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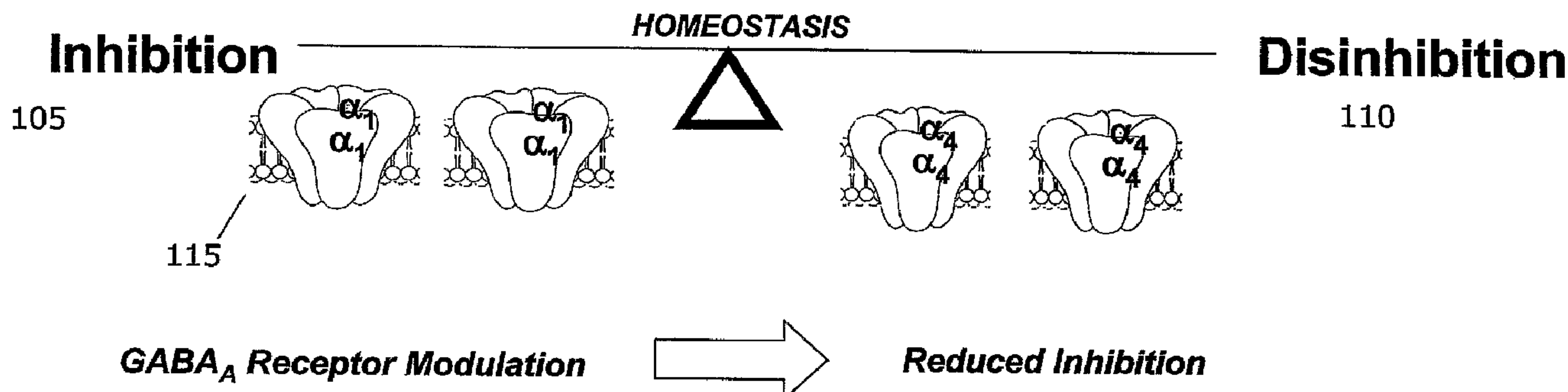
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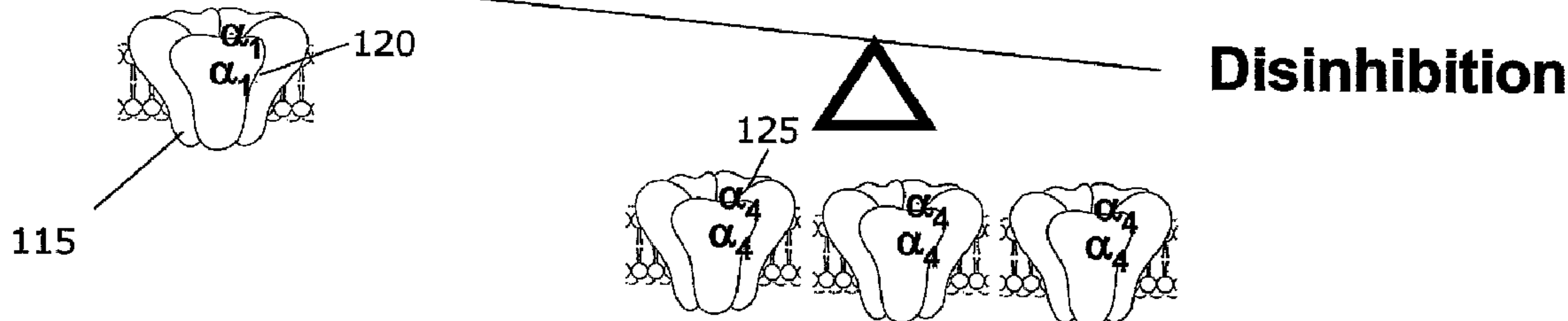
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(57) Abrégé/Abstract:

Compositions for reducing dependency and addiction to substances of abuse are provided. Chloride channels such as the GABAA receptors are altered under conditions of dependency and withdrawal such that the electrophysiological properties of the GABAA receptor containing neurons are altered thereby providing a pathophysiological condition resulting in symptoms of

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dependency and withdrawal such as anxiety. Specifically, under conditions of withdrawal the relative ratio of the $\alpha 1$ receptor subunit decreases relative to the $\alpha 4$ receptor subunit. Endogenous neurosteroid production is also associated with the molecular changes underlying the alterations of GABA-gated chloride channels. Compositions of at least two compounds including at least one inhibitor of neurosteroid production are useful for treating the pathophysiology of addiction, dependency and substance abuse withdrawal.

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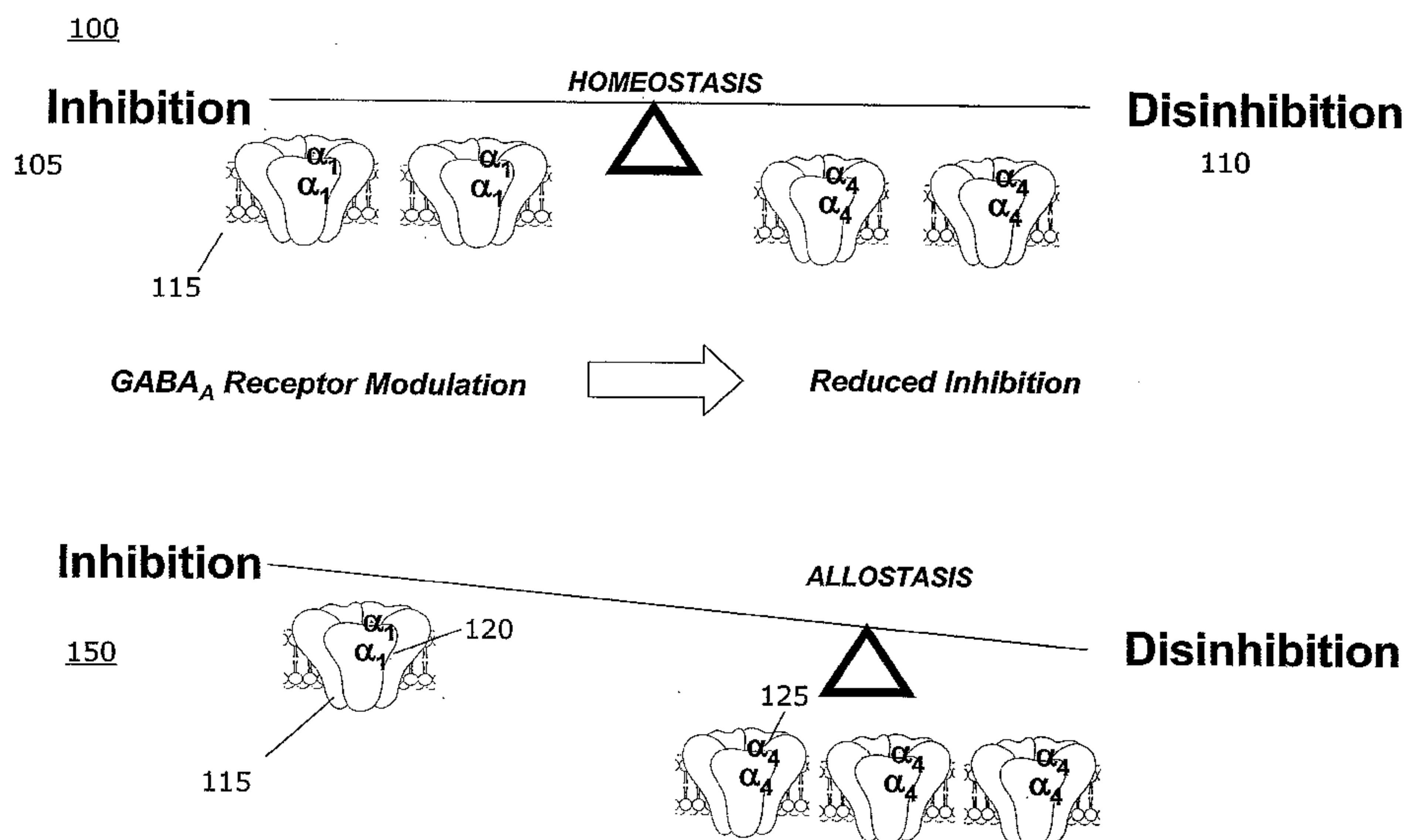
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(54) Title: IMPROVED METHODS OF AND COMPOSITIONS FOR THE PREVENTION OF ANXIETY, SUBSTANCE ABUSE, AND DEPENDENCE



(57) Abstract: Compositions for reducing dependency and addiction to substances of abuse are provided. Chloride channels such as the GABA_A receptors are altered under conditions of dependency and withdrawal such that the electrophysiological properties of the GABA_A receptor containing neurons are altered thereby providing a pathophysiological condition resulting in symptoms of dependency and withdrawal such as anxiety. Specifically, under conditions of withdrawal the relative ratio of the α_1 receptor subunit decreases relative to the α_4 receptor subunit. Endogenous neurosteroid production is also associated with the molecular changes underlying the alterations of GABA-gated chloride channels. Compositions of at least two compounds including at least one inhibitor of neurosteroid production are useful for treating the pathophysiology of addiction, dependency and substance abuse withdrawal.

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IMPROVED METHODS OF AND COMPOSITIONS FOR THE PREVENTION OF ANXIETY, SUBSTANCE ABUSE, AND DEPENDENCE

CROSS-REFERENCE TO RELATED APPLICATIONS

5 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
10 entitled "Methods for Treating Anxiety-Related Diseases", filed on October 21, 2005.

FIELD OF THE INVENTION

 The present invention relates to improved methods of, and compositions for, preventing psychological addiction to and physiological dependence upon exogenous and
15 endogenous substances. More specifically, the present invention relates to methods of, and compositions for, administering a pharmaceutical compound in combination with an inhibitor of neurosteroid production to prevent endogenous neurosteroid production. The present invention also relates to administering a pharmaceutical compound in combination with an inhibitor of neurosteroid production to avoid cross-tolerance effects of both the endogenous
20 and exogenous substance.

 The present invention also relates to methods of, and compositions for, directly or indirectly, preventing the modulation of GABA_A by the progesterone metabolite allopregnanolone. More specifically, the present invention relates to combining the therapeutic activity of conventional pharmaceutical compounds with the therapeutic activity
25 of inhibitors of neurosteroid production that inhibit the production of allopregnanolone.

 The present invention also relates to methods 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.

