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BY HAND

August 9, 2006

Dennis E. Ellis, Executive Director
Colorado Department of Health and Environment
4300 Cherry Creek Drive South
Denver, Colorado 80246-1530

Re: Petition to Add Anxiety to List of Debilitating Medical Conditions Pursuant to Colorado Constitution, Article XVIII § 14 and 6 CCR 1006-2

Dear Mr. Ellis:

On behalf of the undersigned physicians and patients, we hereby submit the enclosed petition, pursuant to 6 CCR 1006-2, to add severe anxiety and clinical depression to the list of debilitating medical conditions for which the medical use of marijuana is authorized under the Colorado Constitution, Article XVIII § 14. The enclosed petition demonstrates beyond doubt that the proposed condition is chronic, debilitating, may be specifically diagnosed, and provides ample scientific evidence that treatment with marijuana may have a beneficial effect, while there is little to no scientific evidence to the contrary.

There are many Coloradoans currently suffering from this debilitating medical condition who are depending on the Department's prompt action on this important petition. Please notify me of when this matter is set for hearing before the Board of Health. Thank you for your attention to this matter.

Respectfully Submitted,

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Robert J. Corry, Jr.

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Brian Vicente, Esq.
Sensible Colorado

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Larisa Lawrence,
Colorado Compassion Club

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Matthew Schnur,
Cannabis Therapeutics

Petition to Include Anxiety and Depression On Amendment 20

To:
Colorado Department of Public Health and Environment

Medical Marijuana Registry
Colorado Department of Public Health and Environment
HSVR-ADM2-A1
4300 Cherry Creek Drive South
Denver, Colorado 80246-1530

Submitted By:
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Reviewed and Edited:
Robert Melamede, PhD, University of Colorado at Colorado Springs
Robert J. Corry, Attorney, Member of NORML
Brian Vicente, Attorney, Executive Director of Sensible Colorado

Submitted this day,(9/13/06), for the people of Colorado suffering from above mentioned diseases.

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I. Introduction

In recent years the medical community has identified new molecular mechanisms of anxiety and depression, as well as the neuroanatomical structures associated with these phenomena. In addition, since the discovery of the cannabinoid receptor over 15 years ago, both human studies and animal models have found cannabinoids to be effective in the treatment of anxiety and depression. In this petition, we intend to prove:

1. Anxiety and depression are diagnosable
2. Anxiety and depression are chronic
3. Anxiety and depression can be debilitating
4. Anxiety and depression can be treated beneficially with the administration of medical marijuana

We shall begin this petition with personal doctoral testimony, enclosing the doctor's curriculum vitae, identifying his qualifications and experience (see attached after works cited). From here, we shall discuss the diagnosis of both diseases, followed by research identifying both mood disorders as chronic and debilitating. At this point, we shall change direction, focusing on the homologous cannabinoid CB1 receptor physiology between all mammals, and prove the validity of using animal models in the study of antidepressant/anxiolytic efficacy of pharmaceuticals. Next, we shall identify specific cannabinoids and their general antidepressant/anxiolytic activity. After these general mechanisms have been validated and discussed, we shall focus more directly on how marijuana shares specific therapeutic activities with currently prescribed mood stabilizers of nearly every class of pharmaceutical available for treatment of these disorders. Finally, we shall compare side effects of every drug mentioned in this paper to marijuana, and identify this plant as one of the safest treatments of these horrific conditions, before closing with subjective testimony by internationally recognized psychologists and medical experts of marijuana's safety and utility in treatment.

II. Personal Testimony:

My name is Dr. David J. Muller and I am a psychiatrist with a practice in Denver, CO. I earned my doctorate at George Washington University in Washington, D.C. and have been practicing psychiatric medicine for over 35 years. Through years of helping people regain control over their quality of life, I have had experience with every known psychological disorder to date.

I encourage my patients to be very candid with me. It is very important for me to know every aspect of a person's lifestyle in order to diagnose a disorder and find the best method of treatment for their condition. This is especially important when referring to substance abuse. There are many cases of psychosis due to substance abuse, whether it is alcohol, pharmaceuticals, or illicit/illegal drugs. There are also cases, particularly in those diagnosed with Depression or Anxiety Disorder, where an illicit drug helps

alleviate symptoms of these diseases. Many people have been using marijuana therapeutically along with prescribed treatment plans and have had great success in overcoming the often disabling symptoms of depression or Severe Anxiety Disorder. These people have been able to rejoin society and have very productive and happy lives.

Many years ago I started taking notice of how effective marijuana was in treating depression and anxiety disorders even though it was contrary to conventional methods. As a doctor I swore the Hippocratic Oath and it is my duty to explore every possible option for those in my care. I take a very conservative approach to medicine because my field deals with the mind and there is very little margin for error. Whenever a new technique, treatment, medication etc. becomes available, I research all relevant material and decide whether it has enough substantiated data before recommending it to my patient. I did the same thing with marijuana and found scientific proof and explanation as to why it is so effective in treating depression and anxiety disorders. The evidence (attached) has shown that marijuana is not only good for helping individuals manage the symptoms of anxiety and depression; some studies also imply that it may help a person overcome the disorders. Such profound results would be inhumane to ignore since depression and anxiety can be life threatening if left untreated.

On behalf of other doctors and patients who would benefit from using marijuana as part of their treatment plan, I am petitioning the Colorado Department of Public Health and Environment to add depression and anxiety disorders to Amendment 20 of the Colorado State Constitution. The Colorado Department of Public Health and Environment requires that a condition must be diagnosable, chronic and debilitating. Included in this petition is a synopsis of each condition along with current methods of treatment, side effects of conventional medications and the benefits of using marijuana.

III. Classification, Identification, and Typical Treatment of Anxiety:

(Reprinted from Rebecca J Frey, PhD, Gale Encyclopedia of Medicine, 2002)

Description

Anxiety disorders are the most common form of mental disturbance in the United States population. It is estimated that 28 million persons suffer from an anxiety disorder every year. These disorders are a serious problem for the entire society because of their interference with patients' work, schooling, and family life. They also contribute to the high rates of alcohol and substance abuse in the United States. Anxiety disorders are an additional problem for health professionals because the physical symptoms of anxiety frequently bring people to primary care doctors or emergency rooms.

DSM-IV defines twelve types of anxiety disorders in the adult population. They can be grouped under seven headings:

- Panic disorders with or without agoraphobia. The chief characteristic of panic disorder is the occurrence of panic attacks coupled with fear of their recurrence.

In clinical settings, agoraphobia is usually not a disorder by itself, but is typically associated with some form of panic disorder. Patients with agoraphobia are afraid of places or situations in which they might have a panic attack and be unable to leave or to find help. About 25% of patients with panic disorder develop obsessive-compulsive disorder (OCD).

- Phobias. These include specific phobias and social phobia. A phobia is an intense irrational fear of a specific object or situation that compels the patient to avoid it. Some phobias concern activities or objects that involve some risk (for example, flying or driving) but many are focused on harmless animals or other objects. Social phobia involves a fear of being humiliated, judged, or scrutinized. It manifests itself as a fear of performing certain functions in the presence of others, such as public speaking or using public lavatories.
- Obsessive-compulsive disorder (OCD). This disorder is marked by unwanted, intrusive, persistent thoughts or repetitive behaviors that reflect the patient's anxiety or attempts to control it. It affects between 2-3% of the population and is much more common than was previously thought.
- Stress disorders. These include post-traumatic stress disorder (PTSD) and acute stress disorder. Stress disorders are symptomatic reactions to traumatic events in the patient's life.
- Generalized anxiety disorder (GAD). GAD is the most commonly diagnosed anxiety disorder and occurs most frequently in young adults.
- Anxiety disorders due to known physical causes. These include general medical conditions or substance abuse.
- Anxiety disorder not otherwise specified. This last category is not a separate type of disorder, but is included to cover symptoms that do not meet the specific *DSM-IV* criteria for other anxiety disorders.

