Medical Marijuana – It's Not Your Grandma's Brownie, Or Is It?

Medical Cannabis: Regulatory Overview

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All conflicts resolved through peer review – Vice-Chair, Illinois State Board of Pharmacy

Objectives

- Compare regulatory differences pertaining to the medical and recreational use of cannabis across the United States.
- Describe potential roles (statutory and non-statutory) for pharmacists and pharmacy technicians in medical cannabis dispensing programs.

Question

A Pharmacist may own and operate a medical cannabis dispensary in Illinois without jeopardizing his/her pharmacist license.

A. Yes
B. No
C. Maybe

Question

A pharmacist or pharmacy technician may be employed in a medical cannabis dispensary in Illinois without jeopardizing his/her professional license.

A. Yes
B. No
C. Maybe

Question

A pharmacist may dispense medical cannabis from a pharmacy in Illinois without jeopardizing his/her professional license or the pharmacy's license.

A. Yes
B. No
C. Maybe

Medical Cannabis Historical Timeline (selected highlights)

- 1500 BC: earliest written reference to medical marijuana in Chinese Pharmacopeia
- 1745-1824: George Washington and Thomas Jefferson grow hemp
- 1850: Marijuana added to the US Pharmacopeia
- 1911: Massachusetts becomes first state to outlaw cannabis
- 1937: 1st marijuana seller convicted under US Federal Law is arrested
- 1942: Marijuana removed from US Pharmacopeia
- 1968: University of Mississippi becomes official grower of marijuana for federal government
- 1970: Controlled Substances Act classifies marijuana as a drug with "no accepted medical use"
- 1976: Marijuana decriminalized in the Netherlands
- 1978: New Mexico passes 1st state law recognizing medical value of marijuana
- 1985: Marinol approved by FDA
- 1988: DEA Judge Francis Young recommends marijuana be placed in Schedule II (overruled in 1989)
- 1991: Federal government suspends IND Compassionate Use Medical Marijuana Program
- 1991: 1st medical marijuana initiative passed in San Francisco
- 1996: California becomes the 1st state to legalize medical marijuana
- AARP Poll finds that 72% of seniors support medical marijuana
- Aug. 2013: Illinois becomes the 20th state to legalize medical marijuana

National Cannabis Legislation

- Medical Cannabis
  - 23 states and the District of Columbia (as of July 2014)
  - State to state differences
    - Controlled substance scheduling/classification
    - Health conditions coverage
    - Ownership and operational management requirements
    - Regulatory departments oversight
    - Law enforcement
  - Recreational Cannabis
    - Colorado and Washington
    - Regulatory differences

Regulatory Differences

- Fees
  - authorized users
  - cultivators
  - dispensers
- Taxes
- Background checks
- Criminal penalties for fraud and abuse
- State registry card transferability
- Possession limits
- Plant growing vs. purchase
- Approved health conditions
- Approved methods of administration
- Age limits for authorized users
- Number of dispensaries and cultivation centers
- Who can grow and dispense
- Health care professionals roles
  - Physicians
  - Pharmacists/pharmacy techs
  - others

Legislated Pharmacy, Pharmacist & Pharmacy Technician Roles

- Connecticut
  - Reclassified as Schedule II
  - Prescription Monitoring Program utilization
  - Dispensary pharmacist
    - Good standing
    - Active license
    - May own dispensary facility
  - Dispensary technician
    - Active pharmacy technician registration within past 5 years
    - Affiliated with a licensed dispensary
    - Registered with the Department
    - 3:1 ratio technicians/dispensary

