Opioid Use and Medical Marijuana: A Review of the Data and an Approach to Underwriting

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Does Chronic Pain Itself Lead to Mortality?

- Studies have shown some mixed but generally negative results.
- One study showed a relative risk of 1.49 for all-cause and 1.68 for circulatory system mortality.
  - Problem - study was not fully adjusted for confounding factors.
- Other studies have shown associations with all-cause, circulatory and cancer mortality.
  - However, these relationships became non-significant when adjusted for comorbid conditions.
  - Especially smoking, physical activity, psychiatric and medical conditions.
- Bottom Line – chronic pain itself does not lead to a significant increase in all-cause or cause-specific mortality.
  - Applies to joint, regional and widespread pain (fibromyalgia) conditions.
Chronic Pain is Associated with Suicide Ideation and Attempts

- Chronic pain is associated with increased risk of suicidal ideation
  - Odds ratio 1.4 - 1.46 after controlled for comorbid conditions
  - Lifetime prevalence is about 20%

- Chronic pain is associated with and increased risk of suicide attempts
  - Odds ratio of 1.94 in one study
  - Lifetime risk 5%-14%

- Risk of completed suicide is at least doubled
  - Drug overdose is the most commonly reported plan for committing suicide
Risk Factors for Suicide with Chronic Pain

- Family history of suicide
- Previous suicide attempt
- Female sex
- Presence of comorbid depression
- Type of pain (migraine with aura, abdominal pain)
- High pain intensity
- Long duration of pain
- Presence of insomnia
- Helplessness and hopelessness about pain
Suicide Risk in Chronic Pain

Based on Interview and Clinical Inventory

- Passive Suicidal Ideation: 19%
- Active Suicidal Ideation: 13%
- Current Plan: 5%
- Previous Attempt: 5%

Smith MT, Pain, 2004; 101:201-208.
Most Deaths with Chronic Pain Occur Secondary to Accidental Drug Overdose

Most often with Opioid Medications
Clinical guidelines for the management of chronic pain changed in 1997
  • American Society of Anesthesiologists
  • American Academy of Pain Medicine

Both guidelines encouraged expanded use of opioid pain medication

Federation of State Medical Boards has also advocated adoption of model policies to promote more compassionate pain management

Result – per capita retail purchases of opioids has increased markedly

With it has come a marked increase in opioid associated overdoses and deaths
Increase in the Retail Purchases of Opioids – 1997-2007

Increase in Retail Purchases by Opioid

- Methadone: 13
- Oxycodone: 9
- Hydrocodone: 4

Relative Increase

Hall A, JAMA, 2008; 300:2613-2620
Accidental Drug Overdose

- Accidental death rates in the US were at their lowest level in 1992.
- Rates have steadily increased since then driven by increased drug overdose death rates.
- Death rates from drug poisoning passed those of motor vehicle accidents in 2009.
- Most drug overdoses are now due to prescription medications.
- Opioids and sedative/hypnotics, especially benzodiazepines, are the principle drivers of this trend.
- *If you are going to worry about MVA related mortality you should be worried about prescription medication overdoses.*
Accidental Drug Overdose

- 50%-80% of individuals with a prescription opioid overdose have a history of chronic pain
- Fatal overdoses are highest in middle age for both unintentional events and suicides
- Prescription drug overdose deaths are more likely in Caucasians
- Risk for prescription overdose is higher in small towns, suburban and rural areas
  - Illicit drug overdose is more common in urban areas
Opioid Concepts

► Tolerance
  • Exposure to a drug over time leads to diminution of its physiologic effects
  • Result is that higher doses are needed to produce the same effects over time

► Withdrawal
  • Physical dependence on the drug
  • Physical symptoms develop if the drug is reduced or withdrawn
  • Symptoms can be severe and include:
    - Diarrhea
    - Sweating
    - Fatigue
    - Anxiety/irritability
    - Shaking
    - Pain, cramps
    - Insomnia
Opioid Concepts

- Physical dependence does **NOT** mean addiction

- Addiction is characterized by the 4 C’s
  - Control – impaired re drug usage
  - Compulsive use
  - Continued use despite harm
  - Craving

