GHB, ECSTASY and KETAMINE Club Drugs

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Ecstasy
- MDMA 3,4 – methylenedioxyamphetamine
- Substituted phenethylamines
- Hallucinogenic amphetamine
  – Similar to mescaline
- Historical use in psychotherapy
- DEA ban on MDMA in 1985
- MDMA often adulterated
**MDMA and Methamphetamine**

1914: E. Merck Pharmaceutical company obtained a patent for MDMA in Germany

1950’s: The US Army conducts animal experiments with MDMA

1965: Alexander Shulgin a chemist at DOW predicts that MDMA is psychoactive

1970’s and early 1980’s: thought to improve interpersonal communications and enhance emotional awareness. MDMA evaluated as adjunct to psychotherapy

Rochester, JA, & Kirchner, JT. (1999). Ecstasy (3,4-methylenedioxymethamphetamine): history, neurochemistry, and toxicology. The journal of the American Board of Family Practice, 12(2), 137-42.

**History of MDMA/Ecstasy**

- 1985: MDMA was placed as Schedule 1 Controlled Substance by DEA citing increasing recreational use and concern over potential neurological damage
- 1990’s and 2000: Popularity increased at “Raves” or dance parties
  - http://www.maps.org/research/mdma/protocol/

Title goes here
**MDMA Mechanism of Action**

- Potent release of brain serotonin and inhibition of serotonin reuptake

- MDMA does NOT cause release of serotonin via exocytosis of serotonin containing secretory vesicles. MDMA causes a reverse in the direction of the normal inward bound serotonin reuptake channel and is taken up into the cell via the serotonin uptake channel and/or through diffusion across the membrane.

- Within the cell MDMA is known to deplete stores of tryptophan hydroxylase (TPH) via acute oxidative inactivation.

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**Amphetamine-Like Effects of MDMA**

- MDMA stimulates sympathetic and central nervous systems due to structural similarity to the endogenous catecholamines

- MDMA has biphasic effect on serotonergic neurons in rats:
  - Acutely serotonin levels fall 3 to 6 hours after drug and return to near normal by 24 hours; Depletion secondary to serotonin secretion from the neurons: Levels decrease again by 1 week Long-term depletion occurs because of toxic degeneration of the serotonergic nerve terminals.
  - Schmidt CJ J Pharmacol Exp Ther. 1987 Jan;240(1):1-7
  - Koesters, SC, et al., 2002; Smith, KM, et al., 2002
  - Image: [www.chem.psu.edu/imagetech/research/andrewsfig1.html](http://www.chem.psu.edu/imagetech/research/andrewsfig1.html)
### Subjective Effects of MDMA
- Altered time perception
- Increased ability to interact with others
- Decreased defensiveness
- Changes in visual perceptions
- Increased awareness of emotions
- Decreased aggression
- Decreased restlessness
- Less impulsive

Leister M et al, J of Nerv Ment Dis, 1992; 180:345-352
McDowell & Kleber, Psychiatric Annals 1994; 24:127-130

### MDMA Adverse Effects
- Mydriasis
- Marked rise in plasma cortisol and prolactin concentrations
- Increase in BP and heart rate
- Bruxism
- Increased restlessness
- Increased anxiety – panic
- Depressed mood
- Nystagmus
- Motor tics
- Headaches
- Anhedonia
- Lethargy
- Anorexia
- Decreased motivation

McDowell & Kleber, Psychiatric Annals 1994; 24:127-130
de la Torre R et al Ann N Y Acad Sci. 2000 Sep;914:225-37
MDMA Adverse Effects

- Hyperpyrexia, rhabdomyolysis and multi-organ failure
  - Prolonged exertion
  - Warm environment
  - Prolonged repetitive activity
  - Disregard for body signals (thirst, exhaustion)
  - Increased muscle tone
- Serotonin syndrome
  - Rapid onset, confusion, diaphoresis, diarrhea, increased muscle tone, rigidity, cardiovascular instability, tremor, myoclonus, muscle contraction
  - Hall & Henry Br J of Anaes 96 (6) 2006

MDMA Research Used Wrong Drug

George Ricaurte, et al. Science September 2002 - paper retracted 1 year later
- People taking MDMA for just one night might later develop Parkinson's disease
- Indicated that 3 consecutive doses of MDMA given to squirrel monkeys and baboons caused damage to dopaminergic neurons
- Animals were injected with MDMA at three-hour intervals to mimic the way humans take the drug; 2 of 10 died within hours after developing hyperthermia.
  
Retraction stated team discovered that all but one of the animals received methamphetamine
PET Scans

New studies suggest long-term MDMA usage may lead to permanent brain damage.

