also known as trimethylxanthine, is a naturally occurring cardiac stimulant and mild diuretic. Caffeine induces nervousness and insomnia in normal individuals, and it increases the level of anxiety in patients prone to anxiety and panic attacks. As an anxiogenic, caffeine changes brain and body functions and results in a rapid release of adrenaline, thereby causing a rapid heartbeat, increased blood pressure, and rapid, shallow breathing.

Caffeine may directly or indirectly act on the GABA receptor $GABA_A$, the activation of which dampens higher neuronal activity. In addition, it has been suggested that

neuroactive steroids modulate the stimulant and anxiogenic effects of caffeine. More specifically, Concas et al. demonstrated that IP administration of caffeine resulted in dose-dependent increases in the plasma and brain concentrations of allopregnanolone as well as in those of its precursors pregnenolone and progesterone. Thus, the effects of caffeine on the plasma and brain concentrations of neuroactive steroids was shown to be similar to those of anxiogenic drugs, including those of direct and indirect inhibitors of the $GABA_A$ receptor complex that induce experimental anxiety in humans. It was also demonstrated that these effects are antagonized by systemic administration of anxiolytic drugs, further demonstrating that both pharmacologic treatments and experimental conditions that induce anxiety-like or conflict behavior also induces increases in the plasma and brain concentrations of neuroactive steroids.

In addition, it is suggested that because caffeine induces both neurotransmitter release and anxiety-like behavior associated with increases in the plasma and brain concentrations of neuroactive steroids that the HPA axis might mediate such actions of caffeine. The transient increase in the brain concentration of allopregnanolone triggered by caffeine may reflect a physiological mechanism for reducing the activation of the neuroendocrine and neurochemical pathways associated with the state of arousal and for limiting the extent of neuronal excitability; consistent with the fact that neuroactive steroids function to counteract overexcitation of the CNS.

Caffeine can induce physical dependence and is addictive, thus long-term use can be problematic due to the development of tolerance and dependency. An abrupt discontinuation of substance use may result in anxiety and confusion. Typical treatments for caffeine dependence and abuse have been based on cognitive-behavioral therapy and weaning a patient off of the drug. These methods, however, fail in that they do not address the physiochemical changes that occur with addiction.

In further support of the effects of caffeine, Jain et al. demonstrated that caffeine produced higher anxiety in animals previously treated with the $GABA_A$ receptor antagonist, bicuculline or either of the various neurosteroid biosynthesis enzyme inhibitors viz. trilostane, finasteride, or indomethacin.

a. PRE-TREATMENT/PATIENT ASSESSMENT PHASE

As described above, prior to admittance into the treatment program of the present invention, each patient should undergo a pre-treatment analysis. The pre-treatment analysis may be used to determine whether a patient is an optimal candidate for the treatment methodology of the present invention. In addition, the pre-treatment process may be

administered to prepare a patient for admittance into the treatment methodology of the present invention.

b. PREPARING A PATIENT FOR TREATMENT WITH THE PROTOCOL OF THE PRESENT INVENTION

i. Placing a Patient in A State of Withdrawal

A patient may be placed in a state of withdrawal by actively inhibiting the upregulation of endogenous neurosteroids and/or causing the downregulation of endogenous neurosteroids. As previously described, this treatment step may be achieved by a) avoiding stress-inducing activities, b) avoiding neurosteroid production enhancing activities, c) avoiding heightened progesterone levels in a patient, d) actively modulating a woman's progesterone levels, or e) actively modulating a male's or female's progesterone levels through the administration of a neurosteroid inhibitor.

i. Other Pre-Treatment Approaches

Caffeine abuse and addiction should follow the basic principles of treatment of substance dependence. These factors include: elimination of the offending substance(s); detoxification as required; medical and psychiatric evaluation for associated conditions and complications; education about addiction, self-care, and recovery; relief of stress and the development of a healthy lifestyle; and psychosocial treatment and support.

It should be appreciated that, regardless of the treatment approach adopted, the patient should cease all pharmacotherapies at least one week prior to the administration of a compound from the class of compounds that modulates GABAA receptor expression.

c. ADMINISTRATION OF A COMPOUND FROM THE CLASS OF COMPOUNDS THAT MODULATES $GABA_A$ RECEPTOR EXPRESSION

Once the pre-treatment protocol has been adhered to and completed, a patient is administered a compound from the class of compounds that modulates $GABA_A$ receptor expression, such as flumazenil, as described above in the general treatment methodology.

d. ADDITIONAL TREATMENT OPTIONS

Once the treatment protocol has been administered, additional treatment options, as described above in the general treatment methodology, may be administered.

e. POST-TREATMENT PHASE OF PROTOCOL

Once the treatment protocol has been administered, a post-treatment protocol is administered, as described above in the general treatment methodology.

f. HYPOTHETICAL TREATMENT EXAMPLE 1

Male, 40 years old, has been using caffeine for 15 years and, under DSM-IV criteria, has been diagnosed as being addicted to caffeine. He also presents with acute headaches upon caffeine withdrawal.

Patient Preparation: Four weeks prior to scheduled treatment, he is initiated on a scheduled finasteride administration of 5 mg per day. Three days prior to scheduled treatment, the finasteride administration is terminated and the patient is instructed to not engage in any stress-inducing activities or ingest any substances that would likely increase neurosteroid production.

Day 1 of Treatment: Male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Male patient is evaluated to determine if a second day of treatment is necessary. If he continues to report feelings of anxiety or cravings, he is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Day 3 of Treatment: Male patient is evaluated to determine if a third day of treatment is necessary. If he continues to report feelings of anxiety or cravings, he is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Male patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, he is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

XII. EXAMPLE 6: PROTOCOL FOR TREATMENT OF ADDICTION TO NON-BENZODIAZEPINE ANXIOLYTICS, SEDATIVES, HYPNOTICS, AND TRANQUILIZERS/BARBITURATES (THE "CNS DEPRESSANTS")

Non-benzodiazepine hypnotics are used for the short term treatment of insomnia (or difficulty in getting to sleep or staying asleep). Some, like chlormethiazole, can be used to help with agitation and restlessness, and to help with alcohol withdrawal symptoms.

Barbiturates are drugs that act as central nervous system (CNS) depressant, producing a wide range of effects – from mild sedation to anesthesia. Today, barbiturates are infrequently used as anticonvulsants and for the induction of anesthesia. Sometimes, two or more barbiturates are combined in a single tablet or capsule.

Barbiturates enhance the functioning of GABA and are general depressants to nerve and muscle tissue. Mild to moderate barbiturate toxicity mimics alcohol intoxication. Severe acute barbiturate toxicity results in CNS problems, including lethargy and coma.

In moderate amounts, barbiturates produce a state of intoxication that is similar to the effects of alcohol. Depending on the dose, frequency, and duration of use, one can rapidly develop tolerance, physical dependence, and psychological dependence on barbiturates. As a user develops tolerance toward the barbiturate, the effective dose is close to the lethal dose. In order to obtain the same level of intoxication, and thus gratification, the tolerant abuser will raise his dose to a near fatal or fatal level.

Nonbenzodiazepine sedatives such as intermediate- or short-acting barbiturates or glutethimide are more likely than benzodiazepines to produce lethal overdose because people who abuse them develop tolerance for their sedative and euphoric effects but not for their respiratory-depressant effects. Therefore, as these people increase their dosages to get high, they suddenly can overdose to respiratory depression. People who are opioid addicted and abuse nonbenzodiazepine sedatives usually need inpatient detoxification before starting MAT or may do better with referral to a long-term, residential program such as a therapeutic community. Nonbenzodiazepine sedatives induce cytochrome P450 3A, an enzyme involved in methadone, levo-alpha acetyl methadol (LAAM), and buprenorphine metabolism, and can make stabilization difficult.

a. PRE-TREATMENT/PATIENT ASSESSMENT PHASE

As described above, prior to admittance into the treatment program of the present invention, each patient should undergo a pre-treatment analysis. The pre-treatment analysis may be used to determine whether a patient is an optimal candidate for the treatment methodology of the present invention. In addition, the pre-treatment process may be administered to prepare a patient for admittance into the treatment methodology of the present invention.

b. PREPARING A PATIENT FOR TREATMENT WITH THE PROTOCOL OF THE PRESENT INVENTION

i. Placing a Patient in A State of Withdrawal

A patient may be placed in a state of withdrawal by actively inhibiting the upregulation of endogenous neurosteroids and/or causing the downregulation of endogenous neurosteroids. As previously described, this treatment step may be achieved by a) avoiding stress-inducing activities, b) avoiding neurosteroid production enhancing activities, c) avoiding heightened progesterone levels in a patient, d) actively modulating a woman's progesterone levels, or e) actively modulating a male's or female's progesterone levels through the administration of a neurosteroid inhibitor.

i. Other Pre-Treatment Approaches

In one embodiment, at least two weeks prior to treatment with a compound from the class of compounds that selectively modulates $GABA_A$ receptor expression, a patient is prevented from taking any CNS Depressant drugs and a benzodiazepine, such as diazepam, is prescribed at a dose of 15 to 25 mg four times daily. Sufficient additional diazepam is administered to suppress signs of increased withdrawal (e.g., increased pulse, increased blood pressure, or increased perspiration). Once a diazepam dose is reached which suppresses signs of withdrawal, it is continued for 2 more days and then decreased by 10% per day.

