Law: Psychedelic Drugs For Mental Health Disorders: Clinical and Legal Issues

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At the conclusion of this lecture the successful learner will be able to:

Describe	Identify	Describe
Describe the important features of post-traumatic stress disorder (PTSD) and major depressive disorder (MDD) with commonly employed non-pharmacologic and pharmacologic treatments	Identify the pharmacologic features of MDMA and psilocybin and clinical trial results when applied to patients with mental health disorders	Describe legal barriers to using psychedelics in patients with mental health disorders and ways to circumvent them at a national or state level

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Disclosures

Dr. White has no relationship with any ineligible companies and therefore nothing to disclose

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MDMA in PTSD

Phase II and III Clinical Trial Overview

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Post-Traumatic Stress Disorder

- Affects nearly 7% of the US population
  - Military/first responders
  - Physical or sexual abuse survivors
  - Health professionals
- Causes impacted people to lose an average of 3.6 workdays/month
- Is a debilitating disorder characterized by avoidance, hypervigilance and flashbacks (re-experiencing aspects of a traumatic event)
- Can be confounded by comorbid anxiety, depression, substance abuse, and suicidal ideation and actions

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PTSD Treatment Options

- VA DoD guidelines: trauma focused psychotherapy preferable to pharmacotherapy if available and the patient is able to access care
- If patients unable or unwilling to attend psychotherapy sessions or sessions are unsuccessful, SSRI or venlafaxine are commonly employed
  - Sertraline and paroxetine reduced CAPS scores 6 to 14 points versus placebo but 28% to 39% of people withdrawing from therapy
  - Venlafaxine reduced CAPS by 9 points with 30% withdrawal rate

• J Clin Pharmacol 2021; https://doi.org/10.1002/jcph.1995

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MDMA Pharmacology – Beneficial Effects

- Why would MDMA enhanced psychotherapy be useful in PTSD?
- Patients unable/unwilling to share their traumatic experience(s)
  - Serotonin release – enhanced mood
  - Oxytocin – increased feeling of bonding or trust
  - Psychedelic effect – create a surreal feeling
  - Mild amphetamine effect – increased energy

- J Clin Pharmacol 2021; https://doi.org/10.1002/jcph.1995

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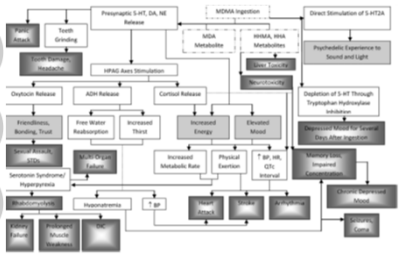
MDMA Pharmacologic Effects – Adverse Effects

- J Clin Pharmacol 2014; https://doi.org/10.1002/jcph.266



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Minimizing Adverse Events with MDMA Enhanced Psychotherapy

- Pharmaceutical grade MDMA – consistent dose, no contaminants of adulterants
- Non-MDMA preparatory session and non-MDMA follow-up sessions
- 2 or 3 MDMA sessions in total
  - Quiet room, multi-hour sessions, trained psychotherapists, no patients with cardiac disease/hypertension, no exercising allowed, unable to leave until the effect completely wears off
- Initial dose with supplementary dose after a couple of hours to reduce C_{max}, extend duration

J Clin Pharmacol 2021; https://doi.org/10.1002/jcph.1995

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MDMA Dosing in Sessions

- Initial doses: Placebo-controlled trials used high 125 mg (Mithoefer et al. 2011) (Mitchell et al.) to variable [80 mg in session 1 and then 80 or 120 mg in sessions 2 or 3] doses
  - Other studies (Oehen et al., Ot'alora et al., Mithoefer et al. 2018) assessed two or three different groups who all received a different initial MDMA dose ranging from high (>125 mg) or medium (50-100 mg) doses compared to low dose (30-49 mg) control therapy
- Supplemental doses: High dose therapy (Mithoefer et al. 2011, Mitchell et al., Oehen et al., Ot Alora et al, and Mithoefer et al. 2018), moderate (Ot'alora et al., Mithoefer et al. 2018), and low (Oehen et al., Ot'alora et al., and Mithoefer et al. 2018) dose MDMA regimens received different supplemental doses of 60-62.5 mg, 37.5-50 mg, or 12.5-20 mg, respectively

