

Ecstasy: Harmless Love Drug or Dangerous Neurotoxin?

Meg Benningfield, MD

Vanderbilt University

(Title Slide)

I. Introduction **(slide 2)**:

- A. Important public health challenge¹
- B. Millions of recreational users worldwide
- C. Animal research suggests irreversible neuronal death¹
- D. Proponents advocate clinical use² for anxiety, adjunct to therapy
- E. May see patients in ED or primary care
- F. This talk will review **(slide 3)**
 - 1. What ecstasy is
 - 2. Who uses it
 - 3. How it works
 - 4. Course and treatment

II. What ecstasy is (chemistry and history)

- A. Chemical name = 3,4-methylenedioxymethamphetamine **(slide 4)**
- B. Street names: E, XTC, Euphoria, X, Love Doves, Hug Drug, Disco Biscuit, Go
- C. Chemical structure: similar to amphetamines, hallucinogens **(slide 5)**
- D. MDMA content in tabs varies, may contain other contaminants **(slide 6)**
 - 1. Methamphetamine
 - 2. Caffeine
 - 3. Dextromethorphan (common ingredient in cough syrup)
 - 4. Ephedrine
 - 5. Cocaine
- E. History of development & use ^{1,2}**(slide 7)**
 - 1. 1912: Developed by Merck as pro-drug, not intended for clinical use

2. 1950s: Classified research by US military
3. 1970s-80s: Used as adjunct to therapy³
 - a. ↑self-esteem, insight, “therapeutic communication”
 - b. Induces warm, empathic feelings
 - c. ↓ fear, defensiveness
 - d. No clinical trials, no empirical evidence
4. 1980s: deaths in recreational users, legislators pursue restriction⁴
5. 1985: Classified Schedule 1 by FDA (no medicinal value)
6. 1980s-1990s: Recreational use ↑; eg. rave parties
7. 2000-present: 2 clinical trials: refractory PTSD, anxiety in cancer patients⁵

F. End section: what it is. Next: who uses it. **(slide 8)**

III. Who uses it

A. Epidemiology **(slide 9)**

1. Used by 9 mil annually worldwide⁶
2. 2.1 mil past year use in US (2008)⁷
3. 8-12th graders: 4.1% in 2008
4. Over 60% 12 graders say “easy to get”

B. Typical user is young (age 18-20), partygoer, poly-drug user **(slide 10)**

C. Pattern of use⁸ **(slide 11)**

1. Enhance dancing, social encounters
2. 1 to 4 pills per occasion
3. Dancing, ↑ temperature, ↑↑ water ingestion → serious consequences
4. Higher lifetime and per episode doses → ↑ risk severe consequences¹
5. Use typically ends after 20s (like many other drugs)⁹

D. Poly drug use common **(slide 12)**

1. >90% ecstasy users also currently use other drugs¹⁰
2. % who used other drugs ≥ 5x in lifetime ¹¹

- a. Alcohol: 100%
- b. Marijuana: 98%
- c. Tobacco 87%
- d. Other hallucinogens: 67%
- e. Amphetamines: 64%
- f. Cocaine: 50%
- g. Opioids: 40%
- h. Nitrous oxide 39%

E. Other risky behaviors also common¹²⁻¹⁶: **(slide 13)**

- 1. More impulsive
- 2. Sexual behavior
 - a. ↑ number of partners
 - b. ↓condom use
- 3. Not known whether these behaviors pre-date ecstasy use

F. End of section: who uses MDMA. Next: how it works

IV. How ecstasy works **(slide 14)**

A. Desired effects: Energy, Empathy, Euphoria¹⁷ **(slide 15)**

B. Common undesired effects¹⁸ **(slide 16)**:

- 1. ↑ BP
- 2. ↑ HR
- 3. ↑ Temperature
- 4. Tremor
- 5. Nausea
- 6. Jaw clenching (trismus)
- 7. Teeth grinding (bruxism)
- 8. Hyponatremia: ↑ water ingestion, sweating → ↓ sodium

