Medicinal Cannabis: Clinical Practice Guidelines and Regulations

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Disclosures

- Research Funding
  - Center for Medicinal Cannabis Research
- Consultant
  - Zynerba Pharmaceutical

Learning objectives

- Discuss the controversy and regulatory issues surrounding medical marijuana
- Discuss opioid/cannabinoid interactions
- Discuss the abuse potential of the cannabinoids
- Review the basic mechanisms and pharmacology of the cannabinoids
- Review the clinical evidence for pain relief

Medical Marijuana Controversy

PRO

- Leaf contains many active constituents making it more efficacious than single component extract
- No lethal dose
  - >16,000 deaths/year from prescription opioids
- Low dependency
- Millennia support safety and efficacy

CON

- Legalization will lead to more recreational use
- Will never meet FDA criteria for approval
- Gateway to drug abuse
- Colorado seeing increase discharges from marijuana toxicity
  - but no deaths

The United States is Going Green with November Elections

- 34 States plus the District of Columbia with legal medical marijuana
- 7 States plus DC with legal recreational use
- Possession limits range from 2 oz. to 24 oz. and 15 plants

Original Investigation

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

Marcus A. Bachhuber, MD; Brendan Saloner, PhD; Chinazo O. Cunningham, MD, MS; Colleen L. Barry, PhD, MPP

Table. Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010

	Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law		
	Primary Analysis	Secondary Analyses	
Independent Variable[a]	Estimate (95% CI)[b]	Estimate (95% CI)[c]	Estimate (95% CI)[d]
Medical cannabis law	−24.8 (−37.5 to −9.5)[e]	−31.0 (−42.2 to −17.6)[f]	−23.1 (−37.1 to −5.9)[e]
Prescription drug monitoring program	3.7 (−12.7 to 23.3)	3.5 (−13.4 to 23.7)	7.7 (−11.0 to 30.3)
Law requiring or allowing pharmacists to request patient identification	5.0 (−10.4 to 23.1)	4.1 (−11.4 to 22.5)	2.3 (−15.4 to 23.7)
Increased state oversight of pain management clinics	−7.6 (−19.1 to 5.6)	−11.7 (−20.7 to −1.7)[e]	−3.9 (−21.7 to 18.0)
Annual state unemployment rate[g]	4.4 (−0.3 to 9.3)	5.2 (0.1 to 10.6)[e]	2.5 (−2.3 to 7.5)

[a] All models adjusted for state and year (fixed effects).

[b] R^2 = 0.876.

[c] All intentional (suicide) overdose deaths were excluded from the dependent variable; opioid analgesic overdose mortality is therefore deaths that are unintentional or of undetermined intent. All covariates were the same as in the primary analysis; R^2 = 0.873.

[d] Findings include all heroin overdose deaths, even if no opioid analgesic was involved. All covariates were the same as in the primary analysis. R^2 = 0.842.

[e] $P \leq .05$.

[f] $P \leq .001$.

[g] An association was calculated for a 1-percentage-point increase in the state unemployment rate.

Medical marijuana policies and hospitalization related to marijuana and opioids

- Hospital discharges 1997-2014
- Medical Marijuana Policies associated with:
  - No change in Marijuana dependence or abuse discharges
  - 23% reduction in Opioid dependence or abuse discharges
  - 13% reduction in Opioid pain reliever overdose discharges

– Shi, Y. Drug and Alcohol Dependence, 2017

Cannabis Use Associated with Decreased Opiate Use

- A retrospective cross-sectional survey of patients with chronic pain
  - 64% decreased opioid use
  - Decreased side effects of medications
  - Improved quality of life

    - Boehnke et al. J Pain, 17:739, 2016

Cannabinoid-Opioid Interaction in Chronic Pain

- 21 subjects with chronic pain taking twice-daily sustained-release morphine or oxycodone
- 5 day inpatient stay, inhaled vaporized cannabis 3X/day
- Average of 27% reduction in pain with no altered plasma opioid levels
- Pulse oximetry did not show any lowered oxygen saturation

Abrams DI, et al. Clin Pharmacol Therap 2011, 90:844-851

Safety of Chronic Cannabis Use

- Multicenter study of 215 chronic pain patients with controlled use of cannabis vs 216 chronic pain patient controls followed for 1 year
- No significant difference in risks between groups

  – Ware et al, J of Pain, 2015.