All *DSM-IV* anxiety disorder diagnoses include a criterion of severity. The anxiety must be severe enough to interfere significantly with the patient's occupational or educational functioning, social activities or close relationships, and other customary activities.

The anxiety disorders vary widely in their frequency of occurrence in the general population, age of onset, family patterns, and gender distribution. The stress and anxiety disorders caused by medical conditions or substance abuse are less age- and gender-specific. Whereas OCD affects males and females equally, GAD, panic disorder, and specific phobias all affect women more frequently than men. GAD and panic disorders are more likely to develop in young adults, while phobias and OCD can begin in childhood.

Anxiety disorders in children and adolescents

DSM-IV defines one anxiety disorder as specific to children, namely, separation anxiety disorder. This disorder is defined as anxiety regarding separation from home or family that is excessive or inappropriate for the child's age. In some children, separation anxiety takes the form of school avoidance.

Children and adolescents can also be diagnosed with panic disorder, phobias, generalized anxiety disorder, and the post- traumatic stress syndromes.

Causes and symptoms

The causes of anxiety include a variety of individual and general social factors, and may produce physical, cognitive, emotional, or behavioral symptoms. The patient's ethnic or cultural background may also influence his or her vulnerability to certain forms of anxiety. Genetic factors that lead to biochemical abnormalities may also play a role.

Anxiety in children may be caused by suffering from abuse, as well as by the factors that cause anxiety in adults.

Diagnosis

Many patients who suffer from anxiety disorders have features or symptoms of more than one disorder. Patients whose anxiety is accounted for by another psychic disorder, such as schizophrenia or major depression, are not diagnosed with an anxiety disorder. A doctor examining an anxious patient will usually begin by ruling out diseases that are known to cause anxiety and then proceed to take the patient's medication history, in order to exclude side effects of prescription drugs. Most doctors will ask about caffeine consumption to see if the patient's dietary habits are a factor. The patient's work and family situation will also be discussed. Laboratory tests for blood sugar and thyroid function are also common.

Diagnostic testing for anxiety

There are several short-answer interviews or symptom inventories that doctors can use to evaluate the intensity of a patient's anxiety and some of its associated features. These measures include the Hamilton Anxiety Scale and the Anxiety Disorders Interview Schedule (ADIS).

Treatment

For relatively mild anxiety disorders, psychotherapy alone may suffice. In general, doctors prefer to use a combination of medications and psychotherapy with more severely anxious patients. Most patients respond better to a combination of treatment methods than to either medications or psychotherapy in isolation. Because of the variety of medications and treatment approaches that are used to treat anxiety disorders, the doctor cannot predict in advance which combination will be most helpful to a specific patient. In many cases the doctor will need to try a new medication or treatment over a six- to eight-week period in order to assess its effectiveness. Treatment trials do not necessarily mean that the patient cannot be helped or that the doctor is incompetent.

There are several reasons why it is important for patients with severe anxiety symptoms to get help. Anxiety doesn't always go away by itself; it often progresses to

panic attacks, phobias, and episodes of depression. Untreated anxiety disorders may eventually lead to a diagnosis of major depression, or interfere with the patient's education or ability to keep a job. In addition, many anxious patients develop addictions to drugs or alcohol when they try to "medicate" their symptoms. Moreover, since children learn ways of coping with anxiety from their parents, adults who get help for anxiety disorders are in a better position to help their families cope with factors that lead to anxiety than those who remain untreated.

Thus, the Gale encyclopedia has identified anxiety disorders as a prevalent condition, affecting millions of Americans. The fact that anxiety related panic attacks are identified as a common reason for emergency room visits, we find the condition to be debilitating. This argument is strengthened further by the fact that an anxiety disorders diagnosis requires the condition to cause interference with work, family, or school.

IV. DSM-IV Criteria and Suggested Questions for the Diagnosis of Depression:

The DSM-IV is used by millions of psychiatrists in both medical and legal settings for the diagnosis of psychiatric conditions. Below is a synopsis of the criteria for diagnosing depression. In determining whether depression is debilitating, we find sleep disturbance, decreased energy, increased or decreased psychomotor activity, decreased concentration, and suicidal tendencies as symptoms. Clearly this condition is both diagnosable and debilitating.

Symptom	**DSM-IV diagnostic criteria**	**Suggested questions**
Depressed mood	Depressed mood most of the day, nearly every day	How has your mood been lately? How often does this happen? How long does it last?
Anhedonia	Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day	Have you lost interest in your usual activities? Do you get less pleasure in things you used to enjoy?
Sleep disturbance	Insomnia or hypersomnia nearly every day	How have you been sleeping? How does that compare with your normal sleep?
Appetite or weight change	Substantial change in appetite nearly every day or unintentional weight loss or gain (≥5% of body weight in a month)	Has there been any change in your appetite or weight?
Decreased	Fatigue or loss of energy	Have you noticed a decrease in

energy	nearly every day	your energy level?
Increased or decreased psychomotor Activity	Psychomotor agitation or retardation nearly every day	Have you been feeling fidgety or had problems sitting still? Have you slowed down, like you were moving in slow motion or stuck in mud?
Decreased concentration	Diminished ability to think or concentrate, or indecisiveness, nearly every day	Have you been having trouble concentrating? Is it harder to make decisions than before?
Guilt or feelings of worthlessness	Feelings of worthlessness or excessive guilt nearly every day	Are you feeling guilty or blaming yourself for things? How would you describe yourself to someone who had never met you before?
Suicidal ideation	Recurrent thoughts of death or suicide	Have you felt that life is not worth living or that you'd be better off dead? Sometimes when a person feels down or depressed they might think about dying. Have you been having any thoughts like that?

Diagnostic Categories For depression and Their Criteria for diagnosis:

Diagnostic category	**DSM-IV criteria**	**Duration**
Major depression	≥5 depressive symptoms, including depressed mood or anhedonia, causing significant impairment in social, occupational, or other important areas of functioning	≥2 weeks
Minor depression	2 to 4 depressive symptoms, including depressed mood or anhedonia, causing significant impairment in social, occupational, or other important areas of functioning	≥2 weeks
Dysthymia	3 or 4 dysthymic symptoms, including depressed mood, causing significant impairment in social, occupational, or other important areas of functioning	≥2 years

Depression is also chronic. Of all patients seeking treatment for depression, over half will have a relapse in symptoms[1a]. Indeed, there is a 60-90% recurrence of a third

major depressive disorder episode (MDD) in patients who have suffered two previous states of depression[2a]. There is also evidence implicating anxiety and depressive disorders as chronic, developing over time. Stressful events in life have been linked to both anxiety and depression[3a, 4a, 5a]. These traumatic effects can be quite chronic, as events in childhood can inflict anxiety and depressive disorders in adults[6a, 7a].

