


**THIS is How Cannabis can Cause Psychosis**



Erik Messamore, MD, PhD  
Expert Opinion & Consultation  
Psychiatry, Psychopharmacology

1

---

---

---

---

---


---

---

---

**Disclaimers**

- I receive no compensation from any industry
- I receive no compensation from any policy-advocacy groups
- I believe that any informed adult who wishes to use cannabis should be able to exercise the right of free choice in an open society that values liberty
- The thoughts, views, and opinions expressed in this presentation are my own and do not reflect or represent the policy or position of Northeast Ohio Medical University



Erik Messamore, MD, PhD

2

---

---

---

---

---


---

---

---

**Objectives**

- Explain psychosis and schizophrenia
- Outline evidence that cannabis can cause psychosis
- Explain how cannabis pharmacology overlaps with psychosis biochemistry
- Explore links between cannabis use and persistent psychosis (schizophrenia)
- Discuss the meaning and significance of cannabis-induced psychosis



Erik Messamore, MD, PhD

3

---

---

---

---

---


---

---

---

**Underestimating Risk**

- One third of US adults believe that smoking or vaping cannabis promotes good health  
Keyhani, S. et al. (2018) 'Risks and Benefits of Marijuana Use: A National Survey of U.S. Adults', *Annals of Internal Medicine*, 169(5), pp. 282-290.
- Half of US adults say that cannabis is no potentially serious side effects  
Keyhani, S. et al. (2018) Mesamore (2019) unpublished national survey results
- Two thirds of youths aged 16 to 19 years are not at all worried that using marijuana will damage their health (Wadsworth et al., 2019)  
Wadsworth, E. and Hammond, D. (2019) 'International differences in patterns of cannabis use among youth: Prevalence, perceptions of harm, and driving under the influence in Canada, England & United States', *Addictive behaviors*, 90, pp. 171-175.



4

---

---

---

---

---

---


---

---

**Underestimating Risk**

**“The bottom line is that there is zero proof that cannabis consumption causes psychosis”**

**Morgan Fox**  
Media Relations Director  
 National Cannabis Industry Association  
<https://local12.com/health/health-updates/marijuana-and-your-mind-new-study-links-pot-to-mental-health-issues>



5

---

---

---

---


---

---

---

---

**What Is Psychosis?**



6

---

---

---

---


---

---


---

---

The most common problem that no one talks about



About 1 in every 11 people will experience symptoms of psychosis at some point in their lives (McGrath, 2015)



7

---

---

---

---

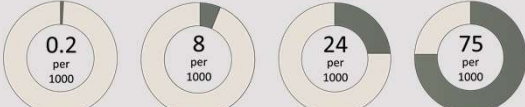
---

---

---


---

Cases per year among adolescents



0.2 per 1000 Suicide    8 per 1000 Diabetes    24 per 1000 Teen birth    75 per 1000 Psychosis

- Hawton, K., Saunders, K. E. A. and O'Connor, R. C. (2012) 'Self-harm and suicide in adolescents', The Lancet, 379(9834), pp. 2373-2382.
- Demmer, R. T. et al. (2013) 'Prevalence of diagnosed and undiagnosed type 2 diabetes mellitus among US adolescents: results from the continuous NHANES, 1999-2010', American journal of epidemiology, 177(7), pp. 1106-1113.
- <https://public.tableau.com/profile/chlidriveds41/Viz-home/Birth-Ratesper1000forFemalesAges15to19byRaceandHispanicOriginSelectedYear1960-2014/Dashboard1>
- Kelleher, J. et al. (2012) 'Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies', Psychological medicine, 42(9), pp. 1857-1863.



8

---

---

---

---

---


---

---

---

Psychosis Is A Symptom

- Indicates that the brain is processing information inefficiently
- When this happens, the brain creates **misperceptions**
- Misperceptions in sensory areas (vision, hearing, touch) → **hallucinations**
- Misperceptions of significance → explanations to explain them → **unusual beliefs (delusions)**



9

---

---

---

---

---

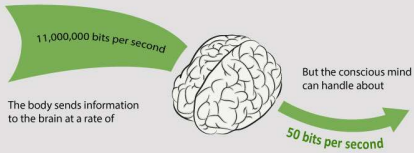
---

---

---

### How Misperceptions of Significance Lead to the Unusual Ideas of Psychosis

- > The brain receives information about the status of the internal workings of the body.
- > The brain also receives information about the world outside the body.