It should be appreciated that, regardless of the treatment approach adopted, the patient should cease all pharmacotherapies at least one week prior to the administration of a compound from the class of compounds that modulates GABAA receptor expression.

c. ADMINISTRATION OF A COMPOUND FROM THE CLASS OF COMPOUNDS THAT MODULATES $GABA_A$ RECEPTOR EXPRESSION

Once the pre-treatment protocol has been adhered to and completed, a patient is administered a compound from the class of compounds that modulates $GABA_A$ receptor expression, such as flumazenil, as described above in the general treatment methodology.

d. ADDITIONAL TREATMENT OPTIONS

Once the treatment protocol has been administered, additional treatment options, as described above in the general treatment methodology, may be administered.

e. POST-TREATMENT PHASE OF PROTOCOL

Once the treatment protocol has been administered, a post-treatment protocol is administered, as described above in the general treatment methodology.

f. HYPOTHETICAL TREATMENT EXAMPLE 1

Male, 32 years old, has been using zalpelon for 5 years and, under DSM IV criteria, has been diagnosed as being addicted to zalpelon.

Patient Preparation: Four weeks prior to scheduled treatment, he is initiated on a scheduled finasteride administration of 5 mg per day. Three days prior to scheduled treatment, the

finasteride administration is terminated and the patient is instructed to not engage in any stress-inducing activities or ingest any substances that would likely increase neurosteroid production.

Day 1 of Treatment: Male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 3 of Treatment: Male patient is evaluated to determine if a third day of treatment is necessary. If he continues to report feelings of anxiety or cravings, he is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Male patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, he is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

g. HYPOTHETICAL TREATMENT EXAMPLE 2

Male, 32 years old, has been using zalpelon for 5 years and, under DSM IV criteria, has been diagnosed as being addicted to zalpelon.

Patient Preparation: Four weeks prior to scheduled treatment, he is initiated on a scheduled finasteride administration of 5 mg per day. Two weeks prior to scheduled treatment, he is prevented from taking any CNS Depressant drugs and is prescribed diazepam at a dose of 15 to 25 mg four times daily. Once the diazepam dose that suppresses signs of withdrawal is reached, it is continued for 2 more days and then decreased by 10% per day. Three days prior to scheduled treatment, the finasteride administration is terminated and the patient is instructed to not engage in any stress-inducing activities or ingest any substances that would likely increase neurosteroid production.

Day 1 of Treatment: Male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 3 of Treatment: Male patient is evaluated to determine if a third day of treatment is necessary. If he continues to report feelings of anxiety or cravings, he is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Male patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, he is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

XIII. EXAMPLE 7: PROTOCOL FOR THE TREATMENT OF ANTI-DEPRESSION DRUG WITHDRAWAL

Clinical depression is a health condition with mental and physical components reaching criteria generally accepted by clinicians (described in greater detail below). Physiological symptoms of depression may be due to changes or imbalances of chemicals which transmit information in the brain, called neurotransmitters. Many modern anti-depressant drugs attempt to increase levels of certain neurotransmitters, like serotonin. Further, it has been shown that progesterone and its effects on GABA have been implicated in depression and anti-depressant dependence. Cessation of a CNS drug, such as selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxides inhibitors, may cause withdrawal, an increased total $GABA_A$ receptor α_4 subunits relative to $GABA_A$ receptor α_1 subunits, which in turn, causes anxiety.

Khemraj et al. demonstrated that allopregnanolone plays a role in the anticonvulsant action of fluoxetine, thus supporting the hypothesis that modulation of $GABA_A$ receptors by

neurosteroid metabolites mediates the anticonvulsant action of fluoxetine. In addition, Pinna et al. suggest that pharmacological profiles of fluoxetine and fluvoxamine are correlated with the ability of these drugs to increase the brain and cerebrospinal fluid content of allopregnanolone, a potent positive modulator of GABA action at $GABA_A$ receptors. This further supports that selective serotonin reuptake inhibitors may act via dual pathways, both regulating levels of free serotonin and increasing levels of endogenous neurosteroid, leading to the "addictive" properties of SSRI's.

By taking away the effect of SSRI's on allopregnanolone, it may be possible to treat patients with higher doses of the drug to regulate levels of serotonin, since it has been demonstrated that the allopregnanolone upregulation occurs at lower doses that serotonin regulation.

a. PRE-TREATMENT/PATIENT ASSESSMENT PHASE

As described above, prior to admittance into the treatment program of the present invention, each patient should undergo a pre-treatment analysis. The pre-treatment analysis may be used to determine whether a patient is an optimal candidate for the treatment methodology of the present invention. In addition, the pre-treatment process may be administered to prepare a patient for admittance into the treatment methodology of the present invention.

b. PREPARING A PATIENT FOR TREATMENT WITH THE PROTOCOL OF THE PRESENT INVENTION

i. Placing a Patient in A State of Withdrawal

A patient may be placed in a state of withdrawal by actively inhibiting the upregulation of endogenous neurosteroids and/or causing the downregulation of endogenous neurosteroids. As previously described, this treatment step may be achieved by a) avoiding stress-inducing activities, b) avoiding neurosteroid production enhancing activities, c) avoiding heightened progesterone levels in a patient, d) actively modulating a woman's progesterone levels, or e) actively modulating a male's or female's progesterone levels through the administration of a neurosteroid inhibitor.

c. ADMINISTRATION OF A COMPOUND FROM THE CLASS OF COMPOUNDS THAT MODULATES $GABA_A$ RECEPTOR EXPRESSION

Once the pre-treatment protocol has been adhered to and completed, a patient is administered a compound from the class of compounds that modulates $GABA_A$ receptor expression, such as flumazenil, as described above in the general treatment methodology.

d. ADDITIONAL TREATMENT OPTIONS

Once the treatment protocol has been administered, additional treatment options, as described above in the general treatment methodology, may be administered.

e. POST-TREATMENT PHASE OF PROTOCOL

Once the treatment protocol has been administered, a post-treatment protocol is administered, as described above in the general treatment methodology.

f. HYPOTHETICAL TREATMENT EXAMPLE 1

Male, 32 years old, has been using fluoxetine hydrochloride for 5 years and, experiences anxiogenic symptoms upon withdrawal, similar to those symptoms in the DMS-IV criteria for addiction.

Patient Preparation: Four weeks prior to scheduled treatment, male patient is initiated on a scheduled finasteride administration of 5 mg per day. Three days prior to scheduled treatment, the finasteride administration is terminated and the patient is instructed to not engage in any stress-inducing activities or ingest any substances that would likely increase neurosteroid production, including fluoxetine hydrochloride.

Day 1 of Treatment: Male patient is administered, via infusion, flumazenil in a therapeutically effective quantity of flumazenil of at least 1.0 mg/day. The total dose and rate are modified by the responsible physician based on an evaluation of the patient's heart rate, blood pressure, and subjective reports.

Day 2 of Treatment: Male patient is evaluated to determine if a second day of treatment is necessary. If he continues to report feelings of anxiety or cravings, he is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Day 3 of Treatment: Male patient is evaluated to determine if a third day of treatment is necessary. If he continues to report feelings of anxiety or cravings, he is again administered flumazenil, via infusion, at a rate of at least 1.0 mg/day.

Post-Treatment: Post-completion of treatment phase, patient is prescribed a post-treatment regimen to follow, which includes, but is not limited to, the administration of pharmaceutical compositions, outpatient therapy, a diet program, and an exercise regimen. Male patient is instructed to attend the outpatient treatment center for several months with decreasing frequency [i.e., once a week for the first three months, once every two weeks during the second three months, and once a month during the third three months]. If feelings of anxiety return, he is scheduled to repeat at least one day, and up to three days, of flumazenil treatment.

The above examples are merely illustrative of the many applications of the system of present invention. Although only a few embodiments of the present invention have been

described herein, it should be understood that the present invention might be embodied in many other specific forms without departing from the spirit or scope of the invention. Therefore, the present examples and embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope of the appended claims. All patents, publications and abstracts cited above are incorporated herein by reference in their entirety.

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
ANALGESICS (PAINKILLERS)	OPIATES		
		ALFENTANIL ALFENTA (alfentanil hydrochloride)	FOR USE DURING GENERAL ANESTHESIA SPONTANEOUSLY BREATHING/ ASSISTED VENTILATION: Induction of Analgesia: 8-20 mcg/kg; Maintenance of Analgesia: 3-5 mcg/kg q 5-20 min or 0.5 to 1 mcg/kg/min; Total dose: 8-40 mcg/kg ASSISTED OR CONTROLLED VENTILATION: Incremental Injection (to attenuate response to laryngoscopy and intubation): Induction of Analgesia: 20-50 mcg/kg; Maintenance of Analgesia: 5-15 mcg/kg q 5-20 min; Total dose: Up to 75 mcg/kg. Continuous Infusion: (To provide attenuation of response to intubation and incision): Infusion rates are variable and should be treated to the desired clinical effect. Induction of Analgesia: 50-75 mcg/kg; Maintenance of Analgesia: 0.5 to 3 mcg/kg/min (Average rate 1 to 1.5 mg/kg/min); Total dose: Dependent on duration of procedure. Anesthetic Induction: Induction of Analgesia: 130-245 mcg/kg; Maintenance of Analgesia: 0.5 to 1.5 mcg/kg/min or general anesthetic; Total dose: Dependent on duration of procedure. At these doses, truncal rigidity should be expected and a muscle relaxant should be utilized; Administer slowly (over 3 minutes); Concentration of inhalation agents reduced by 30-50% for initial hour. MONITORED ANESTHESIA CARE (MAC) (For sedated and responsive, spontaneously breathing patients): Induction of M.C. 3-8 mcg/kg; Maintenance of M.C. 3-5 mcg/kg q 5-20 min or 0.25 to 1 mcg/kg/min; Total dose: 3-40 mcg/kg
		BUPRENORPHINE	Administered sublingually as a single daily dose in the range of 12 to 16 mg/day.

