'E' to 'Bath Salts': Synthetic Psychostimulants and Hallucinogens

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Declarations and Disclaimers

Salaried, academic physician.

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This is a talk about drugs of abuse.

Nearly the entirety of this talk is off-label, if one exists.

Trade, product, and domain names are for identification purposes only and do not constitute endorsement.

My views do not necessarily reflect those of my employers or affiliations.

Question

A 24-year-old female presents with a seizure after attending an evening dance event. Her serum sodium is 120 mEq/L. The agent most likely to cause her symptoms is:

A. Gamma-hydroxybutyrate (GHB)
B. Ketamine
C. Lysergic acid diethylamide (LSD)
D. 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy")
E. "Spice" ("synthetic cannabinoid")

Educational Objectives

For the following substances:

a) Inhalants
b) "Club drugs" – MDMA ("Ecstasy"), GHB, Ketamine, DXM;
c) Hallucinogens – LSD, Mescaline, Psilocybin;
d) New and emerging drugs – Piperazines, Cannabinoid Receptor Agonists ("Spice"), Cathinones ("Bath Salts"), phenethylamine analogues (2C- and DO- series), "FLYs," NBOMe derivatives ("Bombs"), and Botannicals (Kratom, Salvia)

1. Understand their geography, epidemiology, cultural aspects, and/or special populations (GECS).
2. Understand genetics or pre-dispositions (G/PD).
3. Understand their (neuro)physiology (NP).
4. Recognize the presentations of acute and chronic intoxication, abuse, and dependence.
5. Understand potential therapies.

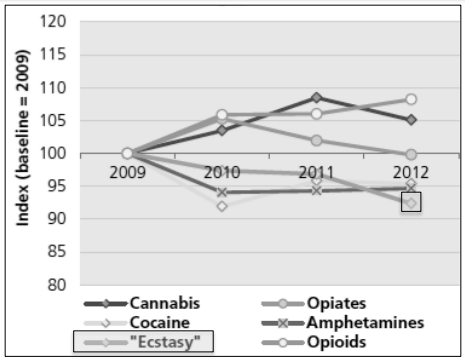
Epidemiological Perspectives

Global Use

Table 1. **Global estimates of users of different drugs, 2012**

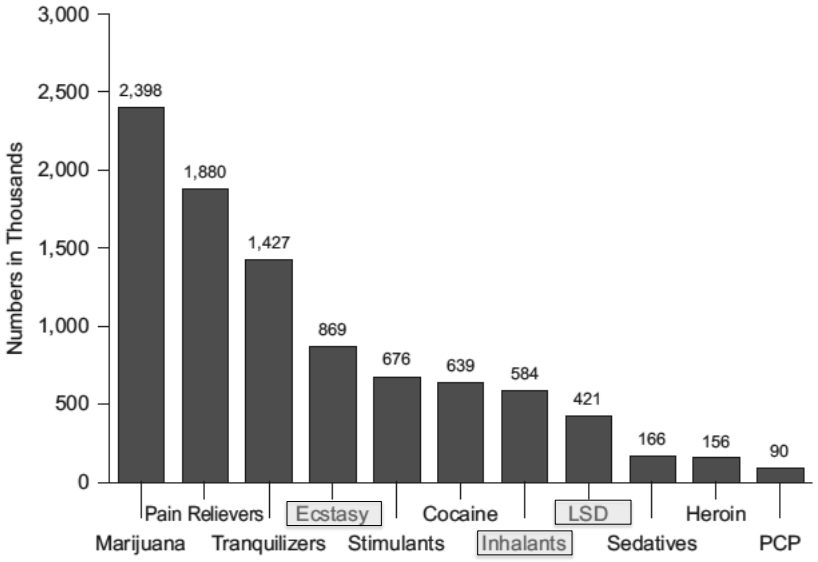
	Number of users (millions of users)			Prevalence (percentage)		
	Best estimate	Low	High	Best estimate	Low	High
Cannabis	177.63	125.30	227.27	3.8	2.7	4.9
Opioids	33.04	28.63	38.16	0.7	0.6	0.8
Opiates	16.37	12.80	20.23	0.35	0.28	0.43
Cocaine	17.24	13.99	20.92	0.37	0.30	0.45
ATS	34.40	13.94	54.81	0.7	0.3	1.2
"Ecstasy"	18.75	9.4	28.24	0.4	0.2	0.6

Trends in the prevalence of use of drugs 2009-2012



UNODC. 2014.

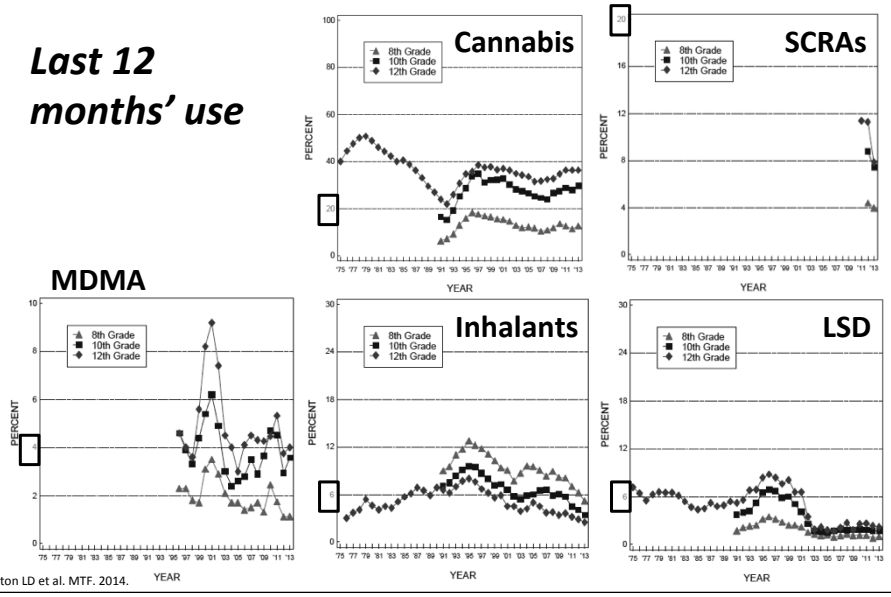
Drug Initiates (Past Year)



SAMHSA, 2013.

Adolescents

Last 12 months' use



Johnston LD et al. MTF. 2014.

