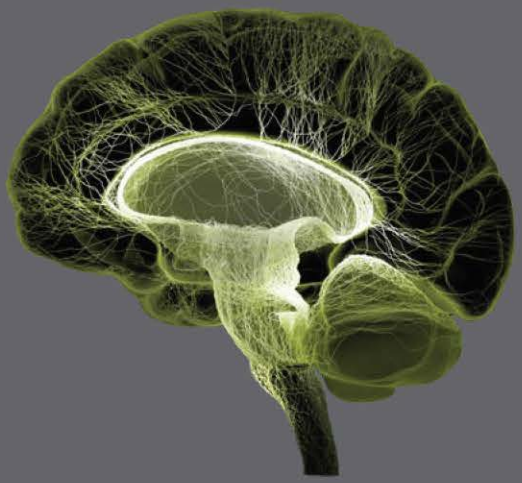
National Institutes of Health

MARIJUANA AND CANNABINOIDS:
A NEUROSCIENCE RESEARCH SUMMIT



March 22–23, 2016

Natcher Conference Center, Building 45
NIH Campus, Bethesda, MD

Meeting Summary

National Institute on Drug Abuse
National Institute on Alcohol Abuse and Alcoholism
National Center for Complementary and Integrative Health
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke

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A Neuroscience Research Summit

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Contents

Background

The National Institutes of Health (NIH) convened the Marijuana and Cannabinoids: A Neuroscience Research Summit (the Summit) on March 22–23, 2016. Multiple NIH Institutes and Centers—the National Institute on Drug Abuse (NIDA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Center for Complementary and Integrative Health (NCCIH), National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke (NINDS)—partnered to organize the Summit. The Summit focused on the neurological and psychiatric effects of marijuana, other cannabinoids, and the endocannabinoid system. Presenters discussed both the adverse and the potential therapeutic effects of the cannabinoid system.[1] The goal of the Summit was to ensure evidence-based information is available to inform practice and policy, particularly important at this time given the rapidly shifting landscape regarding the recreational and medicinal use of marijuana. During lunch breaks at the conference, 126 scientific posters were available that covered the range of topics discussed at the Summit.

More than 2,000 people attended the Summit, either in person or via the videocast. The Summit welcomed more than 60 international guests. NIH Director, Francis S. Collins, M.D., Ph.D., and leaders of the organizing Institutes and Centers addressed Summit participants. Dignitaries from other Federal agencies—Michael Botticelli, Director, National Drug Control Policy, and Robert M. Califf, M.D., Commissioner of Food and Drugs at the U.S. Food and Drug Administration (FDA)—also spoke at the conference.

The Summit had 1.7 million impressions via social media, and 568 unique Twitter accounts used the meeting hashtag (#MJNeuroSummit). Highlights of Summit-related Twitter interactions are available, as well as a videocast recording. Throughout the meeting, attendees were encouraged to submit questions for panelists through question cards available at the meeting or through Twitter.

Summit organizers asked each presenter, an expert in a particular field, to address the following:

- What do we know to date (what does the literature say)?
- How do we know what we think we know (what is the science and data underlying claims)?
- What do we still need to know (for the purpose of generating new science)?

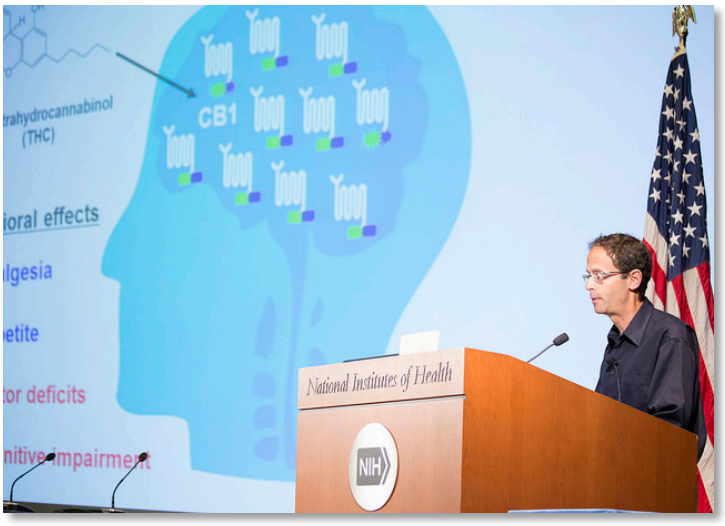
[1] Speakers disclosed any positions and financial interests and acknowledged their colleagues and funders during their presentations.

Understanding the Endocannabinoid System

Co-Moderators: David Shurtleff, Ph.D., NCCIH, and Aidan Hampson, Ph.D., NIDA

The Endocannabinoid System—An Introduction

Benjamin Cravatt, Ph.D., The Scripps Research Institute



Dr. Cravatt provided brief background information on the endocannabinoid system. He described the endocannabinoids, 2-arachidonoylglycerol (2-AG) and anandamide, as the endogenous ligands of the cannabinoid receptors. He also discussed cannabinoid receptor 1 (CB_1), which is the site of action for the active component of marijuana, Δ^9-tetrahydrocannabinol (THC). THC is responsible for the behavioral effects of marijuana—including analgesia, changes in appetite, motor deficits, and cognitive impairment. Dr. Cravatt explained that 2-AG and anandamide are degraded by enzymes, which renders these endocannabinoids inactive. For example, anandamide inactivation is regulated by fatty acid amide hydrolase (FAAH). 2-AG inactivation is regulated by monoacylglycerol lipase (MAGL). Research suggests that 2-AG is a "workhorse" endocannabinoid that is involved in a wide variety of physiological functions, while anandamide is a "stress-responsive" endocannabinoid.

