

WHAT TO REMEMBER ABOUT CANNABIS

HISTORY

Evidence of cannabis (CB) use goes back about 12000 yrs. Starting in Central Asia (Now India, Pakistan and Bangladesh).

Hemp was used by the Greeks and Chinese in antiquity.

It had its start in America in the 1600's, by the English and the Spanish, cultivated primarily for its useful fibers.

Medicinal uses seem to first appear in China, India and the Middle East. Later in South America and Africa.

Chinese uses: 2700 BC, Constipation, Malaria, Rheumatic pains, and "female disorder".

Indian uses: 2000 BC, Fever, Insomnia, Appetite, Headaches and STDs.

Modern Medicine: 1900's, British in India-First studies in Modern Medicine.

Recreational uses: 1930's after repeal of prohibition. Medicinal use was abolished in USA in 1937, with the Marijuana Tax Act. It joined schedule 1 in 1970, after use had exploded in the 1960's. This increase did however spawn greater research interest.

WHY KNOW ABOUT CANNABIS

CB is the most widely used illicit drug in the US, and even the world. There are an estimated 2-3 million users as of 2 years ago, and it is growing all the time. CB has its health implications. In 2011 ER visits for CB related problems rose by 64% compared with 2004. Second only to cocaine, a much more toxic drug. 6-7% of adolescent pre-teens are using CB. Synthetic CB (SC) is growing rapidly in popularity. It is a gateway drug in a variety of ways. Its psychoactive effects, especially in combination with other drugs and alcohol have significant implications for mental health burden of morbidity and financial costs.

CANNABIS IS AN INTERESTING PLANT

Two types of CB. Well known, Sativa and Indica. The Latin name is *Cannabis Sativa*. It contains about 400 compounds, majority of them having never been studied. About 60 are Cannabinoids, having some form of biological activity.

Two types of Cannabinoids: **Cannabinols** and **Cannabidiols**. THC (Delta-9 tetrahydrocannabinol) was purified in 1965. Led to discovery of the **Endocannabinoid System** (ECS). A

biological system in living organisms that makes, regulates and responds to its own cannabinoids.

We make our own cannabinoids, which play important roles pain, inflammation, immunity and muscle control, appetite and other biological functions.

We have drugs that block receptors to cannabinoids, partially mimic them and fully mimic them, and more. It is complex biology (it's always that way). Many of these have the therapeutic effects of CB without psychoactive effects including euphoria. Not clear that this "euphoria" is therapeutic.

The main ingredients are produced in the flowering tips (buds) much less in the stems and leaves. Unfertilized tips (*sensimilla*) have the highest concentration on the plant. Clipping and harvesting skills are highly valued among growers and pay very well. Hashish is a more concentrated processed form, and Hashish oil has the highest concentration of all with 15-50% THC, compared with bud concentrations of 0.5-5%.

SYNTHETIC CANNABINOIDS (SC)

These are not processed CB from natural sources. **Spice** as it is known, is not a single substance, but a diverse group synthetic CB produced in labs as part of research into Cannabis. They have various degrees of effect and have both psychoactive and non-psychoactive clinical effects. Originally sold in head shops, they are not to be confused with Bath Salts or *Cathinone*, a stimulant drug found in *Khat*, a shrub from North Africa, used for making tea and smoking. In ways, similar to cocaine.

Spice, also known as K2, Kush, Pot Pourri, Skunk, Aroma, Moon rocks, Genie and fake marijuana, is a chemical that is sprayed on to other herbs and smoked. These herbs are uncontrolled in the industry and can be toxic and have unknown effects some of which have caused very unpleasant psychoactive effects.

There are 4 groups of SC (cyclohexiphenols, oleamide fatty acids, JWH 018,398, 250 among them). In research and clinical practice, they have been noted to cause anxiety, agitation, hallucinations and paranoia. High heart rate, high blood pressure and blood sugars are also effects. It lasts 3-6 hrs. Cases of renal failure and other physical problems are known to have occurred.

MEDICINAL PROPERTIES AND POTENTIAL

Much of the CB controversy is all about accessing its medicinal benefits. Ethanol Alcohol has nearly no recognizable medical uses, and is not prohibited, despite very serious behavioral, medical and abuse related problems and enormous social cost. We could all use an education about CB.