30 BACKGROUND OF THE INVENTION

 Addiction is an uncontrollable compulsion to repeat a behavior regardless of its negative consequences. Many drugs or behaviors can lead to a pattern of actions recognized as addiction, which include a craving for more of the drug or behavior, increased physiological tolerance to exposure, and withdrawal symptoms in the absence of the stimulus. Although a

distinction is often made between psychological addiction and physical dependence, the terms are used interchangeably throughout this specification.

While addiction is generally thought to apply to illegal narcotics, legal substances, such as prescription and over-the-counter medications, may also cause addiction. While
5 there are many useful, legal prescription and over-the-counter medications that have a positive therapeutic effect, they are limited in use in that there is a tendency of addiction in patients who use these medications.

Substance addiction and abuse is a multi-factorial neurological disease. Over time, repeated exposure to various substances, both endogenous and exogenous, causes
10 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
15 addictions. Rather, addictive behavior arises from an intense desire to manage and/or avoid the anxiety that arises when someone is experiencing withdrawal. Similarly, anxiety-related diseases are caused by behavior that arises from an intense desire to manage and/or avoid the
20 anxiety experienced during endogenous neurosteroid 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. In addition, conventional
25 methods for treating substance abuse require waiting until a patient is addicted to a substance and experiences withdrawal symptoms.

What is therefore needed are improved methods of and compositions for preventing psychological addiction to, and physiological dependence upon, prescription or over the counter medicines.

30 What is also needed is a method for making known prescription or over the counter medicines less addictive and habit-forming.

SUMMARY OF THE INVENTION

The present invention is directed towards improved methods of, and compositions for, preventing psychological addiction to and physiological dependence upon exogenous and endogenous substances. More specifically, the present invention relates to methods of, and compositions for, administering a pharmaceutical compound in combination with an inhibitor of neurosteroid production to prevent endogenous neurosteroid production. The present invention also relates to administering a pharmaceutical compound in combination with an inhibitor of neurosteroid production to avoid cross-tolerance and compounded withdrawal effects of both the endogenous and exogenous substance.

The present invention is also directed towards methods of, and compositions for, directly or indirectly preventing the modulation of GABA_A by progesterone.

The present invention is also directed towards methods of, and compositions for, directly or indirectly preventing the modulation of GABA_A by progesterone metabolite allopregnanolone. More specifically, the present invention is directed towards combining the therapeutic activity of conventional pharmaceutical compounds with the therapeutic activity of inhibitors of neurosteroid production that inhibit the production of allopregnanolone.

Compositions are also provided that include a substance with addictive properties in combination with an inhibitor of neurosteroid production. Methods of administration of these compounds are also provided herein. Such substances with addictive properties may include stimulants, contraceptives, tranquilizers, sedatives, hypnotics, benzodiazepines, analgesics and barbiturates. These compositions may optionally include a modulator of receptor subunit expression.

In one embodiment, the present invention is directed towards compositions of a therapeutically effective dose of a pharmaceutical compound in combination with a therapeutically effective dose of an inhibitor of endogenous neurosteroid production to prevent addiction to, or dependence on, a substance of abuse.

In another embodiment, the present invention is directed towards methods of administering a pharmaceutical compound, without habit-forming or addictive side effects to prevent addiction or reduce dependence, comprising administering a therapeutically effective dose of a pharmaceutical compound in combination with a therapeutically effective dose of an inhibitor of endogenous neurosteroid production to prevent addiction or reduce dependence on the pharmaceutical compound.

It is therefore an object of the invention to provide compositions and methods for reducing dependence on or addiction to substances of abuse.

It is another object of the invention to provide methods and compositions for inhibiting the formation of neurosteroids.

It is another object of the invention to provide compositions and methods for modulating the expression of GABA receptor subunits.

5 Another object of the invention is to provide for the use of a neurosteroid production inhibitor in the preparation of a medicament to prevent addition or dependence on a substance of abuse.

Another object of the invention is to provide for the use of a neurosteroid production inhibitor and a pharmaceutical compound in the preparation of a medicament to prevent
10 addition or dependence on a substance of abuse.

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.

15 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.

20 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
25 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

30 I. INTRODUCTION

The present invention may be understood more readily by reference to the following detailed description of specific embodiments included herein. Although the present invention

has been described with reference to specific details of certain embodiments, thereof, it is not intended that such details should be regarded as limitations upon the scope of the invention.

The present invention is directed towards improved methods of, and compositions for, preventing psychological addiction to and physiological dependence upon exogenous and endogenous substances. As used herein the term "substance of abuse" refers to addiction forming substances such as but not limited to opioids, benzodiazepines, cannabis, caffeine, nicotine, and other drugs that stimulate neural reward pathways and promote addiction. More specifically, the present invention relates to methods of, and compositions for, administering a pharmaceutical compound in combination with an inhibitor of neurosteroid production to prevent endogenous neurosteroid production. The present invention also relates to administering a pharmaceutical compound in combination with an inhibitor of neurosteroid production to avoid cross-tolerance and compounded withdrawal effects of both the endogenous and exogenous substance.

The present invention is also directed towards methods of, and compositions for, directly or indirectly preventing the modulation of GABA_A by progesterone.

The present invention is also directed towards methods of, and compositions for, directly or indirectly preventing the modulation of GABA_A by progesterone metabolite allopregnanolone. More specifically, the present invention is directed towards combining the therapeutic activity of conventional pharmaceutical compounds with the therapeutic activity of inhibitors of neurosteroid production that inhibit the production of allopregnanolone.

In one embodiment, effective prevention of endogenous neurosteroid production and cross-tolerance between endogenous and exogenous substances, requires addressing the underlying pathophysiology that occurs prior to addiction resulting from various substances, namely the conversion of progesterone and deoxycorticosterone (DOC) and their metabolites allopregnanolone and tetrahydrodeoxycorticosterone, which, upon chronic exposure to and withdrawal, result in the increased expression of the GABA_A receptor α_4 subunit relative to the α_1 subunit.

In one embodiment, an effective composition is one which combines the therapeutic activity of a conventional pharmaceutical compound with the therapeutic activity of an inhibitor of neurosteroid production.

In one embodiment, an effective composition is one which prevents psychological addiction to, and physiological dependence upon, prescription or over the counter medicines.

In one embodiment, the present invention is directed towards an effective composition that makes known prescription or over the counter medicines less addictive and habit-forming.

5 In one embodiment, the pharmaceutical compound is selected from the class of compounds that comprise opioids and their derivatives.

In one embodiment, the pharmaceutical compound is selected from the class of compounds that comprise tetrahydrocannabinol and its derivatives.

In one embodiment, the pharmaceutical compound is selected from the class of compounds that comprise benzodiazepines.

10 In one embodiment, the pharmaceutical compound is selected from the class of compounds that comprise tranquilizers, sedatives, hypnotics, and barbiturates.

In one embodiment, the pharmaceutical compound is selected from the class of compounds that comprise contraceptives.

15 In one embodiment, the pharmaceutical compound is selected from the class of compounds that comprise stimulants and their derivatives.

In one embodiment, the inhibitor of neurosteroid production is a 5-alpha-reductase inhibitor. In one embodiment, the 5-alpha-reductase inhibitor is finasteride. In one embodiment, the 5-alpha-reductase inhibitor is dutasteride. In one embodiment, the 5-alpha-reductase inhibitor is an organic medicinal, such as, but not limited to saw palmetto and spironolactone.

20 In one embodiment, the inhibitor of neurosteroid production is a 3-alpha-hydroxysteroid oxidoreductase inhibitor. In one embodiment, the 3-alpha-hydroxysteroid oxidoreductase inhibitor is indomethacin.

25 In one embodiment, dependence upon, tolerance to, and cross-tolerance between endogenous and exogenous substances can further be prevented by optionally administering a pharmaceutical 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. 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.

30 In one embodiment, the compound from the class of compounds that directly or indirectly modulates GABA_A by modulating the expression of the GABA_A receptor α_4 subunit is flumazenil. In one embodiment, flumazenil is administered in a controlled-release formulation. In one embodiment, flumazenil is administered via a subcutaneous implant. In another embodiment, flumazenil is administered via a transdermal patch.

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.

Reference will now be made in detail to specific embodiments of the invention. While the invention will be described in conjunction with specific embodiments, it is not intended to limit the invention to one embodiment.

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 5HT₃ 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 to 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, zalcipelon, 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 zalcipelon or zolpidem, like that of diazepam, induced a marked increase in the amount of α_4 subunit mRNA. These effects of zalcipelon 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 μ M 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 μ M diazepam or 100 mM GHB for ethanol negated the positive modulation of 3 μ M 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 3 α -hydroxy-5 α -pregnan-20-one (allopregnanolone) and 3 α ,21-dihydroxy-5 α -pregnan-20-one (tetradihydrodeoxycorticosterone, 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 (3 α -OH-5 α -pregnan-20-one or 3 α ,5 α -THP) in human brains.

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.

Thus, the endogenous neurosteroid allopregnanolone exhibits withdrawal properties, similar to GABA-modulators, 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.

5 The increase 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, 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.

10 Chronic administration of hormones or contraceptive compounds, and in particular, those containing progesterone, result in the up-regulation of the GABA_A-receptor α_4 subunit. As endogenous neurosteroid levels fluctuate, a person's tolerance liability to certain exogenous substances also fluctuates. For example, but not limited to such example, in a patient with low endogenous hormone levels, the administration of a particular dosage of progesterone that the patient is regularly taking may still result in withdrawal symptomatology, since the patient has developed tolerance to higher levels of progesterone, compounded by both endogenous and exogenous sources. Thus, even with a tolerance to a consistent amount of an endogenous substance, cross-tolerance effects may also be seen due to fluctuating endogenous neurosteroid levels.

15 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 increase 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.

25 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 spectrum 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.

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.

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.

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.

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 particular, 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.

IV. CONVENTIONAL COMPOSITIONS FOR USE IN THE PRESENT INVENTION

Reference will now be made to specific compositions and classes of pharmaceutical compounds for use in the present invention. It should be understood to those of ordinary skill in the art that any number of pharmaceutical compounds that possess addictive properties can be used in the present invention and that the list is not exhaustive. Published dosing and administration literature, available, for example, from the FDA or the Physician Desk Reference (PDR), are incorporated herein by reference.