Now that we have addressed the diagnosis, chronic state, and debilitating factors of anxiety and depression, we begin to focus on the cannabinoid receptor and physiology. In the following discussions we shall demonstrate ligand-receptor mediated causes of depression and anxiety, identify relationships between synaptic transmission systems leading to these disorders, and regulation of the phytocannabinoids and endogenous cannabinoids in specific brain structures associated with alleviating these conditions by conventional methods.

V. Use of Animal Models in Cannabinoid Receptor CB1 Mediated Physiology:

The use of animal models for the study of psychiatric disorders is common in identifying anxiolytic, antipsychotic, anticonvulsant, and antidepressant drugs. Furthermore, the homology of the CB1 cannabinoid receptor and the consequently similar transduction mechanisms between the animal models described below and humans, makes these studies valid in interpreting plant derived CB1 agonists anxiolytic and/or antidepressant activities.

Invertebrate organisms are used as neurobiological models of synaptic transmission. This is due to the simplicity of identifying specific neural pathways being invoked under said experimental conditions. Such neurobiological invertebrate models include the saltwater mollusk *Aplysia californica*[1] and the locust *Schistocerca gregaria*[2]. Furthermore, invertebrates are also used in non-neural models of physiological processes, as in the sea urchin *Stronglyocentrotus purpuratus*, utilized in studies of the molecular mechanisms of fertilization and embryonic development[3].

The CB1 cannabinoid receptor is well conserved across both mammalian and lower species, while the peripheral CB2 receptor shows greater divergence. Indeed, a homolog to the CB1 receptor has been found in the Hydra, and similar to one of the functions in mammals, it induces a feeding response[4]. Salzet et al, 2000 was quoted as saying "the endogenous cannabinoid system is conserved throughout evolution from coelenterates to man"[5] . Both the endogenous cannabinoids anandamide and 2-AG have been identified in the cnidarian *H. vulgaris* and the mollusk *Aplysia*[6]. Besides the discovery of "human" known endocannabinoids in these invertebrates, identification of their hydrolytic enzyme, FAAH, in species of Hydra and Paracentrotus have been isolated[7]. Another endogenous cannabinoid, oleamide, is also hydrolyzed by FAAH. Both oleamide and FAAH were identified in the locust *Schistocerca gregaria* using radiolabeled oleamide. Sites were identified in the brain and gut tissues similar to that of humans[8,9].

Utilization of synthetic cannabinoid agonists allows the identification of putative cannabinoid receptors. Also, these hydrophilic cannabinoid receptor agonists do not bind to lipids, thus the researcher can study only receptor mediated effects. One study, employing the hydrophilic CB1 receptor agonist CP-55,940 radiolabeled with [^{3}H], searched for binding sites in the following species: chicken, turtle, frog, trout, and lamprey. Homologous binding sites were identified in all species except for the lamprey[10]. This suggests both sequence homology and identical brain distribution conservation throughout evolution in many divergent vertebrate species.

In concordance with validating the efficacy of cannabinoid pharmacology at the CB1 receptor between species, a single nucleotide polymorphism is seen in the amino acid sequences of rat and human CB1 receptors[11]. The rat CB1 receptor (473 amino acids) and the human CB1 receptor (472 amino acids) specifically share 97.3% sequence identity, and similarly share the following transduction mechanisms:

- Both species CB1 receptors are linked to negative feedback inhibition of adenylate cyclase formation[12]. This activity has been found to be initiated via a Gi/o mechanism, as determined by the receptors sensitivity to pertussis toxin[13].
- Within the N-terminal domain of the CB1 G-protein coupled receptor, there are 28 amino acids. These amino acids were exactly the same between rat and humans, and that while there are slight differences in both number and type of amino acid between mouse and human, the molecular weights were nearly identical[14].
- Both species receptors have been linked to K^+ concentration alterations[15], as well as lowered Ca^{2+} conductivity[16].
- Besides similar distribution patterns in specific brain regions(discussed below), both rodent and human CB1 receptors show similar densities throughout the life cycle[17].
- There are three N-glycosylation sites all found with high conservation in amino acid type and location in rat, mouse, and human CB1 receptors[18], and one variational N-glycosylation site with variational localization between rodent and human receptors. However, following mutation studies of similar GPC receptors, notably the β-adrenergic & muscarinic receptors; we find that removal of glycosylation sites is not essential to the receptors function[19].
- The "tetrad" of cannabinoid induced effects that are attributable to human physiology have been determined originally in a mouse model. This "tetrad" of effects includes catalepsy, reduced motility, analgesia, and reduction in body temperature[20]. In further examination with the use of synthetic THC analogues, structure activity relationships appear identical between rodents and humans.
- In measuring the concentrations of anandamide in both human and rat brains, it was determined that abundance is identical (20pmol/g wet weight) in all brain regions tested (hippocampus, cerebellum, and striatum) except the thalamus[21].

- In studying the molecular mechanisms of schizophrenia, rodent models are often implemented. When studying the efficacy of antipsychotics, animal models are typically employed, as the neurotransmitters dopamine and glutamate are implicated in the neurobiological mechanisms underlying this disease, and due to the homology of these pathways between species[22]. Specifically, ketamine is utilized to induce a schizophrenic model of psychosis, binding to N-methyl-D-aspartate (NMDA) receptors in both humans and rodents[23]. Antipsychotic pharmacological potential under these models can be detected by c-Fos expression patterns[24]. These patterns are concurrent with antipsychotic activity of cannabidiol (CBD), one of the primary phytocannabinoids, in brain distribution and efficacy in animal models and human[25].

Thus we find that there is validity in using both invertebrate and mammalian species in identifying behavioral and molecular mechanisms of pharmaceutical and endogenous physiology. For the sake of this paper, we shall only focus on human, rat, and mouse related peer reviewed research to deduce the validity of cannabinoids as anxiolytics and antidepressants. We have demonstrated both the sequence homology of the CB1 receptor and FAAH related hydrolysis, as well as G-protein coupling. Presynaptic transmission is regulated by both K^+ and Ca^{2+} currents. Brain distribution of mRNA transcripts, neuroanatomical distribution, and concentration of endogenous cannabinoids are all within similar regions and molarities, respectively.

Now that we have discussed the validity of rodent models in these studies, abundant research is available on the anxiolytic effects of cannabinoids. Both THC, a phytocannabinoid, and nabilone, a synthetic THC analogue, display anxiolytic properties in the elevated plus maze test[26]. Several research papers cite THC as having anxiogenic properties, however, also cite this phenomenon as occurring in predisposed individuals[27], while others regard it as controversial[28]. Other researchers discovered increases in aggression in CB1 knockout mice under the guidelines of the resident intruder test and an increase in the anxiety response in the light-dark box test[29]. CB1 knockout mice also give insight into endocannabinoid control over serotonergic and benzodiazepine mediated anxiolytic activity. These mice were administered the anxiolytic medicines buspirone and bromazepam and submitted to several models of anxiety testing. It was determined that proper efficacy of both these anxiolytics was severely impaired. Thus the authors concluded that 3-dimensional integrity of the CB1 receptor was required for benzodiazepine anxiolytic function[30]. Furthermore, impairment of buspirone, which elicits anxiolytic properties via the $5\text{-}HT_{1A}$ receptor, supports the view that anxiolytic activities of the serotenergic system are under endocannabinoid control[31,32]. Besides CB1 knockout rats, evidence for cannabinoid agonist anxiolytic activity comes indirectly through antagonists. Rimonabant, a CB1 antagonist exerts anxiogenic properties evident in the defensive-withdrawal test[33] and in the elevated-plus maze test[34].

