Marijuana: An Update for Medical Professionals

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September 19, 2014

Disclosures

- No conflict of interest with this content
- Potential perception of conflict:
  - Collaborator: Caron Foundation
  - Consultant: Alvee Laboratories, Braeburn Pharmaceuticals, Millennium Laboratories
  - Founder: The Parents Academy (supported, in part, by Caron Foundation)
  - Managing Partner: Treatment Partners LLC (Two Dreams Outer Banks)
  - Medical Director: Encounter Medical Group, P.C.
  - Partner: EMGlobal LLC
  - Former Consultant: GW Pharmaceuticals

Acknowledgements

- Robert DuPont, Co-chair
- Louis E. Baxter, President ASAM (2010)
- Timken Cermak, Mark L. Kraus, Petros Levounis
- Process
  - Literature review, consensus discussion, field review and findings, conclusions and recommendations regarding the therapeutic value of smoked marijuana and the role of the physician

Objectives

- Examine circumstances leading to current situation
- Explore scientific issues
- Develop recommendations to assist physicians
- Formulate policy recommendations
- Use uniquely qualified perspective of addiction medicine

Take Home Messages

- Differentiate therapeutic potential of specific chemicals delivered in controlled fashion via non-toxic delivery system vs. smoked marijuana
- Consider drug approval within the context of public health
- Apply standard of great care when prescribing controlled substances, considering why a substance is controlled

Approval Essentials

- Close scrutiny by FDA assures (in an ideal world)
  - Standardization by identity, purity, potency, and quality
  - Adequate direction based upon robust body of data from controlled studies for use in approved medical indication
  - Risk/benefit profile elucidated and communicated from well defined controlled studies

Why President's Action?

- Research in therapeutic potential lags behind other modern medications
- Recent discoveries and elucidation of endocannabinoid receptor system coupled with new research tools facilitates analytical, pharmacological, and other preclinical research
- Liberal cannabis distribution puts patients with medical conditions and others at risk in setting of little scientific evidence to guide rational/ethical action

ASAM Paper Outline

- Modern History
- Basis for Cannabinoid Therapeutics
- “Medical Marijuana” in the U.S.
- Reports from Expert Bodies
- Professional Organizations
- The Federal Position
- Federal Departments and Agencies

Outline Continued

- Modern Medications and the FDA
- “Medical Marijuana” and the Modern Medication Model
- Other Countries
- Existing Research
- Oral Cannabinoid Preparations
- Are There Principled Reasons to Exempt Cannabis?

Outline Continued

- Could a Cannabis Preparation Achieve FDA Approval?
- The Significance of Scheduling
- Conclusion
- Recommendations

Understanding the Plant

- Composition of herbal cannabis varies significantly
  - Rich source of variety of compounds
    - Cannabinoids
    - Terpenoids
    - Flavonoids
- Exact content of chemical composition varies
  - Plant genetics
  - Growth conditions
  - Time of harvest
  - Drying conditions

- Many species exist: Cannabis Sativa (Europe), Cannabis Indica (India) and Cannabis ruderalis (Siberia and central Asia)
- 460 known chemical constituents of cannabis
- 66 constituents have a cannabinoid structure
- Δ^9-Tetrahydrocannabinol (Δ^9-THC or THC) most important constituent
- Δ^9-THC is the principal psychoactive component of cannabis
- Delivery systems do not deliver standardized dose
- Smoking to de-carboxylate delivers harmful pyrolytic products

The Plant

Plant Tissue	%THC
Seeds	0.0
Roots	0.0
Stem	0.3
Leaves	0.8
Seeded Female Inflorescence	6.3
Unseeded Female Inflorescence	15.2

Inflorescence

History of Cannabis in Medicine

- Used 4000 years
- 1842 into British medicine by O'Shaughnessy
- Marijuana Tax Act of 1937 made cannabis products less attractive as a treatment option
- 1961 UN Single Convention on Narcotic Drugs banned use
- Schedule I in U.S.

Era of Cannabis Research: 200-1940

- Circa 200 AD: Therapeutic properties of cannabis described in Chinese pharmacopeia
- 1838-1840: Sir W.B. O'Shaughnessy methodically assesses medicinal properties of cannabis, and publishes findings
- 1899: Wood et al. isolate cannabinol from cannabis resin
- 1932: Cahn elucidates part of the structure of cannabinol
- 1940: Todd et al. and Adams et al. simultaneously elucidate the full structure of cannabinol and successfully synthesize it

Era of Cannabinoid Research: 1960-1994

- 1960: Mechoulam (Hebrew University) identifies THC as the principal psychoactive component of cannabis
- 1964: Gaoni and Mechoulam (Hebrew University) elucidate the chemical structure of THC
- 1970-1990: Cannabinoid pharmacology is thoroughly studied
- 1985: Gardner shows cannabinoid-opioid interaction in brain
- 1986: Gardner shows THC activates brain-reward systems

Era 1960-1994, continued

- 1988: Howlett's group finds specific THC binding sites in brain
- 1990: Matsuda et al. clone the CB1 receptor
- 1992: Mechoulam's group (Hebrew University) in collaboration with Pertwee's group (Scotland) identify the first endocannabinoid – Mechoulam names it "anandamide" from the Sanskrit word "anand" meaning "bliss"
- 1993: Munro et al. clone the CB2 receptor

Era of Endocannabinoid Research: 1994-2000

- 1994: Scientists at Sanofi Recherche (France) develop the first CB1 receptor antagonist – SR141716A (Rimonabant)
- 1995: Mechoulam (Hebrew University) isolates and identifies the second endocannabinoid – 2-Arachidonoylglycerol (2-AG)
- 1996: Cravatt et al. (Scripps) clone the first endocannabinoid degrading enzyme – fatty acid amide hydrolase (FAAH)

Era of Research: 1994-2000

- 1998: House of Lords report on medical cannabis
- 1998: Di Marzo et al. propose interactions between endocannabinoids and vanilloid receptors
- 1999: Zygmunt et al. and Smart et al. show that anandamide activates vanilloid receptors

Current Endocannabinoid Research: 2000-

- 2003: Bisogno et al. clone the first endocannabinoid bio-synthesizing enzymes
- 2005: Pertwee et al. (Scotland) discovers an allosteric site on CB1 receptors
- 2005: Sativex® approved for sale in Canada
- 2010: Gardner shows psychoactive (and potentially therapeutic) effects of cannabidiol

Current Research: 2000-

- ????: Discovery of new cannabinoid receptors
- ????: Discovery of new endocannabinoids
- ????: Discovery of new endocannabinoid enzymes
- ????: Cloning of new endocannabinoid transporters
- ????: Discovery of new cannabinoid-based therapies

Different Paths of Opiates and Cannabinoids

- During the 1800s, the active ingredient in opium—morphine—was identified and isolated.
- Other opiates and synthetic medicines rapidly followed
- Opium was not smoked for medical purposes
- ***The paths of medicinal opioid development and recreational use of smoked herbal opium became clearly distinct***

Different Paths continued

- By contrast, the active ingredients in cannabis remained unknown
- Preparations lacked standardizations
- Clinical response varied
- Conditions were numerous
- Better, targeted medications developed
- Fell out of favor with the medical profession

Lipid Transmitters- Endocannabinoids

- Endogenous receptor in form of G-protein coupled receptor (GPCR), stereospecific
- Endogenous lipids bind and activate receptors (CB1 and CB2)
- Purpose of system is to mediate an adaptive response to different pathological stimuli and regulate fundamental physiologic functions

Endocannabinoids, continued

- Pleiotrophy of actions allowed by:
  - Ubiquitous distribution, multiplicity of signal transduction pathways triggered when stimulated
- CNS- memory, learning, pain, appetite, psychoactive state, movement, addiction, and neuroprotection
- Periphery- metabolism, pain, inflammation, cell proliferation, reproductive, cardiovascular

System Function Summary

- To relax
- To eat
- To sleep
- To forget
- To protect

DiMarzo et al 1998

Overview of System

- Lipid precursors lead to production of
  - 2-AG degraded by monoacylglycerol lipase (MAGL) to arachidonic acid
  - AEA degraded by fatty acid amide hydrolase (FAAH) to arachidonic acid
  - Other endocannabinoids (new messengers) by other degradation pathways (new metabolic routes) to other targets/receptors (TRPV1, PPARs, GPRs)

Overview of System, continued

- 2-AG and AEA activate CB1&2 resulting in:
  - ion channel activity
  - protein kinase activity
- Occurs thru retrograde signaling, cell survival, gene expression
- Diverse physiologic effects

MAGL and the Endocannabinoid Retrograde Signaling

- CB receptors and endocannabinoids are involved in synaptic plasticity
  - Modulate signaling by other transmitters
- Depolarization of postsynaptic neuron activates endocannabinoid production

MAGL continued

- Endocannabinoid travels back to pre-synaptic CB1 receptor
  - Inhibits Ca+2 influx and decreases probability of synaptic vesicle release (of other neurotransmitters)
- Temporary or extended dimming of inhibitory (GABA) or excitatory currents (glutamate)
- Co-located with FAAH and CB1 in hippocampus, cerebellum, and amygdala

Characteristics of CB1 and CB2 Receptors

- Both densely distributed throughout the body
- CB1 highly enriched in central nervous system
- Located on axon terminals
- Mediate retrograde signaling (Dendrite → Axon)
- G-protein coupled
- CB2 highly enriched in periphery
  - Especially in immune system
- CB2 also in brain and CNS
  - Fewer than CB1; ~ Same density as μ opioid
  - Nonetheless, CB2s modulate neural signaling

CB1 modulates

- Movement
- Postural control
- Pain and sensory perception
- Memory
- Cognition
- Emotion
- Autonomic and endocrine functions

CB1 Sites

- Brain
- Gut
- Uterus
- Testes

Brain Cannabinoid CB2 Receptors

- Exist in the brain
- Are functionally active in the brain
- Moduate behavior
- CB2 receptor agonists may be clinically useful in anti-addiction pharmacotherapies

Classes of Cannabinoid Molecules

- Phytocannabinoids
  - Occur naturally in the plant, *Cannabis sativa* L
- Endocannabinoids
  - In the body (AEA, 2_AG, etc.)
- Synthetic Cannabinoids
  - Cannabinomimetic compounds from chemical synthesis
    - Dronabinol, Nabilone, HU210, CP55940, SR141716A, etc.)