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			Buprenorphine is also delivered transdermally in 25, 50, and 75 mcg/hour.
		BUTORPHANOL	This formulation of butorphanol is administered every 3-4 hours either as a nasal spray or injected into the buttock or hip muscle or into a vein. The FDA does not regulate Stadol® in most states.
		CODEINE (also METHYL MORPHINE)	Codeine and codeine-combo preparations are usually taken every 4-6 hours. Adults: 15 to 60 mg every 4 to 6 hours (usual adult dose, 30 mg). Children: 1 Year of Age and Older - 0.5 mg/kg of b.d. weight or 15 mg/m2 of b.d. surface every 4 to 6 hours. 200mg (oral) of codeine is about equal to 30 mg (oral) of morphine.
		CODEINON See Hydrocodone for details.	
		PROPOXYPHENE (DARVOCET)	Acetaminophen (Tylenol) and propoxyphene. It is formulated as a tablet taken every 4 hours by mouth.
		DEXTROPROPOXYPHENE	Oral analgesic potency is one-half to one-third that of codeine, with 65 mg approximately equivalent to about 600 mg of aspirin. Dextropropoxyphene is prescribed for relief of mild to moderate pain.
		HEROIN (DIACETYLMORPHINE)	ILLICIT SUBSTANCE/ NO APPROVED DOSING
		DIHYDROCODEINE	Dihydrocodeine is approximately twice as potent as codeine; this is taken into consideration while dosing dihydrocodeine. Codeine Dosage: For the treatment of mild pain to moderate pain: Adults: 15-60mg PO (oral) every 4-6 hours. For the treatment of non-productive cough: Adults: 10-20mg PO (oral) every 4-6 hours. For the treatment of diarrhoea: Adults: 30mg PO (oral)
		FENTANYL	Route of administration: patch, injected, oral transmucosal. The patch is usually changed every 72 hours or as directed by

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			physician. Fentanyl (DURAGESIC®) should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC® 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg oral hydromorphone daily, or an equianalgesic dose of another opioid.
		HYDROCODONE DIHYDROCODEINONE	Five mg of hydrocodone is equivalent to 30 mg of codeine when administered orally. Also, a dose of 15 mg (1/4 gr) of hydrocodone is equivalent to 10 mg (1/6 gr) of morphine. The typical therapeutic dose of 5 to 10 mg is pharmacologically equivalent to 30 to 60 mg of oral codeine.
		HYDROMORPHONE	Dilaudid® is formulated as oral tablets and liquid, rectal suppository, intra-muscular (buttock or hip muscle) injection, and intravenous (I.V.) solution. Dosing is every 4-6 hours for the oral forms and every 6-8 hours for the suppository. An I.V. drip allows for continuous administration and around-the-clock pain relief. It can be given intravenously, intramuscularly, rectally, or orally.
		LAAM Levomethadyl Acetate Hydrochloride, also known as Levo-alpha-acetylmethadol or Levacetylmethadol (LAM)	The initial dose street addicts should be 20 to 40 mg. Each subsequent dose, administered at 48- or 72-hour intervals, may be adjusted in increments of 5 to 10 mg until a pharmacokinetic and pharmacodynamic steady-state is reached. Patients dependent on methadone may require higher initial doses.
		METHADONE	It comes as tablets, dispersible tablets, liquid, and liquid concentrate. Patients take it every 3-4 hours for severe pain and every 6-8 hours for chronic pain.
		MORPHINE and	NO APPROVED DOSING FOR PURE MORPHINE. SEE

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
		MORPHINONE	SALTS.
		MORPHINE SULFATE	MS Contin® comes in the form of tablets, capsules, liquid, and rectal suppository, which are taken every 4 hours. Long-acting tablets and capsules can be taken every 8-12 hours or 1-2 per day, respectively.
		OPIUM (NATURAL)	ILLEGAL – NO FDA RECOMMENDED USAGE
		OXYCODONE	OxyContin® comes in liquid and tablet forms taken every 6 hours. Long-acting tablets are available to take every 12 hours.
		OXYMORPHONE	Injection: Subcutaneous or intramuscular administration: initially 1 mg to 1.5 mg, repeated every 4 to 6 hours as needed. Intravenous: 0.5 mg initially. For analgesia during labor 0.5 mg to 1 mg intramuscularly is recommended. Rectal Suppositories: One suppository, 5 mg, every 4 to 6 hours.
		PETHIDINE (MEPERIDINE)	Adults: The usual dosage is 50 mg to 150 mg intramuscularly, subcutaneously, or orally, every 3 or 4 hours as necessary. Children: The usual dosage is 0.5 mg/lb to 0.8 mg/lb intramuscularly, subcutaneously, or orally up to the adult dose, every 3 or 4 hours as necessary.
		REMIFENTANIL	During Induction of Anesthesia: ULTIVA should be administered at an infusion rate of 0.5 to 1 mcg/kg/min with a hypnotic or volatile agent for the induction of anesthesia. If endotracheal intubation is to occur less than 8 minutes after the start of the infusion of ULTIVA, then an initial dose of 1 mcg/kg may be administered over 30 to 60 seconds. For exact dosing for induction, maintenance and continuation of general anesthesia, including special cases, please refer to FDA Documents.
		SUFENTANIL	Not more than 3 total doses. Each dose must be at least one hour apart.
		THEBAINE	Thebaine is not used therapeutically, but is converted into a variety

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	**SECONDARY DRUG CLASS**	**EXEMPLARY DRUG LISTING**	**DOSAGE**
			of compounds including codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone, nalbuphine, naloxone, naltrexone, buprenorphine and etorphine. It is controlled in Schedule II of the Controlled Substances Act as well as under international law.
		TRAMADOL	Tramadol is approximately 10% as potent as morphine, when given by the IV/IM route. Oral doses range from 50–400 mg daily, with up to 600 mg daily when given IV/IM.
	TETRAHYRDOC ANNIBINOL /THC THC and some other cannibinoids, have analgesic properties.	MARINOL	Marinol: widely available through prescription. It comes in the form of a pill and is also being studied by researchers for suitability via other delivery methods, such as an inhaler or patch. The active ingredient of Marinol is synthetic THC, which has been found to relieve the nausea and vomiting associated with chemotherapy and the loss of appetite associated with various other disease states.
		THC – Herbal and Synthetic	ILLICIT SUBSTANCE – NO FDA-APPROVED DOSAGE

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
		KETAMINE	Intravenous Route: The initial dose of ketamine administered intravenously may range from 1 mg/kg to 4.5 mg/kg (0.5 to 2 mg/lb). The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg (1 mg/lb).Intramuscular Route: The initial dose of ketamine administered intramuscularly may range from 6.5 to 13 mg/kg (3 to 6 mg/lb). A dose of 10 mg/kg (5 mg/lb) will usually produce 12 to 25 minutes of surgical anesthesia.
BARBITURATES			
		ALLOBARBITAL	MRTD (Maximum Recommended Therapeutic Dose) - 3.33000 mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg.
		AMOBARBITAL	Defined Daily Dose - 0.1 g, No data available from FDA.
		APROBARBITAL	MRTD (Maximum Recommended Therapeutic Dose) - 2.67000 mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg. For trouble in sleeping: Adults-40 to 160 milligrams (mg) at bedtime. For daytime sedation: Adults-40 mg three times a day.
		BARBEXACLONE	100mg of barbexaclone is equivalent to 60mg of phenobarbital.
		BARBITAL (VERONAL)	MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg - 10.00000
		BUTABARBITAL	Butabarbital Oral is used to treat the following: Severe Anxiety, Additional Agent to Induce General Anesthesia, Abnormal Trouble Sleeping MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing

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			60 kg – 2.000
		BUTALBITAL Butalbital, 5-allyl-5-isobutylbarbituric acid.	MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg – 5.000 COMMON COMBINATIONS INCLUDE: • Butalbital and acetaminophen • butalbital, acetaminophen, and caffeine • butalbital and aspirin • butalbital, aspirin, and caffeine
		BUTOBARBITAL (SONERYL)	50 mg of Butobarbital is equivalent to 10 mg of Diazepam; Acc. to Nordic Statistics on Medicines, the Defined Daily Dose of Butobarbital is 150 mg. No data available from FDA.
		CYCLOBARBITAL	MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg – 6.67000
		ETHALLOBARBITAL	N.A.
		HEPTABARBITAL	Defined Daily Dose - 0.2 g, No data available from FDA.
		HEXOBARBITAL	MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg – 8.33000
		MEPHOBARBITAL (METHYLPHENOBARBITAL)	Epilepsy: Average dose for adults: 400 mg to 600 mg daily; children under 5 years: 16 mg to 32 mg three or four times daily; children over 5 years: 32 mg to 64 mg three or four times daily. Sedation: Adults: 32 mg to 100 mg optimum dose, 50 mg three to four times daily. Children: 16 mg to 32 mg three to four times daily.
		METHARBITAL	
		METHOHEXITAL	For induction of anesthesia, a 1% solution is administered at a rate of about 1 mL/5 seconds. The dose required for induction may range from 50 to 120 mg or more but averages about 70 mg. The