VI. Effects of Cannabidiol, CBD:

As previously stated, several researchers believe THC to have an anxiogenic effect. If this phenomenon does exist, the efficacy of CBD as both an anxiolytic and antipsychotic clearly diminish the unwanted effect, as evidence indicates in the following tests. The first employed varying concentrations of CBD and THC to rats in the conditioned emotional response[35]. The second utilized the Vogel Conflict test[36], and the last used the elevated plus maze test[37,38]. All these researchers identified CBD as an anxiolytic compound in their tests, and furthermore, could not detect any noticeable side effects. The anxiolytic effects of CBD were diminished however, in doses over 100mg/kg body weight in the elevated plus maze tests, while effective dosages ranged from 2.5-10mg/kg body weight.

The anxiolytic effects of CBD have been investigated in healthy human volunteers as well. It was found that CBD (1mg/kg) completely diminished the anticipatory effects of THC (.5mg/kg) in the human subjects[39]. In a recent double blind study, again on healthy human volunteers, the anti-anxiety efficacy of CBD was compared to ipsapirone and diazepam, two commonly prescribed anxiolytic medicines, under a simulated public speaking test. The researchers concluded that CBD (300mg) was comparable in treatment success to ipsapirone (5mg) and diazepam (10mg), whereas the placebo control showed no efficacy[40]. Specific metabolic evidence is now available in human subjects identifying at least one aspect of the molecular mechanisms of anxiolytic activity of drugs and blood flow patterns correlating to anxiogenic states. Single-photon emission computed tomography is used to investigate localized blood flow in brain tissues. As the author states, the procedure in itself, can be considered an anxiogenic situation and as such, allows successful interpretation of anxiolytic drugs[41]. After studying regional blood circulatory patterns in brain tissues prior to, and after administration of CBD and several currently used anxiolytic medicines, the author concluded “CBD induced a pattern compatible with anxiolytic activity”.

Besides the use of anxiolytics which act on serotenergic and NMDA receptors, antipsychotics are often utilized in the treatment of anxiety. Most conventional and nonconventional antipsychotics are effective due to antagonism at the D_2 dopamine receptor[42]. Two common side effects of conventional antipsychotics (haloperidol being the stereotype) and nonconventional antipsychotics (clozapine being the stereotype) include hyperprolactinemia in blood serum, and Parkinson-like motor side effects as a result of the high density of D_2 receptors in the hypothalamic arcuate nucleus[43]. Recent work has been performed comparing anxiolytic attenuation by CBD and haloperidol in a dopamine based model[44]. It was discovered that CBD (15-60mg/kg) was as effective as haloperidol in alleviating antipsychotic and anxiolytic behaviors, however, CBD did not produce Parkinsonian symptomology (convulsions). Furthermore, only doses exceeding 240mg/kg of CBD were correlated to hyperprolactinemia. Clozapine, a nonconventional antipsychotic, results in fewer motor effects and higher anxiolytic effects because the drug also binds to NMDA receptors, in addition to D_2 receptors[23]. This expands anxiogenic mechanisms to a glutamate based model, in which ketamine is used as an

antagonist at the NMDA receptor. Expanding on previous work, anxiolytic and antipsychotic effects of CBD, haloperidol, and clozapine, were examined under the glutamate based model[45]. Consistent with previous work, haloperidol was the only drug to induce catalepsy, where CBD did not, even at doses reaching 480mg/kg. Furthermore, pharmaceutically induced Fos immunoreactivity for the three drugs has been evaluated[24]. Fos activity is measured in the dorsal striatum with the administration of haloperidol, reflecting the motor side effects. On the other hand, clozapine activates Fos expression only in the prefrontal cotex[24]. Consistent with the distribution patterns of clozapine, CBD activates Fos expression in the prefrontal cortex and not the dorsal striatum[25,46]. The only currently FDA approved cannabinoid in pharmaceutical form is Marinol™, a pill of THC dissolved in sesame oil. After discussing the anxiolytic and antidepressant effects of CBD, we find that marijuana is the only available source of this crucial phytocannabinoid in combating these diseases.

Thus we have demonstrated that anxiety can occur through serotenergic, glutamatergic, and dopaminergic pathways. Identification of currently used medications on these models has been elucidated, and the anxiolytic ability of CBD on these pathways has been verified to be effective.

VII. The Hippocampus, Cannabinoids, Anxiety, and Depression:

Being part of the limbic system, the hippocampus is cited as having regulation over emotion. The CB1 cannabinoid receptor has been identified by multiple research groups utilizing various radiolabeling and immunohistochemical techniques in brain regions associated with the regulation of anxiety and depression, including the amygdala, hippocampus, anterior cingulated cortex, and prefrontal cortex[47,48,49,50].

The main pharmaceuticals utilized in anxiety disorders employ chemicals acting on the serotonergic and NMDA systems in the limbic system[51, 52]. Furthermore, it has been discovered that both antidepressants and anxiolytics, at least in part, elicit their effects by the stimulation of neurogenesis in the hippocampus[53]. Fluoxetine is a commonly prescribed antidepressant that lead to the discovery of neurogenesis in the hippocampus, as this is the primary mechanism by which the drug induces its effect[54, 55]. Unfortunately, this process requires a chronic period of treatment, reflecting the several week time frame before actions of the antidepressant/anxiolytic occur[56]. Studies employing x-irradiation induced disruption of neurogenesis in the hippocampus completely inhibited anxiolytic and antidepressant pharmaceuticals abilities[54].

Exactly how the anxiolytic and antidepressant activity is induced by neurogenesis is unclear. However, researchers have identified underlying mechanisms of addiction in addition to psychiatric disorders related to neurogenesis deficiencies[53, 57]. This was discovered by studies chronically administering opiates, alcohol, nicotine, and cocaine. All previously stated drugs were found to decrease the rate of neurogenesis in the hippocampus[58, 59, 60, 61]. Upon discovery that CB1 receptor knockout mice display a

dramatic decrease in hippocampal neurogenesis[62], researchers immediately began investigating the role of the endocannabinoid system on this process.

Neural stem/progenitor cells are specifically localized within the dentate gyrus of the hippocampus. These cells are capable of exponential differentiation, producing up to several thousand new granule cells each day[63]. New circuitry becomes integrated with existing functional networks[64, 65], and has been correlated with changes in both learning and memory processes integrated in the hippocampus[66]. The importance of these cumulative findings in the antidepressant and anxiolytic activities of cannabinoid agonists comes from the finding that 95% of neural stem/progenitor cells were labeled with the CB1 receptor[67]. In studying the ligands for the activation of hippocampal neurogenesis, the authors identified HU-210, a synthetic agonist with a similar affinity to that of THC, and 2-AG, an endocannabinoid CB1 agonist, as chemicals which greatly increased hippocampal neural stem/progenitor cell mitosis[67].

