Project: Ghana Emergency Medicine Collaborative

Document Title: Drugs of Abuse

Author(s): Tim Albertson, M.D., Ph.D. (University of California- Davis); Jim Holliman, M.D., F.A.E.C.P. (Pennsylvania State University) 2012

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Update on Drugs of Abuse ("some club-drug stuff")

Tim Albertson, M.D., Ph.D.
Professor of Medicine, Pharmacology and Toxicology
UC Davis School of Medicine
CPCS, Sacramento Division

Jim Holliman, M.D.
Penn State University
Overview of Topics

- Gamma hydroxybutyrate (GHB)
  - GHB
  - GHB Analogs
  - GHB / Analog Withdrawal

- Ecstasy: MDMA (Methylenedioxyamphetamine)
Overview of Topics

- Methamphetamine
- Dextromethorphan (DM)
- Ketamine
- Flunitrazepam
- Mescaline
- Inhalants
- Anticholinergics
GHB
(Gamma-hydroxybutyrate)
What is GHB?

- Gamma hydroxybutyrate
- Naturally occurring in brain tissue
  - neurotransmitter-like substance
  - dopamine release in substantia nigra
- Similar structure to GABA
- GABA-B agonist effects
- Approved for narcolepsy 2002
  - Sodium oxybate (Xyrem) Orphan Medical
  - 4.5 gms a night AWP $739 / month limited to certain pharmacies and physicians
GHB

- Investigated as an anesthetic agent: caused myoclonus and delirium; current IND for sleep apnea
- Crystalline salt
- Soluble in water and methanol
- Tasteless
- GBL-gamma-butyrolactone & BD-1,4 butanediol precursor molecules convert to GHB in-vivo
Structure Activity Relationship

\[
\begin{align*}
\text{COOH} & \quad \text{COOH} \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{OH} & \quad \text{NH}_2 \\
\text{GHB} & \quad \text{GABA} \\
\text{gamma} & \quad \text{gamma} \\
\text{hydroxybutyrate} & \quad \text{amino} \\
\ & \quad \text{butyric acid}
\end{align*}
\]
## History of GHB

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960’s</td>
<td>France - Synthesized as an Anesthetic</td>
</tr>
<tr>
<td>1987</td>
<td>Orphan Drug (IND-narcolepsy) ; USFDA</td>
</tr>
</tbody>
</table>
| 1990-1 | Body Builders “Undetectable steroid”  
*Growth hormone stimulator* |
| 1992-5 | Sleep aid, Rave party, Popularity rises |
| 1996 | Sexual enhancer, “Date-Rape” Drug |
| 1997 | Emergence of GHB Analogs  
Emergence of Withdrawal Cases |
| 2000 | Federal Schedule I status |
| 2002 | FDA approval for Narcolepsy : Xyrem |
Slang Names: Gamma Hydroxybutyrate

- Cherry meth
- Easy lay
- G, G caps
- Gamma hydrate
- Georgia home boy
- GHB
- GH Beers
- Liquid E
- Liquid X
- Liquid ecstasy
- Natural sleep 500
- Organic Quaalude
- Oxy sleep
- Scoop
What are GHB Analogs?

- **Organic solvents**
  - √-Butyrolactone, 2(3) Dihydrofuranone,
  - 1,4-Butanediol, Tetramethylene Glycol

- **Converted to GHB in vitro or in vivo**
  - *In vitro using NaOH, heat*
  - *In vivo (Lactonase enzymes) : GBL*
  - *In vivo (alcohol / aldehyde dehydrogenase)*

- **Identical clinical effects to GHB**
Conversion:
Gamma Butyrolactone (GBL)

\[ \text{O} \quad \overset{\text{NaOH + H}_2\text{O}}{\text{in vitro}} \quad \overset{\text{Lactonase}}{\text{in vivo}} \quad \text{C OOH} \]

\[ \text{CH}_2 \]

\[ \text{CH}_2 \quad \text{OH} \]