Key areas for future research on endocannabinoids include:

- Examining crosstalk with other lipid-signaling pathways in the brain,
- Studying additional components in the endocannabinoid system (e.g., other metabolic enzymes, transport mechanisms, and other ligands/receptors), and
- Determining whether endocannabinoid system modulators produce clinically useful subsets of behavioral effects of direct CB_1 agonists.

Cannabinoid Receptors: Where Are They and What Do They Do?

Ken Mackie, M.D., Indiana University

Dr. Mackie reviewed cannabinoid receptors, their signaling, important related concepts, and questions for future research. He reviewed the properties of CB_1 and CB_2 receptors, including their locations, which inform function. CB_1 receptors are found on neurons involved in synaptic plasticity, and CB_1 localization and signaling suggest presynaptic inhibition. Neuronal activation can produce endocannabinoids to activate CB_1 receptors to inhibit synaptic transmission or suppress neuronal excitability. CB_2 receptors are most abundant in immune cells, including microglia. They are highly inducible and may be expressed in some neurons. CB_2 receptors may mediate some of the anti-inflammatory actions of cannabinoids. A number of intriguing studies suggest CB_2 receptors may be a potential therapeutic target that avoids the psychoactivity of CB_1 ligands.

Dr. Mackie summarized what we know about cannabinoid receptors:

- CB_1 receptors mediate most of THC's psychoactivity.
- Endocannabinoids play a role in synaptic plasticity.
- Cannabinoid receptors have a rich and complex pharmacology.

Dr. Mackie summarized what we still need to know:

- What other receptors/proteins interact with cannabinoid receptors, and how do these influence signaling?
- Are there therapeutic opportunities?
- Which CB_1 receptors are being imaged *in vivo*?
- What is the function of CB_1 receptors on astrocytes and mitochondria?

Therapeutic Potential of the Cannabinoid System

Daniele Piomelli, Ph.D., Pharm.D., University of California, Irvine

The endocannabinoids influence fundamental physiological functioning throughout the body. Dr. Piomelli reviewed basic information about cannabinoid receptors, anandamide signaling, and 2-AG signaling. He noted that cannabinoid receptors have a rich repertoire of intracellular transduction mechanisms. Dr. Piomelli discussed receptor activation and various effect sizes and allosteric modulators (AMs), which have little or no effect by themselves, but can enhance the action of an endogenous ligand. Dr. Piomelli also described blockade of CB_1 receptors with neutral antagonists, inverse agonists (e.g., rimonabant), and allosteric and biased modulators. Dr. Piomelli reviewed areas of scientific study about cannabinoid and endocannabinoid signaling related to translational medicine, including FAAH inhibitors.

Dr. Piomelli summarized possible future directions in the therapeutic potential of the cannabinoid system:

- Examine allosteric-positive CB_1 modulators (pain, stress-related disorders);
- Study neutral CB_1 antagonists (obesity, metabolic syndrome);
- Investigate peripherally restricted CB_1 antagonists (obesity, metabolic syndrome);
- Conduct research on global/peripheral FAAH inhibitors (anxiety, post-traumatic stress disorder [PTSD], Autism Spectrum Disorder/nociceptive pain);
- Examine MAGL and 2-AG inhibitors (epilepsy, pain, cancer); and
- Study substrate-selective Cox-2 inhibitors (anxiety).

Brain Development and Function

Moderator: Steve Grant, Ph.D., NIDA

Does Marijuana Harm the Brain?

Kent Hutchinson, Ph.D., University of Colorado Bolder

Dr. Hutchinson reviewed the effect of marijuana and alcohol on brain structure, identified methodological complications, and discussed the effect of different strains on cognition and inflammation. He noted that there are more than 80 cannabinoids. THC (the best studied and perhaps the most psychoactive ingredient in marijuana) and cannabidiol (CBD) have opposing effects, and different genetic "strains" have different levels of cannabinoids. Dr. Hutchinson also identified how marijuana regulations and laws can act as obstacles to research and what might be done about them.

Dr. Hutchinson summarized what we know about marijuana and the brain:

- Marijuana clearly has acute cognitive effects (hours to days) that have negative consequences, especially for young people.
- It is highly unlikely that marijuana causes widespread changes in brain structure (in contrast to alcohol).

Dr. Hutchinson summarized what we still need to know about marijuana and the brain:

- Scientists need to determine the extent to which effects (positive and negative) may depend on the ratio of THC to CBD or other cannabinoids;
- Researchers need to investigate whether high-potency marijuana alters brain structure or function (especially true for new, highly concentrated forms such as "shatter" and "dabs"); and
- New Federal policies and guidance are needed (i.e., "Cole Memo" to universities) to remove impediments to research.

Brain Development and Function: Adolescent Marijuana Use—Influence on Learning, Memory, and Brain Changes

Susan F. Tapert, Ph.D., University of California, San Diego

Dr. Tapert noted the prevalence of marijuana use during adolescence and reviewed the major brain development processes that occur during this period. Currently, it is unclear how use of marijuana and other substances affect these processes. She reviewed research on adolescent marijuana use and learning and memory, including a 3-year study that explored the impact of marijuana use on neuropsychological performance. Dr. Tapert noted that in this area of research, researchers need to determine whether there are pre-existing differences between adolescents who use marijuana and those who do not. This is a critical and complex question reflecting the interaction of neurodevelopment, genes, environment, and personality. It involves looking at how factors such as the propensity for risk-taking affects marijuana use, which in turn influences brain structure and cognition. Two longitudinal adolescent brain development studies—the National Consortium on Alcohol and Neurodevelopment in Adolescence and the NIH ABCD Study—will help shed light on this important question.