"Clubbers"

USA (last 12 months)	US Prevalence	UK (last 12 months)	UK Prevalence
ETOH	87 %	ETOH	94.6 %
Cannabis	69.9 %	Tobacco	59.9 %
Tobacco	50.7 %	Cannabis	53.6 %
Energy Drinks	41.3 %	MDMA	45.2 %
E-cigarettes	23.9 %	Energy Drinks	44.7 %
Opioid painkillers	21.5 %	Cocaine	33.7 %
MDMA	20.7 %	E-cigarettes	23.4 %
Magic Mushrooms	20.4 %	Nitrous Oxide	20.4 %
Benzodiazepines	19.5 %	Ketamine	19.8 %
LSD	17.8 %	Shisha tobacco	15.7 %
Shisha tobacco	15.3 %	Opioid painkillers	14.7 %
Cocaine	14.9 %	Magic Mushrooms	14.7 %
Electronic THC	12.6 %	Benzodiazepines	12.4 %
Nitrous Oxide	8.2 %	LSD	12.2 %

Global Drug Survey. 2014

Drug Seizures

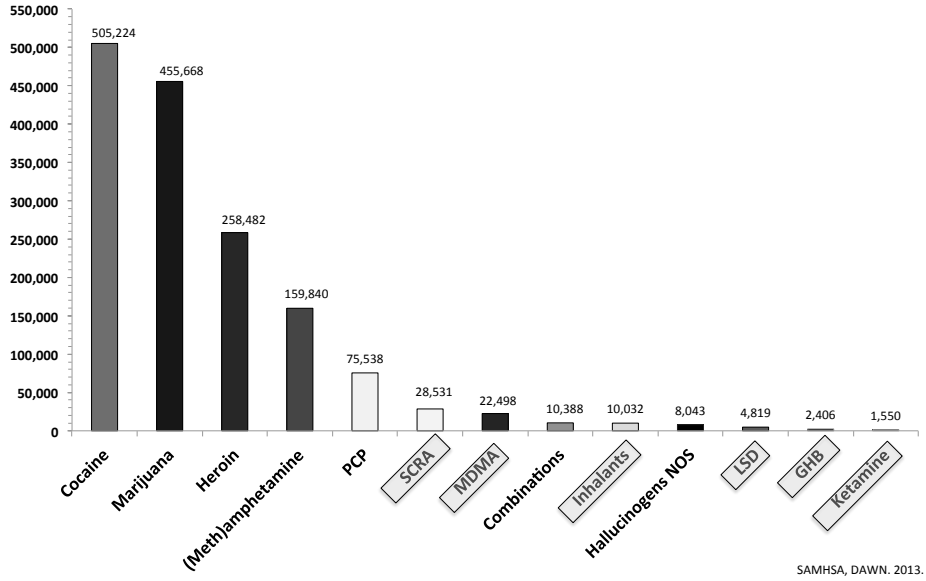
Phenethylamine Reports	Percent
Methamphetamine	83.95%
Amphetamine	4.65%
Methylone	4.38%
MDMA	2.03%
alpha-PVP	1.01%
Lisdexamfetamine	0.79%
MDPV	0.52%
4-MEC	0.49%
2C-I-NBOMe	0.49%
Phentermine	0.25%
MDA	0.15%
2C-C-NBOMe	0.14%
Pentedrone	0.11%
Ephedrine	0.09%
DOC	0.06%
Other phenethylamines	0.89%

Synthetic Cannabinoid Reports	Percent
XLR11	65.38%
UR-144	7.21%
AM-2201	5.13%
PB-22	3.87%
5F-PB-22	3.16%
5F-AKB48	2.42%
AKB48	1.65%
JWH-018 (AM-678)	1.00%
JWH-122	0.73%
JWH-250	0.68%
JWH-210	0.64%
STS-135	0.49%
MAM-2201	0.37%
JWH-081	0.32%
AB-FUBINACA	0.15%
Other	6.80%

	Drug	Number	Percent
1	Cannabis/THC	240,935	31.26%
2	Cocaine	119,323	15.48%
3	Methamphetamine	100,045	12.98%
4	Heroin	74,049	9.61%
5	Oxycodone	23,854	3.09%
6	Hydrocodone	18,834	2.44%
7	Alprazolam	18,428	2.39%
8	XLR11	11,273	1.46%
9	Buprenorphine	5,635	0.73%
10	Amphetamine	5,544	0.72%
11	Clonazepam	5,504	0.71%
12	Methylone	5,215	0.68%
13	Morphine	4,123	0.53%
14	Methadone	3,539	0.46%
15	Noncontrolled, non-narcotic[2]	2,984	0.39%
16	Diazepam	2,883	0.37%
17	Hydromorphone	2,600	0.34%
18	Phencyclidine (PCP)	2,550	0.33%
19	Pseudoephedrine[3]	2,432	0.32%
20	MDMA	2,423	0.31%
21	Carisoprodol	2,249	0.29%
22	Psilocin/psilocibin	2,136	0.28%
23	Codeine	1,628	0.21%
24	1-Benzylpiperazine (BZP)	1,615	0.21%
25	Methylphenidate	1,388	0.18%
	Top 25 Total	661,189	85.77%
	All Other Drug Reports	109,663	14.23%
	Total Drug Reports[4]	770,851	100.00%

USDEA, NFLIS. 2013 Midyear Report, 2014.

Emergency Department Presentations



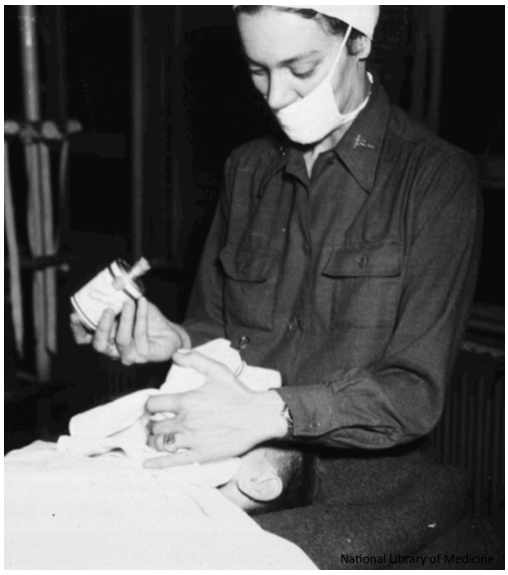
SAMHSA, DAWN. 2013.