Cannabis:
Abuse Potential

- Although cannabis abuse is prevalent, animal studies show that cannabinoids do not seem to be as robust as other agents (heroine, cocaine, nicotine)

Cooper ZV, Haney M. Int Rev Psychiatry, 2009, 104-112

Cannabis:
Conditioned Placed Preference vs Aversion

- High dose THC produces CPA
- Lower doses of THC produces CPP
- Human cannabis smokers also report opposing effects

Braida D, Pozzi M, Cavallini R, Sala M Neuroscience. 2001; 104(4):923-6
Cheer JF, Kendall DA, Marsden CA Psychopharmacology (Berl). 2000 Jul; 151(1):25-30.
Reilly D, Didcott P, Swift W, Hall W Addiction. 1998 Jun; 93(6):837-46.

Cannabis Tolerance

- With chronic cannabis use, tolerance develops to the physiological (i.e cardiovascular) and subjective (i.e. highness) effects.

Benowitz NL, Jones RT J Clin Pharmacol. 1981 Aug-Sep; 21(8-9 Suppl):214S-223S.
Hart CL, Haney M, Ward AS, Fischman MW, Foltin RW Drug Alcohol Depend. 2002 Aug 1; 67(3):301-9.

Cannabis:
Dependence and Withdrawal

- Abrupt termination in habitual users results in withdrawal symptoms similar to opioids
- Dependent on the dose of THC consumed
  - Less likely to occur or symptoms less with lower dose consumption

Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubaran C, Foltin RW Neuropsychopharmacology. 2004 Jan; 29(1):158-70.

Cannabinoids and Sleep

- Prevalence of sleep disturbance high in chronic pain
- Opioids disrupt sleep*
- THC is a sedative while CBD is stimulating**
  - THC alone had no effect of sleep quality
  - Adding CBD reduced stage 3 and increased wakefulness

*Dimsdale JE, et al. J Clin Sleep Med, 2007, 3:33-36

**Nicholson A, et al. J Clin Pharmacol, 2004, 3:305-313

Regulatory and Legal Considerations

- No Federal regulatory oversight of production and distribution of marijuana
- Growers, processors and distributors exist in states with legalization but no federal oversight
  - State oversight varies from state to state
  - Oregon recently passed a bill that designates the Oregon liquor commission to oversee
  - California recently pass 3 bills for more state oversight
- Difficult to predict purity, additives such as pesticides

Regulatory and Legal Considerations

- Laws vary widely from state to state
  - Indicated medical conditions
  - Physician responsibilities
  - Quantity of marijuana possession
  - Oversight of dispensaries
- No state requires a written prescription
- Some states provide physician guidelines (i.e. California)

Regulations for Clinical Research

- As a schedule I, research is challenging
- Research falls under the auspices of a number of agencies
  - DEA, DHHS, FDA, NIDA, some state agencies
- Schedule I DEA license required
  - Approval by DHHS
  - File IND with FDA
  - Review by NIDA, Federal and Local DEA
- University of Mississippi sole supplier through contract with NIDA