Besides having neurogenic properties in the hippocampus, Fluoxetine, electroshock therapy, and cannabinoids have similar effects on synaptic plasticity[68]. Long term potentiation (LTP), is a stimulus frequency dependent form of synaptic plasticity[69], and is considered to be the most accurate model in studying synaptic plasticity relating to memory and learning in all mammals[70, 71, 72]. LTP also occurs in specific hippocampal structures such as the dentate gyrus and CA1 regions, where the CB1 cannabinoid receptor is found to be highly expressed[48, 73,74 ,75, 76]. Both of the endogenous cannabinoids anandamide and 2-AG have been demonstrated to inhibit LTP in the hippocampus[77, 78]. In consensus with the fact that phytocannabinoids elicit homologous pharmacological activity to endocannabinoids by reducing LTP[79] in the hippocampus, all CB1 activation studies with agonists of this receptor have found inhibition of formation of the field potential of LTP[80, 81, 82, 83, 84]. Under models of depressive disorder, varying regimes of stress evoking factors have demonstrated a regulatory influence over hippocampal synaptic plasticity[85, 86, 87, 88]. Fluoxetine and ECS therapy result in increases in dentate connectivity[89, 90, 91], but in doing so reduced any further high frequency induced enhancement of an excitatory post-synaptic potential (EPSP)[68], a requirement for induction of some types of LTP. Thus we find similar mechanisms of inhibition of LTP between marijuana, Fluoxetine, and ECS.

There is a general agreement concerning the short term memory effects of marijuana. These memory impairments have been implicated by selective cannabinoid actions on the CB1 receptor on information processing within the hippocampus[92, 93, 94, 95]. Recent evidence demonstrates a regulatory mechanism of antidepressants is inhibition of cAMP[96, 97]. Multiple studies have confirmed that activation of the CB1 cannabinoid receptor by agonists inhibits cAMP production[98, 99]. Consequently, this reduction in cAMP results in lack of substrate for phosphorylation of cAMP-dependent protein kinase, which has been identified as an essential modulatory mechanism in initiation of LTP[100]. Like Fluoxetine's effects on EPSP, CB1 cannabinoid receptor activation reduces EPSC magnitude in the hippocampal CA1 region[101]. Mood stabilizers like lithium have not only been found to activate G-protein coupled receptors[102, 103, 104], but also show down regulation of the receptor after chronic treatment[105, 106, 107, 108, 109]. The importance of this

in terms of therapeutic application is that like the previously mentioned antidepressants, lithium inhibits cAMP[110, 111]. Other G-protein receptor activating mood stabilizers that inhibit cAMP include carbamazepine[112, 113, 114], which also results in an increase in c-Fos expression[115] similar to CBD, and valproic acid[116]. Even tricyclic antidepressants like trimipramine exert homologous cannabinoid pharmacology on LTP produced via EPSC by glutamatergic transmission[117, 118].

In the previous discussion it seems that memory impairment is a common effect of several antidepressants, including cannabinoids. In this section, we find additional implications of homology between cannabinoids and several anxiolytic medications in this regard. To begin, GABAergic transmission is commonly known to increase by administration of diazepam[119, 120, 121, 122, 123, 124]. Most of the GABA increases by benzodiazepines occur in CA1 neurons of the hippocampus[125, 126]. Cannabinoids have been demonstrated in several models to induce cognitive alterations in mechanisms that resemble increased GABA concentrations in the hippocampus[94, 95]. In addition, phytocannabinoids have been shown to decrease GABA reuptake in CA1 hippocampal regions, which is known to hinder LTP[127, 128]. Memory formation in all mammals is known been to be disrupted upon benzodiazepine activation of the $GABA_A$ receptor[129]. This inhibitory mechanism of memory formation has been identified utilizing diazepam, and is specific to LTP models designed to mimic theta rhythms within the hippocampus[130, 131, 132, 133]. Theta waves localized within the hippocampus are correlated with memory processes[134], as well as emotional states; particularly fear and anxiety[135, 136, 137, 138, 139, 140, 141, 142]. GABA, at all 3 of its receptors, is known to be the major inhibitory neurotransmitter in all mammalian species[143, 144, 145]. Specifically, presynaptic GABA receptors IPSC's are involved in regulation of LTP[126, 146]. CB1 receptors are located on presynaptic terminals of GABAergic interneurons[147, 148], where they demonstrate their inhibition of LTP. In addition, the anxiogenic chemical cholecystokinin[149] is co-expressed in these GABA interneurons[150, 151]. CCK release is regulated by K^+ channels, which CB1 receptor agonists within the hippocampus inhibit[147, 151].

Thus we have demonstrated how both antidepressants and anxiolytics can inhibit LTP in the hippocampus, whether originating from glutamatergic EPSC or GABA IPSC. Memory loss is an effect of these drugs, as part of their therapeutic potential is dependent on inhibition of cAMP and LTP. Cannabinoids have now been demonstrated to exert beneficial effects homologous to many antidepressants and anxiolytics, as well as exert additional therapeutic effects by inhibiting CCK.

VIII. Other Brain Regions Associated With Cannabinoids Antidepressant/Anxiolytic Mechanisms:

Despite various mechanisms of action, enhancement of monoaminergic transmission is a common therapeutic effect of all antidepressants[152]. Decreases in both serotonergic (5-HT) and noradrenergic (NE) transmission is correlated with the advancement of depression[153]. Injections of URB597, a fatty acid amide hydrolase (FAAH) inhibitor which increases endocannabinoid levels, results in neuronal firing

activity and 5-HT outflow from the hippocampus to other brain regions[154]. Furthermore, these authors identify anandamide increases through blockade of its hydrolysis to have similar antidepressant activity to venlafaxine, a 5-HT/NE reuptake inhibitor; nefazodonel, a 5-HT antagonist, and mirtazepine, an adrenergic antagonst[154].

The hypothalamic-pituitary-adrenal (HPA) axis has long been implicated in having a critical role in the pathogenesis of depression and mood disorders[155]. An antidepressants therapeutic efficacy is correlated with its ability to suppress certain types of HPA activation[156, 157, 158]. Depressed patients are found to have elevated cerebrospinal and plasma levels of the HPA hormones corticotrophin-releasing factor (CRF/ CRH) and cortisol[159, 160]. In depressed individuals, the typical glucocorticoid hormone induced negative feedback on the HPA axis doesn't appear to exist as it does in healthy individuals, resulting in hyperactivation of the system in all studies from man[161, 162, 163] and other species[164, 165, 166, 167, 168]. Indeed, patients who do not express an equilibrium of the HPA axis from drug treatment have a higher probability to experience relapse or smaller chances of long term success in treatment[162, 169, 170]. Research employing electrophysiological technologies have identified CB1 cannabinoid receptors in the paraventricular nuclei of the hypothalamus, and like in the hippocampus, are localized to terminals involved in glutamatergic transmission[171]. In addition, these synaptic terminals play an integral role in activating CRH secretory cells[171]. One might think this to be suggestive of an endocannabinoid control over the HPA axis, and many researchers have agreed that cannabinoids can modulate anxiety and depression through HPA axis activation-inhibition[154, 172, 173, 174]. Just two years ago, it was discovered that stress induced increases in the activation of the HPA axis is attenuated by inhibiting endocannabinoid uptake via disruption of this systems signaling through both genetic disruption and/or pharmacological disruption of the CB1 receptor[175, 176]. A major function of the hippocampus is regulation over feedback of outputs of the HPA axis[177, 178, 179], which may demonstrate a connection between the antidepressant/anxiolytic effects of cannabinoids in both the hippocampus and HPA. Endocannabinoid concentrations throughout the brain, but particularly within the HPA, is affected by pharmacological manipulation (antagonism such as SSRI's and dopamine D2 receptors) of monoaminergic receptors [180, 181]. One research group has recently discovered an endocannabinoid regulatory mechanism in the antidepressant activity of the tricyclic pharmaceutical desipramine. They found that after 21 days of treatment with desipramine, the CB1 cannabinoid receptor of both the hippocampus and hypothalamus display up-regulation, while within the prefrontal cortex and amygdala, no changes were identified[182]. Desipramine exerts its pharmacological properties via inhibition of NE reuptake and therefore potentiates noradrenergic synaptic transmission[183, 184]. Studies utilizing both in vivo and in vitro on both rats and humans have demonstrated cannabinoid CB1 receptors of the hippocampus and hypothalamus regulate NE synaptic transmission mechanisms negatively [185, 186]. Therefore, we find that up-regulation of CB1 cannabinoid receptors in these two brain structures decrease NE transmission via an increase in presynaptic CB1 density[182]. In the forced swim test with rodents, increases in plasma corticosterone levels are observed, however, significant reductions in the levels of this glucocorticoid are seen with chronic treatment of desipramine[182]. The reduction in corticosterone by desipramine is inhibited when pretreatment with AM251, a CB1 receptor antagonist, is given before

