Detailed Explanation Justifying Inclusion of "Psychiatric" Conditions onto the List of "Qualifying Conditions" in the Oregon Medical Marijuana Program

A Petition to the Oregon Department of Human Services was submitted through the Advisory Committee on Medical Marijuana on January 26, 2009. The objective of this Petition is to request the Oregon DHS to conduct an expert advisory panel. This process which is described in ORS 475.334 previously met in 2000. The end result of that deliberation was the inclusion of "Agitation Related to Alzheimers Disease" to the list of qualifying conditions of the Oregon Medical Marijuana Act. On February 9, 2009, DHS accepted the recent petition and requested "a detailed explanation for why these conditions should be included…" This document attempts to supply that explanation.

This petition has, as an intention, to revisit psychiatric diseases or mood symptoms and/or diseases in light of nearly a decade of additional research. The addition of much new research, in combination with increasing patient experience has greatly expanded understanding of the wide and deep mechanisms of cannabinoid receptor binding. Societal changes have also cleared away some of the stigma associated with cannabis among legislative and medical leaders.

This paper will evaluate some of the submitted research and written documentation related to: *severe anxiety, agitation, PTSD, depression* and *insomnia.* New scientific research is included as a submission with the petition. It is anticipated that the advisory panel, as part of it's work, will continue the literature search. A number of documents in the petition are abstracts or incomplete descriptions and will need to be obtained. Most of the research papers are complete and are submitted in paper and electronic format. One excellent source of additional research is the *"Petition to Add Anxiety to the List of Debilitating Medical Conditions Pursuant to Colorado Constitution Article XVIII s 14 and 16 CCR 1006-2."* The Colorado petition is included as part of this petition submission. Other documentation is also being submitted with this paper for inclusion in the petition. Rather than describe in detail every single document, I have chosen to briefly describe key findings. Hopefully, the advisory panel will consider every document as having something to contribute.

Clinical Depression and Depressive Symptoms

The research on depression and depressive symptoms indicates that the interaction of the endogenous cannabinoid receptor system with either anandamide, synthetic cannabinoids or natural cannabinoids exert significant influence on areas of the brain like the prefrontal cortex which integrates emotional responses, and hippocampus. The petition includes 13 depression submissions. Nine are research studies.

Jaing et al., (2005) stated that cannabinoids "promote embryonic and -adult hippocampus neurogenesis" producing anti depressant and anti anxiety effects. In the study, the synthetic cannabinoid molecule, HU210, and the endocannabinoid anandamide (AEA)

stimulated cellular growth (neurogenesis) in the hippocampus stem cells of rats. The hippocampus plays a role in motor function in mammals. The link between cannabinoid activation, and depression in diseases of the nervous system like Parkinson's Disease is demonstrated in other research as well.

Barrero et al., (2005) identified a genetic aberration in the cannabinoid receptor gene CNR1, which occurs in some people with Parkinson's Disease depression. " The presence of two long alleles…. was associated with a reduced prevalence of depression." "These data suggest the existence of a relationship between the cannabinoid system and depression in PD patients, through expression of the gene for the CB-1 receptor".

Gobbi et al., (2005) identified "antidepressant like activity" when anandamide decomposition was prevented from occurring. Anandamide is the naturally-occurring (endogenous) THC-like molecule which activates cannabinoid CB-1 receptors located in especially large numbers in the brain. By blocking the breakdown or "hydrolysis" of anandamide, the activity of the molecule is stimulated to continue. According to the authors, this "supports a role for anandamide in mood regulation" based upon an enzyme (fatty-acid amide hydrolase) which blocks intracellular hydrolysis of anandamide and potentiates it's effect. They go on to characterize delta-9 THC as addictive and warn that "it is particularly important that URB597 [a selective inhibitor of FAAH] does not mimic the hedonic and introceptives states evoked by direct-acting cannabinoid agonists". In other words, feeling good is considered a negative side-effect.

In addition to clinical research on cannabinoids, other researchers have surveyed cannabis users for self-reports of antidepressant activity.

Earlywine et al., (2005) surveyed 4400 cannabis users and nonusers. Their results indicated that marijuana users were 30% less depressed than nonusers. Importantly, this study broke users into medical and non-medical cohorts. "Those who use marijuana to battle the symptoms of illness may be depressed because of their illness, not because of marijuana." This paper is included in the form of a press release.
Obtaining the entire study will give greater depth.

Post Traumatic Stress Disorder (PTSD)

The research on PTSD has been late in coming, spurred on by persistent reports from military veterans who served in Vietnam and Iraq. This petition includes written comments by over a dozen people. Most of these comments have been collected since the petition was filed with the ACMM. (Some identifying information on these written comments may compromise confidentiality of the writer. It was left on the sheets in order to facilitate contact from advisory panel members. Otherwise, identifying information should be removed.) The relative lack of basic research into the mechanism of action of cannabinoids on traumatic stress means that the patient record of use is the most substantial evidence available. New Mexico recently added PTSD to it's list of qualifying conditions.