Compositions for use in the present invention include alcohol, nicotine, caffeine, tea, coffee, tobacco, 1-(1-Phenylcyclohexyl)pyrrolidine, 1-(2-Phenylethyl)-4-phenyl-4-acetoxypiperidine, 1-[1-(2-Thienyl)cyclohexyl]piperidine, 1-[1-(2-Thienyl)cyclohexyl]pyrrolidine, 13Beta-ethyl-17beta-hydroxygon-4-en-3-one, 17Alpha-methyl-3alpha,17beta-dihydroxy-5alpha-androstane, 17Alpha-methyl-3beta,17beta-dihydroxy-5alpha-androstane, 17Alpha-methyl-3beta,17beta-dihydroxyandrost-4-ene, 17Alpha-methyl-4-hydroxynandrolone (17alpha-methyl-4-hydroxy-17beta-hydroxyestr-4-en-3-one), 17Alpha-methyl-delta1-dihydrotestosterone (17beta-hydroxy-17alpha-methyl-5alpha-androst-1-en-3-one), 19-Nor-4-androstenediol (3beta,17beta-dihydroxyestr-4-ene; 3alpha,17beta-dihydroxyestr-4-ene), 19-Nor-4-androstenedione (estr-4-en-3,17-dione), 19-Nor-5-androstenediol (3beta,17beta-dihydroxyestr-5-ene; 3alpha,17beta-dihydroxyestr-5-ene), 19-Nor-5-androstenedione (estr-5-en-3,17-dione), 1-Androstenediol (3beta,17beta-dihydroxy-5alpha-androst-1-ene; 3alpha,17beta-dihydroxy-5alpha-androst-1-ene), 1-Androstenedione (5alpha-androst-1-en-3,17-dione), 1-Methyl-4-phenyl-4-propionoxypiperidine, 1-Phenylcyclohexylamine, 1-Piperidinocyclohexanecarbonitrile, 2,5-Dimethoxy-4-(n)-propylthiophenethylamine, 2,5-Dimethoxy-4-ethylamphetamine, 2,5-Dimethoxyamphetamine, 3,4,5-Trimethoxyamphetamine, 3,4-Methylenedioxyamphetamine, 3,4-Methylenedioxymethamphetamine, 3,4-Methylenedioxy-N-ethylamphetamine, 3Alpha,17beta-dihydroxy-5alpha-androstane, 3Beta,17beta-dihydroxy-5alpha-androstane, 3-Methylfentanyl, 3-Methylthiofentanyl, 4-Androstenediol (3beta,17beta-dihydroxy-androst-4-ene), 4-Androstenedione (androst-4-en-3,17-dione), 4-Bromo-2,5-dimethoxyamphetamine, 4-Bromo-2,5-dimethoxyphenethylamine, 4-Dihydrotestosterone (17beta-hydroxyandrost-3-one), 4-Hydroxy-19-nortestosterone (4,17beta-dihydroxyestr-4-en-3-one), 4-Hydroxytestosterone (4,17beta-dihydroxyandrost-4-en-3-one), 4-Methoxyamphetamine, 4-Methyl-2,5-dimethoxyamphetamine, 4-Methylaminorex (cis isomer), 5-Androstenediol (3beta,17beta-dihydroxy-androst-5-ene), 5-Androstenedione (androst-5-en-3,17-dione), 5-Methoxy-3,4-methylenedioxyamphetamine, 5-Methoxy-N,N-diisopropyltryptamine, Acetorphine, Acetyl-alpha-methylfentanyl, Acetyldihydrocodeine, Acetylmethadol, Alfentanil, Allylprodine, Alphacetylmethadol, levo-alphacetylmethadol, Alpha-ethyltryptamine, Alphameprodine, Alphamethadol, Alpha-methylfentanyl, Alpha-methylthiofentanyl, Alpha-methyltryptamine, Alphaprodine, Alprazolam, Aminorex, Amobarbital, Amobarbital suppository dosage form, Amphetamine, Anabolic steroids, Androstenedione (5alpha-androst-3,17-dione), Anileridine, Aprobarbital, Barbital, Barbituric acid derivative, Benzethidine, Benzoylecgonine, Benzphetamine, Benzylmorphine,

Betacetylmethadol, Beta-hydroxy-3-methylfentanyl, Beta-hydroxyfentanyl, Betameprodine,
 Betamethadol, Betaprodine, Bezitramide, Bolasterone (7alpha,17alpha-dimethyl-17beta-
 hydroxyandrost-4-en-3-one), Boldenone (17beta-hydroxyandrost-1,4-diene-3-one),
 Bromazepam, Bufotenine, Buprenorphine, Butabarbital (secbutabarbital), Butalbital,
 5 Butobarbital (butethal), Butorphanol, Calusterone (7beta,17alpha-dimethyl-17beta-
 hydroxyandrost-4-en-3-one), Camazepam, Carfentanil, Cathine, Cathinone, Chloral betaine,
 Chloral hydrate, Chlordiazepoxide, Chlorhexadol, Chlorphentermine, Clobazam,
 Clonazepam, Clonitazene, Clorazepate, Clortermine, Clostebol (4-chloro-17beta-
 hydroxyandrost-4-en-3-one), Clotiazepam, Cloxazolam, Coca Leaves, Cocaine, Codeine,
 10 Codeine, Codeine methylbromide Codeine-N-oxide, Cyprenorphine,
 Dehydrochloromethyltestosterone (4-chloro-17beta-hydroxy-17alpha-methylandrost-1,4-
 dien-3-one), Delorazepam, Delta1-dihydrotestosterone (17beta-hydroxy-5alpha-androst-1-en-
 3-one), Desomorphine, Dexfenfluramine, Dextromoramide, Diampromide, Diazepam,
 Dichloralphenazone, Diethylpropion, Diethylthiambutene, Diethyltryptamine, Difenoxin,
 15 Dihydrocodeine, Dihydroetorphine, Dihydromorphine, Dimenoxadol, Dimepheptanol,
 Dimethylthiambutene, Dimethyltryptamine, Dioxaphetyl butyrate, Diphenoxylate,
 Dipipanone, Diprenorphine, Drostanolone (17beta-hydroxy-2alpha-methyl-5alpha-androstan-
 3-one), Drotebanol, Ecgonine, Estazolam, Ethchlorvynol, Ethinamate, Ethyl loflazepate,
 Ethylestrenol (17alpha-ethyl-17beta-hydroxyestr-4-ene), Ethylmethylthiambutene,
 20 Ethylmorphine, Etonitazene, Etorphin, Etoxeridine, Fencamfamin, Fenethylline,
 Fenfluramine, Fenproporex, Fentanyl, Fludiazepam, Flunitrazepam, Fluoxymesterone (9-
 fluoro-17alpha-methyl-11beta,17beta-dihydroxyandrost-4-en-3-one), Flurazepam,
 Formebolone (2-formyl-17alpha-methyl-11alpha,17beta-dihydroxyandrost-1,4-dien-3-one),
 Furazabol (17alpha-methyl-17beta-hydroxyandrostano[2,3-c]-furan), Furethidine, Gamma
 25 Hydroxybutyric Acid, Glutethimide, Halazepam, Haloxazolam, Heroin, Hydrocodone,
 Hydromorphanol, Hydromorphone, Hydroxypethidine, Ibogaine, Isomethadone, Ketamine,
 Ketazolam, Ketobemidone, Levo-alphaacetylmethadol, Levomethorphan, Levomoramide,
 Levophenacymorphan, Levorphanol, Loprazolam, Lorazepam, Lormetazepam, Lysergic
 acid, Marihuana, Mazindol, Mebutamate, Mecloqualone, Medazepam, Mefenorex,
 30 Meperidine, Meprobamate, Mescaline, Mestanolone (17alpha-methyl-17beta-hydroxy-
 5alpha-androstan-3-one), Mesterolone (1alpha-methyl-17beta-hydroxy-5alpha-androstan-3-
 one), Metazocine, Methadone, Methamphetamine, Methandienone (17alpha-methyl-17beta-
 hydroxyandrost-1,4-diene-3-one), Methandriol (17alpha-methyl-3beta,17beta-
 dihydroxyandrost-5-ene), Methaqualone, Methcathinone, Methenolone (1-methyl-17beta-

hydroxy-5alpha-androst-1-en-3-one), Methohexital, Methyldesorphine, Methyldienolone (17alpha-methyl-17beta-hydroxyestr-4,9(10)-dien-3-one), Methyldihydromorphine, Methylphenidate, Methylphenobarbital (mephobarbital), Methyltestosterone (17alpha-methyl-17beta-hydroxyandrost-4-en-3-one), Methyltrienolone (17alpha-methyl-17beta-hydroxyestr-4,9,11-trien-3-one), Methypylon, Metopon, Mibolerone (7alpha,17alpha-dimethyl-17beta-hydroxyestr-4-en-3-one), Midazolam, Modafinil, Moramide-intermediate, Morpheridine, Morphine, Myrophine, N,N-Dimethylamphetamine, Nabilone, Nalorphine, Nandrolone (17beta-hydroxyestr-4-en-3-one), N-Benzylpiperazine, N-Ethyl-1-phenylcyclohexylamine, N-Ethyl-3-piperidyl benzilate, N-Ethylamphetamine, N-Hydroxy-3,4-methylenedioxyamphetamine, Nicocodeine, Nicomorphine, Nimetazepam, Nitrazepam, N-Methyl-3-piperidyl benzilate, Noracymethadol, Norbolethone (13beta,17alpha-diethyl-17beta-hydroxygon-4-en-3-one), Norclostebol (4-chloro-17beta-hydroxyestr-4-en-3-one, Nordiazepam, Norethandrolone (17alpha-ethyl-17beta-hydroxyestr-4-en-3-one), Norlevorphanol, Normethadone, Normethandrolone (17alpha-methyl-17beta-hydroxyestr-4-en-3-one), Normorphine, Norpipanone, Opium extracts, Opium fluid extract, Opium poppy, Opium tincture, Oxandrolone (17alpha-methyl-17beta-hydroxy-2-oxa-5alpha-androstan-3-one), Oxazepam, Oxazolam, Oxycodone, Oxymesterone (17alpha-methyl-4,17beta-dihydroxyandrost-4-en-3-one), Oxymetholone (17alpha-methyl-2-hydroxymethylene-17beta-hydroxy-5alpha-androstan-3-one), Oxymorphine, Para-Fluorofentanyl, Parahexyl, Paraldehyde, Pemoline, Pentazocine, Pentobarbital, Petrichloral, Peyote, Phenadoxone, Phenampromide, Phenazocine, Phencyclidine, Phendimetrazine, Phenmetrazine, Phenobarbital, Phenomorphan, Phenoperidine, Phentermine, Phenylacetone, Pholcodine, Piminodine, Pinazepam, Pipradrol, Piritramide, Poppy Straw, Prazepam, Proheptazine, Properidine, Propiram, Psilocybin, Psilocyn, Pyrovalerone, Quazepam, Racemethorphan, Racemoramide, Racemorphan, Remifentanil, Secobarbital, Sibutramine, Stanozolol (17alpha-methyl-17beta-hydroxy-5alpha-androst-1-eno[3,2-c]-pyrazole), Stenbolone (17beta-hydroxy-2-methyl—5alpha-androst-1-en-3-one), Sufentanil, Sulfondiethylmethane, Sulfonethylmethane, Sulfonmethane, Talbutal, Temazepam, Testolactone (13-hydroxy-3-oxo-13,17-secoandrosta-1,4-dien-17-oic acid lactone), Testosterone (17beta-hydroxyandrost-4-en-3-one), Tetrahydrocannabinols, Tetrahydrogestrinone (13beta,17alpha-diethyl-17beta-hydroxygon-4,9,11-trien-3-one), Tetrazepam, Thebacon, Thebaine, Thiamylal, Thiofentanyl, Thiopental, Tiletamine, Zolazepam, Tilidine, Trenbolone (17beta-hydroxyestr-4,9,11-trien-3-one), Triazolam, Trimeperidine, Vinbarbital, Zaleplon, Zolpidem, Zopiclone, Vicodin, Hydrocodone, Codan, Hycodan, Hydromet, Hydropane, Mycodone, Tussigon Hydrocodone,

