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Update on Benzodiazepines and Medical Marijuana

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Disclosures

Scott Hambleton, MD:

No conflicts of interest to report
Objectives

• To examine indications for the proper use of benzodiazepines
• To examine indications for discontinuation of therapy and tapering strategies
• To examine evidence for utilization of marijuana for medicinal purposes
Sedative-Hypnotics

- Suppress CNS activity
- Cause effects along a continuum of: calming > sleep > unconsciousness > coma > death
- Used as:
  - Anxiolytics
  - Hypnotics
  - Anti-convulsants
  - Muscle relaxants
  - Anesthesia induction

(Ries, 2014)
GABA

• GABA (Gamma-aminobutyric acid) is the major inhibitory neurotransmitter in the CNS.
• Binds to the GABA Receptors in Neurons in various locations of the brain
• Most sedative hypnotics act on the GABA system. (Roth et al., 2003)
• GABA System extensively studied in the circuit of fear. (Möhler, 2012)
GABA Receptor

• Penatmeric, transmembrane glycoprotein complex with a central ligand gated chloride ion channel.
• Benzodiazepines bind to alpha subunits of the GABA receptor
  • Potentiates effects of GABA by positive modulation of the GABA receptor.
  • Produces antianxiety effects, sedation, amnesia, muscle relaxation, etc.

(Roth et al., 2003)
Benzodiazepines & Respiratory Depression

- Benzodiazepines increase frequency of channel openings induced by GABA.
- Fatal overdose is very rare.
  - (Roth et al., 2003)
Barbiturates, Alcohol & Respiratory Depression

- **Barbiturates and high dose alcohol** (>250mg/dl) cause prolonged opening of the chloride ion channel.
- **Causes fatal overdose** by lethal respiratory depression.
- (Roth et al., 2003)
Benzodiazepine Tolerance

- Tolerance to the **sedative/depressant effects** of benzodiazepines is rapid: days to weeks
- Tolerance to the **anxiolytic/anti-convulsant effects** develops slowly and to a limited extent (weeks to months)
- Tolerance to **amnestic and cognitive impairing effects** do not develop even after years of use
- Deficits in chronic users of memory, attention and visuospatial ability (especially in drinkers/elderly)

(Ries, 2014)
Opioids & Respiratory Depression

• Tolerance to respiratory depression may be slower than tolerance to euphoric and other effects

• Opioids bind receptors in brain stem which inhibit respiratory rhythm generation as well as lowering tidal volume and causing irregular and periodic breathing.
  
  (Bouillon et al., 2003)

• Methadone: lethal respiratory depressive effects can occur in doses as low as 30 mg in non-tolerant persons.
  
  (Ehret et al., 2007)
Benzodiazepines and Overdose

• Michael Jackson: 1958-2009

• Treated for *insomnia*
  by a cardiologist with...

...injections of propofol, lorazepam and midazolam with oral diazepam.
BZ Addiction = BZ Use Disorder

- Primary/Sole BZ addiction is relatively uncommon
  (Ries, 2014)
Benzodiazepines: Two Patterns of Misuse

Two patterns of abuse:

1) Recreational misuse: nonmedical use for purpose of getting high
   a. Intermittent pattern of high doses
   b. Polysubstance users
   c. Often illicitly obtained
   d. Similar to rates of abuse of other illicit substances

2) Chronic quasi-therapeutic use: long term use for a duration inconsistent with accepted medical practice
   a. Older
   b. May or may not have history of alcohol or substance abuse
   c. Chronic pain problems

(Ries, 2014)
Recreational Misusers

- Usually in conjunction with misuse of other substances
  - To either augment the effects of or ameliorate the side effects of or withdrawal from
    - Alcohol
    - Opiates- ‘boost’ the opiate
    - Cocaine/amphetamines- to counter the stimulant/help sleep or ‘come down’

(Ries, 2014)
Benzodiazepines & Polysubstance Misuse

• It is estimated that 80 percent of benzodiazepine misuse occurs within a pattern of polysubstance use, with the highest correlation occurring with concurrent addiction to opioids and alcohol.