Dr. Tapert summarized what we know about adolescent marijuana use and cognition:

- Marijuana adversely influences learning.
- Memory and attention also can show mild long-term effects.
- These outcomes improve with days to weeks of abstinence.

- The effect of marijuana on cognition appears worse with earlier age of onset.
- Some neuroimaging data support these effects of marijuana.

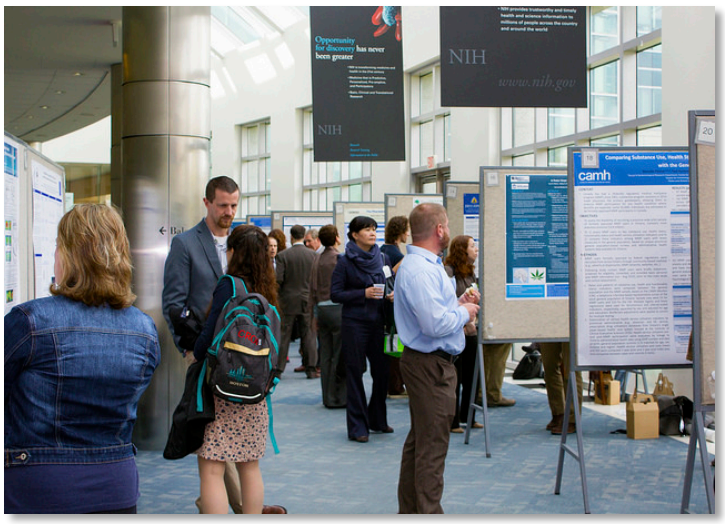
Dr. Tapert summarized what we still need to know about adolescent marijuana use and cognition:

- Can these findings be replicated in a large longitudinal sample?
- Are there sensitive periods in development?
- Is the effect of marijuana different for boys versus girls?
- Is the effect of marijuana different for disadvantaged youth?
- Do the effects of marijuana vary by strain and potency?

Cannabis Use and Cognitive Impairment

Madeline H. Meier, Ph.D., Arizona State University

Dr. Meier summarized current knowledge about cannabis use and cognitive impairment. She discussed methodological issues in this area of research. The field needs prospective longitudinal studies that compare each person to him or herself before and after the initiation of cannabis use. Such studies would conduct cognitive testing during childhood, assess cannabis use during adolescence and young adulthood, and re-test cognitive function during adulthood. This kind of research was conducted in the Dunedin Study; Dr. Meier described the study, its findings, and the researchers' attempts to determine whether other factors could account for the findings.



Dr. Meier summarized what we know about cannabis use and cognitive impairment:

- Cannabis use is associated with cognitive impairment (particularly impairment of verbal learning and memory), and impairment persists following acute intoxication.
- Cannabis-related cognitive impairment is generally subtle.
- More frequent, persistent, and earlier onset cannabis use is associated with greater cognitive impairment.

Dr. Meier summarized what we still need to know about cannabis use and cognitive impairment:

- What is the mechanism underlying the association between persistent cannabis use and IQ decline? (Brain imaging data should help answer this question.)
- What are the parameters of cannabis use sufficient to produce cognitive impairment? Specifically, researchers need to examine quantity, frequency, and age of onset.
- Does cognitive ability recover with abstinence?
- Are there individual differences (e.g., genetics) in susceptibility to cannabis-related cognitive impairment?
- How might strain differences affect cognitive impairment?

Psychosis, Addiction, and Alcohol Interactions

Co-Moderators: David Goldman, M.D., NIAAA, and Wilson Compton, M.D., M.P.E., NIDA

The Association Between Cannabis Use and Psychosis: Clinical, Epidemiological, and Neuroscience Perspectives

A. Eden Evins, M.D., M.P.H., Massachusetts General Hospital

Dr. Evins discussed adolescent cannabis use and the increased risk for psychosis. She outlined factors that can affect the association between adolescent cannabis use and increased risk for psychosis—including early age at first cannabis exposure, frequent/daily use and use of high-potency cannabis, risk factors for psychosis, familial risk, socioeconomic status, drug use, urbanicity, and prior psychiatric symptoms or diagnosis. Dr. Evins described research on the temporal relationship between adolescent cannabis use and psychosis. She also discussed research on whether genetic risk for psychosis confers risk for marijuana use and several hypothesized relationships regarding the association between cannabis exposure and schizophrenia.

Dr. Evins summarized what we know about the association between cannabis use and psychosis:

- There is an association between exposure to cannabinoids and various psychotic outcomes, including the development of schizophrenia.
- The association between cannabis exposure and psychotic outcomes in epidemiologic, laboratory, and animal studies has major dose and developmental stage-of-exposure effects.
- There is interindividual variability in this effect.
- Gene-exposure interactions moderate the risk for cannabis-induced psychosis. We need to learn more about this and develop better measures of exposure for nonlaboratory-based studies.
- Reducing exposure at critical periods has the potential to reduce the incidence and severity of psychotic outcomes and delay their onset.

