

Pharmacology  
Hallucinogens

Jeff Walterscheid, PhD

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**Learning objectives**

Investigating hallucinogens as agonists of the serotonin 2A receptor.

Identities of these substances and their similarity to natural serotonin:  
LSD   NBOMe   Psilocin   MDMA   DMT

Explore pharmacological activity and proposed use in treatment.

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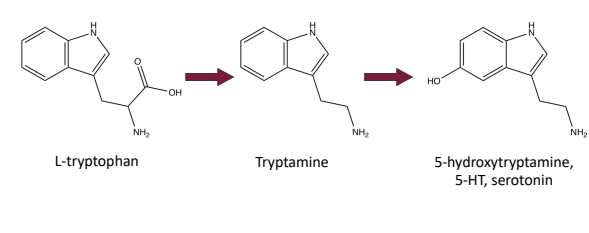
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### Serotonin biosynthesis



NC(Cc1c[nH]c2ccccc12)C(=O)O → NC(Cc1c[nH]c2ccccc12)N → NC(Cc1c[nH]c2cc(O)cc12)N

L-tryptophan      Tryptamine      5-hydroxytryptamine, 5-HT, serotonin

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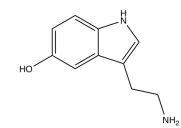
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### Serotonin function

- Produced by enterochromaffin cells in the gut.
- Absorbed by neurons, platelets, and immune cells to be stored and released when needed.
- In the body, it regulates temperature, blood pressure, sensations of touch and pain.
- In the brain, it modulates mood, behavior, sleep, and wakefulness.



NC(Cc1c[nH]c2cc(O)cc12)N

5-hydroxytryptamine, 5-HT, serotonin

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### Neurobiology of the brain

- The brain is an electrochemical computer composed of cells called neurons.
- Neurons release and respond to chemical messengers called neurotransmitters.
- Neurotransmitters are tightly regulated.



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**Hallucinogens mimic serotonin** DRUG IMPAIRMENT.COM

- Neurons absorb and release chemicals such as serotonin, which fills the gap between cells. This gap is called the synapse.
- When serotonin accumulates in the synapse, it reaches a threshold to bind and activate serotonin receptors in the adjacent neuron to propagate a signal.
- But when psychoactive drugs are introduced, there is no regulation so effects are unpredictable.




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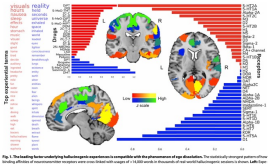
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**Hallucinogens mimic serotonin** DRUG IMPAIRMENT.COM

SCIENCE ADVANCES | RESEARCH ARTICLE

**NEUROSCIENCE**  
**Trips and neurotransmitters: Discovering principled patterns across 6850 hallucinogenic experiences**  
 Galen Ballentine<sup>1</sup>, Samuel Frouin Friedman<sup>2</sup>, Danilo Badoa<sup>1,3\*</sup>



- Under natural circumstances, activation of the serotonin 2A subtype allows you to experience creativity, dreaming, and imagination in a controlled fashion.
- Hallucinogenic drugs activate the serotonin 2A receptor subtype without any scheduling or regulation, so thoughts and perceptions can lead to dangerous behaviors and situations.

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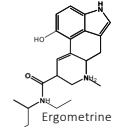
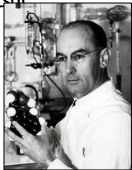
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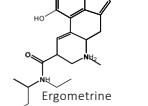
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**History of LSD** DRUG IMPAIRMENT.COM

**1938** Swiss chemist Albert Hofmann was developing a series of medications to intensify uterine contractions, one now known as lysergic acid diethylamide (LSD).



Ergometrine



Serotonin (5-HT)

LSD-25

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**History of LSD** DRUG IMPAIRMENT.COM

**1943** Hofmann absorbed some LSD and experienced its hallucinogenic effects.



Distorted awareness



Altered perception of time and space

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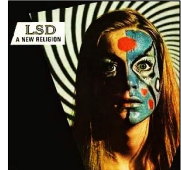
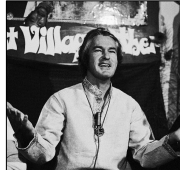
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**History of LSD** DRUG IMPAIRMENT.COM

**1960s** Recreational use spreads among drug enthusiasts.



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**History of LSD** 

**1970s** LSD becomes illegal, so availability and prevalence drops dramatically.



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**LSD has strong affinity to 5HT2AR** 

Psychopharmacology (1991) 136: 403-414 © Springer-Verlag 1991

**ORIGINAL INVESTIGATION**

Christina T. Eggen · Katharine Herrick-Davis  
Keith Miller · Richard A. Channon · Miki Tsuboi

**Agonist activity of LSD and lisuride at cloned 5HT<sub>2A</sub> and 5HT<sub>2C</sub> receptors**

Drug	K <sub>i</sub> (nM)
	5HT <sub>2A</sub>
LSD	1.3 ± 0.6
Lisuride	12 ± 4.6
DOM	225 ± 115
5HT	262 ± 57

• The lower the numbers are, the stronger the drugs are in binding to the serotonin 2A receptor.