  (Longo et al., 2000)

• This should be a major concern for a provider considering initiation of benzodiazepine therapy
Benzodiazepines & Relationship to Future Opioid Use

- Cohort of more than 17,000 men and women followed for 4 to 7 years: benzodiazepine use contributes to later opioid use among subjects who had reported no opioid use to start.
- Benzodiazepine users were more than seven times as likely to have at least 12 prescriptions for opioids than non-benzodiazepine users during the follow-up period.
- 733 million emergency department visits in the same time period and found 32.4% of patients had benzodiazepine or opioid prescriptions.

(Surveit S., et al., 2014)
Figure 1. National Drug Overdose Deaths
Number Among All Ages, by Gender, 1999-2017

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018
Figure 8. National Drug Overdose Deaths Involving Benzodiazepines, by Opioid Involvement, Number Among All Ages, 1999-2017

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018
Controlled Substance Use: MS

- Opioids
  - 2018 – 2.8 million prescriptions
  - 2017 – 3.3 million prescriptions
- Benzos
  - 2018 – 1.2 million prescriptions
  - 2017 – 1.4 million prescriptions

[https://pmp.mbp.ms.gov/statistics/#stat-2](https://pmp.mbp.ms.gov/statistics/#stat-2)

(Stephanie Mueller, Director, MS PMP)
Benzodiazepine Use in 2008 By Age & Sex

(Olson, 2015)
Adverse Benzodiazepine Effects: Acute

- Excessive sedation, fatigue, psychomotor impairment, hypotonia, ataxia with falls (especially elderly)
- Memory and other cognitive impairment
- Autonomic effects - dry mouth, blurred vision, urinary retention, excessive sweating
- Altered sleep physiology
- Dysarthria
- Confusion
- Nausea, vomiting, constipation
- Paradoxical excitement/ anxiety/ hostility
  (Ries, 2014)
Adverse Benzodiazepine Effects: Chronic

Increased rates of:
1) Accidents, falls (hip fractures etc.)
2) Motor vehicle accidents
3) General decline in functional status
4) Cognitive decline/memory impairment
5) Self poisoning
6) Withdrawal
7) Dependence

(Ries, 2014)
Anxiety Disorders: Prevalence

Lifeetime Prevalence of Anxiety Disorders: 33.7% (Bandelow, 2015)

(Graph: Sadock BJ, et al., 2009)
Anxiety Disorders: Treatment

**Pharmacologic:**
- Selective serotonin reuptake inhibitors (SSRIs)
- Tricyclic antidepressants (TCAs)
- Benzodiazepines
- Monamine oxidase inhibitors (MAOIs)
- Other drugs

**Psychological:**
- Supportive and insight-oriented psychotherapy
- Cognitive behavior therapy
- Group therapy
- Residential treatment

(Ries, 2014)
<table>
<thead>
<tr>
<th>Antianxiety Drug</th>
<th>Starting dosage (mg per day)*</th>
<th>Usual dosage (mg per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective serotonin reuptake inhibitors (SSRIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine(Paxil)</td>
<td>5-10</td>
<td>20-60</td>
</tr>
<tr>
<td>Fluoxetine(Prozac)</td>
<td>5-10</td>
<td>20-60</td>
</tr>
<tr>
<td>Sertraline(Zoloft)</td>
<td>12.5-25</td>
<td>50-200</td>
</tr>
<tr>
<td>Citalopram(Celexa)</td>
<td>10</td>
<td>20-40</td>
</tr>
<tr>
<td>Escitalopram(Lexapro)</td>
<td>5</td>
<td>10-30</td>
</tr>
<tr>
<td><strong>Tricylic antidepressants (TCAs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomipramine(Anafranil)</td>
<td>5-12.5</td>
<td>50-125</td>
</tr>
<tr>
<td>Imipramine(Tofranil)</td>
<td>10-25</td>
<td>150-500</td>
</tr>
<tr>
<td>Desipramine(Norpramin)</td>
<td>10-25</td>
<td>150-200</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam(Xanax)</td>
<td>0.25-0.5 TID</td>
<td>0.5-2 TID</td>
</tr>
<tr>
<td>Clonazepam(Klonopin)</td>
<td>0.25-0.5 BID</td>
<td>0.5-2 BID</td>
</tr>
<tr>
<td>Diazepam(Valium)</td>
<td>5-10 BID</td>
<td>5-30 BID</td>
</tr>
<tr>
<td>Lorazepam(Ativan)</td>
<td>0.25-0.5 BID</td>
<td>0.5-2mg BID</td>
</tr>
<tr>
<td>Chlordiazepoxide(Librium)</td>
<td>5-10 BID</td>
<td>25-50 BID</td>
</tr>
<tr>
<td><strong>Monoamine Oxidase Inhibitors (MAOIs)</strong></td>
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<tr>
<td>Phenelzine(Nardil)</td>
<td>15 BID</td>
<td>15-45 BID</td>
</tr>
<tr>
<td>Tranylcypromine(Parnate)</td>
<td>10 BID</td>
<td>10-30 BID</td>
</tr>
<tr>
<td><strong>Serotonin-norepinephrine reuptake inhibitors (SNRIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine(Effexor)</td>
<td>6.25-25</td>
<td>50-150</td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic Acid(Depakote)</td>
<td>125 BID</td>
<td>500-750 BID</td>
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<tr>
<td>Gabapentin(Neurotin)</td>
<td>100-200</td>
<td>600-3400</td>
</tr>
<tr>
<td>Buspirone(Buspar)</td>
<td>5-15 BID or TID</td>
<td>15-30 BID</td>
</tr>
<tr>
<td>Hydroxyzine(Vistaril, Atarax)</td>
<td>12.5-50 BID</td>
<td>50-100 QD</td>
</tr>
<tr>
<td>Propranolol(Atenolol)</td>
<td>10-20 TID</td>
<td>10-40 TID</td>
</tr>
</tbody>
</table>