desipramine. Thus this tricyclic antidepressant's efficacy depends on CB1 receptor functionality. To further support this fact, testing for c-Fos expression in the paraventricular nuclei of the hypothalamus found decreases in c-Fos expression under all stressor models employed, while these reductions in expression levels were again, completely occluded by AM251[182].

IX. Additional Comments on Marijuana's Antidepressant/Anxiolytic Activity:

The enzyme fatty acid amide hydrolase (FAAH) is responsible for the breakdown of both anandamide and 2-AG after their activation of the cannabinoid CB1 receptor[187, 188, 189]. The FAAH enzyme can be pharmacologically blocked by specially designed serine protease inhibitors bearing activated carbonyl groups[190], including URB532 and URB597[191, 192]. URB597 is found to have an anxiolytic effect in rats, and this emotional effect is completely inhibited by Rimonabant, a CB1 receptor antaginonist[190]. The anxiolytic effects of URB597 was determined by the same model used to determine the anxiolytic efficacy of benzodiazepines, where the rodents are found to both spend more time in open compartments and make more entries into them, under the model of the plus maze test[193, 194]. As previously discussed, both phytocannabinoids and endogenous cannabinoids behave as agonists at the CB1 receptor. Thus, competition between anandamide, THC, and CBD for the CB1 cannabinoid receptor can result in higher anandamide levels, which in turn, results in an anxiolytic effect.

Both researchers and medical doctors have found marijuana to be a safe therapeutic treatment for mood disorders. Doctors report of the subjective benefits they see in their patients primary and secondary symptoms of many psychiatric disorders[195, 196, 197, 198, 199].

Most prominently, Harvard professor Dr Lester Grinspoon, pioneer in the use of Lithium for the treatment of bipolar disorder, has advocated the use of medical marijuana as both an antidepressant and mood stabilizer. His case studies demonstrate efficacy and safety in using marijuana to replace other antidepressants, as well as being taken in combination with other drugs[200].

X. A Comparison of Side Effects of Anxiolytics and Antidepressants with Similar Efficacies in Therapeutic Potential to Marijuana:

We have discussed the similarities between various cannabinoids, anxiolytics, and antidepressants. In invoking the Hippocratic Oath, a doctor seeks the treatment most effective in alleviation of the illness while inflicting the least amount of side effects. Before closing the paper, we now turn to the side effects of the medications that have been compared to cannabinoids. Unless otherwise cited, the information is taken from a PDR[201].

Buspar - Buspirone hydrochloride, used in the treatment of anxiety disorders. This drug cannot be used with MAOI antidepressants. Often takes 1-2 weeks of use before desired effects occur. Common side effects include dizziness, dry mouth, fatigue, headache, nausea, nervousness, pain, weakness in hands, and unusual excitement. Less common side effects include anger and/or hostility, blurred vision, confusion, constipation, loss of concentration, depression, rapid heart beat, stomach and abdominal upset, rash, tremors, tingling, urinary incontinence, and vomiting. A special warning on this medication notes that its side effects are completely unpredictable.

Clozapine – Clozaril, a typical antipsychotic used in the treatment of schizophrenia, also finds use as an anxiolytic. May cause agranulocytosis, a lethal white blood cell disorder. As such, patients are required to be monitored for the first 6 months on this medication via weekly blood tests. Approximately 1% patients develop this WBC disease. Seizures also occur in 5% of patients. Common side effects include: Abdominal discomfort, agitation, confusion, constipation, dizziness, fainting, fever, headache, heartburn, high blood pressure, loss or slowness of muscle movement, low blood pressure, nausea, nightmares, heart conditions, salivation, tremors, vertigo, vision problems, vomiting, and weight gain. Less common side effects include: anemia, angina, anxiety, blocked intestine, blood clots, bluish tinge in the skin, breast pain, bronchitis, bruising, involuntary eye movement, delusions, depression, difficult or labored breathing, disorientation, ear disorders, ejaculation problems, fatigue, fluid retention, frequent urination, hallucinations, hives, hot flashes, impacted stool, inability to hold urine, inability to urinate, increase or decrease in sex drive, involuntary movement, memory loss, muscle pain, nose bleed, painful menstruation, paranoia, pneumonia, skin inflammation, slurred speech, stomach pain, vaginal infection, as well as yellow skin and eyes.

Dalmane- Flurazepam Hydrochloride, a benzodiazepine prescribed for anxiety and insomnia. Withdrawal symptoms can occur from abrupt discontinuation of use. Common side effects include: dizziness, drowsiness, falling, lack of muscular coordination, light-headedness, and staggering. Less common side effects may include: bitter taste in mouth, blurred vision, body and joint pain, burning eyes, chest pains, constipation, depression, diarrhea, exaggerated feeling of well-being, genital and urinary tract disorders, hallucinations, headache, heartburn, hyperactivity, itching, loss of appetite, low blood pressure, nausea, rapid, fluttery heart beat,, shortness of breath, intestinal pain, vomiting, and weakness. This medication can have harmful drug interactions with anti-histamines, such as benadril and tavist, narcotic pain killers, such as Tylenol with Codeine, and tranquilizers, such as Librium and Valium.

Diazepam- Valium, A benzodiazepine which can be extremely habit-forming and addictive. Patients may experience withdrawal symptoms upon abrupt discontinuation of use. Common side effects include: fatigue, light-headedness, and loss of muscle coordination, however abdominal and muscle cramps, convulsions, sweating, tremors and vomiting can all be common side effects from abrupt withdrawal. Less common side effects include: anxiety, blurred vision, changes in sex drive, confusion, constipation, depression, difficulty urinating, dizziness, double vision, hallucinations, inability to hold urine, low blood pressure, nausea,

overstimulation, rage, seizures, skin rash, slurred speech, tremors, vertigo, and yellowing of both the eyes and skin. It is also noteworthy that this medication should not be used by patients with acute narrow-angle glaucoma. This drug cannot be prescribed to patients who are taking Prozac, Tagamet, or several anti-seizure drugs such as Dilantin.