C. Rare, serious effects¹⁸ **(slide 17)**:

1. Severe hyperthermia (up to 42° C)¹⁹
2. Rhabdomyolysis (muscle breakdown with potential renal failure)
3. Disseminated intravascular coagulation (disruption of blood clotting)
4. Multi-organ failure (kidneys, liver, pulmonary, cardiac)
5. Seizure (from hyponatremia from ↑water ingestion)
6. Intracranial bleeding or cerebral infarction
7. Death

D. Special case of acute toxicity: serotonin syndrome⁸ (**slide 18**)

1. Also associated with other drugs including antidepressants
2. Hyperactivity (increased movement, restlessness)
3. Confusion (check orientation to person, place, time)
4. Agitation (may be combative)
5. Hyper active reflexes
6. ↑ temperature
7. Tachycardia
8. Shivering
9. Clonus (brisk flexion at ankle → beats of foot extension)
10. Myoclonus (muscle twitching)
11. Ocular oscillations (check for nystagmus)
12. Tremor
13. Mortality 10-15%

E. Dehydration and ↑activity → ↑risk of serious side effects (**slide 19**)

C. Mechanism of action is related to serotonin transmission (**slide 20**)

1. Serotonin distribution in brain. Projects from brainstem to:
 - a. Hippocampus
 - b. Basal ganglia
 - c. Thalamus

- d. Amygdala
 - e. Primary sensory cortex
2. Serotonin contributes to:
 - a. Mood – depression and anxiety
 - b. Regulation of drives: sleep, appetite
 - c. Fight or flight response
 - d. Learning
 - e. Reward
 3. Review of neurotransmitter function (**slide 21**):
 - a. Synthesized in cytoplasm
 - b. Released from vesicles into synaptic cleft
 - c. Bind to post-synaptic receptors (producing effect)
 - d. Re-uptake by transporters (clearing synaptic levels)
 - e. Breakdown by enzymes (monoamine oxidase)
 - f. Pre-synaptic receptors regulate release by feedback loop
 4. Complex effects²⁰ at synapse (**slide 22**)
 - a. MDMA enters cell through serotonin transporter (5-HTT) (**slide 23**)
 - b. Release 5-HT from vesicles → ↑ intracellular 5-HT (**slide 24**)
 - c. Reverses direction 5-HTT → dumps 5-HT into synapse (**slide 25**)
 - d. Inhibits MAO-B → blocks breakdown of 5-HT (**slide 26**)
 - e. Inhibits tryptophan hydroxylase → blocks 5HT synthesis (**slide 27**)
 - f. 5-HT binds 2A receptor → hallucinogenic effects (**slide 28**)
 5. Overall effect is initial ↑ extracellular 5-HT, then overall 5-HT depletion
- D. Ricaurte group:²¹ loss of serotonin neurons with exposure (**slide 29**)
1. Left: serotonin neurons in healthy monkey brain
 2. Right: after exposure to MDMA shows decrease
 3. Density of serotonin neurons not normal after 7 years

E. End section: what it does and mechanism of action. Next: course and treatment.

V. Course and treatment (**slide 30**)

A. Emergency management²² (**slide 31**)

1. 16,000 ED visits mentioning MDMA/year
2. ~1.6 % of the total 958,164 illicit drug visits
3. M=F
4. 75% younger than 26
5. 72% visits related to combined drugs
 - a. 40% alcohol
 - b. 20% cocaine
 - c. 39% marijuana
 - d. ≤5% ketamine, LSD, GHB, amphetamine, meth, heroin

B. Case: 24 year old woman presents to ED ²³ (**slide 32**)

1. Agitated, combative, diaphoretic
2. Visual hallucinations
3. Complained of body tingling
4. No memory of ensuing events
5. Friend reports ingested 100 mg MDMA 2 hours earlier
6. Denied other drugs

C. Emergency management¹⁸ (**slide 33**)

1. If ≤ 1h post ingestion → activated charcoal 50g po/ng to ↓ absorption
2. Close monitoring HR, BP, T
3. Labs:
 - a. ↑BUN, ↑creatinine (dehydration)
 - b. Electrolytes (for hyponatremia, Na<115 to 120 → risk of seizure)
 - c. ↑ liver function tests (presumed from hyperthermia, direct toxicity)
 - d. ↑ CPK (muscle breakdown)

