



# Medical Marijuana in Psychiatry

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Caregiver Collectives in Michigan are assisting thousands of patients today....

Our collective in Ann Arbor is the top rated pick of all collectives in Washtenaw County, MI.

*Great Services, Consultations, and More!*

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- Pull right up to our door and park

#### **Relaxing Atmosphere**

- Come and go as you please

#### **Qualified Caregivers**

- Committed assistance in Michigan

#### **Friendly Staff**

- Creating a relaxed experience



#### **Wheelchair Friendly**

First floor ground level access with one-step ramp.



# Marketing Marijuana



...where patients come first



# The Next Generation of a Drug



# What is a drug?

- Noun: A substance that has a physiological effect when ingested or otherwise introduced into the body
- A drug, broadly speaking, is any substance that, when absorbed into the body of a living organism, alters normal bodily function

# What is Medicine?

- Noun: The science of diagnosing, treating, or preventing disease and other damage to the body or mind.
- Verb: a substance or preparation used in treating disease or injury
- Confers benefit and therapeutic help

# Psychotropic drugs

- Psychotropic drugs are chemicals that alter feelings, emotions, and consciousness in a variety of ways; used in the practice of psychiatry to treat a wide range of mental and emotional illnesses.
- Modern psychotropic drugs are single molecule, often single action chemicals that are synthesized to have a specific action at know targeted brain receptors
- Modern psychopharmaceuticals undergo years of testing to test their safety and efficacy and are subjected to double-blind placebo-controlled testing to prove efficacy before approval by the FDA

# Cannabis sativa

- Hemp plant from which marijuana (leaves, stems, seeds) is derived.
- Contains more than 400 active compounds, 60 are known as cannabinoids
- Delta-9-tetrahydrocannabinol (THC) is the most active cannabinoid, isolated in the 1960's
- THC receptors discovered in the 1990's, CB-1 (brain) and CB-2 (periphery)

# Cannabinoid CB-1 widely distributed throughout brain

Hippocampus (memory, cognition)

Mesolimbic Pathway, Striatum and Nucleus Accumbens (reward circuits)

Frontal cerebral cortex (higher functioning)

Cerebellum and Basal Ganglia (movement and coordination)

Limbic and Paralimbic areas (anxiety, pain, endocrine function)

# Role of Cannabinoids in the Brain

- The endocannabinoid (ECS) system wiring in part of the body's stress response
- Acute stress activates the endocannabinoid system
- In animals acute stress causes behavioral effects, including reduced exploration, defensive postures, and anhedonia. These behavioral manifestations of stress are dampened by the ECS
- In acute stress, a primary role of the ECS is to dampen hypothalamic-pituitary-adrenal (HPA) axis activation

# Not Your Parents' Drug: Marijuana Potency Reaches All-Time High

- From 1970's through 2011 marijuana potency has increased over 1000% due to cultivation/hybridization
- Government sampling University of Mississippi over 3 decades of confiscated samples document THC content
- 1970-1980            1.3- 1.8% THC content
- 1980-mid 1990      2-3 % THC content
- 2000-present        > 1% rise THC content per year
- 2008-2011 THC content 20-30 %, some samples >37%.  
“Medical” marijuana is the most uniformly potent.

# Greater Potency= Greater Addictiveness

- Pharmacologic effect of drugs determined by  
“ HOW MUCH AND HOW FAST”

High concentration marijuana causes intoxication with single inhalation and blood levels reach faster, higher peaks

The degree of the neurochemical “ reward” drives the potential for addiction

Analogy: High from smoking crack cocaine is far greater than inhaling cocaine, which dramatically increases addictiveness

# Delta 9 THC Molecular Effects

- Inhibits adenylate cyclase
- Inhibits N, P /Q calcium channels
- Stimulates potassium channels
- Net effect is depolarization of neurons and overwhelming of the neuronal checks and balances.