State of Illinois Compassionate Use of Medical Cannabis Pilot Program

- 20th state to legalize
- Oversight departments
  - IDFPR
  - Public Health
  - Agriculture
  - Revenue
- 21 Cultivation Centers
- 60 Dispensaries
- Background checks and fingerprinting
- Cannabis knowledge
- Research and substance abuse prevention plan
- Fees (dispensing organization)
  - $5,000 application
  - $30,000 registration
  - $50,000 surity bond
  - $100 dispensing organization agent
  - $5,000 location change
  - $400,000 minimum in liquid assets
- Open a minimum of 35 hrs/week
- Dispensing agent-in-charge
- Inventory control systems
- Recordkeeping systems
- Storage requirements
- Security requirements
- Cleaning and sanitation
- Destruction and disposal
- Qualifying patients
  - Minimum 18 years old
  - Registry identification card: $100 (pt)/$25 (caregiver)
  - Criminal background check
  - Veterans
  - exceptions

State of Illinois Compassionate Use of Medical Cannabis Pilot Program

- Pharmacists and pharmacy technicians are not explicitly mentioned in the Act nor Rules
- Pharmacists and pharmacy technicians are not prevented from receiving a dispensing organization registration, operating a dispensary or being employed by dispensing organizations
- Medical Cannabis Advisory Board
  - Composed of 15 members including a pharmacy representative
  - Review and recommend additional conditions/diseases that would benefit from medical cannabis use
- Physicians must have a physician-patient relationship to certify a qualifying patient
- Physicians cannot hold a direct or indirect economic interest if he/she recommends the use of medical cannabis to qualifying patients or is in a business relationship with one who recommends

Example Approved Debilitating Medical Conditions

- Cancer, glaucoma, positive status for human immunodeficiency virus (HIV), acquired immune deficiency syndrome (AIDS), hepatitis C, amyotrophic lateral sclerosis (ALS), Crohn's disease, agitation of Alzheimer's disease, cachexia/wasting syndrome, muscular dystrophy, severe fibromyalgia, spinal cord disease, including but not limited to arachnoiditis, Tarlov cysts, hydromyelia, syringomyelia, Rheumatoid arthritis (RA), fibrous dysplasia, spinal cord injury, traumatic brain injury (TBI) and post-concussion syndrome, Multiple Sclerosis, Arnold-Chiari malformation and Syringomelia, Spinocerebellar Ataxia (SCA), Parkinson's disease, Tourette's syndrome, Myoclonus, Dystonia, Reflex Sympathetic Dystrophy, RSD (Complex Regional Pain Syndromes Type I), Causalgia, CRPS (Complex Regional Pain Syndromes Type II), Neurofibromatosis, Chronic Inflammatory Demyelinating Polyneuropathy, Sjogren's syndrome, Lupus, Interstitial Cystitis, Myasthenia Gravis, Hydrocephalus, nail-patella syndrome, residual limb pain, or the treatment of these conditions; or any other debilitating medical condition that is added pursuant to statute or by the Department by rule as provided in Section 946.30. (Section 10 of the Act)
- Myoclonic-astatic epilepsy (minors and adults) approved in July 2014 (PA 98-0775)
- Other states: anorexia, nausea, PTSD, cirrhosis, chronic intractable pain,

Issues for Consideration

- Patient counseling
- Patient profiles
- Patient admissions
- Employment
- Student admissions
- Operating motor vehicles
- Primary caregivers
- Housing
- Health and life insurance

Polling Question

Which of the following statements is **true** pertaining to national cannabis legislation?

A. As of July 2014, more than half of all states have approved medical cannabis legislation.
B. There is state-to-state consistency in the quantity of medical cannabis an authorized user may acquire/possess.
C. There is state-to-state consistency in the approved medical conditions for which medical cannabis can be utilized.
D. Age limits for authorized medical cannabis users are dependent upon the medical condition and state regulation.

Polling Question

Which of the following statements is **true** pertaining to the potential roles for pharmacists and pharmacy technicians in medical cannabis dispensing programs?

A. In Connecticut, a pharmacist with an expired pharmacist license may own/operate a medical marijuana dispensary.
B. In Illinois, a pharmacist may serve as a dispensing agent-in-charge of a dispensing organization's dispensary.
C. In Connecticut, the maximum ratio of pharmacy technicians (dispensary technician) to pharmacists (dispensary) is 4:1.
D. In Illinois, a pharmacy technician may *not* be concurrently employed in a pharmacy and medical marijuana dispensary.