Treatment Admissions

Detailed drug	Total [2]	Primary	Secondary	Tertiary	Total [2]	Primary	Secondary	Tertiary
	Number				Percent distribution			
Admissions reporting detailed drug(s)	1,469,165	803,830	464,964	200,371	100.0	100.0	100.0	100.0
Alcohol	486,999	343,753	103,905	39,341	33.1	42.8	22.3	19.6
Marijuana/hashish	305,800	134,818	119,539	51,443	20.8	16.8	25.7	25.7
Cocaine	202,044	62,551	100,824	38,669	13.8	7.8	21.7	19.3
Opiates	304,742	210,406	67,680	26,656	20.7	26.2	14.6	13.3
Stimulants	61,885	32,681	17,390	11,814	4.2	4.1	3.7	5.9
Methamphetamine/speed	49,510	29,165	13,119	7,226	3.4	3.6	2.8	3.6
MDMA (Ecstasy)	4,689	812	1,631	2,246	0.3	0.1	0.4	1.1
Amphetamines	4,733	1,842	1,554	1,337	0.3	0.2	0.3	0.7
Tranquilizers	58,577	9,865	30,095	18,617	4.0	1.2	6.5	9.3
Sedatives/hypnotics	4,734	1,455	1,955	1,324	0.3	0.2	0.4	0.7
Hallucinogens	4,399	816	1,427	2,156	0.3	0.1	0.3	1.1
Other hallucinogens	3,509	659	1,133	1,717	0.2	0.1	0.2	0.9
LSD	890	157	294	439	0.1	*	0.1	0.2
PCP/PCP combinations	7,157	3,392	2,266	1,499	0.5	0.4	0.5	0.7
Inhalants	1,364	452	423	489	0.1	0.1	0.1	0.2
Other drugs	31,464	3,641	19,460	8,363	2.1	0.5	4.2	4.2
Other drugs	29,250	2,984	18,609	7,657	2.0	0.4	4.0	3.8
Other over-the-counter	1,343	372	527	444	0.1	*	0.1	0.2
Ketamine	572	225	167	180	*	*	*	0.1
GHB/GBL	170	27	106	37	*	*	*	*
Diphenhydramine	95	22	35	38	*	*	*	*
Diphenylhydantoin/phenytoin (Dilantin)	34	11	16	7	*	*	*	*

SAMSHA, TEDS. 2014

Inhalants



Inhalants

Sniffing/Snorting Bagging Huffing

Inhalants

Class	Examples
Solvents & aerosols	*Adhesives/contact cements/glues* (benzene, *n*-hexane, toluene, trichloroethane, trichloroethylene, tetrachloroethylene, xylene)
	Carburetor cleaner (methanol, methylene chloride, toluene
	Computer dusters (difluoroethane, tetrafluoroethane)
	Gasoline/kerosene (aliphatic and aromatic hydrocarbons)
	Hairspray (dimethyl ether or alkanes)
	Lighter fluid (butane, ethanol, methanol, stoddard solvent)
	Nail polish remover (acetone)
Gases	Chloroform
	Ether
	Freon (*AC units*)
	Fuel gas
	Nitrous oxide (*whipped cream canisters and cooking sprays*)
Nitrites	*Poppers* (amyl nitrite, isobutyl nitrite)
	Room deodorizers (butyl nitrite, isobutyl nitrite, cyclohexyl nitrite)

GTE 9, 2010

Inhalants (I)

- GECS:
  - Adolescents, American Indian or Alaska Native (5.5%)
  - Low SES, "street children"
  - M = F
- G/PD:
  - Nongenetic factors: monetary and opportunity cost (¢)
- (Neuro)physiology
  - Volatile hydrocarbons: increased inhibitory neurotransmission
  - Varying degrees of enhanced $GABA_A$ transmission
  - $Glycine_{\alpha 1}$ receptor binding
  - N_2O: NMDA receptor inhibition, ↑ dopaminergic transmission
  - Nitrites: NO donation → cytosolic guanylate cyclase → GMP

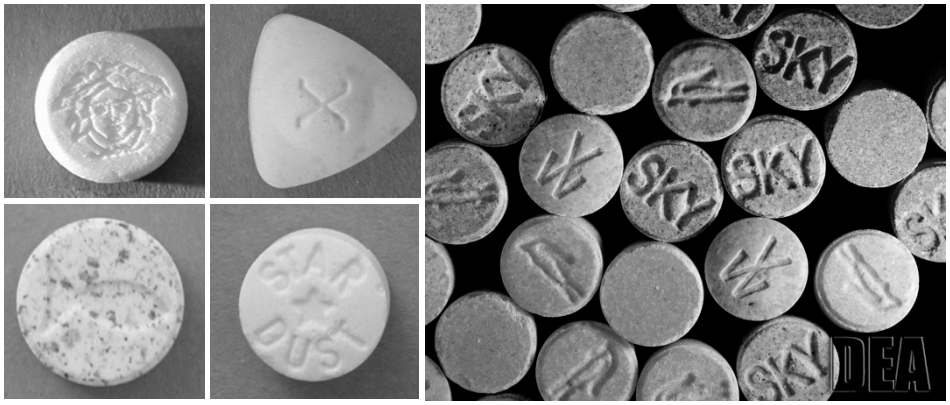
SAMHSA , 2003.

Inhalants (II)

- Goal: rapid, ethanol-like high, "head rush," euphoria, aphrodisiac
- Presentation (intoxication/abuse/dependence)
  - Onset: seconds; duration: minutes
  - Acute
    - NP: hallucinations, headache, drowsiness, impaired motor skills, slurred speech, seizure
    - CV: palpitations, tachycardia, "sudden sniffing death syndrome"
    - Pulmonary: asphyxia, aspiration (chemical pneumonitis)
    - GI: nausea and vomiting
    - Vasodilatation and smooth muscle relaxation (nitrites)
    - Methemoglobinemia (nitrites)
  - Chronic
    - NP: NMDA upregulation, tolerance, cognitive impairment to severe dementia (e.g., toluene leukoencephalopathy), ataxia, depression, irritability
    - PNS: neuropathy (e.g., toluene, *n*-hexane), myelopathy (e.g., N_2O B12 deficiency)
    - GI: hepatotoxicity (halogenated hydrocarbons)
    - GU: renal toxicity, metabolic acidemia, hypokalemia, nephrolithiasis
    - Pulmonary: asthma, pneumonia, bronchitis, asthma, sinusitis
    - Dermatological: mouth sores and/or rash – "glue-sniffer's rash"/"huffer's eczema"
- Therapy
  - Acute: remove source, cardiovascular & ventilatory support, methylene blue (nitrites)
  - Chronic: resource intensive therapy

Hsu, 2012.
SAMHSA , 2003

"Club Drugs"
MDMA ("Ecstasy")



Images. US DEA

US NDIC

MDMA ("Ecstasy")

- "How many people in this crowd have seen molly?" – Madonna @ Miami Ultra Music Festival (2012)

Electric Zoo's Last Day Cancelled Due To Apparent MDMA-Related Deaths (New York City, 2013)

3,4-methylenedioxymethamphetamine *MDMA ("Ecstasy") (I)*

- GECS: CI. Dance events & residences. Weekend use.
  - Co-exposure with EtOH, cannabis, hallucinogens, and stimulants
- G/PD:
  - CYP2D6 PM risk neurotoxicity
  - Associated cannabis abuse/dependence
  - 5-HTTLPR* polymorphism → lifetime risk of primary mood disorders
  - Twins: common genetic + unique environmental effects
  - After initiation: 88% nondependent/10% intermediate/2% dependence
  - Transition to dependence >> LSD
  - Nongenetic factors: monetary and opportunity cost, and motivation
- (Neuro)physiology
  - Induced exocytotic release of 5-HT >> DA & NE
  - NET > SERT> DAT inhibition
  - Subsequent ↓ 5-HT & 5-HIAA
  - Tryptophan hydroxylase inhibition
  - ↑ vasopressin (ADH) secretion

*serotonin transporter gene

Kendler et al. 2003.
Leung et al. 2008.
Martín-Santos et al. 2010.
Sarkar et al. 2010.
Stone et al. 2006.