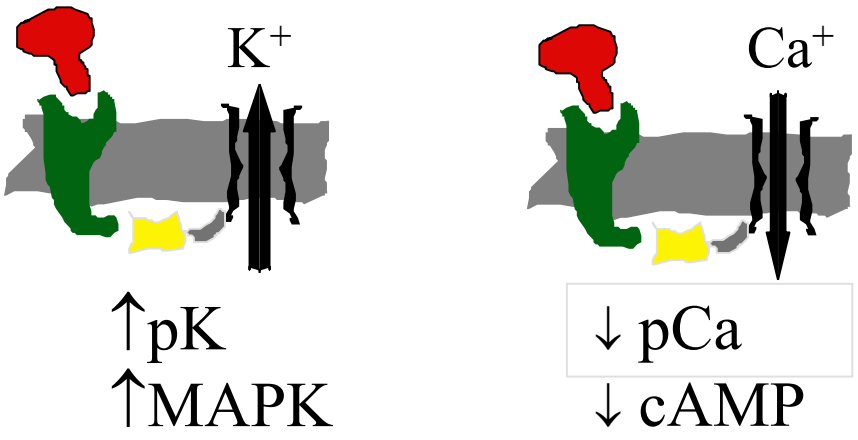
CANNABINOIDS

Two cannabinoid (CB) receptors: CB1/CB2

G protein coupled superfamily 7 TM

-positively to potassium channels and mitogen active protein kinase (MAPK)

-negatively to N-type and P/Q-type calcium channels and adenylate cyclase (responsible for THC psychoactive effects)



CANNABINOID TARGETS

Peripheral Cells: monocytes,B/T and mast cells

CB2-r:

↓Inflammatory cell mediator release

↓Plasma extravasation

↓Sensitization of afferent terminals

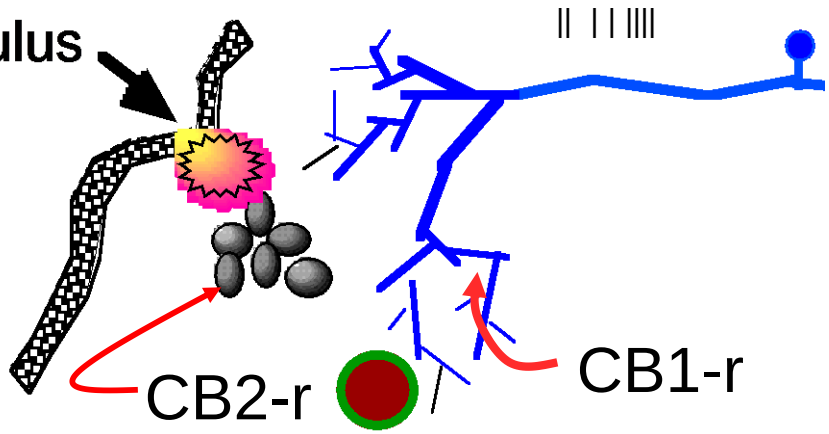
Peripheral terminal of Primary afferent.

CB1-r:

↓Terminal excitability

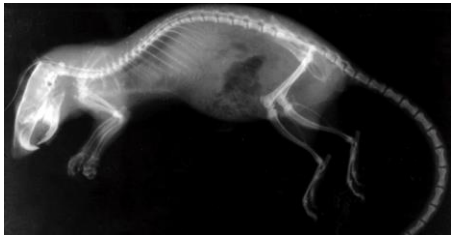
↓Release of pro-inflammatory terminal peptides

CB-r agonists: reduction of elevated terminal excitability otherwise induced by local injury and inflammation.



CANNABINOID TARGETS

Spinal Dorsal Horn



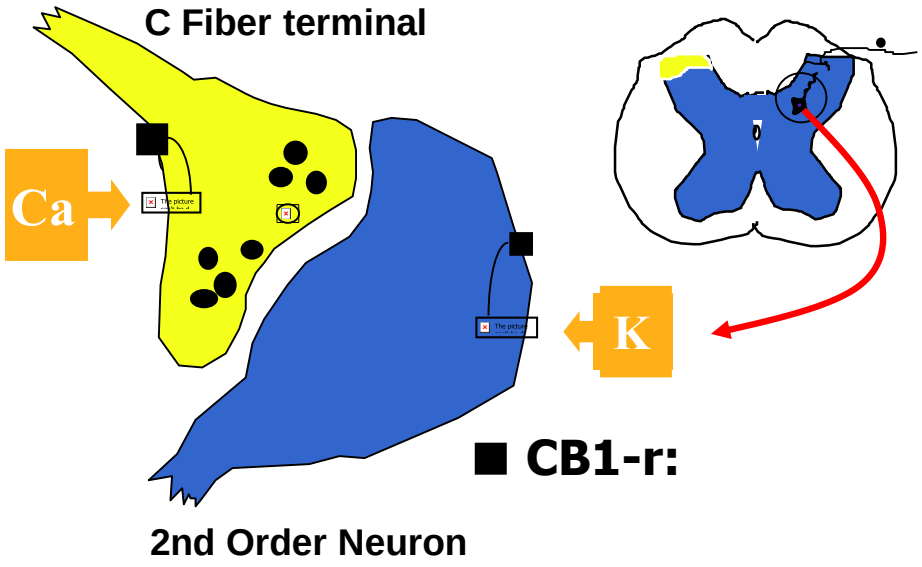
CB1-r: (intrathecal)