• Serotonin (5HT): 262  
LSD: 1.3  
Therefore, LSD is about 200x more likely to bind than serotonin.

• Doses are micrograms instead of milligrams.

Table 1: Affinities of hallucinogens at 5HT<sub>2</sub> receptors.

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## LSD and direct toxicity

**What is a fatal dose of LSD?**

- Most resources point to the equivalent to 1000 times the usual street dose
- This translates into about 200–400 mg of LSD
- However, others have also mistakenly taken these doses and survived with supportive care

Apparently, LSD does not have the degree of physiological toxicity alleged by recent reports in the professional literature and in the media.

**Instead, fatalities are often traced back to:**

- excessive physical restraints
- lack of awareness when in physical danger
- suicidal thoughts and actions
- psychoactive drugs other than LSD

Forensic Science International

Journal homepage: www.elsevier.com/locate/forensi

Review Article

Is LSD toxic?

David E. Nichols<sup>a,\*</sup>, Charles S. Grib<sup>b</sup>

<sup>a</sup>Division of Forensic Science, University of North Carolina, Chapel Hill, NC 27599, USA  
<sup>b</sup>Department of Psychiatry, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA

Fig. 4. Blood plasma concentration of LSD after oral doses of 100 or 200 µg of LSD. See text for further information. Adapted from Odier et al. [10].

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## The real problem with LSD

**Self-inflicted neck wounds under influence of lysergic acid diethylamide**

**A case report and literature review**

Brendan La Dink, PharmD<sup>a,1,2</sup>, Thomas Goguel, PharmD, PhD<sup>3,4</sup>, Alan Bieri, MD<sup>5</sup>, Isabelle More, PharmD, PhD<sup>6,7</sup>, Renaud Boire, MD, PhD<sup>1,2</sup>

Figure 1. Knife found in the immediate vicinity of the body.

**Homicide and LSD**

Arthur Klapfke, MD, John Tracy, MD

**Abstract**

A 22-year-old student killed his girlfriend during a psychotic period which may have been precipitated by ingestion of lysergide. This closely followed another assaultive episode while he was under the influence of drugs. Prior to this, he had not had any untoward drug reaction.

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**Unpredictable effects of psilocin**  DRUG IMPAIRMENT.COM

**FORENSIC SCIENCES** *J Forensic Sci.* July 2016, Vol. 64, No. 4  
doi:10.1111/1751-4033.13362  
Available online at: onlinelibrary.wiley.com

**Unpredictable Behavior Under the Influence of "Magic Mushrooms": A Case Report and Review of the Literature\***


Zsuzsanna Horvath,<sup>1</sup> M.D., Anja-Liljeana Frenzel,<sup>2</sup> M.D., Sarah-Jane Carter,<sup>3</sup> Ph.D., Charles Anthony,<sup>4</sup> M.D., Anne-Sophie Adamski,<sup>5</sup> M.D., Fabian Brähler,<sup>6</sup> Ph.D., and Lorenz Fischer,<sup>7</sup> Ph.D.

**Case study of an 18 year-old male victim:**

- He was at home with friends where they ingested psilocybin mushrooms.
- He undressed in the bathroom and then came out acting unusually aggressive and excited.
- He then ran out on the balcony and jumped.

**Results from investigation:**

- A forensic autopsy found fatal head and thoracic trauma.
- The gastric contents contained partially digested *Psilocybe* mushrooms.
- He had no significant psychiatric history, but wanted to try mushrooms to overcome his shyness.



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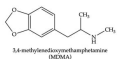
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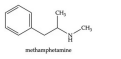
**MDMA is a favored party drug**  DRUG IMPAIRMENT.COM



- MDMA is short for: methylenedioxymethamphetamine
- Although it alters perception like other hallucinogens, it is more of a stimulant:



3,4-methylenedioxyamphetamine (MDA)



methamphetamine

- These properties give flashing lights and thumping music a heightened sensory experience.
- The stimulatory properties promote feelings of high energy and wakefulness.
- Because of its influence on serotonin, users want to touch others and be touched, also known as an entactogen response.