Desipramine- Norpramin, a tricyclic antidepressant which has been known to have fatal reactions when taken with MAOI antidepressants. This medication typically takes 2-3 weeks for signs of improvement to be noticed. Common side effects include: abdominal cramps, agitation, anxiety, black tongue, black, red or blue spots on the skin, blurred vision, breast development in males, confusion, constipation, delusions, disorientation, drowsiness, excessive or spontaneous flow of milk, fatigue, fever, frequent urination or difficulty in urinating, hallucinations, heart attack, heart beat irregularities, hepatitis, high or low blood pressure, high or low blood sugar, hives, impotence, increased or decreased sex drive, inflammation of the mouth, insomnia, intestinal blockage, lack of coordination, loss of appetite, loss of hair, nausea, nightmares, painful ejaculation, ringing in ears, seizures, sore throat, stomach pain, stroke, swelling of testicles, tremors, visual problems, vomiting, weakness, worsening of psychosis, and yellowed skin and whites of eyes. This medication should never be used if you have recently had a heart attack, thyroid disease, seizure disorder, or glaucoma. This drug will have adverse reactions with Prozac, thyroid medications, Proventil, and other drugs that improve breathing.

Effexor- Venlafaxine Hydrochloride, prescribed for the treatment of depression and abnormal anxiety. Fatal reactions are known to occur when taking this medication with the MAOIs Nardil and Parnate. Therapeutic effects typically take several weeks to show visible signs. Common side effects include: abnormal vision, belching, bronchitis, changeable emotions, chest pain, difficult or labored breathing, inflammation of the prostate gland, inflammation of the vagina, irregular uterine bleeding, lockjaw, loss of touch with reality, neck pain, purple patches on the skin, swelling due to fluid retention, vertigo, and weight gain. Less common side effects include: acne, anemia, angina pectoris, arthritis, asthma, bladder pain, blood or plus in the urine, breast pain, bone pain, cataracts, blenching or grinding of teeth, colitis, decreased muscle tone, double vision, eczema, excess menstrual flow, excessive urination, eye disorders or pain, fainting, hair loss, hemorrhoids, high or low blood sugar, high cholesterol, increased sex drive, infection, lack of menstruation, middle ear inflammation, mouth sores, muscle spasms, nerve pain, pneumonia, cirrhosis, rectal and vaginal hemorrhage, seizures, tendonitis, urinary incontinence, and vaginal discharge.

Fluoxetine- Prozac hydrochloride, an antidepressant medication used in extreme cases, as well as in the treatment of obsessive-compulsive disorder. Thus it is also used as an anxiolytic. Fatal reactions are known to occur when Prozac is prescribed in combination with MAOI antidepressants. Relief from depression takes up to four weeks. Common side effects include abnormal dreams, abnormal ejaculation, agitation, amnesia, anxiety, bronchitis, changeable emotions, confusion, conjunctivitis, decreased sex drive, fatigue, dry eyes and mouth, ear pain, flu symptoms, frequent urination, gas, hemorrhage, high blood pressure, impotence,

inability to fall or stay asleep, increased appetite, indigestion, nausea, nervousness, rash, ringing in the ears, sinus or nasal inflammation, tremors, vision problems, vomiting, weight gain, and yawning. Less common side effects include: abnormal gait, abnormal stoppage of menstrual flow, acne, arthritis, asthma, bone pain, breast pain, loss of consciousness, convulsions, dark, tarry stool, difficulty in swallowing, facial swelling due to fluid retention, fever, hair loss, hallucinations, hives, hostility, infections, inflammation of the stomach lining, involuntary movement, irregular heartbeat, lack of muscle coordination, mouth inflammation, muscle spasm, nose bleed, paranoid reaction, pelvic pain, throbbing heartbeat, chest pain, rash, tooth problems, urinary disorders, vertigo, vision disturbances, vomiting, and weight loss. Rare side effects include: antisocial behavior, bleeding gums, blood clots, blood in urine, bloody diarrhea, bruising, coma, deafness, dehydration, diabetes, double vision, enlargement of liver, excess growth of facial hair, excess uterine or vaginal bleeding, eye bleeding, fluid build-up in lungs, gallstones, glaucoma, gout, heart attack, heart failure, hepatitis, high blood sugar, inability to control bowel movements, inflammation of eyes and eyelids, irregular heartbeat, kidney disorders, menstrual disorders, miscarriage, muscle spasms, psoriasis, rheumatoid arthritis, shingles, skin inflammation and disorders, spitting blood, stomach and intestinal hemorrhage, stomach ulcer, stroke, suicidal thoughts, temporary cessation of breathing, urinary tract disorders, and vomiting blood. Prozac cannot be prescribed with other antidepressants and anxiolytics such as Elavil, Xanax, Valium, and Tegretol. It may also not be prescribed with antipsychotics, such as Haloperidol and Clozapine. The effects of this drug have not been evaluated on pregnancy nor breast feeding.

Haloperidol- Haldol, used to treat severe behavior problems including hyperactivity and anxiety. The most significant side effect of this drug is tardive dyskinesia, characterized by severe involuntary muscle spasms and twitches in the face and body which can be permanent. This drug may also have adverse effects with caffeinated beverages and alcohol. Common side effects include: abnormal secretion of milk, acne=like skin reactions, agitation, anemia, anxiety, blurred vision, breast pain, breast development in males, cataracts, catatonic state, chewing movements, confusion, constipation, coughing, deeper breathing, dehydration, depression, dizziness, drowsiness, epileptic seizures, exaggerated feeling of well-being, hair loss, hallucinations, headache, heat stroke, high fever, high or low blood pressure, high or low blood sugar, impotence, inability to urinate, increased sex drive, indigestion, involuntary movements, irregular menstrual periods, liver problems, loss of appetite, muscle spasms, nausea, Parkinson-like symptoms, persistent abnormal erections, physical rigidity, protruding tongue, puckering of mouth, puffing of cheeks, rapid heartbeat, rotation of eyeballs, skin eruptions, sleeplessness, swelling of breasts, twitching in the body, neck, shoulders, and face, vertigo, visual problems, vomiting, wheezing, and yellowing of skin and whites of eyes. Those with Parkinson's disease, severe heart or circulatory disorders, glaucoma, seizures, or who have ever had breast cancer should never use this medications. This drug cannot be used in conjunction with certain antidepressants including Elavil, Tofranil, Prozac, Tegretol, and Lithium. It should also not be used

with other anti-seizure drugs or blood-thinning medications. Furthermore this drug should not be used by women who are pregnant or breast-feeding.

Imipramine- Tofranil, a tricyclic antidepressant which can have fatal effects when used in conjunction with MAOI antidepressants. Improvements typically begin within 1-3 weeks of beginning treatment. Missing a single dose can have adverse effects. Common side effects include: abdominal cramps, agitation, anxiety, black tongue, bleeding sores, blood disorders, blurred vision, breast development in males, confusion, congestive heart failure, constipation or diarrhea, fever, delusions, disorientation, dizziness, drowsiness, episodes of elation or irritability, excessive or spontaneous flow of milk, fatigue, frequent urination or difficulty or delay in urinating, hair loss, hallucinations, headache, heart attack, heart failure, high blood pressure, high or low blood sugar, high pressure of fluid in the eyes, hives, impotence, increased or decreased sex drive, inflammation of the mouth, insomnia, intestinal blockage, irregular heartbeat, light-headedness, loss of appetite, nausea, nightmares, ringing in the ears, seizures, swelling due to fluid retention, especially in the face or tongue, swelling of testicles, tendency to fall, numbness in hands and feet, tremors, visual problems, vomiting, weight gain or loss, and yellowed skin and whites of eyes. This drug should not be prescribed if the patient is at risk or recovering from a heart attack. Patients taking thyroid medication or with narrow-angled glaucoma should not take this medication as well.