Presynaptic - Terminals of small primary afferents (peptidergic and non peptidergic)..partial colocation with TRPV-1-r
Agonist: ↓N/P/Q-VSCC →↓ neurotransmitter release

Post synaptic - neurons: (mRNA): Lam I-V, X
Agonist: ↑K Ch → hyperpolarization →↓ excitability

CB1-r/ CB2-r:
Non neuronal cells (??)

CB1 agonists: reduction of afferent evoked excitation of dorsal horn nociceptive neurons.



CANNABINOID TARGETS

Supraspinal Sites

CB1-r (microinjection)

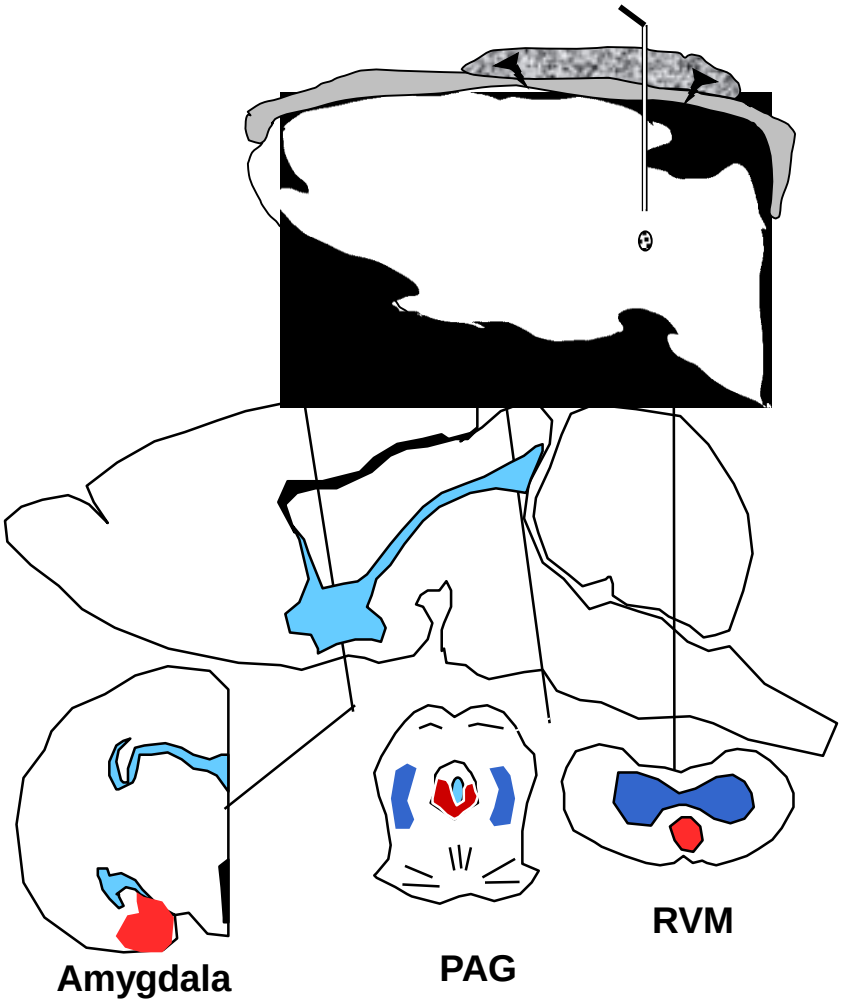
Basolateral Amygdala

Periaqueductal gray

Rostroventral Medulla

Local effects upon nociceptive processing

Activation of bulbospinal pathways…regulating dorsal horn excitability



CB1 agonists: reduction of afferent evoked excitation of dorsal horn nociceptive neurons.