10

---

---

---

---

---

---

---

---

### The Brain Receives A LOT of Information



- |                     |                                 |                         |
|---------------------|---------------------------------|-------------------------|
| Brown clock housing | Desk                            | Wooden table legs       |
| Orange clock face   | Brown desktop                   | Magazines on table      |
| 5 leaves            | White leg                       | Two magazines           |
| Wall                | Blue curtain                    | Shadow on carpet        |
| Clock               | Window                          | 1:20 PM                 |
| Shadows             | Unequal windowpanes             | Woman                   |
| Waste bin           | Variations in light from window | Arm extended            |
| Computer screen     | Purple rug                      | Brown hair              |
| Computer stand      | Brown chair                     | Long hair               |
| Desk                | Soft cushions                   | Neutral face expression |
| Cabinet             | Brown pillow                    | Tan shirt               |
| Drawers             | Square-shaped pillow            | Dark green skirt        |
| Drawer handles      | Tassels on pillow               | Wrinkly knees           |
| Green plan          | Round table                     | Dark shoes              |
| Gray pot            | Glass tabletop                  | Waste bin empty         |
| Potting soil        | Three table legs                | Folds in curtain        |



11

---

---

---

---

---

---

---

---

### Filtering, Flagging, Figuring Out



- This person is inviting me in
- To sit in that chair



12

---

---

---

---


---

---


---

---

### Misperceiving Significance



- Woman, clock, plant, waste bin seem equally important to me
- Is she trying to tell me that time is running out before the plants die?
- Has the plant emerged from the garbage? Is this a sign that invited to discover new life for a new time?



13

---

---

---

---

---


---

---

---

### Summary

- Psychosis is a symptom
- It revolves around misperception
- May involve misperceived sensations (hallucinations)
- Misperceived significance may drive unusual ideas (delusions)
- Psychosis has many causes
  - Over 100 drugs
  - Over 50 medical diseases
  - At least 4 psychiatric conditions



14

---

---

---

---

---


---

---

---

### Schizophrenia

- A longer-term psychiatric condition characterized by
  - Persistent or recurring psychosis
  - Decline in ability to function
  - Not better explained by medical illness
- Affects about 1 in 100 people



15

---

---

---

---


---

---

---

---

## How Cannabis Can Cause Psychosis



16

---

---

---

---

---

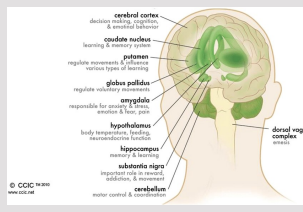

---

---

---

### Pharmacology of THC

- The THC in cannabis mimics the action of a brain-made chemical messenger known as anandamide
- THC activates a specific protein (CB receptor)
- Nerve cells with activated CB receptors change their behavior
  - Mostly by altering the output of neurotransmitter chemicals

17

---

---

---

---

---


---

---

---

### Dopamine

- Very important in the circuits that assign importance or significance to things or events
- Prominently involved in circuits that mediate reward signals or pleasure
- PET scan studies and other neurochemical studies show that many people with psychosis over-produce dopamine and release excessive quantities of dopamine
- Cannabis increases the release of dopamine in human brain



18

---

---

---

---

---

---

---

---

### Cannabis Increases Dopamine Release

- Voruganti, L. N. et al. (2001) 'Cannabis induced dopamine release: an in-vivo SPECT study', *Psychiatry research*, 107(3), pp. 173–177.
- Mason, N. L. et al. (2019) 'Cannabis induced increase in striatal glutamate associated with loss of functional corticostriatal connectivity', *European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology*, 29(2), pp. 247–256.
- Bloomfield, M. A. P. et al. (2016) 'The effects of  $\Delta^9$ -tetrahydrocannabinol on the dopamine system', *Nature*, 539(7629), pp. 369–377.



19

---

---

---

---

---

---

---

---

### Cannabis, Dopamine, Psychosis

- Increased output of dopamine is a very well-known and very important neurochemical cause of psychosis.
- Cannabis can increase the output of dopamine in humans.