Lithium- Eskalith, used to treat both bipolar and manic-depressive illness. As a hit-or-miss drug too low a dose will have no effect while too high a dose will lead to Lithium poisoning. It is recommended to drink a minimum of 10-12 glasses per day to reduce the potential of harmful side effects. Patients are also advised to eat diets including minimal salt. Common side effects that occur upon initial use include: discomfort, frequent urination, hand tremor, mild thirst, and nausea. Other typical side effects include: abdominal pain, black-out spells, cavities, coma, confusion, dehydration, dizziness, dry hair and mouth, fatigue, gas, hair loss, hallucinations, increased salivation, indigestion, involuntary tongue movements, involuntary urination or bowel movements, irregular heartbeat, itching, loss of appetite, low blood pressure, muscle rigidity and twitching, painful joints, poor memory, restlessness, ringing in the ears, seizures, sexual dysfunction, slowed thinking, swelling tightness in chest, vision problems, vomiting, weight gain or loss, This medication should only be used in extreme cases if the patient also suffers from kidney problems, brain or spinal cord disease. Patients should also avoid caffeinated beverages. This drug has adverse reactions with the blood pressure medication Capoten and Vasotec, amphetamines, serotonin boosting antidepressants, anti-inflammatory medications, diuretics, and tetracyclines. Lithium id extremely harmful to babies, and appears in breast milk.

Remeron- Mirtazapine, prescribed for the treatment of major depression. Common side effects include: abnormal dreams and thinking, constipations, dizziness, cry mouth, flu-like symptoms, increased appetite, sleepiness, weakness, and weight gain. Less common side effects include: back pain, confusion, difficult or labored breathing, fluid retention, frequent urination, muscle pain, nausea, swelling of ankles and hands, and tremors. Fatal reactions are known to occur when prescribed in

combination with the anti-depressants Nardil or Parnate. It is unknown whether this drug can be passed to infants through breast milk.

Serzone- Nefazodone Hydrochloride, used in the treatment of severe depression. Common side effects include: blurred or abnormal vision, confusion, constipation, dizziness, dry mouth, nausea, sleepiness, and weakness. Less common side effects include: abnormal dreams, cough, decreased concentration, diarrhea, flu-like symptoms, increased appetite, and water retention. Rare side effects include: breast pain, chills, decreased sex drive, difficulty urinating, fever, lack of coordination, ringing in ears, stiff neck, urinary tract infections, and vaginal inflammation. Serious heart problems can result when combing Serzone with Orap, Seldane, Hismanal, or Propulsid. Fatal reactions can occur with MAOIs.

Tegretol- Carbamazepine, used in the treatment of seizure disorders including epilepsy, neuralgia, alcohol withdrawal, and emotional disorders. Common side effects include: dizziness, drowsiness, nausea, unsteadiness, and vomiting. Other side effects include: abdominal pain, abnormal heart beat and rhythm, abnormal involuntary movement, aching joints and muscles, agitation, anemia, blood clots, blurred vision, chills, confusion, congestive heart failure, constipation, depression, diarrhea, fainting and collapse, fatigue, fever, fluid retention, frequent urination, hair loss, hallucinations, hepatitis, impotence, inability to urinate, inflammation of the mouth, tongue and eyes, involuntary movements of the eyeball, kidney failure, labored breathing, leg cramps, liver disorders, loss of appetite, loss of coordination, pancreatitis, pneumonia, reddish or purplish spots on the skin, ringing in the ears, skin inflammation and scaling, skin pealing, speech difficulties, tingling sensation, worsening of high blood pressure, as well as yellow eyes and skin. This medication should not be taken if you have a history of bone marrow depression or a sensitivity to tricyclic antidepressants.

Marijuana – Potential side effects include: respiratory disorders, decreased pulmonary function, *possible* increased risk of emphysema and pulmonary cardiac arrest, premature ventricular contractions, decreased sperm count and motility, as well as menstrual abnormalities (www.pdrhealth.com).

Marijuana is considerably safer than all of these currently prescribed medications that could potentially be replaced or co-administered with marijuana to reduce the amount of either drug required for therapeutic potential. Other than the potential synergistic effects of medications that lower blood pressure, fatal cannabinoid interactions could not be identified through extensive searches of PubMed and other medical databases. Indeed, some research points to an anxiogenic potential to THC, but fail to propose an accepted molecular mechanism of this phenomena, as clearly as the mechanisms on how THC and other cannabinoids serve to be anxiolytics. The mood elevation and relaxation effects of marijuana is proposed to be elicited primarily by THC[202, 203]. We have previously discussed the efficacy and safety of CBD in various disease models, as well as healthy volunteers, with unanimous agreement in the discovery of no side effects. Given the potential of abuse with any drug that elevates mood and/or acts within the limbic system, medical marijuana should be regulated under direct supervision of a licensed psychiatrist. However, given the therapeutic potential of the cannabinoids, how their antidepressant and anxiolytic activity share homologous

mechanisms of action to the above mentioned medications, and the significantly smaller amount of side effects as well as less harmful, it seems obvious that marijuana might- and indeed does- have a beneficial effect for these debilitating medical conditions. Doctors should be permitted to follow the Hippocratic Oath and be sanctioned to recommend medical marijuana for treatment of these diseases.

XI. Conclusion:

Marijuana has been used for centuries as a medicine and to this day few deaths, if any, have been directly linked solely to marijuana use. In these previous discussions we began by demonstrating homology between rodent and human cannabinoid receptors, identifying a <97% homology, and relatively equal concentrations of the endocannabinoids in the same brain regions. We have shown the similar transduction mechanisms involved by this system between species, and shown how these same animal models are being used for the discovery of new, potentially therapeutic medicines. Furthermore, scientists have performed tests in healthy and diseased human patients with specific cannabinoids, as well as whole plant material, and have found no side effects from CBD, and few side effects from the whole plant material.

In this paper, we have proven with peer reviewed research how the endogenous cannabinoid system plays a regulatory role over the dopaminergic, adrenergic, muscarinic, glutamatergic, GABAergic, and serotonergic systems of the brain in both human and rat. In comparing the side effects of marijuana and the currently prescribed medications for anxiety and depression, one clearly identifies marijuana as the safest potential therapy for these patients. No single antidepressant or anxiolytic has worked successfully on all patients suffering from the same mood disorder. However, marijuana may potentially be a novel therapeutic agent in treating forms of depression and anxiety that conventional treatments do not display a response to. Thus, physicians should be allowed to recommend medical marijuana to their patients as an alternative to typical treatments, in cases of both non-responsiveness to other treatments, or for its similarity in treatment to a conventional pharmaceutical, but safer in terms of their respective side effects.

We have utilized peer reviewed journal publications to identify anxiety and depression as 1. chronic, 2. debilitating, 3. diagnosable, and 4. scientific evidence supporting the fact that marijuana is safe and beneficial for these diseases.

A doctor swears a duty to his/her fellow man above that expected of the average citizen. Their love for humanity, combined with intellectual logic and perseverance, pushes them to discover the best treatments available for that individual patient. The medical research community has identified the mechanisms of how cannabinoids produce anxiolytic and antidepressant effects; in some cases, more is known about marijuana than currently prescribed medications. When a doctor commits to the Hippocratic Oath they swear to “do no harm”, and the authors of this petition request of the Colorado Department of Public Health and Environment to allow our doctors to invoke the

Hippocratic Oath in allowing anxiety and depression patients the ability to utilize medical marijuana.

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