**SSRIs: Start low, go slow and aim high!**
Anxiety and CBT

• The majority of anxiety disorders are optimally treated with cognitive behavioral therapies (CBT)

• CBT and other psychological therapies are evidence based, effective interventions with a sustained impact on anxiety disorders.

• There is a considerable overlap in the symptoms of the major anxiety disorders

• Effective treatments for one often address the other

• Developing simple referral pathways with psychologists, primary care providers can begin to offer alternatives to benzodiazepines.

  (Ries, 2014)
Short Term Indications for Benzodiazepines: 7 - 28 days

- Initial management of panic and agoraphobia
- Alcohol and other drug withdrawal
- Muscle relaxation
- Seizure prophylaxis
- Grief reactions
- NOT for PTSD/trauma (increased risk of abuse)

(Ries, 2014)
Appropriate Use of BZs: Limited

- Benzodiazepines (BZs) are useful for the treatment of anxiety and sleep disorders, but their use is limited by undesirable side effects such as daytime drowsiness, loss of coordination, and liability for addiction.

  (Licata and Rowlett, 2008)
Benzo use and APA Guidelines

“Benzodiazepines and other sedative-hypnotics carry the potential for abuse or dependence and should rarely be prescribed to patients with co-occurring substance use disorders, except as part of a brief detoxification regimen.”

(Gelenberg, et al. APA Practice Guidelines, 2010)
Appropriate Use of BZ

- GAD and panic D/O: SSRI, CBT, self-help
- GAD: limit BZ to 2-4 weeks
- BZ short term only (poor long term outcome)
- Anxiety and Depression: SSRI/SNRI
  (Guebaly et al., 2010)
Chronic BZ Use: Impairment

• “long-term benzodiazepine users were significantly impaired, compared with controls, in all of the areas that were assessed.”
• Meta analysis 13 studies
  (Barker, et al., 2004)
Strategies for Safer Use of Benzodiazepines

- Tell pt in advance will be short term (1-3 months)
- To cover the start of an SSRI
- Start another agent- tell the patient that you are giving BZ short-term while the other meds start to work
- Use longer acting benzodiazepines like clonazepam (klonopin©): less reinforcing
- Prescribe no more than month’s supply; Recheck monthly
- Maximize the other agents/modalities