20

---

---

---

---

---

---

---

---

### Glutamate

- Over half of the connections between brain cells use glutamate as their chemical message. In terms of number of connections, it's the #1 neurotransmitter
- Glutamate is like the gas pedal. It excites, activates nerve cells
- Critically involved in sensory perception
- Critically involved in shaping nerve circuits and forming memories
- Drugs that reduce the strength of the glutamate signal produce psychosis
- The primary action of THC is to inhibit the release of glutamate (like taking the foot off the gas pedal)



21

---

---

---

---

---

---

---

---

### Glutamate: Caught In The Act

“Compared to individuals who were not sensitive to the psychotomimetic effects of Δ9-THC, individuals who developed transient psychotic-like symptoms (≅ 70% of the sample) had significantly lower baseline Glx and a 2.27-times higher increase following Δ9-THC administration.”

Colizzi, M. et al. (2019) 'Delta-9-tetrahydrocannabinol increases striatal glutamate levels in healthy individuals: implications for psychosis', Molecular psychiatry, doi:10.1038/s41380-019-0374-8.

- 70% of volunteers given THC experienced transient psychosis
- The ones susceptible to psychosis symptoms had:
  - higher baseline glutamate activity (gas pedal was more active)
  - greater inhibition of glutamate release (release of gas pedal was more pronounced)



22

---

---

---

---

---

---

---

---

---

---

### GABA

- 30% to 40% of nerve cell connections use GABA to communicate. It's the #2 neurotransmitter.
- GABA is an inhibitory signal – it's like the brake.
- THC inhibits the release of GABA – (like taking the foot off the brake)
- If anxiety centers (like the amygdala) are under GABA's control, then "taking the foot off the brake" essentially revs up the anxiety engine.



23

---

---

---

---

---

---

---

---

---

---

### Taking The Foot Off The Brake in the Amygdala (the anxiety control center)

“The principal findings of this study are that a **modest dose** of delta-9-THC resulted in the **acute induction of anxiety symptoms in the healthy volunteers** studied here and the severity of anxiety induced by delta-9-THC was **directly correlated with the baseline availability of CB1 receptors in the amygdala**, a region that has been linked to anxiety and fear processing both in health, and under the influence of delta-9-THC.”

Bhattacharyya, S. et al. (2017) 'Acute induction of anxiety in humans by delta-9-tetrahydrocannabinol related to amygdalar cannabinoid-1 (CB1) receptors', Scientific reports, 7(1), p. 15025.

- Differences in anxiety sensitivity to THC may be explained by the availability of CB receptors in the amygdala



24

---

---

---

---

---

---

---

---


---

---



**Summary: Significant Overlap**

- Pharmacological effects of THC
  - Increasing dopamine release
  - Decreasing glutamate release
- The most important biochemical changes consistently observed in psychosis
  - Greater synthesis and release of dopamine
  - Diminished responsiveness to glutamate



25

---

---

---

---


---

---

---

---

**What's The Evidence That Cannabis Can Cause Psychosis?**



26

---

---

---

---

---


---

---

---

**Medical Textbooks from the Original Medical Marijuana Era**

- The mid-19<sup>th</sup> to early 20<sup>th</sup> century was a very drug friendly time
- Cannabis was routinely used as a medicine
- Cannabis preparation, use, and side effects were described in medical textbooks
- Potentially severe mental status risks were routinely noted



27

---

---

---

---

---

---

---

---


### Medical Textbooks from the Original Medical Marijuana Era

“Occasionally, a species of intoxication is induced, with hallucinations or complete delirium... Among those who use it habitually, it is said ultimately to impair the mental faculties”  
*A Treatise on Therapeutics, and Pharmacology, or Materia Medica, 1868*

“Hallucinations occur, but they are not usually agreeable; they are often painful and are replaced by stupor”  
*A Practical Treatise on Materia Medica and Therapeutics, 1893*

“In large doses it will produce hallucinations... Its habitual use will cause insanity.”  
*Materia Medica and Clinical Therapeutics, 1905*

“The most common effect, however, is the development of insanities which have been known for many years”  
*A Textbook of Materia Medica, Pharmacology and Therapeutics, 1908*




---

---

---

---

---

---

---

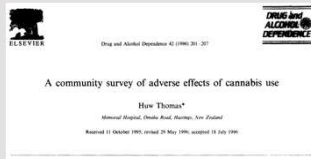
---

---

---


28

### Consumer Surveys



- 22% of those who had used cannabis reported acute anxiety or panic attacks following cannabis use
- 15% reported psychotic symptoms after use

2. After taking cannabis have you ever had strange, unpleasant experiences such as hearing voices or becoming convinced that someone is trying to harm you, or that you are being persecuted? (YES/NO)




---

---

---

---

---

---

---

---

---


---

29

### Summary of Multiple Surveys Involving 3,000 Cannabis Consumers

Side Effect	% of Cannabis Consumers Who Reported it
Become less social	63%
Impaired concentration	55%
Paranoia	51%
Impaired memory	50%
Anxiety	40%
Impaired thinking	40%
Poor sleep	39%
Depressed mood	37%
Hallucinations	20%
Irritability	8%

Green, B., Kavanagh, D. and Young, R. (2003) 'Being stoned: a review of self-reported cannabis effects', *Drug and alcohol review*, 22(4), pp. 453-460.




