New and Emerging Drugs of Abuse

Gregory C. Janis
Disclaimers and Apologies
Cocaine use declining

Admissions to Minneapolis/St. Paul area addiction treatment programs with cocaine as the primary substance problem: 2002 - 2010

SOURCE: Minnesota Department of Human Services, Drug and Alcohol Abuse Normative Evaluation System (DAANES), May 2011.
European Monitoring Center for Drugs and Drug Addiction – 2010 report

• In 2009, 24 new synthetic psychoactive substances reported including:
  – 9 new synthetic cannabinoids
  – 5 phenethylamines
  – 2 tryptamines
  – 4 synthetic cathinones

• Report describes an “increasingly complex ecstasy market”
New Drugs Emerging

• 10% of high school seniors (2010) had used synthetic cannabinoids in the last year.

• National Incidents
  – Blain (2C-E)
  – Oklahoma (BrDragonfly),
  – Demi Moore (synthetic cannabinoids?)
### Exposures to selected drugs reported to Hennepin Regional Poison Center: 2009 through 2011

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
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<tbody>
<tr>
<td>Synthetic Cannabinoids</td>
<td>-</td>
<td>28</td>
<td>149</td>
</tr>
<tr>
<td>Bath Salts</td>
<td>-</td>
<td>5</td>
<td>144</td>
</tr>
<tr>
<td>2C-E and analogs</td>
<td>5</td>
<td>10</td>
<td>23</td>
</tr>
</tbody>
</table>

Synthetic Cannabinoids accounted for ~20 national poison control calls in 2008; and ~6,000 calls in 2011
Most of the “new” drugs are not new, but rediscovered
The internet has allowed the rapid dissemination of previously difficult to obtain knowledge of drugs.
Synthetic Cannabinoids
From Innocent Beginnings

• 1980’s pharma and basic researchers began creating synthetic cannabinoids
  – Gain basic understanding of cannabinoid receptors: distribution, SAR, subtypes
  – Develop novel pharmaceuticals for: appetite stimulation, nausea, pain reception
Some agonists are obviously related to THC, others are not

Anandamide

Delta$^9$ THC

CP 47,497

HU-210

JWH-018

Potencies of the synthetic agonists typically exceed THC by 10 to 200X
• Most JWH cannabinoids are easily synthesized.
• Sprayed onto inactive plant material
• Packaged and marketed masquerading as:
  – Herbal incense
  – Potpourri
Synthetic Cannabinoid Pharmacology

• CB₁ receptor binding; similar to THC
  – G protein coupled receptor
  – Associated w/ K & Ca channels
    – Learning & memory, wakefulness, novelty seeking

• Likely Serotonergic activity
  – Hallucinations
Symptoms of synthetic cannabinoid use

- Many effects and symptoms generally similar to THC.
  - Tachycardia
  - Time disturbances
  - Cognitive and memory effects
- Faster onset, quicker elimination.
- Psychedelic interference consisting of color and sound changes.
- Serotonin syndrome
Serotonin Syndrome

- Agitation or restlessness
- Diarrhea
- Fast heart beat
- Hallucinations
- Increased body temperature
- Loss of coordination
- Nausea
- Overactive reflexes
- Rapid changes in blood pressure
- Vomiting
JWH’s are NOT Synthetic Marijuana

Vomiting, convulsions, hallucinations, blood pressure elevation are not generally associated with marijuana.

Chemical Toxicity?
Legalities

• 5 Compound scheduled by US DEA:
  • JWH-018
  • JWH-073
  • JWH-200
  • CP-47,497
  • CP-47,497 C8

• Compounds scheduled in MN
  • CP-47,497
  • CP-47,497 C8
  • HU-210
  • HU-211
  • JWH-018
  • JWH-019
  • JWH-073
  • JWH-200
  • JWH-250
  • JWH-007
  • JWH-015

But......
More than 200 described CB$_1$ agonists

- Following the DEA ban:
  - Products switched to non-scheduled but equally active components
  - Sold with statements of “50 state legal”
    - Maybe “yes” maybe “no”
    - Does anyone actually know?
Synthetic Cannabinoid Trends

• Local pockets of dominant ingredients
  – House blends
  – JWH-250
• We have never seen HU-210, JWH-200
• JWH-018 declined following DEA ban
  – But is still present and maybe increasing
  – Why?
• AM-2201 (essentially 5 fluoro JWH-018)
Bath Salts, Plant Food and Research Chemicals
Phenylethylamines

- MDMA / amphetamine derivatives
Synthesized, evaluated, and described over 200 simple hallucinogens after a 1967 experience with MDMA

everything he saw and thought "had been brought about by a fraction of a gram of a white solid, but that in no way whatsoever could it be argued that these memories had been contained within the white solid ... I understood that our entire universe is contained in the mind and the spirit. We may choose not to find access to it, we may even deny its existence, but it is indeed there inside us, and there are chemicals that can catalyze its availability."
Trials in A-1

July 1, 1974, 0.070 mg, 11:00 PM ATS. There was almost some tooth-rubbing at about 11:30, but a bit slow. No effect. Go a bit slowly.

