Marijuana: Addiction, Mental Health, and Policy

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Harvard Medical School
Boston, June, 2019
It’s clearly not simple…

Is MJ harmful? Yes for some:
- For kids, there are lasting detrimental cognitive effects of heavy use
- For some, high potency MJ exposure increases risk of psychotic illness
- On roadways and workplaces, MJ intoxication is a public safety risk

Is MJ medicine? Yes, components of MJ are medicine for some:
- CBD for children with some forms of epilepsy now FDA approved
- For some with spasticity due to MS, for some THC for severe weight loss.
- For ALL other indications, there are too few, poor quality data to know.
- Our group is poised to study epidiolex for chronic back pain in a clinical trial with PET imaging

Effective regulation using a public health framework is key to mitigating risk
Permitting cannabis use is one thing, Promoting it is another…
Can We Please Stop Pretending Marijuana Is Harmless?

By Dr. Sushrut Jangi October 08, 2015

“…underscoring the **incredible momentum to legalize marijuana** is the misconception that the drug can’t hurt anybody. It can, especially young people.”
<table>
<thead>
<tr>
<th></th>
<th>At Birth</th>
<th>6 Years Old</th>
<th>14 Years Old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image</td>
<td><img src="http://etec.ctlt.ubc.ca/510wiki/Brain-based_Learning" alt="At Birth" /></td>
<td><img src="http://etec.ctlt.ubc.ca/510wiki/Brain-based_Learning" alt="6 Years Old" /></td>
<td><img src="http://etec.ctlt.ubc.ca/510wiki/Brain-based_Learning" alt="14 Years Old" /></td>
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Image retrieved from: [http://etec.ctlt.ubc.ca/510wiki/Brain-based_Learning](http://etec.ctlt.ubc.ca/510wiki/Brain-based_Learning)

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Brain Maturation Proceeds ‘Back to Front’

Anandamide

THC
**Receptor Binding in Brain Tissue**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Potency relative to THC</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-Delta9-THC</td>
<td>1</td>
</tr>
<tr>
<td>Anandamide</td>
<td>.47*</td>
</tr>
</tbody>
</table>

*The affinity of anandamide for cannabinoid receptors ranges from about one-fourth to one-half that of THC. The differences depend on the cells or tissue that are tested and on the experimental conditions, such as the binding assay used.

Content of THC in marijuana has increased over time

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THC vs. Anandamide


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Adolescent Cannabis Use, Especially of High THC Potency, Increases Risk for Psychosis