(Ries, 2014)
### TABLE 1. Pharmacokinetic Properties of Benzodiazepines

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Dosage Equivalent (mg)</th>
<th>Onset of Action</th>
<th>Relative Lipophilicity</th>
<th>Active Substance</th>
<th>Elimination Half-life (hours)</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam (Klonopin®)</td>
<td>0.25 mg</td>
<td>Intermediate</td>
<td>( {\text{+}}^{1/2} )</td>
<td>Clonazepam</td>
<td>18-50</td>
<td>Oxidation, Nitrodeuction</td>
</tr>
<tr>
<td>Alprazolam (Xanax®)</td>
<td>0.5 mg</td>
<td>Intermediate</td>
<td>+++</td>
<td>Alprazolam</td>
<td>6-20</td>
<td>Oxidation</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Alphabutyroxyalprozolam</td>
<td>6-10</td>
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</tr>
<tr>
<td>Triazolam (Halcion®)</td>
<td>0.5 mg</td>
<td>Fast ,</td>
<td>+++</td>
<td>Triazolam</td>
<td>1.7-3.0</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Lorazepam (Ativan®)</td>
<td>1.0 mg</td>
<td>Intermediate</td>
<td>++</td>
<td>Lorazepam</td>
<td>10-20</td>
<td>Conjugation</td>
</tr>
<tr>
<td>Estazolam (ProSom®)</td>
<td>2.0 mg</td>
<td>Intermediate</td>
<td>0</td>
<td>Estazolam</td>
<td>8-24</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Diazepam (Valium® and others)</td>
<td>5.0 mg</td>
<td>Fast</td>
<td>++++</td>
<td>Diazepam</td>
<td>30-100</td>
<td>Oxidation</td>
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<td>Desmethyldiazepam</td>
<td>30-200</td>
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<td>Oxazepam</td>
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<td>Desmethyldiazepam</td>
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<td>Oxazepam</td>
<td>30-200</td>
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<td>Oxazepam</td>
<td>30-200</td>
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<td>Oxazepam</td>
<td>30-200</td>
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<td></td>
<td></td>
<td>Oxazepam</td>
<td>30-200</td>
<td></td>
</tr>
<tr>
<td>Chloralhydrate (Librium®</td>
<td>10.0 mg</td>
<td>Intermediate</td>
<td>++</td>
<td>Chloralhydrate</td>
<td>5-100</td>
<td>Oxidation</td>
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<tr>
<td>and others)</td>
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<td></td>
<td></td>
<td>Desmethylchloralhydrate</td>
<td>18</td>
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<td></td>
<td></td>
<td>DesmethylchloralhydrateDiazepam</td>
<td>14-95</td>
<td>Oxidation</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>DesmethylchloralhydrateDiazepam</td>
<td>30-200</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>DesmethylchloralhydrateDiazepam</td>
<td>30-200</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DesmethylchloralhydrateDiazepam</td>
<td>30-200</td>
<td></td>
</tr>
<tr>
<td>Oxazepam (Serax®)</td>
<td>15.0 mg</td>
<td>Slow</td>
<td>++</td>
<td>Oxazepam</td>
<td>3-21</td>
<td>Conjugation</td>
</tr>
<tr>
<td>Flurazepam (Dalmane®)</td>
<td>30.0 mg</td>
<td>Fast</td>
<td></td>
<td>Flurazepam</td>
<td>0.5-3.5</td>
<td>Oxidation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hydroxyethylflurazepam</td>
<td>1-4</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Desalkylflurazepam</td>
<td>0.5-3.5</td>
<td>Oxidation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Desalkylflurazepam</td>
<td>1-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Desalkylflurazepam</td>
<td>0.5-3.5</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Temazepam (Restoril®)</td>
<td>30.0 mg</td>
<td>Slow</td>
<td>+++</td>
<td>Temazepam</td>
<td>10-12</td>
<td>Conjugation</td>
</tr>
<tr>
<td>Quazepam (Doral®)</td>
<td>30.0 mg</td>
<td>Fast</td>
<td>++++</td>
<td>Quazepam</td>
<td>20-120</td>
<td>Oxidation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oxoquazepam</td>
<td>20-120</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Desalkylflurazepam</td>
<td>20-120</td>
<td></td>
</tr>
<tr>
<td>Buspirone (BuSpur®)</td>
<td>15.0-30.0 mg (usual dose)</td>
<td>Rapid peak; very slow onset (&gt;7 da)</td>
<td>1-Pyrimidinylpiperazine</td>
<td>2-11</td>
<td>Oxidation</td>
<td></td>
</tr>
<tr>
<td>Zolpidem (Ambien®)</td>
<td>10.0 mg</td>
<td>Rapid</td>
<td></td>
<td>Zolpidem</td>
<td>2.5KE120</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Zaleplon (Sonata®)</td>
<td>10.0 mg</td>
<td>Rapid</td>
<td></td>
<td>Zaleplon</td>
<td>1</td>
<td>Oxidation</td>
</tr>
</tbody>
</table>
Benzodiazepines - Potency