# THC pharmacology

- THC metabolized through cytochrome p450 system
- $\frac{1}{2}$  life THC 20-57 hours depending on route of use
- $\frac{1}{2}$  life 11-OH THC active metabolite 12-36 hours
- 90% THC eliminated at 5 days
- Because of fat-solubility, metabolites still detectable in urine 13 days after use
- Regular users still excreting drug at 45 days
- Heavy users still excreting drug at 90 days

# Cannabinoids increase dopamine

- Dopamine is the reward chemical of the brain
- Cannabinoids release dopamine in the ventral-tegmental mesolimbic pathway
- In vitro cannabinoids cause abnormal neuronal firing and bursting activity in the midbrain, area underlying learning and execution of goal-directed activities
- The powerful activation of mesolimbic pathway circuits underlies the reinforcing, rewarding effects of ALL drugs of abuse
- Cannabinoids share the same action as all drugs of abuse including morphine and opiates.

# Animal Models with THC

- The hallmark of a drug's potential for abuse is that animals will work to obtain it.
- Squirrel monkeys were first trained to inject themselves with intravenous cocaine, which they could do by pressing a lever ten times. When saline was substituted for the cocaine, the monkeys stopped pressing the lever, but when saline was in turn replaced by a solution of THC, the monkeys quickly resumed their pressing behavior, giving themselves about thirty injections during a one-hour session.
- "These findings suggest that marijuana has as much potential for abuse as other drugs of abuse, such as cocaine and heroin." (Nature Neuroscience 2010)

# Psychiatric syndromes in marijuana users

- Mood disorders
- Anxiety disorders
- Attentional Disorders and Motivational disorders
- Psychotic Disorders and Schizophrenia
- Marijuana use is “The Great Imitator”, inducing symptoms of multiple diagnoses

# Hijacking the brain's dopamine system leads to addiction

- Dopamine release regulated by genes and environment.
- Dopamine is the primary driver of reward and learning behaviors
- Dopamine systems are interconnected with other chemical systems of the brain, serotonin, GABA glutamate, norepinephrine and others.
- Dopamine release enhancement results in over-stimulation of these pleasure-pathway nerves in the brain.

# Anxiety disorders

- Panic attacks are a frequent symptom of acute marijuana intoxication and can recur for weeks to months after single episode of use.
- Patients with preexisting anxiety disorders resort to “self-medicating” with cannabis, but suffer cyclic withdrawal and heightened anxiety and are refractory to traditional therapies such as SSRI’s.
- Possible mechanism of panic: Cannabinoids diminish GABA, an inhibitory chemical, lowering nature’s Valium-like “calming” transmitter.

# Mood disorders

- Preexisting depression or other mood symptoms may predispose to development of substance abuse
- Substance abuse in turn exacerbates and intensifies mood disorders
- In Baltimore 15 year prospective study of 2000 nondepressed volunteers, marijuana users were 4-5 times more likely to develop depression than nonusers
- Mood chemicals serotonin, dopamine and norepinephrine systems dysregulated by marijuana use

# Complicating the Picture

- Marijuana use can obscure definitive diagnosis of psychiatric disorders.
- Marijuana withdrawal symptoms occur in regular users, peaking at 2-3 days and lasting 2-3 weeks causing drug cravings, sleep impairment, anxiety, mood changes and cognitive complaints.
- Marijuana use causes treatment resistance in depressed users, antidepressants may not relieve the symptoms.
- Abstinence must be total of clinical outcomes are poor.

# Teen MJ use and Depression

- Depressed teens are more than twice as likely to use marijuana and to become dependent on it.
- Teens who smoke MJ at least once a month are 3 times more likely to have suicidal thoughts or suicide attempts than non-users
- Teen girls are at greater risk for depression and MJ use: 12% of teen girls experience depression vs. 4% of boys.
- Teen girls who smoke marijuana are 5 times more likely to develop symptoms of depression or anxiety

# Drug use Prevalence

Percent of persons 12 years of age and over with any illicit drug use in the past month: 8.7% (2009)

- Percent of persons 12 years of age and over with marijuana use in the past month: 6.6% (2009)
- Percent of persons 12 years of age and over with any nonmedical use of a psychotherapeutic drug in the past month: 2.8% (2009)
- Source: UM Survey Health, United States, 2010