- J Clin Pharmacol 2021; https://doi.org/10.1002/jcph.1995

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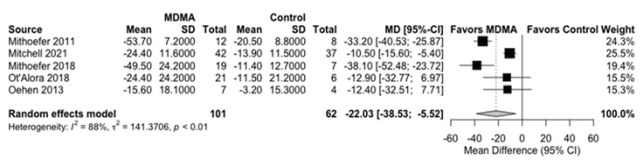
MDMA Psychotherapy CAPS Score Reductions



J Clin Pharmacol 2021; https://doi.org/10.1002/jcph.1995

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Exploring Heterogeneity

- Same direction of effect in all trials
- Differences in magnitude of effect may be due to:
  - MOST LIKELY: Different baseline CAPS scores with greater reductions in more severe disease
    - The average patient in Mitchell et al. had a baseline CAPS score of 44 units, just under the cutoff for severe disease, while the average patient had average CAPS scores of ~65 (Oehen et al.), ~79 (Mithoefer et al. 2011), ~87 (Mithoefer et al. 2018), and ~90 units (Ot'alora et al.)
    - Among active controlled trials, Oehen et al. has a less robust reduction in CAPS scores from baseline with high dose MDMA-assisted psychotherapy than the Mithoefer et al (2018) or Ot'alora et al trials
  - OTHER POTENTIAL FACTORS: Different dosing regimens, duration of follow-up, control groups, and patient populations unlikely related to heterogeneity

- J Clin Pharmacol 2021; https://doi.org/10.1002/jcph.1995

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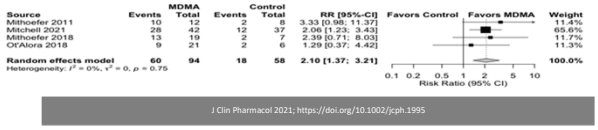
No Longer Meets CAPS PTSD Criteria



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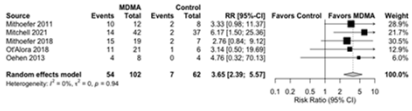
Clinically Significant Drop in CAPS



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Crossover Effects

- Oehen et al. the four participants originally in the low dose MDMA group responded to open label high dose MDMA treatment with a 52% decrease in CAPS-IV score over the course of treatment; 50% no longer met criteria for PTSD diagnosis
- In Mithoefer et al. 2011, the open-label phase of the study included 7 of the 8 participants from the original placebo group
  - All subjects showed clinically meaningful reductions in CAPS-IV score after MDMA therapy was used, which averaged 48% lower than baseline.
- Ot'alora et al., switched participants who originally received low dose MDMA to open label high dose MDMA therapy and achieved a 47% reduction in CAPS scores from the end of the blinded portion of the study
- Mithoefer et al. 2018, switched participants who originally received low dose MDMA to open label high dose MDMA therapy and achieved a reduction in CAPS-IV score of 27 units and 33% of six participants no longer met PTSD diagnostic criteria

- J Clin Pharmacol 2021; https://doi.org/10.1002/jcph.1995

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- J Clin Pharmacol 2021; https://doi.org/10.1002/jcph.1995

MDMA Psychotherapy – Adverse Events

Mitchell et al hemodynamics: systolic (146±19 vs. 118±16mmHg), diastolic blood pressure (87±10 vs. 76±10mmHg), and pulse (92 vs. 66 bpm) - MDMA versus placebo

Adverse Event	Placebo or Low Dose MDMA	Moderate or High Dose MDMA
Aggregate of Phase II Trials		
Anxiety	48%	72%
Jaw Clenching	19%	64%
Reduced Appetite	23%	49%
Dizziness	19%	40%
Nausea	19%	40%
Depressed Mood	3%	8%
Irritability	0%	6%
Panic Attack	0%	6%
Mitchell et al. 2021 (Phase III)		
Muscle Tightness	11%	63%
Reduced Appetite	11%	52%
Nausea/Vomiting	11%/0%	30%/9%
Excessive Sweating	2%	20%
Restlessness	0%	15%
Jaw Clenching	2%	13%
Dizziness	5%	13%
Jittery	0%	11%
Pyrexia	2%	7%
Anxiety	0%	7%
Blurred Vision	2%	9%

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MDMA Psychotherapy – Long Term Effects

- Jerome et al. reported results of questionnaire sent to the participants in the Phase II trials 12 months after their last MDMA session
- Five-point scale, with 1 being slight and 5 being large or severe
  - 86% of participants said their benefits were a 4 or 5
- 84% had improved feelings of well-being
- 72% had less excess vigilance
- 71% had fewer nightmares
- 69% had less avoidance
- 69% had less anxiety
- 66% had improved sleep
- 1.2% felt worse