MDMA ("Ecstasy") (II)

- Goal: euphoric, aphrodisiac, &/or entactogenic experience
- Presentation (intoxication/abuse/dependence)
  - Onset (50-200 mg): 30-45 min; duration: 4-6 hours
  - Adulteration: PMA, (Me)amphetamine, caffeine, DXM, piperazines, cathinones
  - Acute
    - NP: ↑ arousal, energy, talkativeness, euphoria; ataxia, anxiety, paranoia, hallucinations
    - Thermal stress and acute hyperthermia
    - Hyponatremia (free water, ADH, salt loss)
    - CV: tachycardia, HTN, dysrhythmia, collapse
    - Nausea, vomiting, bruxism, myalgias, rhabdomyolysis, DIC
  - Chronic
    - ↓ 5-HIAA & SERT density
    - NP: impaired inhibition, verbal memory, and visual/spatial performance
      Mood and anxiety disorders
    - GI: hepatotoxicity
    - CV: myocardial damage; valvular heart disease
- Therapy
  - Acute: supportive care, sedation, cooling, [cyproheptadine]
  - Chronic

Licht et al. 2012.
Martín-Santos et al. 2010.
Parrot, 2012.
Steinkellner et al. 2011.
van Holst et al. 2011.

"Club Drugs"
GHB

US DEA

Gamma-hydroxybutyrate (*GHB*) *(I)*

- GECS
  - CIII as "sodium oxybate" Rx for narcolepsy
  - Precursors: gamma butyrolactone (GBL) and 1,4-butanediol (1,4-BD)
  - Used in combination (ETOH, cannabis, MDMA)
  - Teens & young adults; M > F
  - Dance events, "after-parties," & private homes
  - Others: Body builders. DFSA victims. Aphrodisiac seekers
- G/PD: unknown
- NP
  - Endogenous NT (GABA → SSA → GHB)
  - γ-butyrolactone (*GBL*) & 1,4-butanediol (*1,4-BD*) → GHB
  - $GABA_B$ and GHB-specific agonism
  - ↑ dopamine in nucleus accumbens
  - ↑ prolactin and GH hormone levels
  - Absent analgesic or spasmolytic properties

EMCDDA, 2008.
Schep et al. 2012.

GHB (II)

- Goal: euphoria, relaxation, and disinhibition
- Presentation
  - Onset: 15 minutes; duration: ~3 - 4 hours
  - Acute
    - Relaxation → euphoria → incoordination → agitation, combativeness, confusion, CNS and respiratory depression, coma (50 mg/kg)
    - Maintains the natural sleep stages
    - Nausea, vomiting, myoclonus, bradycardia, hypothermia
  - Chronic
    - Withdrawal syndrome (1 - 12 hours)
- Therapy
  - Acute: supportive care
  - Chronic: benzodiazepines (± second line agents)

Bialer PA, 2002.

"Club Drugs"
Ketamine

US DEA

Ketamine (I)

- GECS
  - CIII anesthetic for diagnostic, surgical, & airway procedures, et al.
  - Teens & young adults; M > F
  - Multiple settings: dance events, parties, private homes, school
  - Other populations: DFSA ("Predatory Drug").
- G/PD: Prior drug exposure
- NP
  - NMDA noncompetitive receptor antagonism (*S(+)* > *R(-)* isomer)
  - Mild α- and β- adrenergic agonism, nicotinic antagonism
  - Dissociative anesthesia
  - Selective interruption of brain association pathways
  - Somatesthetic sensory blockade
  - Thalamoneocortical, reticular-activating & limbic system depression

JHP Pharmaceuticals LLC, 2012. Udesky, 2005.

Ketamine (II)

- Goal: "K-land" ± "K-hole"
- Presentation (intoxication/abuse/dependence)
  - Onset: rapid (IV); duration: $t_{1/2\alpha \rightarrow \beta}$ = 15 min → 2.5 hr (IV); other routes
  - Acute
    - NP: Depersonalization, derealization, NDE/NBE, panic, paranoia, hallucinations, confusion, delusions, hallucinations, delirium, behavioral toxicity
    - GI: Abdominal pain ("K cramps")
    - GU: LUTS (Lower Urinary Tract Symptoms)
    - Hypertension
  - Chronic
    - GU: Painful bladder, ureteral obstruction, papillary necrosis
    - GI: hepatitis, cholestasis
    - NP: cognitive, memory, and attention impairment
      May trigger mania or schizophrenia; depression
      Upregulation of dopamine D_1 receptors in dorsolateral prefrontal cortex
- Therapy
  - Acute: supportive care
  - Chronic: GU modalities

Daly et al. 2011.
D'Souza, 2012.
Jansen, 2000.
Persson, 2010.
Sear, 2011.
Winstock, 2012.
Wood et al. 2011.

"Club Drugs"
Dextromethorphan

US NDIC

Dextromethorphan (DXM) (I)

- GECS
  - FDA approved 1958. Unscheduled antitussive; c.f. levorphanol (CII)
  - Prescription restricted (< 18 yrs.) in California and NY
  - Potential "free base" extraction
  - Younger adolescents, caucasian
- G/PD:
  - CYP2D6 substrate → dextrorphan (DXO) [active]
  - Rapid metabolizers may be more susceptible to psychotropic effects
- NP
  - Absent significant μ-opioid affinity
  - NMDA noncompetitive receptor antagonism (at the "PCP site")
  - σ-1 agonism; SERT inhibition; nAChR antagonism; VDCC antagonism

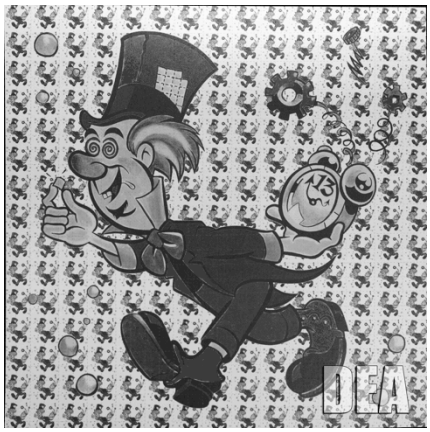
Franklin et al. 1992. Lessenger, et al. 2008. Romanelli et al. 2009. US FDA, 2010.