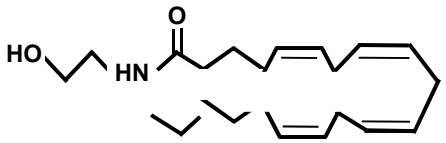
Endocannabinoids- Lipid Transmitters

- *N*- arachidonoylethanolamine (AEA) or anandamide
  - Partial agonist at CB1
- 2- arachidonoylglycerol (2-AG)
  - CB1 and CB2
  - 170 times as plentiful as AEA
  - Monoacylglycerol lipase (MAGL) important in regulation of levels

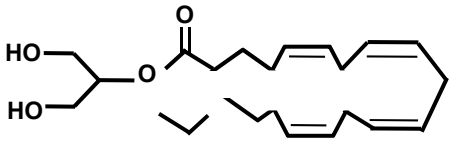
Endocannabinoids, continued

- Noladin ether
- Virodhamine
- *N*-arachidonoyl-dopamine (NADA)

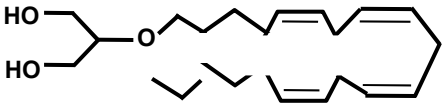
Endocannabinoids



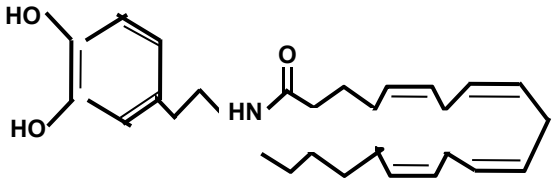
Anandamide



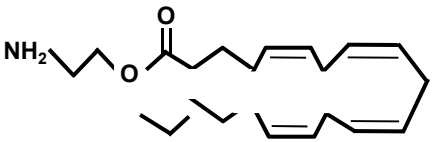
2-Arachidonoylglycerol



Noladin ether

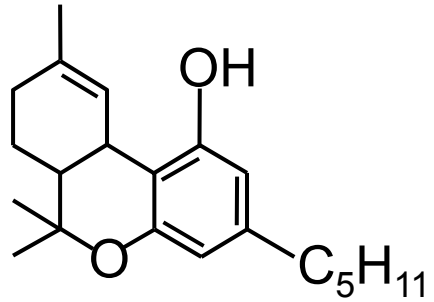


N-Arachidonoyldopamine

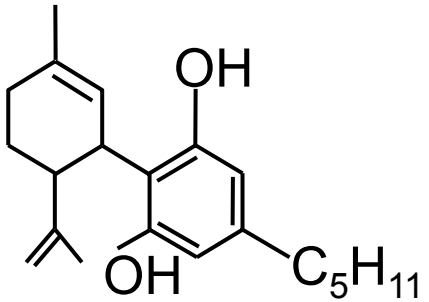


Virodhamine

Two Principle Cannabinoids



Δ^9-THC

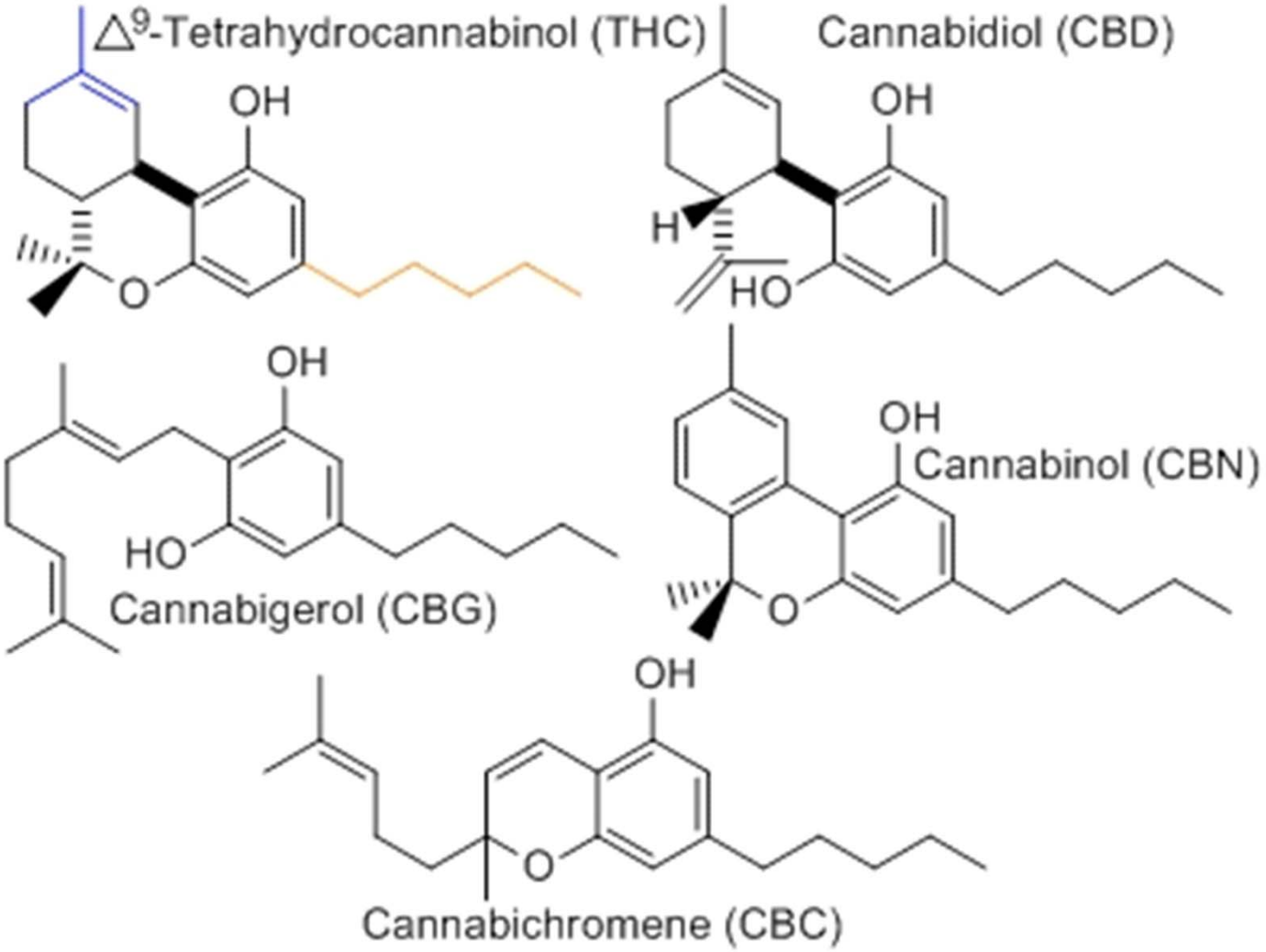


CBD

- Like D9-THC, CBD is a natural constituent of cannabis
- Unlike D9-THC, CBD has low affinities for CB1 & CB2 receptors
- Unlike D9-THC, CBD lacks psychotropic activity

Pertwee, R.G. (2004) Pharmacology of cannabidiol. In: *Cannabinoids.* Ed. V. Di Marzo, pp. 32-83, Kluwer Academic/Plenum Publishers, New York

Natural Cannabinoids



Other Receptors Activated by Cannabinoids

- Cannabidiol (CBD) receptors
- Transient Receptor Potential Cation V1 receptors (TRPV1; Capsaicin receptors)
- G-coupled Protein Receptor 55 (GPR55)
- G-coupled Protein Receptor 119 (GPR119)
- Peroxisome Proliferator-Activated receptors (PPARs)
- Others

Pharmacological Strategy

- Exploit properties of the cannabinoid system while minimizing the psychotropic effects of the molecule(s) used

