Perspectives in medical use of cannabis and health consequences

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Cannabis: not a new medicine
Substances contained in cannabis

483 known compounds in the plant:
- tetrahydrocannabinol (THC)

84 other cannabinoids:
- cannabidiol (CBD)
- cannabinol (CBN)
- tetrahydrocannabinabivarin (THCV)
- cannabigerol (CBG)
Lots of media information
Lots of anecdotal information
Petition: allow veterans diagnosed with PTSD use of medicinal cannabis Nationwide.
The endogenous cannabinoids

- Anandamide
- Virodhamine
- N-arachidonoyldopamine
- 2-Arachidonoylglycerol
- Noladin ether

Cannabinoid Targets for Drug Discovery
Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

- Brain Development
- Memory and Cognition
- Motivational Systems & Reward
- Appetite
- Immunological Function
- Reproduction
- Movement Coordination
- Pain Regulation & Analgesia
Distribution of Brain CB1 Receptors

- Hippocampus – Memory and Learning
- Amygdala – Novelty, Emotion, Appetitive Behaviour
- Basal Ganglia & Motor Cerebellum – Real Time Coordination, Selective Attention and Time Sense
- Nucleus Accumbens - Reward Mechanisms
- Cortex & Frontal Lobe - Executive Function, Judgment, Synthesis, Evaluation
Retrograde Signaling & the Cannabinergic System
Pre-synaptically located CB1 cannabinoid receptors regulate GABA Release from Axon Terminals

Katona et al., 1999
Hájos et al., 2001
Piomelli et al., 2003
Example of findings regarding medicinal use of cannabis


- **Higher Concentration THC improves post surgical/traumatic neuropathic pain** *(Ware, et al. 2010. CMAJ. 2010 Oct 5;182(14)*)

- **Cannabis improves MS spasticity in placebo controlled randomized study** *(Corey-Bloom, et al. (2012) CMAJ 184(10); 1143-1150)*

- **Dronabinol was found effective for appetite stimulation** *(Beal, et al. (1995). Journal of Pain and Symptom Management. 10;2. 89-97)*
Medicinal Uses for Cannabinoids

- Analgesic
- Anticonvulsive
- Sedative
- Anti-depressive
- Hypnotic
- Anti-asthmatic
- Immunomodulation
- Memory Enhancing
- Anesthetic
- Appetite Stimulation
- Antipyretic

- Neuropathic Pain
- Anti-emetic
- Antirheumatic
- Anti-migraine
- Anti-neuralgic
- Reduction of fatigue
Cannabis appears to have treatment value in patients with anxiety (social phobia).
Pharmacol Biochem Behav.

Antidepressant-like effect of delta9-tetrahydrocannabinol and other cannabinoids isolated from Cannabis sativa L.
El-Alfy et al., 2010

cannabigerol (CBG) and cannabinol (CBN)
no antidepressant-like action

cannabichromene (CBC) and cannabidiol (CBD)
significant antidepressant-like effect
Role for cannabinoids in schizophrenia treatment?
Some evidence for cannabinoid involvement

• Heavy MJ use associated with increased risk of psychosis in some studies; THC itself can produce acute psychosis
• Human PET studies show increase in CB1 binding in various brain regions in untreated schizophrenia
• Serum/CSF anandamide increased during onset of psychotic symptoms, but not in heavy MJ users
• Higher CSF anandamide associated with less likely transition to psychosis in “high risk” cases
• In psychosis cases treated with cannabidiol, improvement in negative symptoms associated with greater anandamide rise

Cannabinol and cannabidiol exert opposing effects on rat feeding patterns. Farrimond et al., 2012.

Δ(9)-tetrahydrocannabinol-induced
- Increase in food consumption

Cannabinol
- increase in appetitive behavior and food intake

Cannabidiol
- reduction in food intake

an alternative to psychotropic Δ(9)-tetrahydrocannabinol-based medicines since cannabinol is considered to be non-psychotropic.
Treatment of refractory epilepsy—especially in children—using cannabidiol (CBD).

Little published evidence is available to prove or disprove the efficacy and safety of CBD in patients with epilepsy.

Clinical evidence suggesting efficacy in HIV-associated neuropathic pain

Efficacy in spasms associated with multiple sclerosis

Cannabidiol: promise and pitfalls. Welty et al., 2014
Amygdala FAAH and anandamide: mediating protection and recovery from stress.

A long-standing literature linking endo-cannabinoids to stress, fear, and anxiety has led to growing interest in developing novel anxiolytics targeting Inhibition of FAAH (Fatty acid amide hydrolase) facilitates long-term fear extinction

Inhibiting FAAH as a mechanism to therapeutically mitigate the effects of traumatic stress.

Gunduz-Cinar et al., 2013
Clinical endo-cannabinoid deficiency revisited: can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome?

underlying endo-cannabinoid deficiencies play a role in migraine, fibromyalgia, irritable bowel syndrome

Smith and Wagner, 2014
dronabinol and nabilone for chemotherapy-associated nausea and vomiting
HIV (Human Immunodeficiency Virus) wasting

Nabiximols (a cannabis extract)
treatment of
- spasticity
- intractable pain

marijuana extracts
for seizure disorders
The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis.
Goldenberg et al., 2017.

- Pain
- Multiple sclerosis
- Inflammatory bowel disorders

- Small improvements in quality of life.
- HIV patients: reduced quality of life.