- e. Urine drug screen for other drugs of abuse
 - f. Clotting profile (for disseminated intravascular coagulation)
 - g. Arterial blood gas (for metabolic acidosis: pH<7.3)
4. ECG (look for tachycardia, non-specific ST-T changes, peaked Ts, arrhythmias)
5. Treatment of acute effects (**slide 34**)
- a. Hyperthermia: cooling blanket
 - b. Agitation: diazepam 0.1-0.3 mg/kg po/iv (~5-30 mg)
 - c. Hyponatremia: fluid restrict, usually self-corrects
 - d. Hypertensive crisis (BP> 180/120): labetalol (40-80 mg iv q10min)
 - e. Hypotension: fluids
 - f. Admit to ICU, ventilate if needed, fluid resuscitation to maintain BP, etc.
6. Case outcome (**slide 35**)
- a. Required ICU admission with intubation
 - b. Resuscitated with fluids
 - c. Agitation treated
 - d. All complications resolved over 7 days
- D. Heavy use may → depression, anxiety, paranoia^{13;24;25} but no clear causal relationship (**slide 36**)
- E. Persistent use may → abuse or dependence—ecstasy itself or other drugs used ^{11;26} (**slide 37**)
1. Drug abuse is ≥1 in 12 months (**slide 38**)
- a. Inability to fulfill role obligations
 - b. Use in physically hazardous situations
 - c. Legal problems
 - d. Social or interpersonal problems
 - e. Never met criteria for dependence
2. Drug dependence is ≥3 in 12 months (**slide 39**)
- a. Larger / longer than intended
 - b. Desire or attempts to cut down

- c. Time spent
 - d. Give up activities
 - e. Ongoing use despite problems
 - f. Tolerance: need amount for desired effect
 - g. Withdrawal: stop or ↓use results in physiological signs/symptoms
3. DSM criteria are for drug class. Some debate where ecstasy fits (**slide 40**)
- a. Most classify as hallucinogen
 - b. Some stimulant effects like amphetamine
 - c. Lacks amphetamine-specific withdrawal profile
- F. Screening/brief intervention (5A's) to be determined for each drug used (**slide 41**)
- 1. Assess consumption of ecstasy and other drugs
 - 2. Advise—provide education about potential danger of use
 - 3. Agree on goals (patient centered)
 - 4. Assist in motivation to decrease use or abstain
 - 5. Arrange for referral to treatment as needed
- G. SBIRT is collaborative (**slide 42**)
- 1. Goal: enhance motivation for change
 - 2. Principles summarized by acronym FRAMES
- H. Case 2: management of chronic complications (**slide 43**)
- 1. 26 yo M presents to primary care with
 - a. Chest pain
 - b. Trouble breathing
 - c. Trouble sleeping
 - d. Stopped going to work, class
 - e. History of chronic ecstasy use (**slide 44**)
 - f. Now using benzodiazepines acquired from friend
 - g. Developed tolerance

- h. Knows he should cut back, but feels shaky if stops using
- i. Requests prescription for more "nerve pills"

2. Patient requires treatment for benzodiazepine dependence and anxiety (**slide 45**)

VI. Summary of what we have covered (**slide 46**)

- A. MDMA used by millions worldwide
- B. Alters neurotransmission, especially serotonin
- C. Potential serious acute and long term side effects
- D. Emergency management of acute effects
- E. Screening and brief intervention for problematic use
- F. Intervention with chronic use followed by benzodiazepine dependence