Significance of Findings

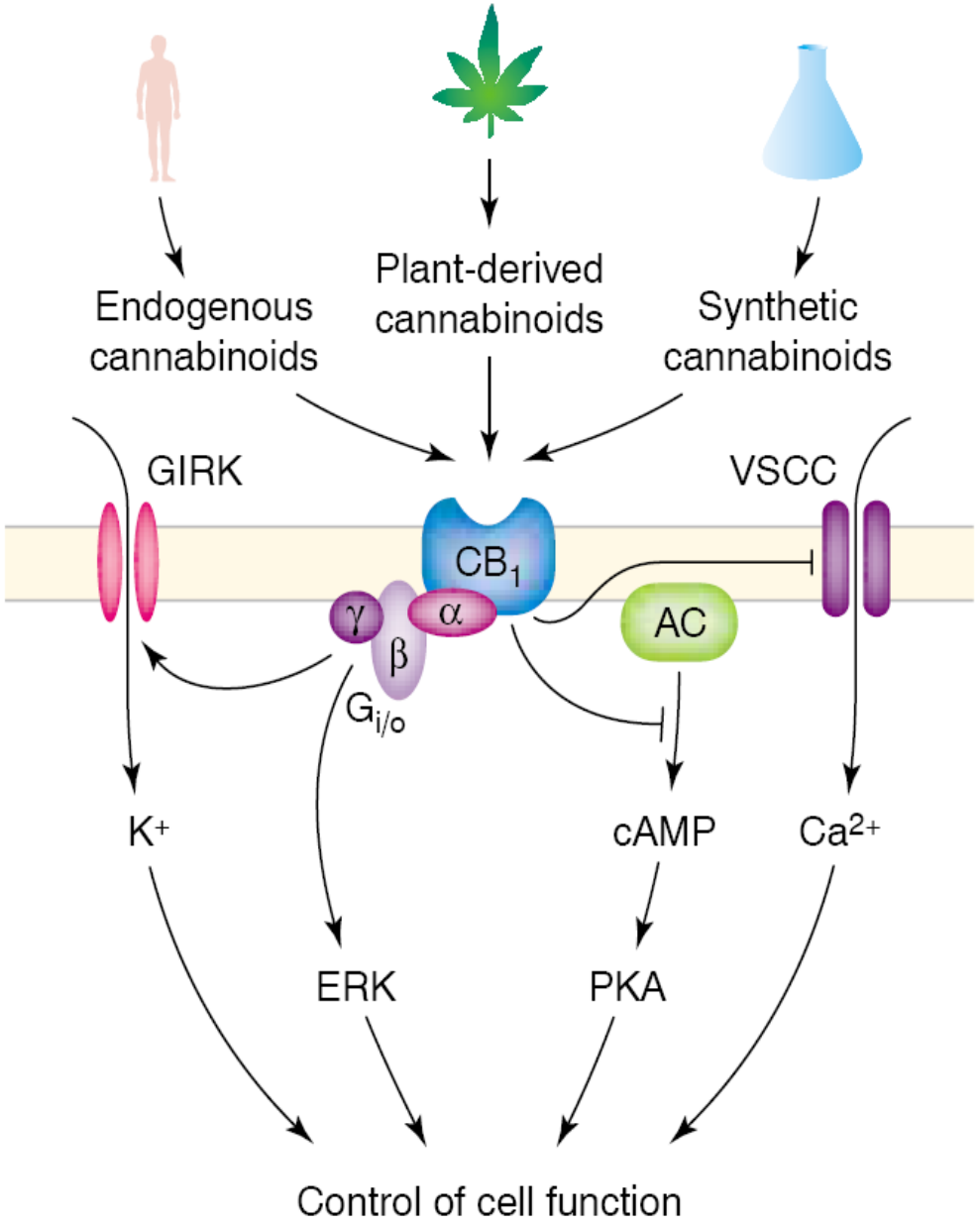
- Cloning of CB1 and CB2 enabled discovery of endogenous agonists and enzymes that catalyze endocannabinoid inactivation
- Endocannabinoids that are produced endogenously following onset of pathology may act in site- and time-specific manner to minimize consequences of condition

Significance, continued

- The endogenous endocannabinoids may differ significantly from THC and synthetic CB1 and CB2 agonists in their ability to limit extension of insult, injury
  - Preclinical data supports this view: animal benefit in neuropathic pain, anxiety, irritable bowel syndrome, proliferation and migration of CA cells
- Clinical target at degrading enzymes to prolong pro-homeostatic actions

Important Take-Home Messages

- Endocannabinoids are neurotransmitters, may have protective function in response to injury/insult
- Cannabinoids (e.g., THC) modulate neural activity
- Endocannabinoids are involved in synaptic re-modeling
- Cannabinoids (e.g., THC) can modulate synaptic re-modeling
- Depending upon the specific CNS circuits involved, cannabinoids can have a host of actions on brain, cognition, and behavior (some beneficial, some not)



CB1 Receptors

G-Protein ($G_{i/o}$) Coupled

Inhibition
Ca^{++} Channels
cAMP/PKA

Activation
K+ Channels
MAPK (Erk)

Overall Effects mainly inhibitory via presynaptic receptors

diagram from: Guzman et al. *Trends Pharmac. Sci*. 22:19, 2001

What WE Know

- Unimpeachable Preclinical Research Indicates That There Are Many Diseases (Some Currently Totally Untreatable) That Can Be Successfully Treated By Cannabinoid Agonists or Antagonists

What We Know

- Unimpeachable Preclinical Research Indicates That There Are Many Ways In Which The Endocannabinoid System of The Body Can Be Manipulated to Produce Either Cannabinoid Agonist or Antagonist Actions

Potential Cannabinoid Therapies

- Diseases of Energy Metabolism
  - Appetite Dysregulation
  - Obesity
  - Dyslipidemia
  - Peripheral Energy Metabolism Dysregulation
  - Cachexia
  - Anorexia
  - Type II Diabetes

Potential Therapies

- Pain
  - Somatosensory Pain
  - Neuropathic Pain
- CNS Disorders
  - Closed Head Brain Trauma
  - Neurotoxicity
  - Stroke
  - Spinal Cord Injury
  - Multiple Sclerosis

Potential Therapies

- CNS Continued
  - Multiple Sclerosis
  - Parkinson's Disease
  - Huntington's Disease
  - Tourette's Syndrome
  - Tardive Dyskinesia
  - Dystonia
  - Amyotrophic Lateral Sclerosis
  - Alzheimer's Disease

Potential Therapies

- CNS Continued
  - Epilepsy
  - Anxiety
  - Depression
  - Insomnia
  - Post-Traumatic Stress Disorder
  - Schizophrenia
  - Drug and Alcohol Addition
  - Nausea and Emesis

Potential Therapies

- Cardiovascular & Respiratory
  - Hypertension
  - Hypotension
  - Circulatory Shock
  - Myocardial Reperfusion Injury
  - Atherosclerosis
  - Cardiopathies
  - Asthma
- Inflammation

Potential Therapies

- Eye Disorders
  - Glaucoma
  - Retinopathy
  - Intraocular Pressure
- Reproductive Disorders
- Musculoskeletal Disorders
  - Arthritis
  - Osteoporosis
  - Post-Fracture Bone Healing

Potential Therapies

- GI and Liver Disorders
  - Inflammatory Bowel Disease
  - Ulcerative Colitis
  - Hepatitis
  - Cirrhosis – Encephalopathy
  - Cirrhosis – Liver Fibrosis
  - Cirrhosis – Vasodilatation
- Cancer
  - Cancer Cell Proliferation
  - Colorectal Cancer

Ways to Extend Cannabinoid Effect

- Provide more
  - Dump into system
  - Encourage synthesis
- Block re-uptake
- Block degradation
- Synergistic actions to change receptor reactivity
- Others?, more “sticky” versions

Potential Cannabinoid Therapies - Tools

- Endocannab Uptake Inhibitors – AM404, UCM707, AM1172
- FAAH Inhibitors – URB597, OL135, BMS1, SA47, PF750
- MAGL Inhibitors – URB602, OMDM169, JZL184
- Dual CB1/CB2 Agonists – WIN55512, CP55940, HU210
- Anandamide Analogues – Methanandamide, Metfluoroanand.
- Selective CB1 Agonists – ACEA, ACCP

Potential Therapies- Tools

- Selective CB2 Agonists – HU308, JWH015, JWH133, AM1241
- 2-AG Synthesis Inhibitors – O3640, O3891, OMDM188, O5596
- CB1 Antagonists/Inverse Agonists – SR141716A, AM251
- CB1 Neutral Antagonists – AM4113, PIMSR1
- CB2 Antagonists/Inverse Agonists – SR144528, AM630
- CB1 Receptor Allosteric Modulators – ORG27596, ORG29647

What is “Medical Marijuana?”

- Home remedy
- Dietary supplement
  - Numerous botanicals- taken by mouth, supplements the diet (vitamins, minerals, herbs, other botanicals, amino acids, enzymes, organ tissues, glandulars, and metabolites)
  - DSHEA of 1994 places under general umbrella of foods, not drugs- cannot make disease claim
- FDA approved medicine
  - OTC v. Prescription drug

Botanical Drug

- Intended for diagnosis, cure, mitigation, treatment or prevention of disease
- Consists of vegetable materials available as a solution, powder, tablet, capsule, elixir, topical or injection
- Complex mixtures, lack distinct active ingredient, substantial prior human use
- Some (cascara, psyllium, senna, etc.) are OTC with published safety, efficacy data

Why Do We Care About the FDA Process?