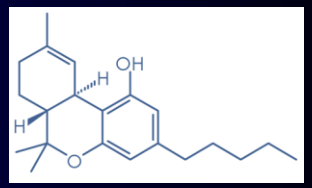
Cannabinoid Refers to a Variety of Compounds

- Endocannabinoids
  - Endogenous cannabinoids
- Phytocannabinoids
  - Derived from cannabis plants
- Synthetic

Clinical Pharmacology of Marijuana

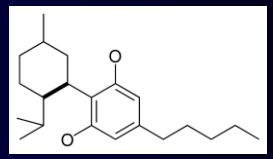
- Marijuana contains more than 500 compounds of which approximately 107 are called the cannabinoids
- delta-9-tetrahydrocannabinol (THC) is the main psychoactive cannabinoid in marijuana
- Cannabinoids are extremely lipid soluble
- Besides THC . There are varying proportions of other cannabinoids, cannabidiol (CBD),cannabinol (CBN) and others
- Lethal doses in humans are not known

Tetrahydrocannabinol (THC)



- Principal psychoactive compound
- Partial CB1 and CB2 agonist
- Low receptor efficacy and affinity
- 11-OH-THC main metabolite and psychoactive
- Medicinal Effects
  - Analgesic
  - Anti-inflammatory
  - Antiemetic
  - Antispasmodic
  - Sedation

Cannabidiol (CBD)



- May have different medicinal applications than THC
- Very low affinity for CB1 and CB2
- Minimal psychoactive effect
- 5-HT1A receptor agonist
  - Antidepressant, Anxiolysis
- Allosteric modulator of μ- and δ-opioid receptors
  - Analgesia
- Other: Anti-psychotic, antiepileptic

CBD:THC Interaction

Schizophrenia Research 162 (2015) 153–161

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Review

A systematic review of the antipsychotic properties of cannabidiol in humans

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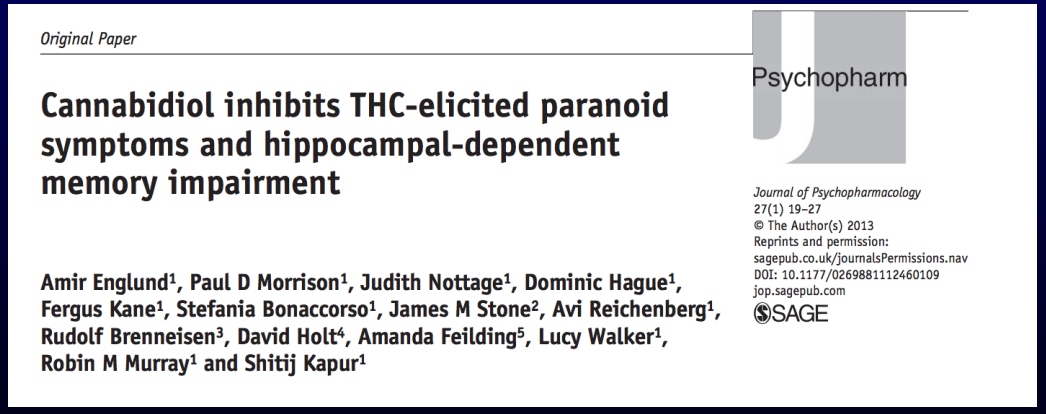


Original Paper

Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment

Amir Englund[1], Paul D Morrison[1], Judith Nottage[1], Dominic Hague[1], Fergus Kane[1], Stefania Bonaccorso[1], James M Stone[2], Avi Reichenberg[1], Rudolf Brenneisen[3], David Holt[4], Amanda Feilding[5], Lucy Walker[1], Robin M Murray[1] and Shitij Kapur[1]