Percocet, Oxycodone, Xanax, Alprazolam, OxyContin, Lortab, Tramadol, Lexapro,
 Escitalopram, Neurontin, Gabapentin, Valium, Diazepam, Lisinopril, Lipitor, Atorvastatin,
 Amoxicillin, Zolof, Sertraline, Naproxen, Lyrica, Pregabalin, Morphine, Clonazepam,
 Alprazolam, Adderall, Darvocet, Klonopin, Clonazepam, Seroquel, Quetiapine, Methadone,
 5 Trazodone, Flexeril, Cyclobenzaprine, Cyclobenzaprine, Prednisone, Cymbalta, Duloxetine,
 Lorazepam, Cephalexin, Atenolol, Phentermine, Soma, Carisoprodol, Levaquin,
 Levofloxacin, Propoxyphene, Norvasc, Amlodipine, Metformin, Amitriptyline, Ativan,
 Lorazepam, Gabapentin, Ambien, Zolpidem, Diazepam, Ultram, Tramadol, Protonix,
 Pantoprazole, Mobic, Meloxicam, Zocor, Simvastatin, Doxycycline, Skelaxin, Metaxalone,
 10 Sitrex, Guaifenesin, Phenylephrine, Paxil, Paroxetine, Toprol, Metoprolol, Acetaminophen,
 Promethazine, Topamax, Topiramate, Plavix, Clopidogrel, Risperdal, Risperidone, Prozac,
 Fluoxetine, Clindamycin, Wellbutrin, Bupropion, Nexium, Esomeprazole, Clonidine,
 Effexor, Venlafaxine, Synthroid, Levothyroxine, Furosemide, Carisoprodol, Keflex,
 Cephalexin, Provigil, Modafinil, Lamictal, Lamotrigine, Vytorin, Zyrtec, Viagra, Sildenafil,
 15 Abilify, Aripiprazole, Diclofenac, Methocarbamol, Concerta, Methylphenidate, Diovan,
 Valsartan, Hydroxyzine, Metronidazole, Biaxin, Clarithromycin, Celebrex, Celecoxib,
 Methadose, Lasix, Furosemide, Prevacid, Lansoprazole, Ritalin, Methylphenidate, Zetia,
 Ezetimibe, Nabumetone, Zithromax, Azithromycin, Ibuprofen, Flagyl,
 Celexa, Citalopram, Temazepam, Altace, Ramipril, Singulair, Montelukast, Levothyroxine,
 20 Actos, Pioglitazone, Etodolac, Lunesta, Eszopiclone, Omnicef, Cefdinir, Robaxin,
 Methocarbamol, Roxicet, Zyprexa, Olanzapine, Elavil, Amitriptyline, BuSpar, Buspirone,
 Voltaren, Benicar, Olmesartan, Avelox, Moxifloxacin, Coreg, Carvedilol, Citalopram,
 Phenergan, Promethazine, Adipex, Phentermine, Coumadin, Warfarin, Ranitidine, Advair,
 Ketek, Telithromycin, TriCor, Fenofibrate, Lithium, Relafen, Nabumetone, Suboxone,
 25 Buprenorphine, DuraDex, Fioricet, Omeprazole, Reglan, Metoclopramide, Roxicodone,
 Naprosyn, Naproxen, Demerol, Meperidine, Lovastatin, Prolex, Baclofen, Percodan,
 Strattera, Atomoxetine, Allegra, Fexofenadine, Flomax, Tamsulosin, Meclizine, Avandia,
 Rosiglitazone, Paroxetine, Pediatex, Carbinoxamine, Rozerem, Ramelteon, Zanaflex,
 Tizanidine, Verapamil, Zantac, Ranitidine, Bupropion, Avapro, Irbesartan, Diltiazem,
 30 Enalapril, Enalaprilat, Tizanidine, Aciphex, Rabeprazole, Lactinex, Cialis, Tadalafil,
 Prilosec, Omeprazole, Dextropropoxyphenol, Dextromethorphan, Ethchlorvynol, Fentanyl, Gamma-
 hydroxybutyrate, Glutethimide, Hydromorphone, Ketamine, Levo-alpha-acetylmethadol,
 Meperidine, Meprobamate, Methamphetamine, Methaqualone, Methadone, Methcathinone,
 Morphine, Nicotine, Opium, Paraldehyde, Phencyclidine, Flunitrazepam, Paracetamol,

NSAIDs, Opiates, Tetrahydrocannabinol, Aspirin, Celecoxib, Diclofenac, Diflunisal, flurbiprofen, Ibuprofen, Ketoprofen, Ketorolac, Meloxicam, Naproxen, Piroxicam, Rofecoxib, Valdecoxib, Alfentanil, Buprenorphine, Carfentanil, Codeine, Codeinone, Dextropropoxyphene, Diamorphine, Dihydrocodeine, Fentanyl, Hydromorphone, Nalbuphine, Oxymorphone, Pentazocine, Pethidine (Meperidine), Propoxyphene, Remifentanil, Sufentanil, Tramadol, Amobarbital, Aprobarbital, Butabarbital, Butalbital, Hexobarbital, Methylphenobarbital, Pentobarbital, Phenobarbital, Secobarbital, Sodium thiopental, Talbutal, Thiobarbital, Allobarbital, Barbexaclone, Barbital, Butobarbital, Cyclobarbital, Ethallobarbital, Heptabarbital, Mephobarbital, Metharbital, Methohexital, Primidone, Proxibarbal, Reposal, Secobarbital, Thiopental, Vinbarbital, Vinylbital, Adinazolam, Alprazolam, Bromazepam, Brotizolam, Camazepam, Chlordiazepoxide, Cinolazepam, Clobazam, Clonazepam, Clorazepate, Clotiazepam, Cloxazolam, Diazepam, Doxefazepam, Estazolam, Ethyl loflazepate, Etizolam, Fludiazepam, Flunitrazepam, Flurazepam, Gidazepam, Halazepam, Ketazolam, Loprazolam, Lorazepam, Lormetazepam, Medazepam, Midazolam, Nimetazepam, Nitrazepam, Nordazepam, Oxazepam, Pinazepam, Orthotricyclen, Watson 240-0.5, Tri-sprintec tab, Sezonel, Alene, Miciona, Triguilar, Apre, Metr, Mivelle, Prazepam, Quazepam, Temazepam, Tofisopam, Triazolam, Valerian, and St. John's Wort (collectively referred to as "Conventional Compositions").

Specific classes of Conventional Compositions are discussed below. Exemplary compositions that fall within the classes of compositions listed below are provided in Table 1. It should be noted that the list contains exemplary compounds for use with the present invention and is not exhaustive.

a. CONTRACEPTIVE COMPOUNDS

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 cycle.

Contraceptive medications contain hormones (estrogen and progesterone, or progesterone alone). The medications are available in various forms, such as pills, injection (into a muscle), topical (skin) patches, and slow-release systems (vaginal rings, skin implants, and contraceptive infused intrauterine devices. The rate of absorption of progesterone is highly dependent upon the administration route.

In particular, the altered tolerance liability of a person to exogenous sources of progesterone and other hormones may be due to the cross-tolerance effects between administered and endogenous progesterone. As mentioned above, endogenous levels of

progesterone and its metabolites such as allopregnanolone, fluctuate, thus resulting in the altered tolerance liability of a patient to administered progesterone.

b. STIMULANTS

Stimulants can be used as recreational drugs or therapeutic drugs to increase alertness.

5 They are also used to boost endurance and productivity as well as to suppress appetite. The class of compounds that comprises stimulants includes, but is not limited to caffeine, amphetamines, ecstasy, and cocaine.

10 Stimulants increase the amount of norepinephrine and dopamine in the brain, which increases blood pressure and heart rate, constricts blood vessels, increases blood glucose, and increases breathing. Effects can feel like an increase alertness, attention, and energy along with a sense of euphoria.

Stimulants can be addictive in that individuals begin to use them compulsively. Taking high doses of some stimulants repeatedly over a short time can lead to feelings of hostility or paranoia. Additionally, high doses of a stimulant may result in dangerously high
15 body temperatures and an irregular heartbeat.

i. CAFFEINE

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
20 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
25 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
30 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.

ii. PRESCRIPTION STIMULANTS

Attention Deficit Disorder is often treated using stimulant medications, the most popular of which includes methylphenidate, which is more commonly known by its trade name, Ritalin; amphetamine, which may be sold as a mixture with dextroamphetamine and commonly known by its trade name Adderall; and dextroamphetamine, which is more commonly known by its trade name Dexedrine. These drugs are known to enhance brain activity and were used historically to treat asthma, obesity, neurological disorders, and a variety of other ailments, before their potential for abuse and addiction became apparent.

c. ANALGESICS

An analgesic, more commonly referred to as painkillers is any member of the group of drugs used to relieve pain and to achieve analgesia. They include paracetamol, the non-steroidal anti-inflammatory drugs such as aspirin, and the opioids, such as morphine.

i. OPIOIDS

“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, hydromorphone, 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.

ii. TETRAHYDROCANNIBOL

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. 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.

