Psychedelics for the Treatment of Depression: Focus on 5-HT$_{2A}$
This program is paid for by Otsuka Pharmaceutical Development & Commercialization, Inc. and Lundbeck, LLC.

Speakers are paid consultants and/or employees of Otsuka Pharmaceutical Development & Commercialization, Inc.
Objectives

1. Describe the prevalence and burden of depression in the US
2. Define and review the history of psychedelics in therapeutic approaches, focus on psilocybin
3. Review the neurobiology of psychedelics, role of serotonin 5-HT$_{2A}$, and results from current psychedelic research
4. Discuss challenges associated with psychedelic-assisted therapies
Prevalence Of Depression

- Affects approximately 8% of American adults in a given year\(^1\)
- Nearly twice as common in women than in men\(^{1,3}\)
- Of the adults reporting MDD, 63.8% reported severe impairment, representing 4.5% of adults in the US\(^2\)

<table>
<thead>
<tr>
<th>Depression Rate by Adult Age Group</th>
<th>18-25</th>
<th>26-49</th>
<th>50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>US depression rate</td>
<td>13.1</td>
<td>7.7</td>
<td>4.7</td>
</tr>
</tbody>
</table>

1. Brody et al 2018 NCHS Data Brief No 303

The projected median time between MDD onset and first contact with a care provider\(^4\) is 8 years.

The information provided by PsychU is intended for your educational benefit only. It is not intended as, nor is it a substitute for medical care or advice or professional diagnosis. Users seeking medical advice should consult with their physician or other health care professional.
The Personal Burden Of MDD Can Be Significant And Wide-Ranging

Marital dissatisfaction/discord and negative parenting behaviours are strongly related to symptoms of depression.¹

MDD is significantly associated with chronic physical disorders including arthritis, asthma, cancer, diabetes, cardiovascular disease and pain.¹

Personal earnings and household income of people with MDD are substantially lower than those without depression.¹

People with MDD have the highest number of days away from work of any physical or mental disorder.¹

**Psychedelics**

- **Psychedelics** are psychoactive substances that alter perception, mood, and numerous cognitive processes\(^1\).
- The classic serotonergic psychedelics are classified by the DEA as Schedule I Substances and include LSD, psilocybin, dimethyltryptamine (DMT), and mescaline\(^2,3\).
  - Historical use in healing and religious rituals\(^1\)
  - Extensively studied in 1950s and 60s\(^1\)
  - Associated with the counter-culture movement of the 1960s and 1970s\(^2\)
  - Resurgence of research on the potential therapeutic benefits\(^4\)

---

**Timeline**

1938 - LSD discovered\(^4\)
1950 - Psilocybin "Good Friday Experiment"\(^1\)
1962 - Controlled Substances Act\(^1\)
1970 - Psilocybin granted FDA "Breakthrough Therapy" status for treatment-resistant depression\(^5\)
1990 - Research resumed, first clinical trials initiated in early 2000’s\(^2\)
2000 - Psilocybin granted FDA "Breakthrough Therapy" status for MDD\(^5\)
2018
2019

**Approximately 1,000 studies on potential therapeutic uses of psychedelics**\(^1\)

---

LSD, lysergic acid diethylamide; DMT, N,N-dimethyltryptamine; DEA, Drug Enforcement Administration; FDA, Food and Drug Administration; MDD, Major Depressive Disorder

2. Dos Santos RG and Hallak JEC. *Neurosci Biobehav Rev*. 2020;423-434
Psilocybin effects have been shown to correlate with 5-HT<sub>2A</sub> occupancy and plasma psilocin<sup>5</sup>

- **Psychedelics bind to additional 5-HT receptor subtypes, possibly contributing to the therapeutic effects<sup>6</sup>**

---

6. Dos Santos RG and Hallak JEC. *Neurosci Biobehav Rev.* 2020;423
**5-HT<sub>2A</sub> Receptors**

- Implicated in various physiological functions and neuropsychiatric disorders<sup>1</sup>
- One of at least 14 identified 5-HT receptor subtypes<sup>2</sup>
- 5-HT<sub>2A</sub> receptors are G-protein coupled that modulate neurotransmission, including GABA and glutamate signaling<sup>1</sup>
- Evidence of “functional selectivity” (aka biased signaling), potentially resulting in ligand-specific differences in signaling pathways following activation of this receptor<sup>3</sup>

5-HT, serotonin; GABA, gamma-aminobutyric acid; β-arr, beta-arrestin

---

1. Guiard BP and Di Giovanni G. *Front in Pharm.* 2015;6(46)
5. Dos Santos RG and Hallak JEC. *Neurosci Biobehav Rev.* 2020;423-434

---

The information provided by PsychU is intended for your educational benefit only. It is not intended as, nor is it a substitute for medical care or advice or professional diagnosis. Users seeking medical advice should consult with their physician or other health care professional.
5-HT$_{2A}$ Receptor Localization & Links to Depression

- 5-HT$_{2A}$ is widely distributed with high expression in areas of brain involved in sensory processing and cognition$^1$
- Increased cortical expression of 5-HT$_{2A}$ is seen in depressed and suicidal patients$^1$
- Hippocampal expression is decreased in depressed patients$^1$
- Expressed in regions of the Default Mode Network$^2$
  - Set of regions whose activity is high at rest and low during focused attention on the external environment$^3$
  - Major Depressive Disorder is associated with hyper-connectivity within this network and increased network activity during rumination$^4$
  - Psychedelics acutely decrease resting-state connectivity within this network$^2$