<table>
<thead>
<tr>
<th>drug</th>
<th>comparative dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>diazepam</td>
<td>5mg</td>
</tr>
<tr>
<td>alprazolam</td>
<td>0.5mg</td>
</tr>
<tr>
<td>clonazepam</td>
<td>0.25mg</td>
</tr>
<tr>
<td>lorazepam</td>
<td>1mg</td>
</tr>
<tr>
<td>chlordiazepoxide</td>
<td>25mg</td>
</tr>
<tr>
<td>temazepam</td>
<td>10mg</td>
</tr>
<tr>
<td>estazolam</td>
<td>1mg</td>
</tr>
<tr>
<td>triazolam</td>
<td>0.25mg</td>
</tr>
</tbody>
</table>

- 2mg klonopin equivalent to what dose of valium?
- 40mg!!!

(Adapted from Ries, 2014)
Warning Signs for High Risk Patients

- History of substance misuse
- Concurrent polysubstance misuse
- Illicitly obtained benzodiazepines
- Inaccurate patient report about amount of BZ consumed
- Unsuccessful attempts to decrease or discontinue use
- Chronic opiate use

(Ries, 2014)
Sedative, Hypnotic, or Anxiolytic Withdrawal

- Two (or more) of the following, developing within several hours to days after the cessation of (or reduction in) anxiolytic use...

(DSM 5)
Sedative, Hypnotic, or Anxiolytic Withdrawal, cont’d.

1) Autonomic hyperactivity (sweating or pulse >100)
2) Hand tremor.
3) Insomnia.
4) Nausea or vomiting.
5) Transient visual, tactile, or auditory hallucinations or illusions.
6) Psychomotor agitation.
7) Anxiety.
8) Grand mal seizures.

(DSM 5)
Predictors of Inability to Discontinue and Withdrawal Severity

• **Pharmacologic Variables:**
  1) Higher daily dose
  2) Short half-life
  3) Chronic use
  4) Rapid taper

• **Patient Variables:**
  1) Diagnosis of Panic Disorder but not GAD
  2) Higher pre-taper levels of anxiety and depression
  3) Co-occurring substance use disorder
  4) Personality disorders (traits)

(Ries, 2014)
Long term use of Benzodiazepines

• Long term use is ≥ 8-12 months
• 90% experience withdrawal symptoms, whether withdrawn slowly or rapidly
• Gradual taper off alprazolam after long-term treatment of panic disorder results in rebound panic and anxiety, exceeding pretreatment levels in 50-90% of patients.

(Saddock et al., 2009)
4 Week Taper: Is this reasonable?

- Post Acute Withdrawal Syndrome (PAWS) can last 18-24 months
- Repair of GABA receptor will usually not occur in 4 weeks
  - Prolonged risk of seizures
  - Ineffective in 32-42% of chronic users
  - 4 week taper will often result in intolerable side effects

- Long term BX users are most difficult to treat (compared to other substances)- Author’s opinion
BZ Tapering Strategies

- Ashton Manual: convert to Valium, then taper
- Dry tapering
- Tapering Strips
- Micro-tapering
- BEST STRATEGY (Author’s opinion):
  - Benzodiazepine Information Coalition:
    - Maximum 5-10% of current dose every 2-4 weeks
    - Typically 10 months
BZ Tapering: Additional Strategies:

- Weekly visits for assessment, support, and to provide prescription
- Consider carbamazepine, imipramine, phenobarbital, trazodone, or medically directed detox as inpatient
- Cognitive behavior therapy: aids discontinuation and prevents relapse to panic disorder
  
  (Ries, 2014)
Other Treatments for Insomnia

- Treat Underlying Conditions
  - Anxiety/Depression
  - Obstructive Sleep Apnea
  - GERD
  - CHF/COPD

- Sleep Hygiene

- Meds
  - Mirtazapine (Remeron®)
  - Trazodone
  - TCAs: Amitriptyline (Elavil®)
  - Hydroxyzine (Vistaril®/diphenhydramine (Benadryl®)
  - Melatonin
  - Ramelteon (Rozerem®)

(Ries, 2014)
References


References


References

References


• Substance Abuse and Mental Health Services(SAMHSA), 2011 National Survey on Drug Use and Health(NSDUH).