- Multiple, prospective epidemiologic studies
- Consistent association, cannabis use precedes psychosis, independent of confounding and intoxication effects
- The association is stronger with:
  - Early age at first cannabis exposure
  - Frequent/daily use and use of high potency cannabis
  - Risk factors for psychosis present
  - Outcome = Psychotic disorder dx vs. psychotic symptoms
- Association attenuated by control for familial risk, SES, other drug use, urbanicity, prior psychiatric symptoms.
<table>
<thead>
<tr>
<th>Author / Country</th>
<th>Subjects</th>
<th>Follow up</th>
<th>Adjust. OR</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreasson 1987,* # Zammit 2002* / Sweden</td>
<td>50,053</td>
<td>15, 25 years</td>
<td>3.1 (1.7, 5.5)</td>
<td>Conscript cohort</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 50x use 2.5 (1.2, 5.1) &gt; 5 yrs. bet. use &amp; dx</td>
<td>* Schizophrenia diagnosis # dose response relationship No evidence age exposure effect</td>
</tr>
<tr>
<td>van Os 2002 ** / The Netherlands / NEMESIS</td>
<td>4,045</td>
<td>3 years</td>
<td>2.8 (1.2, 6.5) use; 1.9 (1.3-2.9) linear trend dose</td>
<td>Population based</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORs higher for diagnosis vs sx</td>
<td>* ORs higher for diagnosis vs sx # dose response relationship</td>
</tr>
<tr>
<td>Weiser 2002 * / Israel</td>
<td>9,724</td>
<td>4-15 years</td>
<td>2.0 (1.3, 3.1)</td>
<td>Population based</td>
</tr>
<tr>
<td>Fergusson 2005 # @/ New Zealand Christchurch</td>
<td>1,055 assessed at age 16, 18, 21 and 25</td>
<td>7 years</td>
<td>IRR=1.8 (1.3, 2.4) in daily users</td>
<td>Birth cohort, @ odds psychosis increased with earlier exposure, extensive control for confounding</td>
</tr>
<tr>
<td>Arseneault 2002 * @ / New Zealand Dunedin</td>
<td>1,253</td>
<td>15 years</td>
<td>3.1 (0.7, 13.3)</td>
<td>Birth cohort, * schizophreniform dx age 26</td>
</tr>
<tr>
<td>Miettunen 2008 # / Finland</td>
<td>6,330</td>
<td>14 years</td>
<td>2.2 (1.7, 2.9) ever vs never</td>
<td>Population based, outcome is 3+ prodromal sx</td>
</tr>
<tr>
<td>Henquet 2005 # / Germany</td>
<td>2,437 aged 14-24</td>
<td>4 years</td>
<td>1.7 (1.1, 1.5)</td>
<td>Population based, adjusted for predisposition for psychosis</td>
</tr>
<tr>
<td>Wiles 2006 / United Kingdom</td>
<td>8,580</td>
<td>1.5 years</td>
<td>1.5 (0.55, 3.94)</td>
<td>Population based</td>
</tr>
<tr>
<td>Moore 2007 # / Meta Analysis 11 cohorts</td>
<td>Adjusted ORs</td>
<td></td>
<td>2.1 (1.5, 2.8) in regular users</td>
<td>Henquet 2005 # Meta Analysis pooled OR = 2.1 (1.7, 2.5)</td>
</tr>
<tr>
<td>Marconi 2016 # / Meta Analysis 10 studies</td>
<td>66,816</td>
<td>Un-adjusted ORs:</td>
<td>1.97 (1.7, 2.3) use, 3.9 (2.8, 5.3) in heavy users</td>
<td>OR: 5.1 (2.8, 5.3) for ICD or DSM Dx of schizophrenia, schizophreniform disorder</td>
</tr>
</tbody>
</table>
### Case Control Studies: Strong Dose Effect

**Higher potency = Greater risk psychosis**

<table>
<thead>
<tr>
<th>Author/Year/Country</th>
<th>Number of cases</th>
<th>Odds ratio (95% CI)</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiForti 2009 / UK</td>
<td>280 cases FEP</td>
<td>No difference in ever use 2.1 (0.9, 8.4)</td>
<td>Case-control Population Control</td>
</tr>
<tr>
<td></td>
<td>174 controls</td>
<td>&gt; 5 yrs. use 6.4 (3.2, 28.6) Daily use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(age, gender, ethnicity, education, employment)</td>
<td>6.8 (2.6, 25.4) High THC use</td>
<td></td>
</tr>
<tr>
<td>DiForti 2015 / UK</td>
<td>410 cases FEP</td>
<td>No difference in ever use 3.0 (1.9, 7.8)</td>
<td>Case-control Population Control</td>
</tr>
<tr>
<td></td>
<td>370 controls</td>
<td>No difference in duration of use 2.9 (1.5, 3.6)</td>
<td></td>
</tr>
<tr>
<td>Giordano 2014 / Sweden*</td>
<td>5456 with Hospital Dx of Schiz, each matched with 5 schizophrenia free controls</td>
<td>10.4 (9.0, 12.1) vs. gen. pop. 5.1 (4.2, 6.2) vs. full siblings 1.98 (1.6, 2.5) vs. full siblings with 7 years between MJ use and schizophrenia and fully controlling for confounding</td>
<td>Co-relative case-control with full sibling, half sibling, and 1st cousin comparisons</td>
</tr>
</tbody>
</table>
Those with Adolescent Cannabis Use Have Greater Severity of Illness Schizophrenia
Males with schizophrenia with v. without cannabis use before age 18-20 followed for 21 years had:

- Higher median **duration of first hospital stay** (59 vs. 30 days)
- Greater median **number of hospitalizations** (10 vs. 4)
- Greater total **hospital days** (547 vs. 184)
- Greater odds of **having >20 hospitalizations** OR=3.1 (1.3–7.3)
- Greater odds of hospital stay **>2 years** OR=2.4 (1.1–7.4)

Controlling for personality disorder, family SES, IQ, marital status, urban residence, risky use of alcohol, and other drug use

THC Causes Transient Psychotic Symptoms in a Greater Proportion of Those with Schizophrenia than Healthy Volunteers

D'Souza, et al., Biol Psych 2005
THC Effect on Psychotic and Cognitive Symptoms in Healthy Volunteers is Variable and is Attenuated by CBD

- Psychotic effect of THC attenuated by CBD pretreatment: implications for high THC, low CBD potency cannabis effect on psychosis outcomes
- High inter individual variation in THC induced psychotic symptoms in volunteers: Implications for gene-environment interaction

Battacharyya et al., Neuropsychopharmacology, 2010, above; Englund, et al., J Psychopharm 2013
Marijuana Related Psychotic Symptoms Among Primary Care Patients

Routine pediatric visits, mean age 16.6

- Hallucinations (27%)
- Paranoia/Anxiety (33.6%)
- Any psychotic symptom (42.9%)

Significantly higher rates among youth with depressive sx, CUD

Teen MJ use increasing since commercialization

Percent of students who used MJ in past 3 months

- 2015-16: 10%
- 2016-2017: 11%
- 2017-2018: 12%
- 2018-2019: 19%

100% ↑ use since 2015

Percent of students who used MJ once a week or more in past 3 months

- 2015-16: 5%
- 2016-17: 6%
- 2017-2018: 8%
- 2018-2019: 11%

117% ↑ use since 2015

Percent of students who use MJ daily

- 2015-16: 1%
- 2016-2017: 3%
- 2017-2018: 3.5%
- 2016-2019: 5%

268% ↑ use since 2015

Percent of people who used MJ in past 3 months

- 2015-16: 0.00%
- 2016-2017: 2.00%
- 2017-2018: 4.00%
- 2018-2019: 6.00%

Percent of students who use MJ one or more times per week

- 2015-16: 1%
- 2016-2017: 3%
- 2017-2018: 3.5%
- 2018-2019: 5%

% participants that use MJ daily
Cannabis abstinence in youth improves memory

Users who Abstain for 30 Days

Users who continue to use cannabis

THC Concentrations in Urine

Attention

Memory

Schuster et al., J Clin Psych 2018
In youth aged 12 – 19 in MA surveyed in their school

Problem cannabis use and Cannabis Use Disorder symptoms are associated with significantly more prodromal psychotic symptoms
In youth aged 12 – 19 in MA surveyed in their school

Problem cannabis use and Cannabis Use Disorder symptoms are associated with significantly more symptoms of Major Depressive Disorder.
In youth aged 12 – 19 in MA surveyed in their school

Problem cannabis use and Cannabis Use Disorder symptoms are associated with significantly more anxiety symptoms.
In youth aged 12 – 19 in MA surveyed in their school

Those with a diagnosed mental health disorder use significantly more MJ, use MJ more frequently, and are more likely to have cannabis use disorder.
Cannabis Withdrawal Syndrome Lasts Longer in Adolescents with a Comorbid Psychiatric Illness

Schuster et al., Preventive Medicine, 2018
Randomized Trial of Medical Marijuana Cards vs. Waitlist

Assessing adults, aged 18-55, seeking medical marijuana cards for:
- Pain,
- Insomnia,
- Depression, or
- Anxiety

Funded by
- MGH ECOR
- RO1DA042043

<table>
<thead>
<tr>
<th>Active Study Group</th>
<th>Waitlist Control Group</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>2 week</td>
<td>2 week</td>
</tr>
<tr>
<td>1 month</td>
<td>1 month</td>
</tr>
<tr>
<td>3 month</td>
<td>3 month</td>
</tr>
<tr>
<td>6 month follow-up</td>
<td>6 month follow-up</td>
</tr>
<tr>
<td>12 month follow-up</td>
<td>12 month follow-up</td>
</tr>
</tbody>
</table>
AIMS: Randomized Trial of Medical Marijuana Cards vs. Waitlist

