FUTURE TRENDS IN DRUGS OF ABUSE

Jonathan J. Lipman, PhD

Stanley Kubrick’s 1971 view of the future:
The korova milkbar

“Stanley Kubrick’s 1971 view of the future: The korova milkbar

“...The Korova Milk Bar sells Milk Plus: milk plus synthemesc, vellocet, or drencom, which is what we were drinking. This will sharpen you up and make you ready for a bit of the old ultraviolence.”

Anthony Burgess [1962]

Scope

- Novel GABA tranquilizers
- Buprenorphine and "mixers"
- Stimulants
- MDMA as reference
- Pyrovalerone and MDPV
- Cathinones
- Hallucinogens
- Salvia – k receptor agonist
- Stimulants including Piperazines and 2C

hallucinogens
- Cannabinoids and similar drugs
- New illicit combinations
- Kratom
- “Fake ethicals”

DISCLAIMER

NEITHER THE PUBLISHER NOR THE AUTHORS ASSUME ANY LIABILITY FOR ANY INJURY AND OR DAMAGE TO PERSONS OR PROPERTY ARISING FROM THIS WEBSITE AND ITS CONTENT.
Directions

**ETHICALS**
- New combinations of old drugs
- New combinations of new drugs

**ETHNobotanicals**
- New markets for old ethnods
- Translational research chemicals
- Research modified ethnobotanicals

*"FAKES" – real drugs masquerading as different drugs

**Novel agents**
- Novel phenylethylamines combining stimulant and hallucinogenic properties
- Novel brief-acting hallucinogens
- Novel synthetic cannabinoids
- GABA agonists including GABA precursors
- Newer opioids

**NIDA 2010 Drug Use Survey (U.Mich)**
- Proportion of children using illicit drugs in grade school:
  - Grade 8: 16%
  - Grade 10: 30%
  - Grade 12: 38%
- Greatest increase was in marijuana use
- Alcohol use continued to decline among teens
- Amphetamine abuse incidence has declined since 2002: 11% to 7%
  - (Adderall > Ritalin), but not as much as new prescription use has increased.
- About 1 in 5 12th graders admit to having ever used Adderall
- Vicodin abuse declined to 8% in grade 12, OxyContin use increased to 5.1%
- Solvents, hallucinogens, "rave drugs" held steady

**NIDA Drug Use Survey 1975-2004**

**Ethical (licit) amphetamine**
- The United States spends approximately $2.2 billion dollars per year for medication to treat ADHD and consumes over 80% of the world's methylphenidate (Woodworth, 2000; Marsa, 2005).
- About 80% of the prescriptions for amphetamine and methylphenidate are written for children (Woodworth, 2000)
- more than four-fold increase in amphetamine production in the United States between 1986 and 1995
- seven-fold increase in methylphenidate and twenty-five fold increase in amphetamine between 1991 and 2000.
Sedation and tranquility

GABA, agonists and precursors as a drug

GABA –A  ANTAGONISTS

| Ro 15-4513 (α4β3δ antagonist) | Ro 15-1788 (flumazenil) |

GABA B: Baclofen(lioresal, novartis)

- Baclofen intoxication: report of four cases and review of the literature
- Lee TH, Chen SS, Su S & Yong SS
- Abstract
- Four cases of baclofen intoxication are reported, with a review of 33 cases from the literature. Analysis of these 37 cases suggests that there are two types of baclofen intoxication syndrome. Patients with acute intoxication present with four major clinical manifestations: encephalopathy (disturbance of consciousness), respiratory depression, muscular hypotonia, and generalized hyporeflexia. Patients with chronic intoxication present with hallucinosis, impaired memory, cataonia, or acute mania. The acute intoxication syndrome has a faster onset, shorter duration, more severe clinical manifestations
- Baclofen intoxication, although it may cause grave encephalopathic manifestations and electroencephalographic findings, has a benign outcome if actively managed.
GABA-B agonists

Beta Phenyl Gamma Aminobutyric Acid

H$_2$N\[\begin{array}{c} & \text{phenibut} \\ & \text{4-amino-3-phenylbutyric acid} \end{array}\]BACLOFEN