References


Medical Marijuana

Scott Hambleton, MD, DFASAM
Medical Director, Mississippi Physician Health Program
Cannabinoids

- Diverse chemical compounds that bind cannabinoid receptors ($\text{CB}_1$ and $\text{CB}_2$) and inhibit GABA release
  - Endogenous cannabinoids:
    - Anandamide (AEA)
    - 2-AG
  - Phytocannabinoids (over 100 found in cannabis):
    - $\Delta^9$-THC
    - Cannabidiol
    - THC: Cannabidiol in most plants is 20:1
  - Synthetic cannabinoids (Spice, K2, Moon Rocks)
Marijuana Potency

- Potency (THC content)
  - 1985: 3.48%
  - 2012: 13.19%

  (Univ Miss, Potency Monitoring Program Quarterly Report #120, March 26, 2013)

- Average potency 2014: ≈ 15%

  (NIDA, Jan 2014)
Localization of THC binding sites (CB$_1$ Receptors)

THC binds CB$_1$ receptors in VTA causes DA release by NA
Cannabis Use Disorder

- Cannabis dependence: 9-10% lifetime risk
  - 17% with initiation during adolescence
- Colorado: 18 to 25 age past year cannabis use increased significantly after “medical” cannabis legalization (35 percent in 2007 to 2008 to 43 percent in 2010 to 2011)
Potential Clinical Uses

- Refractory emesis
- Appetite Stimulation for Cachexia
- Movement Disorders
- Anticonvulsant Effect (Dravet Syndrome: Severe Myoclonic Epilepsy of Infancy)
- Analgesia
Knowledge Gap

• Cannabis is Schedule I:
  • limited research opportunities for prospective RCTs; Double blinded w/ placebo
• Extensive data not yet available regarding:
  • Pharmacological properties
  • Toxicity
  • Safety/tolerability
  • Efficacy
  • Risk/benefit profile for use in specific medical conditions
Medical Marijuana: Research Issues

• Most studies use oral THC preparations rather than smoked cannabis
• Most studies exclude participants with H/O major psychiatric comorbidities or substance abuse
• Most studies confounded by uncontrolled variables
  • Concomitant tobacco use
  • Comorbid illnesses
Medical Marijuana: Research Issues

- Cannabinoids are insoluble in water and subject to degradation by temperature and light; thus, optimal delivery systems or dosage forms are difficult to design.
- Various dosage forms (smoked, vaporized, baked goods, teas, elixirs, etc.)
  - Do not provide a known and reproducible dose;
  - Data on efficacy and adverse events are not being collected in a reliable manner.
8 Hour Prescriber Course

• Required to prescribe marijuana in Florida
  • No data on concentration of active ingredients
  • No data on appropriate dosage
  • No parameters for determination of misuse
  • “like trying to prescribe St John’s wort instead of Prozac”
Existing Research is Inconsistent

• *National Academies 2017 Report*

• *Versus*

• *Annals of Internal Medicine 2017 Systematic Review of 27 clinical trials entitled*
• National Academies 2017 Report
• “Health Effects of Cannabis and Cannabinoids”
• Review of >10,000 abstracts
• doi.org/10.17226/24625
National Academies Report

• Conclusive or Substantial Evidence for Effectiveness of cannabis/cannabinoids
  • Treatment of chronic pain in adults (cannabis)
  • Treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids)
  • Improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)

(doi.org/10.17226/24625)
The use of medicinal cannabis has become increasingly accepted in the United States and globally (1, 2). Eight states and the District of Columbia have legalized cannabis for recreational purposes, and 28 states and the District of Columbia have legalized it for medical purposes (3). Between 45% and 80% of persons who seek medical cannabis do so for pain management (4, 5). Among patients who are prescribed long-term opioid therapy for pain, up to 39% are also using cannabis (6, 7). Physicians will increasingly need to engage in evidence-based discussions with their patients about the potential benefits and harms of cannabis use. However, little comprehensive and critically appraised information exists about the benefits and harms of using cannabis to treat chronic pain. The objectives of this systematic review were to assess the efficacy of cannabis for treating chronic pain and to provide a broad overview of the short- and long-term physical and mental health effects of cannabis use in chronic pain and general patient populations.