DXM (II)

- Goal: pleasant altered mood and perception
- Presentation (intoxication/abuse/dependence)
  - Onset: 15-30 minutes; duration: 6 hours
  - Acute
    - Dose dependent PCP/ketamine mimic
      - Plateau 1 (1.5-2.5 mg/kg): Mild inebriation, stimulation, and GI effects
      - Plateau 2 (2.5-7.5mg/kg): Similar to ethanol intoxication (nystagmus, slurred speech, ataxia, lethargy, memory impairment), occasional mild hallucinations
      - Plateau 3 (7.5-15 mg/kg): Altered consciousness, agitation, paranoia, hallucinations, psychosis
      - Plateau 4 (>15-30 mg/kg): Depersonalization, derealization, c.f. PCP/ketamine.
    - Hypertension, tachycardia, diaphoresis
    - Respiratory depression
    - [Serotonin syndrome]
  - Chronic
    - Psychological and physical dependence
- Therapy
  - Acute: supportive care. Co-formulary. May cause (+) UDS for PCP
  - Chronic: rare detoxification

Boyer, 2004. Lessenger, et al. 2008. Romanelli et al. 2009. US FDA, 2010.

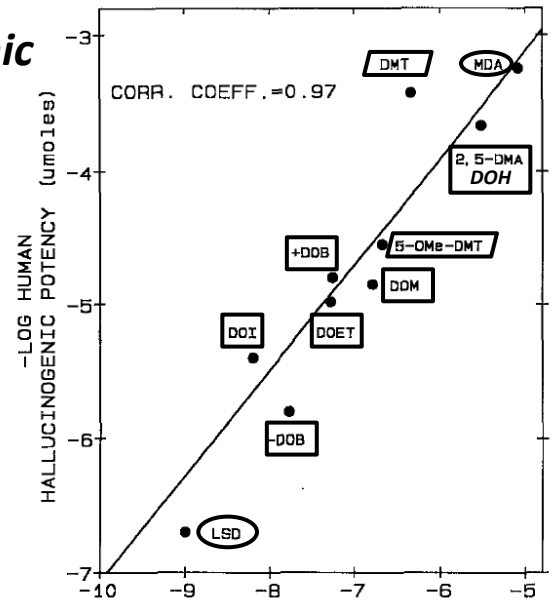
Hallucinogens
LSD



Blotter Sheet

Capsules / Powder

Hallucinogenic Potency

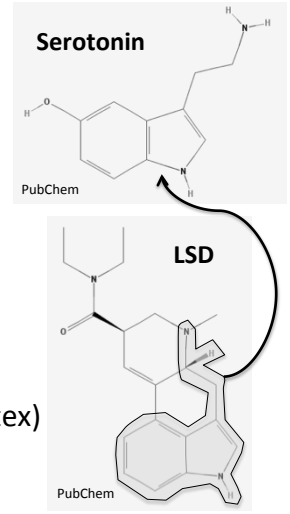


5-HT$_2$ receptor binding LOG KI [HUMAN] nM

Sadzot et al. 1989.

LSD (Lysergide) (I)

- GECS
  - LSD-25 (1938); Delysid (Sandoz Laboratories, 1947). CSA CI (1966, 1970)
- G/PD: Cannabis use, caucasian
  - "Candy flip": LSD + MDMA
- (Neuro)physiology
  - Active stereoisomer [(+)-D (*6aR,9R*)-LSD]
  - 5-HT_{2A} receptor partial agonist (frontal cortex)
  - 5-HT_{2C}, 5-HT_{1A} receptor agonism
  - Triggered glutamate release
  - NMDA receptor modulation
  - Dopamine receptor stimulation



Fantegrossi et al. 2008.
Sadzot et al. 1989.
Sanders-Bush et al. 1988.
Wilcox et al. 2002.
Winter, 2009.

LSD (II)

- Goal: hallucinogenic effects
- Presentation (intoxication/abuse/dependence)
  - Onset (50-100 μg): 30-60 min; duration: 10-12 hours
  - Acute
    - NP: perceptual alterations, synesthesia, depersonalization, altered mood and cognition, anxiety, dysphoria, behavioral toxicity
  - Chronic
    - < dependence risk c.f. MDMA (weaker reinforcing effects)
    - Hallucinogen persisting perceptual disorder (HPPD, "flashback")
- Therapy
  - Supportive care

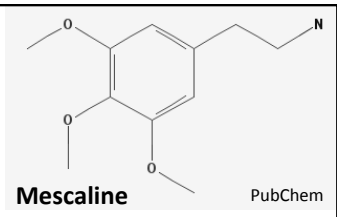
Fantegrossi et al. 2008.

Hallucinogens
Mescaline

Peyote

San Pedro

Mescaline (I)



Mescaline PubChem

- GECS
  - Isolated 1896
  - CSA CI, [⃠] Native American Church
  - Cacti: peyote (*Lophophora williamsii*) and San Pedro (*Trichocereus pachanoi)*
- G/PD
  - Transition to dependence > LSD
  - "Love trip" = MDMA and mescaline
- (Neuro)physiology
  - 5-HT_{2A} and 5-HT_{2C} receptor partial agonist
  - Negligible 5-HT_{1A} receptor affinity

Stone et al. 2006.
Winter, 2009.

Mescaline (II)

- Goal: hallucinogenic effects
- Presentation (intoxication/abuse/dependence)
  - Onset (6-12 buttons, 300-500 mg): 1-3 hours; duration: 10-12 hours
  - Acute
    - NP: hallucinations, illusions, perceptual alterations
    - GI: nausea, vomiting
    - Mydriasis, tachycardia, hypertension, headache
  - Chronic
    - Absent psychological or cognitive deficits in NAC members
- Therapy
  - Supportive

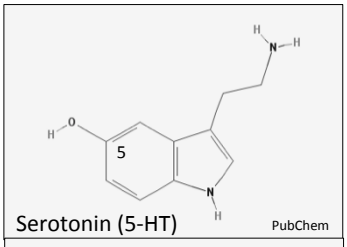
Halpern et al. 2005.