July 4, 1974, 0.060 mg, 10:30 AM ATS. No effect.

July 5, 1974, 0.665 mg, 8:25 AM ATE. No Effect. General stimulation in P.R. but losing response in I.P. No effect.

Aug. 8, 1974, 0.14 mg, 8:30 AM ATE. General stimulation in P.R., but losing response in I.P. No effect.

Sept. 1, 1974, 0.175 mg, 10:00 AM ATE. No effect.

Jan. 10, 1975, 0.26 mg, 9:55 AM ATE. No effect.

Jan. 18, 1975, 0.50 mg, 10:15 AM ATE. 2:30 PM (12:45 pm) very lightly spaced walking. Still lightly spaced - getting a bit done.

5:45 (9:00) a bit more. A burn of intense rubbing.

10:45 (9:15) have no response. No motion. No relief. Can't reach it. Scan of tongue - no trouble. No relief by far. He has a bit of speech. Is this a washout? Need more elixir? - note I the second of Jan. 11, 1975. No no washout effect. The no relief effect?
Phenylethylamines I have Known and Loved

- Systematic SAR investigation of hallucinogenic stimulants
- Details synthesis, dosing, effects
Activity of Phenylethylamines

- Mixed 5-HT receptor agonists
- Serotonin dumping
- Some NE and dopamine activity
- Structural variants alter spectrum of activity, potency and ADME

- Buyer beware!
  
  $2C-I \neq 2C-E \neq LSD$
2C-E, 2C-I, 2C-B Symptoms

• Complex visual and auditory effects.
• Tachycardia
• Systolic BP up
• Time distortions
• Twitching, grimacing
• Grinding teeth
• Serotonin syndrome
Flies and Dragonflys

• Oklahoma incident
  – Massive OD’s – wrong drug
• Steric rings increase potency and inhibit metabolism.
• “I really don’t know how many days I was tripping; three, maybe four.”
Br Dragonfly’s 5-HT activity

- Sub mg quantities for hallucinations
- Peripheral vasoconstrictor, can cause near immediate seizures.
- Rupture of blood vessels in the esophagus, eyes and sinuses.
- Loss of control of involuntary processes in the gut; continuous vomiting and diarrhea result.
- 2 days of vasoconstriction = gangrene
Khat or Qat

• Leaves of *catha edulis* slowly chewed
• Historically consumed in North African and Arabian cultures as a social activity.

“O, thou blessed that contains no demon, but a fairy! When I follow thee thou takest me into regions overlooking Paradise. My sorrows are as nothing. My rags are become as robes of silk. My feet are shod, not worn and bleeding. I lift up my head – O Flower of Paradise!”  - Arabian traditional song in praise of khat
Cathinone

- Active ingredient in khat.
- Slow mastication of khat results in relatively mild stimulation.
- Chronic use may lead to stimulant-induced psychosis / schizophrenia.
- Khat use is generally isolated to populations with historical use.
- Difficult to detect use; cathinone is metabolized to norephedrine.
The stimulant properties of purified or synthetic cathinone are much more similar to amphetamine.
Cathinone Derivatives

- Amphetamine
- Methylone
- MDPV
- Pyrovalerone
- Centroton
- Cathinone
- Mephedrone
## Designer Cathinones

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<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Methylone</td>
<td>Mephedrone</td>
<td>MDPV</td>
<td>DMMC</td>
</tr>
<tr>
<td>Fluphedrone</td>
<td>Butylone</td>
<td>Ephedrine</td>
<td>Ethcathinone</td>
</tr>
</tbody>
</table>

And at least 50 other compounds (and growing)
Pharmacology of Cathinones

- Weak non-selective 5-HT agonists
- Norepinephrine and weak dopamine reuptake inhibitors or transmitter releasing
- Structural variants alter spectrum of activity, potency and ADME
- Users report:
  - Flying euphoria, clarity of vision, color enhancement, invincibility, increased libido, hallucinations from some derivatives.
Designer Cathinone Symptoms

• Clinical:
  – Panic attacks, prolonged anxiety, irregular and increased heart rate, hypertension, grinding of teeth, insomnia, increased body temperature, erratic behavior.
Benzyl Piperazinines; BZP and TFMPP