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			usual dosage in adults ranges from 1 to 1.5 mg/kg. Maintenance of anesthesia may be accomplished by intermittent injections of the 1% solution or, more easily, by continuous intravenous drip of a 0.2% solution. Intermittent injections of about 20 to 40 mg (2 to 4 mL of a 1% solution) may be given as required, usually every 4 to 7 minutes. For continuous drip, the average rate of administration is about 3 mL of a 0.2% solution/minute (1 drop/second).
		PENTOBARBITAL	The usual adult dosage of NEMBUTAL Sodium Solution is 150 to 200 mg as a single IM injection; the recommended pediatric dosage ranges from 2 to 6 mg/kg as a single IM injection not to exceed 100 mg. The rate of IV injection should not exceed 50 mg/min for pentobarbital sodium.
		PHENOBARBITAL	Pediatric Oral Dosage (as recommended by the American Academy of Pediatrics): Preoperative: 1 to 3 mg/kg. Adult Oral Dosage: Daytime sedative: 30 to 120 mg daily in 2 to 3 divided doses. Bedtime hypnotic: 100 to 320 mg. Anticonvulsant: 50 to 100 mg 2 to 3 times daily.
		PRIMIDONE	Adult Dosage: Patients 8 years of age and older who have received no previous treatment may be started on primidone according to the following regimen using Primidone 250 mg tablets. Days 1-3: 100 to 125 mg at bedtime; Days 4-6: 100 to 125 mg b.i.d.; Days 7-9: 100 to 125 mg t.i.d.; Day 10-maintenance; 250 mg t.i.d. For most adults and children 8 years of age and over, the usual maintenance dosage is three to four 250 mg primidone tablets daily in divided doses (250 mg t.i.d. or q.i.d.). If required, an increase to

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			five or six 250 mg tablets daily may be made but daily doses should not exceed 500 mg q.i.d. Pediatric Dosage: For children under 8 years of age, the following regimen may be used: Days 1-3: 50 mg at bedtime; Days 4-6: 50 mg b.i.d.; Days 7-9: 100 mg b.i.d.; Day 10-maintenance: 125. mg t.i.d. to 250 mg t.i.d. For children under 8 years of age, the usual maintenance dosage is 125 to 250 mg three times daily, or 10-25 mg/kg/day in divided doses.
		SECOBARBITAL	For oral dosage form (capsules): For trouble in sleeping: Adults-100 milligrams (mg) at bedtime. Children-Dose must be determined by your doctor. For daytime sedation: Adults-30 to 50 mg three or four times a day. Children-Dose is based on body weight or size and must be determined by your doctor. The usual dose is 2 mg per kilogram (kg) (0.9 mg per pound) of body weight three times a day. For sedation before surgery: Adults-200 to 300 mg one or two hours before surgery. Children-Dose is based on body weight and must be determined by your doctor. The usual dose is 2 to 6 mg per kg (0.9 to 2.7 mg per pound) of body weight one or two hours before surgery. However, the dose is usually not more than 100 mg. For injection dosage form: For trouble in sleeping: Adults-100 to 200 mg injected into a muscle, or 50 to 250 mg injected into a vein. Children-Dose is based on body weight or size and must be determined by your doctor. The usual dose is 3 to 5 mg per kg (1.4 to 2.3 mg per pound) of body weight, injected into a muscle. However, the dose is usually not more than 100 mg. For sedation before dental procedures: Adults-Dose is based on body weight and must be determined by your doctor. The usual dose is 1.1 to 2.2 mg per kg (0.5 to 1 mg per pound) of body weight, injected into a

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			muscle ten to fifteen minutes before the procedure. Children-Dose must be determined by your dentist. For sedation before a nerve block: Adults-100 to 150 mg, injected into a vein. For sedation before surgery: Children-Dose is based on body weight and must be determined by your doctor. The usual dose is 4 to 5 mg per kg (1.8 to 2.3 mg per pound) of body weight, injected into a muscle.
		TALBUTAL (Lotusate®), also called 5-allyl-5-sec-butylbarbituric acid.	MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg – 3.30000
		THIOBARBITAL	N.A.
		THIOPENTAL Pentothal (Thiopental Sodium for Injection, USP).	Use in Anesthesia: Moderately slow induction can usually be accomplished in the "average" adult by injection of 50 to 75 mg (2 to 3 mL of a 2.5% solution) at intervals of 20 to 40 seconds, depending on the reaction of the patient. Once anesthesia is established, additional injections of 25 to 50 mg can be given whenever the patient moves. Use in Convulsive States: For the control of convulsive states following anesthesia (inhalation or local) or other causes, 75 to 125 mg (3 to 5 mL of a 2.5% solution) should be given as soon as possible after the convulsion begins. Convulsions following the use of a local anesthetic may require 125 to 250 mg of Pentothal given over a ten minute period. Use in Psychiatric Disorders: For narcoanalysis and narcosynthesis in psychiatric disorders, premedication with an anticholinergic agent may precede administration of Pentothal. After a test dose, Pentothal (Thiopental Sodium for Injection, USP) is injected at a slow rate of 100 mg/mm (4 mL/min of a 2.5% solution) with the patient counting backwards from 100. Shortly after counting becomes confused but before actual sleep is produced, the injection

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			is discontinued. Allow the patient to return to a semidrowsy state where conversation is coherent. Alternatively, Pentothal may be administered by rapid I.V. drip using a 0.2% concentration in 5% dextrose and water. At this concentration, the rate of administration should not exceed 50 mL/min.
		VINBARBITAL Vinbarbital (5-Ethyl-5-(1-methyl-1-butenyl)barbituric acid).	MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg – 3.33000
		VINYLBITAL Butylvinyl	Defined Daily Dose - 0.15 g, No data available from FDA.
BENZODIAZEPINES			
		ALPRAZOLAM	Dosage Depends on Disorder: Oral (For anxiety or nervous tension): Start: 0.25 mg to 0.5 mg 3 times daily. Maximum: 4 mg in 24 hours. Oral (For panic disorder): Start: 0.5 mg 3 times daily. Increases: 1 mg daily in 3 to 4 day intervals. Maximum: 10 mg in 24 hours.
		BROMAZEPAM	Not commercially available in the U.S.
		BROTIZOLAM	Brotizolam is not approved for sale in the United States or Canada.
		CAMAZEPAM	Defined Daily Dose - 30 mg, No data available from FDA.
		CHLORDIAZEPOXIDE	For relief of mild and moderate anxiety disorders and symptoms of anxiety: 5 mg or 10 mg, 3 or 4 times daily. For relief of server anxiety disorders and symptoms of anxiety: 20 mg or 25 mg, 3 or 4 times daily. Geriatric patients or in the presence of debilitating disease: 5 mg, 2 to 4 times daily.
		CLONAZEPAM	Seizure Disorders: Adults: The initial dose for adults with seizure disorders should not exceed 1.5 mg/day divided into three doses.

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			Dosage may be increased in increments of 0.5 to 1 mg every 3 days until seizures are adequately controlled or until side effects preclude any further increase. Maintenance dosage must be individualized for each patient depending upon response. Maximum recommended daily dose is 20 mg. Pediatric Patients: Klonopin is administered orally. In order to minimize drowsiness, the initial dose for infants and children (up to 10 years of age or 30 kg of body weight) should be between 0.01 and 0.03 mg/kg/day but not to exceed 0.05 mg/kg/day given in two or three divided doses. Dosage should be increased by no more than 0.25 to 0.5 mg every third day until a daily maintenance dose of 0.1 to 0.2 mg/kg of body weight has been reached, unless seizures are controlled or side effects preclude further increase. Whenever possible, the daily dose should be divided into three equal doses. If doses are not equally divided, the largest dose should be given before retiring. Panic Disorder: Adults: The initial dose for adults with panic disorder is 0.25 mg bid. An increase to the target dose for most patients of 1 mg/day may be made after 3 days. The recommended dose of 1 mg/day is based on the results from a fixed dose study in which the optimal effect was seen at 1 mg/day. Higher doses of 2, 3 and 4 mg/day in that study were less effective than the 1 mg/day dose and were associated with more adverse effects. Nevertheless, it is possible that some individual patients may benefit from doses of up to a maximum dose of 4 mg/day, and in those instances, the dose may be increased in increments of 0.125 to 0.25 mg bid every 3 days until panic disorder is controlled or until side effects make further increases undesired. To reduce the inconvenience of somnolence, administration of one dose at bedtime may be