GBL

GHB
Gamma Butyrolactone (GBL)
Slang Names:
Gamma Butyrolactone or Dihydro Furanone

- Blue Nitro
- Firewater
- Furanone Extreme
- Gamma G
- GBL
- GH Release
- Insom-X
- Invigorate
- Jolt
- Liquid Libido
- Regenerize
- ReneTrient
- Revivarant
- Revivarant-G
Renewtrient and Blue Nitro, GHB precursors, have been removed from the market.
Slang Terms:
1,4 Butanediol or Tetramethylene glycol

- Biocopia PM
- Borametz
- BVM
- Enliven
- FX
- NRG3
- Inner G
- Thunder Nectar
- Pro G
- Promusol
- Rest-eze
- Revitalize Plus
- Serenity
- SomatoPro
Incidence: GHB and Precursors

Source Undetermined
Pathology

- Structurally similar to GABA
- Stimulates $\text{GABA}_B$ receptors
- Influences dopamine release from substantia nigra
- Readily crosses the BB barrier
GHB / Analogs: Clinical Presentation

- Vomiting, Coma, Bradycardia
- Myoclonic jerking
- Loss of protective airway reflexes
  - Aspiration risk
- Hypothermia, Mild respiratory acidosis
- HOTN when combined with ethanol
Effects

**“DESIRED”**
- Euphoria
- Mood elevation
- Hallucinations
- GH-Muscle growth?
- Amnesia

**UNDESIRED**
- Decreased HR, RR
- Coma
- Excessive salivation
- Absence-like sz’s
# Emergency Department (ED) Course of Gamma Hydroxybutyric Acid (GHB) Intoxication Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Intubated</th>
<th>Duration of Intubation</th>
<th>Time in ED if Not Admitted</th>
<th>Number Admitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chin et al. (n = 88)</td>
<td>13 %</td>
<td>179 min</td>
<td>NR</td>
<td>11 %</td>
</tr>
<tr>
<td>Mahon et al. (n = 8)</td>
<td>50 %</td>
<td>80 min</td>
<td>NR</td>
<td>0 %</td>
</tr>
<tr>
<td>Li et al. (n = 7)</td>
<td>57 %</td>
<td>210 min</td>
<td>360 min</td>
<td>43 %</td>
</tr>
<tr>
<td>Garrison &amp; Mueller (n = 78)</td>
<td>10 %</td>
<td>NR</td>
<td>180 min</td>
<td>4 %</td>
</tr>
</tbody>
</table>
Case Study ..... 

- 26 y/o F with chronic insomnia doubled her dose of Blue Nitro (GBL) : 3 oz.
  - Vomiting within 15 minutes
  - Pt was unresponsive within 30 minutes
  - Myoclonic jerking
  - EMS was called
  - VS: BP 120 / 70, HR 50, RR 22, T 35
Case Study continued …..

- Unresponsive to pain, GCS 3.
- CT scan normal, glucose 125
- No response to naloxone or flumazenil
- Woke up within 4 hours
- Discharged
- Urine Toxicology screen negative
<table>
<thead>
<tr>
<th>Kinetics Aspect</th>
<th>Time/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Coma</td>
<td>within 30 minutes</td>
</tr>
<tr>
<td>Peak</td>
<td>1 hour</td>
</tr>
<tr>
<td>T 1/2</td>
<td>Short</td>
</tr>
<tr>
<td>Duration</td>
<td>1 to 6 hours (Average 2.5 hr)</td>
</tr>
<tr>
<td>Most patients</td>
<td>require &lt; 5 hr observation</td>
</tr>
</tbody>
</table>
Emergence Delirium

- Myoclonic jerking motions
- Confusion, agitation, combativeness
  - Transient symptoms (< 30 minutes)
  - Symptoms worsen with stimulation
- Treatment
  - Supportive Care
  - Minimize stimulation. “Back off”
GHB / Analogs: Diagnosis

- History of use and circumstances
- Clinical Presentation
- Short Duration
- Role of Laboratory
  - Suspected assault
  - Obtain sample within 12 hours
  - National Medical Laboratories
GHB / Analogs: Treatment