- Protect patient health and safety
  - promote quality, safety and efficacy of medications
- Testing for body of risk/benefit and pharmacological data
- Registration/inspection ensures manufacturing quality control tools
- Promotional activities of manufacturers limited
- Products prescribed/dispensed under the supervision of licensed health providers

Modern Regulatory Approval Requirements

- Quality
- Safety
- Efficacy

Quality

- Product Composition
- Characterization
- Quantification of components
- Standardization / Consistency
- Stability / Storage

Safety

- Animal data, including:
  - Carcinogenicity
  - Reproductive and chronic toxicology
  - Genotoxicology
  - Safety pharmacology
- Clinical data
  - Several hundred patient-years of data required
  - Reports of all adverse events (mild/moderate/severe – related and unrelated)
  - Immediate regulatory notification of serious adverse events

Efficacy

- Multiple Phase II & Phase III placebo-controlled clinical trials for each target clinical indication

Hazards of Marijuana Contrasted with Pharmaceutical Product

- Harmful constituents of smoked marijuana
  - Bronchial irritation and pyrolytic compounds in a bad delivery system
- Potential for abuse
  - Reward
- Recreational users seek the “high”
  - Manage therapeutic window
- Lack standardization with contamination
  - Fungi, heavy metals, variance

Contrasts, continued

- No regulation of sources of manufacture and distribution
  - Distribution chain monitoring
- Lack of patient information and support
  - Unable to study in RCTs, lack information to advise
- Liability
  - Insurance does not cover recommendation of illegal product, patients are on their own

Contrasts, continued

- Stigma
  - Illegality of product, not covered by heath care insurance, stress/anxiety/ inconvenience associated with illegal product
- Access
  - Not contained within health care environments
- Public health considerations
  - Undermines prevention- perception of risk

Does “Medical Marijuana” Fit into the FDA Paradigm?

- Composition (% of THC) of herbal cannabis varies significantly
  - Depends on strains, cultivation and storage, etc.
- North American cannabis bred to exhibit (only) high levels of THC
  - No meaningful levels of other cannabinoids such as CBD
- Delivery systems (smoked/vaporized, baked goods, teas) do not provide a standardized dose
  - Smoking delivers harmful combustion products to the lungs
  - Vaporization does not completely eliminate PAHs
- Contamination with microbes, heavy metal, and pesticides a real possibility

Does "Medical Marijuana" Currently Fit into the FDA Paradigm?, continued

- Distribution does not take place within regulated supply chain for pharmaceuticals
  - "Collectives" and "cooperatives"
- No collection of adverse event or efficacy data
  - Impossible to know who is really benefiting or being harmed
- Medical advice being given by untrained and unlicensed individuals
  - Broad efficacy claims
  - Often no meaningful physician supervision
  - No labeling with risk information or instructions for use
- Patients cannot obtain health insurance coverage

What Would it Take for a Cannabis Product to Secure FDA Approval?

- Herbal material grown by clones under rigorous conditions, ideally computer controlled greenhouses, to produce standardized starting materials
  - Under international policies of last 85 years, US imports, rather than cultivates, psychoactive herbal material and manufactures finished products in US
- Need to incorporate **an extract** ("Botanical Drug Substance") into an appropriate delivery system;
  - No precedent for administering **any** crude herbal material in a manner that reliably achieves a reproducible dose, produces no carcinogens

FDA Approval, continued

- Sponsor must manufacture and test product in accordance with FDA “Guidance for Industry: Botanical Drug Products”
  - Guidance allows some leniency in early research; by Phase 3 /NDA, all NCE standards must be met
  - Blinded, placebo-controlled large clinical studies must examine specific medical condition in specific population
  - Sponsor must conduct abuse liability testing and prepare risk management plan

What About the DEA?

- DEA must register clinical and preclinical research sites and importer/manufacturer
- After NDA, DEA must reschedule product
  - FDA approval satisfies “currently acceptable medical use in the US” **for that product**

Rationale for Cannabis-Based Medicines

- Recent research revealed that both principle components of cannabis have important pharmacological effects
  - THC: analgesic, anti-spasmodic, anti-tremor, anti-inflammatory, appetite stimulant, anti-emetic
  - CBD- anti-inflammatory, anti-convulsants, anti-psychotic, anti-oxidant, neuroprotective, immunomodualtory
- Different ratios may be important clinically

Cannabinoid and Cannabis-Derived Products

- Synthetic THC
  - Pure, synthetic THC (dronabinol) in sesame oil (gelatin capsule); oral;
  - FDA approved for nausea & vomiting with cancer chemotherapy & HIV-wasting disease; off-label use for pain, sleep
- Nabilone
  - Nabilone (a synthetic THC analogue); oral;
  - FDA approval for N&V; off-label use for pain

Products, continued

- Ajulemic acid:
  - Synthetic cannabinoid analogue;
  - Oral
  - Debate about the degree of psychoactivity at therapeutic doses
  - Being studied in US for interstitial cystitis
- Phyto-cannabinoids

Production

- Breeding
- Cultivation
- Drying
- Extraction
- BDS content
- BDP

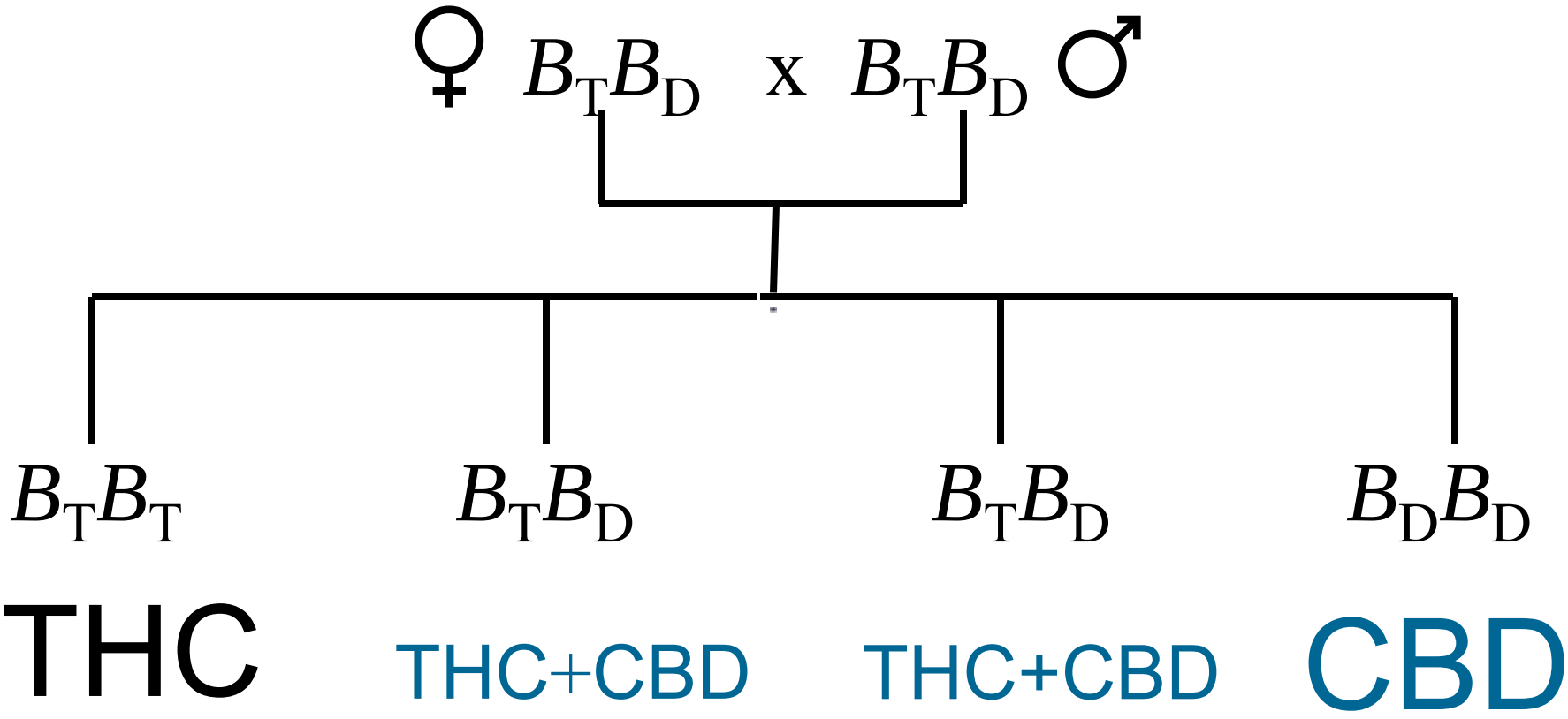
Crop Uniformity

- Uniform Genetics
- Precise Propagation Timings
- Tightly Controlled Temperature
- Near Uniform Light Intensity
- Automated Irrigation

Crop Uniformity, continued

- Growth Medium
- Tightly Controlled Plant Nutrition
- Pest and Disease Prevention and ‘Organic’ Control
- Attention to detail by trained staff