Although considered illegal in the United States, in some areas, cannabis is prescribed under strict supervision for medicinal purposes. Medically, cannabis is most often used as an appetite stimulant and pain reliever for certain terminal illnesses. It is also used to relieve glaucoma and certain neurological illnesses, such as epilepsy, migraine and bipolar disorder.

d. BARBITURATES

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.

e. BENZODIAZEPINES

5 The term benzodiazepine refers to a class of drugs with hypnotic, anxiolytic, anticonvulsant, amnestic and muscle relaxant properties. Benzodiazepines are divided into three groups – short-acting (less than six hours); intermediate-acting (six to ten hours); and long-acting (strong sedative effects that persist).

10 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
15 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,
20 administering a benzodiazepine antagonist to counteract the drug's effects. These methods, however, fail in that they do not address the physiochemical changes that occur with addiction.

f. NON-BENZODIAZEPINE ANXIOLYTICS, SEDATIVES, HYPNOTICS, AND TRANQUILIZERS

25 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.

Due to the effects that these drugs have on the brain, as described above, they can sometimes produce a type of dependence (or addiction) in some people if taken regularly
30 every night for more than about four to six weeks.

g. ANTI-DEPRESSION DRUGS

Clinical depression is a health condition with both mental and physical components. 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 oxidase 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.

i. Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective serotonin reuptake inhibitors relieve depression by increasing the availability of one of the body's natural mood-enhancing chemicals, the neurotransmitter serotonin. Recent research indicates that SSRIs trigger chemical activity along more than one track at a time. Fluoxetine (Prozac®), paroxetine (Paxil®), and sertraline (Zoloft®) all show a dramatic, positive effect (10 to 30-fold) on the levels of allopregnanolone, a steroid made in the brain, which modulates mood and plays a role in heightened anxiety and depression found in severe premenstrual disorders and other conditions.

In this GABA-pathway, allopregnanolone boosts mood-enhancing neurotransmitter receptors by increasing how many and how long certain openings in the ion channels remain open. Recent clinical studies suggest that fluoxetine and fluvoxamine increase the brain and cerebrospinal fluid content of allopregnanolone.

V. COMPOUNDS THAT INHIBIT NEUROSTEROID BINDING ON THE GABA_A RECEPTOR.

In one embodiment, the present invention is directed towards a method of using a compound from a class of compounds that competitively bind to the GABA_A receptor neurosteroid binding site. In one embodiment, the compound is one that inhibits allopregnanolone from binding to the GABA_A receptor. In another embodiment, the compound is one that, upon withdrawal, does not result in the increase of the α_4 subunit relative to the α_1 subunit.

For example, but not limited to such example, Maitra et al. (1998) demonstrated that the 3beta-pregnane isomers epipregnanolone and isopregnanolone both inhibited the ability of allopregnanolone and alphaxalone to potentiate GABA_A receptor function.

VI. 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 5 α -dihydroprogesterone into allopregnanolone.

As shown in Figure 4, progesterone is first converted to 5 α -dihydroprogesterone via an enzyme called 5 α -reductase. 5 α -dihydroprogesterone is then converted to 5 α ,3 α -pregnanolone (allopregnanolone) via the 3 α -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 5 α -reductase inhibitor is capable of acting as a Type I inhibitor, a Type II inhibitor, or a combination thereof, and inhibits the 5 α -reductase enzyme from converting progesterone to 5 α -dihydroprogesterone and thus from creating progesterone metabolite allopregnanolone.

There are currently accepted dosing regimens for 5-alpha-reductase inhibitors. In one embodiment, an individual is administered a therapeutically effective amount of a 3-alpha-hydroxysteroid oxidoreductase inhibitor which blocks the conversion of progesterone metabolite 5 α -dihydroprogesterone into allopregnanolone. One exemplary 3-alpha-hydroxysteroid oxidoreductase is indomethacin or analogs or derivatives thereof. There are currently accepted dosing regimens for 3-alpha-hydroxysteroid oxidoreductase inhibitors. 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.

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.

a. 5α -REDUCTASE INHIBITORS

5 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.

i. FINASTERIDE

Finasteride is a synthetic 4-azasteroid compound, and is a 5α -reductase inhibitor.
10 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.

15 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
20 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,
25 dizziness, headache, impotence, and testicular pain.

ii. 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-
30 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.

5 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,
10 impotence, inability to have or keep an erection, loss in sexual ability, desire, drive, or performance, or swelling of the breasts or breast soreness.

iii. 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
15 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
20 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.

b. Other Inhibitors of Neurosteroid Production

The present invention further includes the use of 3α -hydroxysteroid oxidoreductase
25 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
30 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.

VII. COMPOUNDS THAT MODULATE THE EXPRESSION OF CERTAIN GABA_A RECEPTOR SUBUNITS

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.

In one embodiment, the present invention is directed towards using a compound from 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.

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.

a. 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.

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, 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 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 0.5 mg/day and 20 mg/day, between 0.5 mg/day and 15 mg/day, between 1.0 and 3.0 mg/day, and or between 1.5 and 2.5 mg/day. In one embodiment, the dose is in the range of 1.0 mg/day and 3.0 mg/day. 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. A larger dose may be administered over short periods of time, such as 3 mg doses administered within 6 minutes.

VIII. NOVEL COMPOSITIONS THAT COMBINE CONVENTIONAL COMPOSITIONS WITH INHIBITORS OF NEUROSTEROID PRODUCTION

As described herein, reference will be made to specific pharmacological compounds for use in the present invention. While the invention will be described in conjunction with specific embodiments, it is not intended to limit the invention to one embodiment. It should be understood by one of ordinary skill in the art that a plurality of drug combinations are possible. The present invention contemplates operating in a dosing range of established safety and efficacy in order to maximally decrease the production of allopregnanolone while administering a pharmacological compound.

Prior to prescribing any medication, the physician in charge should make a determination, prior to treatment, if a patient diagnosed with any symptom or disorder, other than substance dependence, should receive medication for this disorder. For example, a patient diagnosed with arterial hypertension should be prescribed with the appropriate medication or continue with any existing medication if they are not contraindicated for use with the compositions used in the treatment methodology of the present invention.

The present invention is broadly directed toward the combination of any Conventional Composition, in any dosage form or amount, with any Inhibitor of Neurosteroid Production, in the same dosage form and in any amount. For purposes of illustration, specific novel compositions will be described below. It should be appreciated that the actual dosage and administration route of the Conventional Compositions vary greatly and depend upon the

status of an individual patient. It should also be appreciated that, accordingly, the actual dosage and administration route of the Inhibitor of Neurosteroid Production will vary as well. However, a person of ordinary skill in the medical art would be able to appropriately select a dosage amount for the Conventional Composition and the Inhibitor of Neurosteroid
5 Production should be provided in the same dosage form and in a sufficient amount to be therapeutically effective at blocking neurosteroid production.

As used herein, a “therapeutically effective amount” of a composition of the present invention refers to a sufficient amount to reduce or prevent neurosteroid production. The therapeutically effective amount is also an amount effective to reduce, alleviate or ameliorate
10 symptoms of dependency such as for example, anxiety. A reduction or amelioration of the symptoms may be determined using standard clinical tests where a reduction or amelioration of the symptoms indicates a therapeutically effective amount has been administered. Examples of such clinical tests are the Hamilton Anxiety Rating Scale and the Beck Anxiety Inventory for anxiety where an improvement in an individual’s test score indicates a
15 therapeutically effective amount has been administered. Therapeutically effective amounts for use in humans can be determined from animal models. For example, a dose for humans can be formulated to achieve circulating concentration that has been found to be effective in animals. Useful animal models of anxiety are well known in the art.

a. FORMULATIONS

The compounds useful in the present invention, or pharmaceutically acceptable salts thereof, can be delivered to a patient using a wide variety of routes or modes of administration. Suitable routes of administration include, but are not limited to, inhalation, transdermal, oral, rectal, transmucosal, intestinal and parenteral administration, including intramuscular, subcutaneous and intravenous injections. These methods also include the use
25 of the aforementioned compounds in the manufacture of compositions, drugs or medicaments useful for reducing the production of neurosteroids. The claimed methods also include the use of the aforementioned compounds in the manufacture of compositions, drugs or medicaments useful for treating, reducing or ameliorating addictive properties of certain substances.

The term “pharmaceutically acceptable salt” means those salts which retain the biological effectiveness and properties of the compounds used in the present invention, and which are not biologically or otherwise undesirable. Such salts may be prepared from inorganic and organic bases. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, and magnesium salts. Salts derived
30

from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, substituted amines including naturally-occurring substituted amines, and cyclic amines, including isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, and N-ethylpiperidine. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example carboxylic acid amides, including carboxamides, lower alkyl carboxamides, di(lower alkyl) carboxamides, and the like.

The compounds, or pharmaceutically acceptable salts thereof, may be administered singly, in combination with other compounds, and/or in cocktails combined with other therapeutic agents. Of course, the choice of therapeutic agents that can be co-administered with the compounds of the invention will depend, in part, on the condition being treated.

The active compounds (or pharmaceutically acceptable salts thereof) may be administered per se or in the form of a pharmaceutical composition wherein the active compound(s) is in admixture or mixture with one or more pharmaceutically acceptable carriers, excipients or diluents. Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the compounds may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained as a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or

sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

For administration orally, the compounds may be formulated as a sustained release preparation. Numerous techniques for formulating sustained release preparations are described in the following references--U.S. Pat. Nos. 4,891,223; 6,004,582; 5,397,574; 5,419,917; 5,458,005; 5,458,887; 5,458,888; 5,472,708; 6,106,862; 6,103,263; 6,099,862; 6,099,859; 6,096,340; 6,077,541; 5,916,595; 5,837,379; 5,834,023; 5,885,616; 5,456,921; 5,603,956; 5,512,297; 5,399,362; 5,399,359; 5,399,358; 5,725,883; 5,773,025; 6,110,498; 5,952,004; 5,912,013; 5,897,876; 5,824,638; 5,464,633; 5,422,123; and 4,839,177; and WO 98/47491.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in a conventional manner.