# Escalation of MJ in High School

- Daily Marijuana use increased among 8th, 10th, and 12th graders from 2009 to 2010. Among 12th graders it was at its highest point since the early 1980s at 6.1 percent.
- The perceived risk of regular marijuana use also declined among 10th and 12th graders, suggesting future trends in use may continue upward.
- In addition, most measures of marijuana use increased among 8th graders between 2009 and 2010 (past year, past month, and daily), paralleling softening attitudes for the last 2 years about the risk of using marijuana.
- Regular marijuana use among HS students now at 21.4% is now greater than cigarette use at 19.4%. Occasional use is 43 %

(Univ Mich. Monitoring the Future (MTF) Survey, 2010)

# Teen depression

- Casual substance use like cannabis can significantly reduce the efficacy of antidepressant therapy in adolescents with treatment-resistant major depressive disorder (Treatment of Resistant Depression in Adolescents (TORDIA) study)

# Attention-Deficit Disorders

- Preexisting ADD/ ADHD does increase risk of lifetime marijuana use
- Marijuana use increases symptoms of ADD/ADHD and can induce similar symptoms in formerly non ADD patients
- Prefrontal cortex --the “executive brain”-- activity diminished in both ADD patients and marijuana users

# Memory and Marijuana

- Neuropsychological testing reveals cognitive deficits in MJ users.
- Marijuana disrupts short-term memory, working memory, and attentional skills (Fletcher, et al., 1996)
- Marijuana induces deficits in mathematical skills, verbal expression and memory retrieval (Block and Ghoneim, 1993)
- Marijuana causes short-term memory deficits that persist for long periods (Schwartz, et.al., 1989), and residual neuropsychological effects persist even after long abstinence (Pope and Yurgelun-Todd. 1996)

# Brain Imaging in Teens

- Functional MRI of abstinent adolescent users show abnormalities in prefrontal cortex(PFC), the” executive” part of the brain
- Earlier age of marijuana use = greater abnormalities on fMRI
- MRI abnormalities continue beyond 28 days of abstinence
- **Abstinent adolescent marijuana users show altered fMRI response during spatial working memory, problem solving.**
- Alecia D. Schweinsburg,<sup>ae</sup> Bonnie J. Nagel,<sup>f</sup> Brian C. Schweinsburg,<sup>bd</sup> Ann Park,<sup>e</sup> Rebecca J. Theilmann,<sup>bc</sup> and Susan F. Tapert<sup>bde\*</sup>

# Marijuana and the Hippocampus: In vitro

- In vitro: THC is toxic for hippocampal neurons at low concentrations, but toxicity increased with potency
- Mechanism of toxicity is likely oxidative stress (activation of a cascade of the PLA 2 COX pathway), whereby cell membranes, nucleic acids and proteins are oxidized leading to cell death
- THC caused cell shrinkage, nuclear damage and DNA breakage in hippocampal neurons
- THC is neurotoxic at concentrations as low as 0.5 1.0 mM, comparable to THC levels in human plasma after a single marijuana cigarette

# In Vivo: Hippocampal Damage

Clinical studies using f MRI show marijuana users have shrinkage of the hippocampal complex, the area pivotal for memory and learning as well as regulation of emotion and thought

Hippocampal damage decreases the ability to acquire new information or to recover previously learned knowledge

The hippocampus in heavy users showed volume reductions or 12%, particularly left hippocampus) as well as shrinkage of the amygdala by 7.1 % ((Arch Gen Psychiatry 2008; 65:694-701)

Left hippocampal volume shrinkage correlated with cumulative exposure to the drug.

Left hippocampal atrophy is seen in schizophrenia patients

# Schizophrenia and Psychosis

- Risk of developing psychosis with marijuana is 41% across entire population, higher among heavy users.
- Younger users and higher potency marijuana increases risk for psychosis
- Users exhibit subclinical psychosis frequently, which may progress to clinical thresholds with ongoing use

# Schizophrenia

- Normal onset in early adulthood
- First episode of psychosis confers highest risk for suicide (ages 18-26)
- Downward, deteriorating course is naturalistic pattern unless effective treatments are given.
- Each episode of psychosis causes damage to critical brain structures, so age of onset and treatment resistance are of great importance to functionality
- Marijuana use, by accelerating onset or by inducing psychosis, correlates with worsened outcomes

# Cannabis and Psychosis: Longitudinal Studies

- German study 1923 individuals age 14-23 showed MJ users were 70% more likely over 10 years to develop psychotic symptoms by age 26.
- Swedish study of 50,000 men over 15 years : Adolescent marijuana use increased risk of developing schizophrenia 6-fold
- Large New Zealand study of 1037 patients Dunedin Birth Cohort Study, those who used MJ before age 16 were 4 times as likely to have schizophreniform symptoms at age 26.