Bibliography

- IL Compassionate Use of Medical Cannabis Pilot Program Act http://www.ilga.gov/legislation/ilcs/ilcs3.asp?ActID=3503&ChapterID=35 (accessed: July 21, 2014)
- IL Compassionate Use of Medical Cannabis Pilot Program Rules: Departments of Financial and Professional Regulation; Agriculture; Public Health; and, Revenue. http://www2.illinois.gov/gov/mcpp/Pages/update-07182014.aspx (accessed: July 21, 2014)
- http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881 (accessed: July 21, 2014)
- State of Connecticut Palliative Use of Marijuanahttp://www.cga.ct.gov/current/pub/chap_420f.htm (accessed: July 21, 2014)

Medical Marijuana – It's Not Your Grandma's Brownie, Or Is It?

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September 13, 2014

The speaker has no conflicts of interest to disclose with regard to this presentation.

Objectives

- Identify which clinical indications have robust evidence for the effectiveness of medical marijuana.
- List potential adverse effects and safety issues associated with the use of medical marijuana.

Polling Question (use ARS device)

What is your stance on medical marijuana?

A. Pro
B. Con

Audience Response Question (use cell phone)

- Name an indication for which you have seen medical marijuana used (or requested) at your practice site.

A History Lesson

- Medical marijuana (MM) was introduced to the medical community in Europe in 1839
- Admitted to US Pharmacopoeia in 1850
- Used therapeutically in the U.S. until mid-1930s
- 1937: Law prohibiting use passed by Congress (against the advice of the AMA)
- Removed from US Pharmacopoeia in 1942
- ~40-50% of the US population has used in their lifetime

J Psychoactive Drugs. 2011 Apr-Jun;43(2):128-35

Formulations: Synthetic

Compound	Approved in the US?	Indications	Formulations
Dronabinol (Marinol®) Schedule III	Y	• Second-line treatment of CINV • Anorexia/weight loss in patients with AIDS	Oral capsules
Nabilone (Cesamet®) Schedule II	Y	• Second-line treatment of CINV	Oral capsules
Nabiximols (Sativex)	N	• Second-line treatment of spasticity in adults with MS • Neuropathic pain in patients with MS • Intractable cancer pain	Cannabis-derived liquid extract available as an oromucosal spray.

Marinol Prescribing information
Cesamet Prescribing Information
Sativex Prescribing Information
Pharmacotherapy 2013;33(2):195-209.

Formulations: Botanical

- "Medical cannabis" or "medical marijuana"
- Schedule I
  - *Cannabis sativa* or *cannabis indica*
  - Contains > 60 active components
    - Δ^9-tetrahydrocannabinol (THC) is most psychoactive

$C_{21}H_{30}O_2$ (molecular weight = 314.47)

Pharmacodynamics

- CB1 receptors
  - Basal ganglia (motor activity)
  - Cerebellum (motor coordination)
  - Hippocampus (short-term memory)
  - Neocortex (thinking)
  - Hypothalamus and limbic cortex (appetite and sedation)
  - Periaqueductal gray dorsal horn (pain modulator)
  - Immune cells
- CB2 receptors
  - Immune cells
  - Brain on microglia (Alzheimer's Disease)

Pharmacotherapy 2013;33(2):195-209.

Pharmacodynamics

- THC
  - Most psychoactive component of marijuana
  - ↑ heart rate
  - ↑ Euphoria
  - ↓ Alertness
  - ↓ Motor instability

Pharmacotherapy 2013;33(2):195-209.