- Pain relief versus addictive behavior
  - Individuals seeking pain relief focus on the pain
    - Willing to try other treatments
  - Addicts focus on the drug
Risk Factors for Dependence

- Younger age
- Male sex
- Smokers
- Unmarried status
- Past history of substance abuse
  - Includes history of non-opioid abuse
- History opioid abuse in past
  - Especially if the abuse was severe
- Family history of substance abuse
- Psychiatric disorder
- History of childhood sexual abuse
- Increased duration of use
Do Not Need to Be Dependent or Addicted to Misuse Opioids
Signs of Abuse

- Obtaining prescriptions from multiple physicians
  - “Doctor shopping”
- Obtaining prescriptions from multiple pharmacies
  - Even more concerning
- Filling prescriptions early
- Reluctance to use other means to control pain
- Bullying or abusing the medical staff
- Presence of a psychiatric condition
  - PTSD is especially problematic
Problem Use of Opioids in Individuals with PTSD

PTSD With or Without Another Mental Health Diagnosis

- Higher Dosage
- Longer Duration of Use
- Multiple Opioids
- Concurrent Sedatives
- Early Refills

Relative Risk

## Dependence Risk Builds as Number of Risk Factors Increases

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Only</td>
<td>2.33</td>
</tr>
<tr>
<td>Age + Severe Pain</td>
<td>3.59</td>
</tr>
<tr>
<td>Age + Severe Pain + Depression</td>
<td>4.63</td>
</tr>
<tr>
<td>Age + Severe Pain + Depression + Psych Meds</td>
<td>8.01</td>
</tr>
<tr>
<td>Age + Severe Pain + Depression + Psych Meds + History Severe Dependence</td>
<td>14.8</td>
</tr>
<tr>
<td>Age + Severe Pain + Depression + Psych Meds + History Severe Dependence + Prior Opioid Abuse</td>
<td>56.36</td>
</tr>
</tbody>
</table>

Opioid Dosage

- Different opioids have different potency
- Assessing the daily exposure may be difficult when different drugs are used
  - Especially if multiple drugs are used
- Solution – Morphine Equivalent
- Different drugs are compared with morphine as the standard measure
- Morphine is given the potency of 1
  - Heroin also has a relative potency of 1
- Other drugs are given a potency value relative to this standard
- The total daily dose of opioids can then be expressed as a morphine equivalent dose
# Morphine Equivalent Conversion Factors

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Morphine Eqiv Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Avinza, Kadian, MS Contin, Oramorph SR</td>
<td>1</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Darvon, Darvon-N, Darvocet, Balacet</td>
<td>0.23</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Ultram, Rybix, Ryzolt, Syapryn, Tramalgan</td>
<td>0.10</td>
</tr>
<tr>
<td>Codeine</td>
<td>Tylenol with codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxycontin, Oxyir, Percodan, Percocet, Roxicet, Tylox, Combunox</td>
<td>1.5</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Lortab, Maxidone, Norco, Vicodin, Xodol, Zydone, Ibudone</td>
<td>1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Dilaudid, Dilaudid HP</td>
<td>4</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Demerol</td>
<td>0.10</td>
</tr>
<tr>
<td>Fentanyl transmucosal</td>
<td>Fentora, Onsolis</td>
<td>0.13</td>
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<tr>
<td>Fentanyl transdermal</td>
<td>Duragesic</td>
<td>2.4</td>
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<tr>
<td>Oxymorphone</td>
<td>Opana, Opana ER</td>
<td>3</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>Levo-Dromoran</td>
<td>11.0</td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadose, Dolophine</td>
<td>3</td>
</tr>
</tbody>
</table>
There is No Universally Accepted Definition of “High Dose” by Morphine Equivalent Standards

Tolerance is an Issue

Differential Effects Depending on Duration of Treatment
Risk of Overdose and Death Increases with the Opioid Dosage
Risk of Overdose by Dosage

Hazard Ratio by Dosage in Morphine Equivalent Dose

Risk of Fatal Prescription Opioid Overdose by Dosage

Opioid Dosage in Morphine Equivalents

Bohnert AS, JAMA, 2011; 305:1315-1321.
Red Flags for Opioid Overdose Mortality

- Male sex
- Smoking
- Middle age
- Caucasian
- Presence of a psychiatric condition
  - Especially ADD, obsessive compulsive disorder, depression, PTSD
- Use of a sedative/hypnotic
  - Especially benzodiazepines
- Use of methadone
- Use of fentanyl
- Evidence to suggest alcohol abuse
  - Alcohol criticism
  - DWI, CDT, high HDL, clinical factors
Red Flags for Opioid Overdose Mortality