Reference List

- (1) Green AR, Mehan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacological Reviews* 2003;55:463-508.
- (2) Pentney AR. An exploration of the history and controversies surrounding MDMA and MDA. *Journal of Psychoactive Drugs* 2001;33:213-221.
- (3) Grinspoon L, Bakalar JB. Can drugs be used to enhance the psychotherapeutic process? *Am J Psychother* 1986;40:393-404.
- (4) Green AR, Cross AJ, Goodwin GM. Review of the Pharmacology and Clinical-Pharmacology of 3,4-Methylenedioxymethamphetamine (Mdma Or Ecstasy). *Psychopharmacology* 1995;119:247-260.
- (5) Doblin R. A clinical plan for MDMA (Ecstasy) in the treatment of posttraumatic stress disorder (PTSD): partnering with the FDA. *J Psychoactive Drugs* 2002;34:185-194.
- (6) United Nations Office on Drugs and Crime. UNODC World Drug Report. 2007. Vienna.
- (7) Substance Abuse and Mental Health Services Administration. Results from the 2008 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-36, HHS Publication No. SMA 09-4434). 2009. Rockville, MD.
- (8) Parrott AC. Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. *Human Psychopharmacology-Clinical and Experimental* 2001;16:557-577.
- (9) von Sydow K, Lieb R, Pfister H, Hofler M, Wittchen HU. Use, abuse and dependence of ecstasy and related drugs in adolescents and young adults - a transient phenomenon? Results from a longitudinal community study. *Drug and Alcohol Dependence* 2002;66:147-159.

- (10) Substance Abuse and Mental Health Services Administration. Results from the 2008 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-36, HHS Publication No. SMA 09-4434). 2009. Rockville, MD.
- (11) Cottler LB, Womack SB, Compton WM, Ben-Abdallah A. Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria. *Human Psychopharmacology-Clinical and Experimental* 2001;16:599-606.
- (12) McElrath K. MDMA and sexual behavior: Ecstasy users' perceptions about sexuality and sexual risk. *Substance Use & Misuse* 2005;40:1461-1477.
- (13) Singer LT, Linares TJ, Ntiri S, Henry R, Minnes S. Psychosocial profiles of older adolescent MDMA users. *Drug and Alcohol Dependence* 2004;74:245-252.
- (14) Sterk CE, Klein H, Elifson KW. Young Adult Ecstasy Users and Multiple Sexual Partners: Understanding the Factors Underlying this HIV Risk Practice. *Journal of Psychoactive Drugs* 2008;40:237-244.
- (15) Theall KP, Elifson KW, Sterk CE. Sex, touch, and HIV risk among ecstasy users. *Aids and Behavior* 2006;10:169-178.
- (16) Wu LT, Parrott AC, Ringwalt CL, Patkar AA, Mannelli P, Blazer DG. The high prevalence of substance use disorders among recent MDMA users compared with other drug users: Implications for intervention. *Addict Behav* 2009;34:654-661.
- (17) Gouzoulis-Mayfrank E, Daumann J. Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: how strong is the evidence for persistent brain damage? *Addiction* 2006;101:348-361.
- (18) Hall AP, Henry JA. Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management. *British Journal of Anaesthesia* 2006;96:678-685.
- (19) Dar KJ, McBrien ME. MDMA induced hyperthermia: Report of a fatality and review of current therapy. *Intensive Care Medicine* 1996;22:995-996.
- (20) Capela JP, Carmo H, Remiao F, Bastos ML, Meisel A, Carvalho F. Molecular and Cellular Mechanisms of Ecstasy-Induced Neurotoxicity: An Overview. *Molecular Neurobiology* 2009;39:210-271.
- (21) Ricaurte GA, Forno LS, Wilson MA et al. (+/-)3,4-Methylenedioxymethamphetamine Selectively Damages Central Serotonergic Neurons in Nonhuman-Primates. *Jama-Journal of the American Medical Association* 1988;260:51-55.
- (22) DAWN Series D-30. DHHS Publication No. (SMA) 08-4339. 2008. Rockville, MD.
- (23) Brown C, Osterloh J. Multiple Severe Complications from Recreational Ingestion of Mdma (Ecstasy). *Jama-Journal of the American Medical Association* 1987;258:780-781.
- (24) Parrott AC, Lasky J. Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. *Psychopharmacology (Berl)* 1998;139:261-268.
- (25) Parrott AC, Sisk E, Turner JJD. Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. *Drug and Alcohol Dependence* 2000;60:105-110.
- (26) Cottler LB, Leung KS, Ben Abdallah A. Test-re-test reliability of DSM-IV adopted criteria for 3,4-methylenedioxymethamphetamine (MDMA) abuse and dependence: a cross-national study. *Addiction* 2009;104:1679-1690.

