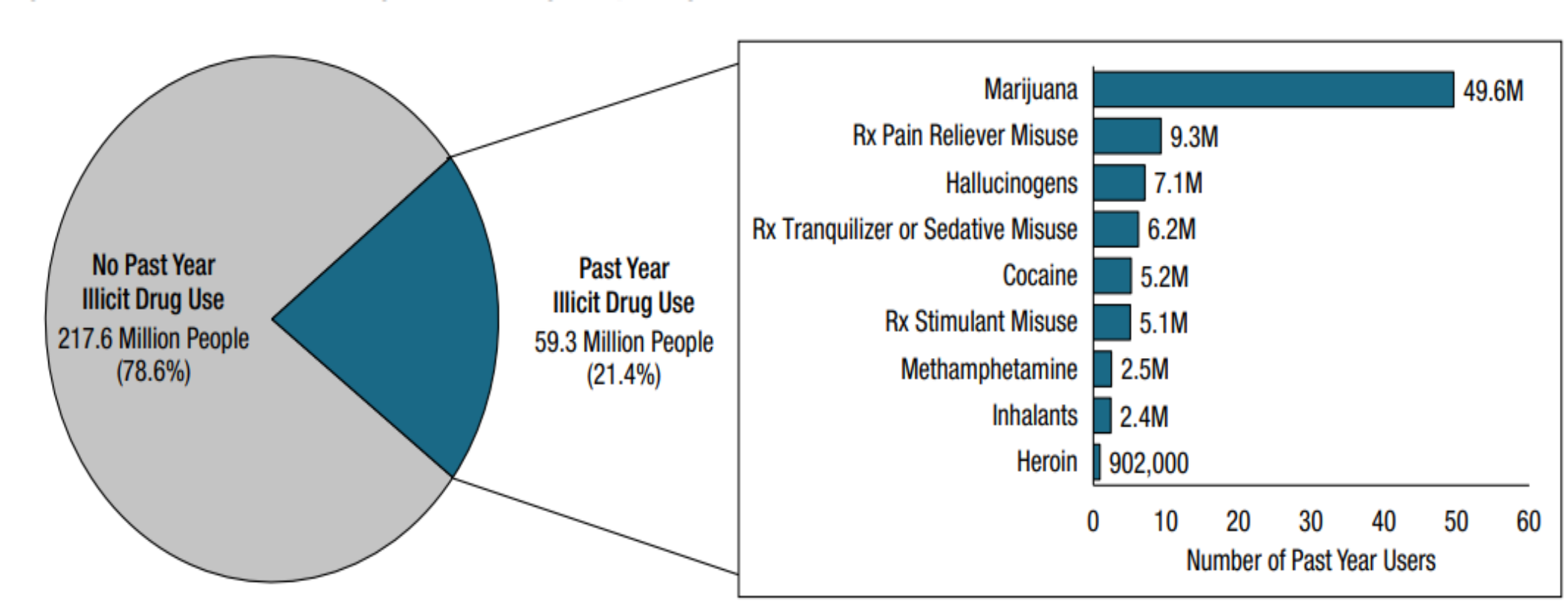
Overview of Cannabinoids

Olawale Ojo M.B.Ch.B, MS

Most used illicit substance

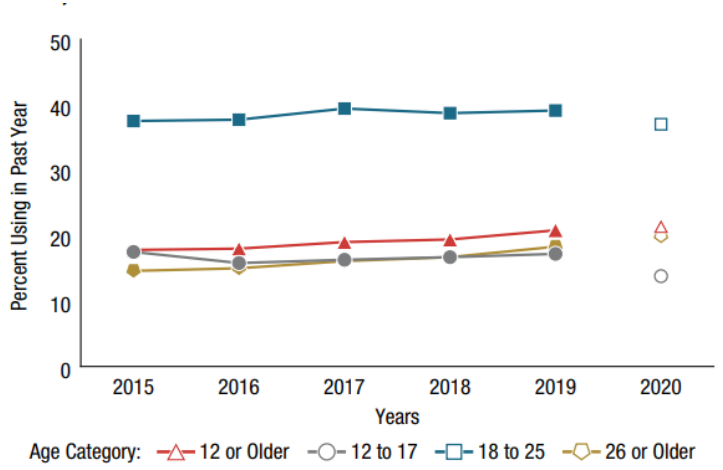


Rx = prescription.

Note: The estimated numbers of past year users of different illicit drugs are not mutually exclusive because people could have used more than one type of illicit drug in the past year.

- In 2020, 17.9 percent of people aged 12 or older (or 49.6 million people) used marijuana in the last year.
- The percentage was highest among young adults aged 18 to 25 (34.5 percent or 11.6 million
- An important gateway drug
- Comorbidity with other SUD disorders
  - Alcohol use disorder – 50%
  - Nicotine use 53%
- Comorbid with psychiatric disorder
  - 11% Major depressive disorder
  - 24% Any anxiety disorder
  - 13% bipolar I disorder
  - 30% Antisocial Personality Disorder (PD)
  - 18% Paranoid PD
- Adolescents CUD- 60% - conduct disorder, ADHD; 33% - anxiety, depression, PTSD

2020 National Survey on Drug Use and Health



Note: There is no connecting line between 2019 and 2020 to indicate caution should be used when comparing estimates between 2020 and prior years because of methodological changes for 2020. Due to these changes, significance testing between 2020 and prior years was not performed.

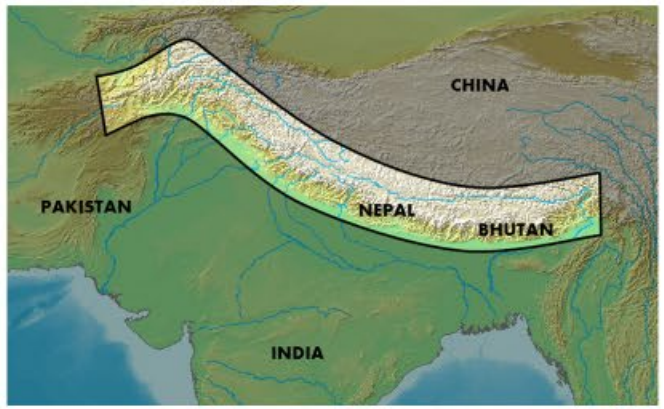
Figure 10 Table. Past Year Illicit Drug Use: Among People Aged 12 or Older; 2015-2020

Age	2015	2016	2017	2018	2019	2020
12 or Older	17.8	18.0	19.0	19.4	20.8	*21.4*
12 to 17	17.5	15.8	16.3	16.7	17.2	*13.8*
18 to 25	37.5	37.7	39.4	38.7	39.1	*37.0*
26 or Older	14.6	15.0	16.1	16.7	18.3	*19.9*

Note: The estimate in 2020 is italicized to indicate caution should be used when comparing estimates between 2020 and prior years because of methodological changes for 2020. Due to these changes, significance testing between 2020 and prior years was not performed.

Possible origins

Central Asia



Himalayan Mountains

Three subspecies

Cannabis sativa

Cannabis indica

Cannabis ruderalis

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Administration

- Smoke
  - rolled as blunts, joints, spiffs, bongs, pipes, hookahs
  - Whole plant-THC content 1-5%
  - Unfertilized flower (sinsemilla) THC content 7-15%
- Vaped, ingested
  - Hashish: resin with 10-20% THC
  - Hash oil: concentrated resin 20-80%
- Edibles- food, usually in fat/oil

Cannabinoids

Δ9-tetrahydrocannabinol (THC)

Δ9-tetrahydrocannabivarin (THCV)

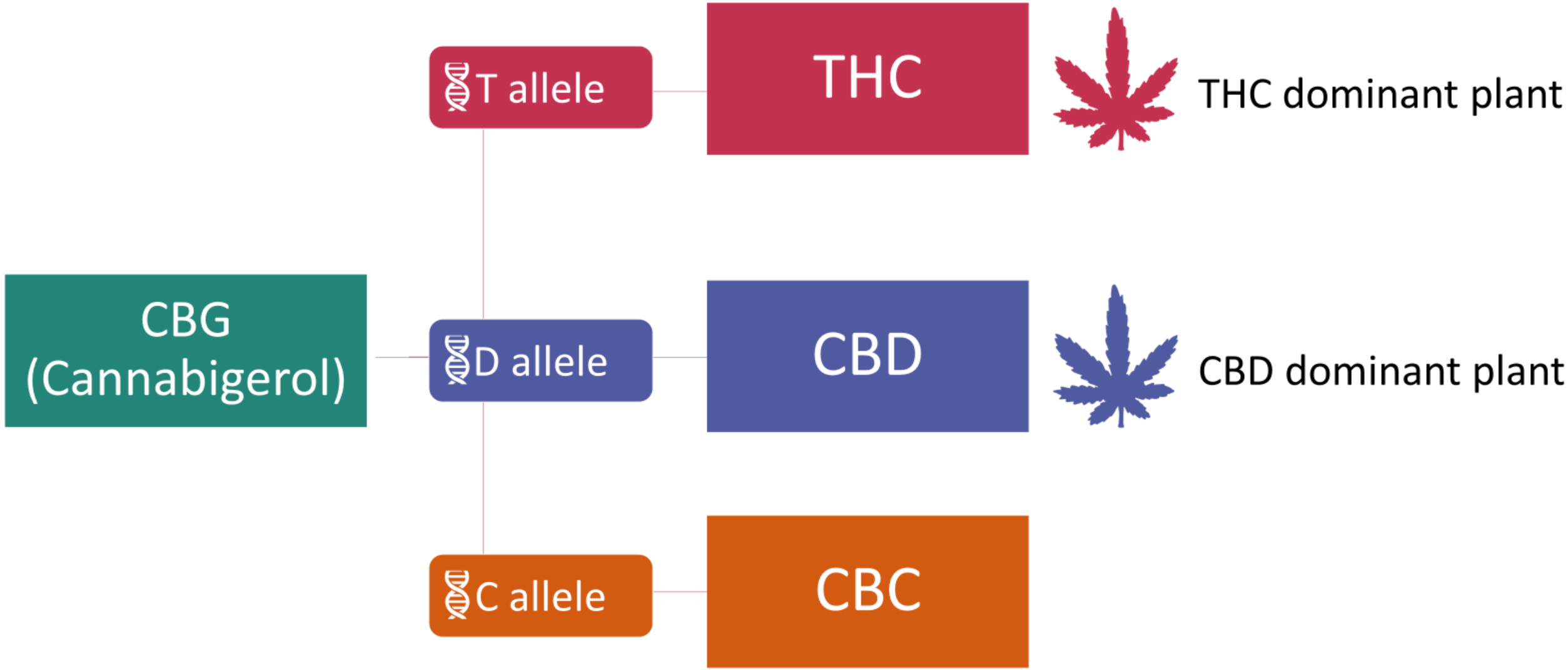
Cannabidiol (CBD)

Cannabinol (CBN)

Cannabigerol (CBG)

Cannabichromene (CBC)

Clarke R. & Watson D. (2007) Cannabis and natural cannabis medicines, in ElSohly MA (ed.) Marijuana and the cannabinoids. Totowa, New Jersey: Humana press Inc. pp. 1-15.



Clarke R. & Watson D. (2007) Cannabis and natural cannabis medicines, in ElSohly MA (ed.) *Marijuana and the cannabinoids.* Totowa, New Jersey: Humana press Inc. pp. 1-15.

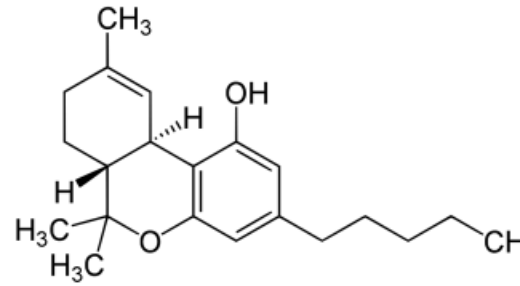
PSYCHOPHARMACOLOGY INSTITUTE

Pollinated plant

- Energy:
- Seed production

Unpollinated plant (Sinsemilla)

- Energy
- Cannabinoid production
- Sinsemilla: without seeds
- T allele dominant
- High THC, no CBD



Increase in mean %THC

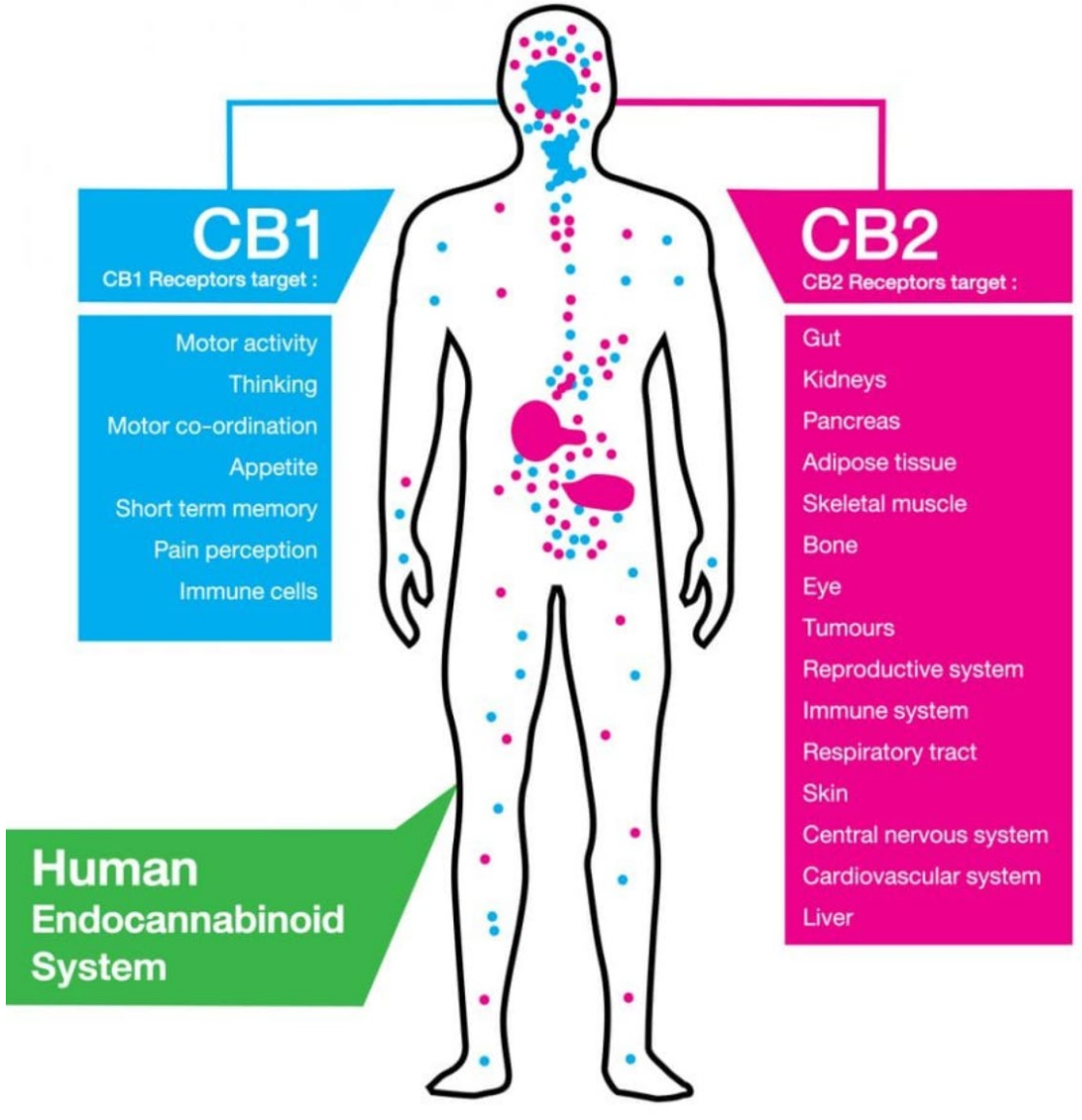
- 3.4% in 1990
- 8.5% in 2008

THC/CBD ratio

In a 2012 study by Englund et al

- Session 1- Pretreated with CBD, before given THC
- Session 2- pretreated with placebo
- Findings
  - Low PANSS scores in CBD group
  - Post-THC paranoia in CBD group
  - Episodic memory was poorer in placebo group
- THC/CBD ratio may be a factor in predicting serious

THE NEUROBIOLOGY



Endogenous cannabinoid system

2 Major Cannabinoid receptor types (G protein coupled)

- CB1 receptors: Found predominantly in the brain at nerve terminals where they mediate inhibition of transmitter release – Psychoactive effects: Memory, mood, sleep, appetite and pain
- CB2 receptors: Found mainly on immune cells in the brain, heart, cardiovascular system, nervous system, reproductive system, and immune system

Intoxication

- Intoxication within 30 minutes inhaled or 2-3 hours if ingested
- Typically, last 3–4 hours (longer if ingested)
- Effect peak in 4 hours but may persist for 12-24 hours
- Severity depends on
  - Dose
  - Method of administration
  - Characteristics of the individual
  - Rate of absorption
  - Tolerance
  - Sensitivity to the effects of cannabis.

Acute intoxication

- Conjunctival injection
- Cannabis odor on clothing
- Yellowing of finger tips (from smoking joints)
- Chronic cough
- Exaggerated craving and impulse for specific foods, sometimes at unusual times of the day or night
- Euphoria
- inappropriate laughter

- grandiosity
- Sedation
- lethargy
- Impairment in short-term memory
- Difficulty carrying out complex mental processes
- Impaired judgment
- Distorted sensory perceptions – time
- Impaired motor performance – slow movements
- Dry mouth
- Tachycardia

Withdrawals

Begins 24–72 hours of cessation, peaks within the first week, last approximately 1–2 weeks

- Sleep difficulties may last over 30 days
- Irritability, anger, or aggression
- Nervousness or anxiety
- Sleep difficulty (e.g., insomnia, disturbing dreams)
- Decreased appetite or weight loss
- Restlessness
- Depressed mood
- Physical symptoms- abdominal pain, shakiness/tremors, sweating, fever, chills, or headache

Other Cannabis-Induced Disorders

- Cannabis-induced psychotic disorder
- Cannabis-induced anxiety disorder
- Cannabis-induced sleep disorder
- Cannabis intoxication delirium

Cannabis Use Disorder

- Affects psychosocial, cognitive, and health functioning
- poor higher executive function
- Amotivational syndrome- lack of goal directed activity
- Accidents
- Respiratory illnesses as in tobacco smokers (high levels of carcinogens in smoke)
- Other mental disorders - a causal factor psychotic disorders
- Cannabinoid hyperemesis syndrome

Effects of cannabis on memory

- Significant and localized hippocampal volume reductions and global reduction in bilateral amygdala volume – makes it difficult to form new memories and increases the risk of psychotic symptoms and depression and anxiety
- THC dampens down the activity of hippocampal neurons, below the level needed to trigger the formation of a memory
- With chronic THC exposure and continual suppression of hippocampal neuron activity, the neurons start to lose connections to other neurons, making it harder to form and retrieve memories

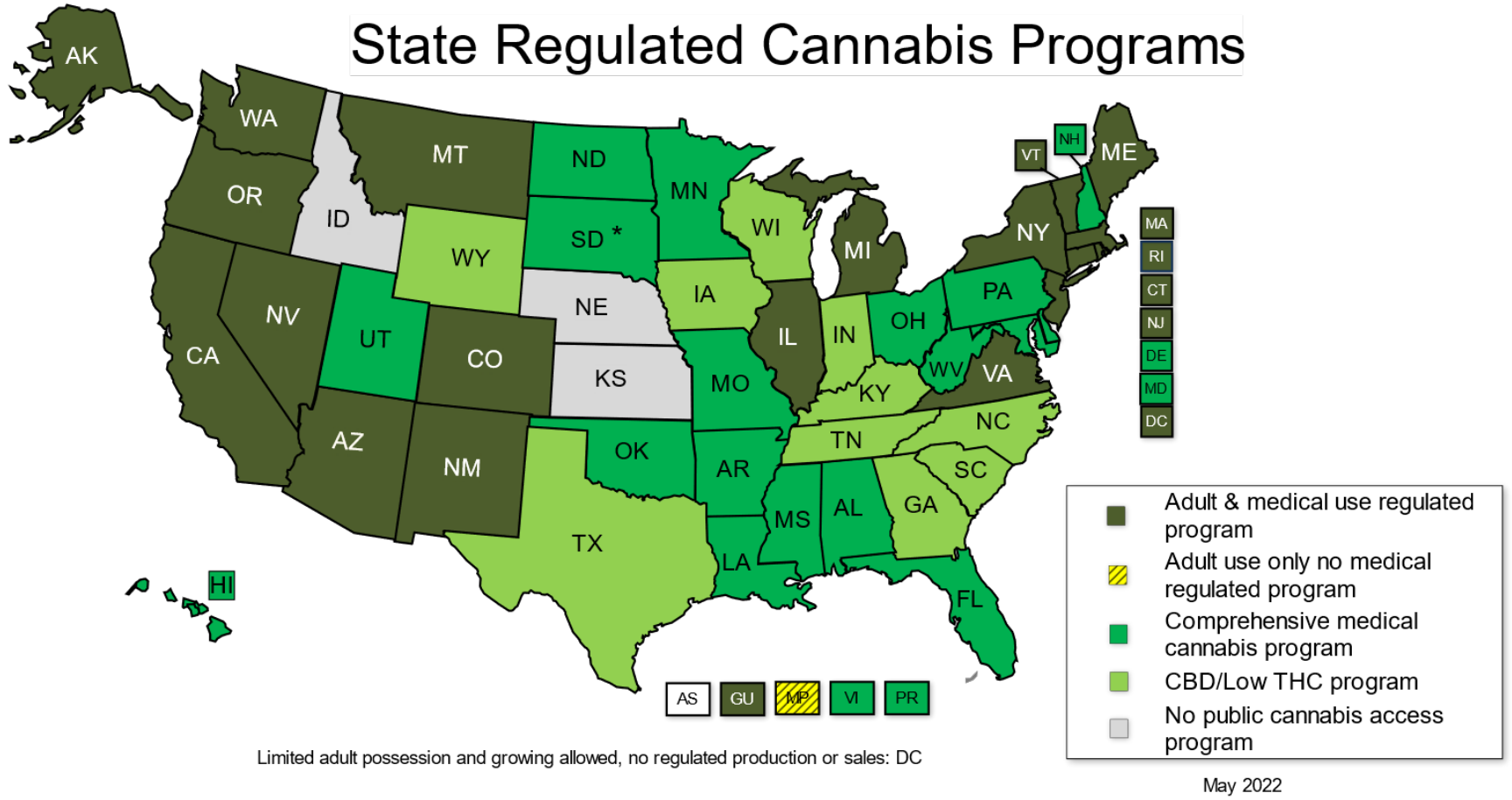
Effects of cannabis on cognition

- In the Dunedin Study, birth cohort of 1,037 individuals followed from birth to age 38.
- Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38
- Neuropsychological testing was conducted at age 13 and again at age 38
- Findings
  - Cognitive problems for persistent cannabis users.
  - Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline.
  - Cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset.
- Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents.

Treatment

- Intoxication
  - Supportive treatment, with quiet room and reassurance, low dose benzodiazepines, and low dose antipsychotics for psychotic features usually effective if needed
- Withdrawals
  - Supportive care, N-Acetylcysteine, gabapentin
- Use Disorder
  - CBT, MET

Medical Marijuana



Medical Marijuana

- THC studies for pain and spasticity in neuropathy from HIV, cancer pain, multiple sclerosis
- CBD studies seizure disorders especially childhood epilepsy
- Limited evidence in psychiatric disorders
- FDA approved dronabinol and nabilone for chemotherapy induced nausea and appetite stimulation in AIDS

Delta 8

- Little natural amount in cannabis plant
- Delta-8 THC has psychoactive and intoxicating effects
- Synthesized using unsafe chemicals to make delta-8 THC often in uncontrolled or unsanitary settings
- Delta-8 THC products often involve use of potentially harmful chemicals to create the concentrations of delta-8 THC claimed in the marketplace.

Delta 8

- 104 reports of adverse events in patients who consumed delta-8 THC between December 1, 2020, and February 28, 2022.
  - 77% involved adults, 8% involved pediatric patients less than 18 years of age, and 15% did not report age.
  - 55% required intervention (e.g., evaluation by emergency medical services) or hospital admission.
  - 66% described adverse events after ingestion of delta-8 THC-containing food products (e.g., brownies, gummies).
  - Adverse events included, but were not limited to: hallucinations, vomiting, tremor, anxiety, dizziness, confusion, and loss of consciousness.

Delta 8 and Delta 10

National poison control centers received 2,362 exposure cases of delta-8 THC products between January 1, 2021 (i.e., date that delta-8 THC product code was added to database), and February 28, 2022.

- 58% involved adults, 41% involved pediatric patients less than 18 years of age, and 1% did not report age.
- 40% involved unintentional exposure to delta-8 THC and 82% of these unintentional exposures affected pediatric patients.
- 70% required health care facility evaluation, of which 8% resulted in admission to a critical care unit; 45% of patients requiring health care facility evaluation were pediatric patients.
- One pediatric case was coded with a medical outcome of death.

Synthetic Cannabis-

Return of the living dead! Bad batch of K2 sends ANOTHER wave of 'zombies' staggering through Brooklyn just days after dozens overdosed

- **At least three were hospitalized on Thursday after overdosing in Brooklyn**
- **Pictures show them staggering down a sidewalk and slumped in drug stupor**
- **Comes days after 25 were hospitalized for K2 overdoses a few miles away**
- **K2 has been known to induce paranoia, confusion, vomiting and hallucinations**
- **Cops say the illicit drug is often manufactured in China and sells for just $1**
- **NYPD has made 36 arrests and says nearly 100 have overdosed in recent days**

By KEITH GRIFFITH FOR DAILYMAIL.COM
PUBLISHED: 22:15 EDT, 25 May 2018 | **UPDATED:** 23:45 EDT, 27 May 2018

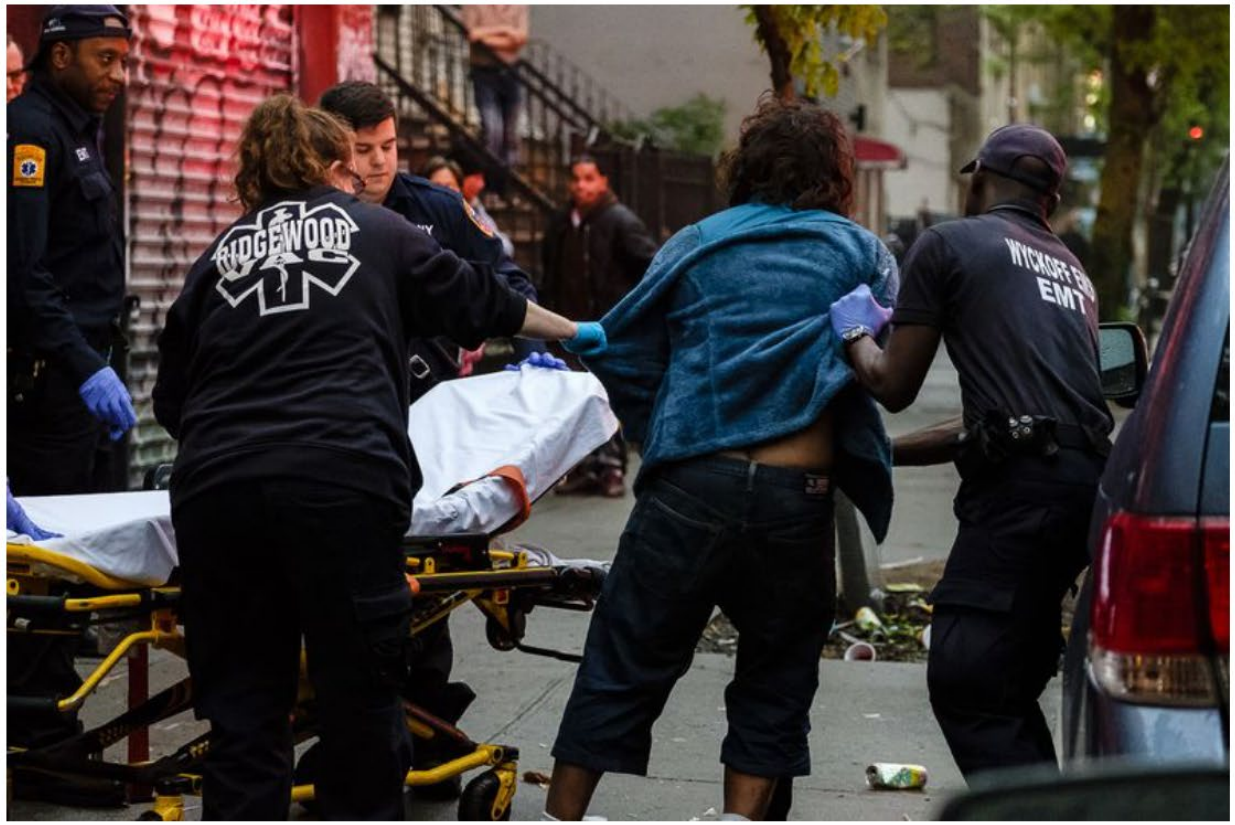
Another wave of K2 'zombies' has descended on **Brooklyn**, as the area fights an epidemic of overdoses tied to a bad batch of the illicit drug.

Paramedics peeled three overdose victims from the sidewalk at around 12.30pm on Thursday at the intersection of Ralph Avenue and Eastern Parkway in the Brooklyn neighborhood of Crown Heights.

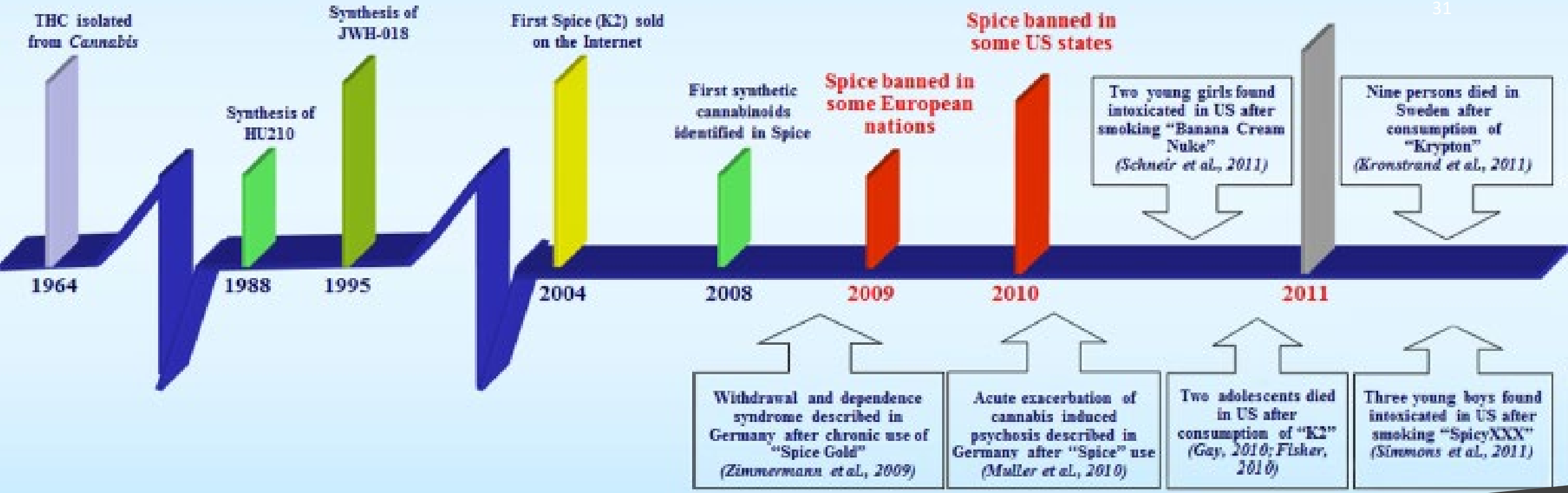
Cops say a batch of bad K2 packed in baggies showing Scooby-Doo and a scantily clad woman labeled 'Fairly Legal' has sent nearly 100 to the hospital in recent days.

'Zombieland' K2 overdoses outrage Brooklyn leaders

By GRAHAM RAYMAN, MIKEY LIGHT and LEONARD GREENE
SEP 10, 2018 AT 5:30 PM



EMTs tend to apparent K2 overdose victims in May at Broadway and Myrtle Ave. in Brooklyn, a common sight at the corner locals call



Timeline of Synthetic Cannabinoid Products

- SOURCE: Fattore & Fratta. (2011). *Frontiers in Behavioral Neuroscience, 5*(60), 1-12.

Early Synthetic Cannabinoids

Name		Synthesized by
JWH-018	JWH-073	John Huffman
HU-208	HU-210	Hebrew University
AM-694		Alexandros Makriyannis
CP-47-497		Pfizer
WIN55222-2		Sterling-Winthrop

U.S. Drug Enforcement Administration, Diversion Control Division. (2016). Synthetic Cannabinoids and Synthetic Cathinones Reported in NFLIS, 2013–2015. Springfield, VA: U.S. Drug Enforcement Administration.

- Colorful packaged as Herbal highs, Incense, Potpourri and Deodorizers
- Labelled “Not For Human Consumption” or “Do Not Ingest”
- Sprayed on Plant material
- Smoked but also available as resins, herbal infusions and liquids for vaping

BRANDS

Spice	Amsterdam Gold	Annihilation	Black Mamba	Blue Cheese
Bombay Blue	ExtremeClockwork	OrangeDevil's Weed	EcsessExodus	DamnationMary
JoySpice	Tai High Hawaiian Haze	Genie	Joker	AK-47


BLACK GIANT
Psycho
AK-47
Joker
ScoobySnax

APPEAL

- Hard to detect in UDS
- Easily purchased in small retail stores (like gas stations, bodegas, corner stores)
- Easy to purchase online
- Marketed alternative to marijuana

EPIDERMIOLOGY

- Difficult to determine the prevalence
  - The ingredients are unknown and ever changing
  - Testing is not done frequently

AMERICAN ASSOCIATION OF POISON CONTROL CENTERS

Month	Number of Cases				
	2022	2021	2020	2019	2018
January	55	88	81	89	145
February	35	84	95	120	191
March	44	96	69	97	175
April	52	118	65	102	309
May	43	107	81	112	178
June	42	82	118	113	175
July	0	68	120	105	157
August	0	62	169	85	172
September	0	68	129	83	199
October	0	75	95	93	97
November	0	47	114	73	97
December	0	115	66	91	98
Total	**271**	**1,010**	**1,202**	**1,163**	**1,993**

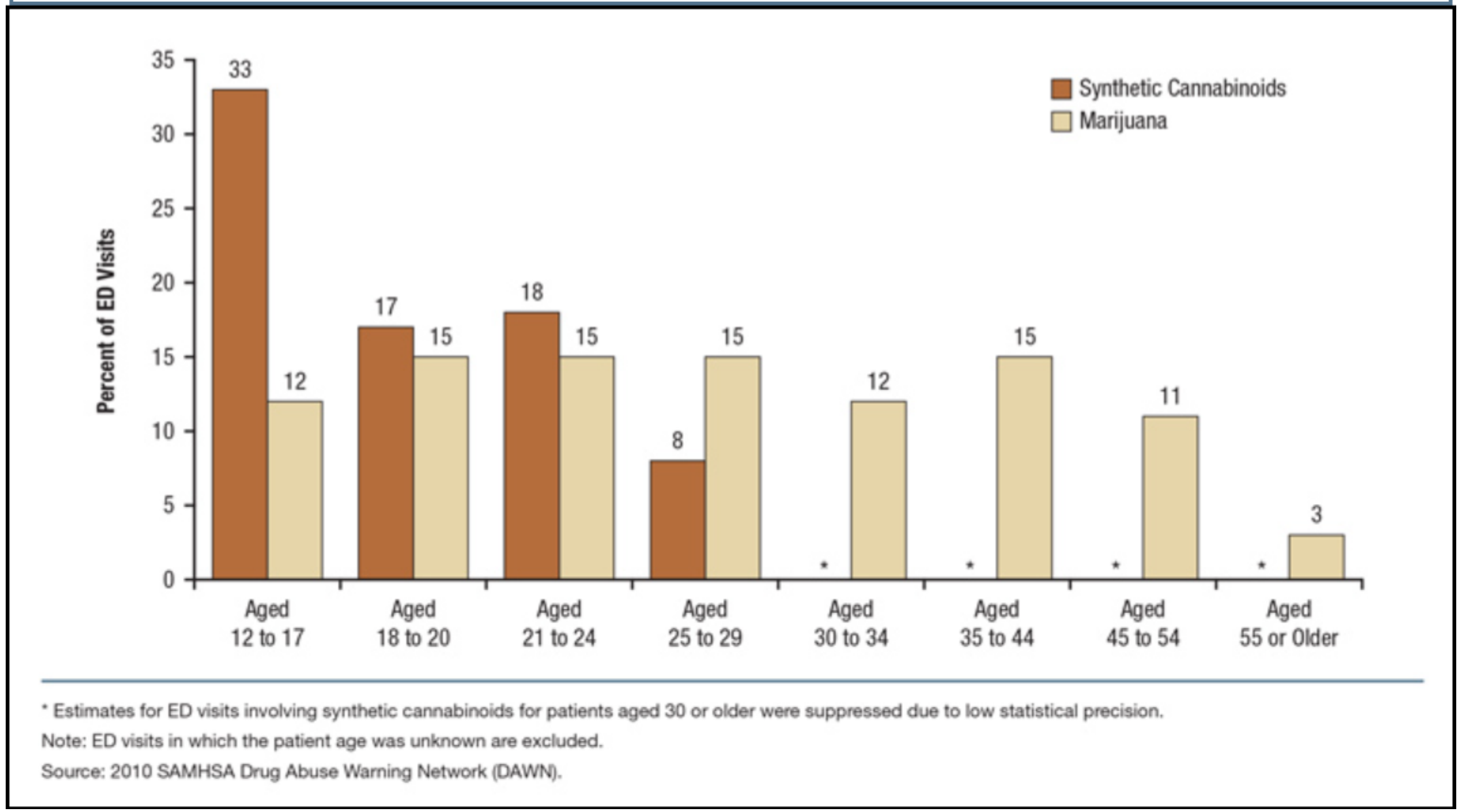
Month	Number of Cases				
	2017	2016	2015	2014	2013
January	188	292	355	181	177
February	155	282	273	167	252
March	157	302	270	205	253
April	165	207	1,511	251	266
May	193	228	1,205	312	277
June	195	170	655	337	230
July	167	224	740	280	186
August	139	211	721	441	204
September	162	175	629	395	213
October	234	155	614	439	200
November	101	279	454	357	208
December	103	178	365	316	200
Total	**1,959**	**2,703**	**7,792**	**3,681**	**2,666**

Emergency Room Visits Related to Synthetic Cannabis: DAWN, 2011

- 70% Male
- 55% under age 21
- 3% in ICU or substance treatment facilities

2010 ED visits SC compared to MJ

Figure 3. Age Distribution of Synthetic Cannabinoid and Marijuana-Related Emergency Department (ED) Visits: 2010



* Estimates for ED visits involving synthetic cannabinoids for patients aged 30 or older were suppressed due to low statistical precision.

Note: ED visits in which the patient age was unknown are excluded.

Source: 2010 SAMHSA Drug Abuse Warning Network (DAWN).

Figure 2.5 Distribution of synthetic cannabinoid reports within region, 2019[1]

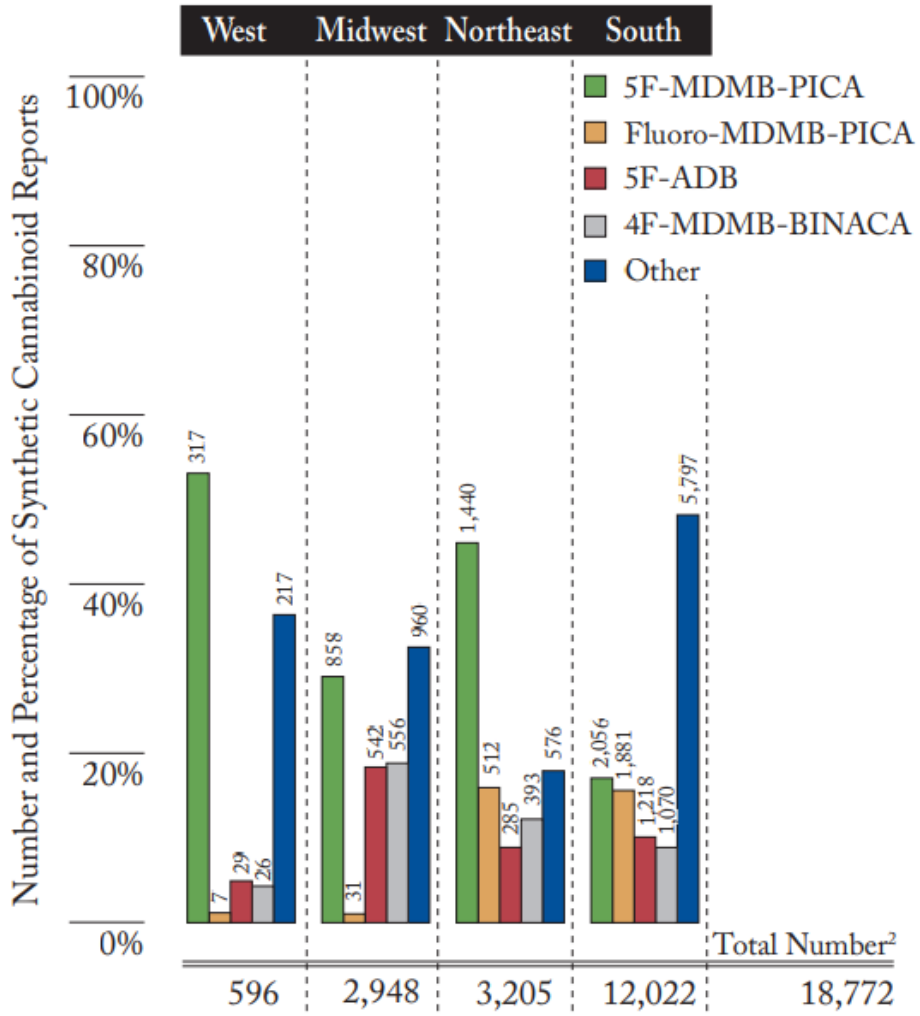


Table 2.5 ***SYNTHETIC CANNABINOIDS***
Number and percentage of synthetic cannabinoid reports in the United States, 2019[1]

Synthetic Cannabinoid Reports	Number	Percent
5F-MDMB-PICA	4,671	24.88%
Fluoro-MDMB-PICA	2,431	12.95%
5F-ADB	2,075	11.06%
4F-MDMB-BINACA	2,044	10.89%
FUB-AMB	1,170	6.23%
MDMB-4en-PINACA	1,029	5.48%
Fluoro-MDMB-BINACA	994	5.30%
FUB-144	300	1.60%
MMB-FUBICA	263	1.40%
ADB-FUBINACA	122	0.65%
Fluoro-ADB	103	0.55%
APP-BINACA	88	0.47%
5F-EDMB-PINACA	68	0.36%
4-CN-CUMYL-BUTINACA	64	0.34%
Fluoro-EDMB-PINACA	49	0.26%
Other synthetic cannabinoids	3,301	17.59%
Total Synthetic Cannabinoid Reports[2]	18,772	100.00%
Total Drug Reports	1,521,360	

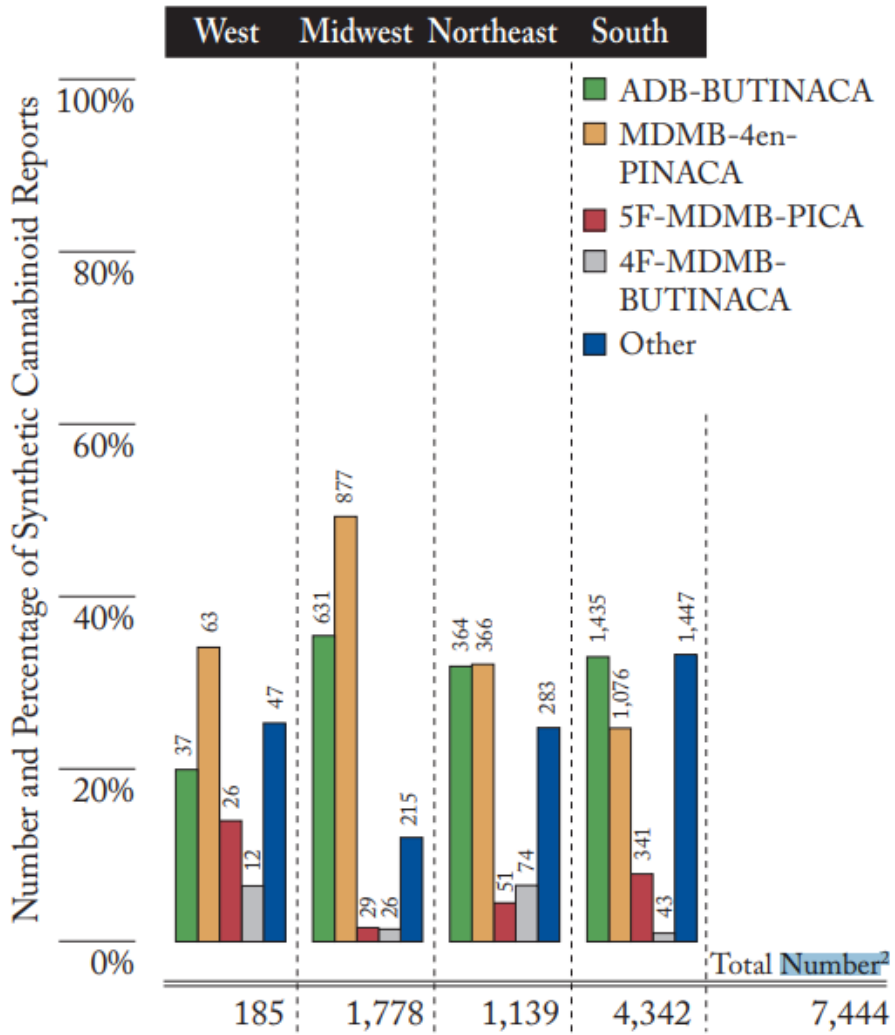
[1] *Includes drug reports submitted to laboratories from January 1, 2019, through December 31, 2019, that were analyzed by March 31, 2020.*

[2] *Numbers and percentages may not sum to totals because of rounding.*

Table 2.5 *SYNTHETIC CANNABINOIDS*
Number and percentage of synthetic cannabinoid reports in the United States, January 2021–June 2021[1]

Synthetic Cannabinoid Reports	Number	Percent
ADB-BUTINACA	2,467	33.14%
MDMB-4en-PINACA	2,382	32.00%
5F-MDMB-PICA	448	6.01%
4F-MDMB-BUTINACA	156	2.09%
ADB-4en-PINACA	78	1.05%
4F-MDMB-BUTICA	77	1.03%
5F-EMB-PICA	74	0.99%
4CN-CUMYL-BUTINACA	70	0.94%
Fluoro-EMB-PICA	65	0.87%
5F-ADB	55	0.74%
ADB-HEXINACA	55	0.74%
FUB-AMB	54	0.73%
Fluoro-MDMB-BUTICA	52	0.70%
Fluoro-MDMB-PICA	49	0.66%
Fluoro-ABUTINACA	37	0.50%
Other synthetic cannabinoids	1,325	17.80%
Total Synthetic Cannabinoid Reports[2]	7,444	100.00%
Total Drug Reports	678,902	

Figure 2.5 Distribution of synthetic cannabinoid reports within region, January 2021–June 2021[1]



National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services.

NFLIS-DRUG 2019 ANNUAL REPORT

Synthetic Cannabinoids (K2/Spice) Trends & Statistics

Monitoring the Future Study: Trends in Prevalence of Synthetic Marijuana (K2/Spice) for 8th Graders, 10th Graders, and 12th Graders; 2020 (in percent)*

Drug	Time Period	8th Graders	10th Graders	12th Graders
Synthetic Marijuana (K2/Spice)	Past Year	[1.6]	2.5	2.4

* Data in brackets indicate statistically significant change from the previous year. Previous MTF Data

February 11, 2020

Marijuana contains

- THC is a partial agonist at mainly CB1 which mediates psychoactive effects
- Cannabidiol which is a partial agonist at mainly CB2 and functionally balances actions on CB1

Synthetic cannabinoids selectively bind to CB1

- SC have greater binding affinity
- Has greater potency
- Longer half-life
- No significant actions at CB2 receptor
- Psychoactive metabolites

ASSESSMENT

- Diagnosis often made by history and/or presence of typical cannabis intoxication signs (e.g., conjunctival redness) in the absence of a drug test positive for THC.
- Look for paraphernalia, packaging; obtain collateral information
- Synthetic cannabinoids are not detected by routine drug screening tests.
- Diagnosis is suggested by sudden onset of unexplained psychosis; cognitive impairment; or kidney, neurological, or cardiovascular problems.

INTOXICATION

Symptoms similar to Cannabis intoxication	Subjective high
	Sedation
	Increased appetite
	Dry Mouth
	Tachycardia
	Conjunctival injection
	Seizures
	Hallucinations (5 times more likely with SC)
	Paranoia

INTOXICATION

Symptoms unlike Cannabis intoxication	Agitation
	Hypertension (unlike hypotension in marijuana use)
	Acute kidney injury
	Coagulopathy with contamination by pesticide- Brodifacoum
	Seizures
	Coma

WITHDRAWAL

Like cannabis withdrawal symptoms but more intense

- Anxiety
- Depression
- Insomnia
- Cravings
- Headache
- Chills
- Decreased appetite

TREATMENT

Symptomatic treatment during intoxication or withdrawal

Fever- Acetaminophen

Agitation/Anxiety- Benzodiazepines

Psychosis- Antipsychotics

Suicidal ideas- Antidepressants

summary

- Lack of information on the chemical contents, and quality
- Research is needed to better understand the side effects and long-term consequences associated with the use of synthetic cannabinoids
- More toxicological identification of these new drugs, more information on the sources of them, as well as their distribution and patterns of use is needed to curtail future increases in use

Reference

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