Hohmann et al., (2005) theorizes that the endogenous cannabinoid system modulates stress-induced analgesia. Stressed-induced analgesia is analgesia that results from activation of opioid or non-opioid mechanisms. "Here we show that an opioid-independent form….termed stress-induced analgesia is mediated by the release of endogenous marijuana-like compounds in the brain." This lends weight to the subjective experience of cannabis users, especially those suffering from severe pain, that cannabis modulates the pain perception and decreases associated anxiety.

Marsicano et al., (2002) describes the acquisition and storage of "aversive memories" as one of the basic functions of the nervous system, and that these aversive memories will gradually diminish over time if they are not reinforced. This research supposed that "the endogenous cannabinoid system has a central function in the extinction of aversive memories." The researchers concluded that "…endocannabinoids facilitate extinction of aversive memories through their selective inhibitory effects on local inhibitory networks in the amygdala."

This petition includes 15 new patient comments, five of which are from veterans. Comments by users significantly underscore the perception of relief through herbal cannabis: C. M. relates personal experiences as an active duty nurse *"treating victims of major trauma, watching young people die." "The use of medical marijuana continues to alleviate the PTSD and it's effects on my life. Marijuana definitely influences my quality of life."*

OMMP Patient # 161570 relays memories of abuse, molestation, depression, anxiety and disability. She has taken a number of pharmaceuticals including Prozac, Wellbutrin, Seroquel. *"…using cannabis will stop the memories and divert my mind to allow me to take care of my responsibilities…" "Cannabis makes it possible for me to relax…., to go places outside my home, relieves depression symptoms, alleviates anxiety, and helps me go to sleep."*

D. P. writes: *"I have been using cannabis to alleviate symptoms of PTSD for years. I was in Vietnam in 1966 and the experience left indelible scars that would not heal, and weren't even acknowledged or identified for years. It has been common knowledge for a long time among PTSD veterans (and many mental health professionals who treat them) that cannabis is an effective treatment for these symptoms."*

There is strong evidence that cannabis assists some victims of trauma to compartmentalize the horror of the experience. This symptom relief needs to be evaluated in the context of substance use disorders which are prevalent in people with PTSD. It appears that the inclusion of PTSD into the list of qualifying conditions seems justified if considered in the context of living hell experienced by many people with PTSD.

Severe Anxiety

"Anxiety" is defined as significant psychological stress, apprehension or worry. More simply, it relates to a state of higher arousal. Anxiety is a normal experience in most people. In other people it compromises functioning. The petition includes 11 document citations under this classification.

Di Marzo et al., (2003) provides an excellent discussion of cannabinoid neurochemistry. The authors state: "Endocannabinoid signaling might be seen as an adaptive response to stimuli or conditions that pose a threat to the organism and to the brain in particular." "Via… inhibitory actions, endocannabinoid are able to compensate both at the neurochemical and behavioral level, for the abnormal neurotransmission caused by these conditions."

Patal, et al., (2006) describes a model of anti anxiety effects modulated through the effect of anandamide on the endogenous cannabinoid signaling system. "These data indicate that activation of CB-1 cannabinoid receptors reduces anxiety-like behaviors in mice and further support an anxiolytic role for endogenous cannabinoid signaling." As with PTSD, this research lends weight to the use of herbal cannabis by people to treat unwanted symptoms of anxiety. Cannabis appears to reduce anxiety from any cause, be it Alzheimer's Disease, traumatic experiences or other sources.

Musty et al., (2005) is included as an abstract in this petition. The review describes the activation of various locations in the brain, particularly the hypothalamus, and hippocampus- as increased due to activation of CB-1 receptors in those areas. Interestingly, they relate that CB-1 antagonists are anxiolytic, but that agonists (like cannabis) "seem to have biphasic effects. Low doses seem to be anxiolytic, while high doses are antigenic." It would be interesting to compare the dosage with the disease condition and see if people with anxiety states report using low-dose therapy.

Additionally, the petition includes articles by Marx and O'Connell:

Marx et al., (2006) contains a good discussion of the neurobiology of cannabinoids on a number of physiological processes including, weight loss, anxiety, pain, tissue and brain inflammation, cancer cell growth, PTSD. The article discusses Rimonabant, a selective CB-1 receptor inhibitor and it's potential as a weight loss medication. According to the authors, "Even phobias and posttraumatic stress disorder (PTSD) may be amenable to treatment with cannabinoid boosters." Patients have long ago discovered this treatment; researchers are more interested in formulating pharmaceuticals.