- Party Pills
- Stimulating and empathetic
- Abuse relatively isolated to “dance scene”
- Highly variable legal status
BZP Pharmacology

BZP: Similar pharmacology to amphetamine
   NE, 5-HT, & DA reuptake inhibition and dumping

BZP + TFMPP for a MDMA like experience

Buyer beware! DanceSafe.org
Submitted ecstasy tablets

<table>
<thead>
<tr>
<th>Photo</th>
<th>Name</th>
<th>Contents</th>
<th>Location</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="36x36" alt="Photo" /></td>
<td>Pink Stripper</td>
<td>TFMPP, BZP</td>
<td>Montreal</td>
<td>2/01/12</td>
</tr>
<tr>
<td><img src="36x36" alt="Photo" /></td>
<td>Purple Nike</td>
<td>TFMPP, BZP, Caffeine</td>
<td>Victoria, BC</td>
<td>2/01/12</td>
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<tr>
<td><img src="36x36" alt="Photo" /></td>
<td>White Ying Yang</td>
<td>TFMPP, BZP, Caffeine</td>
<td>Salt Lake</td>
<td>12/27/11</td>
</tr>
<tr>
<td><img src="36x36" alt="Photo" /></td>
<td>Blue Heart</td>
<td>MDMA, BZP</td>
<td>Philadelphia</td>
<td>3/30/11</td>
</tr>
</tbody>
</table>
"Turn On Tune In Drop Out"
Dr. Timothy Leary
1920-1996
Tryptamines

Bufotenin

Serotonin

Psilocin
Synthetic Tryptamines
Tryptamine Pharmacology

- Selective agonist of 5-HT$_{2A}$
- Likely potentiation of tryptophan neuromodulation
Effects of Tryptamines

- Mild euphoria at best
- Time distortion
- Mild sedation to catatonic
- Religious experience
- Vomiting, convulsions
- Conscious respiration
Kratom

- Leaves of the *Mitragyna speciosa korth*
- Native to South East Asia
- Historically masticated for both stimulating and opioid-like effects
Kratom Pharmacology

- Mitragynine and 7-Hydroxy mitragynine (primary actives)
- mu opioid receptor agonist
- Alpha adrenergic receptor agonist
- Structurally unrelated to opiates
Kratom Use

- Legal status in U.S.
- Sold as extracts and as plant material
- Frequently mixed with tramadol

- Abused for opiate-like effects
  - Drug treatment centers and court ordered abstinence
Dextromethorphan (DXM)

- **Available OTC in > 100 products**
  - Typical adult dose of 15-30 mg, 4 times daily
  - Active at sigma-opioid receptors with little affinity for mu or delta (analgesic, CNS depressant).

- **Abuse Dosing:**

<table>
<thead>
<tr>
<th>PLATEAU</th>
<th>DOSE (MG)</th>
<th>BEHAVIORAL EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>100 - 200</td>
<td>Mild stimulation</td>
</tr>
<tr>
<td>2nd</td>
<td>200 - 400</td>
<td>Euphoria and hallucinations</td>
</tr>
<tr>
<td>3rd</td>
<td>300 - 600</td>
<td>Distorted visual perceptions, loss of motor coordination</td>
</tr>
<tr>
<td>4th</td>
<td>500 - 1500</td>
<td>Out-of-body sensations</td>
</tr>
</tbody>
</table>
DTM Activity and Toxicity

• At High doses DTM or dextrorphan:
  – Antagonizes NDMA receptors
    • Dissociative
  – Non-selective 5-HT agonist

• High dosing often accompanied with high APAP
• Variable CYP2D6 metabolism
Desomorphine (Krokodil)

Home Synthesized from OTC Codeine

- 10X morphine potency, fast onset, short acting, little respiratory depression or nausea.
Krokodil
the power of addiction

• Highly addictive
• Long, hard detoxification
• No real purification
  – Users injecting residue HCl, gasoline, I₂,
• Injection site rots away
• <2 year life expectancy
Federal Legalities of New Drugs

- DEA emergency scheduling powers
  - DEA is required by law to evaluate:
    - Patterns & scope of abuse, risk to public health

- Analog Drug Act of 1986
  - Similar structure to a schedule 1 or 2
  - Similar pharmacology
    - (similar or greater stimulant, depressant, or hallucinogenic effect)
  - Intended for human consumption
There is no list of analogs

- A few published DEA opinions on specific drugs
- Each analog case must be tried and proven independently
- Most challenges on “similar structure”
the cat and mouse game of designer drugs

- Manufacturers and distributors are aware that the analog act is challenging to prosecute.