- J Clin Pharmacol 2021; https://doi.org/10.1002/jcph.1995

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MDMA Psychotherapy – Place in Therapy

- Trauma specific psychotherapy still first line therapy
- MDMA assisted psychotherapy an option before moving the SSRI or venlafaxine therapy
  - Indirect evidence suggests larger MDMA benefit, fewer withdrawals
  - Need direct comparison to be certain
  - Only 2-3 MDMA enhanced sessions means drug adherence less of an issue
- The impact of SSRI or venlafaxine therapy on MDMA psychotherapy
  - Animal data suggests that SSRI therapy might negate some of the elevation in mood associated with illicit MDMA use

- J Clin Pharmacol 2021; https://doi.org/10.1002/jcph.1995

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Conclusions for MDMA in PTSD

- PTSD is a debilitating disease that requires additional therapeutic options
- MDMA assisted psychotherapy is a novel option for those refractory to trauma specific psychotherapy alone
  - Therapy is intermittent, patients must be carefully selected and well supported throughout the session
  - Benefits might be greater in those with more severe disease
  - Benefits are long-lasting after the last MDMA session
- Illicit MDMA products should be avoided and MDMA not explicitly tied into psychotherapy sessions are unlikely to provide benefits and could cause harm

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Self Assessment Question 1

- **What pharmacologic effects of MDMA would benefit people undergoing psychotherapy?**
  A. Oxytocin bonding effect
  B. Serotonin mood elevation effect
  C. Psychedelic surreal effect
  D. All of the above

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Self Assessment Question 1

- What pharmacologic effects of MDMA would benefit people undergoing psychotherapy?
  A. Oxytocin bonding effect
  B. Serotonin mood elevation effect
  C. Psychedelic surreal effect
  D. All of the above

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Self Assessment Question 2

- **What was the degree of moderate-term benefit that MDMA psychotherapy provided?**
  A. Doubling of people no longer meeting CAPS criteria for PTSD
  B. Quadrupling of people no longer meeting CAPS criteria for PTSD
  C. No reduction in people meeting CAPS criteria for PTSD

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Self Assessment Question 2

- What was the degree of moderate-term benefit that MDMA psychotherapy provided?
  A. Doubling of people no longer meeting CAPS criteria for PTSD
  B. Quadrupling of people no longer meeting CAPS criteria for PTSD
  C. No reduction in people meeting CAPS criteria for PTSD

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Self Assessment Question 3

- **Which of the following was not a major adverse event seen when MDMA was administered?**
  A. Jaw clenching
  B. Temporary blindness
  C. Muscle tightness

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Self Assessment Question 3

- Which of the following was not a major adverse event seen when MDMA was administered?
  A. Jaw clenching
  B. Temporary blindness
  C. Muscle tightness

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Psilocybin in Depression and Anxiety

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Depression

- NIMH estimates 19.4 million US adults (7.8%) have at least one episode of major depression in a year
- Episodes of major depression more common among:
  - Women (10% vs. Men 6%)
  - People 18 and 25 years old (15%)
  - People who describe themselves as being of two or more races or ethnicities (14%)
- 3% of US adults may have chronic depression (major depressive disorder)

- https://www.healthline.com/health/depression/facts-statistics-infographic#depression-types

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Anxiety

All Anxiety Types	40 million adults in US affected (18.1% of the population)
Generalized Anxiety Disorder	GAD affects 6.8 million adults (3.1% of the U.S. population)
	Women are twice as likely to be affected as men.
	GAD often co-occurs with major depression.
Panic Disorder (PD)	PD affects 6 million adults (2.7% of the U.S. population)
	Women are twice as likely to be affected as men.
Social Anxiety Disorder	SAD affects 15 million adults (6.8% of the U.S. population)
	SAD is equally common among men and women

https://adaa.org/understanding-anxiety/facts-statistics

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Standard Pharmacologic Treatments for Depression and Anxiety

- Enhancing synaptic serotonin and/or norepinephrine
  - Without antidepressants: ~20 to 40 out of 100 people who took placebo noticed an improvement within six to eight weeks
  - With SSRIs/SNRIs/Tricyclics: ~40 to 60 out of 100 people who took an antidepressant noticed an improvement in their symptoms within six to eight weeks
- Benzodiazepines
  - Partially effective in ~70% of people but possible withdrawal symptoms after therapy stops

- https://www.ncbi.nlm.nih.gov/books/NBK361016/

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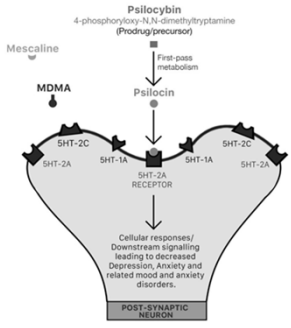
Psilocybin Pharmacology