Drug users: darker = less serotonin activity

MDMA and psychiatric Disorders

- Much of the literature is from case reports.
- Patient developed florid paranoid psychosis after long-term MDMA use and EEG changes intermittent paroxysmal discharges.
- Patient developed atypical paranoid psychosis with Fregoli syndrome (delusional disorder) and complex-partial seizures with secondary generalization after first dose.


- Temporal pathway - childhood symptoms of anxiety and depression may precede use of MDMA.
  - Anja C Huizink et al BMJ 2006;332:825-828

What is the impact of Ecstasy on the brain across the lifespan?

- baby in womb, baby, child, teenager, adult, pensioner
MDMA Adverse Effects
- Serious acute illness are relatively rare
- Dilutional hyponatremia – cerebral edema
- Liver failure
  - In some cases it is a function of hyperpyrexia, shock and DIC
  - Other case reports of liver failure independent of hyperthermia
- Impaired driving – maybe fatal

MDMA and Cognitive Problems
- Multiple studies suggest memory and cognitive deficits proportional to the amount and duration of use
  - Verbal memory
  - Working memory
  - Episodic memory tasks
  - Attention
  - Frontal-executive function
- Do SSRI's provide neuroprotection?

De-coding the Message
- “Y” may be replaced by “E”
- “E” & “X” may be capitalized, hyphenated or underlined to accentuate it.
- “Drop & Roll” refers to dropping pills & rolling on MDMA.
RAVE

- All night dance party
- Electronically synthesized repetitive loud (techno) mind-numbing music
- Dress: “Lack of pretense” - baggy pants, glow sticks, infant toys, pacifiers, beads
- Diminished distinction based on physicality and sexual orientation
- Description of atmosphere: “safety, acceptance, hyper connectivity”
- Philosophy “Peace, Love, Unity and Respect”

Candy Flipping—LSD & MDMA
Hippy Flipping—Shrooms & MDMA
Love Flipping—Mescaline & MDMA
Kitty Flipping—Ketamine & MDMA
Elephant Flipping—PCP & MDMA
Robo Flipping—DXM & MDMA
Nexus Flipping—2-CB (Nexus) & MDMA
Lucky Flipping—2-CT-7 (Lucky 7) & MDMA
Time Flipping—DMT & MDMA
Adam & Eve in the garden of Eden—MDMA, MDEA & MBDB
Raves Today—Big Business

- Music, Venue, People, Drugs
- Noncommercial music - Independent artist distribute directly to DJs
- DJ can be the main draw for raver audience
- Now held in legal spaces: concert halls, sports centers, parking lots. Called: Venues or Concerts not Raves
- Many raves held on Holidays such as Valentines Day, Halloween and New Years Eve
- Usually no age restriction (no alcohol)
- Kids don’t live in small towns... They live in the Wide Web World. It is easy to find a rave near you!

Eye Candy

GHB
History of GHB

1960: Studied for induction of a sleep-like state with cardiovascular stability

1963: Naturally occurring chemical in the human brain

1960’s Anesthetic, abandoned because of poor analgesic effects


1970’s: first studied for treatment of narcolepsy/cataplexy

1980’s: marketed as a “fat burner and muscle developer”
  - Takahara et al Stimulatory effects of GHB on growth hormone and prolactin release in humans Journal of Clinical Endocrinology & Metabolism 1977;44(5)1014

1990: GHB banned by FDA from OTC sales

1990s: GHB replaced by precursor GBL gamma-butyrolactone

History of GHB

- 1990’s: Studied for treatment of opiate and alcohol withdrawal and maintenance therapy for alcohol dependence
- 1999 FDA recall of GBL containing products – replaced by 1,4-butanediol
- 1999 FDA declared 1,4-BD a Class I Health Hazard


History of GHB

- 2000: GHB implicated in drug facilitated sexual assault: President Clinton signed the Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act
- 2002: Zyrem (sodium oxybate) is approved for the treatment of cataplexy in patients with narcolepsy as a Schedule III but Schedule I for illicit use
- 2005: FDA approves Zyrem indication for the treatment of excessive daytime sleepiness in patients with narcolepsy
- 2005: Phase II trial of Zyrem for the treatment of fibromyalgia

GHB Survey Study

- Convenient sample - recruited by a newspaper advertisement
- 120 callers
- 42 came in for an interview
- Male 76%
- Caucasian 73%
- Heterosexual 70%
- Employed 69%
**GHB/GBL Analogs and Reported Uses**
- Gamma-Butyrolactone
- 2(3H) Furanone dihydro
- 1,4 Butanediol
- Sodium oxybate
- ZYREM
- Improve sleep
- Insomnia
- Dancing
- Avoid drug testing
- Antidepressant
- Antianxiety
- Socialize
- Weight lifting