- Evidence of regular marijuana use
- More than one opioid prescription
- Obtaining prescriptions from multiple providers
- Obtaining prescriptions from multiple pharmacies
  - Prescription drug monitoring programs (PDMPs)
  - Adopted by 42 states
  - Some sharing of data by 20 states
- Period of change in regimen – tolerance comes in to play
  - New onset of use
  - Restarting after a period of abstinence
  - Changing from one opioid to another
    - Especially with methadone
Fatal Opioid Overdose by Age – New Mexico Study

Percentage of Deaths with Prescription Drug Overdose by Age

Positive Drug Tests in Pain Clinic Users

Percentage Positive in 10,922 Specimens from 31 Clinics in 6 States

- Amphetamine: 1.5%
- Cocaine: 2.8%
- Barbiturates: 2.8%
- Fentanyl: 4.2%
- Cannabinoids: 8.9%
- Methadone: 11.6%
- Benzodiazepines: 21.9%
- Opiates: 82.4%

% Positive
Risk of Overdose Death by Type of Opioid

Methadone
Fentanyl
Hydromorphone
Oxycodone

Odds Ratio

Medication Related Accidental Overdose Death

Hazard Ratios by Psychiatric Condition

- Schizophrenia
- Other Anxiety
- PTSD
- Other Depression
- Major Depression
- Opioid Use
- Stimulant Use
- Cannabis Abuse
- Alcohol Use

Methadone is Particularly Problematic in Terms of Overdose Death

Represents 4.5% - 18.5% of Opioids Distributed by State

Accounted for 39.4% of Single Drug Opioid Deaths
Methadone

**Advantages for pain relief**
- Long duration of action
- Relatively low cost
- Availability in a liquid formulation

**Disadvantages/risks**
- Increased potency
  - Morphine equivalent factor of 3
- Long and unpredictable half-life
  - Associated with accumulation and respiratory depression
  - Cannot be used like other opioids
- Most patients and non-specialist physicians are unfamiliar with its idiosyncrasies
- Multiple interactions with other drugs, especially benzodiazepines
- Ability to cause cardiac rhythm disturbances
Methadone – Red Flags

- Never used for acute pain, breakthrough pain or on an “as needed” basis
- Not a drug of first choice
- Should never be used in someone naïve to opioids
- Special caution if an applicant is starting or being switched to methadone
- Combination of methadone and benzodiazepines is especially high risk
  - Potential for severe respiratory depression
Good Case Factors

- Low dose of opioids
- Followed by pain specialist
- Stable dosage over time
- No evidence to suggest drug seeking behavior
- Willing to use alternative means of controlling pain
- No significant psychiatric comorbidity
- No use of benzodiazepines
- Functional at home and work
- Good compliance with therapy
- Regular follow-up
Final Pearl – 2/3 of Patients Saw a Physician in the Month Before Overdose Death
Medical Marijuana
Marijuana

- Derived from plant *Cannabis sativa*
  - Marijuana is derived from the crushed leaves, flowers and stems of the plant
  - Hashish is its concentrated resin

- Contains more than 460 active chemicals and 60 different cannabinoids

- Two major active ingredients
  - **Delta-9-tetrahydocannabinol (THC)**
    - Psychoactive ingredient
    - Varies in potency with derivative of cannabis plant
    - Average THC content has increased over time with cultivation
      - 2% - 1980, 4.5% - 1997, 8.55% - 2006
  - **Cannabidiol**
    - More peripheral effects
    - May counteract some of the THC psychoactive effects
Marijuana - Historical Aspects