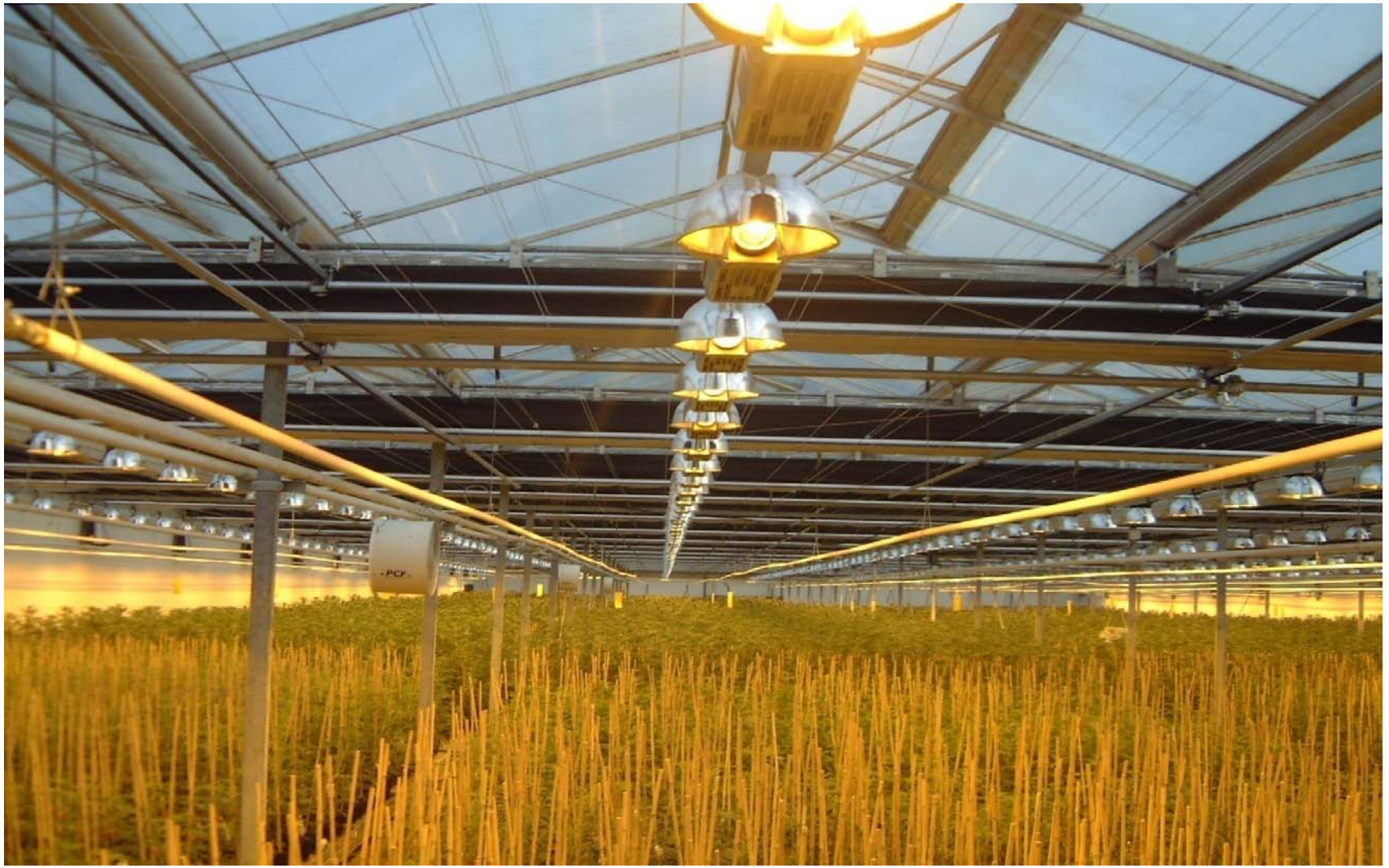
Phyto-Cannabinoid Biosynthesis
‘Co-dominant Monogenic Control’



G5 M13 CBD Plant

G1 M1 THC Plant

Cultivation



Drying

Extraction

Delivery System

- Desirable characteristics: reliable dose with predictable effect
- Relief of symptoms
- Minimal side effects
  - Psychoactivity
  - Harmful impurities

Should Cannabis be Rescheduled?

- If a cannabis-derived product were FDA approved, must cannabis itself be moved to Schedule II, like opium and cocaine?
- Conversely, must cannabis be rescheduled in order for such a product to reach the market?
- Split scheduling appears to be possible.
  - Marinol (Schedule III) and Cesamet (Schedule II) vs. THC (Schedule I);
  - Xyrem (Schedule III) vs. GHB (Schedule I)

What Would Rescheduling Achieve?

- FDA does not approval bulk substances/ active ingredients for direct prescriptive use
- **Even if "cannabis" itself were moved to Schedule II, a specific cannabis or cannabis-based product would need FDA approval to be available by prescription**
- Might at most speed up the obtaining of initial research registrations

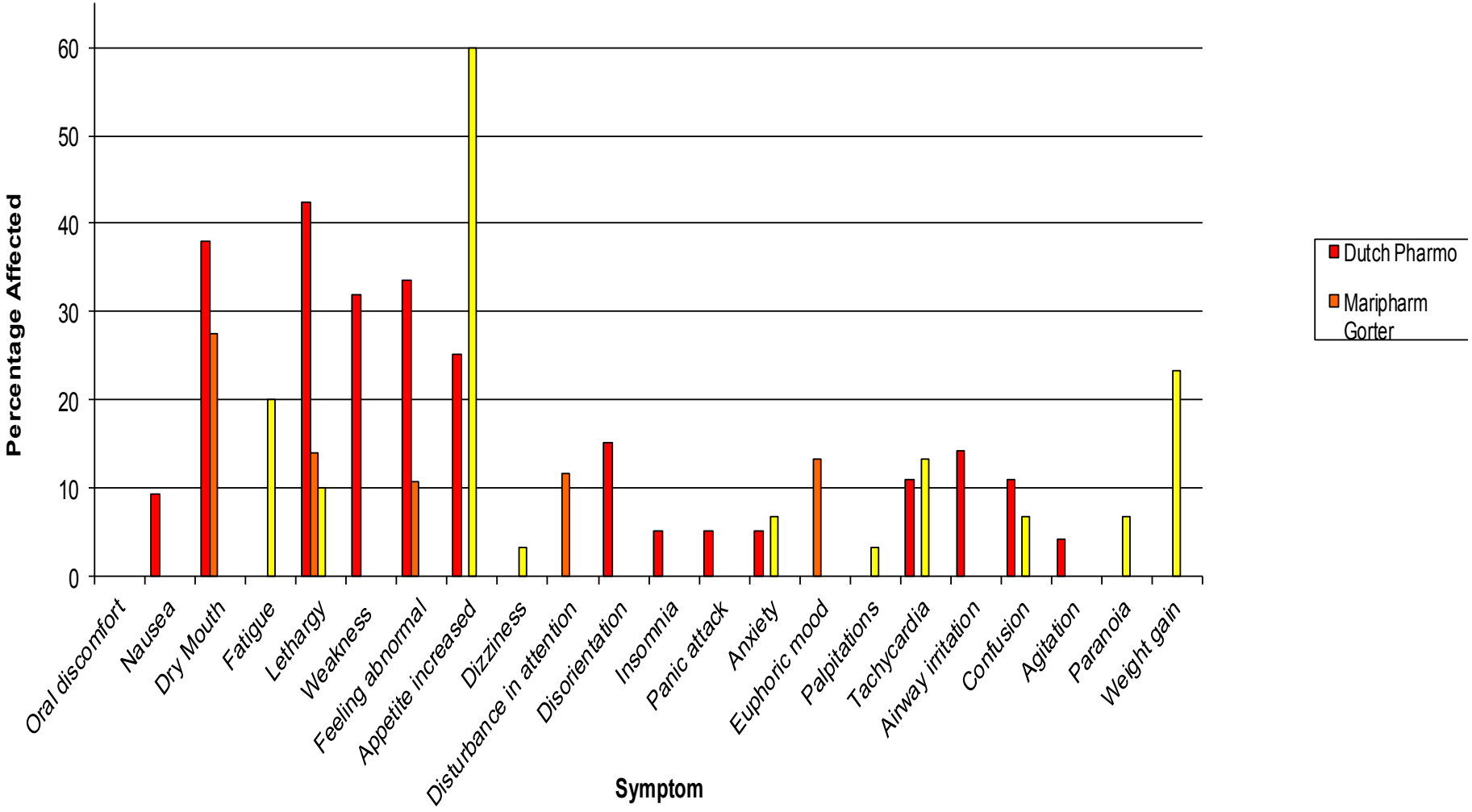
Giving Cannabis a Free Pass = ?

- By creating an exception for cannabis, we are preventing the development of Q, S &E data that would allow it to become broadly accepted as a true medication
- The vast majority of patients want a product that is standardized by composition and dose and about which their physicians can offer meaningful advice

There's More Than THC!

- Cannabis used centuries ago would have involved a 1:1 CBD:THC ratio
- THC (tetrahydrocannabinol):
  - is analgesic, anti-spasmodic, anti-tremor, anti-inflammatory, appetite stimulant, anti-emetic
- CBD (cannabidiol):
  - does not bind to CB1 cannabinoid receptor, but does bind to other receptors in the body;
  - is anti-inflammatory, analgesic, anti-convulsant, anti-psychotic, anti-oxidant, neuroprotective;
  - reduces the negative effects of THC
  - has been bred out of modern herbal cannabis!

AE of Standardized Smoked Medicinal Cannabis



Adapted from Russo, EB 2008. Cannabinoids in management of difficult to control pain. Therapeutics & Clinical Risk Management 4(1):245-259

It Takes Time!