**GHB/GBL Preparations**
- Blue Nitro
- Blue Nitro Vitality
- G3
- Gamma G
- GHRE
- Invigorate
- Jolt
- Remforce
- Renewtrient
- Revitalize Plus
- Revivarant
- Serenity
- Solar Water
- SomatoPro
- Thunder Nectar
- Verve
- Weight Belt Cleaner
- ZEN
- [www.ashesonthesea.com/ghb/analog s.htm#trinka2](http://www.ashesonthesea.com/ghb/analogs.htm#trinka2)

**GHB**
- Water-soluble four-carbon molecule
- Formed from the precursor gamma-butyrolactone (GBL)
- Recipe: GBL, heat to dissolve with sodium hydroxide
- Often sold as clear salty liquid
- Dose is the number of caps
GHB Pharmacology

- Cap concentration varies 500mg-5g
  - Jo Ellen Dyer SF Poison Control Center
- Rapidly absorbed, peak conc 20-60 min
- Half life is 20 minutes
- Almost completely oxidized to carbon dioxide
- Readily crosses the blood brain barrier and placenta

GHB Mechanism of Action

- Neurotransmitter or neuromodulator in mammalian brain
- Structurally related to GABA (gamma-aminobutyric acid) and is a metabolite of GABA
  - It does not bind to GABA₆ receptors; bind noncompetitively to GABA₁ but only when present in amounts larger than occur naturally
- High and low-affinity GHB receptor sites that are highly specific for GHB and whose distribution differs from GABA receptors

Galloway, GP, et al., 2000

GHB Mechanism of Action

- Highest density of GHB receptors is in the hippocampus, cortex, and dopaminergic areas (striatum, olfactory tracts, and substantia nigra)
- GHB inhibits dopamine release and activates tyrosine hydroxylase, that together act to increase central dopamine levels which could be associated with the reinforcing effects of GHB
GHB Use
Survey Study N=42

- How often do you use GHB
  - Every day 21.4%
  - 1-6 days/ week 35.7%
  - 1X/month or less 42.9%
- How many times per day
  - Once 28.6%
  - 2-3 times 42.9%
  - 4 or more 28.6%
- How much do you use at a time?
  - < 1 capful 9.5%
  - 1-3 capfuls 73.8%
  - > 3 capfuls 14.3%
  - Other 2.4%

A dose of GHB

- Sleep studies - 50 - 60 mg/kg/night 2 doses
- Alcohol studies - 50 - 150 mg/kg day divided doses
- Sodium Oxybate - 4.5 grams initial dose ½ at bedtime, ½ 2-4 hours later
- Titrator 1.5 grams q 2 weeks Max 9 grams
- Solution 500 mg/ml 1 month supply $750
- Central Pharmacy Xyrem Risk management System

Subjective Effects of GHB
Reported by > 50% of participants

- Euphoria
- Increased sexuality
- Wellbeing
- Relaxation
- Talkative
- Tranquility
- Tranquility
- Drowsy
- Optimism
- Increased energy
- Giddiness
- Increased sensitivity to sound
- Feeling silly
- Sweaty
- Loss of consciousness

Adverse Effects Associated with GHB

- Nausea
- Vomiting
- Enuresis
- Feeling drunk
- Disorientation
- Confusional state
- Respiratory depression in combination with other depressants
- Sleep walking
- Sleep paralysis
- Cataplexy
- Headache
- Blurred vision
- Dizziness
- Coma
- Overdose

Factors Associated with GHB Overdose

- Loss of Consciousness
- Alcohol Use
- Other Drug Use
- Unknown GHB Concentration
- Amnesia
- Anesthesia
- Suicide
- Withdrawal
- Confusion

GHB Abuse

- Tolerance
  - Down regulation of inhibitory GABA-A, GABA-B, GHB receptors
- Decreased GHB Consumption
- Dysinhibition of Excitatory Neurotransmitters
  - (Glutamate, NMDA, Norepinephrine, Dopamine)
- Withdrawal
- Anxiety
- Restlessness
- Insomnia
- Tremor
- Confusion
- Delirium
- Hallucinations
- Tachycardia
- Hypertension
- Nausea
- Vomiting
- Diaphoresis
### Temporal Pattern of the Symptoms of GHB Withdrawal