Phenibut

- Less potent than Baclofen
- Effects: Baclofen-like: drowsiness (63%). Other common CNS effects include asthenia, confusion, dizziness, fatigue, ... ataxia, coordination disorders, euphoria,, dysarthria, dystonic reaction, hallucinations, paresthesias, slurred speech, tinnitus, and tremor have been reported. Seizures and hallucinations have been reported with overdose situations
- withdrawal involving severe anxiety, tremors "agitation, psychosis, hallucinations and a complaint of insomnia" similar to Baclofen withdrawal

Gamma Hydroxy Butyrate

(AKA: GHB, 4-hydroxybutanoic Acid, Sodium Oxybate)

- 1960s widely used in Europe as hypnotic and an anesthetic in childbirth
- 1960s Sold as legal "aphrodisiac" (eu)
- 1970s US introduced as "Na Oxybate" - Xyrem® by Jazz Pharmaceuticals) schedule C-III for Cataplexy treatment
- Acts at a specific GHB receptor, as well as through the GABA-B receptor

Gamma Hydroxy Butyrate

(AKA: GHB, 4-hydroxybutanoic Acid, Sodium Oxybate)

- Patient should prepare both nighttime doses prior to bedtime.
- Take the first dose while sitting up in bed, immediately before lying down to go to sleep
- Take the second dose 2½ to 4 hours later
Gamma Hydroxy Butyrate (GHB)

- 9g/day for night-time (in bed) treatment of daily cataplexy attacks (Xyrem) – to induce sleep to discourage daytime attacks
- **Adverse reactions** include increased libido and euphoria “The rapid onset of sedation, coupled with the amnestic features of sodium oxybate, particularly when combined with alcohol, has proven to be dangerous”
- Withdrawal syndrome includes: insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, and tachycardia

Illicit GHB

- “Dangerous party drug GHB has grown in popularity in Kansas” -- Dec 2010
- Stimulates GH release – bodybuilders
- US OTC sale banned in 1990 [“entheogenic reaction” kits”]

GHB Emergency – future antagonist

- Central nervous system depression
- Respiratory depression
- Bradycardia
- Hypothermia

Coming soon, possibly: Selective GABA B antagonist (for baclofen or GHB overdose)

GABA / GHB Precursors

*One Comma Four*  
“One Four Bee” or “One Four B-O-O”  
Gamma Butyro Lactone (GBL, US Schedule 1)
GABA Precursors: GBL and 1,4 Butanediol

- 1.4 Butanediol 1 liter
- $119.00
- Cas #: 110-63-4
  - Health: 1
  - Flammability: 1
  - Reactivity: 0

Stimulants

- Yellow Lab
- Black Lab
- Chocolate Lab
- Mutt Lab

Novel Stimulants & Hallucinogens

- PiHKAL: A Chemical Love Story (1991)
- TiHKAL: The Continuation (1997)
Phenylethylamines

The “Essential Amphetamines” (differ from safrole or myristicin by only one molecule of ammonia)
- PMA (para-methoxy-amphetamine)
- 2,4-DMA (2,4-dimethoxy-amphetamine)
- 3,4-DMA (3,4-dimethoxy-amphetamine)
- AMDA (3,4-methylenedioxy-amphetamine)
- MMDA (2-methoxy-4,5-methylenedioxy-amphetamine)
- MMDA-3a (2-methoxy-3,4-methylenedioxy-amphetamine)
- MMDA-2 (2-methoxy-4,5-methylenedioxy-amphetamine)
- MDMA (3,4-methylenedioxy-amphetamine)
- MMDA-3a (2-methoxy-3,4-methylenedioxy-amphetamine)
- MMDA-2 (2-methoxy-4,5-methylenedioxy-amphetamine)
- TMA (3,4,5-trymethoxyphenethylamine)
- TMA-2 (2,4,5-trymethoxyphenethylamine)
- DMMDA (2,5-dimethoxy-3,4-methylenedioxy-amphetamine)
- DMMDA-2 (2,3-dimethoxy-4,5-methylenedioxy-amphetamine)