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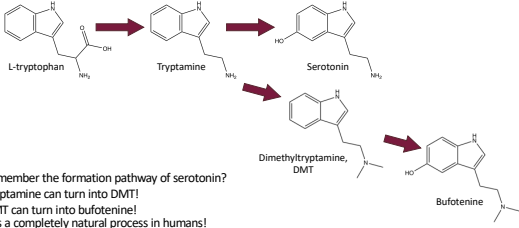
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**Serotonin and DMT** 



NC(Cc1c[nH]c2ccccc12)C(=O)O → NC(Cc1c[nH]c2ccccc12)N → NC(Cc1c[nH]c2cc(O)c12)N → CN(C)C(Cc1c[nH]c2cc(O)c12)N → CN(C)C(Cc1c[nH]c2cc(O)c(O)c12)N

- Remember the formation pathway of serotonin?
- Tryptamine can turn into DMT!
- DMT can turn into bufotenine!
- It is a completely natural process in humans!

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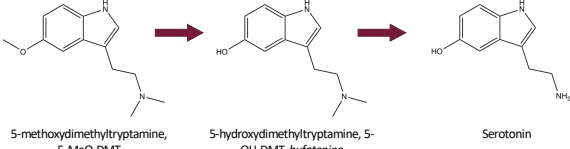
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**Related tryptamines** 



CN(C)C(Cc1c[nH]c2cc(OC)c12)N → CN(C)C(Cc1c[nH]c2cc(O)c12)N → NC(Cc1c[nH]c2cc(O)c12)N

5-methoxydimethyltryptamine, 5-MeO-DMT      5-hydroxydimethyltryptamine, 5-OH-DMT, bufotenine      Serotonin

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### Binding potency comparisons

European Neuropsychopharmacology (2016) 26, 1327-1337  
**Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens**  
 Anna Rickitt<sup>1</sup>, Olivier D. Monin<sup>1</sup>, Marius C. Hoener<sup>2</sup>, Matthias E. Liechti<sup>1\*</sup>

- Binding studies show LSD and psilocin have among the strongest drug affinities for the serotonin receptor.
- Doses are relatively low, so toxicology detection is very challenging.

**Binding potency**

Substance	Ki (µM)
LSD	~0.05
5-MeO-NET	~0.05
Psilocin	~0.05
4-OH-1E-T	~0.1
5-MeO-1P-T	~0.15
DMT	~0.2
4-OH-DMT	~0.3
DMT	~0.4
5-MeO-DMT	~0.5

*Ki (µM)*  
smaller numbers = more potent

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### Receptor activation compared

European Neuropsychopharmacology (2016) 26, 1327-1337  
**Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens**  
 Anna Rickitt<sup>1</sup>, Olivier D. Monin<sup>1</sup>, Marius C. Hoener<sup>2</sup>, Matthias E. Liechti<sup>1\*</sup>

- The semi-synthetic tryptamines are stronger activators, but effects are fleeting.
- Doses are higher than LSD, but the metabolites disappear into natural biochemicals.

**Activation potency**

Substance	Ki (µM)
5-MeO-NET	~0.05
5-MeO-1P-T	~0.05
4-OH-1E-T	~0.05
DMT	~0.1
4-OH-DMT	~0.15
DMT	~0.2
LSD	~0.3
Psilocin	~0.5

*Ki (µM)*  
smaller numbers = more potent

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### Social acceptance of hallucinogens

salon

**More States May Legalize Psychedelic Mushrooms**

**GOP New Hampshire Lawmaker Files Bill To Legalize Psychedelics Like LSD And Psilocybin**

**In defiance of federal drug law, mushroom dispensaries are popping up across North America**

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**Summary** 

- Hallucinogens mimic the effects of serotonin, but they are more potent and longer lasting.
- LSD is a synthetic drug that causes wild hallucinations and poses a safety risk to users and those around them.
- NBOMe is a more refined form of LSD with a proven history of acute fatal toxicity.
- Psilocin is a natural hallucinogen from magic mushrooms that can lead to unsafe situations.
- MDMA is a classic synthetic club drug known for its mixture of psychedelic and stimulatory properties.
- DMT is a naturally occurring tryptamine in the body that can be enriched to produce a short term psychedelic experience.
- There is continued interest in hallucinogens as treatments for depression and anxiety, but safety is still at risk.

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# Hallucinogen Pharmacology

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