For administration by inhalation, the active compound(s) may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active compound(s) may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or transcutaneous delivery (for example subcutaneously or intramuscularly), intramuscular injection or a transdermal patch. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A further embodiment of the present invention is related to a nanoparticle. The compounds of the present invention may be incorporated into the nanoparticle. The nanoparticle within the scope of the invention is meant to include particles at the single molecule level as well as those aggregates of particles that exhibit microscopic properties.

Methods of using and making the above-mentioned nanoparticle can be found in the art (U.S. Patent Nos. 6,395,253, 6,387,329, 6,383,500, 6,361,944, 6,350,515, 6,333,051, 6,323,989, 6,316,029, 6,312,731, 6,306,610, 6,288,040, 6,272,262, 6,268,222, 6,265,546, 6,262,129, 6,262,032, 6,248,724, 6,217,912, 6,217,901, 6,217,864, 6,214,560, 6,187,559, 5 6,180,415, 6,159,445, 6,149,868, 6,121,005, 6,086,881, 6,007,845, 6,002,817, 5,985,353, 5,981,467, 5,962,566, 5,925,564, 5,904,936, 5,856,435, 5,792,751, 5,789,375, 5,770,580, 5,756,264, 5,705,585, 5,702,727, and 5,686,113).

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to 10 calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredient is contained in a therapeutically or prophylactically effective amount, i.e., in an amount effective to achieve therapeutic or 15 prophylactic benefit, as previously discussed. Of course, the actual amount effective for a particular application will depend on the condition being treated and the route of administration. Determination of an effective amount is well within the purview of those skilled in the art, especially in light of the disclosure herein.

b. METHODS OF USE

20 The methods of the present invention include the use of the aforementioned compounds in the manufacture of compositions, drugs or medicaments useful for reducing the addictive and habit-forming properties of certain compounds in the classes described above. These methods also include the use of the aforementioned compounds in the manufacture of compositions, drugs or medicaments useful for reducing the production of 25 neurosteroids. The claimed methods also include the use of the aforementioned compounds in the manufacture of compositions, drugs or medicaments useful for reducing the tolerance of certain compounds in the classes described above.

c. EXEMPLARY COMPOSITIONS

30 The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are intended neither to limit nor define the invention in any manner. 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.

5 Example 1

An orally administered tablet comprises between 100 mg and 1000 mg, preferably 300, 325, 400, 500, 650, or 750 mg, of VICODIN[®] and 0.1 to 150 mg, preferably 5 mg, of finasteride.

10 Example 2

An orally administered tablet comprises between 100 mg and 1000 mg, preferably 325, 500, or 650 mg, of PERCOCET[®] and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 3

15 An orally administered tablet comprises between 0.1 and 5 mg, preferably 0.25, 0.5, 1, 2, or 3 mg, of XANAX[®] and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 4

20 An orally administered tablet comprises between 1 mg and 200 mg, preferably 10, 20, 40, or 90 mg, of PROXAC[®] and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 5

25 An orally administered tablet comprises between 1mg and 50 mg, preferably 2, 5, or 10 mg, of VALIUM[®] and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 6

30 An orally administered tablet comprises between 1 mg and 200 mg, preferably 5, 10, 20, 30, 40, 80, 100, or 160 mg, of OXYCONTIN[®] and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 7

An orally administered tablet comprises between 10 mg and 1000 mg, preferably 100, 325, 500, and 650mg, of DARVOCET[®] and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 8

An orally administered tablet comprises between 1 mg and 50 mg, preferably 5, 6.25, or 10 mg, of zolpidem and 0.1 to 150 mg, preferably 5 mg, of finasteride.

5

Example 9

An orally administered tablet comprises between 1 mg and 200 mg, preferably 10, 12.5, 20, 30, or 40 mg, of PAXIL[®] and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 10

10

An orally administered tablet comprises between 0.5 mg and 100 mg, preferably 2.5, 5, 10, 15, or 20 mg, of diazepam and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 11

15

An orally administered tablet comprises between 0.5 mg and 100 mg, preferably 2.5, 5, 10, 15, or 20 mg, of methadone and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 12

20

An orally administered tablet comprises between 0.01 mg and 1000 mg of any of the aforementioned conventional compositions and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 13

25

An orally administered tablet comprises between 0.01 mg and 1000 mg of any of the aforementioned conventional compositions and 0.1 to 1000 mg of any of the inhibitors of neurosteroid production.

Example 14

30

An orally administered capsule comprises between 150 mg and 750 mg, preferably 500 mg, of VICODIN[®] and 0.1 to 100 mg, preferably 0.5 mg, of dutasteride.

Example 15

An orally administered capsule comprises between 100 mg and 1000 mg, preferably 500 mg, of PERCOCET[®] and 0.1 to 100 mg, preferably 0.5 mg, of dutasteride.

Example 16

An orally administered capsule comprises between 1 mg and 250 mg, preferably 10, 20, or 40mg, of PROZAC[®] and 0.1 to 100 mg, preferably 0.5 mg, of dutasteride.

5

Example 17

An orally administered capsule comprises between 1 mg and 50 mg, preferably 10, 15, 2.5, 20, or 5 mg, of VALIUM[®] and 0.1 to 100 mg, preferably 0.5 mg, of dutasteride.

Example 18

10 An orally administered capsule comprises between 1 mg and 200 mg, preferably 5 mg, of OXYCONTIN[®] and 0.1 to 100 mg, preferably 0.5 mg, of dutasteride.

Example 19

15 An orally administered capsule comprises between 0.5 mg and 100 mg, preferably 2.5, 5, 10, 15, or 20 mg, of diazepam and 0.1 to 100 mg, preferably 0.5 mg, of dutasteride.

Example 20

An orally administered capsule comprises between 1 mg and 500 mg, preferably 10, 15, 30, 20, 100, 120 mg, of morphine and 0.1 to 100 mg, preferably 0.5 mg, of dutasteride.

20

Example 21

An orally administered capsule comprises between 10 mg to 1000 mg, preferably 100, 200 or 400 mg, of CELEBREX[®] and 0.1 to 5 mg, preferably 0.5 mg, of dutasteride.

25

Example 22

An orally administered tablet comprises between 1 mg and 100 mg, preferably 15, 30, or 60 mg, of codeine and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 23

30 An orally administered tablet comprises between 1 mg to 500 mg, preferably 25, 50, or 100 mg, of ZOLOFT[®] and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 24

A nicotine patch having between 0.1 to 150 mg, preferably 5 mg, of finasteride therein.

While the examples are presented in terms of pharmaceutical compositions in the form of tablets and capsules, it should be appreciated that they could take a solution or injectable dosage form. Moreover, it should be appreciated that for those substances without defined dosage regimens, such as alcohol, caffeine, and nicotine, an inhibitor of neurosteroid production can be added as required to achieve a reduction in dependence.

10 Example 25

A solution comprising any amount of wine, beer, or other alcoholic beverage, such as 6 ounces, 12 ounces, 1 pint, or 1 quart, and 0.1 to 150 mg, preferably 5 mg, of finasteride dissolved therein.

15 Example 26

An orally administered tablet comprises 0.25 mg norgestimate, 0.035 mg ethinyl estradiol, and 0.1 to 150 mg, preferably 5 mg, of finasteride.

Example 27

20 An orally administered tablet comprises between .5mg and 1 mg of norethindrone, 0.035 mg ethinyl estradiol, and 0.1 to 150 mg, preferably 5 mg, of finasteride.

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
30 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/m ² 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 cannabinoids, 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	ILLCIT 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.
BARBITURATE S			
		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

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
			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

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
			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

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
			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

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
			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-1-1-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.

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
			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.

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
			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

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
			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 unmedicated 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

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
			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.

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
HORMONES/CONTRACEPTIVES	ESTROGENS include: ethinyl estradiol and mestranol. PROGESTERON ES 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 pills, 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 are 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/ethinyl 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 scheduled 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

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
			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 is 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, severely 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

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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

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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.

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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.
		TRANLYCYPROMINE (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 doses 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	<i>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.</i> 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): <i>By mouth:</i> Oral dosing has not been studied in well-conducted trials in humans, and therefore no specific dose can be recommended. <i>By injection:</i> 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 this 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
DOPAMINE	ERGOT	Kaempferol, Myricetin, Isorhamnetin	The dose of bromocriptine will be different for different patients.
		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	

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		<i>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.</i> 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
			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	Methylphenidate 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. <i>Spancule</i> 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
			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. <i>Spansule</i> 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 neurosteroid production inhibitor in the manufacture of a medicament to prevent addiction or dependence on a substance of abuse.
2. Use of a neurosteroid production inhibitor and a pharmaceutical compound in the manufacture of a medicament to prevent addiction or dependence on a substance of abuse.
3. The use of claims 1 or 2 wherein the neurosteroid production inhibitor is a 5- α -reductase inhibitor.
4. The use of claim 3 wherein the 5- α -reductase inhibitor is finasteride.
5. The use of claim 4 wherein the finasteride is between about 0.1 and 150 mg.
6. The use of claim 4 wherein the finasteride is about 5 mg.
7. The use of claim 4 wherein the finasteride is administered at between about 0.1 and 150 mg/day.
8. The use of claim 4 wherein the finasteride is administered at about 5mg/day.
9. The use of Claim 2, wherein the pharmaceutical compound is a stimulant, contraceptive, tranquilizer, sedative, hypnotic, benzodiazepine, analgesic or barbiturate
10. A composition comprising a therapeutically effective dose of a pharmaceutical compound in combination with a therapeutically effective dose of an inhibitor of endogenous neurosteroid production to prevent addiction to or dependence on a substance of abuse.
11. The composition of claim 10 wherein the pharmaceutical compound is a stimulant, contraceptive, tranquilizer, sedative, hypnotic, benzodiazepine, analgesic or barbiturate
12. The composition of claim 11 wherein the stimulant is amphetamine, methylphenidate, dextroamphetamine, or mixtures thereof.
13. The composition of claim 12 wherein the stimulant comprises between 5 mg and 20 mg of methylphenidate.
14. The composition of claim 12 wherein the stimulant comprises between 5 mg and 60 mg of dextroamphetamine.
15. The composition of claim 12 wherein the stimulant comprises between 2.5 mg and 60 mg of a mixture of amphetamine and dextroamphetamine.
16. The composition of claim 11 wherein the contraceptive is ethinyl estradiol, mestranol, norethynodrel, norethindrone, norethindrone acetate, norgestimate, desogestrel, ethyndiol

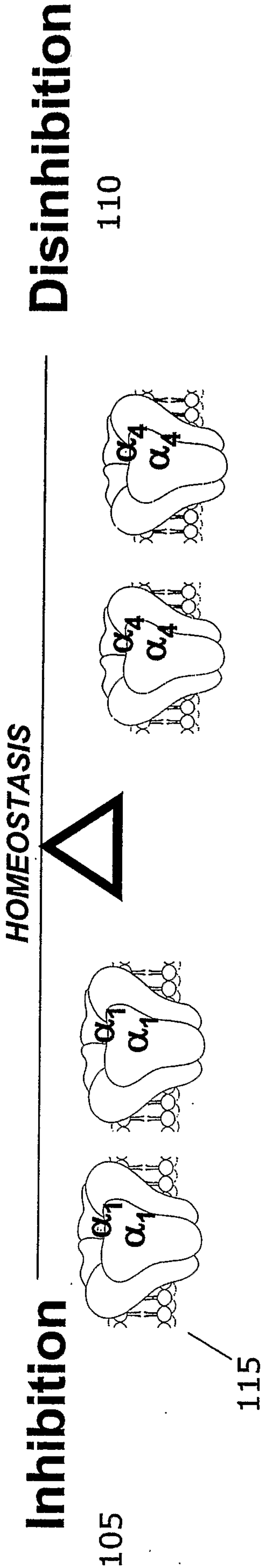
diacetate, norgestrel, levonorgestrel, medroxyprogesterone acetate, drospirenone or combinations thereof.