Dr. Evins summarized what we need to know about the association between cannabis use and psychosis:

- Scientists need to understand the precise nature of the association between cannabis use and the development of schizophrenia, including who is at risk.
- They need to discover the genetic factors that moderate the impact of cannabinoid exposure on the risk for psychosis.
- Research is needed to clarify the molecular/neurophysiologic mechanisms underlying cannabinoid effects on the adolescent brain.
- Work is needed to clarify the effect of cannabinoids on neurodevelopmental processes and brain structures relevant to psychotic disorders.
- Scientists should determine whether there are identifiable protective factors that make those exposed to cannabis less likely to develop psychosis/schizophrenia in those at risk.
- Researchers should determine whether there is a physiologic basis for the observation that many with schizophrenia regularly use cannabis.

Addiction to Cannabis: Phenomenology, Prevalence, Outcomes, and Probability

Alan J. Budney, Ph.D., Geisel School of Medicine at Dartmouth

Dr. Budney reviewed the biological, behavioral, and epidemiological evidence for the addictive potential of cannabis. He also discussed studies related to cannabis dependence and withdrawal syndrome. Dr. Budney noted the prevalence of past-year cannabis use disorder and rates of cannabis abuse. He reviewed the extensive literature on randomized clinical trials (RCTs) for behavioral treatments for cannabis use disorders among adults and adolescents. Research suggests ways to enhance delivery systems and improve access. Dr. Budney highlighted the importance of targeting concurrent tobacco use and addressing treatment nonresponse, particularly by using innovative technology. He also reviewed the factors that influence cannabis addiction—including pharmacology, biological vulnerability, and intrapersonal factors. He discussed the changing environmental landscape of cannabis laws and regulations and the recent considerations of edible cannabis, new products, and devices for vaping.

Dr. Budney summarized what we know about addiction to cannabis:

- Cannabis has addictive potential.
- Cannabis use disorder is common, resembles other substance use disorders, and may be increasing.
- Interventions for cannabis use disorder have demonstrated efficacy, but there is much room for improvement.
- The factors that influence the probability of cannabis use disorder are similar to those that affect other substance use disorders.
- Changing laws and regulations will impact the development and prevalence of cannabis use disorder.

Dr. Budney summarized what we still need to know about addiction to cannabis:

- Scientists need to determine how to translate knowledge into more effective prevention and treatment for cannabis use disorder and work on efficacy and dissemination.
- Researchers should determine how to communicate accurate information about cannabis use and its associated risks to the public.
- Scientists need to determine how to address the changing legal and regulatory systems to minimize the impact on rates and consequences of cannabis use disorder.

Marijuana and Alcohol Interactions: Comorbidity, Consequences, and Mechanisms

Loren H. Parsons, Ph.D., The Scripps Research Institute

Dr. Parsons reviewed patterns of drug use in the United States, noting that marijuana is the third most commonly used substance after alcohol and tobacco, according to results from the 2014 National Survey of Drug Use and Health. He discussed the subjective effects of concurrent alcohol and marijuana use. He also outlined the adverse effects associated with concurrent or simultaneous alcohol and marijuana use—including binge drinking, alcohol dependence, depression, and social consequences. Dr. Parsons reviewed the relationships between alcohol use disorder and marijuana use disorder among adolescents and young adults. He discussed the neuropharmacology of alcohol and THC as well as the neurochemistry of acute alcohol and THC exposure.

Dr. Parsons summarized what we know about marijuana and alcohol interactions:

- Compared with either drug independently, concurrent marijuana and alcohol use increases the odds of developing:
  - Binge drinking;
  - Substance use disorder/drug dependence (particularly alcohol use disorder/alcohol dependence); and
  - Major depressive disorder.
- Cannabinoids and alcohol produce similar pharmacologic effects and similar neuroadaptations following extended exposure.
- Endocannabinoid signaling influences the motivational effects of alcohol.
- Dysregulated endocannabinoid function may contribute to alcohol use disorder and alcohol dependence.

Dr. Parsons summarized what we still need to know about marijuana and alcohol interactions:

- What is the biological basis (genetic and pharmacologic) for the interactive effects of these drugs on vulnerability to substance use disorder and drug dependence?
- Are there specific vulnerability factors (such as age and stress)?
- What is the impact of the strain of marijuana (CBD and other phytocannabinoids) or route of administration (edibles versus smoked versus vaped)?
- In terms of treatment, is comorbid marijuana and alcohol addiction a distinct entity or an exaggeration of each independent disorder?

Therapeutic Potential: Epilepsy and Multiple Sclerosis

Moderator: Alan L. Willard, Ph.D., NINDS

Mechanisms of Cannabinoid Signaling in Epilepsy

Ivan Soltesz, Ph.D., Stanford University

Dr. Soltesz described the characteristics and epidemiology of epilepsy. He reviewed the mechanistic aspects of cannabinoid signaling as it relates to epilepsy, considering the preclinical evidence for cannabinoids in seizure control, and evaluating the potential risk factors and confounds in the research. He noted that there are many different subtypes of epilepsy, and many are treatment resistant. Current treatment is antiepileptic medications or surgery, but these have major side effects.

Dr. Soltesz summarized what we know about cannabinoid signaling and epilepsy:

- CB_1 receptor signaling is highly cell-type specific and affects select inhibitory and excitatory synapses.
- CB_1 receptor agonists typically decrease seizures in chronic epilepsy in animal models.
- CB_1 receptor numbers increase on inhibitory but decrease on excitatory terminals in chronic epilepsy.
- CBD is typically anticonvulsant.
- Seizures/injury induce rapid, robust changes in endocannabinoid signaling.