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>Early (1-24 hours)</th>
<th>Progressive (1-6 days)</th>
<th>Episodic when waning (7-14 days)</th>
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</thead>
<tbody>
<tr>
<td>Anxiety/Restlessness</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Delirium</td>
<td>+++</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Tachycardia</td>
<td>+</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Diaphoresis</td>
<td>+</td>
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</tr>
</tbody>
</table>

**Key:** Mild = +, Moderate = ++, Severe = +++

### GHB Withdrawal - Clinical Concerns
- Patients present to the ER with anxiety, confusion, and hallucinations - early manifestation withdrawal
- Antipsychotic are started and high dose benzodiazepines or barbiturates are delayed
- Agitated delirium develops with dehydration
- Restraints are need for the patient safety
- Autonomic changes independent of withdrawal severity
- Treatment setting: psychiatry, ICU, medical floor?
- Recommendation: start treatment early with benzodiazepines – load to sedation – patients are generally resistant to the sedative effects

### GHB -like Drugs Summary
- Evolving drug distribution system
  - Designed to defy FDA ban
  - Marketed as health aids
  - Internet sales
  - Sold by some body builders and personal trainers
- Drugs effects – amnesia, hypnotic, anxiolytic, myorelaxant, anesthetic
- GHB tolerance, dependence and withdrawal
- Major toxicity - Overdose
Take a little ‘K’ and
Meet the
“K- Monster”

PCP and Ketamine

History of Ketamine

- 1962: Developed and initially promoted as a fast acting general anesthetic
- 1970’s: Approved for human use by federal government, and as a result became popular as a battlefield anesthetic
- Late 1970’s and early 1980’s: Abuse began to increase across the country, especially among certain sub-cultures (e.g., mind explorers and New Age spiritualists)

University of Maryland, http://www.cesar.umd.edu/cesar/drugs/ketamine.asp
History of Ketamine

- Mid-1980s: Another increase in the social-recreational use was beginning to be linked to various dance or rave cultures
- 1999: Classified as a Schedule III controlled substance in August 1999, creating more stringent controls of the drug
- Late 1990: Ketamine and the treatment of pain
  - Low dose ketamine infusion
  - Ketamine tablets
  - Intranasal ketamine

Ketamine Mechanism of Action

- N-methyl-D-aspartate (NMDA) receptor antagonist
  Binds NMDA receptor, thus causing a blockade of calcium flow through these channels - Blockade of calcium associated with altered perception, memory, and cognition
- Some evidence suggests that ketamine can inhibit the reuptake of serotonin, dopamine, and norepinephrine
- NMDA blockade is associated with increased dopamine release in prefrontal cortex and midbrain
- NMDA blockade resulting from ketamine binding has also been linked to activation of serotonin systems, particularly serotonin 1A receptors

Ketamine

- Central nervous system depressant
- Rapid acting-acting dissociative anesthetic
  - General anesthesia characterized by catalepsy, catatonia, and amnesia, but not necessarily involving complete unconsciousness
- Sedative-hypnotic, analgesic and hallucinogenic properties
- Structurally similar to PCP and dextromethorphan
- N-methyl-D-aspartate (NMDA) antagonist

Ketamine

- Administration: intranasal, oral, smoked, injected
- 10 ml vials provide 5 doses
- Sell for $20 a dosage unit
- Rapid onset of effects
- Duration of effects 4-6 hours
- Street names: Special K, Vitamin K, KitKat, Blind squid, Super acid

Ketamine

- Muscle spasm
- Blurred vision
- Nystagmus
- Lack of coordination
- Dizziness
- Slurred speech
- Psychological effects
- Tolerance
- Dependence
- Anesthesia
- Cataplexy
- Immobility
- Tachycardia
- Increased blood pressure
- Profound insensitivity to pain
- Amnesia, slurred speech
Ketamine – “Special K”
- K-land desired state
- Dissociative effects called a “K-hole” – your brain is active but your body isn’t, “like you’re in a tunnel, your hear echoes, you’re in a semi-conscious state”
- Used at rave/dance club scene, "not as popular as in past"
- "like living inside a big cotton ball," “everything is in slow motion”
- flashbacks

Toxicity and Adverse Effects
- Emergence reactions: common during recovery, include unpleasant dreams, confusion, hallucinations and irrational behavior (children less susceptible), reduced by prior administration of a benzodiazepine
- “Out-of-body” state/experience: a psychological dissociation, “near death experience”
- “Flashbacks”

Conclusion Club Drugs
- NIDA’s “Initiative to Combat Club Drugs”
- www.clubdrugs.org
- Ecstasy and the Rave Culture
- GHB-like drugs
- Ketamine