METHODS

Topic Development

This article is part of a larger report commissioned by the Veterans Health Administration (8). A protocol describing the review plan was posted to a publicly accessible Web site before the study began (9). The authors of this review are independent of the Veterans Health Administration (8).}

• Annals of Internal Medicine
• Systematic Review of 27 clinical trials
• “The effects of cannabis among adults with chronic pain and an overview of general harms: A systematic review”
Annals of Internal Medicine
Systematic Review

- Limited evidence that cannabis may alleviate neuropathic pain in some patients
- Insufficient evidence exists to demonstrate analgesic effects in patients with other types of chronic pain.

*(Ann Intern Med. 2017;167(5):319-331)*
Psychomotor Adverse Effects:

• Dose-dependent impairment of:
  • Object distance
  • Shape discrimination
  • Reaction time
  • Information processing
  • Perceptual motor coordination
  • Signal detection
  • Tracking behavior
  • Slowed time perception

(Ries et al., 2014)
Cognitive Impairing Adverse Effects:

- Acute effects:
  - Complex reaction time
  - Perception
  - Reading
  - Arithmetic performance
  - Recall and memory

- 20 year prospective study:
  - Persistent and dependent users lost 6 IQ points
  - Nonusers gained 1 IQ point

- Cannabis use is neurotoxic when use begins in teen years

(Ries et al., 2014)
National Academies Report: Adverse Effects

• Conclusive or Substantial Evidence for a **statistical association** between cannabis smoking and:
  • More frequent chronic bronchitis episodes (long-term cannabis smoking)
  • Increased risk of motor vehicle crashes
  • Lower birth weight of offspring (maternal cannabis smoking)
  • the development of schizophrenia or other psychoses, with the highest risk among the most frequent users
    ([doi.org/10.17226/24625](https://doi.org/10.17226/24625))
AMA: Cannabis Legalization for Recreational Use

• Cannabis is a dangerous drug and as such is a serious public health concern.
• Sale of cannabis for recreational use should not be legalized.
AMA: Cannabis Legalization for Recreational Use

• Discourages cannabis use, especially by persons vulnerable to the drug's effects and in high-risk populations such as youth, pregnant women, and women who are breastfeeding.
AMA: Cannabis Legalization for Recreational Use

- AMA supports public health based strategies, rather than incarceration, in the handling of individuals possessing cannabis for personal use.
AMA: Cannabis Legalization for Medicinal Use

- Calls for further adequate and well-controlled studies of marijuana and related cannabinoids for use in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy and the application of such results to the understanding and treatment of disease.
AMA: Cannabis Legalization for Medicinal Use

- AMA urges that marijuana's status as a federal schedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines, and alternate delivery methods.
AMA: Cannabis Legalization for Medicinal Use

• AMA supports research to determine the consequences of long-term cannabis use, especially among youth, adolescents, pregnant women, and women who are breastfeeding.
AMA: Cannabis Legalization for Medicinal Use

- AMA urges legislatures to delay initiating the legalization of cannabis for recreational use until further research is completed on the public health, medical, economic, and social consequences of its use.
ASAM: Public Policy Statement on Medical Marijuana

• ASAM asserts that cannabis, cannabis-based products, and cannabis delivery devices should be *subject to the same standards that are applicable to other prescription medications and medical devices*
ASAM: Public Policy Statement on Medical Marijuana

• These products should not be distributed or otherwise provided to patients unless and until such products or devices have received marketing approval from the Food and Drug Administration.
ASAM: Public Policy Statement on Medical Marijuana

- ASAM rejects smoking as a means of drug delivery since it is not safe.
ASAM: Public Policy Statement on Medical Marijuana

- ASAM recommends its members and other physician organizations and their members reject responsibility for providing access to cannabis and cannabis-based products until such time that these materials receive marketing approval from the Food and Drug Administration.
PARK CAR, LOOK FOR PHONE FOR 5 MIN
WITH THE LIGHT FROM YOUR PHONE
• Thank you!
References:


References:
