Current Trends in Addiction Medicine

C. Chapman Sledge, MD, DFASAM
Cumberland Heights
Nashville, TN
ccsledge@gmail.com
@ccsledge

Synthetic Cannabinoids and Substituted Cathinones

Synthetic Cannabinoids

- JWH compounds (Aminoalkylindoles)
  - JWH 018, JWH 073, JWH 200, JWH 250
- CP compounds (Cyclohexylphenols)
  - CP47,497, Cannabicyclohexanol
- Classical Cannabinoids (Dibenzopyrans)
  - HU 210, HU 243

Synthetic Cannabinoids

- Pharmacology
  - Detailed pharmacology not yet elucidated
  - Agonist v. partial agonist at CB1 receptor
  - Greater potency than THC
  - Lipid soluble
  - Variable duration
  - Urinary metabolite excretion
    - NOT readily detectable

Synthetic Cannabinoids

- John William Hoffman developed over 450 compounds related to research of the newly described endocannabinoid receptors

Synthetic Cannabinoinds

- Compared to THC:
  - Much greater receptor affinity
  - Much longer duration of action
  - Much more potent
  - More severe withdrawal syndrome

Synthetic Cannabinoids

- First appeared in Europe in mid 2000's
- First reported in US in late 2000's

Synthetic Cannabinoids

- Various states began banning specific compounds in 2010
- Specific substances banned by DEA in 2011
- Synthetic Drug Abuse Prevention Act signed by President Obama

Synthetic Cannabinoids

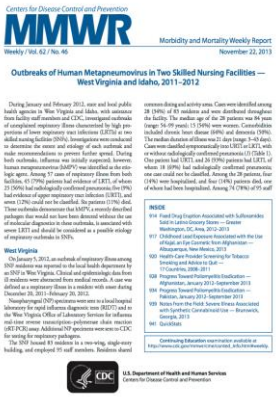
- Typically smoked
- More recent rise in "vaping"

Synthetic Cannabinoids

- After ban, 20% US HS Seniors had used Synthetic Cannabinoids

Synthetic Cannabinoids

- By 2011, 11% US HS Seniors had used Synthetic Cannabinoids



Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Weekly / Vol. 62 / No. 46

November 22, 2013

Outbreaks of Human Metapneumovirus in Two Skilled Nursing Facilities — West Virginia and Idaho, 2011–2012

During January and February 2012, state and local public health agencies in West Virginia and Idaho, with assistance from facility staff members and CDC, investigated outbreaks of coinfluenza-like respiratory illness characterized by high proportions of lower respiratory tract infections (LRTIs) at two skilled nursing facilities (SNFs). Investigators were conducted to determine the extent and etiology of each outbreak and make recommendations to prevent further spread. During both outbreaks, influenza was initially suspected; however, human metapneumovirus (hMPV) was identified as the etiologic agent. Among 57 cases of respiratory illness from both facilities, 45 (79%) patients had evidence of LRTI, of whom 21 (56%) had radiologically confirmed pneumonia; five (9%) had evidence of upper respiratory tract infection (URTI), and seven (12%) could not be classified. Six patients (11%) died. These outbreaks demonstrate that hMPV, a recently described pathogen that would not have been detected without the use of molecular diagnostics in these outbreaks, is associated with severe LRTI and should be considered as a possible etiology of respiratory outbreaks in SNFs.

West Virginia

On January 5, 2012, an outbreak of respiratory illness among SNF residents was reported to the local health department by an SNF in West Virginia. Clinical and epidemiologic data from 10 residents were abstracted from medical records. A case was defined as a respiratory illness in a resident with onset during December 20, 2011–February 20, 2012.

Nasopharyngeal (NP) specimens were sent to a local hospital laboratory for rapid influenza diagnostic tests (RIDT) and to the West Virginia Office of Laboratory Services for influenza real-time reverse transcription–polymerase chain reaction (rRT-PCR) assay. Additional NP specimens were sent to CDC for testing for respiratory pathogens.

The SNF housed 83 residents in a two-wing, single-story building, and employed 95 staff members. Residents shared common dining and activity areas. Cases were identified among 28 (34%) of 83 residents and were distributed throughout the facility. The median age of the 28 patients was 84 years (range: 56–99 years); 15 (54%) were women. Comorbidities included chronic heart disease (68%) and dementia (50%). The median duration of illness was 21 days (range: 3–43 days). Cases were classified symptomatically into URTI or LRTI, with or without radiologically confirmed pneumonia (3) (Table 1). Nine patients had URTI, and 28 (93%) patients had LRTI, of whom 18 (69%) had radiologically confirmed pneumonia; one case could not be classified. Among the 28 patients, four (14%) were hospitalized, and four (14%) patients died, one of whom had been hospitalized. Among 74 (78%) of 95 staff

INSIDE

Continuing Education examination available at http://www.cdc.gov/mmwr/mmwrcontinued_edu.html#weekly

CDC U.S. Department of Health and Human Services Centers for Disease Control and Prevention

Morbidity and Mortality Weekly Report

Notes from the Field

Severe Illness Associated with Synthetic Cannabinoid Use — Brunswick, Georgia, 2013

On August 23, 2013, the Georgia Poison Center was notified of eight persons examined in an emergency department in Brunswick, Georgia, after smoking or inhaling fumes from synthetic cannabinoids. The Georgia Poison Center notified the Georgia Drug and Narcotics Agency, which informed the Georgia Department of Public Health (DPH). The Brunswick emergency department was asked to report any additional patients who reported use of synthetic cannabinoid to the Coastal District Health Department. DPH investigators reviewed recent medical records of patients who had gone to the emergency department and found that 22 patients had been examined after using synthetic cannabinoids during August 22–September 9, 2013.

The 22 patients were aged 16–57 years (median: 25 years); 18 (82%) were male. Patients experienced hyperglycemia (13 [59%]), hypokalemia (nine [41%]), acidosis (seven [32%]), tachycardia (13 [59%]), nausea/vomiting (eight [36%]), confusion/disorientation (seven [32%]), aggression (seven [32%]), somnolence/unresponsiveness (seven [32%]), and seizures (three [14%]). Complications included pneumonia (two patients), rhabdomyolysis (one), and myocardial infarction (one). Six (27%) patients were admitted to the intensive care unit; five (23%) required assisted ventilation; none died. Serum from seven of the initial eight patients was tested for synthetic cannabinoid by the Clinical and Environmental Toxicology Laboratory at the University of California, San Francisco. Five tested positive for ADB-PINACA (N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide), a previously unrecognized synthetic cannabinoid related to indole compounds recently identified in Europe and Japan (1).

Law enforcement authorities removed the synthetic cannabinoid from the implicated Brunswick smoke shop,* which sold all types of tobacco products and smoking paraphernalia. The product, "Crazy Clown," was tested by the Georgia Bureau of Investigation Crime Laboratory, which identified ADB-PINACA, an indazole classified under Georgia law as Schedule 1 on the basis of its close relationship to Schedule 1 compounds already specified. The smoke shop owners were charged on September 10, 2013, with possession of a Schedule 1 controlled substance with intent to distribute; no additional patients who used synthetic cannabinoids have been reported by the ED.

Synthetic cannabinoids are designer drugs often smoked as a marijuana alternative. Despite laws prohibiting synthetic cannabinoid sales, they are still widely available, and recent increases in reports of synthetic cannabinoid use and adverse health effects have occurred (2,3). Common adverse effects include altered mental status and tachycardia. Clinicians examining patients with suspected drug abuse and these symptoms should consider synthetic cannabinoid intoxication (4). Public health authorities can raise awareness of adverse events associated with synthetic cannabinoids and establish mechanisms for surveillance by partnering with poison centers, health-care providers, and law enforcement.

Reported by

Cherie Drenzek, DVM, Georgia Dept of Public Health; Robert J. Geller, MD, Alaina Steck, MD, Justin Arnold, DO, Gaylord Lopez, PharmD, Georgia Poison Center; Roy Gerona, PhD, Dept of Laboratory Medicine, Univ of California, San Francisco. Laura Edison, DVM, EIS Officer, CDC. ***Corresponding contributor:*** *Laura Edison, [illegible], 404-657-6452.*

References

1. Uchiyama N, Kawamura M, Kikura-Hanajiri R, et al. Identification of two new-type synthetic cannabinoids, [illegible] and detection of five synthetic cannabinoids, AM-1220, AM-2233, AM-1241, CB-13 (CRA-13), and AM-1248, as designer drugs in illegal products. Forensic Toxicol 2012;30:114–25.
2. [illegible] L, [illegible] W. Beyond THC: the new generation of cannabinoid designer drugs. Front Behav Neurosci 2011;5:60.
3. CDC. Acute kidney injury associated with synthetic cannabinoid use—multiple states, 2012. MMWR 2013;62:93–8.
4. Lapoint J, James LP, Moran CL, Nelson LS, Hoffman RS, Moran JH. Severe toxicity following synthetic cannabinoid ingestion. Clin Toxicol (Phila) 2011;49:760–4.

*The initial eight patients reported buying the synthetic cannabinoid from the same smoke shop. Additional patients interviewed also named the smoke shop as the source.

MMWR - November 22, 2013

- 6 – ICU admissions
- 5 – Mechanical ventilation
- 0 – deaths

MMWR - November 22, 2013

- August 2013
- Reports to GA Poison Control Center from hospital in Brunswick, GA
- 22 patients examined after using synthetic cannabinoinds
- Ages 16 – 57 years
- 82% male
- “Crazy Clown’’ purchased in local tobacco shop

Synthetic Cannabinoids

MMWR - November 22, 2013

- 13 – hyperglycemia
- 13 - tachycardia
- 9 – hypokalemia
- 8 – nausea / vomiting
- 7 – acidosis
- 7 – disorientation / confusion (DEA agent)
- 7 – aggression
- 7 - somnalence / unresponsiveness
- 3 – seizures
- 2 – pneumonia
- 1 – rhabdomyolysis
- 1 – myocardial infarction (30 y/o)

Synthetic Cannabinoids

"Spice / K2"

- Serious Adverse Effects
  - Agitated Delerium
  - Cardiotoxicity
  - Anxiety
  - Psychosis
  - Seizures
  - Dependence
  - Death
  - Kidney Injury
  - Coma
  - Elevated HR
  - Panic Attacks
  - Suicidal ideation
- Management is supportive

CDC MMWR, June 12, 2015

- Between 1/1/15 and 4/1/15: 330% increase in Poison Control Center calls related to Synthetic Cannabinoinds
  - 349 calls in January 2015
  - 1501 calls in April 2015
- Agitation, tachycardia, lethargy, n/v, confusion
- 11% life threatening
- 15 deaths


Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Weekly / Vol. 64 / No. 22 June 12, 2015

Health Effects of Cut Gas Lines and Other Petroleum Product Release Incidents — Seven States, 2010–2012

INSIDE

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

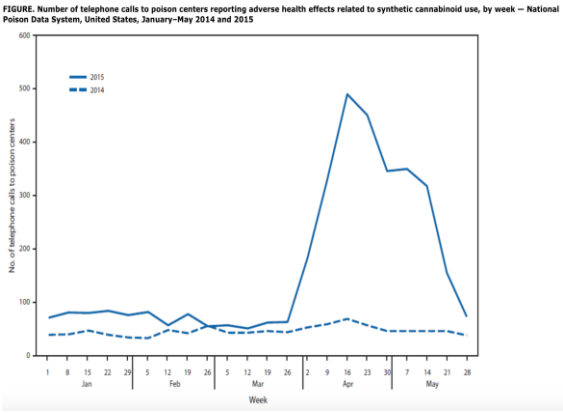


FIGURE. Number of telephone calls to poison centers reporting adverse health effects related to synthetic cannabinoid use, by week — National Poison Data System, United States, January–May 2014 and 2015


Morbidity and Mortality Weekly Report

Notes from the Field

Increase in Reported Adverse Health Effects Related to Synthetic Cannabinoid Use — United States, January–May 2015

New England Journal of Medicine

- July 9, 2015
- Synthetic Cannabinoid-related Illness and Death

NEJM

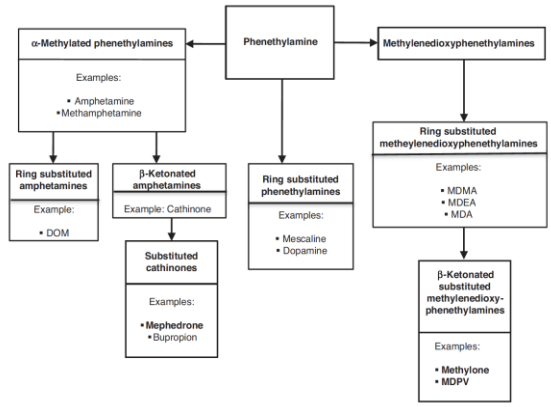
- Motivations
  - 91% Curiosity / experimentation
  - 89% To feel good / to get high
  - 71% To relax
  - 71% to get high / avoid UDS

"Bath Salts / Plant Food"

- Mephedrone
  - Synthesized from cathinone
  - Initially synthesized in 1929
  - Appeared in Europe as drug of abuse 2007
    - By 2009, 4th most abused drug in UK
- Other Phenethylamines
  - MDPV (Methylenedioxypryovalerone)
  - Methylone

NEJM

- Recent increase in clusters of severe toxicity and death (3/2015 -5/2015)
- First cluster was in Gainesville, FL
- From 2014 through 4/2015
  - Mississippi Department of Health reported 1200 ER visits and 17 deaths related to synthetic cannabinoids



Substituted Cathinone

- Khat
  - Flowering plant
  - Africa and Arabian peninsula
  - Leaves are chewed for stimulant effect
  - Documentation of use in Ancient Egypt
  - Primary active ingredient is Cathinone
    - Metabolites include
      - Cathine
      - Norephedrine

Substituted Cathinones

- Product variability
  - Other stimulants not uncommon (cocaine, amphetamine, caffeine)
  - Ketamine
  - Benzocaine, lidocaine, procaine
- By 2009, 4th most commonly abused drug in UK
- Majority of MDMA sold in UK in 2009 was mephedrone

Substituted Cathinones

- Pharmacology
  - DA, NE, 5HT release and reuptake inhibition
  - Similar to amphet/ MA / MDMA / cocaine
  - Variable duration
    - Euphoria 2-4 hrs
    - Physical effects 2-8 hrs
  - 0.25 – 1 gm dose
  - Binge up to 5 gm

Substituted Cathinones

- Physical Effects
  - Elevated HR / BP
  - Pupillary dilation
  - Arrythmia
  - MI
  - Hyperreflexia
  - Seizure
  - rhabdomyolysis
  - Death – direct toxicity or indirect (DIC)

  Hyperthermia
  Diaphoresis
  Bruxism
  CVA
  Myoclonus
  Serotonin Syndrome (MDPV)

Substituted Cathinones

- First appearance in US 2009

US Poison Control Centers

Year	Calls
2009	0
2010	304
2011	6138

Substituted Cathinones

- 70 to 80% of ER presentations include agitated delirium
- May include combative violent behavior
- Psychosis may be pronounced

Substituted Cathinones

- Behavioral / Psychiatric Symptoms
  - Agitation
  - Anxiety
  - Anorexia
  - Self-mutilation
  - Profound Depression
  - Attention / Memory disturbance

  Panic Attacks
  Insomnia
  Psychosis
  Suicidal Ideation

Substituted Cathinones

- 70 to 80% of ER presentations include agitated delirium
- May include combative violent behavior
- Psychosis may be pronounced

- Treatment is supportive
- Benzodiazepines, antipsychotics, propofol

Ban

- Specific substances targeted

Substituted Cathinones

- '2nd Generation' products developed to circumvent ban
- Alpha – Pyrrolidinovalerophenone
- Alpha – PVP
- FLAKKA

Ban

- Majority of states enacted emergency legislation to ban synthetic intoxicants
- Federal Analog Act not enforced due to label "not for human consumption"
- DEA ultimately banned known and potential compounds

Flakka

- Alpha PVP
- Synthesized in China
- Sold online as a variety of products
- 5gm for $40, standard dose is 0.1gm, $.80 per dose

Substituted Cathinones

- '2nd Generation' products developed to circumvent ban
- Alpha – Pyrrolidinovalerophenone
- Alpha - PVP

Flakka

- Agitated delirium
- Prolonged psychosis

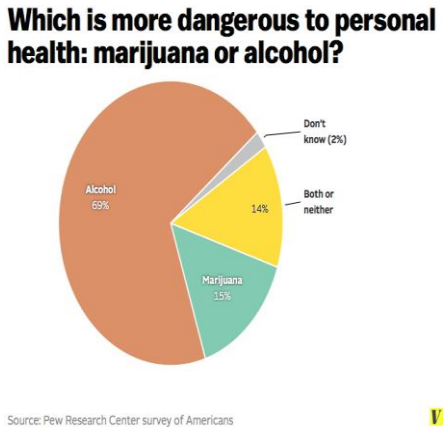
Flakka

- For the first 3 months of 2015, cathinones exceeded cocaine arrests in Broward County

Cannabis

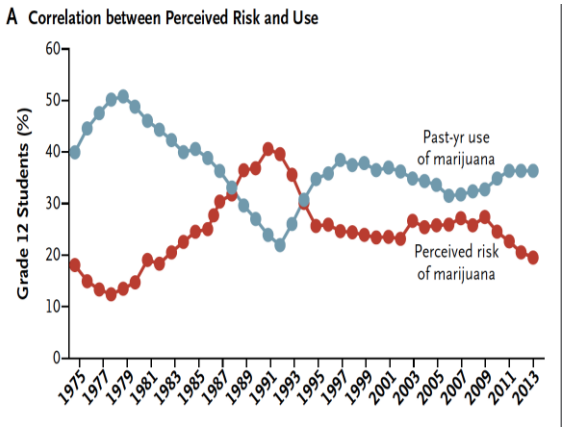
Substituted Cathinones

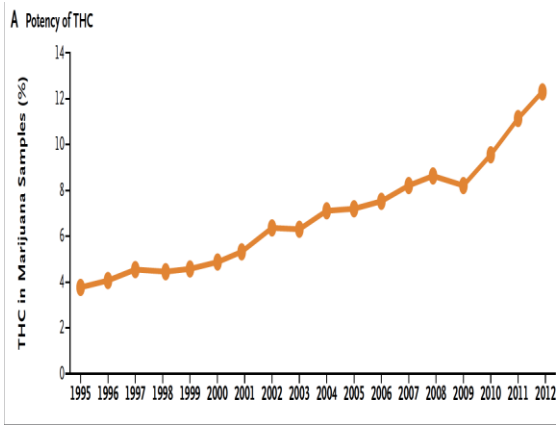
- In 2015, 679 festival attending young adults who reported using MDMA consented to hair testing
- 50% samples contained MDMA
- 47.9% samples contained Substituted Cathinones, most notably alpha PVP



Substituted Cathinones

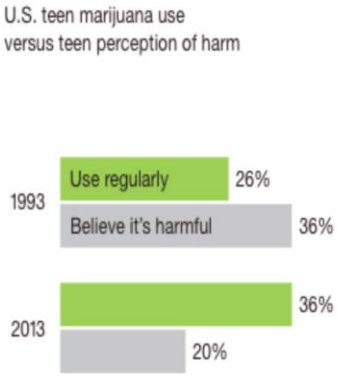
- In 2015, 679 festival attending young adults who reported using MDMA consented to hair testing
- 50% samples contained MDMA
- 47.9% samples contained Substituted Cathinones, most notably alpha PVP
- Majority of MDMA sold in Europe is Substituted Cathinones





NEJM June 5, 2014

- ADVERSE EFFECTS OF MARIJUANA USE
- Volkow, Compton
- Review of 77 academic publications



NEJM June 5, 2014

- ADVERSE EFFECTS OF MARIJUANA USE
- Risk of ***addiction***
  - 9% of MJ users become addicted
  - 16% if onset in teens
  - 25% to 50% if daily use

NEJM June 5, 2014

- ADVERSE EFFECTS OF MARIJUANA USE
- Volkow, Compton

NEJM June 5, 2014

- ADVERSE EFFECTS OF MARIJUANA USE
- ***Brain Development***
  - Impaired connectivity in specific regions
  - Precuneus – alertness / self conscious awareness
  - Hippocampus – learning / memory
  - Prefrontal cortex – executive function
  - Lower IQ as adult

NEJM June 5, 2014

- ADVERSE EFFECTS OF MARIJUANA USE
- ***Gateway***
  - Decrease in mesolimbic dopamine activity
  - May lead to other drug use to stimulate dopamine activity

NEJM June 5, 2014

- ADVERSE EFFECTS OF MARIJUANA USE
- Relationship to ***Psychiatric Illness***
  - Associated with anxiety / depression, though causality lacking
  - Increased incidence of psychosis
  - Precipitation of schizophrenia in genetically susceptible individuals

NEJM June 5, 2014

- ADVERSE EFFECTS OF MARIJUANA USE
- ***Academic performance / lifetime achievement***
  - Impaired school performance (+/- reversible)
  - Increased dropout
  - Lower income
  - Increased public assistance
  - Increased unemployment
  - Increased criminal acitivity
  - Lower life satisfaction

Table 2. Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

Effect	Overall Level of Confidence*
Addiction to marijuana and other substances	High
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Medium
Diminished lifetime achievement	High
Motor vehicle accidents	High
Symptoms of chronic bronchitis	High
Lung cancer	Low

* The indicated overall level of confidence in the association between marijuana use and the listed effects represents an attempt to rank the strength of the current evidence, especially with regard to heavy or long-term use and use that starts in adolescence.

Volkow ND et al. N Engl J Med 2014;370:2219-2227.

NEJM June 5, 2014

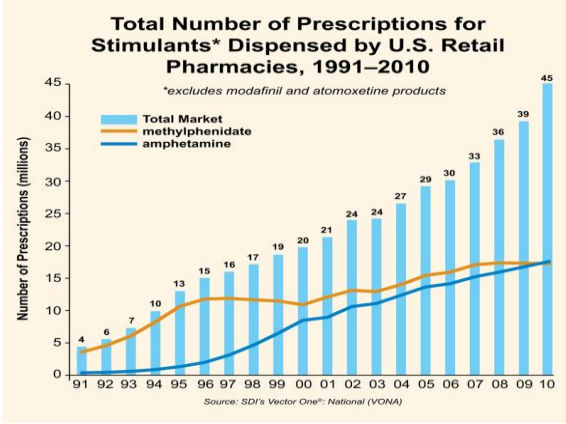
- ADVERSE EFFECTS OF MARIJUANA USE
- ***MVA***
  - Driving ability impaired with acute and chronic use
  - Most common illicit drug identified in fatal accidents
  - Minimum detectable blood level (1ng / ml)
    - 3-7 times increase in MVA
  - BAC 0.08%
    - 5 times increase in MVA

Co-Occurrence of Substance-Related and Other Mental Health Disorders Among Adolescent Cannabis Users

- Zaman, et al
- Journal of Addiction Medicine
- June 2015

Co-Occurrence of Substance-Related and Other Mental Health Disorders Among Adolescent Cannabis Users

85% admissions to Boston Children's Hospital Adolescent Substance Abuse Program have diagnosis of Cannabis dependence, abuse, or problematic use



Co-Occurrence of Substance-Related and Other Mental Health Disorders Among Adolescent Cannabis Users

Co-occurrence of substance related disorders and other mental health disorders was the rule, not the exception

Prevalence

- Top 200 drugs for 2012 (Sales)
  - 33. Vyvanse
  - 37. Methylphenidate ER
  - 70. Adderall XR
  - 105. Focalin XR
  - 132. Amphetamine salts ER (Global)
  - 135. Amphetamine salts ER (Teva)
  - 137. Provigil
  - 175. Nuvigil
  - 183. Amphetamine salts (Teva)

Prescription Stimulants

Prevalence

- March 2015
  - 7. Vyvanse

Prevalence

- DEA allows only a certain amount of amphetamine to be commercially produced each year.
- Quota approved by congress each year

Prevalence

- DEA allows only a certain amount of amphetamine to be commercially produced each year.
- Quota approved by congress each year
- 1990 – 417 Kg produced
- 2000 – 9007 Kg produced
- 2012 – 25,300 Kg produced

Prevalence

- DEA allows only a certain amount of amphetamine to be commercially produced each year.
- Quota approved by congress each year
- 1990 – 417 Kg produced

Prevalence

- DEA allows only a certain amount of amphetamine to be commercially produced each year.
- Quota approved by congress each year
- 1990 – 417 Kg produced
- 2000 – 9007 Kg produced
- 2012 – 25,300 Kg produced
- *AND THEY RAN OUT!!!*

Prevalence

- DEA allows only a certain amount of amphetamine to be commercially produced each year.
- Quota approved by congress each year
- 1990 – 417 Kg produced
- 2000 – 9007 Kg produced

Prevalence

- Department of Defense
- Active Military
- 10 fold increase in stimulant prescriptions from 2005 to 2010
  - 18 million prescriptions for stimulants in 2010

The Selling of Attention Deficit Disorder

- New York Times
  - December 14, 2013

The Selling of Attention Deficit Disorder

- New York Times
  - December 14, 2013
- Sales of prescription stimulants
  - 2002 – $1.7 billion
  - 2012 - $9 billion

The Selling of Attention Deficit Disorder

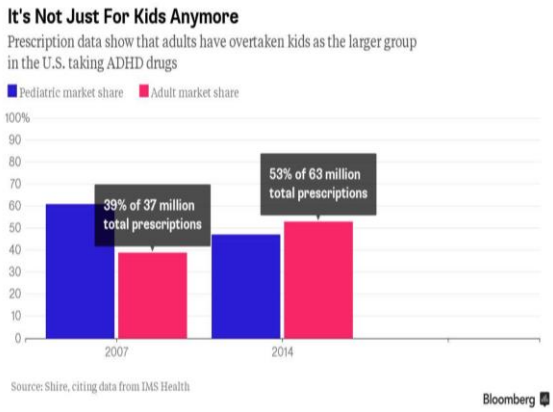
- New York Times
  - December 14, 2013
- 15% high school age diagnosed with ADHD

The Selling of Attention Deficit Disorder

- New York Times
  - December 14, 2013
- New Market?

The Selling of Attention Deficit Disorder

- New York Times
  - December 14, 2013
- Children on prescription stimulants
  - 1990 – 600,000
  - 2012 – 3,500,000



The Selling of Attention Deficit Disorder

- New York Times
  - December 14, 2013
- New Market?
  - Adults 20-39
    - 2007 – 5.6 million prescriptions
    - 2012 – 16 million prescriptions

Non-Medical Use

- N=1253
- Medical use for ADHD – 3%
- ADHD with Non-Medical Use – 33% (F>M)
- Non-ADHD with Non-Medical Use – 18%

  - Arria, 2008

The Selling of Attention Deficit Disorder

- New York Times
  - December 14, 2013
- New Market?
  - Adults 20-39
    - 2007 – 5.6 million prescriptions
    - 2012 – 16 million prescriptions
  - Women 20-39
    - 750% in stimulant prescriptions

Non-Medical Use

- Mixed Amphetamine Salts – 89%
- Methylphenidate – 26%
- Methylphenidate ER – 14%

  - Arria, 2008

College

Non-Medical Use

- Route of Administration
  - Oral – 77%
  - Crushed / snorted – 15%

  - Arria, 2008

Non-Medical Use

- How obtained
  - Friend with prescription – 79%
  - Friend without prescription – 16%
  - Free – 72%
  - Stealing - <1%
  - Internet – 0%
    - Arria, 2008

Non-Medical Use

- Non-Medical Use significantly associated with higher rates of binge drinking and higher rates of adverse consequences of alcohol use
  - 50% Non-Medical User with positive CAGE screen
- Non-Medical Users 65% positive screen (DAST-10) with 3 or more drug-use related problems compared to 18% Non Users
  - Sepulveda, 2011

Non-Medical Use

- Non-Medical Use was strongly associated with alcohol and marijuana dependence
  - ADHD with Non-Medical Use were more likely cannabis dependent than non-ADHD with Non-Medical Use
- Non-Medical Use was associated with past year use of Cannabis, Inhalants, Hallucinogens, Cocaine, MDMA, Opioids, Sedative Hypnotics
  - ADHD with Non-Medical Use demonstrated strongest association with illicit drug use

Arria, 2008

Non-Medical Use

- For ADHD, Non-Medical Use higher (55% v. 33%) for those who were diagnosed and prescribed stimulants in college as opposed to prior to college
- 80% of Non-Medical Users who identified "to get high" as motivation for Non-Medical Use initiated treatment in college
  - Sepulveda, 2011

Non-Medical Use

- No statistical significant differences in Non-Medical Use for those reporting active symptoms of ADHD
  - Sepulveda, 2011

Non-Medical Use

- Diversion
  - 36% ADHD reported diversion of stimulant medication
  - 57% Non-Medical Use reported diversion
  - 20% non-use reported diversion
  - Adderall and Adderall XR most often diverted
    - Sepulveda, 2011

Motivation

- N=689 college students
- Help concentration 58%
- Increase alertness 43%
- Counteract effects of other substances 8%
- To get high 43%
- No significant difference in gender
  - Teter, 2005

Cognitive Enhancement

- American Academy of Neurology, Committee on Ethics, Law, and Humanities:
- Physicians are allowed to grant requests for stimulant drugs to improve cognition in healthy patients……BUT, they are not obliged to do so.
  - Lavierre, 2009

Motivation

- N= 1253 College Freshmen
- Improve concentration / study – 73%
- Curiosity – 18%
- Enhance wakefulness to party / drink / go out – 9%
- Get high / feel good / have fun – 7%
- Peer pressure – 5%
- Others:
  - weight loss, stay awake to drive, pass breathalyzer, stay awake for no particular reason
  - Arria, 2008

Cognitive Enhancement

- American Academy of Neurology, Committee on Ethics, Law, and Humanities:
- Physicians are allowed to grant requests for stimulant drugs to improve cognition in healthy patients…