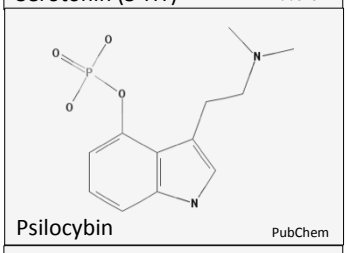
Hallucinogens
Psilocybin

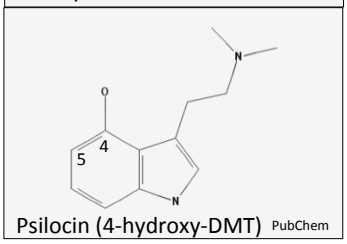
US DEA

Psilocybin (I)

- GECS: used by the ancients;
  isolated and synthesized 1958; Sandoz USP 3,183,172 (1965) as tranquilizer and psychotherapeutic prior to CI scheduling
  Use > mescaline
- G/PD
  - MDMA & other hallucinogens
  - MAO substrate
- (Neuro)physiology
  - Psilocybin → psilocin
  - 5-HT_{2A} > 5-HT_{2C} receptors







Hoffman et al. 1958. Licht et al. 2012. Stone et al. 2006. Winter, 2009.

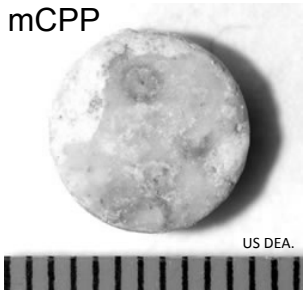
Psilocybin (II)

- Goal: hallucinogenic effects
- Presentation (intoxication/abuse/dependence)
  - Onset (5 g): 30-120 min; duration: 4-6 hours
  - 1 µg LSD ≈ 100 µg psilocybin ≈ 1000 µg mescaline
  - Acute
    - As for other hallucinogens, i.e. perceptual alterations, synesthesias, unusual thoughts, ego loss, anxiety, impaired cognition,
      Midriasis, tachycardia, nausea, hyper-reflexia, tremor
- Therapy
  - Supportive

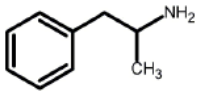
Passie et al. 2002

New and (Re)Emerging Drugs
Piperazines

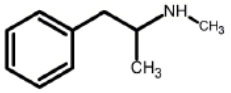
Piperazines (I)



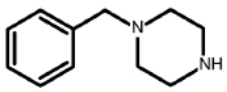
Amphetamine



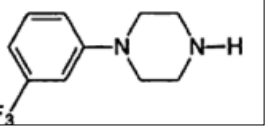
Methamphetamine



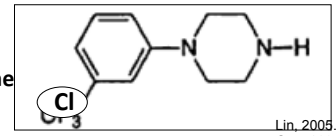
BZP
1-Benzylpiperazine



TFMPP
1-[3-trifluoromethyl-phenyl]-piperazine



mCPP
3-chloro-phenylpiperazine



Lin, 2005.
Gee, 2005.

Piperazines (II)

- GECS: CI
  - Previously "legal high"
  - Youth and young adults in social settings (bars, dance parties, etc.)
  - "Ecstasy" users (MDMA mimics as capsule/tablets)
- G/PD:
  - MDMA clients
  - Potential CYP450 and COMT differences
- (Neuro)physiology
  - DA release & DA re-uptake inhibition (BZP)
  - Postsynaptic DA receptor agonism (BZP)
  - ↑ circulating NE (BZP)
  - 10-fold lower potency than D-amphetamine (BZP)
  - 5-HT_1 and 5-HT_2 receptor agonism (TFMPP)
  - 5-HT reuptake inhibition (TFMPP)
  - Minimal dopamine, more serotonergic effects (mCPP)

Cohen et al. 2011.
Gee et al. 2008.
Lin et al. 2009.

Piperazines (III)

- Goal: euphoria and amphetamine-like effects
- Presentation (intoxication/abuse/dependence)
  - Onset (50-100 mg ingestion): minutes; duration: several hours
  - Acute
    - NP: anxiety, agitation, hallucination, seizures, insomnia, migraines
    - CV: palpitations, tachycardia
    - GI: vomiting, anorexia, abdominal pain
    - Diaphoresis, mydriasis, tremors, hot/cold flashes
  - Chronic
    - Insomnia, fatigue, mood swings, confusion and irritability
- Therapy
  - Supportive care (special attention to seizures)

Cohen et al. 2011.
Gee et al. 2008.
Lin et al. 2009.

Synthetic Cannabinoid Receptor Agonists (SCRAs)

US DEA

SCRAs ("Spice")

- GECS: CI
  - "The term 'cannabimimetic agents' means any substance that is a cannabinoid receptor type 1 (CB1 receptor) agonist as demonstrated by binding studies and functional assays." – specific naming of several AM-, CP-, JWH-, RCS-, and SR- compounds*
  - Major U.S. increase, rapidly changing constituents
  - Young adults
  - Current cannabis users (24% last month)
- G/PD: insufficient data
- (Neuro)physiology
  - CB_1 / CB_2 agonism
  - Active metabolites (variable effects)
  - Lack cannabidiol ("neuroprotective") in cannabis

*Synthetic Drug Abuse Prevention Act of 2012 [FDASIA. Public Law 112-144, 126 Stat. 993]. Gunderson et al. 2014

SCRAs ("Spice") (II)

- Goal: pleasant, potent high; relaxation; UDS evasion
- Presentation (intoxication/abuse/dependence)
  - Onset: rapid; duration of action: JWH-018 (1–2 hours); CP 47,497-C8 (5–6 hours)
  - Acute
    - "Cannabinoid tetrad": analgesia, catalepsy, hypothermia, suppressed locomotor activity
    - NP: agitation, hallucinations, panic attacks, paranoia, acute psychosis; incoordination, sedation, coma, seizure
    - CV: Hypertension, MI, CVA
    - Acute kidney injury (ATN, AIN)
  - Chronic
    - Withdrawal: craving, nausea, irritability, insomnia, headaches, diaphoresis, hypertension, tachycardia
- Therapy
  - Supportive care

Brents, 2011. Compton, 1992. Pendergraft et al. 2014. Vandrey, 2011. Zimmermann, 2009.

Cathinones ("Bath salts")

US DEA

Cathinones ("Bath salts") (I)

- GECS: CI: MDPV,* mephedrone,* methylone
  - Urban, youth; M > F
- G/PD: stimulant users
- (Neuro)physiology
  - 5-HT, DA and NE release (*variable*)
  - 5-HT, DA and NE reuptake inhibition (*variable*)
  - Methylone ≈ MDMA at NET and DAT, < MDMA at VMAT2
  - Mephedrone: < MDMA for [5-HT]; > MDMA for [dopamine]
  - Pyrovalerone: NET and DAT inhibition, minimal SERT inhibition

*Synthetic Drug Abuse Prevention Act of 2012 [FDASIA. Public Law 112-144, 126 Stat. 993] Prosser et al. 2012

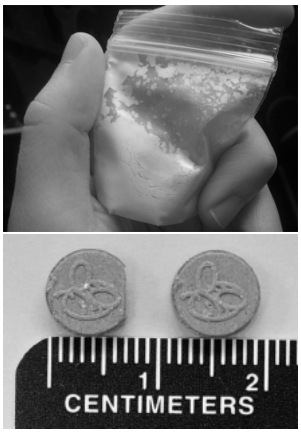
Cathinones ("Bath salts") (II)

- Goal: consistent, stimulant high
- Presentation (intoxication/abuse/dependence)
  - Onset (25-250 mg): ~minutes post insufflation, ~15-45 min post ingestion; duration of action: ~3 hours)
  - Acute (sympathomimetic effects)
    - NP: agitation, delusions, hallucinations, paranoia, insomnia Headaches, seizure
    - GI: Nausea, abdominal pain, anorexia
    - CV: Tachycardia, palpitations, chest pain, MI
    - Mydriasis, bruxism, diaphoresis
  - Chronic
    - Craving, addiction [self-reported] in 50% of users
- Therapy
  - Supportive care, sedation, cooling

Benzie, 2011.
Prosser et al. 2012.
EMCDDA, 2011.