- First used medically in Central Asia and China
- Documented use 5000 years ago
- 1830’s - Irish physician – WB O’Shaughnessy wrote a paper advocating its use
  - Indications – pain, vomiting, convulsions, spasticity (similar to current recommendations)
- 1854 – listed in US Dispensary
- 1937 – Marijuana Tax Act – essentially eliminated its use from medical practice
- 1942 – removed from the US Dispensary
- 1970 – US Congress itself declared marijuana to have no medical value
  - Bypassed the usual review process in the Controlled Substances Act
  - Designated a Schedule 1 drug – no medical use, high abuse potential
    - Others in class – heroin, quaaludes, LSD
- 1999 Institute of Medicine review of literature declared some potential benefit
  - Appetite stimulant, treatment of nausea and vomiting, severe pain, spasticity
Marijuana - Historical Aspects

- 1996 - California became first state to permit medical use of marijuana
- Now 21 states and District of Columbia have laws permitting use of medical marijuana (as of 4/17/14)
- Laws vary in structure
  - Most establish a patient registry
  - Some but not all allow dispensaries
  - Many laws are vague in what conditions it can be used to treat
  - May not require an established relationship with a physician – just a prescription
- 12 states have pending legislation (as of April 16, 2014)
- Colorado and Washington legalized recreational use of marijuana as of elections in November 2012
- Problem – marijuana is still a Schedule 1 drug under Federal Law
Department of Justice to take a “trust but verify” approach to new state laws
May not impinge on state laws in some cases
Federal government reserves the right to enforce the schedule 1 status if states don’t carefully regulate threats to public safety
Key priorities will drive federal enforcement policy
Key Priorities for Federal Enforcement

➤ Distribution of marijuana to minors
➤ Revenue from sales going to criminal enterprises, gangs or cartels
➤ Diversion of marijuana to states where it is illegal
➤ Use of state authorized marijuana sales to traffic in other drugs
➤ Violence and use of firearms in the cultivation or distribution of marijuana
➤ Drugged driving or adverse other public health consequences of marijuana use
➤ Growing of marijuana on public lands
➤ Prevention of marijuana possession or use on federal property
Schedule 1 Status Under Federal Law Makes Study of the Medical Uses of Marijuana Very Difficult

Only Federally Authorized Source of Cannabis for Medical Study is a Strain Grown at the University of Mississippi

Only Through an Application to the National Institute of Drug Abuse
Endocannabinoid System – 2 Different Receptors

- Moderator system
  - Regulates neurotransmitter release at the level of the synapse
  - Functions in parallel and conjunction with the adrenergic, cholinergic and dopaminergic systems
  - Effects in the central and autonomic nervous systems

- CB1 receptors
  - Psychoactive effects
  - Located primarily in CNS and gut

- CB2 receptors
  - Located only in periphery
  - Associated with neuroinflammation and pain, host defense, digestion
CB1 Receptors – Primary Binding Site for THC

- Concentrate in specific areas of CNS
- Those associated with pleasure, movement, learning memory and pain
- Mesolimbic system - reinforce pleasurable activities
- Cerebellum and basal ganglia - affect motor tone and coordinated movement
- Hippocampus – modulate mood
- Hippocampus, prefrontal cortex – concentration, short-term memory, attention and tracking behavior
- Hypothalamus – vegetative functions
- Food intake receptors – appetite ("munchies")
- Spinal cord – pain pathways, analgesia
- Central reward center – can lead to addiction
- Near absence in the brainstem – negates severity of overdose effects
A Lethal Human Overdose from Marijuana has *Never* Been Reported
CB2 Receptors

- Not found in the CNS
- Located only in peripheral cells
  - Neurons
  - Immune cells
- Activation leads to multiple actions
  - Immunosuppression
  - Anti-inflammatory effects
  - Reduced pain sensation
Marijuana is Fat Soluble
Concentrates in Adipose Tissue
Marijuana Testing

► Urine testing
  • Most commonly used format
  • Tests for metabolites
  • Duration when test can be positive varies depending on cutoff level used, amount of drug absorbed and frequency of use
    - Usually 1-3 days for acute use
    - Up to a month or more for chronic users
    - Due to fat solubility of the drug

► Blood testing and oral fluid
  • Tests for both parent drug and metabolites (blood) or metabolites (oral fluid)
  • Usually only for a few hours after use
  • Up to 1-2 days for heavy users