- Improved technology and discovery of endocannabinoid receptor system means that we are only at the early stages of developing modern medications, i.e., numerous preclinical studies, gradually moving into clinical trials, etc.
- At some point soon, will be same distinction as there is with smoked opium (recreational use only) and modern opiate medications

More Research Needed: Formulation is Important

- Cannabis plant is the unique source of cannabinoids
- Over 60 cannabinoids in total, each with their own--often complementary—pharmacology, especially CBD
- Also other pharmacologically active components, e.g., terpenes, flavonoids

Products of the Future

- Preparations of different cannabinoids (both synthetic and botanically-derived) and cannabinoid ratios, e.g., CBG, CBN, THCV, etc.
- Targeting CB2 and other receptors, not just CB1
- Modulating the endocannabinoid receptor system

One Possible Product

- Nabiximols (Sativex®) contains a defined (1:1) ratio of THC and CBD , as well as other minor cannabinoids, terpenes, etc.
- Finished pharmaceutical product derived from extracts of two unique strains of the cannabis plant
  - One strain is predominantly THC
  - Other strain predominantly CBD (cannabidiol), a non-psychoactive cannabinoid
  - Also contains other plant components, such as terpenes, flavonoids, etc.
- Novel delivery system—oromucosal spray
  - Intermediate onset of action, 15-40 minutes
  - Allows patients to individualize their dose
  - Each spray provides 100 mcl. of product, comprising 2.7mg. THC and 2.5mg. CBD

Natural Pain Systems

- Cannabis
- Opium poppy
- Chili peppers
- Willow bark

Is there a deficiency of the endocannabinoid system in treatment resistant conditions?

What is the Evidence?

- Agonists
  - Fibromyalgia patients (Schley et al 2006)
  - Intestinal pain and motility in IBS (Massa and Monory 2006)
- CB1 Antagonist- SR141716A (Rimonabant)
  - Hypergesia in mice (Richardson et al 1997)

Evidence, continued

- Anti-inflammatory effects
  - Migraine (Russo 1998, 2001)
- Glutamatergic system
  - Cannabinoids presynaptically inhibit glutamate release (Shen et al 1996)
- Cannabidiol
  - Inhibits glutamate neurotoxicity (Hampson et al 1998)
  - TRPV1 antagonist (Bisogno et al 2001)

Characteristics and Nature of Cannabinoids

- Lipid soluble, slow and erratic oral absorption, therefore, challenges in formulation
- Shelf life issues
- Smoked cannabis leads to rapid onset and high peak levels

Characteristics, continued

- AEs increase with increased blood level
- Tolerance develops to effects
- Intoxication is undesirable AE
- Withdrawal is a possibility

Managing the Nature of Cannabinoids

- Formulation challenges
- Storage and stability issues
- Managing AEs
  - Rate of absorption
  - Route of administration

RCTs of cannabinoids

Drug	N=	RCT Indication	Trial Duration
Ajulemic Acid	21	Neuropathic pain	7 day crossover
Cannabis, smoked	50	HIV neuropathy	5 days
Cannabis, smoked	21	Chronic neuropathic pain	5 days
Nabilone	419	Pain 2° spasm, MS	15 weeks
Nabilone	65	Post-herpetic neuralgia	4 weeks
Nabilone	30	Post-operative pain	Single doses, daily

RTCs, continued

Drug	N=	RCT Indication	Trial Duration
Synthetic THC	24	Neuropathic pain, MS	15-21 day crossover
Synthetic THC	40	Post-operative pain	Single dose
Nabilone	41	Post-operative pain	3 doses in 24 hours
Nabiximols	20	Neurogenic pain	Series of 2-week N-of-1 crossover blocks
Nabiximols	24	Chronic intractable pain	12 weeks, N-of-1
Nabiximols	48	Brachial plexus avulsion	6 weeks in 3 two-week crossover

RTCs, continued

Drug	N=	RCT Indication	Trial Duration
Nabiximols	66	Central neuropathic pain in MS	5 weeks
Nabiximols	125	Peripheral neuropathic pain	5 weeks
Nabiximols	56	Rheumatoid arthritis	Nocturnal dosing for 5 weeks
Nabiximols	117	Pain after spinal injury	10 days
Nabiximols	177	Intractable cancer pain	2 weeks
Nabiximols	135	Intractable lower urinary tract symptoms in MS	8 weeks

Sativex ®

Sativex

- Sativex is indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

Method of Administration

- Sativex is for oromucosal use only
- Sativex is intended to be used in addition to the patient's current anti-spasticity medication.
- Treatment must be initiated and supervised by a physician with specialist expertise in treating this patient population.

Titration of Dose

DAY	AM DOSE	PM DOSE	TOTAL
1	0	1	1
2	0	1	1
3	0	2	2
4	0	2	2
5	1	2	3
6	1	3	4
7	1	4	5

DAY	AM DOSE	PM DOSE	TOTAL
8	2	4	6
9	2	5	7
10	3	5	8
11	3	6	9
12	4	6	10
13	4	7	11
14	5	7	12

Maintenance Period

- Following titration period, patients advised to maintain the optimum dose achieved
- Median dose in clinical trials for patients is eight sprays per day
- Once the optimum dose has been achieved, patients may spread the doses throughout the day according to individual response and tolerability
- Re-titration upwards or downwards may be appropriate if there are any changes in the severity of the patient's condition, changes in their concomitant medication or development of adverse reactions
- Doses of greater than 12 sprays per day are not recommended

Review by the Physician

- Initial evaluation of the severity of spasticity related symptoms and of the response to standard anti-spasticity medication before starting
- Indicated in moderate to severe spasticity not responsive to other anti-spasticity medication
- Review response after four weeks of treatment.
- Stop if no response
- Seek 20% improvement in spasticity related symptoms on a 0-10 patient reported numeric rating scale
- Re-evaluate periodically.

Contraindications

- Hypersensitivity to cannabinoids or to any of the excipients
- Known or suspected history or family history of
  - Schizophrenia, or other psychotic illness
  - Severe personality disorder
  - Other significant psychiatric disorder other than depression associated with underlying condition.
- Breast feeding women

Precautions and Warnings

- Mild or moderate dizziness is common
- Not recommended for use in children or adolescents
- Alterations in pulse rate and blood pressure observed
- Fainting episodes
- Not recommended in patients with serious cardiovascular disease
- Caution when treating patients with a history of epilepsy, or recurrent seizures.

Warnings, continued

- Psychiatric symptoms such as anxiety, illusions, changes in mood, and paranoid ideas reported
- Disorientation (or confusion), hallucinations and delusional beliefs or transient psychotic reactions reported
- No specific studies carried out in patients with significant hepatic or renal impairment
- Several THC metabolites may be psychoactive, effects may be exaggerated or prolonged with renal or hepatic disease
- May not be legal in other countries to travel with Sativex®

Warnings, continued

- Contains ethonol, 12 sprays a day contains less than 0.5 g
- Risk of falls in patients with reduced spasticity but insufficient strength to maintain posture or gait
- CNS effects can increaser personal safety risk such as with food and hot drink preparation.
- Warn about additive risk with muscle relaxants (baclofen, etc.)

Warnings, continued

- Sativex® may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly
- Avoid alcoholic beverages
- Alcohol and Sativex® may impair driving, machine operation, and increase risk of falls

Application Site Problems

- Application site reactions reported
  - Application site pain
  - Oral pain and discomfort
  - Mouth ulceration
  - Regular inspection of the oral mucosa is advised

Drug – Drug Interactions

- Metabolized by the cytochrome P450 enzyme system.
- The *in vitro* inhibitory effects of Sativex® on the major CYP450 enzymes CYP3A4 and CYP2C19 occurs at concentrations substantially higher than the maximum observed in clinical trials
- In an *in vitro* study with 1:1% THC botanical drug substance (BDS) and CBD BDS, no relevant induction of cytochrome P450 enzymes was seen for CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzymes in human hepatocytes, at doses of up to 1µM (314 ng/mL)

With CYP3A4 Inhibitors

- Concomitant treatment with the CYP3A4 inhibitor ketoconazole produced an increase in Cmax and AUC of THC (1.2- and 1.8-fold, respectively), its primary metabolite (3- and 3.6-fold, respectively) and of CBD (2- and 2-fold, respectively)
  - If itraconazole, ritonavir, clarithromycin initiated, consider new titration

CYP3A4 Inducer Treatment

- Rifampicin produced reductions in Cmax and AUC of THC (40% and 20% reduction, respectively), its primary metabolite (85% and 87% reduction, respectively) and CBD (50% and 60% reduction, respectively)
  - Rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort should be avoided
  - Careful titration is recommended, notably within the two weeks following the stop of the inducer
  - Hypnotics, sedatives and drugs with potential sedating effects should be avoided

Anti-Spasticity Agents

- Reduction in muscle tone and power may lead to increased risk of falls in patients taking anti-spasticity agents with Sativex®

Undesirable Effects

- Over 1500 patients with MS in placebo controlled trials and long-term open label studies
- Up to 48 sprays per day used
- Most common adverse reactions in the first four weeks of exposure were dizziness and fatigue.
- Reduced with recommended dose titration schedule

Overdose

- No experience of deliberate overdose
- In a thorough QT study in 257 subjects, with 18 sprays taken over a 20-minute period twice daily, signs and symptoms of overdose/poisoning were observed
  - Dizziness, hallucinations, delusions, paranoia, tachycardia or bradycardia with hypotension
- Three of 41 Ss presented with transient toxic psychosis
  - Twenty-two subjects still completed the 5-day study period.
- Treatment should be symptomatic and supportive

Mechanism of Action

- CB1 and CB2 receptors at nerve terminals, have role in retrograde regulation of function, THC partial agonist at both
- Endocannabinoids may modulate the effects of neurotransmitters
- In animal models of MS and spasticity, CB receptor agonists have been shown to ameliorate limb stiffness and improve motor function
- Effects are prevented by CB antagonists
- CB1 knockout mice show more severe spasticity
- In the CREAE (chronic relapsing experimental autoimmune encephalomyelitis) mouse model, Sativex® produced a dose-related reduction in the hind limb stiffness.

