Cannabinoid Therapeutics: Marijuana and Beyond
Chair: Igor Grant, M.D.

Advances in understanding the molecular mechanisms underlying cannabinoid effects, coupled with increased public acceptance that cannabinoids might have therapeutic benefits have spurred renewed interest in the cannabinoids as medicines. The objectives of this panel are 1) to present the results of recently completed clinical trials on marijuana conducted at the University of California's Center for Medicinal Cannabis Research (CMCR); 2) to link the positive findings from these trials to on-going research aimed at understanding the underlying molecular mechanisms; 3) to review the potential of novel molecules whose capacity to modulate the endocannabinoid system may form the basis for a future generation of pharmaceuticals.

The first paper by Ron Ellis, M.D., Ph.D., will present the results of clinical trials with smoked marijuana in patients with painful peripheral neuropathy, indicating a therapeutic effect. The second paper by Jody Corey-Bloom, M.D., Ph.D., will describe the effects of smoked marijuana on spasticity in patients with Multiple Sclerosis. The third paper by Daniele Piomelli, Ph.D., will review recent pre-clinical studies aimed at understanding how modulation of the endocannabinoid system may form the basis of therapeutic effects. The fourth paper by Alexandros Makryannis, Ph.D., will review the development of new molecules whose capacity to act as agonists, antagonists, and otherwise modulate the endocannabinoid system and its targets may form the basis of a new generation of pharmaceuticals. The discussant is Raphael Mechoulam, Ph.D., who first characterized the structure of tetrahydrocannabinol, and later discovered the CB1 receptor. Dr. Mechoulam will discuss the future potentials of cannabinoid-based therapeutics.

Smoked medicinal cannabis for neuropathic pain in HIV infection: A randomized clinical trial

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Background. Neuropathic pain continues to be a major clinical problem in HIV infection despite management with opioids, nonsteroidal anti-inflammatory agents (NSAIDs) and adjunctive pain modifying therapies. Cannabinoid receptors in the central and peripheral nervous system have been shown to modulate pain perception.

Methods. This was a double-blind, phase 2, placebo-controlled crossover trial of smoked cannabis for the short-term treatment of neuropathic pain due to HIV-associated distal, sensory predominant polyneuropathy (DSPN). Inclusion criteria were documented HIV infection, meet stringent diagnostic criteria for DSPN, and have neuropathic pain refractory to treatment using at least two prior classes of analgesics. Under direct observation, subjects smoked active cannabis ranging in potency between 1 and 8% THC, or placebo four times a day for 5 consecutive days during each of two treatment weeks in a randomized order. A washout of two weeks separated the treatment periods. A masked dose escalation-titration protocol was used to accommodate individual differences in sensitivity to the analgesic and adverse effects of cannabis. The principal outcome measure was change in pain intensity as measured by the Descriptor Differential Scale (DDS) from baseline to the end of each treatment week.

Subjects. Between February, 2002 and November, 2006, 127 subjects were screened, 34 enrolled and 28 completed treatment with both active and placebo cannabis. Enrollees (33 men, 1 woman) had a mean age of 49.1 years, education 13.9 years, and 32 (94%) were on combination antiretroviral therapies; 76% had been exposed to neurotoxic dideoxynucleoside antiretrovirals. Most subjects (31/34, 91%) had some previous experience with cannabis, though all subjects were asked to discontinue outside cannabis use for the duration of this study. Concurrent analgesics were NSAIDs in 26% and adjunctive medications in 62%.

Results. Among subjects completing both treatment periods, the mean ($\pm$ sd) baseline DDS was 11.1 ($\pm$ 4.0). Pain relief was greater during the active cannabis treatment week than during the placebo week (mean difference in DDS change, 2.6 ($\pm$ 5.1) points; p=0.016, Wilcoxon rank test), corresponding to pain reduction from moderate to very mild. At least 50% pain reduction was reported by 29% of subjects during cannabis treatment versus 18% during placebo treatment. Adverse effects, most frequently cough, were generally mild and self-limited. Two subjects were unable to tolerate smoked cannabis, one due to intractable cough and another due to cannabis-related acute psychosis.

Conclusions. In study completers, smoked cannabis added to stable concurrent analgesics was effective and well-tolerated for the short-term relief of refractory pain due to DSPN in HIV infection.

Short-Term Effects of Medicinal Cannabis on Spasticity in Multiple Sclerosis

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Background. Spasticity is a common and disabling symptom for many patients with multiple sclerosis (MS). In some patients, treatment with agents such as baclofen, benzodiazepines, or tizanidine is limited by unacceptable side effects. For others, severe spasticity persists despite adequate dosing. Thus, the possibility of alternative treatment options is appealing. Evidence that cannabis relieves spasticity produced by MS is largely anecdotal; potential therapeutic effects, in addition to risk and safety issues regarding medicinal cannabis use, remain to be clarified. In the current study, we sought to assess the short-term safety and efficacy of smoked medicinal cannabis vs. placebo over 17 days in MS patients with spasticity in the outpatient setting.

Methods. Single-center, prospective, randomized, placebo-controlled crossover trial conducted between 2003 and 2005 in adults with MS and spasticity. Subjects were randomly assigned to smoke either cannabis (approximately 4% tetrahydrocannabinol) or identical placebo cigarettes once daily for three consecutive days with assessments before and after treatment. Following a washout interval of 11 days, subjects crossed over to the opposite condition for three consecutive days, again with assessments before and after treatment. The primary outcome measure was the Ashworth Spasticity Scale. Secondary outcome measures included effects on cognition (Paced Auditory Serial Addition Task [PASAT]) and pain (Visual Analog Scale [VAS]).