► Hair
  • Tests for metabolites
  • Can be positive up to 90 days
Pharmacology

- THC is rapidly absorbed when smoked
  - Peak serum concentrations in 10-20 minutes
  - Peak clinical effects in 30 minutes
  - Heavy users absorb it more efficiently

- Oral use produces similar physical effects
  - But – absorbed more slowly and erratically
  - Peak concentrations in 1-3 hours
  - Levels are lower than with smoking

- Because of the more rapid onset and easier titration of effects most medical users prefer using the drug via smoking
Toxicology

- **Tolerance may develop** with chronic use
  - Need increasing doses to produce comparable effects

- **Cannabis withdrawal syndrome exists**
  - Anxiety, irritability, depressed mood, restlessness
  - Disturbed sleep
  - GI symptoms
  - Decreased appetite
  - Symptoms begin first week of abstinence, last several weeks
  - Overall milder than withdrawal from other drugs
    - Likely due to slow leaching of drug from fat stores

- **Overall lifetime risk of marijuana dependence is 9%**
  - Characterized by the 4 C’s – similar to other drugs
  - No risk of new onset dependence after age 25
Lifetime Risk for Dependence

Percentage Risk for Dependence by Substance

Adverse Effects – Lung Cancer

- Association with lung cancer in some studies but not all
- 50-70% more carcinogens than tobacco
  - 1/3 more tar retention in lungs than tobacco smoke
- Smoke is more deeply inhaled and held in lungs longer
- In one study lifetime cannabis use (< 20 joints was not associated with lung cancer)
- However, heavy use (> 10.5 joint-years of exposure) – had RR of 5.7
- 1 joint per day is roughly equivalent to 1 pack of cigarettes per day in terms of lung cancer risk
- Another study followed Swedish conscripts for 40 years
- Users > 50 times at age 18-20 had a HR of 2.12 compared to never users
- Roughly equivalent to ½ pack of cigarettes per day
- HR of 11-50 times = 1.68
Adverse Events – Lung Disease

- Smoking marijuana increases blood carboxyhemoglobin level – 5 fold
- Short term, acute use may lead to bronchodilation
  - Used for asthma in the past
- Associated with an increased frequency of bronchitis
  - Inflammation in the airways
- Emphysema risk is not increased
- 1 pack/day of cigarettes is roughly equivalent to 7.9 marijuana joints/day in terms of lung effects in one study
Adverse Events - Psychiatric

- Odds ratio for psychosis – 2.1-2.3
- Increases the risk of schizophrenia and possibly bipolar disorder and depression
- Appears to unmask risk in predisposed individuals
- Risk is dose dependent
- Risk appears to flow both ways
  - Marijuana users have worse psychosis
  - Psychotic individuals are more likely to use marijuana
Risk of Psychosis with Marijuana Usage

Odds Ratio by Amount of Usage

Risk is Particularly High in Adolescence

- Puberty is characterized by cerebral reorganization
  - Especially the frontal lobes
- Developing brain is vulnerable to the effects of cannabinoids
- Increases the risk of schizophrenia
- Persistent adverse effects in daily and weekly users
  - Memory deficits
  - Reduced attention
  - Reduced processing speed
  - Abnormal social behavior
  - Susceptibility to anxiety and depression disorders
  - Marijuana dependence
  - Greater risk of other drug dependence
Adverse Events – Cardiovascular and Bone

► Associated with multiple physiologic effects
  • Sinus tachycardia
  • Vasodilation
  • Hypertension
  • Arrhythmias

► Associated with acute MI
► Associated with infarctions in other organs
► Isolated reports of cerebral vasospasm and arteritis
► Associated with significant bone loss and osteoporosis
Effect on Driving is Mixed

- Some studies show an impairment of driving skills in a dose related fashion
  - Highly variable between individuals – may be due to tolerance in heavy users
- Effect on accident rate is mixed in various studies
  - Problem – urine drug screens may not reflect acute intoxication
- Recent study showed a significant association of marijuana use with motor vehicle crashes
- Combination of marijuana with alcohol or opioids is particularly bad
  - Risk is higher than with either of the combination alone
Association of Marijuana with Motor Vehicle Crashes