1. Observe behavior of MM patients in first months of use, including potential progression to addiction
   a) Target Symptoms, Side Effects
   b) Concomitant medication use, e.g. opioids
   c) Temporal pattern of MM use and loss of control over intake of other substances

2. Effects of MM on working memory, attention, executive function, and decision-making

3. Assess how MM affects prefrontal cortical brain function
MM cardholders double their use after getting their MM cards, begin to obtain cannabis products at dispensaries

Preliminary results for an ongoing trial.

n = 52 MM
n = 31 WLC
Because we can’t know what is in the products people purchase as ‘Medical Marijuana’, we conduct a full analysis of 11 cannabis metabolites in urine at each visit.

- THC
- 11OH-THC
- THC-COOH
- THC-glucuronide
- THCV
- THCV-COOH
- CBD
- CBN
- CBG
- CBD-glucuronide
- CBDV
- CBC
No Detectable CBD in 1/3 of Med MJ Patients Purchasing CBD Products at Dispensaries

86 Participants:
Reported use of Medical MJ products with CBD only or CBD + THC

32.6%:
Of participants had no CBD detected in urine

67.4%:
Had at least one urine that contained CBD metabolites
To Date MM users report minimal to no effect on PAIN...

Preliminary results for an ongoing trial
n = 52 MM
n = 31 WLC
little effect on SLEEP…

Preliminary results for an ongoing trial
n = 52 MM
n = 31 WLC
and little to no benefit for anxiety and depression...

Preliminary results for an ongoing trial
n = 52 MM
n = 31 WLC
While Medical MJ purchased at MA dispensaries had No CBD for 1/3 of Patients and little efficacy, there were side effects consistent with high THC products…

- 45 Psychiatric AEs
  - 18 Psychotic
  - 20 Worsening of Depression
  - 7 Anxiety
- 27 Gastrointestinal
  - 20 Nausea/vomiting/abdominal pain
- 17 Other CNS
  - (headache, 16 migraines or cluster headache)
'I was taking what I thought was CBD oil, and apparently it wasn't what I thought it was. I started feeling the effects when I was driving, which was really scary. I got home as quickly as I could. I felt so high I didn't know where I was and couldn't focus, and the only way I got home was the noises from GPS. I was paranoid that I might have hit someone or something, but I checked my car and there was no damage.'
In Summary

- MJ use in adolescence is associated with mental health disorders, cannabis use disorder, and cognitive decline that is potentially reversible.

- Substantial epidemiologic evidence suggests some of these relationships are causal.

- New high potency THC oils, dabs, vapes, and edibles are driving up THC exposure and changing the clinical picture, probably increasing the risk for psychosis.

- American Acad Peds recommends counseling all adolescents: ‘Non-use is best for health.’ First Episode Psychosis programs advising sibs not to use.

- ‘Medical’ marijuana in MA is not reliably tested or labeled

- Aside from pediatric epilepsy and MS, there is little rigorous data to support ANY medical claims

With pressure mounting on state legislatures across the country to legalize recreational marijuana, a coalition of eight state Medical Societies, including the Medical Society of Delaware, is calling for thorough consideration before rushing to legislate. “Public health should be our number one concern here, not commercializing a drug for state tax dollars. It is unconscionable to put money over the medical well-being of our citizens, the priority must be health first.” Andrew Dahlke, president of the Medical Society of Delaware.

“data from states that have legalized recreational marijuana shows an increase in car accidents and an increase in teen use.” From statement released by the coalition.

Coalition is of the Medical Societies of New York, Connecticut, New Jersey, Delaware, New Hampshire, Massachusetts, Pennsylvania, and the Ohio State Medical Association.
Physicians and scientists, from every major medical school and hospital in Massachusetts, are signing onto a call for MA to regulate marijuana using a public health framework, putting public health ahead of commercial interests. Permitting cannabis use is one thing, Promoting it is another…