O'Connell (2005) in his article: "Cannabis use in Adolescence: Self Medication for Anxiety" describes adolescents who used cannabis to unwittingly treat ADD and ADHD. He used detailed surveys with nearly 4000 patients whom he noticed were apparently able-bodied, mostly young men. The article discusses use patterns, use of other drugs, school careers and symptom groups. The article concludes: "The previously unrecognized role of cannabis as effective self-medication for symptoms experienced by adolescents also explains why so many adults have continued to use it despite social and legal penalties."

Agitation

Agitation is a symptom classification which includes physiological markers of increased sympathetic nervous system stimulation (muscle tension and blood pressure), but behaviorally manifests in potentially violent, loud, extreme emotional outbursts. The petition contains seven documents including two research studies and two research reviews.

Uriguen et al., (2004) describes how basic endocannabinoid signaling is effected by blockage or removal of CB-1 receptors in mice. Anxiety reduction drugs are *less* effective when the CB-1 receptor in mice is inactive. "The results of this study provide clear evidence that the cannabinoid CB-1 receptor plays a key role in the regulation and treatment of anxiety-like behaviors." This illustrates the importance of the cannabinoid signaling system as a regulator and modulator for cannabinoid agonists and subsequent mood. It also lends credence to patient reports of mood regulation and decreased anxiety or agitation after using cannabis.

The advisory panel might consider the addition of bipolar disorder onto the list, knowing the high mortality rate of untreated or poorly treated symptoms. Providing psychiatrists the option of recommending treatment with cannabis would be reasonable and prudent so long as the patient has ongoing psychiatric care.

Ashton et al., (2005) is a literature review that describes the dearth of research of cannabis on Bipolar Affective Disorder. They relate case reports from other clinicians about effective symptom management through cannabis. "…[T]he evidence discussed above shows that both THC and CBD have pharmacological properties that could be therapeutic in patients with BAD." The authors suggest further research.

Grinspoon (1998) is in abstract form. It discusses case reports of the use of cannabis as a mood stabilizer. These patients related cannabis as more effective than conventional drugs, or that is was used to increase compliance with pharmacotherapy. This study may be obtained from PubMed (PMID: 9692379.)

Insomnia

The petition requests the inclusion of insomnia either as a symptom or a disease. To that end there are seven documents. Included among these is:

Rodriguiez et al., (2003, 2006) Each of these studies identifies cannabinoid-based molecules as responsible for promoting sleep. The first study shows that anandamide increases the level of adenosine in the basal forebrain of rats. (Adenosine is an enzyme that affects metabolism, muscle contraction and is present in all cells). In the second study, rats who were administered cannabidiol (CBD) a constituent molecule, showed an increase in dopamine release, resulting in increased sleep behavior. The authors

concluded "…that CBD modulates waking via activation of neurons in the hypothalamus and DRD [dorsal raphe nucleus]. Both regions apparently involved in the generation of alertness."

Non specific Research

The petition includes 14 citations which have no direct symptom or disease link with petitioned conditions, but do contain relevant information. I will not review these documents.

Previous Research Documents

Attached to this petition is one document I am requesting be included as part of the research base:

Correy (2006) is a petition to add anxiety to Colorado's list of qualifying conditions. Included with the petition is an extensive bibliography of research citations which should allow the present advisory panel to gain additional research.

Conclusion

Since 2000, the evidence base surrounding cannabis and psychosis has not materially changed, as it has in research on agitation and depression. As a result, I have omitted inclusion of schizophrenia or psychotic symptoms into this petition. If agitation as a symptom finds acceptance on the list of qualifying conditions, it is possible that psychotic agitation could be treated with cannabis at the discretion of the treatment providers and patient.

Today there is an explosion of cannabinoid research occurring world wide. The restrictive legal framework in the United States has placed the US in a distinct disadvantage. There are new formulations which utilize combinations of cannabinoids, like Sativex, or single molecular forms like Marinol and Rimanobant. It is beyond the scope of this panel to evaluate these new products, however cannabinoid medicine clearly represents an emerging field of medicine, and many new products will appear in the decades to come. Some of these drugs, like Rimonabant, act by blocking or antagonizing receptors, others act as agonists or activators. Little is actually known about the long-term effects of these single molecule drugs on the complex biochemical pathways in humans. Herbal cannabis is likely to remain a reasonable alternative for a number of diseases and symptoms due to the enormous knowledge which has accumulated through large-scale patient use. For this reason, I request the DHS to give significant "evidentiary weight" to patient accounts if there is consistency of reports.

Enclosed with this letter is a list of patients who have expressed an interest in testifying in person, and a list of potential expert panel members. I am in the process of contacting medical professionals to submit written comments and will forward this when complete.

Thank-you to the Oregon Department of Human Services for accepting this petition. I truly hope that it will be conducted with highest regard to people who suffer from illness- and those who advance medical practice- free from manipulation or coercion. I also request that this letter be included as a part of the record of this singular event.

Respectfully submitted,

Edward Glick
Date: March 30, 2009