5-HT, Serotonin

2. Dos Santos RG and Hallak JEC. Neurosci Biobehav Rev. 2020;423-434

The information provided by PsychU is intended for your educational benefit only. It is not intended as, nor is it a substitute for medical care or advice or professional diagnosis. Users seeking medical advice should consult with their physician or other health care professional.
**Psychedelics:**

**Neurobiological Effects of 5-HT<sub>2A</sub> Activation**

**Neuroplasticity:** The ability of the brain to reorganize neuronal synapses and pathways in response to interactions with the environment (i.e. learning, injury, or drug actions)<sup>1,2</sup>

Psychedelics increase neuritogenesis, spinogenesis, and synaptogenesis, forms of neuroplasticity<sup>3</sup>

TrkB, mTOR, and 5-HT<sub>2A</sub> signaling underlie psychedelic-induced plasticity<sup>3</sup>

Psychedelics also exert potent anti-inflammatory effects through 5-HT<sub>2A</sub> receptor activation<sup>4</sup>

5-H, serotonin; TNFα, Tumor necrosis factor alpha; mTOR, mammalian target of rapamycin

---

1. Gulyaeva NV. *Biochem (Moscow).* 2017;82(3):237-242

---

**The information provided by PsychU is intended for your educational benefit only. It is not intended as, nor is it a substitute for medical care or advice or professional diagnosis. Users seeking medical advice should consult with their physician or other health care professional.**
Psilocybin-Assisted Therapy Sessions

<table>
<thead>
<tr>
<th>Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Interpersonal atmosphere between individual and study monitors¹</td>
</tr>
<tr>
<td>• Psychoeducation¹</td>
</tr>
<tr>
<td>• Explanation of study logistics¹</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing Sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pleasant surroundings, eye mask, and headphones/music²</td>
</tr>
<tr>
<td>• Two monitors present for non-directive support, but mostly uninterrupted inner “journey”³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Post-sessions where individuals discuss their experiences during the session, usually with the lead monitor¹</td>
</tr>
<tr>
<td>• Individuals generate their own insights and ideas from the experience¹</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Subjective Measures of mediating effects of the psychedelic experience (i.e. MEQ30 and ASC)⁴,⁵</td>
</tr>
<tr>
<td>• Outcome measures (i.e. HAM-D, MADRS, QIDS, and BDI)³</td>
</tr>
</tbody>
</table>

MEQ30, Mystical Experience Questionnaire; ASC, Altered State of Consciousness Rating Scale; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; QIDS, Quick Inventory of Depressive Symptomatology; BDI, Beck Depression Inventory

5. Roseman L et al. Front in Pharmacol. 2018;8:974
Psychedelic Research: Psilocybin

- In 2006, Griffiths et al published a double-blind clinical study in naïve volunteers showing significant positive changes in behavior and attitudes\(^1\)

- Acute psilocybin effects include reduced negative mood, increased positive mood, and reduced amygdala response to negative affective stimuli\(^2\)

- Two randomized controlled trials assessed patients with potentially life-threatening cancer and a DSM-IV diagnosis that included anxiety and/or mood symptoms\(^3,4\)
  - Unprecedented positive relief of anxiety and depression\(^5\)

Persisting Effects of Psilocybin Experience\(^6\)

- Significant reductions in measures of anxiety and depression were found at follow-up (avg 4.5 yrs)

- Participants appraised the psilocybin session as increasing life satisfaction or wellbeing at a rate of 86%

---

Psychedelic Research: DMT & LSD

- Ayahuasca is a plant based preparation that contains DMT and monoamine-oxidase inhibitors, which decrease the metabolism of DMT and allow for psychoactive brain concentrations\(^1\)

- Preclinical assessments, studies in healthy volunteers, and clinical studies in patient populations, suggest that ayahuasca has antidepressant and anxiolytic properties\(^1\)

- In a double-blind randomized placebo controlled trial in 29 patients with treatment resistant depression, a single dose of ayahuasca resulted in a significant antidepressant effect compared to placebo\(^2\)

- Ongoing clinical trial assessing the benefits of LSD-assisted psychotherapy in patients with major depressive disorder\(^3\)
  - LSD and psilocybin alleviate depressive-like symptoms in the rodent forced swim test\(^4\)

N,N-Dimethyltryptamine (DMT); lysergic acid diethylamide (LSD)

1. Dos Santos RG and Hallak JEC. Neurosci Biobehav Rev. 2020;423-434
Challenges with Psychedelic-Assisted Therapies

Patient Population Considerations
Not recommended for individuals with psychotic disorders, or a family history of schizophrenia or bipolar I or II disorder.

Certain medications may alter the effects of a hallucinogen and individuals taking them should be excluded from participation.

Clinical Trial Design
Blinded Placebo Control
Study Personnel

Therapeutic vs Recreational Use
Young adults who use hallucinogens have problems with a range of addictive substances and unhealthy behaviors.

No Significant Adverse Events in Modern Trials
Reports of elevated blood pressure and heart rate, psychological discomfort (e.g. anxious or dysphoric reactions), physical discomfort (e.g. nausea/vomiting and headaches). Can be managed with appropriate safeguards.

Download The PsychU App Today!

All of Your Resources In One Spot

- Webinars & Live Events
- Resource Library
- Psychiatric Scales Collection
- Patient & Caregiver Corner

Download Now

© 2020 Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, MD          Lundbeck, LLC.
Psychedelics for the Treatment of Depression: Focus on 5-HT$_{2A}$