Pharmcodynamics

- Cannabidiol (CBD)
  - Major non-psychotropic compound found in cannabis
  - Inverse agonist
    - ↓ psychotropic effects of THC
  - Enhances activity of endogenous cannabinoid
  - Amount differs across products and formulations
  - May have some anti-inflammatory properties

Pharmacokinetics

- Smoking
  - 50% of THC converted to smoke
  - 50% of remaining THC is exhaled again as smoke
  - Small amount of remaining THC metabolized in lung

	Smoking	Oral
Bioavailability	0.10-0.25	0.05-0.2
Peak concentrations	Within minutes	1-3 hours
Distribution t ½	30 minutes	3.8 hours
Terminal t ½	30 hours	25 hours

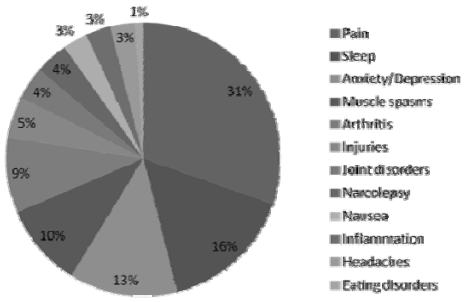
Pharmacotherapy 2013;33(2):195-209.

Patterns of Use

- Frequency of use
  - 67% used daily; 10% used 3x/day
- Time of day
  - 52% used in the evening
- Formulation
  - 86% smoked; 24% oral; 22% vapor
- Prior therapies
  - 79% had failed prescription therapy
  - 48% had failed physical therapy

J Psychoactive Drugs. 2011 Apr-Jun;43(2):128-35

Patient ID Cards Issued by MDs



J Psychoactive Drugs. 2011 Apr-Jun;43(2):128-35

Why Patients Use Marijuana

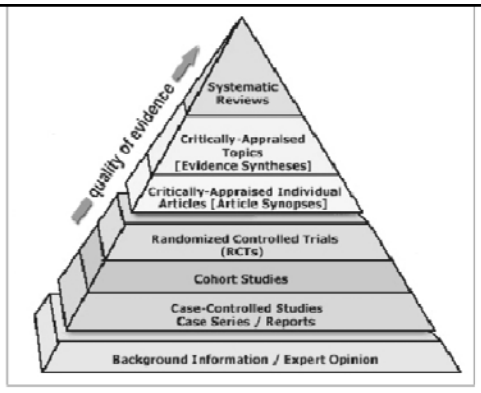
Condition	%	Condition	%
Pain	81%	Depression	26%
Sleep	71%	Concentration/focus	23%
Relaxation	55%	Anger management	22%
Headaches	41%	Cramps	19%
Anxiety	38%	Panic attacks	17%
Appetite	38%	Energy	16%
Nausea/vomiting``	28%		

J Psychoactive Drugs. 2011 Apr-Jun;43(2):128-35.

Clinical Efficacy

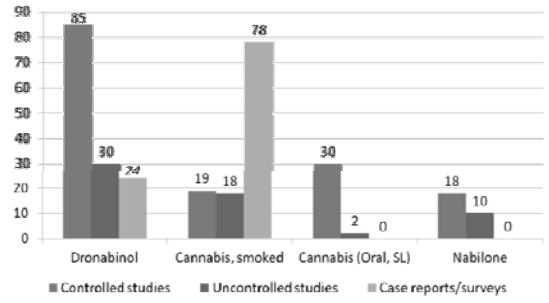
Quantity of Evidence

- Pubmed search for "cannabis" OR "marijuana, smoking" OR "medical marijuana" OR "cannabinoids" OR "dronabinol"
  - 16,473 publications
  - 921 clinical trials
  - 1,881 review articles
  - 167 systematic reviews
    - 135 within the last 10 years
    - 83 within the last 5 years



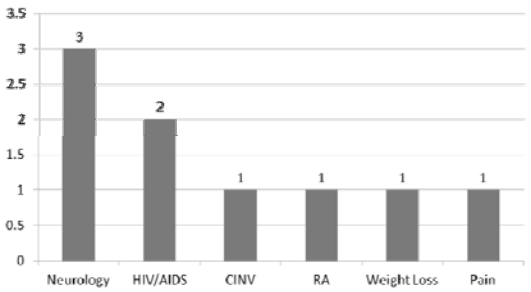
http://openi.nlm.nih.gov/imgs/512/330/2759611/2759611_IJO-42-104-g001.png