Lowe H. Molecules. 2021;26(10):2948. doi:10.3390/molecules26102948

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Psilocybin in Depression

- Patients (n=19) with treatment-resistant depression who received two doses of the drug (10 mg followed by 25 mg, one-week apart) as part of an open-label clinical trial (no control group)
- The mean depression score (QIDS-SR16) went from 16.9 ± 5.1 at baseline to 8.8 ± 6.2 (change = −8.1 ± 6, p < 0.001) a day after the 25-mg dose
- Benefits maintained at 5 weeks (change = −8 ± 5.1, p < 0.001)

Carhart-Harris RL, Sci Rep 2017;7:13187.
https://doi.org/10.1038/s41598-017-13282-7

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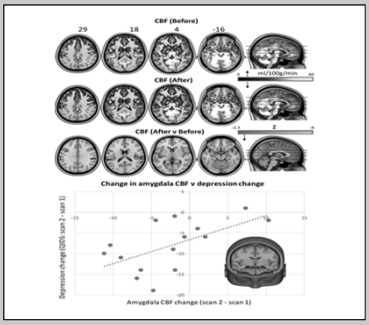
Psilocybin and Brain Blood Flow

- fMRI data were collected from 16 of 19 patients
- Post-treatment decreases in blood flow in the temporal cortex, including the amygdala
  - Decreased amygdala blood flow correlated with treatment response



Carhart-Harris RL, Sci Rep 2017;7:13187.
https://doi.org/10.1038/s41598-017-13282-7

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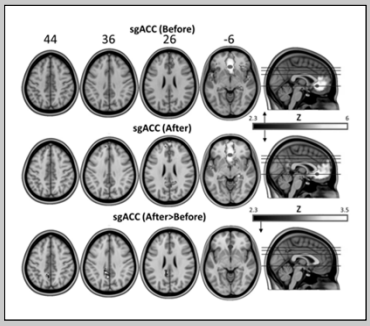
Psylocybin and Resting State Functional Connectivity

- Increased ventromedial prefrontal cortex-bilateral inferior lateral parietal cortex RSFC was predictive of treatment response at 5-weeks
- Decreased parahippocampal-prefrontal cortex RSFC was also predictive of response



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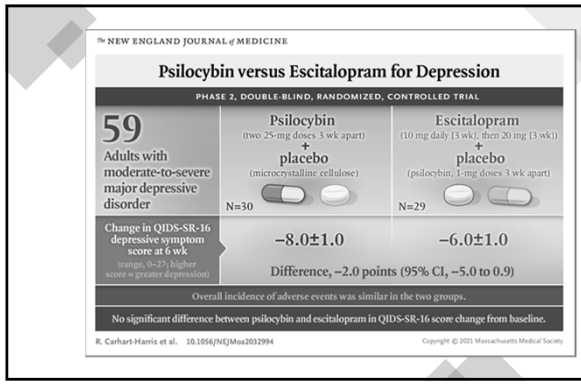

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Meta-Analysis of Trials in Depression and Anxiety in Cancer

- Patients had depression and anxiety associated with life-threatening cancer and assessed with the Becker Depression Index (BDI) and State-Trait Anxiety Inventory (STAI) scales
  - Ross et al. 2016. n=29, R, DB, PC; two doses (0.3 mg/kg)
  - Griffiths et al. 2016. n=51, R, DB; two doses: low (0.3-0.4 mg/kg) vs. higher dose (1-3 mg/kg) psilocybin
  - Grob et al. 2011. n=12, controlled; one dose 0.2 mg/kg
- Psilocybin of 25mg = **0.35 mg/kg** for 70 kg person

Vargas AS. Biomedicines **2020**;*8*:331.
https://doi.org/10.3390/biomedicines8090331

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Results of Meta-Analysis

- BDI: WMD = -4.59 (-4.21 to -0.97)
- STAI-Trait = -5.91 (-7.85 to -3.96)
- STAI-State = -6.03 (-8.90 to -3.16)
- No statistical heterogeneity (I^2=0%) seen in any result but used fixed effect model
  - Random effects model is more appropriate since the control groups (niacin for 2, lower dose psilocybin for 1), doses in active group, and durations were different
  - Depression score would not have been significant with random effects model

Vargas AS. Biomedicines **2020**;*8*:331.
https://doi.org/10.3390/biomedicines8090331

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Conclusions for Psilocybin in Depression and Anxiety