CB has central (brain and spine) effects when it crosses the blood-brain barrier (BBB), and peripheral effects on the body.

Two types of CB receptors in our bodies are well known, but there are probably more. CB1, and CB2. Many CB compounds have effects of different potency on both receptors. Some don't cross the BBB and have no psychoactive effects. Some are effective as transdermal patches, or can be ingested.

HIV-AIDS, due to its urgent need for novel therapies was a first testing ground for some of these compounds. It treated neuropathic pain, anorexia and weight loss, emesis, seizures and movement disorders. It was also found to help in Glaucoma.

Then it found uses in other serious disorders like Multiple Sclerosis (MS) and Parkinson's. Treating painful muscle spasticity, appetite and sleep disorders. Non-psychoactive therapeutic compounds would be important here as these disorders can cause hallucinations, delusions and significant mood symptoms which CB can complicate.

Analgesia, relief from pain. Primarily related to CB1. Especially in nerve pain (neuropathic pain), an area where opiates don't do so well. Problem with natural CB is that it is short acting. Blocking CB1 receptors causes increased pain (CB blocker: *Rimonabant*).

CB1 receptors increase naturally in affected nerve sites that are a source of pain. The nerve will therefore respond to drugs that block the re-uptake and breakdown of Endocannabinoids (EC). There will also develop changes in receptor concentrations and responses (affinity and effectiveness) after exposure to these agents for a while. These re-uptake and breakdown blocking agents are not like smoking natural CB, because they respond to the body's own levels of EC production and breakdown. Anti-depressants do the same thing with endogenous catecholamines.

EC and CB from exogenous sources get incorporated into the metabolic processes of the lipoxygenase prostaglandin pain pathway. They are broken down by COX 2 enzymes. Therefore, COX2 inhibitors can prolong the analgesia of CB and EC. Remember that COX2 inhibitors increased our risk of heart attack and stroke. Does CB reduce this risk? Some studies suggest so.

CB2 treats inflammatory pain (not neuropathic), modulates immune responses through interactions in the marrow and other sources of lymphocyte production (spleen, nodes, etc.). Interestingly it also enhances bone density. Immune proteins called cytokines regulate pain and inflammation.

There are a number of CB2 active compounds in existence that treat pain and inflammation without psychoactive effects.

Interestingly: CB reduces the development of tolerance and withdrawal in opiate use for analgesia but not in other areas. This reduces opioid related morbidity and adverse effects. Blocking opioids can inversely release EC activity. Thought to be a mechanism for **LDN** (low-dose naltrexone) to treat chronic pain (superior to Lyrica, Cymbalta and Savella). Naltrexone does reduce CB dependence and the high through the dopamine pathway. Naltrexone worsens pain only in persons on opiates.

Opioid, and Substance P receptors respond to CB and EC also. CB binds with the opioid receptors forming Dimers that enhance the affinity and effect of both. Exogenous CB interacts with endogenous opioids.

DXM or dextromethorphan, alone and in combination with LDN also relieves pain. LDN relieves pain in MS like CB. These effects may be EC mediated. Other conditions with severe inflammatory problems, like RA and Crohn's might also benefit from treatment with CB.

The strange case of increased EPS, movement disorders in opiate addicted persons can be explained by the opioid-EC balance in the CNS. These tracts co-occur in the spine.

Cardiovascular effects of CB exist. Can cause severe low blood pressure, decreased rate and contractility. This can be therapeutic in HTN and dangerous in congestive heart failure (CHF). EC have a natural role in BP regulation in disease states.

Glaucoma, the most commonly joked about excuse for having possession of medicinal marijuana. Ironically has mixed results and so far, not better than conventional treatments, nor necessarily helpful in conventional treatment non-responders. There is a theory that it lowers vascular pressure on the eye thereby reducing ocular pressure.

THE DARK SIDE?

Recreational use, abuse and dependence. There is CB **tolerance and withdrawal**, but only really in heavy users. The lifetime risk of developing dependence in CB users is about 9%.