---

---

---

---

---

---

---


---

---

---

30

But What About Proving It?



31

---

---

---

---

---


---

---

---

### Human Clinical Laboratory Studies

- Administer THC or cannabis extracts to human volunteers (without mental illness)
- Observe if signs of psychosis emerge



32

---

---

---

---

---

---

---

---

### Human Clinical Laboratory Studies


**Review**

**Human Laboratory Studies on Cannabinoids and Psychosis**

Mohamed Sherif, Rajiv Radhakrishnan, Deepak Cyril D'Souza, and Mohini Ranganathan

"Human laboratory studies provide the clearest evidence that cannabinoid agonists can induce a range of transient positive, negative, and cognitive symptoms and psychophysiological deficits relevant to psychosis."

- This review article identified 68 studies
- Studies reveal perceptual, mood, and cognitive, and brain wave changes from THC that are identical to those seen in people with psychosis or with schizophrenia



33

---

---

---

---

---

---

---

---

### Placebo-Controlled Clinical Trials

- The double-blind, placebo-controlled clinical trial is the gold standard for medical evidence
- Participants are randomly assigned to active treatment (THC) or identical-appearing inactive treatment (placebo).
- Neither the patients taking the pills nor the doctors/study staff administering them and observing the effects know if the pills are active or placebo.
- This design eliminates biased experience and biased observation
- THC is an FDA-approved medication and has undergone this sort of testing



34

---

---

---

---

---

---

---

---

---

---

### Placebo-Controlled Clinical Results for THC

**Common Adverse Reactions**

The following adverse reactions were reported in clinical trials at an incidence greater than 1%.

System Organ Class	Adverse Reactions
General	Asthenia
Cardiovascular	Palpitations, tachycardia, vasodilation/ facial flush
Gastrointestinal	Abdominal pain*, nausea*, vomiting*
Central Nervous System	Dizziness*, euphoria*, paranoid reaction*, somnolence*, thinking abnormal*, amnesia, anxiety/nervousness, ataxia, confusion, depersonalization, hallucination

\* Actual incidence 3% to 10%

- Adverse reactions to low-dose THC (2.5 mg twice per day)
- Source: Marinol prescribing information (FDA website)
- (average joint delivers 12 mg THC)



35

---

---

---

---

---

---

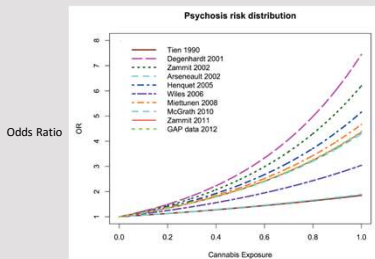
---

---

---

---

### Ten population-based studies show that the risk of psychosis increases with degree of exposure



Marconi, A. et al. (2016) 'Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis', Schizophrenia bulletin, 42(5), pp. 1262-1269.



36

---

---

---

---

---

---

---

---

---

---

### Summary: Cannabis Can Cause Psychosis

- Consumer surveys
- Human clinical laboratory studies
- Double-blind, placebo-controlled clinical trials
- Higher exposure (dose, duration of use) associates with higher risk of psychosis



37

---

---

---

---

---

---

---

---

### Cannabis and Schizophrenia



38

---

---

---

---

---

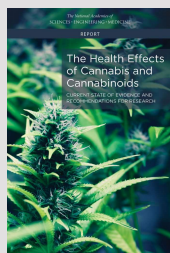
---

---

---

### National Academies Report

- **The National Academies of Sciences, Engineering and Medicine** is an **independent** scientific advisory organization.
- Several legal marijuana states (AZ, AK, CA, OR, WA) were among the co-sponsors of the report.



The full-text report is at:  
<https://www.nap.edu/read/24625/chapter/1>



39

---

---

---

---

---

---


---

---

**National Academies Report**

“CONCLUSION 12-1 There is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.”

