Ecstasy: Harmless Love Drug or Dangerous Neurotoxin?

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(Title Slide)

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

A. Important public health challenge[1]

B. Millions of recreational users worldwide

C. Animal research suggests irreversible neuronal death[1]

D. Proponents advocate clinical use[2] 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. Methampehtamine
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 therapy[3]
    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 restriction[4]
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 patients[5]

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 worldwide[6]
    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 use[8] **(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 consequences[1]
    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 drugs[10]
    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 common[12-16]: **(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, Euphoria[17] **(slide 15)**

B. Common undesired effects[18] **(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 effects[18] **(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 syndrome[8] **(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 effects[20] 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 management[22] **(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 management[18] **(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, arrythmias)

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): labetolol (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

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