The “Magical Half Dozen” Hallucinogenic phenylethylamines
- Mescaline (3,4,5-trimethoxyphenethylamine)
- DOM (2,5-dimethoxy-4-ethylamphetamine)
- 2-CB (2,5-dimethoxy-4-bromophenethylamine)
- 2-C (2,5-dimethoxy-4-ethylphenethylamine)
- 2C-T (2,5-dimethoxy-4-(N-propyl)thiophenethylamine)
- 2C-T-7 (2,5-dimethoxy-4-(N-propyl)thiophenethylamine)

Safrole and Myristicin

A “List 1” drug chemical precursor in the USA “banned” by the FDA as a carcinogen in rats

Naturally found in: Sassafras (root beer). Root bark oil is 75% safrole
- Cinnamon
- Nutmeg
- Camphor laurel
- Black pepper

MDMA “Ecstasy”

MDMA History

- 1912 Synthesized by Merck from Saffrole seeking a hemostasis agent
- Pharmacology noted similar to ephedrine
- 1954 US Army research
- 1970 used recreationally in US
- 1976 drug introduced to Shulgin
- 1977 Shulgin introduced MDMA to Leo Zeff who popularized its use in psychotherapy
- 1980s spread throughout UK rave culture
MDMA history

- Shulgin in his laboratory
- “I feel absolutely clean inside, and there is nothing but pure euphoria. I have never felt so great, or believed this to be possible.”
- The cleanliness, clarity, and marvelous feeling of solid inner strength continued through the rest of the day, and evening, and into the next day. I am overcome by the profundity of the experience...” (Shulgin 1978)

- http://thedea.org/drughistory.html

MDMA History

- 1985: Intending to place MDMA in schedule 1, DEA opens hearing on MDMA under Judge Frances Young
- 1986: Judge Young decision: safe and useful under medical supervision, therefore Schedule 3
- 1986: DEA action: rejects Judge Young’s ruling and places MDMA in Schedule 1
- DEA action appealed: MDMA transiently becomes “legal” while appeal is before the courts
- 1988: Appeal court upholds lower court ruling: MDMA, being medically useful, should be in schedule 3
- March 1988: DEA ignores the court and places MDMA back in Schedule 1

MDMA toxicity

- Rave. Emergency room personnel call the hyperthermic effect of ecstasy “Saturday night fever”

MDMA Adverse Effects

- Depend on dose and chronicity
- Very similar to methamphetamine (psychosis related to Morbid Risk)
- Hypertension, sympathetic drive, sweating, hyperpyrexia
- Persistent reduction in brain serotonin and dopamine (8 weeks, in baboons) and human CSF 5-HIAA
- Both acute and chronic learning and memory deficits, most pronounced in regular users


**MDMA Adverse Effects**

Table 2: Group mean scores (± S.E.) for the SCL-90, IVT and EPI/EPITABILES, questionnaires

<table>
<thead>
<tr>
<th></th>
<th>Non-users controls</th>
<th>Light MDMA users</th>
<th>High MDMA users</th>
<th>ANOVA group effect</th>
<th>Tukey post comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCL-90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitization</td>
<td>7.4 ± 0.3</td>
<td>11.7 ± 1.4</td>
<td>15.3 ± 1.7</td>
<td>*</td>
<td>Non</td>
</tr>
<tr>
<td>Emotional sensitivity</td>
<td>7.4 ± 0.3</td>
<td>10.5 ± 1.3</td>
<td>16.4 ± 1.9</td>
<td>*</td>
<td>Non</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.9 ± 0.3</td>
<td>11.2 ± 1.6</td>
<td>12.2 ± 1.5</td>
<td>*</td>
<td>-</td>
</tr>
<tr>
<td>Depression</td>
<td>10.7 ± 1.1</td>
<td>16.0 ± 2.4</td>
<td>16.4 ± 2.0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>SIQ</td>
<td>4.9 ± 0.2</td>
<td>7.3 ± 0.2</td>
<td>12.0 ± 0.5</td>
<td>**</td>
<td>Non, NH</td>
</tr>
<tr>
<td>Fluency</td>
<td>3.8 ± 0.3</td>
<td>6.4 ± 1.2</td>
<td>9.7 ± 1.6</td>
<td>**</td>
<td>Non</td>
</tr>
<tr>
<td>Prospective memory</td>
<td>5.8 ± 0.2</td>
<td>7.4 ± 1.2</td>
<td>9.8 ± 1.5</td>
<td>**</td>
<td>Non, NH</td>
</tr>
<tr>
<td>Paracetal-alcohol</td>
<td>3.0 ± 0.1</td>
<td>7.8 ± 1.0</td>
<td>9.9 ± 1.0</td>
<td>**</td>
<td>Non, NH</td>
</tr>
<tr>
<td>Psychosis</td>
<td>3.5 ± 0.2</td>
<td>7.9 ± 1.1</td>
<td>12.7 ± 0.1</td>
<td>**</td>
<td>Non, NH</td>
</tr>
<tr>
<td>Appetite</td>
<td>0.9 ± 0.1</td>
<td>0.7 ± 0.0</td>
<td>1.7 ± 0.9</td>
<td>*</td>
<td>Non, NH</td>
</tr>
</tbody>
</table>