- Most manufacturing is overseas
  - China and the former Soviet Republics
# Legality of Emerging Drugs

<table>
<thead>
<tr>
<th>Phenylethylamines</th>
<th>Cathinones</th>
<th>Pyrovalerones</th>
<th>Tryptamines</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C-I</td>
<td>Methylone</td>
<td>MDPV</td>
<td>DMT</td>
<td>Kratom</td>
</tr>
<tr>
<td>2C-E</td>
<td>Ethylone</td>
<td>MDPBP</td>
<td>MeO DALT</td>
<td>Desomorphine</td>
</tr>
<tr>
<td>2C-B</td>
<td>Butylone</td>
<td>MDPPP</td>
<td>MeO DIPT</td>
<td>MDAI</td>
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<tr>
<td>2C-T7</td>
<td>3,4-DMMC</td>
<td>Alpha-PPP</td>
<td>Bufotenine</td>
<td>Dextromethorphan</td>
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<td>2C-T2</td>
<td>Ethcathinone</td>
<td>Pyrovalerone</td>
<td>AET</td>
<td>Salvinorum</td>
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<tr>
<td>Bromo fly</td>
<td>Mephedrone</td>
<td>Naphyrone</td>
<td>NMT</td>
<td>BZP</td>
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<td>Bromo dragonfly</td>
<td>Methedrone</td>
<td>Alpha-PVP</td>
<td>AMT</td>
<td>TFMPP</td>
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<tr>
<td>bromobutterfly</td>
<td>Buphedrone</td>
<td>Alpha-PBP</td>
<td>DALT</td>
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<tr>
<td>DiMeO Br amphet</td>
<td>Methcathinone</td>
<td>MOPPP</td>
<td>DIPT</td>
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<td>DiMeO 4-Me amphet</td>
<td>Flephedrone</td>
<td>MOPBP</td>
<td>MeO AMT</td>
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<tr>
<td>4-MEC</td>
<td></td>
<td></td>
<td>HO DIPT</td>
<td></td>
</tr>
<tr>
<td>Pentylone</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**DEA Scheduled; Likely Analog; Maybe; Not Federally Scheduled**
How to keep up with the ever evolving drug scene
Legitimate Sources of Information

The Cops

The Government

Your friendly MEDTOX sales associate
Internet

Drug Forums

Erowid.org

Bluelight.ru

Suppliers / Distributers

All legal herbal
Research chemicals
MDAI Research
Pure Chemicals.net
Identifying unknowns from submitted samples and purchased samples
Some may tell you
HPLC-TOF HR MS Analysis of Drug Products
Sample F35043210: “Benzo Fury”

Broad LC gradient with HR TOF MS detecting all ions between 50 – 1000 m/z

One Peak detected which does not match our library of reference standards.
High Resolution Mass spectrometry measures the exact mass of a species with enough accuracy to define the elemental composition due to the mass defect of each element.

<table>
<thead>
<tr>
<th>Element</th>
<th>Exact Mass</th>
<th>Mass Defect</th>
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<tbody>
<tr>
<td>$^{12}\text{C}$</td>
<td>12.000000</td>
<td>0</td>
</tr>
<tr>
<td>$^{16}\text{O}$</td>
<td>15.994915</td>
<td>-0.005085</td>
</tr>
<tr>
<td>$\text{H}$</td>
<td>1.007825</td>
<td>+0.007825</td>
</tr>
<tr>
<td>$^{14}\text{N}$</td>
<td>14.003074</td>
<td>+0.003074</td>
</tr>
</tbody>
</table>
HR MS Analysis of Detected Peak

Exact Mass and Isotopic Pattern is characteristic of two Potential Formula: C11H13NO and CH11N7OF2

Only C11H13NO is sensible.
Rarely more than two logical formula exist for a single mass.
Database Search Yields ~ 1000 Structures with that formula
Potential compounds are evaluated for structural commonalities with drugs of abuse.
The mass spectrometer fragments the target compound, yielding structural information.
Potential structures are subjected to a theoretic fragmentation analysis and compared to actual fragmentation.
In most cases, one potential candidate remains