- **Supportive Care**
  - Approximately 35% patients require airway protection

- **Gastrointestinal Decontamination**
  - Limited Value
  - Consider Charcoal in massive ingestions

- **Education regarding Dependence**
GHB Dependence : Case Study

- 29 year old male started taking GHB for the "anabolic effects" 2 yrs ago
- Gradually increased dose to 4 to 6 "capfuls" every 4 hours
- Discontinued the GHB cold turkey
- Arrived in ED 24 hr after his last dose
Case Study continued ….

- Patient was highly agitated
- Visual and auditory hallucinations
- Delusional, paranoid
- Tremulous, diaphoretic

- VS: HR 110, BP 160 / 112, T 99.1
Case Study continued ...

Patient received:
- Ativan: 90 mg in the first 24 hours
- Phenobarbital, Haloperidol

10 day withdrawal course

Discharged symptom and drug free
GHB Withdrawal

- Similar to ETOH and sedative-hypnotic withdrawal.

- Symptoms start within a few hours of discontinuation.

- Seen with long-term use or daily use.
GHB Withdrawal: Clinical Presentation

Onset: 1 to 6 hours

Progression of sx's over 1 to 3 days

Symptoms
  - Agitation, hallucinations, paranoia
  - Tremulous, diaphoretic
  - Tachycardic, hypertensive
  - Hyperthermia, Rhabdomyolysis possible

Duration: 5 to 15 days
GHB Withdrawal: Management

- **AGGRESSIVE TREATMENT EARLY**

- Benzodiazepines
  - High doses may be required

- Barbiturates

- Antipsychotics

- Unproven Therapy
  - Baclofen (GABA-B agonist)
Stimulants of Abuse

- Methamphetamine
- Methylene dioxymethamphetamine: MDMA (Ecstasy)
- Cocaine
- Ketamine / PCP (phencyclidine)
- Dextromethorphan
Rave Party : Case Study ...

18 year old F was at a Rave party with a friend. She was drinking ethanol and using the following:

- **Midnight** 1 tablet of Ecstasy
- **3 am** Snorted 1 line of Ketamine
- **5 am** Drank a “capful” of GHB

At 6:30 am patient found slumped in bathroom, cyanotic. EMS called.
Case Study continued …. 

- In ED, comatose but not cyanotic.
- Intubated for airway protection.
- No response to flumazenil or narcan
- VS: HR 58, BP 110 / 60, RR 16, p 5mm, T 37

- ICU admission. Woke up at 12 hours
- Extubated, discharged
Ketamine: Clinical Presentation

- Dissociative anesthetic

- Clinical Presentation
  - Separation of perception and sensation
  - Nystagmus, hallucinations, lethargy, sz
  - Tachycardia, HTN, RR depression
  - Hyperthermia

- Duration
  - 2 to 4 hours
Ketamine Treatment

- Supportive
- Sedation
Phencyclidine Effects

- Tremors, agitation, hallucinations: visual and auditory.
- Tachycardia, HTN.
- Wernicke-Korsakoff syndrome.

Treatment is same as for ketamine
Methamphetamine

- First synthesized by a Japanese pharmacologist in 1893
- Ephedrine most common precursor
- Red phosphorus-hydriotic acid most common reduction method.
- D-isomer: CNS stimulant effects.
- L-isomer: peripheral sympathomimetic activity.
Structures

- Phenethyllamine
- Amphetamine
- Methamphetamine
Production

- Ephedrine
- Methamphetamine
Pathology

- Increase release of neurotransmitters from nerve terminals.
- Serotoninergic and dopaminergic ATP decrease.
- 5HT and D2 depletion.
- Apoptosis
- Endothelial injury.
- Reactive oxygen species.
Model of Methamphetamine Neurotoxicity