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			desirable. Treatment should be discontinued gradually, with a decrease of 0.125 mg bid every 3 days, until the drug is completely withdrawn.
		CLOTIAZEPAM	Clotiazepam is not approved for sale in the United States or Canada
		CLORAZEPATE	ORAL: START: 15 mg/daily INCREASES: As needed. MAXIMUM: 60 mg in 24 hours
		CLOXAZOLAM	Cloxazolam is not approved for sale in the United States or Canada.
		DELORAZEPAM	Defined Daily Dose - 3 mg, No data available from FDA.
		DIAZEPAM	Management of Anxiety Disorders and Relief of Symptoms of Anxiety: Depending upon severity of symptoms – 2 mg to 10 mg, 2 to 4 times daily. Symptomatic Relief in Acute Alcohol Withdrawal: 10 mg, 3 or 4 times during the first 24 hours, reducing to 5 mg, 3 or 4 times daily as needed. Adjunctively for Relief of Skeletal Muscle Spasm: 2 mg to 10 mg, 3 or 4 times daily. Adjunctively in Convulsive Disorders. 2 mg to 10 mg, 2 to 4 times daily. Geriatric Patients, or in the presence of debilitating disease: 2 mg to 2.5 mg, 1 or 2 times daily initially; increase gradually as needed and tolerated. Pediatric patients: Because of varied responses to CNS-acting drugs, initiate therapy with lowest dose and increase as required. Not for use in pediatric patients under 6 months. 1 mg to 2.5 mg, 3 or 4 times daily initially; increase gradually as needed and tolerated.
		ESTAZOLAM	The recommended initial dose for adults is 1 mg at bedtime; however, some patients may need a 2 mg dose. In healthy elderly

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			patients, 1 mg is also the appropriate starting dose, but increases should be initiated with particular care. In small or debilitated older patients, a starting dose of 0.5 mg, while only marginally effective in the overall elderly population, should be considered.
		ETIZOLAM	Etizolam is not approved for sale in the United States or Canada.
		FLUDIAZEPAM	Defined Daily Dose – 0.75 mg, No data available from FDA.
		FLUNITRAZEPAM	Flunitrazepam has not been approved by the Food and Drug Administration for medical use in the United States. It is available only by private prescription in the United Kingdom
		FLURAZEPAM	Dosage should be individualized for maximal beneficial effects. The usual adult dosage is 30 mg before retiring. In some patients, 15 mg may suffice. In elderly and/or debilitated patients, 15 mg is usually sufficient for a therapeutic response
		HALAZEPAM	For oral dosage form (tablets): For anxiety: Adults-20 to 40 milligrams (mg) three or four times a day. Children younger than 18 years of age-Use and dose must be determined by your doctor. Older adults-20 mg one or two times a day.
		HALOXAZOLAM	Defined Daily Dose – 7.50 mg, No data available from FDA.
		LOPRAZOLAM	It is available in 1mg tablets. The usual adult dose is 1 - 2 mg at bedtime, the higher dose being recommended for patients who have previously been treated with benzodiazepines for severe persistent insomnia. An initial dose of 0.5 mg – 1.0 mg is recommended in elderly and debilitated patients.
		LOREZEPAM	The usual range is 2 to 6 mg/day given in divided doses, the largest dose being taken before bedtime, but the daily dosage may vary from 1 to 10 mg/day. For anxiety, most patients require an initial dose of 2 to 3 mg/day given b.i.d. or t.i.d.

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			For insomnia due to anxiety or transient situational stress, a single daily dose of 2 to 4 mg may be given, usually at bedtime. For elderly or debilitated patients, an initial dosage of 1 to 2 mg/day in divided doses is recommended, to be adjusted as needed and tolerated.
		MEDAZEPAM	Defined daily dose as used in the Nordic Statistics on Medicines – 20 mg; No data available from FDA.
		MIDAZOLAM	For preoperative sedation/anxiolysis/amnesia. Intramuscular -The recommended premedication dose of VERSED for good risk (ASA Physical Status I & II) adult patients below the age of 60 years is 0.07 to 0.08 mg/kg IM (approximately 5 mg IM) administered up to 1 hour before surgery. The dose must be individualized and reduced when IM VERSED is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients who have received concomitant narcotics or other CNS depressants. In a study of patients 60 years or older, who did not receive concomitant administration of narcotics, 2 to 3 mg (0.02 to 0.05 mg/kg) of VERSED produced adequate sedation during the preoperative period. The dose of 1 mg IM VERSED may suffice for some older patients if the anticipated intensity and duration of sedation is less critical. Intravenous - VERSED 1 mg/mL formulation is recommended for sedation/anxiolysis/amnesia for procedures to facilitate slower injection. Both the 1 mg/mL and the 5 mg/mL formulations may be diluted with 0.9% sodium chloride or 5% dextrose in water. 1. Healthy Adults Below the Age of 60: Titrate slowly to the desired effect (eg, the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 2.5 mg should be given

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			over a period of at least 2 minutes. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint. If narcotic premedication or other CNS depressants are used, patients will require approximately 30% less VERSED than unpremedicated patients. 2. Patients Age 60 or Older, and Debilitated or Chronically Ill Patients: Titrate slowly to the desired effect (eg, the initiation of slurred speech). Some patients may respond to as little as 1 mg. No more than 1.5 mg should be given over a period of no less than 2 minutes. If additional titration is necessary, it should be given at a rate of no more than 1 mg over a period of 2 minutes, waiting an additional 2 or more minutes each time to fully evaluate the sedative effect. Total doses greater than 3.5 mg are not usually necessary. Epileptic fit: 10mg intranasally or as buccal.
		NIMETAZEPAN	MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg - 0.08330
		NITRAZEPAM	Nitrazepam shortens the time required to fall asleep and lengthens the duration of this sleep. Typically, it may work within an hour and allow the individual to maintain sleep for 4 to 6 hours. It is no longer available in the United States.
		NORDAZEPAM	Defined Daily Dose – 15 mg, No data available from FDA.
		OXAZEPAM	Mild to moderate anxiety, with associated tension, irritability, agitation or related symptoms of functional origin or secondary to organic disease: 10 to 15 mg, 3 or 4 times daily. Severe anxiety syndromes, agitation, or anxiety associated with depression: 15 to 30 mg, 3 or 4 times daily. Older patients with anxiety, tension, irritability, and agitation: Initial dosage – 10 mg, 3 times daily. If necessary, increase

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			cautiously to 15 mg, 3 or 4 times daily. Alcoholics with acute inebriation, tremulousness, or anxiety on withdrawal: 15 to 30 mg, 3 or 4 times daily.
		OXAZOLAM	20 mg is equivalent to 10 mg of Diazepam. MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg - 1.0000
		PINAZEPAM	MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg - 0.33300
		PRAZEPAM	MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg - 1.00000
		QUAZEPAM	The recommended initial dose is 15 milligrams daily. Your doctor may later reduce this dosage to 7.5 milligrams.
		TEMAZEPAM	While the recommended usual adult dose is 15 mg before retiring, 7.5 mg may be sufficient for some patients, and others may need 30 mg. In transient insomnia, a 7.5 mg dose may be sufficient to improve sleep latency. In elderly and/or debilitated patients it is recommended that therapy be initiated with 7.5 mg until individual responses are determined.
		TETRAZEPAM	Defined Daily Dose – 100 mg, No data available from FDA.
		TOFISOPAM	Tofisopam is not approved for sale in the US or Canada. However, Vela Pharmaceuticals of New Jersey is developing the D-enantiomer (dextofisopam) as a treatment for IBS.
		TRIAZOLAM	The recommended dose for most adults is 0.25 mg before retiring. A dose of 0.125 mg may be found to be sufficient for some patients (e.g., low body weight). A dose of 0.5 mg should be used only for exceptional patients who do not respond adequately to a trial of a

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			lower dose since the risk of several adverse reactions increases with the size of the dose administered. A dose of 0.5 mg should not be exceeded. In geriatric and/or debilitated patients the recommended dosage range is 0.125 mg to 0.25 mg. Therapy should be initiated at 0.125 mg in this group and the 0.25 mg dose should be used only for exceptional patients who do not respond to a trial of the lower dose. A dose of 0.25 mg should not be exceeded in these patients.

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
HORMONES/CONTRACEPTIVES			
	ESTROGENS include: ethinyl estradiol and mestranol. PROGESTERONES include: Norethynodrel, norethindrone, norethindrone acetate, norgestimate, desogestrel, ethyndiol diacetate, norgestrel, levonorgestrel, drospirenone.	See other columns.	Hormone-Containing Contraceptives General Dosing Information: Combination contraceptives are those containing both estrogen and progesterone. Several types of combination birth control pills exist, including monophasic pills, biphasic pills, triphasic pils, and 91-day cycle pills. USE: Starting at the beginning of the pill pack, take one each day at approximately the same time every day to increase efficacy. WHEN TO BEGIN: The following regimens may be used when first starting on birth control pills: • Taking one pill each day, starting on the fifth day after the onset of menses and continuing for 21 or 28 days. • Beginning pills on the first day of the menstrual period. • Beginning on the first Sunday after the menstrual period starts. 21-DAY PILL CONTAINER: Take one pill daily for 21 days, stop for 7 days, then resume taking the pills with a new container of pills. 28-DAY PILL CONTAINER: Start with the first pill in the container and swallow one daily for 28 days. Do not stop taking the pills. The last 7 ae usually placebos. 91-DAY PILL CONTAINER: One pill is taken daily for 12 weeks, followed by one week of inactive pills. A menstrual period occurs during the week of inactive pills, so women on this regimen have a period only once every three months. Monophasic Pills: Alesse, Brevicon, Demulen, Desogen, Levlen, Levlite, Loestrin, Microgestin, Modicon, Necon, Nelova, Nordette, Norinyl, Ortho-Cept, Ortho-Cyclen, Ortho-Novum, Ovcon, Ovral,