• Close structural isomers can be indistinguishable.
<table>
<thead>
<tr>
<th>Product</th>
<th>Active</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eight Ballz</td>
<td>MDPV</td>
<td>-</td>
</tr>
<tr>
<td>Cloud 9</td>
<td>3,4 Dimethylmethcathinone</td>
<td>-</td>
</tr>
<tr>
<td>Ivory Gold</td>
<td>MDPV</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Bliss</td>
<td>MDPV</td>
<td>-</td>
</tr>
<tr>
<td>Tran Quility</td>
<td>MDPV</td>
<td>Caffeine</td>
</tr>
<tr>
<td>Rush, Plant Feeder</td>
<td>-</td>
<td>Caffeine</td>
</tr>
<tr>
<td>Sky Vanilla</td>
<td>-</td>
<td>Caffeine</td>
</tr>
<tr>
<td>Gogaine</td>
<td>MDAI</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>4-Meo-PCP</td>
<td>4, Methoxy Phencyclidine</td>
<td>-</td>
</tr>
<tr>
<td>Ivory Wave Ultra</td>
<td>MDPV</td>
<td>-</td>
</tr>
<tr>
<td>White Rush</td>
<td>MDPV</td>
<td>-</td>
</tr>
<tr>
<td>Vanilla Sky</td>
<td>MDPV</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Benzo Fury</td>
<td>1-1-Benzofuran-6yl-propan-2 amine</td>
<td>-</td>
</tr>
<tr>
<td>Charly Sheen</td>
<td>MDAI</td>
<td>Lidocaine</td>
</tr>
</tbody>
</table>

Buyer beware!! What everyone thinks they know, might be wrong.
Our Goal: Detecting Drugs of Abuse in Biological Fluids
We know what is being ingested, but....

• Route of elimination?
• Phase I metabolism?
• Phase II metabolism?
• Rate of elimination?

• Scientific literature may or may not exist.
• Clues from similar compounds; maybe.
• Route of elimination?
• Assume some urinary elimination.
• Phase II metabolism?
• Enzymatic hydrolysis for good measure.
Strategy # 1
The Big Gun for Little Targets

- Assume some drug is excreted either unchanged or as a Phase II metabolite of the parent.
- High horsepower instrumentation to detect ng or pg drug levels.
High Horsepower Strategy

• Often successful.
  – Kratom, MDPV, mephedrone, etc.

• Almost as often, assay is too sensitive for real samples.
  – Kratom assay range: 1 to 500 ng/mL
  – Positive samples often > 10 µg/mL
  • Flooding instrumentation
Monitoring for parent will not always work

- If parent drug is not excreted, it can’t be detected.

- No reports of any detected JWH parent drugs in urine, and some species don’t appear to circulate either.
Plan B

• In vitro metabolism studies
  – Does not always accurately reflect human metabolism.

• Predict metabolites
  – Not always simple or obvious.

• Test known positive samples or a lot of samples that might be positive.
Scanning for metabolites by looking for mass shifts

<table>
<thead>
<tr>
<th>Transition</th>
<th>Mass Shift</th>
<th>Transition</th>
<th>Mass Shift</th>
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</thead>
<tbody>
<tr>
<td>Oxidation</td>
<td>+ 16</td>
<td>Decarbonylation</td>
<td>- 28</td>
</tr>
<tr>
<td>Carboxylation</td>
<td>+ 30</td>
<td>Alcohol dehydration</td>
<td>-18</td>
</tr>
<tr>
<td>Reduction</td>
<td>+ 2</td>
<td>Demethylation</td>
<td>- 14</td>
</tr>
<tr>
<td>Acetylation</td>
<td>+ 42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2X Oxidation</td>
<td>+ 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylation</td>
<td>+ 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkene to dihydrodiols</td>
<td>+ 34</td>
<td>Desalkylation</td>
<td>Compound specific</td>
</tr>
</tbody>
</table>

MS / MS techniques to further filter data
Comparing parent vs metabolite MSMS fragmentation provides metabolite structural information.
Elucidating Metabolites by MS Fragmentation Analysis

The presence of an alkyl modification will result in a shift in only these peaks
Identified biological markers of drug use; Now what?

• Validating the discriminative accuracy of procedure.

• Controlled dosing studies
  – Good luck!

• Known users
  – Maybe

• Likely users
  – Large, blind screening studies
With limited access to known samples and spotty scientific information, eliminating the risk of false positives is paramount.
Screen and Confirmation procedures

- Antibody based screening procedures generally don’t yet exist

- Complimentary instrumental methods
  - LC-TOF and LC-MS/MS
  - Different LC-MS/MS procedures
Full fragmentation fingerprinting analysis

Full fragmentation analysis via quadrupole linear ion trap instruments generate a higher level of confidence than MRM based methods alone.
Metabolites

The coexistence of metabolites substantiates the use of the parent compound
Designer Drugs Du Jour

- Synthetic Cannabinoids
  - JWH-018, JWH-250, AM-2201

- MDPV, Mephedrone, Fluphedrone

- MeO DALT
FIN

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Melissa Goggin
Amy Tann
Ryan Russ

Susan Puskas

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