Evidence Summary



http://www.cannabis-med.org/english/studies.htm#_Toc307501840

Systematic Reviews: Effectiveness



Pain: Efficacy

- Meta-Analysis of 18 trials
  - Many had attrition bias
  - None controlled for blinding
  - Study using smoked marijuana excluded
- Formulations
  - 10 with oromucosal spray
  - 8 with capsules
- Efficacy:
  - Effect size -0.61 (-0.84, -0.37)

Pain Med. 2009 Nov;10(8):1353-68

Pain: Adverse Effects

Adverse Effects	OR (95% CI)	P-value
Euphoria	4.11 (1.33-12.72)	0.01
Blurred vision, visual hallucinations	8.34 (4.63-15.03)	<0.00001
Disorientation, confusion	3.24 (1.51-6.97)	0.003
Speech disorders	4.13 (2.08-8.20)	<0.0001
Ataxia, muscle twitching	3.84 (2.49-5.92)	<0.00001
Numbness	3.98 (1.87-8.49)	0.0003
Impaired memory	3.45 (1.19-9.98)	0.02
Attention, thought disturbances	5.12 (2.34 -11.21)	<0.0001

Pain Med. 2009 Nov;10(8):1353-68

Neurologic Disorders

- Systematic review of 34 studies by the AAN
  - Multiple sclerosis, epilepsy, movement disorders
  - Studies graded according to classification scheme of American Academy of Neurology (AAN)
  - Studies grouped by product formulation:
    - Oromucosal spray (Nabiximols)
    - Oral cannabis extract (OCE)
    - Smoked/vaporized marijuana

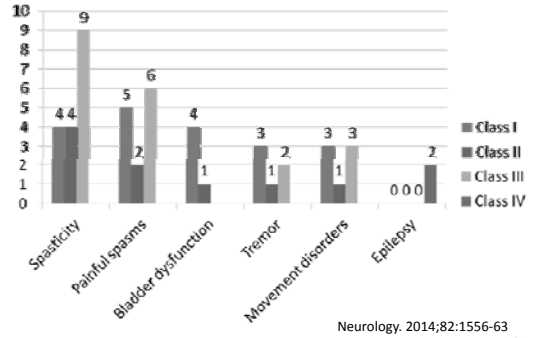
Neurology. 2014;82:1556-63

AAN Classification Scheme

Class I	RCT with all of the following a. Concealed allocation b. Primary outcomes defined c. inclusion/exclusion criteria defined d. Dropouts accounted for and >80% completion rate e. Appropriate description of methods for non-inferiority or superiority studies
Class II	RCT lacking one of the criteria listed in class I Cohort studies that match b-e above
Class III	All other controlled trials where outcome is independently assessed or derived from objective measurement
Class IV	Doesn't meet criteria for Class I-III; consensus or expert opinion

http://www.neurology.org/content/suppl/2014/04/26/82.17.1556.DC1/Appendix_e-4.pdf

Neurology: Quality of Evidence



Neurology. 2014;82:1556-63

Condition: AAN	Oral cannabis extract (OCE)	Nabiximols	Smoked Marijuana
Spasticity in MS	• *Effective*: subjective endpoints, objective endpoints @ 1 year • *Ineffective*: Objective endpoints @ 12-15 weeks	• *Probably effective*: subjective endpoints @ 6 weeks • *Probably ineffective*: objective endpoints @ 6 weeks	• *Probably effective*: subjective endpoints, objective endpoints @ 1 year • *Probably ineffective*: Objective endpoints @ 12-15 weeks
Central pain or painful spasms in MS	Effective	Probably effective	Unclear efficacy
Bladder dysfunction in MS	Probably ineffective	Probably effective	Probably ineffective
Tremor in MS	Probably ineffective	Possibly ineffective	Probably ineffective
Epilepsy	Insufficient evidence	Insufficient evidence	Insufficient evidence