Psilocybin was synthetically produced, not directly from mushrooms

Studies in depression are promising with consistent benefits across preliminary studies but not proven

Most effective dose not currently known but best studied is two 25 mg doses 30 days apart

Additional studies underway that will determine effectiveness

Anxiolytic effect promising but not as well studied, only based on studies in cancer patients who also had depression

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Self Assessment Question 4

- **What is most accurate about psilocybin's known impact on anxiety?**
  - A. It was assessed in people with anxiety related to cancer
  - B. It was assessed in multiple populations with strong results
  - C. It was studied in performance anxiety only

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Self Assessment Question 4

- **What is most accurate about psilocybin's known impact on anxiety?**
  - **A. It was assessed in people with anxiety related to cancer**
  - B. It was assessed in multiple populations with strong results
  - C. It was studied in performance anxiety only

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Legal Implications of Clinical Psychedelic Use

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Legal Barriers to Using Psychedelics

- MDMA and psilocybin are DEA Schedule I drugs
  - Schedule I drugs, substances, or chemicals: no currently accepted medical use and a high potential for abuse
  - Examples: heroin, LSD, non-hemp marijuana, methaqualone, peyote, 3,4-methylenedioxymethamphetamine (MDMA/ecstasy), psilocybin
- Cannabidiol was schedule I, but the DEA removed the Epidiolex version when the FDA approved it for the treatment of rare childhood seizure disorders

https://www.dea.gov/drug-information/drug-scheduling#:~:text=Schedule%20I%20drugs%2C%20substances%2C%20or,)%2C%20methaqualone%2C%20and%20peyote.

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Avoiding Prosecution: Cannabis Example

- Cannabis (THC > 0.3%) is still Schedule I, but federal congressional legislation prohibits the federal government from spending any money to prosecute people using it in states with established medical marijuana programs
  - Cannabis cannot legally cross state lines

https://en.wikipedia.org/wiki/Rohrabacher%E2%80%93Farr_amendment#:~:text=The%20Rohrabacher%E2%80%93Farr%20amendment%20(also,of%20state%20medical%20cannabis%20laws.

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Making the Switch: CBD Example

- Cannabidiol (CBD) was schedule I, but the DEA removed the Epidiolex version (THC < 0.1%) when the FDA approved it for the treatment of rare childhood seizure disorders
  - This is the only form of CBD that can make any health claims or be marketed to improve health
- Hemp derived CBD (THC < 0.3%) was removed from Schedule I status by the Agriculture Improvement Act of 2018, Pub. L. 115-334 (2018 Farm Bill)
  - None of these products can legally be sold or marketed to treat, mitigate, or impact human health

https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd#othercbdapproved

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Federal Options for MDMA and Psilocybin

- A single MDMA drug product by a single manufacturer will likely submit for the FDA indication to treat psychotherapy refractory PTSD
  - At the end of exclusivity, generic versions will likely be able to be approved
  - If the FDA approves it, the DEA will remove the Schedule I designation and allow the use of that single product for human use
- Psilocybin could be allowed to be sold if states create their own medical psilocybin programs, but the drug would have to be made and used in that state
  - Need legal change to prevent federal prosecution while it remain Schedule I
- Psilocybin could follow the same route as Epidiolex CBD or MDMA and apply for FDA approval with subsequent DEA removal of Schedule I
  - Only synthetic version would be FDA approved and not Schedule I

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Legal Conclusions

- The FDA approval will not automatically mean use is legal in the US
- The DEA will have to move the drugs off Schedule I status
  - This is tricky because the US has international treaties with mutual banning of Schedule I drugs that will have to be revisited and reconciled with cosignatory countries
- There is precedent to make the drug available either through a Federal or State process by following the cannabis or CBD examples

https://www.deadiversion.usdoj.gov/mtgs/pharm_train/conf_2016/april_2016/presentations_2016/harper-avila.pdf

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Self Assessment Question 5

- **What is true about the legal status of MDMA and psilocybin?**
  - A. They are both schedule II drugs
  - B. They are schedule I drugs but will automatically lose that schedule once FDA approved
  - C. The DEA will need to decide whether to remove the schedule I designation if the FDA approves one of both of them for clinical use

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Self Assessment Question 5

- What is true about the legal status of MDMA and psilocybin?
  - A. They are both schedule II drugs
  - B. They are schedule I drugs but will automatically lose that schedule once FDA approved
  - **C. The DEA will need to decide whether to remove the schedule I designation for a proprietary version if the FDA approves one of both of them for clinical use**

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