Dr. Soltesz summarized what we still need to know about cannabinoid signaling and epilepsy:

- Scientists should further investigate the tonic CB_1 receptor control of neurotransmitter release in epilepsy.
- They should study the postsynaptic cannabinoid pathway in epilepsy.
- Research should identify the CBD targets that mediate anticonvulsant action.
- Researchers should examine the long-term effects of CBD and THC on brain development.
- Studies are needed on the mechanisms of anti-epileptogenic actions of cannabinoids.

Cannabinoids for Treatment of Pediatric Epilepsy: The Hype and the Evidence

Amy Brooks-Kayal, M.D., Children's Hospital Colorado (CHCO)

Dr. Brooks-Kayal noted that CBD has not been approved by the FDA as a treatment for epilepsy; therefore, she discussed its off-label use. She reviewed the Children's Hospital Colorado experience with the use of medical marijuana for pediatric epilepsy patients and other available medical evidence supporting the therapeutic use of cannabinoids in epilepsy. She also presented current regulatory information and restrictions surrounding medical use of cannabinoids and discussed how to monitor and counsel patients who pursue medical cannabinoid use. Dr. Brooks-Kayal mentioned the unique challenges that medical marijuana has posed for health care providers at CHCO. She added that until we have better evidence, CHCO's policy states that providers do not recommend the use of cannabinoids for treatment of epilepsy outside of clinical trials.

Dr. Brooks-Kayal summarized what we know about cannabinoids for the treatment of pediatric epilepsy:

- CBD has activity against seizures in some preclinical models.
- There is initial evidence suggesting that CBD may reduce seizures in some children with refractory epilepsy.
- There is evidence of multiple adverse effects of CBD and other marijuana products, including potential long-term cognitive and behavioral effects.

Dr. Brooks-Kayal summarized what we still need to know about cannabinoids for the treatment of pediatric epilepsy:

- What is the rate of response to CBD versus placebo effect?
- What types of seizures/epilepsy syndromes does it work for?
- What is the optimal dose?
- What are the drug interactions and how do they affect CBD efficacy?
- What are the short- and long-term adverse effects?

Multiple Sclerosis and Cannabinoids: Therapeutic Potential

David Gloss, M.D., Charleston Area Medical Center

Dr. Gloss noted that all data he presented were taken from off-label studies. He reviewed the evidence found in low-risk-of-bias trials in multiple sclerosis, identified areas where there is enough evidence to make treatment recommendations, and discussed the side effects. Dr. Gloss described multiple sclerosis and its symptoms—including dysesthesias, spasms and/or pain, visual complaints, bladder problems, and fatigue. He outlined animal models, which are very important in multiple sclerosis research.

Dr. Gloss summarized what we know about multiple sclerosis and cannabinoids:

- Cannabinoids seem to be effective at controlling specific cardinal symptoms of multiple sclerosis—spasticity and central pain—as indicated by several high-quality RCTs.
- THC/oral cannabinoids seem to be ineffective at controlling tremor and bladder symptoms in multiple sclerosis.
- Clinicians should warn multiple sclerosis patients contemplating cannabinoid use about the risks of dizziness, dry mouth, psychoactive effects (e.g., confusion), and visual changes.

Dr. Gloss summarized what we need to know about multiple sclerosis and cannabinoids:

- Researchers should conduct comparative effectiveness studies; currently, it is difficult to understand when to use them.
- The field needs long-term safety data, as there are concerns with the short-term data.
- Scientists need to understand why these medications work in multiple sclerosis, specifically.

Psychomotor Performance and Detection

Moderator: Steven Gust, Ph.D., NIDA

Effect of Cannabis on Human Psychomotor Performance

Marilyn Huestis, Ph.D., University of Maryland School of Medicine

Dr. Huestis summarized current knowledge on the effects of cannabis on human psychomotor performance. She reviewed information on cannabis use and motor vehicle crashes and fatalities. Dr. Huestis also explained types of tolerance and discussed the development of tolerance for various effects of cannabis. She described research on the THC blood concentrations that occur after smoking cannabis. Currently, there is no simple, accurate, roadside behavioral impairment test for drugged driving. Dr. Huestis reviewed research on the effects of experience with THC on psychomotor impairment. She briefly touched on cannabinoid monitoring in blood, oral fluid, and breath. Using oral fluid, cannabinoids can be tested at the roadside to indicate recent cannabis intake. Testing devices are now available. An important question is: Are there markers of recent cannabis smoking/inhalation?

Dr. Huestis summarized what we know about the effects of cannabis on human psychomotor performance:

- Cannabis is the most common illicit drug identified in motor vehicle crashes and fatalities in the United States and generally worldwide (according to National Highway Traffic Safety Administration and National Forensic Laboratory Information System data).
- Cannabis significantly increases (about doubles) the odds ratio for motor vehicle crashes or fatalities (with some exceptions) (see PMID 22323502).
- The combination of cannabis and alcohol increases psychomotor impairment (sometimes additive, sometimes

synergistic); generally, cannabis is found in combination with other drugs.
- Cannabis medicalization and legalization may pose public safety issues.
- There is no single blood THC concentration that indicates impairment in all occasional and chronic, frequent, cannabis users.
- A combination of cannabis and alcohol is more impairing than either alone.
- Oral fluid offers onsite monitoring of recent cannabis intake.
- Tolerance can develop for some effects of cannabis, but it is not complete for any effect and it does not occur for all effects.
- THC blood concentrations drop rapidly after end of smoking/inhalation; its metabolites in blood drawn from drugged driving suspects can dissipate 1.5 to 4 hours after the arresting incident.
- We do not have a simple, accurate, roadside behavioral impairment test.