Page 295



40

---

---

---

---


---

---

---

---

“But It’s Only A Concern For People With Genetic Risk For Schizophrenia”



41

---

---

---

---

---

---

---


---

**Prospective Study from New Zealand (Dunedin Cohort)**

- Carefully followed the lives of 1,038 kids born during a single one-year period (that ended in 1973)

Cannabis Use By Age 15	Likelihood of Schizophrenia-Spectrum Diagnosis at Age 26
Used cannabis 3 times or more	<b>10%</b>
Used cannabis 2 times or less	<b>3%</b>

Arseneault, L. et al. (2002) 'Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study', *BMJ*, 325(7374), pp. 1212–1213.



42

---

---

---

---

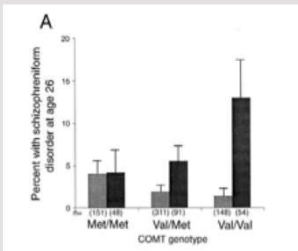
---

---

---

---

### Genetic Risk in the Dunedin Cohort



- COMT gene metabolizes dopamine
- COMT gene comes in 3 combinations
  - Met/Met
  - Val/Met
  - Val/Val
- Adolescent cannabis use had
  - no added schizophrenia risk for Met/Met group
  - 2.5-fold added risk for Val/Met group
  - 10-fold added risk for Val/Val group

Caspi, A. et al. (2005) 'Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction', *Biological psychiatry*, 57(10), pp. 1117-1127.



43

---

---

---

---

---

---

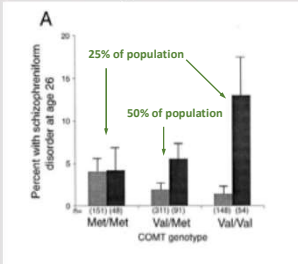
---

---

---

---

### "It's only a concern for people with genetic risk for schizophrenia"



- 75% of the population carries a COMT gene combination that was associated with cannabis-linked added schizophrenia risk



44

---

---

---

---

---

---

---

---

---

---

### Summary

- It might be true that cannabis-associated schizophrenia is only a concern for people with genetic risk factors for schizophrenia
- But family history of mental illness is a very poor guide
- Schizophrenia risk genes are carried by many people without family history of mental illness
- An identical twin of someone with schizophrenia has 100% of their twin's genes, but only a 50% risk of developing schizophrenia
  - Environmental triggers are important
  - Cannabis appears to be an environmental trigger
  - If true, then it's causing some schizophrenia cases that could have been avoided



45

---

---

---

---

---

---


---

---

---

---

**But You Can't PROVE That Cannabis Can Cause Schizophrenia!**



46

---

---

---

---

---

---

---

---

**Would Anyone Ever Do This Kind Of Study?**

20,000 Young, Healthy Non-Smokers


Random Assignment

- 10,000 Smoke Every Day
- 10,000 Placebo-Smoke Every Day

10-Year Follow Up

How Many New Cases of Cancer Have We Caused?

- We can't and don't and will never set up studies to "prove" harmful outcomes like schizophrenia
- Instead, we look for evidence of probable cause



47

---

---

---

---

---


---

---

---

**Showing Probable Cause**

- Is it biochemically plausible that cannabis could cause schizophrenia? (yes)
- Can we create schizophrenia-like changes in animals by giving them cannabis, or by tweaking their cannabinoid system? (yes)
- Can we create features of schizophrenia in human volunteers under controlled conditions in the clinical laboratory? (yes)
- Is there a relationship between cannabis use and schizophrenia in population studies? (yes)
- Does greater degree of cannabis exposure correlate with higher risk of schizophrenia? (yes)



48

---

---

---

---

---


---

---

---



## The Significance of Cannabis-Induced Psychosis



49

---

---

---

---

---


---

---

---

### Forecasts Substantially Higher Risk of Developing a Persisting Severe Mental Illness

- 46% likelihood of receiving a schizophrenia-spectrum diagnosis within 8 years, based on Finnish long-term followup study of 18,500 people first diagnosed with substance-induced psychosis  
Nieminen-Pynttari, J. A. et al. (2013) 'Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases', The Journal of clinical psychiatry, 74(1), pp. e94-9.
- 47% likelihood of being diagnosed with either schizophrenia or bipolar disorder after an initial diagnosis of cannabis-induced psychosis in a Danish study that followed 6,788 individuals.
  - Half of these conversions to schizophrenia or bipolar disorder occurred with 4.4 years after the initial substance-induced psychosis episode