- Basic cognitive functions generally unimpaired (simple reaction time, choice reaction time, number vigilance, Stroop, trail-making)
- Cognitive functions affected:
  - Reduced memory for new information (Rivermead Behavioral Memory, Supraspan word recall)
  - Impaired higher executive functioning (Wisconsin card sort, Tower of London)
  - Increased impulsiveness on questionnaires and Matching Familiar Figures Test

**Rivermead Behavioral Memory Test**

Perform tasks that involve:
- Associating a name to a face
- Remembering the location of a hidden object
- Recalling a spatial route
- Distinguishing previously presented faces from new ones
- "remembering to remember" tasks when cued

**Novel stimulants**

Relatives of PYROVALERONE
“Ethical” Pyrovalerone
(Centroton [Wander], Thymergix [Joulli])

- Antidepressant stimulant
- Amphetamine-like SNDRI, NA-DA Reuptake Inhibitor (cf bupropion)
- Tx of ADHD, narcolepsy, anorectic for obesity
- Schedule V in the US (only stimulant in that category)

Methamphetamine

“illicit” Methylene Dioxo Pyrovalerone MDPV

- First US seizure March 2008
- Ring substituted pyrovalerone
- Amphetamine-like SNDRI stimulant, high doses cause panic attacks, psychosis
- Duration 3-4h, 5-20mg dose
- WS similar to amphetamine: depression, lethargy, HA, anxiety

Methylene dioxy pyrovalerone (MDPV, methylone)

US TRADE NAMES:
- Cloud 9
- Ivory Wave
- Ocean
- Charge Plus
- White Lightning
- Scarface
- Hurricane Charlie
- Red Dove
- White Dove

CATHINONES
Cathinone

- The recreational use of Khat (Quat, Gat, Miraa) is endemic to NE Africa. The fresh leaves are chewed.
- Khat does not travel – used fresh
- Cathinone and CATHINE are the main active ingredients
- December 1980 – WHO requests cathinone studies
- In 1993 the drug remained unknown in the US
- 1993 DEA added cathinone to schedule 1
- The plant still (2011) remains largely unknown in the US

Cathinone Synthesis

Figure 1 - Ephedrine (or pseudoephedrine) undergoes reduction to give methamphetamine and oxidation to afford methcathinone.

DEA Micromgram Journal Dec 2010

Cathinones

The sale of Khat (the plant) is legal in Israel, Oman, Yemen, United Kingdom, and the Horn of Africa.

Cathinones

- Cathinones
- Methcathinone
- Methamphetamine
- Bupropion

Cathinone Synthesis

- Methcathinone (4 Methyl)
- Methcathinone was first synthesized (from ephedrine) in 1928 in Russia
- It was used as an antidepressant in the USSR 1930 – 1950, after which it was adopted as a recreational drug
- Bupropion
**Synthetic Meth-Cathinones**

- Methcathinone (2a)
- bk-MCDB (2b)
- 4-methylmethcathinone (2c)

**Western Recreational Cathinones**

- **METHCATHINONE**
  - Ephedrine (Europe)
  - Beta ketone, bk, ketone (Australia)
  - Woolen Warrior, wooly (NZ)
  - Cat (South Africa)
- **4-METHYL-METHCATHINONE**
  - Mephedrone, MMC, meow-meow

---

**Methcathinone Pharmacology**

- Pharmacology similar to amphetamine
- Very strong affinities for the DA and NA transporters.
- Affinity for the serotonin transporter < methamphetamine
- Effects usually last from four to six hours
- Binge-crash cycle, like amphetamine

**Methcathinone Effects (per manufacturer)**

- Feelings of euphoria
- Increased alertness
- Dilated pupils
- Rapid breathing
- Increased heart rate
- “Inability to stop talking”
- Increased empathy and sense of communication
- Both decreased and increased sexual function and desire
- “Loss of cognitive ability relating to the distinction of relative importance of matters” (i.e. one might spend days thinking that he or she is being productive but later realize that the activity and/or product was not even necessary)
Khat: Ohio 2006

Piperazines

- Originally developed as antihelminthics for use in farm animals and (1950s) humans
- Human use abandoned due to "side effects"
- Introduced as potential antidepressants (1970s)
- Abandoned as "too amphetamine-like"

- Amphetamine-like, but lower potency
- Euphoria, alertness, wellbeing
- Hallucinogenic at higher doses

Piperazines

- Named for their similarity to piperidine (piper nigrum / black pepper)
- Anchor Piperazine
- Water Wormer,
- Happy Jack Kennel Wormer,
- Happy Jack Puppy Paste,
- Pipa-Tabs, Pipfuge,
- Purina Liquid Wormer,
- Sergeant’s Worm-Away

N-Benzylpipirazine Pharmacology

- Sympathomimetic
- SNRI, with
- alpha-2 antagonism, and also;
- nonselective 5-HT agonist
- 5-HTA2 agonism may explain hallucinogenic effect at high doses
### Piperazine Effects

- Dilated pupils
- Blurred vision
- Dry mouth
- Extreme alertness
- Confusion
- Agitation
- EPS (dystonia, akathisia)
- Headache
- Dizziness
- Vomiting
- Hallucinations
- Tachycardia
- Hypertension
- Urinary retention

(Christchurch NZ hospital ED)
61 pts presented on 80 occasions

- 2 cases of seizures (status) with metabolic acidosis in otherwise neurologically NORMAL patients
- No deaths reported except in combination with other drugs (MDMA is common)

Users report: feeling that it helps them to reach higher levels of mood, sociability, and energy

### N-BZP

- 2000 Piperazine based drugs began to appear in Europe
- 2002 Schedule 1 in USA
- 2007 New Zealand – 5 million doses sold
- Legal in Canada,
- Has no name-brand following in the US

### BZP

### Pipirazine Emergency

- No specific antidote
- Treatment symptomatic and supportive.
- Since they are amphetamine-like in effect: monitor for tachycardia, hypertension, seizures and rhabdomyolysis
US MONITORING of BZP

- We have – as yet - no survey category for BZP, seized doses tend to be lumped in with other drugs as “ecstasy mimics”

“Ecstasy Mimic” Tabs Containing N-BPZ and TFMP

- N-Benzylpiperazine
- Trifluoro-methyl piperazine (TFMP)

“Ecstasy Mimic” Tablets

- ACTUALLY CONTAINING BZP and TFMP

Hallucinogens

- Kappa agonists
- 2-C hallucinogens
Salvia Divinorum

- Mazatecs of Oaxaca, Mexico (Maria Sabina, curandera)
- Traditionally, ingested as a quid or smoked for its psychoactive properties
- Exerts potent hallucinatory actions, oral 5-60 min

Salvinorin A: A potent naturally occurring non-nitrogenous opioid selective agonist, Roth et al (PNAS September 3, 2002 vol. 99 no. 18 11934-11939)

Salvia Divinorum “Diviner’s Sage”

- Salvinorin A terpenoid
- (no N atoms, not an alkaloid)
- Active in ug range (10-20 leaves)
- Kappa opioid agonist (displaces bremazocine)
- D2 partial agonist \( EC_{50}=40-90 \text{ nM} \)
- No effect at 5HT2A receptor
Human psychopharmacology and dose-effects of salvinorin A, a kappa opioid agonist hallucinogen present in the plant *Salvia divinorum*

Matthew W. Johnson et al (Johns Hopkins / NIH funded)
Drug & Alcohol Dependence, Available online 4 December 2010

- Subjects in the study were experienced hallucinogen users
- 16 ascending doses, different sessions, 0.375 μg/kg to 21 μg/kg.
- Inhaled: Onset 2 min, duration 20 min
- Reported very different experiences from those caused by hallucinogens such as LSD and psilocybin.
- Intense experiences characterized by disruptions in vestibular and interoceptive signals (e.g., change in spatial orientation, pressure on the body) and unusual and sometimes recurring themes across sessions such as revisiting childhood memories, cartoon-like imagery, and contact with “entities.”
- Johnson: “With salvia, the subjects described leaving this reality completely and going to other worlds or dimensions and interacting with entities.”
- “These are very powerful, very intense experiences.”