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			Yasmin, Zovia. Monophasic pills have a constant dose of estrogen and progestin in each of the hormonally active pills through the entire cycle (21 days of ingesting active pills). Several of the brands listed above may be available in several strengths of estrogen or progesterone, from which doctors choose according to a woman's individual needs. Biphasic Pills: Jenest, Mircette, Necon 10/11, Nelova 10/11, and Ortho-Novum 10/11 Biphasic Pills typically contain two different progesterone doses. The progesterone dose is increased about halfway through the cycle. Triphasic Pills: Cyclessa, Estrostep, Ortho-Novum 7/7/7, Ortho Tri-Cyclen, Ortho Tri-Cyclen LO, Tri-Levlen, Tri-Norinyl, Triphasil, Trivora Triphasic pills gradually increase the dose of estrogen during the cycle (some pills also increase the progesterone dose). Three different increasing pill doses are contained in each cycle. Ninety-One Day BCP: Levonorgestrel/ethynl estradiol (Seasonale) These pills are monophasic birth control pills that have been approved for use on a daily basis for 84 days without interruption. Users have fewer schedules menstrual cycles (only 1 period every 3 months). Topical Contraceptive Patch: Norelgestromin/ethinyl estradiol (Ortho Evra) A new patch is applied on the same day of the week, each week for three weeks in a row. The first patch is applied on either the first day of the menstrual period or on the Sunday following menses. On the fourth week, no patch is applied. Another 4-week cycle is started by applying a new patch following the 7-day patch free period.

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			Long-Acting, Injectable, Progesterone-Only Contraceptives: Medroxyprogesterone acetate (Depo-Provera) The first injection is given within five days following the onset of menstruation. After that, an injection is needed every 11-13 weeks. Unlike pills, the injection works right away. Progesterone-Only Pills: Norethindrone (Nor-QD) Progesterone-only pills, also known as mini-pills, are not used widely in the US. POPs are ingested once daily, every day. They may be started on any day, and there are no pill-free days or different colored pills to track. Since progesterone is the only hormonal ingredient, estrogen-related side effects are avoided. Vaginal Ring: Etonogestrel/ethinyl estradiol (NuvaRing) The ring is self-inserted into the vagina. Exact positioning is not required for it to be effective. The vaginal ring must be inserted within 5 days of the onset of the menstrual period, even if bleeding is still occurring. During the first cycle, an additional method of contraception is recommended. The ring remains in place continuously for three weeks. It is removed for one week. The next ring is then inserted one week after the last ring was removed.
NON-BENZODIAZEPINE ANXIOLYTICS SEDATIVES HYPNOTICS TRANQUILIZERS			
		CHLORAL HYDRATE	The usual hypnotic dose is 500 mg to 1 g, taken 15 to 30 minutes

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DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			before bedtime or ½ hour before surgery. The usual sedative dose is 250 mg three times daily after meals. Generally, single doses or daily dosage should not exceed 2 g.
		CHLORAL BETAINE	Chloral betaine 707 mg (chloral hydrate 414 mg) Dose: 1–2 tablets with water or milk at bedtime, max. 5 tablets (2 g chloral hydrate) daily
		CLOMETHIAZOLE (or CHLOMETHIAZOLE)	MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg - 6.40000
		DIPHENHYDRAMINE	Adults: 25 to 50 mg three or four times daily. Children (over 20 lb): 12.5 to 25 mg three to four times daily. Maximum daily dosage not to exceed 300 mg.
		ETHCHLORVYNOL	Due to the problems it can cause, it is unusual for ethchlorvynol to be prescribed for periods exceeding seven days.
		PROMETHIAZINE.	Administration of 12.5 to 25 mg Phenergan by the oral route or by rectal suppository at bedtime will provide sedation in children. Adults usually require 25 to 50 mg for nighttime, presurgical, or obstetrical sedation.
		ZALPELON (imidazopyridine)	The recommended dose of Sonata for most nonelderly adults is 10 mg. For certain low weight individuals, 5 mg may be a sufficient dose. Although the risk of certain adverse events associated with the use of Sonata appears to be dose dependent, the 20 mg dose has been shown to be adequately tolerated and may be considered for the occasional patient who does not benefit from a trial of a lower dose.
		ZOLPIDEM (pyrazolopyrimidine)	The recommended dose for adults is 10 mg immediately before bedtime, indicated for the short-term treatment of insomnia.
		ZOPICLONE	The usual dose is 7.5 mg at bedtime. This dose should not be exceeded. Depending on clinical response and tolerance, the dose

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			may be lowered to 3.75 mg. Geriatrics: In the elderly and/or debilitated patient an initial dose of 3.75 mg at bedtime is recommended. The dose may be increased to 7.5 mg if the starting dose does not offer adequate therapeutic effect.
STIMULANTS			
		CAFFEINE	Caffeine Oral is used to treat the following: Absence of Breathing in the Newborn Caffeine Oral may also be used to treat: Drowsiness, Low Energy Caffeine citrate is indicated for the short term treatment of apnea of prematurity in infants between 28 and <33 weeks gestational age. Caffeine Citrate: Loading Dose - 20 mg/ kg Maintenance Dose - 5 mg/ kg
		NICOTINE	NICOTROL Inhaler is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. NICOTROL Inhaler therapy is recommended for use as proof of a comprehensive behavioral smoking cessation program. It it supplied as 42 cartridges each containing 10 mg (4 mg is delivered) nicotine. Initial Treatment: Up to 12 Weeks : 6 -16 cartridges/day Gradual Reduction (if needed) - 6 -12 Weeks: No tapering strategy has been shown to be superior to any other in clinical studies.
OTC MEDICATIONS			
		DEXTROMETHORPHAN	Now prescription only in the United States. MRTD (Maximum Recommended Therapeutic Dose) in mg/kg-

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			body weight (bw)/day based upon an average adult weighing 60 kg - 2.00000
MISCELLANEOUS			
		GHB Gamma-hydroxybutyrate	It has been used as a general anesthetic, and a hypnotic in the treatment of insomnia. GHB has also been used to treat clinical depression, and improve athletic performance. In the US, the FDA permits the use of GHB to reduce the number of cataplexy attacks in patients with narcolepsy. In Italy, GHB is used for the treatment of alcoholism (50 to 100 mg per kg per day, in 3 or more divided doses), both for acute alcohol withdrawal and medium to long term detoxification. LD50 of GHB is estimated to be between 1100mg/kg and 2000 mg/kg in rodents and is almost certainly lower in humans.
		MEPROBROMATE	Meprobromate is available in 200 mg and 400 mg tablets for oral administration. Symptoms of meprobromate overdose include coma, drowsiness, loss of muscle control, severly impaired breathing, shock, sluggishness, and unresponsiveness. Death has been reported with ingestion of as little as 12 g of meprobromate and survival with as much as 40g.
		METHQUALONE	In the United States, the marketing of methaqualone pharmaceutical products stopped in 1984, and methaqualone was transferred to Schedule I of the CSA.
		NITROUS OXIDE	Nitrous Oxide is a weak general anesthetic, and is generally not used alone. It has a very low short-term toxicity and is an excellent analgesic. In general anesthesia it is often used in a 2:1 ratio with oxygen in addition to more powerful general anesthetic agents. Possession of nitrous oxide is illegal in most localities in the United

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			States for the purposes of inhaling or ingesting if not under the care of a physician or dentist.
		PCP Phencyclidine	Not available for medicinal use.
HERBAL MEDICINALS		VALERIAN ROOT (Valeriana officinalis, Valerianaceae)	Dosing not regulated/approved by FDA. Large doses are known to cause withdrawal symptoms when stopped, as it is mildly addictive. Those with liver disease are advised not to use valerian. Valerian is the source of valeric acid.
		SALVINORIN A Salvinorin A is the main active psychotropic constituent of the plant Salvia divinorum (diviner's sage, Mexican mint).	N.A. Salvinorin A is a dissociative hallucinogenic compound that is active at the extremely low doses of 0.2 - 0.5 mg, second only to LSD in quantitative potency, making it the most potent naturally occurring drug known to date. A dose of 200 to 500 micrograms produces profound hallucinations when smoked. Its' effects in the open field test in mice and loco motor activity tests in rats are similar to mescaline.
		ST. JOHN'S WORT Refers to the species Hypericum perforatum.	The dosage of St John's wort preparations vary greatly between formulations, due to variability in the plant source and preparation processes. The doses of St. John's wort extract used in clinical trials generally range from 350 to 1800 mg daily (equivalent to 0.4 to 2.7 mg hypericin depending on the preparation). The recommended dosage for various forms of St John's wort as recommended by the British Herbal Medicine Association Scientific Committee (1983) are as follows:dried herb: 2-4 g or by infusion three times daily liquid extract 2-4 mL (1:1 in 25% alcohol) three times daily tincture 2-4mL (1:10 in 45% alcohol) three times daily