50

---

---

---

---

---


---

---

---

### Quitting vs Continuing After a Cannabis-Induced Psychosis

- "Patients who completely abstained from cannabis after the 1st episode had no relapse of psychiatric illness.
  - They showed marked improvement in socio-occupational functioning as well.
- All those who relapsed to cannabis use had a recurrence of illness.
- Half the patients with predominantly non-affective psychosis progressed to an independent psychiatric disorder within 5.75 years.
- Abstinence later in the course of illness did not improve outcome significantly.
- *This was a small sample (57 cases of CIP identified, 35 could be followed up)*



51

---

---

---

---

---

---

---

---

### Summary

- Having an episode of cannabis-induced psychosis proves that the affected cannabis consumer has:
  - the genetic vulnerability, and/or
  - the psychological vulnerability, and/or
  - the neurological wiring that makes psychosis possible.
- An episode of cannabis-induced psychosis signals extremely high risk (nearly 50%) of eventually progressing to schizophrenia or bipolar disorder.
- This would be a good time to reduce exposure to risk factors and to enhance resilience factors.



52

---

---

---

---

---

---

---

---

### Conclusions

- Cannabis can cause psychosis through its effects on dopamine, serotonin, glutamate, and GABA neurotransmitter signals
- Depending on dose and setting, between 1% to 20% of consumers may experience psychosis during cannabis use.
- Cannabis use is associated with approximately 3-fold increased risk of developing schizophrenia
- An episode of cannabis-induced psychosis means that
  - the affected person's brain is capable of experiencing psychosis
  - there may be up nearly 50:50 risk of progressing to schizophrenia or bipolar disorder



53

---

---

---

---

---

---

---

---

### Conclusions

- An episode of cannabis-induced psychosis means that
  - the affected person's brain is capable of experiencing psychosis
  - there may be up nearly 50:50 risk of progressing to schizophrenia or bipolar disorder
- The ability for cannabis to cause psychosis or schizophrenia is:
  - Biochemically plausible
  - Suggested by animal studies
  - Proven (for psychosis) by human clinical laboratory studies
  - Consistent with population studies
- This is something that should be as widely-known and publicized – so that people have the chance to avoid finding out the hard way



54

---

---

---

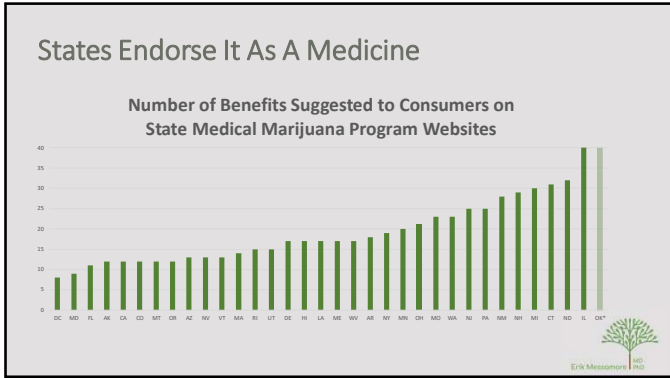
---

---

---

---

---



55

---

---

---

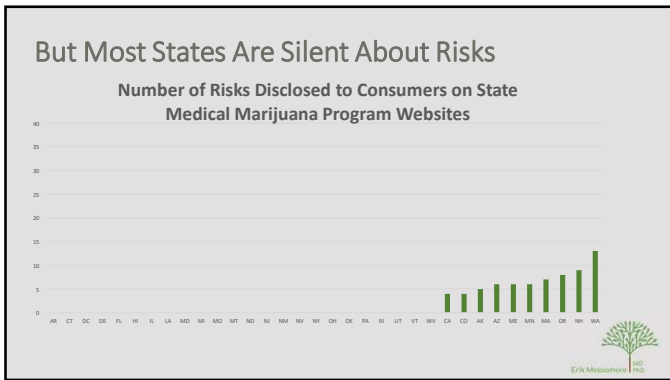
---

---

---

---

---



56

---

---

---

---

---

---

---

---

**Erik Messamore, MD, PhD**  
Expert Opinion & Consultation  
Psychiatry, Psychopharmacology

ErikMessamore.com  
 Erik Messamore  
 @ErikMessamoreMD

57

---

---

---

---

---

---

---

---