Dr. Huestis summarized what we still need to know about the effects of cannabis on human psychomotor performance:

- How will the American public balance the right to drive with public safety risk?
- Scientists need a greater understanding of the psychomotor effects of residual THC.
- Researchers need to learn much more about the degree of tolerance development and dissipation.
- Can we develop a sensitive and specific, objective, onsite behavioral test that can identify drug impairment (even with multiple drug intake)?
- Can we attain the required sensitivity for an onsite breath cannabis test?

Therapeutic Potential: Pain and PTSD/Anxiety

Co-Moderators: John Williamson, Ph.D., NCCIH, and Susan Borja, Ph.D., NIMH

Harnessing the Therapeutic Potential of the Endocannabinoid Signaling System to Suppress Pain

Andrea Hohmann, Ph.D., Indiana University

Dr. Hohmann discussed animal research describing how cannabinoids produce antinociception (i.e., relief from pain), as well as well-known behavioral side effects. She touched upon therapeutic targets and work on strategies for separating the therapeutic efficacy and side effects (e.g., psychoactivity, addiction) of cannabinoids in animal models of pathological pain. These strategies included targeting cannabinoid CB_2 receptors, use of brain-permeant and brain-impermeant inhibitors of endocannabinoid deactivation, allosteric modulators of cannabinoid CB_1 receptor signaling, and nonpsychoactive phytocannabinoids (e.g., CBD). She reviewed preliminary clinical findings on cannabinoids in the treatment of chemotherapy-induced neuropathic pain and briefly summarized results of published RCTs of cannabinoids for pain that largely support efficacy of cannabinoid-based therapeutic interventions.

Dr. Hohmann summarized what we know about the therapeutic potential of the endocannabinoid signaling system to suppress pain:

- Cannabinoids suppress pain processing through CB_1- and CB_2-specific mechanisms. Spinal, supraspinal, and peripheral cannabinoid mechanisms suppress pain.
- Cannabinoid CB_2 agonists show promise for suppressing pathological pain without the unwanted side effects of CB_1 agonists.
- Endocannabinoids suppress pain under physiological conditions. 2-AG is a retrograde endocannabinoid messenger that suppresses pain through activation of an mGlu5-DGLα-CB_1 pathway.

- Endocannabinoids are metabolized by multiple enzymes. Enzymes implicated in endocannabinoid deactivation (e.g., FAAH, MAGL) are therapeutic targets but are not selective for endocannabinoids.
- Allosteric modulators of CB_1 signaling suppress pathological pain in preclinical studies.
- Cannabis contains many active constituents and is not the same as THC.
- CBD, a nonpsychoactive ingredient in cannabis, shows therapeutic potential.

Dr. Hohmann summarized what we still need to know about the therapeutic potential of the endocannabinoid signaling system to suppress pain:

- What are the signaling pathways responsible for the therapeutic efficacy of CB_2 agonists?
- What are the physiological roles of other lipids hydrolyzed by FAAH, MAGL, and other active products derived from endocannabinoid metabolism?
- Are CB_1-positive allosteric modulators potentially superior to other cannabinoid-based therapeutics?
- What is the mechanism of action and therapeutic potential of CBD and other phytocannabinoids?
- How does the therapeutic potential of brain-permeant versus brain-impermeant inhibitors of endocannabinoid deactivation compare?
- How do we improve translation of preclinical findings to clinical populations?
- What are the factors that distinguish responders from nonresponders in clinical trials (e.g., genetics, sensitivity to side effects, and sex differences)?
- How can we better understand comorbid disease states, which may be particularly responsive to cannabinoid-based therapies, at preclinical and clinical levels?

The Therapeutic Potential of Cannabis in the Treatment of Neuropathic Pain

Barth Wilsey, M.D., University of California, San Diego

Dr. Wilsey reviewed the events that led California's legislature to establish the University of California Center for Medicinal Cannabis Research (CMCR). CMCR sponsored studies involving medicinal cannabis at all five medical schools in the state. Dr. Wilsey briefly outlined health conditions studied over the past 15 years at these institutions, including neuropathic pain and multiple sclerosis.

Dr. Wilsey reviewed findings from additional studies on medicinal cannabis for the treatment of neuropathic pain, spasticity, and other less frequently studied conditions. He also discussed patient and physician survey data on the use of medicinal cannabis, research on adverse events from medicinal cannabis, and existing knowledge gaps.

Dr. Wilsey summarized what we know about the therapeutic potential of cannabis in the treatment of neuropathic pain:

- Cannabis demonstrates efficacy in the treatment of neuropathic pain.
- Chronic pain is a common indication for cannabis in surveys.
- Cannabis has a reasonably acute safety profile.

Dr. Wilsey summarized what we still need to know about the therapeutic potential of cannabis in the treatment of neuropathic pain:

- Scientists need to study drug delivery methods other than smoking.
- Researchers need to determine the best combination of cannabinoids for analgesia.

- Studies are needed to improve masking of the psychoactive effects of cannabinoids in order to improve the ability of clinical trials to distinguish an effective treatment from a less effective or ineffective intervention.
- Research should determine whether cannabinoids have a synergistic interaction with opioids.