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
ANTI-DEPRESSION DRUGS			
		CITALOPRAM HBR (CELEXA)	Celexa (citalopram HBr) is indicated for the treatment of depression. Celexa (citalopram HBr) should be administered at an initial dose of 20 mg once daily, generally with an increase to a dose of 40 mg/day. Dose increases should usually occur in increments of 20 mg at intervals of no less than one week
		ESCITALOPRAM OXALATE LEXAPRO™	LEXAPRO (escitalopram) is indicated for the treatment of major depressive disorder and Generalized Anxiety Disorder (GAD). The recommended dose of LEXAPRO is 10 mg once daily.
		FLUOXETINE HYDROCHLORIDE	Prozac is indicated for the treatment of: Major Depressive Disorder: a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. The maximum fluoxetine dose should not exceed 80 mg/day. Obsessive Compulsive Disorder: a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. The maximum fluoxetine dose should not exceed 80 mg/day. Bulimia Nervosa: the recommended dose is 60 mg/day, administered in the morning. Panic Disorder: Treatment should be initiated with a dose of 10 mg/day. After 1 week, the dose should be increased to 20 mg/day.
		PAROXETINE HYDROCHLORIDE	Major Depressive Disorder: The recommended initial dose is 20 mg/day. Some patients not responding to a 20-mg dose may benefit from dose increases, in 10-mg/day increments, up to a maximum of 50 mg/day. Obsessive Compulsive Disorder: The recommended dose of PAXIL in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10-mg/day increments. The maximum dosage should

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			not exceed 60 mg/day. Panic Disorder: The target dose of PAXIL in the treatment of panic disorder is 40 mg/day. The maximum dosage should not exceed 60 mg/day. Social Anxiety Disorder: The recommended and initial dosage is 20 mg/day. Generalized Anxiety Disorder: The recommended starting dosage and the established effective dosage is 20 mg/day. Posttraumatic Stress Disorder: The recommended starting dosage and the established effective dosage is 20 mg/day.
		FLUVOXAMINE MALEATE (LUVOX).	Fluvoxamine is indicated in the treatment of depression and for Obsessive Compulsive Disorder (OCD). The recommended starting dose for LUVOX Tablets in adult patients is 50 mg, administered as a single daily dose at bed time. The maximum therapeutic dose should not to exceed 300 mg per day.
		SERTRALINE HYDROCHLORIDE	Major Depressive Disorder and Obsessive-Compulsive Disorder: ZOLOFT treatment should be administered at a dose of 50 mg once daily. Panic Disorder, Posttraumatic Stress Disorder and Social Anxiety Disorder: ZOLOFT treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily. Premenstrual Dysphoric Disorder: ZOLOFT treatment should be initiated with a dose of 50 mg/day, either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment.
		AMITRIPTYLINE	For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than are other depressive states. Oral Dosage: 75 mg of amitriptyline HCl a day in divided doses. If necessary, this may be increased to a total of 150 mg per day. Intramuscular Dosage: Initially, 20 to 30 mg (2 to 3 ml) four times a day.

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
		DESIPRAMINE HYDROCHLORIDE	Desipramine hydrochloride is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression. The usual adult dose is 100 to 200 mg per day. Dosages above 300 mg/day are not recommended. Not recommended for use in children.
		NORTRIPTYLINE	Nortriptyline HCl is indicated for the relief of symptoms of depression. Endogenous depressions are more likely to be alleviated than are other depressive states. It is not recommended for children. Usual Adult Dose - 25 mg three or four times daily. Doses above 150 mg/day are not recommended. Elderly and Adolescent Patients - 30 to 50 mg/day, in divided doses, or the total daily dosage may be given once a day.
		DULOXETINE HYDROCHLORIDE	Cymbalta is indicated for the treatment of major depressive disorder (MDD) and pain associated with diabetic peripheral neuropathy. Major Depressive Disorder: Cymbalta should be administered at a total dose of 40 mg/day Diabetic Peripheral Neuropathic Pain: Cymbalta should be administered at a total dose of 60 mg/day given once a day
		VENLAFAXINE Effexor	Effexor (venlafaxine hydrochloride) is indicated for the treatment of major depressive disorder. The recommended starting dose for Effexor is 75 mg/day, up to a maximum of 375 mg/day, generally in three divided doses
		PHENELZINE SULFATE	The usual starting dose of Nardil is one tablet (15 mg) three times a day. Maintenance dose may be as low as one tablet, 15 mg, a day or every other day, and should be continued for as long as is required.
		TRANYLCYPROMINE (Parnate)	For the treatment of Major Depressive Episode Without Melancholia. The usual effective dosage is 30 mg per day, usually given in

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			divided doses; may be extended to a maximum of 60 mg per day. When tranylcypromine is withdrawn, monoamine oxidase activity is recovered in 3 to 5 days, although the drug is excreted in 24 hours.
		MIRTAZEPINE	Indicated for the treatment of major depressive disorder. The recommended starting dose for REMERON® (mirtazapine) Tablets is 15 mg/day, up to a maximum of 45 mg/day.
		NEFAZODONE HYDROCHLORIDE SERZONE®	SERZONE (nefazodone hydrochloride) is indicated for the treatment of depression. When deciding among the alternative treatments available for this condition, the prescriber should consider the risk of hepatic failure associated with SERZONE treatment. The recommended starting dose for SERZONE (nefazodone hydrochloride) is 200 mg/day
		TRAZODONE HYDROCHLORIDE DESYREL	DESYREL is indicated for the treatment of depression. An initial dose of 150 mg/day in divided doses is suggested, up to but not in excess of 600 mg/day in divided doses.
		BUPROPION HYDROCHLORIDE WELLBUTRIN (bupropion hydrochloride)	WELLBUTRIN is indicated for the treatment of depression. The usual adult dose is 300 mg/day, given 3 times daily. WELLBUTRIN should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day. When Wellbutrin is used in combination with an SSRI to offset sexual side effects, the usual dose is 75 mg per day.
		Isocarboxazid	The maximum daily dose of isocarboxazid is 60mg.
		Moclobemide	Depression: The initial dose is 300mg daily in 2 or 3 divided doses. Social Phobia: The recommended dose is 600mg daily in 2 or 3 divided doses. A single 300mg dose of moclobemide inhibits 80% of monoamine oxidase A (MAO-A) and 30% of monoamine oxidase B (MAO-B),

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			blocking the decomposition of norepinephrine, serotonin and, to a lesser extent, dopamine. No reuptake inhibition on any of the neurotransmitters occurs.
		Selegiline	10 mg per day administered as divided doses of 5 mg each.
NEUROSTEROID INHIBITORS	5-ALPHA-REDUCTASE INHIBITORS		
		FINASTERIDE	The recommended dosage is 1 mg orally once per day. It may be administered with or without meals. An alternate dosage of 5 mg orally once per day is also included. It may be administered with or without meals. In general, daily use for three months or more is necessary before benefit is observed. Continued use is recommended to sustain benefit, which should be re-evaluated periodically. Withdrawal of treatment leads to reversal of effect within 12 months. In clinical studies, single doses of finasteride up to 400mg and multiple doses of finasteride up to 80 mg/day for three months did not result in adverse reactions.
		DUTASTERIDE	The recommended therapeutic dose of dutasteride is 0.5 mg taken orally once per day. Dutasteride pharmacokinetics has not been investigated in subjects less than 18 years of age. No dose adjustment is necessary in the elderly. In volunteer studies, single doses of dutasteride up to 40 mg (80 times the therapeutic dose) for 7 days have been administered without significant safety concerns. In a clinical study, daily doses of 5 mg (10 times the therapeutic dose) were administered to 60 subjects for 6 months with no additional adverse effects to those seen at therapeutic does of 0.5 mg.

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
		SAW PALMETTO	Tablets/Capsules. A dose of 160 mg twice daily or 320 milligrams daily (containing 80% to 90% liposterolic content) for up to 11 months has been taken by mouth. Higher doses may be used under medical supervision. Berries. A dose of one to two grams of ground, dried, or whole berries daily has been taken by mouth. Tincture. A dose of two to four milliliters (1:4) three times daily has been taken by mouth. Fluid Extract of Berry Pulp. A dose of one to two milliliters (1:1) three times daily has been taken by mouth. Rectal Suppositories. A dose of 640 milligrams once daily has been used. Rectal use of saw palmetto is no better than taking saw palmetto by mouth. Tea. Tea made from berries may not be effective because the proposed active ingredient does not dissolve in water.
		SPIRONOLACTONE	Treatment protocols may involve continuous spironolactone use at 50mg to 200mg per day or cyclic use; for example, 50mg or 100mg twice daily from the 4^{th} to the 22^{nd} day of the menstrual cycle. Numerous treatment protocols involving spironolactone have been used in different studies, but no particular treatment approach has been shown to be significantly superior.
	3-ALPHA REDUCTASE INHIBITORS		
		INDOMETHACIN	Indomethacin can be administered in the form of capsules (25 mg and 50 mg); sustained-release capsules (75 mg); a suspension (25 mg/ml); or a suppository (50 mg). The recommended dose for adults is 50-200 mg per day split into 2-3 doses.