$O_2, H_2O_2, OH, NO$

DNA Damage

P53 Regulated Genes
- Bax

$\uparrow$ P53

$\uparrow$ ROS

Terminal Degeneration Apoptosis

$\downarrow$ Bcl-2

$\uparrow$ Bax/Bcl-2

Cytochrome Release

$\uparrow$ Caspase Activation

Lena Carleton, University of Michigan
A: Acute overdose toxic model
e.g. 4 x 5 mg/kg

- Entry into cells by DAT and cationic lipophilicity
- Enters intracellular organelles including mitochondria and vesicles
- Raises organelle pH and alters enzyme activity. DA released from vesicles and oxidized
- Loss of DA function
- Mitochondrial permeability transition pore opens
- \( \uparrow \) Ca

Cell death

B: Chronic binge (continuous) model
e.g. 15 mg/kg/day \times 14 \text{ days}

- Increased glutamate release
- Increased DA release
- Increased Ca\(^{2+}\) efflux
- Increased RONS

Apoptotic cascades

- AIF cytochrome C
- Caspase 9

Source Undetermined
Signs and Symptoms

- **Action phase**
  - Skin picking
  - Head banging
  - Pacing
  - Paranoid psychosis
  - Extreme suspiciousness

- **Resolution phase**
  - Exhaustion
  - Fatigue
  - Sleep
  - Depression
Other Signs and Symptoms

- Pulmonary hypertension
- Dyspnea
- Pleuritic chest pain
- Anorexia/weight loss
- Ulcers
- Rhabdomyolysis
TESS DATA

Methamphetamine Exposures Without Concomitants, 2001
(Cardiovascular Effects)

Source: American Association of Poison Control Centers Toxic Exposure Surveillance System, 2001
Methamphetamine and the ED

- 6 months UCDMC ED ending February 1997
- 461 methamphetamine (+) patients
- Caucasian males without health insurance
- Increase use of ambulances and acute hospitalization
- Significant association with trauma: blunt 33% and penetrating 4%
- Altered LOC (23%), Abd pain (13%), suicide (8%), chest pain (8%), skin infections (6%)
Methamphetamine and Trauma

- UCDMC Level 1 Trauma Center
- Retrospective Study 1989 to 1994
- Results:
  - 18,004 pts; 3.1 / 1000 population per year
  - + methamphetamine defined as urine > 1000 ng / ml
  - Rates increased from 7.4 to 13.4 %
  - Cocaine rates 5.8 to 6.2 %
Methamphetamine and Trauma

- Decrease in ethanol from 43% to 35%
- Meth (+) most common in Caucasian or Hispanic
- Cocaine (+) most common African American
- Meth (+) in MVA or MCA’s
- Cocaine (+) in assaults, GSW’s or stab wounds

Schermer and Wisner, J Am Coll Surg 1999; 189: 442-449
Treatment

Don’t forget to r/o other causes:

– Look-alike diseases: e.g. Pheo, scorpion bites.

– Drugs: e.g. LSD, psilocybin-hallucinations, etc.

– Elevated temperature: e.g. malignant hyperthermia, NMS, anticholinergic syndrome.

– Seizures: e.g. cocaine, ETOH withdrawal.

– CVS: e.g. GHB withdrawal.
Treatment (cont.)

- Control stimulant effects
- Decontamination
- Control hyperthermia: how?
- Control seizures: how?
- Be careful of physical restraints.
- Treat psychiatric conditions.
What is Ecstasy (MDMA)?

- 3,4-Methylenedioxymethamphetamine
- Sympathetic effects mild in low doses
- Potent releaser of serotonin

Overdose
- Symptoms similar to amphetamines
- Risk of serotonin syndrome
- Risk of hyponatremia
  - SIADH and / or increased water intake
History of Ecstasy

- 1914: Patented as Appetite suppressant
  - *Never Marketed*
- 1970’s: Use by psychiatrists
- 1980’s: “LSD of the 60’s”
- 1990’s: Increasing abuse, Rave party use
- 2000: Continuing abuse
- Illicit adulterants common
Illicit Ecstasy Tablets