Salvia Legality

- Banned by law
- Sales to minors prohibited
- Import/sale restricted

Salvia


  *Salvinorin* derivatives and uses thereof

  **Abstract**
  The invention features *salvinorin* compositions that are selective for kappa opioid receptors; methods of treating mania by using a selective kappa receptor agonist; and methods of treating mood disorders, such as depressive disorders and manic disorders, using *salvinorin* compositions.

- Inventors: Bequin; Cecile (Lexington, MA), Carlezon; William A. (Lincoln, MA), Cohen; Bruce M. (Lexington, MA), He; Minsheng (Allston, MA), Lee; David Yue-Wei (Cambridge, MA), Richards; Michele R. (Mansfield, MA), Liu-Chen; Lee-Yuan (Media, PA) Assignee: The McLean Hospital Corporation (Belmont, MA)
- Appl. No.: 11/079,825 Filed: March 14, 2005

2-C Hallucinogens
### 2-C Hallucinogens

**2C** general name for the 25 member family of psychedelic phenylethylamines containing methoxy groups on positions 2 and 5 of the benzene ring.

![2-C structure](image)

- Synthesized by Shulgin in 1974
- Dose 16-24 mg
- Short acting hallucinogen
- Low efficacy 5-HT 2A partial agonist (euphoria)
- 5-HT 2C agonist (hallucinations)
- DEA Sched 1 in 1995

### 2-CB

- **Seroquel**
- **Ki at 5-HT 2A = 0.2 nM**
- Hallucinogen
- **5-HT 2A agonist**
- **2-CB**
- **Ki at 5-HT 2A = 0.2 nM**
- **Partial agonist**
- **5-HT 2C agonist**
- **Ki at 5-HT 2A = 0.2 nM**

### Hallucinogens

- **Mescaline**
- **Ki at 5-HT 2A = 0.2 nM**
- **5-HT 2A agonist**
- **Ki at 5-HT 2A = 0.2 nM**

- **LSD**
- **Ki at 5-HT 2A = 0.2 nM**
- **5-HT 2A agonist**

- **DOC**
- **Ki at 5-HT 2A = 0.2 nM**
- **5-HT 2A agonist**

- **DOB**
- **Ki at 5-HT 2A = 0.2 nM**
- **5-HT 2A agonist**

### “Ecstasy Mimic” DOC and DOB

- **BLOTTER CONTAINING A MIXTURE OF**
- **4-CHLORO-2,5-DIMETHOXYAMPHETAMINE [DOC]**
- **4-BROMO-2,5-DIMETHOXYAMPHETAMINE [DOB]**

Seized: DEA 2010 WARNER ROBINS, GA
Abused OPIATES and combinations

Buprenorphine:

Suboxone / Subutex Tablets and Film

- Oct 2002: Introduced at high dose to US by Reckitt Benckiser via Boehringer (Schering-Plough in EU)
- 2007: Chicago's West Side: "easy to purchase" for $2 to $5 per tablet.
- 2008: Vermont: 14% of prescription opioid abusers reported that buprenorphine was their "primary opioid of abuse."
- 2010: The Tennessean newspaper reported on the 100x increase in the number of buprenorphine prescriptions from 2002 to 2009, going from about 50,000 to more than 5 million. Tennessee has more buprenorphine users per capita than 43 other states in the country. State Medicaid prescriptions for buprenorphine have more than doubled in the last year and half, according to TennCare.
- 2010: Washington DC: street price: $8-20 per tablet
- 2010: Austin TX: street price: $10 per tablet

Buprenorphine

Pictures in a child's coloring book, impregnated with Buprenorphine

Legal/Illegal Marijuana

- DEA Jan 2009: Seized in Flagstaff AZ (on 16 Nov 2010 AZ passed their "medical marijuana law")
- "Investigative intelligence indicated that the "Incredible Edibles" foods are products of a marijuana distributor in California" (CA passed MML in 1996)
Canna Cola: 35-65 mg THC per bottle

Marijuana Sprinkled With Morphine Sulphate Powder

DEA 2009, Vista CA (very rare)

Synthetic “Cannabinoids”

DEA 2009 Seizure

- “Spice Gold,” “Spice Silver,” “Spice Diamond,” “Genie,” and “Yucatan Fire”
- “Duquenois-Levine color test +ve for THC
- But did not contain cannabis - contained HU-201
HU-210

THC
CB1 \( K_i = 40 \text{ nm} \)
CB2 \( K_i = 36 \text{ nm} \)

HU-210
CB1 \( K_i = 234 \text{ pM} \) (100-800 times more potent)


January 2010 Synthetic Cannabinoid Seizures

- “Duquenois-Levine color test of the suspected hashish resulted in a green color that did not transfer to the chloroform layer”
- GC/MS identified
  - JWH-018
  - JWH-073

Naphthoylindoles

THC
CB1 \( K_i = 40 \text{ nm} \)
CB2 \( K_i = 36 \text{ nm} \)

CP-47,497 Pfizer CB1 2.1 nM


October 2010 “Spice” Seizures

October 2010 DEA Identified JWH-018 and 3-fluoromethylcathinone

October 2010 UTAH Seizures

Hashish mimic
Oregon 2010
The next big thing?

Kratom – An Indole Alkaloid
With μ-agonism

- Addictive (WHO 1975)
- Mitragynine has a highly unusual but well-documented history as both a depressant (high dose) and a stimulant (low dose)
- Has the chemical structure of a psychedelic (Jansen and Prast, 1988)
- 7-OH mitragynine is a Mu opioid agonist > morphine in gpi and rat tail flick

Kratom (Mitragyna Speciosa)

- Member of the Rubiaceae (coffee) family
- Indigenous to southeast Asia, notably Thailand and Malaysia
- Kratom is the Thai name for M. speciosa
- Known as “Biak Biak” in Malaysia.
- DEA (2010) “drug of concern”:
- “Widely available on the internet”

Kratom

- The Kratom tree can reach over 50 feet in height and over 15 feet in diameter
- Leaves traditionally used brewing tea, smoking, or chewing, for medicinal purposes, and as a substitute for opium
- Kratom (2010) is not a controlled substance in the United States. However, it is controlled in Thailand, Malaysia, and Myanmar (Burma).
- In 2004, mitragynine and Kratom were both placed in Schedule 9 (the most restrictive level) of the Australian National Drugs and Poisons Schedule.
Fakes

Quaalude Mimic

DEA March 2009
QUAALUDE MIMIC TABLETS (ACTUALLY CONTAINING DIAZEPAM) IN DUPAGE COUNTY, ILLINOIS

Fakes

Oxtcontin mimic

OXYCONTIN MIMIC TABLETS ACTUALLY CONTAINING HEROIN 50MG, DEXTROMETHORPHAN, AND CAFFEINE

Fakes

Hydrocodone mimic

HYDROCODONE MIMIC TABLETS (ACTUALLY CONTAINING ALPRAZOLAM) IN TAMPA, FLORIDA

DEA 2010
Fakes Oxycontin mimic

OXCONTIN MIMIC TABLETS (ACTUALLY CONTAINING TRAMADOL, DICYCLOMINE, AND DIAZEPAM) IN TARRYTOWN, NEW YORK

DEA 2009

New Combinations

- DEA 2009:
- the first submission to the Western Laboratory of combination tablets containing BZP, MDMA, TFMP, and methamphetamine

Stroop Color-Word Test

Ki: Binding affinity/Equilibrium dissociation constant
EC50: Concentration of an agonist at which the effect of the agonist is exactly halfway between baseline and the maximal effect
L: Ligand concentration
P: Protein (receptor) concentration
C: P+L complex concentration
Kd: Dissociation constant

Ki = EC50 (1+[L/Kd])

Kd = [P][L]/[C]

Agonist Parameters Definitions

John Ridley Stroop 1935