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	**SECONDARY DRUG CLASS**	**EXEMPLARY DRUG LISTING**	**DOSAGE**
CLASS OF COMPOUNDS THAT SELECTIVELY MODULATES $GABA_A$ RECEPTORS			
		FLUMAZENIL (Romazicon)	ROMAZICON is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose. Reversal of Conscious Sedation: The recommended initial dose of ROMAZICON is 0.2 mg (2 mL) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a second dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). Reversal of General Anesthesia in Adult Patients: The recommended initial dose of ROMAZICON is 0.2 mg (2 mL) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). Management of Suspected Benzodiazepine Overdose in Adult Patients: the recommended initial dose of ROMAZICON is 0.2 mg (2 mL) administered intravenously over 30 seconds. If the desired

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			level of consciousness is not obtained after waiting 30 seconds, a further dose of 0.3 mg (3 mL) can be administered over another 30 seconds. Further doses of 0.5 mg (5 mL) can be administered over 30 seconds at 1-minute intervals up to a cumulative dose of 3 mg.
		MILTIRONE	*The below doses are based on scientific research, publications, traditional use, or expert opinion. Many herbs and supplements have not been thoroughly tested, and safety and effectiveness may not be proven. You should read product labels, and discuss doses with a qualified healthcare provider before starting therapy.* Standardization: There is no widely accepted standardization or well-studied dosing of miltirone, and many different doses are used traditionally. Adults (18 years and older): *By mouth:* Oral dosing has not been studied in well-conducted trials in humans, and therefore no specific dose can be recommended. *By injection:* In research from the 1970s, an 8 milliliter injection of miltirone (16 grams of the herb) was given intravenously (diluted in 500 milliliters of a 10% glucose solution) for up to four weeks for ischemic stroke. Safety and effectiveness have not been established for this route of administration and it cannot not recommended at his time. Children (younger than 18 years): There is not enough scientific evidence to recommend the safe use of danshen in children, and it should be avoided due to potentially serious side effects.
	FLAVONOIDS	They have been classified according to their chemical structure, and are usually subdivided into 6 subgroups: Flavonols, including Quercetin,	N.A.

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
		Kaempferol, Myricetin, Isorhamnetin Flavones, including Luteolin, Apigenin Flavanones, including Hesperetin, Naringenin, Eriodictyol Flavan-3-ols, including (+)-Catechin, (+)-Gallocatechin, (-)-Epicatechin, (-)-*Epigallocatechin, (-)-Epicatechin 3-gallate, (-)-Epigallocatechin 3-gallate, Theaflavin, Theaflavin 3-gallate, Theaflavin 3'-gallate, Theaflavin 3,3' digallate, Thearubigins Isoflavones, including Genistein, Daidzein,Glycitein Anthocyanidins, including Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin	
DOPAMINE	ERGOT		The dose of bromocriptine will be different for different patients.

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			change your dose over several weeks as needed. Teenagers less than 15 years of age and children—Use and dose must be determined by your doctor. For pituitary tumors: Adults and teenagers 15 years of age or older—At first, 1.25 milligrams (mg) two or three times a day taken with meals. Then your doctor may change your dose over several weeks as needed. Teenagers less than 15 years of age and children—Use and dose must be determined by your doctor.
PRESCRIPTION STIMULANTS		METHYLPHENIDATE	Methylphendiate comes in 5 mg, 10mg and 20 mg tablets. ADULTS Tablets: Administer in divided doses, 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patient may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. FOR CHILDREN, DOSAGES SHOULD BE INITIATED IN INCREMENTS Days 1-3: One 5 mg tablet per day Days 4 -6: Two 5 mg tablets per day Add one pill every fourth day until a dosage of 20 mg per day is achieved. Daily dosage above 60 mg is not recommended.
		ADDERALL.	Attention Deficit Disorder with Hyperactivity: Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained. In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours. Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. Narcolepsy: Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response. Narcolepsy seldom occurs in children under 12 years of age; however, when it does, dextroamphetamine sulfate may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.
		DEXEDRINE	Narcolepsy. Usual dose 5 to 60 mg per day in divided doses, depending on the individual patient response. Narcolepsy seldom occurs in children under 12 years of age; however, when it does Dexedrine (dextroamphetamine sulfate) may be used. The suggested initial dose for patients aged 6 to 12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g. insomnia or anorexia), dosage should be reduced. *Spansule* capsules may be used for once-a-day dosage wherever appropriate. With tablets give first dose on awakening, additional doses (1 or 2) at intervals of 4 to 6 hours.

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
AGONISTS	ALKALOIDS		*Follow your doctor's orders or the directions on the label.* The following information includes only the average doses of bromocriptine. *If your dose is different, do not change it* unless your doctor tells you to do so. The number of capsules or tablets that you take depends on the strength of the medicine. Also, *the number of doses you take each day, the time allowed between doses, and the length of time you take the medicine depend on the medical problem for which you are taking bromocriptine.* For *oral* dosage forms (capsules and tablets): For infertility, male hormone problem (male hypogonadism), starting the menstrual cycle (amenorrhea), or stopping abnormal milk secretion from nipples (galactorrhea): Adults and teenagers 15 years of age or older—At first, 1.25 to 2.5 milligrams (mg) once a day taken at bedtime with a snack. Then your doctor may change your dose by 2.5 mg every three to seven days as needed. Doses greater than 5 mg a day are taken in divided doses with meals or at bedtime with a snack. Teenagers less than 15 years of age and children—Use and dose must be determined by your doctor. For lowering growth hormone (acromegaly): Adults and teenagers 15 years of age or older—At first, 1.25 to 2.5 milligrams (mg) once a day taken at bedtime with a snack for three days. Then your doctor may change your dose by 1.25 or 2.5 mg every three to seven days as needed. Doses greater than 5 mg are divided into smaller doses and taken with meals or at bedtime with a snack. Teenagers less than 15 years of age and children—Use and dose must be determined by your doctor. For Parkinson's disease: Adults and teenagers 15 years of age or older—At first, 1.25 milligrams (mg) one or two times a day taken with meals or at bedtime with a snack. Then your doctor may

TABLE 1 – EXEMPLARY LISTING OF PHARMACOLOGICAL COMPOUNDS AND SUGGESTED DOSAGES FOR USE WITH THE PRESENT INVENTION

DRUG CLASS	SECONDARY DRUG CLASS	EXEMPLARY DRUG LISTING	DOSAGE
			Attention Deficit Disorder with Hyperactivity. Not recommended for pediatric patients under 3 years of age. In pediatric patients from 3 to 5 years of age, start with 2.5 mg daily, by tablet daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained. In pediatric patients 6 years of age and older, start with 5 mg once or twice daily, daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. *Spansule* capsules may be used for once-a-day dosage wherever appropriate. With tablets, give first dose on awakening additional doses (1 or 2) at intervals of 4 to 6 hours.

CLAIMS

We claim:

1. Use of a $GABA_A$ receptor expression modulator in the manufacture of a medicament to treat addiction to antidepressants, opiates, nicotine or marijuana.
2. The use of claim 1 wherein the $GABA_A$ receptor modulator is flumazenil.
3. The use of claim 2 wherein the flumazenil is administered between 0.5 and 10 mg/day.
4. The use of claim 2 wherein the flumazenil is administered between 1.5 and 2.5 mg/day.
5. Use of a neurosteroid production inhibitor in the manufacture of a medicament to treat addiction to antidepressants, opiates, nicotine or marijuana.
6. The use of claim 5 wherein the neurosteroid production inhibitor is a 5-α-reductase inhibitor.
7. The use of claim 6 wherein the 5-α-reductase inhibitor is finasteride.
8. The use of claim 7 wherein the finasteride is administered at about 5mg/day.
9. A method of treating addiction to anti-depressants, opiates, nicotine or marijuana comprising the step of administering a compound that selectively modulates $GABA_A$ receptor expression.
10. The method of claim 9 wherein the compound is flumazenil.
11. The method of claim 10 wherein flumazenil is administered in a therapeutically effective quantity.
12. The method of claim 11 wherein the therapeutically effective quantity of flumazenil is between 0.5 mg/day and 10 mg/day.
13. The method of claim 10 wherein flumazenil is administered at a rate of between 0.1 and 0.3 mg over predetermined time intervals for a total administration of between 0.5 mg/day and 10 mg/day.
14. The method of claim 13 wherein the predetermined time interval is in the range of 1 and 15 minutes.
15. The method of claim 10 wherein flumazenil is administered at a rate of between 0.1 and 0.3 mg over predetermined time intervals for a total administration of between 1.0 mg/day and 3.0 mg/day.
16. The method of claim 10 wherein flumazenil is administered at a rate of between 0.1 and 0.3 mg over predetermined time intervals for a total administration of between 1.5 mg/day and 2.5 mg/day.

17. The method of claim 9 further comprising the step of administering an inhibitor of neurosteroid production prior to the step of administering the compound that selectively modulates $GABA_A$ receptor expression.
18. The method of claim 17 wherein the inhibitor of neurosteroid production is a 5-alpha-reductase inhibitor.
19. The method of claim 18 wherein the 5-alpha-reductase inhibitor is finasteride.
20. The method of claim 19 wherein the finasteride is administered in a therapeutically effective quantity.
21. The method of claim 20 wherein said therapeutically effective quantity of finasteride is 5 mg/day.
22. A method of treating addiction to anti-depressants, opiates, nicotine or marijuana comprising the steps of:

    assessing a patient for treatment compatibility;

    preparing the patient for treatment; and

    administering a compound that selectively modulates $GABA_A$ receptor expression to the patient.
23. The method of claim 22 wherein the step of preparing the patient for treatment includes withdrawing the patient from current treatment.
24. The method of claim 22 wherein the step of preparing the patient for treatment includes placing the patient in a state of withdrawal.
25. The method of claim 24 wherein the patient is a female patient and the female patient may be placed in a state of withdrawal by actively modulating said patient's progesterone levels with contraceptives.
26. The method of claim 24 wherein the patient is placed in a state of withdrawal by administering an inhibitor of neurosteroid production.