Odds Ratio for Increased Crash Risk by Study and Indicator of Use

Probability of Responsibility for a Motor Vehicle Accident

Responsibility by Substance

Index of Responsibility

In General, Marijuana Use is Associated with a Higher Probability of Risk Taking Behavior
Marijuana is **NOT** the First Choice Drug for **ANY** Medical Condition

Research is Limited Due to Schedule 1 Status
Medical Uses of Marijuana – 5 Major Conditions

- Severe nausea and vomiting
  - Cancer chemotherapy and other conditions

- Weight loss and cachexia
  - Cancer, HIV disease, other conditions

- Spasticity associated with neurologic disease
  - Multiple sclerosis, Parkinson’s disease, spinal cord injuries

- Pain syndromes
  - Neuropathic pain, migraines, musculoskeletal disorders

- Glaucoma
Issues with Medical Marijuana

► Many laws are vague re what conditions are appropriately treated with marijuana
► Many states only require a prescription
  • No ongoing relationship with a physician
  • De facto legalization
► Most users smoke the “medication”
  • Only 2 oral meds are available for use for nausea and vomiting
    – Dronabinol
    – Nabilone
► Users prefer plant derived marijuana as onset earlier, easier to titrate
  • Only medication available in which the specific dose cannot be measured
  • No standardization of purity
► Novice users find the psychoactive effects of THC difficult to tolerate
Issues with Medical Marijuana

- Most current users of medical marijuana were previous heavy, regular recreational users.
- Example – study from California on applicants for use of medical marijuana:
  - 90% had tried the drug before age 20
  - 90% had admitted daily or near daily use prior to application
  - 85% had tried other illegal drugs
- Four fold increase in the use of cocaine and methamphetamine in pain patients using marijuana.
Percentage Trying Illegal Drugs Among Medical Marijuana Applicants

Percentage by Drug Males and Females

- **Heroin**
  - Females: 10%
  - Males: 20%

- **PCP**
  - Females: 30%
  - Males: 40%

- **Methamphetamine**
  - Females: 45%
  - Males: 55%

- **Cocaine**
  - Females: 65%
  - Males: 75%

- **LSD**
  - Females: 50%
  - Males: 60%

Marijuana and Opioid Use

- Marijuana users are more likely to abuse or misuse opioids
- More likely to use other illicit drugs
- More likely to be involved with diversion of opioids
- Clearly has significant adverse effects on driving
  - Considered an absolute contraindication to operating a motor vehicle
- Marijuana abuse disorder with use of opioids increases the risk of overdose mortality
Medication Related Accidental Overdose Death

Hazard Ratios by Psychiatric Condition

- Schizophrenia
- Other Anxiety
- PTSD
- Other Depression
- Major Depression
- Opioid Use
- Stimulant Use
- Cannabis Abuse
- Alcohol Use

Hazard Ratio

Summary Medical Marijuana

- Most medical marijuana patients are heavy, regular cannabis users.
- Most medical marijuana patients smoke the drug.
- Due to the lung function, lung cancer and vascular effects of inhaled marijuana, the baseline risk of regular users is closer to that of tobacco smokers than non-smokers.
- Use in adolescence is problematic:
  - Effect on the developing brain with long-term cognitive effects.
  - Increased probability of abuse/dependence.
  - Associated with a greater probability of psychiatric illness.
  - More likely to have adverse outcomes.
  - More likely to misuse or abuse licit and illicit drugs.
The Mortality Associated with Medical Marijuana is Not From the Drug Itself but the Company It Keeps

Medical Conditions that are Being Treated

Social and Behavioral Aspects Associated with Chronic Heavy Use
Underwriting Medical Marijuana

- Most medical conditions for which it is used are largely high risk conditions
  - Exceptions – pain and glaucoma

- Ideally under regular care and supervision of a physician
  - If not – more like recreational use

- No indication or suspicion of misuse or abuse, history of withdrawal symptoms

- Use in individuals under age 18 is very high risk

- Caution in individuals with any significant psychiatric illness, now or in past

- Beware evidence of alcohol or other substance abuse currently or in the past

- Current regular use of opioids is a red flag
  - Especially if any opioid risk factors are present

- Be alert to any significant driving criticism
  - Especially with a history of a DWI or concurrent use of opioids

- High risk with certain medical conditions
  - COPD, CAD, poorly controlled asthma, history of tobacco related cancers