17. The composition of claim 16 wherein the contraceptive comprises 150 mg of medroxyprogesterone acetate.
18. The composition of claim 11 wherein the tranquilizer, sedative or hypnotic is chloral hydrate, chloral betaine, chlomethiazole, diphenhydramine, ethchlorvynol, promethiazine, zalpelon, zolpidem, zopiclone or combinations thereof.
19. The composition of claim 10 wherein the inhibitor of neurosteroid production is finasteride
20. The composition of claim 19 wherein the finasteride is between about 0.1 and 150 mg.
21. The composition of claim 20 wherein the finasteride is about 5mg.
22. The composition of any of claims 10 to 21 further comprising a pharmaceutically acceptable carrier.
23. A method of preventing addiction or reducing dependence to a pharmaceutical compound comprising administering a therapeutically effective dose of the pharmaceutical compound in combination with a therapeutically effective dose of an inhibitor of endogenous neurosteroid production wherein the therapeutically effective doses are effective to prevent addiction or reduce dependence on the pharmaceutical compound.
24. The method of claim 23 wherein the pharmaceutical compounds is a stimulant, contraceptive, tranquilizer, sedative, hypnotic, benzodiazepine, analgesic or barbiturate.
25. The method of claim 24 wherein the stimulant is amphetamine, methylphenidate, dextroamphetamine, or mixtures thereof.
26. The method of claim 25 wherein the stimulant comprises between 5 mg and 20 mg of methylphenidate.
27. The method of claim 25 wherein the stimulant comprises between 5 mg and 60 mg of dextroamphetamine.
28. The method of claim 25 wherein the stimulant comprises between 2.5 mg and 60 mg of a mixture of amphetamine and dextroamphetamine.
29. The method of claim 23 wherein the contraceptive is ethinyl estradiol, mestranol, norethynodrel, norethindrone, norethindrone acetate, norgestimate, desogestrel, ethyndiol diacetate, norgestrel, levonorgestrel, medroxyprogesterone acetate, drospirenone or combinations thereof.
30. The method of claim 29 wherein the contraceptive comprises 150 mg of medroxyprogesterone acetate.

31. The method of claim 24 wherein the tranquilizer, sedative or hypnotic is chloral hydrate, chloral betaine, chlomethiazole, diphenhydramine, ethchlorvynol, promethazine, zalpelon, zolpidem, zopiclone, or combinations thereof.
32. The method of claim 23 wherein the inhibitor of neurosteroid production is finasteride
33. The method of claim 32 wherein the finasteride is between about 0.1 and 150 mg.
34. The method of claim 32 wherein the finasteride is about 5mg.
35. The method of claim 23 further comprising a therapeutically effective dose of a compound that modulates expression of GABA_A subunits.
36. The method of claim 35 wherein the compound that modulates expression of GABA_A subunits is flumazenil.

Figure 1

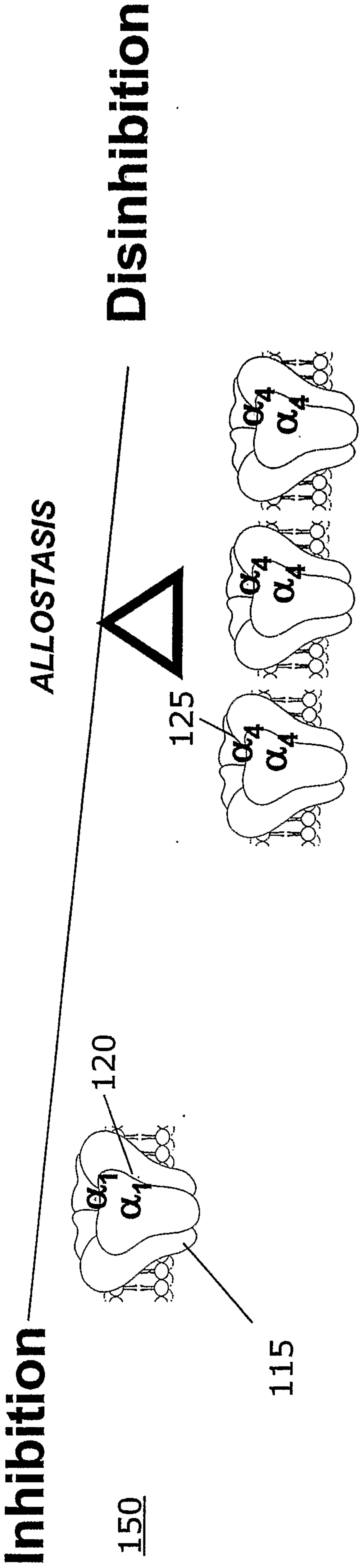
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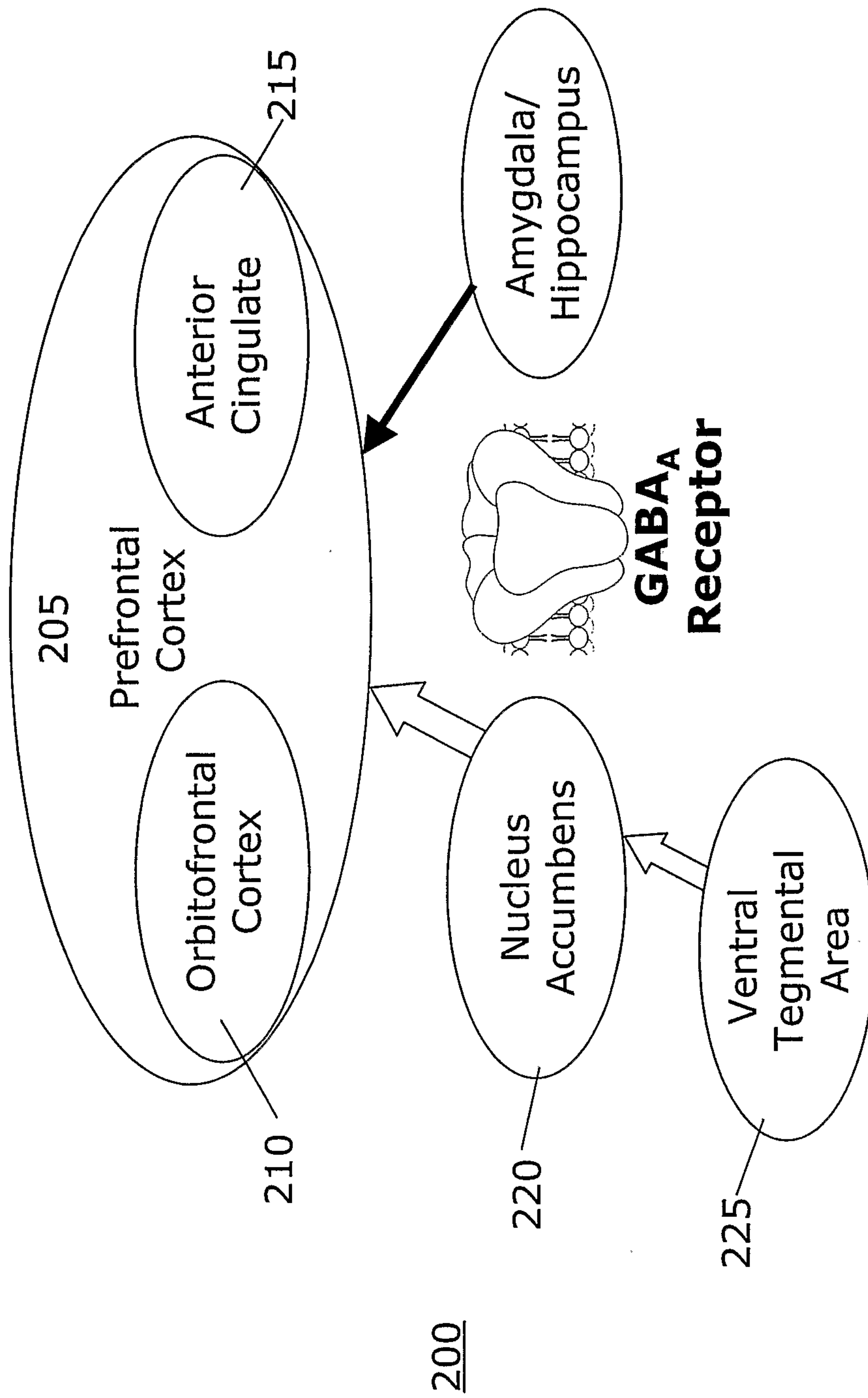
1/6