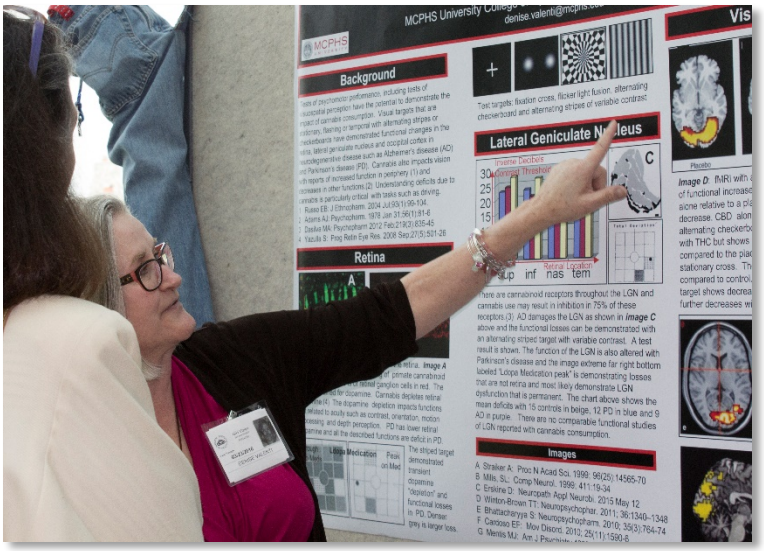
Cannabinoids and the Processing of Fear and Anxiety: Preclinical Studies

Cecilia J. Hillard, Ph.D., Medical College of Wisconsin

Dr. Hillard explained the survival value of fear and anxiety. Anxiety responses have a normal and appropriate range, and those that are out of proportion to the stimulus are pathological. She reviewed research on endocannabinoid-CB_1 receptor signaling in brain regions involved in the processing of anxiety and fear. She also discussed animal research on anxiety behaviors as they relate to CB_1 receptor signaling and endogenous cannabinoids. According to animal research, direct CB_1 receptor agonists affect anxiety behaviors in a biphasic manner, with low doses reducing anxiety and high doses increasing anxiety (see PMID 23785142). Dr. Hillard reviewed approaches to elevating CB_1 receptor signaling that have therapeutic potential for anxiety.

Dr. Hillard summarized what we know about cannabinoids and the processing of fear and anxiety:

- CB_1 receptor signaling is necessary for appropriate responses to a perceived threat and for appropriate extinction of aversive memories.
- Elevation of anandamide/CB_1 receptor signaling reduces anxiety and increases the extinction of fear.
- Direct CB_1 receptor agonists and MAGL inhibition do not produce the same spectrum of effects as FAAH inhibition.



Dr. Hillard summarized what we still need to know about cannabinoids and the processing of fear and anxiety:

- Is reduced CB_1 receptor signaling part of the etiology of stress-induced anxiety and risk for PTSD?
- Is there an opportunity for a personalized approach to treatment of anxiety and PTSD using cannabinoid-based therapy?

What is the Therapeutic Potential of Cannabis in PTSD and Anxiety Disorder Treatment? Evidence from Human Studies

Christine A. Rabinak, Ph.D., Wayne State University

Dr. Rabinak described the role of the amygdala in processing threats. She reviewed neuroimaging research on cannabinoids and endocannbinoid signaling and threat responses in the amygdala. Dr. Rabinak also discussed PTSD and its associations with changes in endocannabinoid signaling and in CB_1 receptor availability in the brain. She described Pavlovian fear extinction, a paradigm for animal research that can be used to understand PTSD and anxiety disorders, and the possibility that pharmacological agents could be used to enhance fear extinction learning.

Dr. Rabinak summarized what we know about the therapeutic potential of cannabis in PTSD and anxiety disorder treatment:

- Acute THC and CBD reduce amygdala reactivity to threat.
- PTSD is associated with reduced peripheral endocannabinoids and increased CB_1 receptor availability in the brain.
- An acute dose of THC pre-extinction facilitates extinction learning and increases activation of the ventromedial prefrontal cortex and hippocampus during extinction recall.

Dr. Rabinak summarized what we still need to know about the therapeutic potential of cannabis in PTSD and anxiety disorder treatment:

- What is the long-term impact of cannabinoid treatment?
- What is the optimal dosing and timing of treatment?
- Is there a therapeutic potential of cannabinoids for anxiety treatment in children?

Policy Research: Challenges and Future Directions

Co-Moderators: Susan Weiss, Ph.D., NIDA, and Michael Hilton, Ph.D., NIAAA

Cannabis Policy

Mark Kleiman, Ph.D., NYU Marron Institute of Urban Management and BOTEC Analysis Corporation

Dr. Kleiman pointed out that current research is not optimized to support policymaking, especially around the complex questions of regulating legal cannabis availability rather than the simpler yes/no question of whether to legalize it at all. He stressed the importance of studying cannabis as actually used, including both the chemical composition of various plant varieties and extracts and patterns of voluntary consumption, and said that studies that try to measure the effects of "marijuana use" generically often fail to make these key distinctions. There is no good reason to expect uniformity of effects over wildly varying preparations and use patterns. In studying damage, the focus should be on very heavy users, whose numbers have been rising sharply. To what extent can that increase be attributed to rising potency and THC/CBD ratios and to falling effective (potency-adjusted) prices? A useful statistic not currently gathered is the annual number of person-hours spent under the influence of cannabis.

More knowledge is also needed about the desired subjective effects of nonmedical cannabis use, and how those effects vary with the mixes of active compounds in different cannabis preparations and with dosage level and frequency. The folk-belief that cannabis intoxication enhances the enjoyment of music, for example, is empirically testable but as yet untested. There would be both research and policy value in establishing standard dose of THC to serve the same purposes as the "standard drink" of alcohol.