Drug Enforcement Agency, Wikimedia Commons
Pathology

- Similar to other amphetamines in causing release of catecholamines.
- Alpha and beta-adrenergic agonist.
- Can cause SIADH by an unclear mechanism.
Effects

**DESIRED**
- Increased energy
- Euphoria
- Empathy
- Visual hallucinations

**UNDESIRED**
- Jaw clenching
- Paranoia
- Hot / cold flashes
- Hyperpyrexia
- Seizures
Clinical Signs and Symptoms

- Rhabdomyolysis
- Hyponatremia
- DIC
- Renal failure
- Hepatotoxicity
- Aplastic anemia : rare
Illicit MDMA Adulterants

Assayed tablets have contained:

- MDMA
- MDMA with Caffeine
- Dextromethorphan 122 to 143 mg / tablet
- Caffeine
- Ephedrine, Pseudoephedrine, PPA
- Placebo
Treatment

- Similar to amphetamines and derivatives
- Controlling cerebral edema from hyponatremia important.
- Pneumomediastinum also an issue
- Controlling hyperthermia predicts survival in several studies
Dextromethorphan: Case Study ..... 

14 year old M ingested 30 Coricidin tablets to get high. At 2.5 hours:
- Lethargic, slurred speech, hallucinating
- Flushed, tremulous
- Nystagmus present

- VS: HR 114, BP 170 / 100, T 97.8, p 7mm
Dextromethorphan (DXMF) Abuse

- Many DXMF containing OTC products
- Coricidin: many combinations
  - DXMF 30 mg, CTM, APAP, PPA, etc.
- Teenage DXMF abuse is rising
- Easy OTC availability
Dextromethorphan

- Therapeutic doses: mild CNS effects
- High doses: significant CNS effects
- Specific DXMF receptors (opiate - sigma)
  - Anticholinergic-like symptoms
  - Hallucinations, delusion, dysphoria
- Opiate kappa and mu receptors
  - Opiate effects
Dextromethorphan: Treatment

- Gastrointestinal decontamination
- Narcan may be useful
- Supportive Care
- Laboratory
  - Rule out aspirin and acetaminophen
Mescaline

Source Undetermined
Characteristics

- Derived from peyote cactus.
- Hallucinogen.
- Can mimic an acute gastroenteritis
Mescaline Treatment

- Supportive
Flunitrazepam

- Used throughout Europe.
- Not approved in the US.
- One of the “date-rape” drugs.
- By weight 10x more potent than diazepam.
- Produces effects within 15 mins.
New Rohypnol tablets include a dye that make the drug visible if slipped into a drink
Pathology

- A benzodiazepine working on the $\text{GABA}_A$ receptor.

- Lipid soluble rapidly crossing the BB barrier.
Effects

“DESIRED”
- Euphoria
- Hallucinations
- Disinhibition
- SM relaxation
- Sedation
- Memory impairment

UNDESIRED
- Hypotension
- Drowsiness
- Apnea
- Urinary retention
- Tremors
Supportive care.

AC, lavage (use with caution, may be contraindicated)

Benzodiazepine antagonists (flumazenil):

NO!! (very few indications).
Inhalant Abuse

- Freon Propellants
- Xylene, Toluene
- Gasoline Fumes

United States Department of Defense, Wikimedia Commons
Anticholinergic Abuse

- Antihistamines
- Jimson Weed

Anticholinergic Syndrome:
- Mad as a hatter
- Blind as a bat
- Hot as Hades
- Dry as a bone
- Red as a beet
Summary

- **GHB / GHB Analogs**
  - Classic Symptoms in Overdose
  - Withdrawal Symptoms

- **Rave Parties**
  - Multiple drugs commonly used

- **Rising OTC Dextromethorphan Use**
  - Rule out aspirin and acetaminophen
Summary

- Methamphetamine is a major problem
- Older drugs of abuse have not gone away
  - PCP
  - LSD
  - Heroin
  - Cocaine
  - Ethanol
  - Marijuana