GABA_A Receptor Modulation

Reduced Inhibition



2/6

Figure 2

4/6

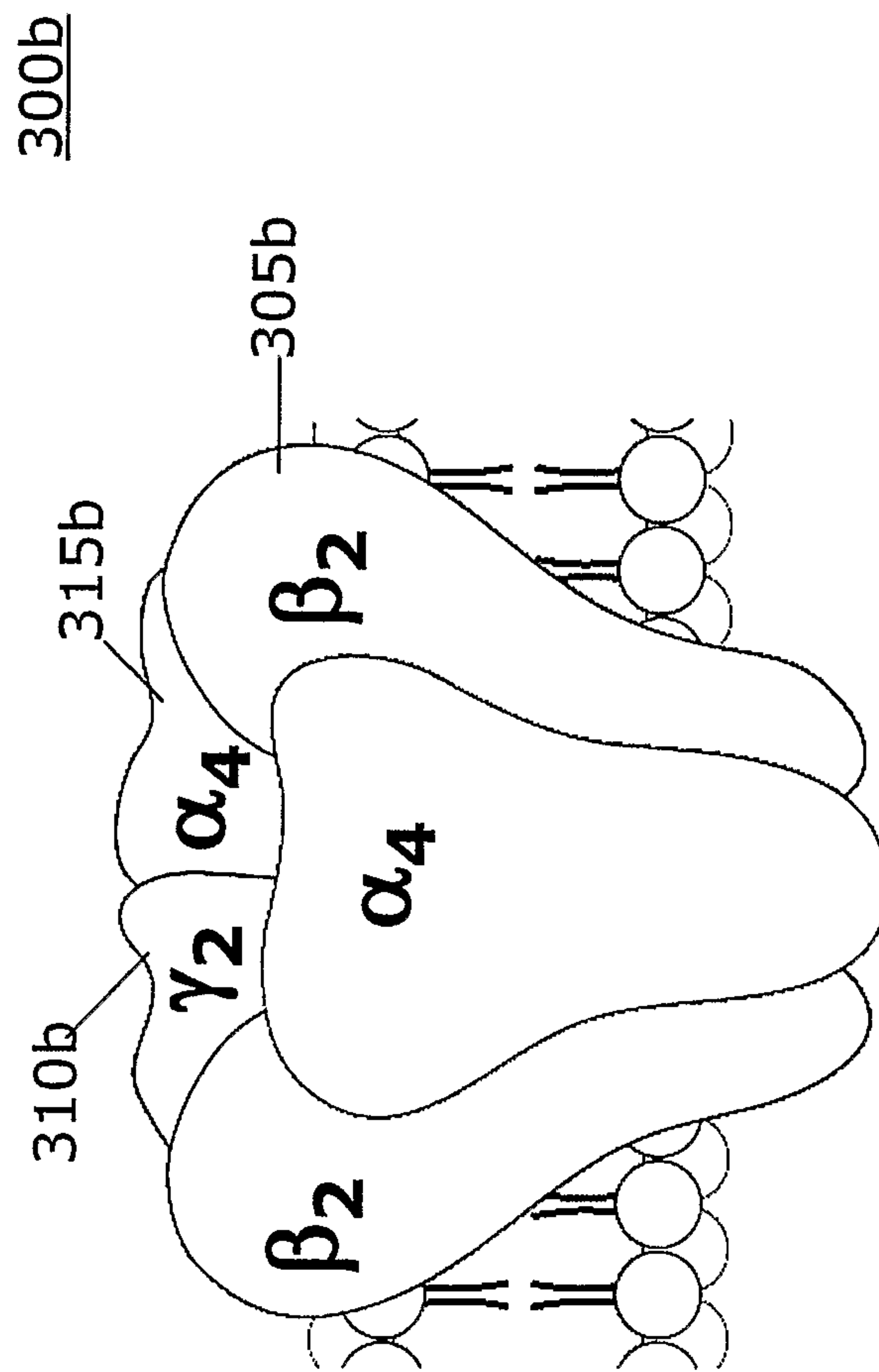
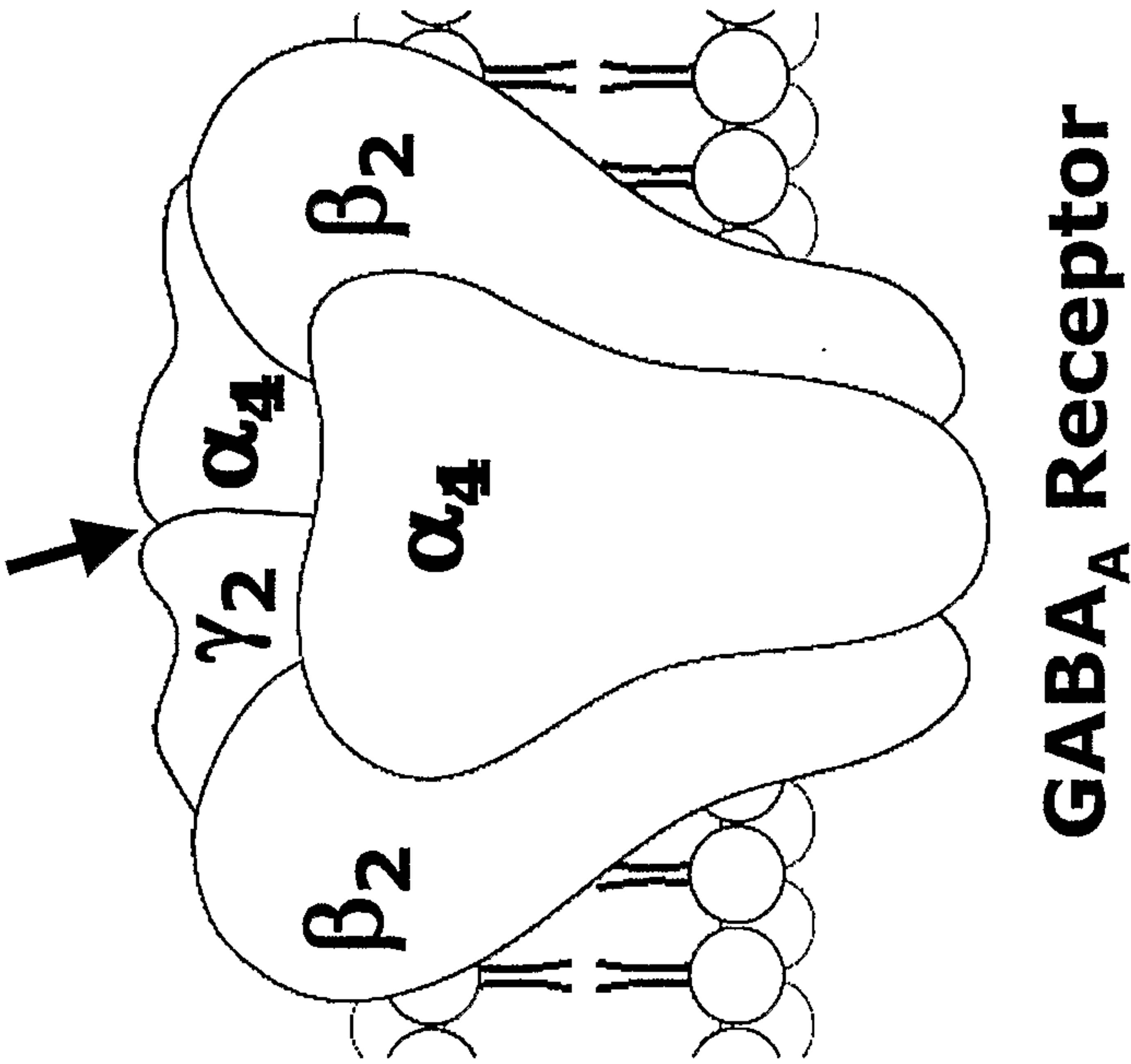
Figure 3b

Figure 3c

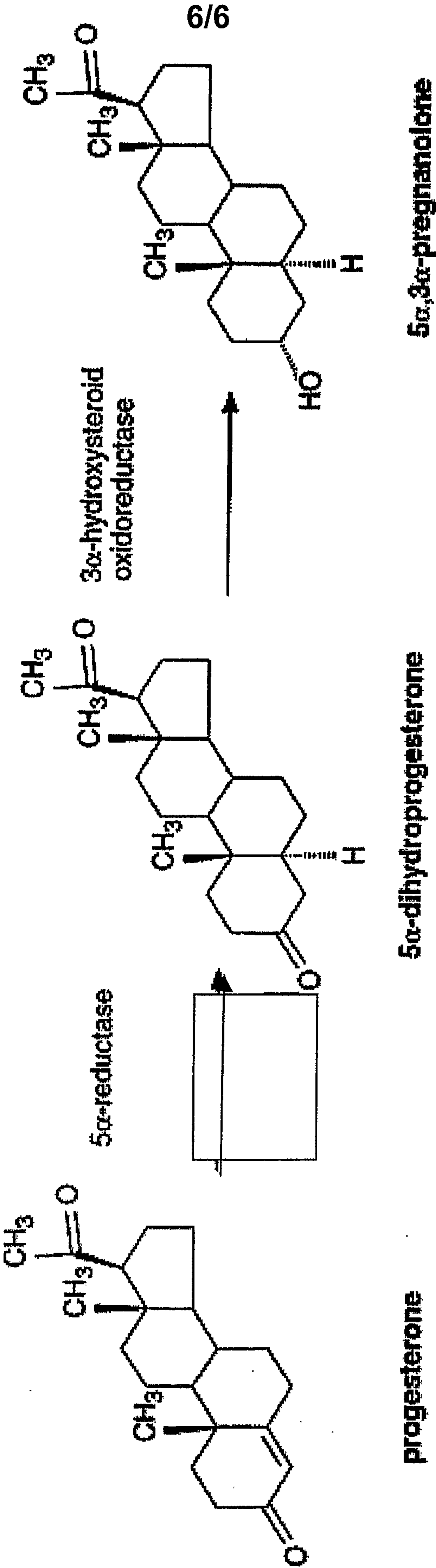
**BDZ does not bind
at α_4 subunits**



Withdrawal

**Depression
Anxiety
Impulsivity
Dysphoria**

Figure 4



Inhibition

HOMEOSTASIS

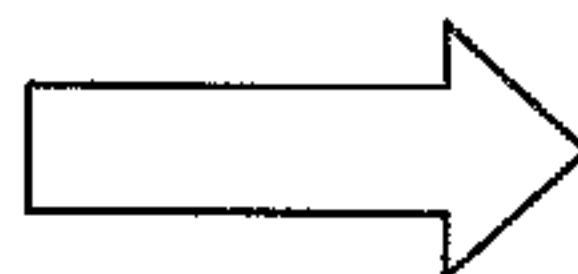
Disinhibition

105

110

115

GABA_A Receptor Modulation



Reduced Inhibition

Inhibition

ALLOSTASIS

Disinhibition

150

115

120

125