Psychopharm

Journal of Psychopharmacology
27(1) 19–27

DOI: 10.1177/0269881112460109
jop.sagepub.com
SAGE

CBD could reduce the incidence of psychoactive effects induced by THC

Other Cannabis Compounds with Medicinal Properties

- Myrcene
  - Analgesic effect
    - Blocked by naloxone or yohimbine
  - Anti-inflammatory effect
    - Through PGE2 inhibition
- Linalol
  - Possible reduction of stress
- Limonene
  - Adenosine agonist
- Caryophyllene
  - CB2 agonist
  - Antiinflammatory
  - Beta-caryophyllene is an FDA approved dietary supplement
- Humulene
  - Antiinflammatory

    Effects similar to dexamethsone
  - Inhibits TNFα and IL1B

Clinical Pharmacology of Marijuana: Route-Dependent Pharmacology - Inhaled

- Leaf combustion results in release of all cannabinoids in the smoke
- Vaporization results in the selective release of cannabinoids and some terpenes
- Peak venous blood levels occur soon after initiating smoking
- Duration is short (<2 hours)

Clinical Pharmacology of Marijuana: Route-Dependent Pharmacology - Oral

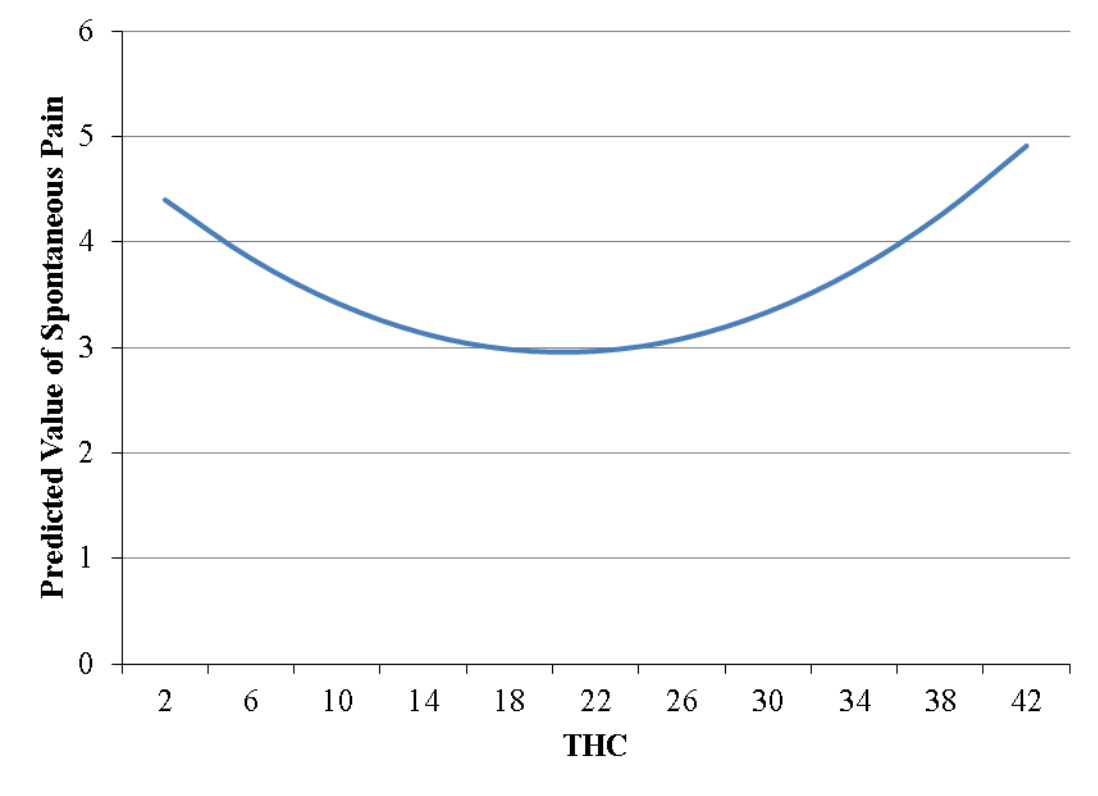
- Oral ingestion of THC or marijuana is quite different than inhalation
- Maximum THC and other cannabinoid blood levels are only reached 1-4 hours after an oral dose
- Onset of psychoactive and other pharmacologic effects is much slower and unpredictable with oral delivery
- Oral absorption and peak plasma levels can increase with ingestion of a fatty meal
- Bioavailability ranges from 5-20 percent (large 1st pass effect and erratic absorption from stomach and intestines)