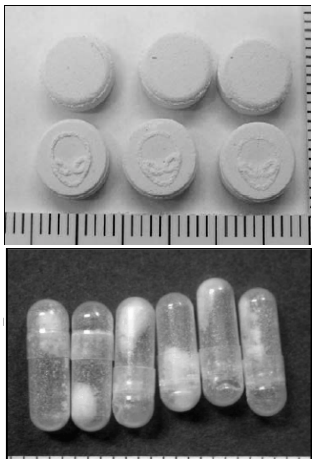
Phenethylamine analogues

2C-B



2C-E

2C-I

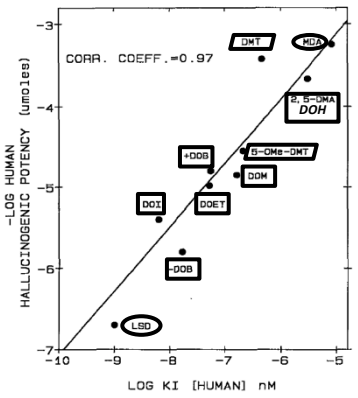


Images, US DEA

Phenethylamine analogues (I)

- GECS
  - Young adults
  - Club goers
  - LSD/MDMA mimics (capsules/ tabs/blotters)
- G/PD: insufficient data
- (Neuro)physiology
  - 2C-series (2,5-DM-PEAs)*
  - DO-series (2,5-DMAs)§
  - 5-HT_2 receptor agonism

5-HT_2 receptor binding

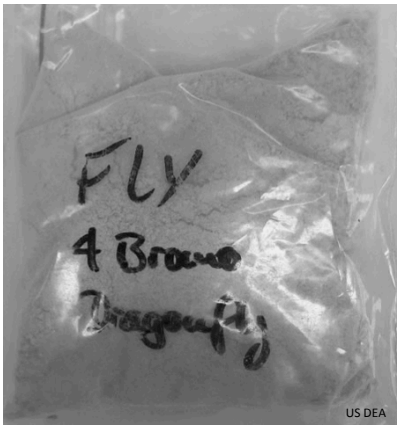


*2,5-dimethoxy-phenethylamines; §2,5-dimethoxy-amphetamines

Phenethylamine analogues (II)

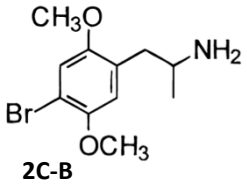
- Goal: euphoric, entactogenic experience
- Presentation (intoxication/abuse/dependence)
  - Onset: 1-3 hours, duration (1.5-3 mg): 16-30 hours
  - Acute
    - NP: hallucinations (visual), stimulation, insomnia
    - Nausea, chest pain
    - Peripheral vasoconstriction (limb ischemia)
  - Chronic
- Therapy
  - Supportive care, with attention to amphetamine-like effects

"FLYs"

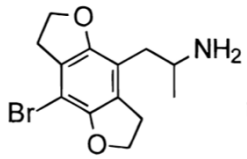


"FLYs" (I)

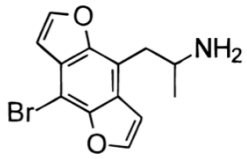
- GECS: U.S., U.K., Scandinavia
- G/PD: Cannabis use, caucasian
- (Neuro)physiology
  - 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C} (partial) agonism
  - Triggered glutamate release and NMDA receptor modulation
  - Dopamine receptor stimulation



2C-B



2-C-B-FLY



Bromo-DragonFLY

"Reprinted with permission from Parker MA, Marona-Lewicka D, Lucaites VL, Nelson DL, Nichols DE. A novel (benzodifuranyl)aminoalkane with extremely potent activity at the 5-HT2A receptor. J Med Chem. 1998 Dec 17;41(26):5148-9. Copyright 1998, American Chemical Society." Chambers et al. 2001.

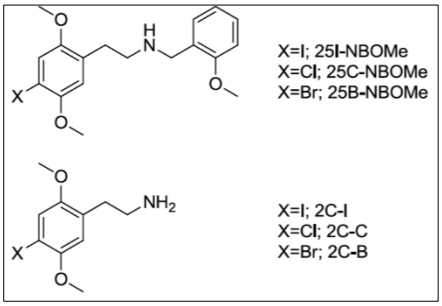
"FLYs" (II)

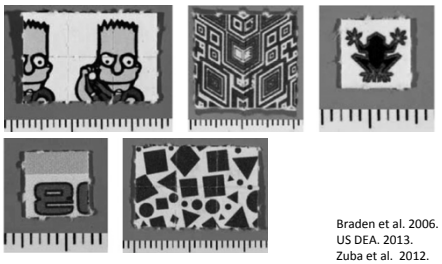
- Goal: hallucinogenic ± entactogenic experience
- Presentation (intoxication/abuse/dependence)
  - Acute
    - Onset (500-1000 µg): hours; duration: 2-3 days
    - NP: Hallucinations, agitation, time dyssynchrony; seizures; behavioral toxicity
    - Diaphoresis
    - Peripheral vasoconstriction (limb ischemia)
  - Chronic
    - Insufficient data
- Therapy
  - Supportive care

Thorlacius et al. 2008.
Wood et al. 2009.

25-NBOMe series ("Bombs")

- GECS: C1
  - Research tool for 5-HT_{2A} receptor study (2003)
  - LSD mimics (powder/tabs/ blotters); liquid
  - Parties, music events, internet
  - M ≥ F
- G/PD: unknown
- (Neuro)physiology
  - 5-HT_{2A} agonism
  - 2C-I-NBOMe (K_i = *0.044 nM*)
  - 2C-I (K_i = *0.73 nM*)





Braden et al. 2006.
US DEA. 2013.
Zuba et al. 2012.