Neurology 2014;82:1556-63

Rheumatoid Arthritis

- 2005 UK Survey
  - Arthritis was listed as one of the top 5 reasons for seeking marijuana
- One published clinical trial (n=58)
  - Multi-center, double-blind, randomized, parallel-group
  - Standardized concentrations of CBD/THC
  - Sativex® vs. placebo for 5 weeks at night
  - Primary efficacy variable: Change in pain on movement score (0-10) from baseline
  - Secondary variables: pain at rest, sleep quality, and morning stiffness

Int J Clin Pract. 2005;59(3):291-5.
Rheumatology. 2006;45:50-52.

Rheumatoid Arthritis

Outcome	Δ from baseline	95% CI	P-value
Morning pain on movement	-0.95	-1.83,- 0.02	0.044
Morning pain at rest	-1.04	-1.90, -0.18	0.018
Morning stiffness	-0.09	-0.58, 0.23	0.454
Quality of sleep	-1.17	-2.20, -0.14	0.027

- Adverse Effects
  - Dizziness (26% vs. 4% in placebo)
  - Light-headedness (10% vs. 4% in placebo)
  - Dry mouth (13% vs. 0% in placebo)
- Quality of Evidence
  - Very small sample size
  - Short duration
  - Customized dosing
  - Clinical significance?

Rheumatology. 2006;45:50-52.

Patient ID Cards Issued by MDs

Condition	%	# Trials	Condition	%	# Trials
Pain	31%	+++	Joint disorders	4%	+
Sleep disorders	16%	++	Narcolepsy	4%	-
Anxiety/Depression	13%	+	Nausea	3.4%	+++
Muscle spasms	10%	+++	Inflammation	3%	++
Arthritis	9%	+	Headaches /Migraines	3%	++
Injuries (knee, ankle, foot)	5%	+++	Eating Disorders	1%	+++

+ 1-3 trials
++ 3-10 trials
+++ > 10 trials

J Psychoactive Drugs. 2011 Apr-Jun;43(2):128-35

Why Patients Use Marijuana

Condition	%	# Trials	Condition	%	# Trials
Pain	81%	+++	Depression	26%	+
Sleep	71%	++	Improved concentration /focus	23%	-
Relaxation	55%	-	Anger management	22%	+
Headaches	41%	+	Cramps	19%	+
Anxiety	38%	+	Panic attacks	17%	+
Appetite	38%	+++	Energy	16%	-
Nausea/vomiting	28%	+++			

+ 1-3 trials
++ 3-10 trials
+++ > 10 trials

J Psychoactive Drugs. 2011 Apr-Jun;43(2):128-35.

Safety Concerns

Audience Response Question (use cell phone)

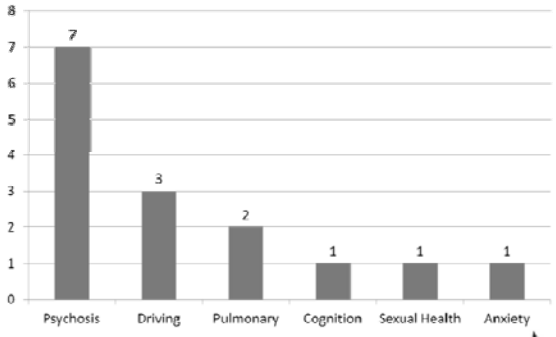
- Name one adverse effect you would be concerned about (or have seen) in patients using medical marijuana.

Adverse Effects

Short-term Use	Long-term or Heavy Use
• Impaired short-term memory • Impaired motor coordination • Altered judgment • Paranoia/psychosis	• Addiction • Altered brain development • Effects on education • Cognitive impairment • Decreased life satisfaction • Chronic bronchitis • Risk of chronic psychosis

N Engl J Med 2014;370:2219-27.