Clinical Pharmacology of Marijuana: Route-Dependent Pharmacology - Sublingual

- Sublingual delivery is an attractive route of administration
- A sublingual spray containing the cannabis-based extract (CBME) combination of THC and CBD is currently in approved in Canada for multiple sclerosis
- The plasma levels achieved are similar to oral delivery but more titratable and predictable (Peak in about 1 hour, duration up to 4 hours).

THC Plasma Levels and Pain Relief

Therapeutic window of pain relief occurs between 16-31 ng/ml plasma level of THC



BJCP British Journal of Clinical Pharmacology

Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

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Keywords
cannabinoids, chronic non-cancer pain, neuropathic pain, systematic review

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Accepted Article

Fifteen of the eighteen trials that met the inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared with placebo and several reported significant improvements in sleep. There were no serious adverse effects. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity and led to withdrawal from the studies in only a few cases.

This article is linked to a themed issue in the British Journal of Pharmacology on Respiratory Pharmacology. To view this issue visit http://dx.doi.org/10.1111/bph.2011.163.issue-1

Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis.

[4, 5] there is increasing attention on their potential role in the management of pain [6–9]. A previous systematic review done a decade ago identified the need for further randomized controlled trials (RCTs) evaluating cannabinoids in the management of chronic pain indicating that there was insufficient evidence to introduce cannabinoids into widespread use for pain at that time [10]. A subsequent review identified a moderate analgesic effect but indicated this may be offset by potentially serious harm [11]. This conclusion of serious harm mentioned in the more recent review is not consistent with our clinical experience. In addition there have been a number of additional

ment guidelines for reporting systematic reviews that evaluate health care interventions [12].

Systematic search

A literature search was undertaken to retrieve RCTs on the efficacy of cannabinoids in the treatment for chronic pain. The databases searched were: PubMed, Embase, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library (Wiley), ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search Premier (EBSCO), Clinical Trials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline.

Cannabis and Driving

- States with Medical Marijuana Laws have fewer traffic fatalities
  - Fatality Analysis Reporting System 1985-2014
    - Age 15-24 – 11% reduction
    - Age 25-44 – 12% reduction
    - Age 45 and older – no significant change
  - State specific immediate reductions
    - California – 16%
    - New Mexico – 17.5%
    - However, there has been a gradual increase since laws passed

Am J Pub Health, 2016 doi:10.2015/AJPH.2016.303577

Cannabis Use and Driving

- Very little research on Driving
- Appears to have much less affect on motor skills than alcohol
- However, combination of alcohol and cannabis can result in severe impairment
- General rule
  - Ingestion – no driving for 8 hours
  - Transmucosal – no driving for 4 hours
  - Inhalation – no driving for 2 hours

Patient Selection and Monitoring
Still Unclear and Unanswered Questions

- Should they be as strict as opioids?
- Role of UDT
- Role of Patient Agreements
- Concurrent use of opioids or wean first
- Dosing

UCSD Pain Clinic Approach to Medical Marijuana

- Failure of conservative therapies
  - Consider before chronic opioids
- Provide authorization via the DPH application
- Referral to Naturopathic Doctor experienced in cannabis delivery and dosing
- If using chronic opioids, wean first
  - Consider introducing cannabis during wean for compliant patients
- Follow up: document type and dose if known
- Consider UDT