Results. Thirty patients (11 males, 19 females) completed the trial. Mean age was 50.8 ($\pm$7.7) years and mean education was 15.2 ($\pm$2.1) years. Mean EDSS score was 5.3 ($\pm$1.5). No serious adverse events occurred. Active treatment reduced Ashworth Total Scores by an average of 2.739 points (95% bootstrap CI = [2.203, 3.144]) more than placebo [$t(29) = 11.7$, $p<0.0001$]. Treatment order did not have a statistically significant effect on outcome [$t(21.309) = 0.268$, $p=0.792$). In addition, active treatment reduced Pain VAS scores by an average of 5.278 points (95% bootstrap CI = [2.482, 10.013]) more than placebo [$t(29) = 2.83$, $p=0.0083$]. On the PASAT, however, total correct scores for the active treatment group worsened by an average of 8.667 points (95% bootstrap CI=[4.098, 14.308]) compared to placebo [$t(28)=3.31$, $p=0.0026$].

Discussion. Smoked cannabis was effective in reducing spasticity and pain in this small study and, although generally well tolerated, resulted in significant immediate cognitive effects. Larger, long-term studies will be needed to confirm these findings and assess the overall clinical usefulness of smoked cannabis for spasticity in MS.

ENDOCANNABINOID REGULATION OF PAIN, ANXIETY AND MOOD

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Background. The major psychoactive constituent of cannabis, Δ^9-tetrahydrocannabinol, affects pain sensation and emotional states in humans and laboratory animals by activating brain CB_1-type cannabinoid receptors. A primary endogenous ligand of these receptors is anandamide, the amide of arachidonic acid with ethanolamine. Anandamide is released in select regions of the brain and is deactivated through a two-step process consisting of transport into cells followed by intracellular hydrolysis by fatty-acid amide hydrolase (FAAH). Our lab has developed a potent and selective FAAH inhibitor, URB597, and investigated its pharmacological properties in live animals.

Results. URB597 inhibits FAAH activity *in vivo* with an ID50 of 0.15 mg/kg (ip, rat). As doses of 0.1-0.3 mg/kg (ip) URB597 exerts potent anxiolytic-like effects in the rat elevated plus maze and isolation-induced ultrasonic vocalization tests. At the same doses, URB597 elicits marked antidepressant-like effects in the mouse tail-suspension test and the rat forced-swim test. Moreover, URB597 reduces hyperalgesia and allodynia in a rat model of neuropathic pain (loose sciatic nerve ligature). These behavioral actions of URB597 (i) are accompanied by increases in the firing activity of serotonergic neurons in the dorsal raphe nucleus and noradrenergic neurons in the nucleus locus coeruleus; (ii) are prevented by the CB_1 antagonist rimonabant; and (iii) are maintained upon repeated URB597 administration. Unlike direct CB_1 agonists, URB597 does not exert rewarding effects in the conditioned place preference test or produce generalization to the discriminative effects of Δ^9-THC in rats. Finally, URB597 does not maintain self-administration or enhance Δ^9-THC self-administration in squirrel monkeys.

Discussion. Pharmacological blockade of anandamide deactivation produces anxiolytic-like, antidepressant-like and analgesic effects in rats and mice. These actions are not associated with other behavioral responses typical of direct-acting cannabinoid agonists – such as place preference or self-administration –– and are accompanied by changes in serotonergic and noradrenergic transmission in select regions of the brain. These findings suggest that anandamide contributes to the regulation of pain and emotion, and that anandamide deactivation might be the target for novel analgesic, anxiolytic and antidepressant drugs.

Ligand Modulators of the Endocannabinoid System as Therapeutic Drugs

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Background. Our current knowledge of the endocannabinoid system includes CB1 and CB2, two $G_{i/o}$ GPCRs involved in a number of signaling mechanisms. The endogenous molecules that modulate this biochemical system are represented by arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG). Furthermore, the levels of these endocannabinoids are modulated by a number of metabolizing and deactivating enzymes as well as by a transporter system that remains to be fully characterized. Modulation of the endocannabinoid system either directly (through CB1/CB2) or indirectly (through enzymatic or transport inhibition) provides opportunities for the design and development of small ligands capable of effecting physiological changes and, thus, serve as potential drug candidates.

Methods. A number of medicinal chemistry efforts are currently underway to develop such medications. The approaches for such work involve high throughput screening approaches followed by lead optimization using classical medicinal chemistry concepts. Alternatively, the design of novel ligands is based on the intimate knowledge of the 3D-structure of the protein (receptor or enzyme) with which they interact. This target-based drug design utilizes a combination of computational and biophysical methods.

Results. Earlier work had led to the development of the CB1/CB2 agonist nabilone as a medication for chemotherapy-induced nausea and pain. Very recently a novel CB1 selective inverse agonist was developed for the treatment of obesity and metabolic disorders under the name Acomplia. Furthermore, a number of ongoing efforts aim at the development of novel compounds for other therapies, as will be described. These include CB2 agonists for the treatment of neuropathic pain, CB1 agonists for the treatment of cachexia, as well as FAAH antagonists for the treatment of pain and neurodegeneration.

Discussion. The endocannabinoid system has been recognized as an important "druggable" target for medication development. There is an excellent chance that within the next few years novel cannabinergic medications will become available.