Has all the properties of an abuse drug, a reward pathway, euphoric and sensory enhancing properties, rapid onset of action and mechanisms for rapid delivery of drug to the brain.

Withdrawal, is the opposite of the clinical effects of using CB.

- 1 Insomnia.
- 2 Anorexia.
- 3 Anxiety.
- 4 Irritability.
- 5 Depression (mood).
- 6 Tremor.

But it is more of an affective than physiological withdrawal. The intensity varies, as will all substances, but is comparable to nicotine withdrawal.

Withdrawal is a negative reinforcer of use and increases rates of relapse (higher than with other drugs). Not much is known about whether other compounds in CB play a role.

BEHAVIORAL EFFECTS

The old stereotype “amotivational syndrome” is not really proven, but seems to be observed frequently. Many consumers of mental health services express significant concern over the fact that many psychotropic medications cause weight gain, sedation, cognitive interference, and often apathy. Ironically, CB can do all that *and* exacerbate mental health symptoms, and I have yet to hear a single client make the comparison. Why?

The reason seems to be that our medications don't cause or induce euphoria for one. CB can *reduce* movement disorders and related adverse effects induced by anti-psychotics. CB induces paranoia in persons with primary psychotic disorders, where's the euphoria associated with that?

It's a complicated subject with many individual variances, and there can be euphoria followed by paranoia, and then there's stigma and culture.

Heavy users tend to experience the complications of CB, not surprisingly.

Cognition: Reduces recent and short-term memory. Reduces goal directed activity. Reduces concentration and fine motor skills. Age is a factor. So is dose. Anxiety is as well, Cannabidiols can reduce anxiety. If anxiety is impairing concentration than it can help. Heavy and long-term users experience reductions in functional IQ. Its effects on cognition most pronounced if use starts in the teens. EC plays a role in memory suppression which may indicate a role in PTSD and GAD.

Psychosis: EC system known to play a role in Schizophrenia. EC blocker Rimonabant will increase symptoms in Schizophrenia, but so does THC. So, other components in CB may have a beneficial role. It is believed to induce onset of Schizophrenia by 5-6 times in individuals with a first degree relative with a primary psychotic disorder, and about 1.7-2 times in others of those who start in their early teens. Induces symptoms in those with an established primary psychotic disorder. Little connection drawn between CB use, psychosis and violence. However, paranoia, and co-morbid substance use (especially alcohol and cocaine) are independent risk factors for violence associated with psychiatric disorders.

Depression: Many confounding factors reported in research, but. This is very commonly seen in practice. There are studies pointing to CB playing a role, but others that do not support the assertion and it is not worked out. I did not see any clear connection with suicide rates so far.

Anxiety: Initial use causes a sensation of relaxation for most. As the effect continues, paranoia can set in which induces anxiety. Long-term use is frequently associated with high levels of anxiety, but not like with stimulants, or the rebound effects from alcohol and benzodiazepines.

NON-BEHAVIORAL EFFECTS

Not really the focus of our talk today, but it's helpful to mention the following:

Respiratory: Many of the carcinogenic mutagens in Tobacco (Tbc) are in CB. Direct links to cancer in CB users are lacking. Same for COPD. This is possibly related to the frequency of use. It's much easier to smoke a pack of cigarettes, than a pack of joints. CB has been shown to cause inflammation, cough and increased shortness of breath. The combined use of CB and Tbc has been shown to increase cancer risk than either alone.

Reproductive: Reduces fertility in males and females. CB stores in fat reserves and thus is found in breast milk and can affect infants.

Cardiovascular: Reduces blood pressure, heart rate and myocardial contractility. This may be beneficial in those with hypertension. Not good for athletes as such effects can reduce exercise tolerance and endurance. It's bad in CHF, as it can reduce stable and compensated CHF states and counter the effects of cardiovascular medications.

OPEN DISCUSSION POINTS

How do clinician's view the role of CB among our patients, peers and children?

Drug use is reinforced in the population in many ways. Does opposing that reinforcement help or hinder our relationships with our patients?

How should we approach the subject of CB use now and in the future?

Any cases or experiences to share?

Many Thanks!

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