Published Systematic Reviews: Safety



Driving

- Dose-related impairment in cognitive and psychomotor skills
- Cannabis intoxication can impair many skills necessary for driving
  - Reaction time
  - Perception
  - Short-term memory
  - Attention
  - Motor skills
  - Tracking
  - Skilled activities

Drug Alcohol Depend. 2004;73:109-19.

Driving: Collisions

- Asbridge, et al
  - 9 studies (4 "high quality", 5 "medium quality")
  - N ranged from 631- 32,543
  - Collision risk with marijuana use OR 1.92 (1.35-2.73)
- Li, et al
  - 9 studies (5 case-control, 2 cohort, 2 cross-sectional)
  - N ranged from 110-626
  - Collision risk with marijuana risk OR 2.66 (2.07-3.41)

BMJ. 2012;344:e536.
Epidemiol Rev. 2012;34:65-72.

Driving

- Marijuana users had increased risk of responsibility in fatal crashes
  - OR 3.17 (95% CI 2.56-3.94) vs. non-users

THC Conc (ng/mL)	Unadjusted OR	95% CI
<1	2.18	1.22-3.89
1-2	2.54	1.86-3.48
3-4	3.78	2.24-6.37
≥5	4.72	3.04-7.33

BMJ. 2005;331:1371.

Pulmonary: Function

- Systematic Review
  - 14 studies; 10 cross-sectional, 3 cohort, 1 case series
  - Mean quality score 12.6 (range 6-18)

Outcome	Results
Short-term: airway response	9/12 studies found an increase in bronchodilation after a marijuana challenge
Long-term: pulmonary function	9 studies. No consistent results on FEV1/FVC ratio or airway hyperreactivity
Long-term: respiratory complications	14 studies. All found respiratory complications with long-term use including cough, sputum production, wheezing, bronchitis, dyspnea, pharyngitis, worsening asthma/CF, hoarse voice and abnormal chest sounds

Arch Intern Med. 2007; 167:221-8.
J Epidemiol Community Health. 1998 Jun;52(6):377-84.

Pulmonary: Lung Cancer

- Systematic Review
- 19 studies; 4 experimental, 7 cohort, 6 case-control, 2 case-series
- Results
  - Increased exposure to tar compared to tobacco
  - Alveolar macrophages in marijuana smokers have less tumoricidal activity vs. non-smokers
  - Increased histopathological abnormalities in bronchial mucosa vs. non-smokers (additive with tobacco)
  - No clear association with a diagnosis of lung caner

Arch Intern Med. 2006; 166:1359-67.

Additional Safety Concerns

- Effects on brain development
  - Cognition
  - School performance
- Mental illness
  - Anxiety
  - Psychosis
- "Gateway" drug
- ↑risk of MI, stroke, TIA
- Sexual Health
- Drug interactions

Cochrane Databast Syst Rev 2008;3: CD004837
Hum Psychopharmacol Clin Exp 2009; 24:515-23
J Sex Med 2011;8:971-975.
J Addict Med 2011;5(1):1-8.

Summary

- Marijuana may have a role in some disease states
  - Quantity and quality of evidence varies by formulation and disease state
- Dosing is not "exact"
- Adverse effect profile may limit use
- More rigorous studies are needed

Which of the following indications have the most robust published evidence supporting the use of medical marijuana? (use ARS device)

A. Rheumatoid arthritis
B. Narcolepsy
C. IBD
D. Pain
E. All of the above

Which of the following is *not* a safety concern with the use of medical marijuana?

A. Impaired driving
B. Impaired sexual health
C. Precipitating psychosis
D. Cognitive impairment
E. All of the above are safety concerns

The risk for a fatal motor vehicle collision increases in a dose-related fashion in drivers who use marijuana.

A. True
B. False

On the pyramid of evidence, which of the following types of published literature ranks the highest?

A. Case report
B. Case-control study
C. Randomized, controlled trial
D. Meta-analysis
E. Cohort study

Thank you!

Polling Question
(use ARS device)

What is your stance on medical marijuana?

A. Pro
B. Con