Clinical Experience

- Sativex has been studied at doses of up to 48 sprays/day in controlled clinical trials of up to 19 weeks duration in more than 1500 patients with MS
- In the pivotal trials to assess the efficacy and safety of Sativex for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) the primary efficacy measure was a 0 to 10 point Numeric Rating Scale (NRS) on which patients indicated the average level of their spasticity related symptoms over the last 24 hours where 0 is no spasticity and 10 is the worst possible spasticity

Clinical Experience, First Phase III trial

- In a first Phase 3 placebo controlled trial over a 6-week treatment period the difference from placebo reached statistical significance but the difference between treatments of 0.5 to 0.6 points on the 0-10 point NRS was of questionable clinical relevance.
- In a responder analysis 40% Sativex and 22% placebo responded to treatment using the criterion of greater than a 30% reduction in NRS score.

Clinical Experience, Second Phase III Trial

- A second 14 week Phase 3 study failed to show a significant treatment effect
- The difference from placebo on the NRS score was 0.2 points.
- It was postulated that a clinically useful treatment effect in some patients might be partly masked by data from non-responders in the analyses of mean changes

Clinical Experience, Second Phase III

- In analyses comparing NRS scores with patient global impression of change (PGI)
  - 19% NRS response was estimated to represent a clinically relevant improvement on the PGI and a response of 28% “much improved” on the PGI
  - In post hoc exploratory combined analyses of the above two studies, a 4-week trial period using a 20% NRS response threshold was predictive of eventual response defined as a 30% reduction.

Clinical Experience, Third Phase III Trial

- A third Phase 3 trial incorporated a formalized 4-week therapeutic trial period prior to randomization
- The aim of the trial was to assess the benefit of continued treatment for patients who achieve an initial response to treatment.
- 572 patients with MS and refractory spasticity all received single blind Sativex for four weeks

Clinical Experience, Phase III Trial

- After four weeks on active treatment 273 achieved a reduction of at least 20% on the spasticity symptom NRS
- 241 met the entry criteria for randomization
- Reported mean change from the start of treatment of -3.0 points on the 10 point NRS.
- These patients were then randomized to either continue to receive active or switch to placebo for the 12 week double-blind phase
- Received total of 16 weeks treatment overall.

Clinical Experience, Phase III Trial

- During the double-blind phase the mean NRS scores for patients receiving Sativex generally remained stable (mean change from randomization in NRS score -0.19), while the mean NRS scores for patients switched to placebo increased (mean change in NRS score was +0.64 and median change was +0.29). The difference* between treatment groups was 0.84 (95% CI -1.29, -0.40).
- * Difference adjusted for centre, baseline NRS and ambulatory status
- Of those patients who had a 20% reduction from screening in NRS score at week 4 and continued in the trial to receive randomized treatment, 74% (Sativex) and 51% (placebo) achieved a 30% reduction at week 16.

Marinol ®

Dronabinol/Marinol®

- Dronabinol is used to prevent nausea and vomiting that may occur after treatment with cancer medicines. It is used only when other kinds of medicine for nausea and vomiting did not work. This medicine is also used to increase appetite in patients with acquired immunodeficiency syndrome (AIDS)

Medical Problems, Warnings

- The presence of other medical problems may affect the use of this medicine
- Alcohol abuse or dependence
- Drug abuse or dependence
- Bipolar disorder (manic or depressive states)
- Heart disease
- Hypertension
- Mental illness
- Seizures

Dosing

- Dose varies
- For increasing appetite in patients with AIDS:
  - Adults and teenagers—Initial dose 2.5 milligrams (mg) two times a day, taken before lunch and supper, not more than 20 mg a day.
- For nausea and vomiting caused by cancer medicines:
  - Adults and teenagers—Dose is based on body surface area

Drug-Drug Interactions

- Additive with other CNS depressants
- Causes drowsiness, lightheadedness, false sense of well-being
- Postural hypotension
- Thought disorders
- OD requires ER visit
- Concern for drug-drug interactions

Side Effects- Infrequent

- Changes in mood, confusion, delusions
- Tachycardia
- Feelings of unreality, hallucinations
- Loss of memory, problems with memory
- Mental depression
- Nervousness or anxiety
- Problems with memory

Side Effects- Rare

- Blurred vision
- Chills
- Postural dizziness, faintness, or lightheadedness
- Sweating
- Unusual tiredness or weakness

Overdose

- Being forgetful
- Time sense distortions
- Sensory distortions
- Constipation
- Decrease in motor coordination
- Drowsiness (severe)
- Dryness of the mouth (severe)
- False sense of well-being
- Feeling sluggish

Overdose, continued

- Panic reaction
- Problems in urinating
- Redness of the eyes
- Seizures
- Slurred speech
- Unusual drowsiness or dullness

Marinol- Effects

- Marinol has mild to moderate analgesic effects and can be used to treat pain by altering transmitter release on dorsal root ganglion of the spinal cord and in the periaqueductal gray
- Produces relaxation, alteration of visual, auditory, and olfactory senses, fatigue, and appetite stimulation
- Anti-emetic properties
- Acutely increases aggression during withdrawal

Marinol- Effects, continued

- Partial agonist results in down regulation of cannabinoid receptors
- Tolerance is irregularly developed for certain effects
- Tolerance to side effects more likely than primary effects, this may increase therapeutic window
- Mile antioxidant activity sufficient to protect neurons against oxidative stress, such as glutamate induced excitation

Marinol- Effects, continued

- It has long been known that, in humans, cannabis increases appetite and consumption of food, results from activity in gastro-hypothalamic axis
- CB1 activity in the hunger centers in the hypothalamus increases the palatability of food when levels of a hunger hormone ghrelin increase prior to consumption
- Involved with signaling hormones such as cholecystokinin and leptin, reduces gastric emptying and transmission of satiety signals to hypothalamus
- Cannabinoid signals are reduced by leptin release

Marinol- Effects, continued

- A study in mice suggested that based on the connection between palatable food and stimulation of Dopaminein nucleus accumbens, cannabis may also stimulate hedonic value of food
- Complicated mechanism of action

Multiple Sclerosis

- *Spasticity*. Based on the results of 3 high quality trials and 5 of lower quality, oral cannabis extract was rated as effective, and THC as probably effective, for improving patient's subjective experience of spasticity. Oral cannabis extract and THC both were rated as possibly effective for improving objective measures of spasticity
- *Centrally mediated pain and painful spasms*. Based on the results of 4 high quality trials and 4 low quality trials, oral cannabis extract was rated as effective, and THC as probably effective in treating central pain and painful spasms
- *Bladder dysfunction*. Based on a single high quality study, oral cannabis extract and THC were rated as probably ineffective for controlling bladder complaints in multiple sclerosis

Neurodegenerative Disorders

- *Huntington disease*. No reliable conclusions could be drawn regarding the effectiveness of THC or oral cannabis extract in treating the symptoms of Huntington disease as the available trials were too small to reliably detect any difference
- *Parkinson disease*. Based on a single study, oral cannabis extract was rated probably ineffective in treating levodopa-induced dyskinesia in Parkinson disease
- *Alzheimer's disease*. A 2011 Cochrane Review found insufficient evidence to conclude whether cannabis products have any utility in the treatment of Alzheimer's disease

CNS Disorders

- *Tourette syndrome*. The available data was determined to be insufficient to allow reliable conclusions to be drawn regarding the effectiveness of oral cannabis extract or THC in controlling tics
- *Cervical dystonia*. Insufficient data was available to assess the effectiveness of oral cannabis extract of THC in treating cervical dystonia
- *Epilepsy*. Data was considered insufficient to judge the utility of cannabis products in reducing seizure frequency or severity

Toxicity

- The estimated lethal dose of intravenous Dronabinol in humans is 30 mg/kg
- Typical medicinal dosage administered is two 2.5 mg capsules daily
- Lethal dose for such a person would be 960 of those capsules infused intravenously
- Non-fatal overdoses have occurred: Significant CNS symptoms in antiemetic studies followed oral doses of 0.4 mg/kg (28 mg/70 kg) of dronabinol capsules

THC Research Findings

- Meta analysis of cannabis and THC clinical trials conducted by the American Academy of Neurology found that of 1619 persons treated with cannabis products (including some treated with smoked cannabis and nabiximols)
- 6.9% discontinued due to side effects (compared to 2.2% of 1,118)
- Nausea, weakness, behavioral or mood changes, suicidal ideation, hallucinations, dizziness, and vasovagal symptoms, fatigue, and feelings of intoxication were each described
- single death rated by the investigator as "possibly related" to treatment, seizure followed by aspiration pneumonia

THC Cognitive Effects

- A 2011 systematic review evaluated published studies of the acute and long-term cognitive effects of cannabis
- THC intoxication impairs cognitive functioning acutely, affects ability to plan, organize, solve problems, make decisions, and control impulses
- impact may be greater in novice users; if habituated to high level ingestion withdrawal may reduce cognition
- Studies of long-term effects on cognition with conflicting results, from no difference between long-term abstainers and never-users and others finding long term deficits.