# MJ affects gene expression

- Cannabis use was significantly associated with earlier age at onset of psychotic disorder (AOP; average difference 2.7 years,  $P < 0.001$ ), showing dose-response effects with higher frequency and earlier age at first use

(Am Journal Medical Genetics: Neuropsychiatric Genetics 2011 vol 166, 363-369)

# Genetics of Psychosis

- Risk of psychosis may relate to COMT gene (catechol-O-methyltransferase) gene responsible for metabolism of dopamine
- Risk of psychosis may relate to COMT gene (catechol-O-methyltransferase) gene responsible for metabolism of dopamine, the chemical producing the high with drugs
- MET gene sequence is normal, VAL gene abnormal
- MET/VAL genotype increases risk of psychosis 2 fold
- VAL/VAL genotype increases risk 10 times (25% of population)

# Mechanism of Damage: BDNF

- Cannabis decreases Brain Derived Neurotrophic Factor (BDNF).
- BDNF is a neurotrophin that is involved in the regulation of the genesis, differentiation, survival, and repair of neurons
- BDNF modulates neuroplasticity and adaptive processes underlying learning and memory.
- Acute and repeated exposure to cannabis in adolescence and young adulthood may further compound an already abnormally developing brain by altering BDNF levels in a nonphysiologic manner.
- The effects of cannabinoids on BDNF provide a mechanism by which exposure to cannabinoids may interfere with normal brain development and contribute to the development of some neuropsychiatric disorders.

# Medical Marijuana is Viral

Your teen or preteen has access to medical marijuana through diversion/reselling in every community

No barriers to getting a card creates armies of dealers and growers

Marijuana use has been “normalized” by decriminalization.

Teens regard marijuana as safer than alcohol and other drugs

Yes, MJ is a gateway drug to ecstasy, methamphetamine, hallucinogens for over 30% of users

# Developing Brains are Vulnerable

- Studies show that marijuana use in adolescence may be associated with persisting neurocognitive abnormalities, which could have important implications for future functioning among these youths.
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- Cannabinoid metabolites remain detectable in urine for at least 4 days and 27 days on average in heavy users, so even casual use exposes the brain to incessant pharmacologic effects that may reorganize neural networks and possibly affect brain structure permanently.

# Marijuana is Not Medicine

- Physicians do not support this legislation!
- True forces behind legalization: George Soros, Peter Lewis (Progressive Insurance), John Sperling (Univ. Phoenix)
- Lindesmith Center \$ 4 mil Soros, pro-MJ think tank, Open Society Institute (OSI) influential.
- Drug Policy Foundation, now Drug Policy Alliance (DPA), 7 offices in USA, \$3.5 mil, \$1.7 mil Soros seed money.
- DPA funds pro- marijuana research studies in articles for review by for Science, JAMA and Brit Med Journal and other mainstream journals
- Soros et.al., financially behind all marijuana legalization initiatives in California, Nevada, Arizona, Texas, Michigan

# Marijuana is Not Medicine

- Definition of A DRUG: A substance that has a physiological effect when ingested or otherwise introduced into the body, in particular

Definition of a Medicine: A drug or agent with a purpose of preventing disease and other damage to the body or mind

Contrast : The definition of “TO DRUG”: Administer a **drug** to (someone) in order to induce stupor or insensibility.

# Family Members and Citizens

- Educate yourself and your family, friends and schools
- Major studies suggest that cannabis use among psychologically vulnerable adolescents should be strongly discouraged by parents, teachers, and health practitioners
- Community Resources: Get help when you or your teens are using
- Political action: your state representatives, your local zoning board and city council to keep dispensaries out of your communities
- Other states have recognized the damage done by drug legalization and have reversed the laws (eg., Montana)