Inconclusive results
Cannabinoids in treatment-resistant epilepsy: A review. O'Connell et al., 2017

Treatment-resistant epilepsy that affects 30% of epilepsy patients

Placebo-controlled, randomized trials with cannabidiol (CBD)

We lack valid data on the safety, efficacy, and dosing of artisanal preparations available from dispensaries

Open-label studies with 100mg/ml CBD have provided additional evidence of its efficacy along with an adequate safety profile in children and young adults with a spectrum of treatment-resistant epilepsy
Whether "medical marijuana" should be accorded the status of a legitimate pharmaceutical agent has long been a contentious issue.

Should cannabis be approved for medical use by a vote of the people as already has been done in 13 states? Or should medical marijuana be scientifically evaluated for safety and efficacy as any other new investigational drug?

Should the approval of medical marijuana be governed by the same statute that applies to all other drugs or pharmaceutical agents, the Food, Drug, and Cosmetic Act (FD&C Act), after the appropriate regulatory agency, the Food and Drug Administration (FDA), has evaluated its safety and efficacy?

If not, should medical marijuana be exempted from scientific review and, instead, be evaluated by the Congress, state legislatures, or popular vote?

I will argue that advocacy is a poor substitute for dispassionate analysis, and that popular votes should not be allowed to trump scientific evidence in deciding whether or not marijuana is an appropriate pharmaceutical agent.
- Pre-clinical studies: cells, experimental animals

Clinical trials: in-human-studies

- Phase 0: Pharmacodynamics and Pharmacokinetics (15-20)

- Phase 1: Screening for safety, determine a safe dosage range, and identify side effects (80)

- Phase 2: Establishing the efficacy of the drug, usually against a placebo to see if it is effective (100–300)

- Phase 3: Final confirmation of safety and efficacy, to confirm its effectiveness, monitor side effects, compare it to commonly used treatments (1,000–3,000)

- Phase 4: Studies during sales (post marketing studies)
Medications approved by:

Court?

Referendum?

Acclamation?

Scientific trials?
No smoked medication is easy to manage in a clinical setting

(Kleber and DuPont, Am. J. Psychiatry, 2012)

Clinical trials should be prospective, organized, with systematic exposures of patients to an intervention.

Clinical trials need long term follow up

Clinical trials should be placebo-controlled randomized

(Feifel, 2009)
A functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of adolescent cannabis use on developing adult psychosis.

**COMT valine158 allele**
Psychotic symptoms if they used cannabis

**COMT methionine allele**
No such adverse influence
Schizophr Bull.
Gene-environment interplay between cannabis and psychosis.
Henquet et al., 2008
The epidemiological literature in the past 20 years shows that regular cannabis use induces:

- risk of accidents
- dependence
- poor psychosocial outcomes
- mental health problem in adulthood

Some researchers still argue that these relationships are explained by shared causes or risk factors.

Hall, 2014
One in six teenagers who regularly smoke the drug become dependent on it.

Cannabis doubles the risk of developing psychotic disorders (schizophrenia).

Cannabis users do worse at school.

Heavy use in adolescence appears to impair intellectual development.

One in ten adults who regularly smoke the drug become dependent on it.

Cannabis users are more likely to go on to use harder drugs.

Driving after smoking cannabis doubles the risk of a car crash.

Smoking it while pregnant reduces the baby’s birth weight.

Hall, Addiction 2014
Adverse health effects of marijuana use.

Volkow et al., N. Engl J Med., 2014

- Acute psychosis
- Chronic psychosis
- Depression
- Anxiety
- Suicidal thoughts
- Personality disturbances
- Lack of motivation
lower levels of arousal in response to negative emotions compared to abstinent cannabis users and controls

a persistent hyperactivity of hypothalamus-pituitary-adrenal (HPA) axis

impaired hormonal reaction to negative emotions, in comparison with healthy subjects.

reduced sensitivity to negative emotions
Cold color bar shows regions where gray matter volume is lower in regular smokers compared with occasional ones.
Cannabis and schizophrenia

Shared risk factors: parallel development of co-occurring disorders

Causal model: in vulnerable or non-vulnerable population

Self-medication model
Strokes are possible complications of cannabinoids use. Wolff and Jouanjus, 2017.

Cannabis may be considered as a risk factor of stroke until research shows evidence of an underlying mechanism that, alone or in association with others, contributes to the development of stroke.

As of today, reversible cerebral vasoconstriction triggered by cannabinoids use may be a convincing mechanism of stroke in 27% of cases.

One of the mechanisms: the generation of reactive oxygen species leading to an oxidative stress, which is a known mechanism in stroke in humans.
While a myriad of studies have examined cannabis use in all its various forms, often these research conclusions are not appropriately synthesized, translated for, or communicated to policy makers, health care providers, state health officials...
In conclusion

- Cannabinoids appear to be promising as medications.

- A rigorous approach will permit to recognize their value.

- The same approach that is applied to any other new medication

- The studies should target single cannabinoid substances

- Smoking as way of administration is inappropriate

- Undesirable side effects should be reported accurately in long term trials and considered before prescription
In conclusion

- Cannabinoids may induce dependence
- Cannabinoids may induce bronchitis and cardiovascular disorders
- Cannabinoids may contribute to car accidents
- Cannabinoids interfere with emotional development of adolescents
- Cannabinoids use is significantly associated with co-occurring mental health disorders, in particular psychosis
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