The Effects of Liberalizing Marijuana Policies on Use and Harms: Why Research Has Not Told Us Much

Rosalie Liccardo Pacula, Ph.D., RAND Corporation

Although some may think of it as a recent issue, state marijuana policy reforms have been taking place since the 1970s. Dr. Pacula reviewed the definitions and trends in decriminalization, medical marijuana, and legalization. She discussed the reasons why research to date is not definitive on the effects of marijuana policy. Policy heterogeneity is important and should be included in research. Definitions of decriminalization and medical marijuana matter. Research in this area should consider how marijuana laws have been implemented and how they have changed over time.

Dr. Pacula summarized what we know about the effects of liberalizing marijuana policies on use and harms:

- Marijuana liberalization policies continue to evolve within states, not only across states.
- Evaluations of policy effects are just beginning to focus on policy dimensions rather than policy labels.
- Current science suggests that particular dimensions of marijuana policies influence use more than other dimensions.
- Medical marijuana laws have clearly increased marijuana use among adults; however, evidence on the effects among youth is lacking.

Dr. Pacula summarized what we still need to know about the effects of liberalizing marijuana policies on use and harms:

- How do these policies influence: (a) the evolution of new products and (b) harmful use by adults and youth?
- How do these policies influence simultaneous co-use with alcohol and tobacco?

Regulating Retail Marijuana: Lessons Learned from Tobacco Control

Stanton A. Glantz, Ph.D., University of California, San Francisco

Dr. Glantz reviewed research on the health effects of tobacco and marijuana. He discussed the dynamic marijuana policy environment and the expanding marijuana industry. A legalized market will open up the opportunities for a lucrative market in which corporate players will seek to maximize consumption to maximize profits through innovations in product design and aggressive marketing. To counter these inevitable pressures, Dr. Glantz suggested that a public health framework is needed for marijuana. In this framework, the policy environment would develop a marijuana prevention and control program aimed at the general population and produce hard-hitting mass media education campaigns modeled on successful tobacco control programs that would be implemented concurrently with any marijuana legalization. This framework would include comprehensive public usage laws, strict marketing and advertising restrictions, taxation, and state-of-the-art graphic warning labels. Finally, policies should use tax revenue to fund an education campaign as well as a robust marijuana-related research program. In this public health framework, marijuana would be legal, but with declining numbers of people wanting to use it.

Dr. Glantz made the following public health recommendations:

- Robust demand reduction should be launched concurrently with legalization.
- Independent oversight committees should comprise public health officials and researchers exclusively—with no industry connections involved.
- Comprehensive marijuana prevention and control programs should be modeled on the best evidence-based tobacco control programs.
- Marijuana should be included in existing smoke-free laws, without exemptions.
- Marijuana tax revenue should be dedicated to fund ongoing research on both the harms and therapeutic potential of marijuana as well as education.
- Marijuana marketing and advertising should be restricted to inside licensed retail stores to minimize the exposure of youth, young adults, and vulnerable populations.

Dr. Glantz summarized what we know about regulating retail marijuana based on tobacco control:

- Tobacco and marijuana use among youth are intertwined.
- Marijuana has potential adverse health effects.
- Major corporate interests, including tobacco, see marijuana as a future profit center.
- Protecting public health has not been a priority in marijuana legalization.
- Tobacco, not alcohol, is a good model for marijuana legalization.

Dr. Glantz summarized what we still need to know about regulating retail marijuana based on tobacco control:

- Researchers need to determine the short- and long-term health effects of marijuana use as well as dual use with tobacco and alcohol.
- Information is needed on the evolving patterns and determinants of marijuana, tobacco, and alcohol use.
- Researchers should examine marijuana marketing and promotion strategies and how to counter them.
- Information is needed on effective (and ineffective) marijuana warning labels and educational messages.
- Researchers should study effective marijuana tax policy to promote public health.
- Studies should consider the legal marijuana industry as a disease vector, including its influence on policy.

Policy Surveillance Resources

Rosalie Liccardo Pacula, Ph.D., RAND Corporation

Dr. Pacula described the Prescription Drug Abuse Policy System (PDAPS). PDAPS is a NIDA-funded resource that provides data on prescription drug abuse and medical marijuana laws. She also discussed the Drug Abuse Policy Surveillance System (DAPSS), a pending project with NIDA that will include longitudinal data on recreational marijuana, medication-assisted treatment, and drugged driving laws. If approved, the DAPSS resource is expected in late 2016. LawAtlas is a policy surveillance portal that is maintained by the Policy Surveillance Program, a national program of the Robert Wood Johnson Foundation at Temple University. This resource provides cross-sectional data on recreational marijuana (since 2015) and more than 35 other health policies (e.g., which states ban texting while driving or give nurse practitioners authority to prescribe medications). Each resource provides interactive maps, legal text, and rigorous data for these topics.

Recreational Use of Cannabis to be Included in the Alcohol Policy Information System

Michael Hilton, Ph.D., NIAAA

NIAAA's Alcohol Policy Information System (APIS) provides detailed information on a wide variety of alcohol-related policies in the United States at both state and Federal levels. Detailed state-by-state information is available for 35 policies. APIS also provides a variety of informational resources of interest to alcohol policy researchers and others involved with alcohol policy issues. Dr. Hilton reported that APIS will include information on recreational use of cannabis. He reviewed the unique challenges involved—including developing a taxonomy for cannabis policy. Dr. Hilton identified the variables that NIAAA proposes to cover in APIS regarding recreational marijuana. He remarked that we know that public policy can affect the levels of adverse consequences for legal substances and that science can influence public policy. We still need to know the long-term impact of marijuana on adolescent brain development.

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