"Bombs" (II)

- Goal: hallucinogenic experience
- Presentation (intoxication/abuse/dependence)
  - Onset (100 to 800 µg): 15-120 min; plateau: 2-4 h; duration: insufflation (4-6 h), sublingual (6-10 h)
  - Acute
    - NP: tactile, visual and auditory perceptual alterations, aggression, seizures (including status), psychomotor agitation and agitated delirium
    - CV: tachycardia, hypertension
    - Pulmonary: tachypnea
    - GU: acute kidney injury
    - Diaphoresis, metabolic acidosis, rhabdomyolysis, thermal stress and acute hyperthermia, behavioral toxicity
  - Chronic
    - Insufficient data
- Therapy
  - Aggressive supportive care, sedation, cooling

Armenian et al. 2014.
Hill et al. 2013.
Nikolaou et al. 201.

Botannicals

Salvia

Kratom

Salvia (Salvia divinorum) (I)

- GECS:
  - Mint family herb
  - Traditional: Oaxaca/Mazatec: ceremonial and medicinal (chewed, drinks)
  - Other groups: adolescents & young adults (pipe, water bong)
- G/PD: M > F
- (Neuro)physiology
  - Salvinorin A (abundant in leaves)
  - *κ*-opioid receptor (KOR) agonist
  - Absent 5-HT_{2A} receptor binding affinity

Babu, 2008.

Salvia divinorum (II)

- Goal: hallucinations
- Presentation (intoxication/abuse/dependence)
  - Onset (200-500 µg by inhalation): rapid (< 1 minute); duration: ~15-30 minutes
  - Ineffective via ingestion
  - Acute
    - NP: incapacitation, spatiotemporal dislocation, laughter, vivid hallucinations, behavioral toxicity, occasional agitated delirium
    - "Post-trip": fatigue, dizziness, amnesia, psychotic disturbances
- Therapy
  - Supportive care

Babu, 2008.

Kratom (Mitragyna speciosa korth) (I)

- GECS
  - Tree
  - Traditional (Thailand/Malaysia): hard labor, indigenous medicine (chewed)
  - Other groups: "legal high" seekers; chronic pain therapy; opioid users (reduce tolerance, withdrawal mitigation)
- G/PD:
- (Neuro)physiology
  - Mitragynine & 7-hydroxymitragynine (among > 20 alkaloids)
  - Mitragynine shares structural similarity to yohimbe
  - Mu and kappa opioid receptor agonism
  - Central alpha$_2$ agonism
  - Dopamine (D_2) effects
  - Serotonin effects

Babu et al. 2008.
Boyer, 2008.

Kratom (II)

- Goal: enhanced labor productivity, opioid "high," pain mitigation and management
- Presentation (intoxication/abuse/dependence)
  - Onset: 5 to 10 min; duration 2-5 hours
  - Acute (dose dependent stimulant/opioid effects)
    - Moderate euphoria, miosis, pruritis, agitation, constipation
    - Nausea, vomiting, diarrhea
    - Seizures
  - Chronic
    - Anorexia, weight loss, hyper-pigmentation, urinary frequency, psychosis, intrahepatic cholestasis
    - Withdrawal: cravings, anxiety, "dread," restlessness, diaphoresis, pruritis
- Therapy
  - Acute: supportive care
  - Chronic: opioid substitution, antiemetics, benzodiazepines, central α-agonists

Babu et al. 2008. Boyer et al. 2008. Kapp et al. 2011. McWhirter et al. 2010.

Compound	Selected Alternative, Slang, and Street Terms
Cannabinoid Receptor Agonists	Synthetic, Spice, Black Mamba, Bombay Blue, Fake Weed, Genie, Herbal, Incense, Potpourri, Smoking Blend, Zohai, synthetic cannabinoid receptor agonists (SCRAs)
Cathinones	Bath Salts, Plant Food, Research Chemical, Blue Silk, Cloud Nine, Drone, Energy-1, Ivory Wave, Lunar Wave, Meow Meow, Ocean Burst, Pure Ivory, Purple Wave, Red Dove, Snow Leopard, Stardust, Vanilla Sky, White Dove, White Knight, White Lightening
Dextromethorphan	DXM, CCC, Triple C, Skittles, Robo, Red Hots, Velvet
"FLYs"	Bromo-Dragonfly, B-Fly, 3c-Bromo-Dragonfly, DOB-Dragonfly, ABDF
GHB	G, Georgia Home Boy, Grievous Bodily Harm, Easy Lay, Liquid Ecstasy, Liquid X, Scoop, Goop
Inhalants	Air blast, Amys, Bang, Boppers, Glading, Gluey, Head cleaner, Locker room, Poor man's pot, Rush, Snappers, Shoot the breeze, Whippits
Ketamine	Special K, Super K, Vitamin K, K, Kit Kat, Cat Valium, Purple
Kratom	Thang, Kakuam, Thom, Ketum, Biak
LSD	Acid, Blotter, Stamps, Dots, Mellow Yellow, Trips, Paper, A-bombs, Window Pane
MDMA	Molly, E, Ecstasy, Beans, Clarity, Disco Biscuit, Go, Hug Drug, Lover's Speed, Peace, X, Adam, XTC
Mescaline	Buttons, Cactus, Mesc, Peyote, Peyoto, San Pedro
NBOMe derivatives	N-Bomb, 25B-NBOMe (25B); 25C-NBOMe (25C, C-Boom, Cimbi-82, Dime, Pandora, Vortex); 25I-NBOMe (25-I, Bom-25, Smiles, N-Bomb, Smiley Paper, Solaris); Holland film
Piperazines	BZP, A2, Legal E, Legal X, Party Pills, P.E.P. pills, A2, Social Tonic
Psilocybin	Magic Mushrooms, Mushrooms, 'Shrooms, Boomers, Sacred Mushrooms
Salvinorum A [*Salvia divinorum*]	Maria Pastora, Sally-D, Salvia, Sage of the Seers, Diviner's Sage, Magic Mint, Purple Sticky, Lady Salvia
2C-series	2C-B (2's, Nexus, Toonies, Bromo, Spectrum, Venus); 2C-I (i); 2C-T-7 (Blue Mystic, T7, Beautiful, Tripstay, Tweety-Bird Mescaline)
DO-series	DOI (D.O.I.); DOM (STP)
NBOMe-series	25C-NBOMe (C-Boom, Pandora, Dime, Vortex, Cimbi-82); 25I-NBOMe (Smiles, N-Bomb, 25-I)

Question

A 24-year-old female presents with a seizure after attending an evening dance event. Her serum sodium is 120 mEq/L. The agent most likely to cause her symptoms is

A. Gamma-hydroxybutyrate (GHB)

B. Ketamine

C. Lysergic acid diethylamide (LSD)

D. 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy")

E. "Spice" ("synthetic cannabinoid")

References

Please see handout.