THC- Cognition, continued

- Discrepancies between studies may reflect greater long term effects among heavier users relative to occasional users, and greater duration of effect among those with heavy use as adolescents compared to later in life.
- Second systematic review focused on neuroimaging studies found little evidence supporting an effect of cannabis use on brain structure and function
- 2003 meta analysis concluded that any long term cognitive effects were relatively modest in magnitude and limited to certain aspects of learning and memory

Other Long Term Effects

- A 2008 NIH study
- 19 chronic users
- 28 gm to 272 g weekly
- 24 controls
- Elevated levels of apolipoprotein C-III (apoC-III) in chronic smokers
- Increase of apoC-III induces hypertriglyceridemia

THC Antagonists

- Effects reduced by the CB_1 receptor inverse agonist rimonabant (SR141716A), opioid blockers (i.e. Naloxone, etc.)
- Alpha 7 nicotinic receptor antagonist (methlyllycaconitine) blocks self-administration comparable to varenicline on nicotine administration
- Cannabidiol is indirect antagonist against cannabinoid agonists, reduces anandamide and TRC agonists on CB1 and CB2

THC- Pharmacological Actions

- The pharmacological actions of THC and analogues result from partial agonist activity at the cannabinoid receptor CB1 (Ki=10nM), located mainly in the central nervous system, and the CB2 receptor (Ki=24nM[62]), mainly expressed in cells of the immune system
- Psychoactive effects of THC are primarily mediated by its activation of CB1G-protein coupled receptors, which result in a decrease in the concentration of the second messenger molecule cAMP through inhibition of adenylate cyclase

CB1 and CB2

- The presence of these specialized cannabinoid receptors in the brain led researchers to the discovery of endocannabinoids, such as anandamide and 2-arachidonoyl glyceride (2-AG)
- THC targets receptors in a manner far less selective than endocannabinoid molecules released during retrograde signaling, as the drug has a relatively low cannabinoid receptor efficacy and affinity
- In populations of low cannabinoid receptor density, THC may act to antagonize endogenous agonists that possess greater receptor efficacy.

THC, continued

- THC is a lipophilic molecule and may bind non-specifically to a variety of entities in the brain and body, such as adipose tissue]
- THC, similarly to cannabidiol, albeit less potently, is an allosteric modulator of the μ- and δ-opioid receptors

THC Biotransformation

- THC is metabolized mainly to 11-OH-THC
- Psychoactive metabolite and is further oxidized to 11-nor-9-carboxy-THC (THC-COOH)
- More than 100 metabolites identified, but 11-OH-THC and THC-COOH are the dominating metabolites
- Metabolism occurs mainly in the liver by cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP3A4
- More than 55% of THC is excreted in the feces and ~20% in the urine. The main metabolite in urine is the ester of glucuronic acid and THC-COOH and free THC-COOH. In the feces, mainly 11-OH-THC was detected

Dronabinol

- Dronabinol is the INN for a pure isomer of THC, (–)-trans-Δ9-tetrahydrocannabinol,[75] which is the main isomer found in cannabis
- Sold as Marinol®, generally referred to as dronabinol
- Available as a prescription drug (under Marinol) in several countries In U. S. is schedule III drug, non-narcotic, low risk of physical or mental dependence
- Marinol approved by the U.S. FDA in the treatment of anorexia in AIDS patients, as well as for refractory nausea and vomiting of patients undergoing chemotherapy

Dronabinol and Nabilone

- Overdose usually presents with lethargy, decreased motor coordination, slurred speech, and postural hypotension
- FDA estimates the lethal human dose of intravenous dronabinol to be 30 mg/kg (2100 mg/ 70 kg)
- An analog of dronabinol, nabilone, is available commercially in Canada under the trade name Cesamet
- Cesamet has received FDA approval and began marketing in the U.S. in 2006
- Nabilone is a Schedule II drug

Nabilone

- Nabilone has shown modest effectiveness in relieving fibromyalgia
- The main settings that have seen published clinical trials of nabilone include movement disorders such as Parkinson's syndrome, chronic pain, dystonia and spasticity neurological disorders, multiple sclerosis, and the nausea of cancer chemotherapy
- Nabilone is also effective in the treatment of inflammatory bowel disease, especially ulcerative colitis
- Medical marijuana patients report that nabilone is more similar in effect to CBD than THC, indicating that it has more of a therapeutic effect on the body than a "high" effect on the mind

Nabilone, continued

- Chemotherapy based preferences for traditional anti-emetics v. cannabinoid based therapy
- Study comparing nabilone with anti-emetics, conducted before the development of modern 5-HT3 antagonist anti-emetics, revealed that patients taking cisplatin chemotherapy preferred H-based abtiemetics but patients taking carboplatin chemotherapy preferred nabilone to control nausea and vomiting

Nabilone, continued

- One study compared the efficacy and tolerability of nabilone with that of dihydrocodeine in the treatment of neuropathic pain
- Nabilone was not as effective as dihydrocodeine in controlling pain, and caused a higher incidence of minor adverse drug reactions than did dihydrocodeine
- One critic of the study has suggested that nabilone might be best suited for the treatment of patients suffering from central and spasticity-related pain, however, these patients made up only a small fraction of the study's population, and the study was not designed to identify subgroups which might have responded more favorably to treatment than others

Nabilone, continued

- A clinical trial performed in Canada reviewed the use of nabilone to treat nightmares in individuals suffering from post-traumatic stress syndrome
- The study found that nighttime administration of nabilone reduced the frequency and/or intensity of nightmares in 34 out of 47 (72%) of patients
- 28 reported complete cessation of nightmares

Nabilone- Projections on Usefulness

- Study had no placebo control, but warrants future investigation into the use of cannabinoid therapy in the treatment of post-traumatic stress syndrome and other disorders involving recurrent nightmares
- As endocannabinoids play a significant role in regulating long-term depression, perhaps downregulating the CB1 system can help remove the highly potentiated, hippocampal/amydygalia memories of the fear
- Perhaps CB1 agonists make one less likely to remember a dream, or even make REM sleep happen without significant involvement of the limbic system.

Nabilone, Adverse Effects

- Nabilone can increase, rather than decrease, post-operative pain
- In the treatment of fibromyalgia, adverse effects limits the useful dose
- Adverse effects of nabilone include dizziness/vertigo, euphoria, drowsiness, dry mouth, ataxia, sleep disturbance, dysphoria, headache, nausea, disorientation, depersonalization, asthenia and increased appetite

Other Clinical Targets

- Marijuana withdrawal
- CNS and psychiatric conditions
- Wasting

What's Coming?

- Generic versions of Synthetic THC, including hard or room temperature capsules
- Cannabis-derived pharmaceutical products
- CB2 agonists
- THC-precursor suppositories
- Transdermal THC delivery
- Inhaled THC

What's Coming?

- THC tablets
- THC syrup
- 50 states with "medical marijuana" laws?
- State level "legal" marijuana
- Federal laws decriminalizing medical use (or any use) of marijuana?
- All of it?

ASAM Recommendations

- ASAM recommends its members and other physician organizations and their members reject responsibility for providing access to cannabis and cannabis-based medications until such time that these materials receive marketing approval from the Food and Drug Administration.

ASAM Recommendations

- ASAM asserts that cannabis, cannabis-based medications, and cannabis delivery devices should be subject to the same standards that are applicable to other prescription medications and medical devices and that these medications or devices should not be distributed or otherwise provided to patients unless and until such medications or devices have received marketing approval from the Food and Drug Administration.

ASAM Recommendations

- ASAM rejects smoking as a means of drug delivery since it is inherently unsafe

ASAM Recommendations

- ASAM supports the need for federal regulatory standards for drug approval and distribution. ASAM recognizes that states can enact limitations that are more restrictive but rejects the concept that states could enact more permissive regulatory standards. ASAM discourages state interference in the federal medication approval process

ASAM Recommendations

- ASAM rejects a process whereby State and local ballot initiatives approve medicines because these initiatives are being decided by individuals not qualified to make such decisions (based upon a careful science-based review of safety and efficacy, standardization and formulation for dosing, or provide a means for a regulated, closed system of distribution for marijuana which is a CNS drug with abuse potential)

ASAM Recommendations

- ASAM asserts that physician organizations operating in states where physicians are placed in the gate-keeping role have an obligation to help licensing authorities assure that physicians who choose to discuss the medical use of cannabis and cannabis-based products with patients:

ASAM Recommendations

- Adhere to the established professional tenets of proper patient care, including
  - History good faith examination of the patient
  - Development of a treatment plan with objectives
  - Provision of informed consent, including discussion of risks, side effects, and potential benefits

ASAM Recommendations

- Periodic review of the treatment's efficacy
- Consultation as necessary
- Proper record keeping that supports the decision to recommend the use of cannabis

ASAM Recommendations

- Have a *bona fide physician-patient relationship with the patient, i.e., should have a pre-existing and ongoing relationship with the patient as a treating physician;*
- Ensure that the issuance of “recommendations” is not a disproportionately large (or even exclusive) aspect of their practice

ASAM Recommendations

- Not issue a recommendation unless the physician has adequate information regarding the composition and dose of the cannabis product
- Have adequate training in identifying substance abuse and addiction

Resources

- ASAM website for Policy Statements (http://www.asam.org)
- CLAAD for Citizen's Petition, membership, news (http://claad.org)
- Two Dreams for clinical information (http://www.twodreams.com)

Thank You!

Questions?