What the emergency physician should know about ……

The new psychoactive substances

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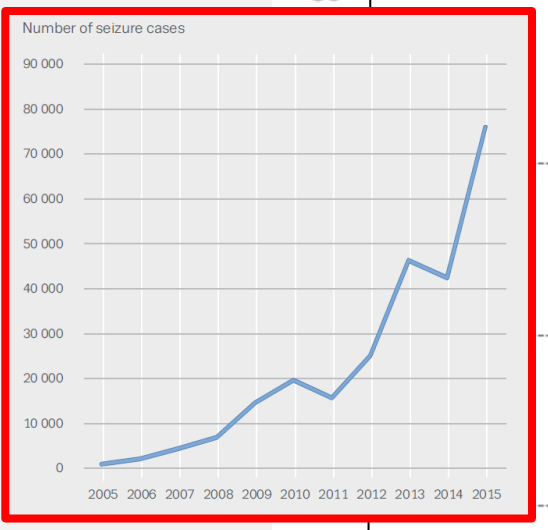
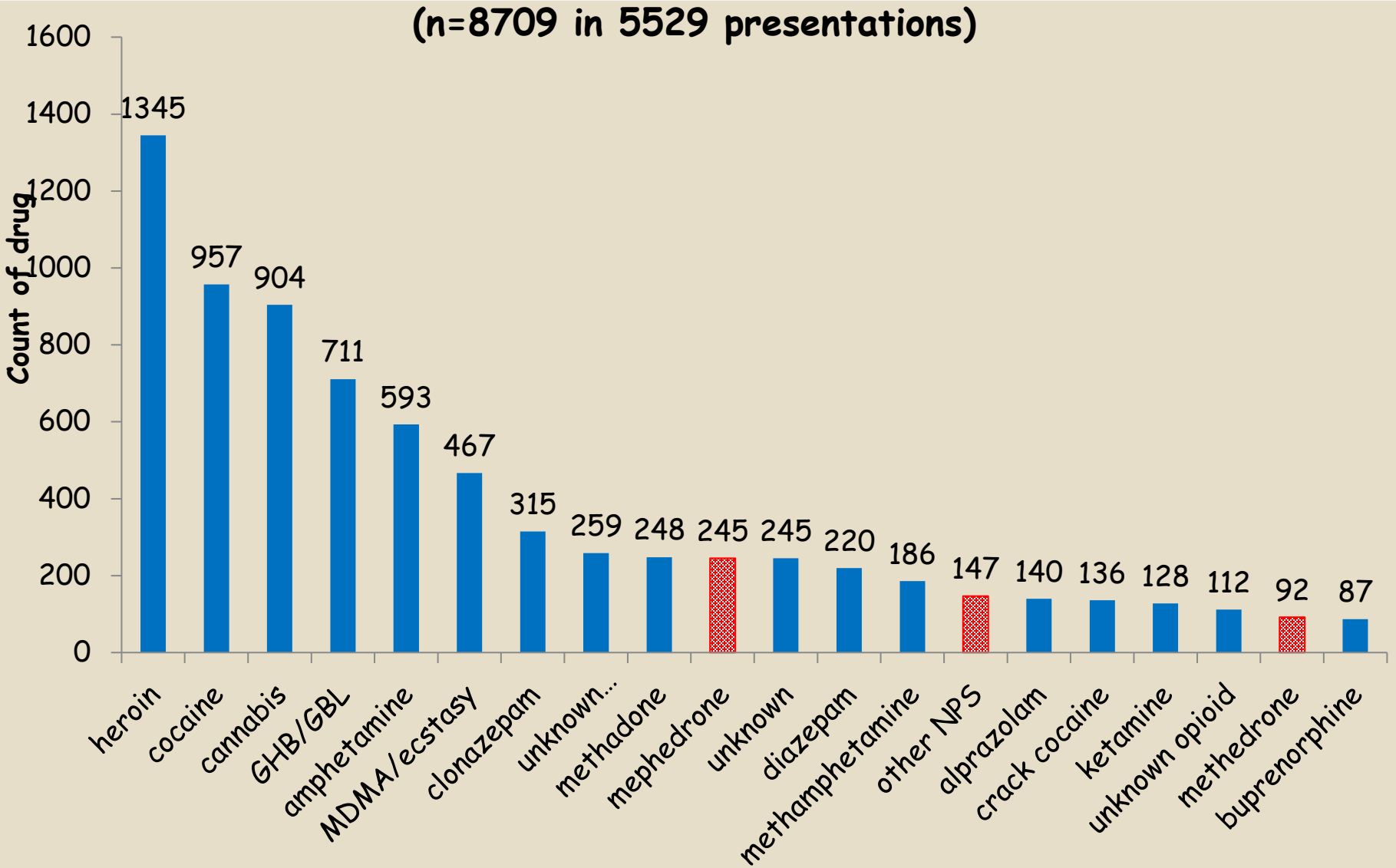
NPS notified to the EU Early Warning System

Denominations: "designer drugs" "legal highs", "research chemicals", "bath crystals", "bath salts", "plant food", "spice" or "herbal incense"



European Drug Report 2016

Top 20 most commonly reported drugs in the ED in Europe



EuroDEN, Clin Tox 2015

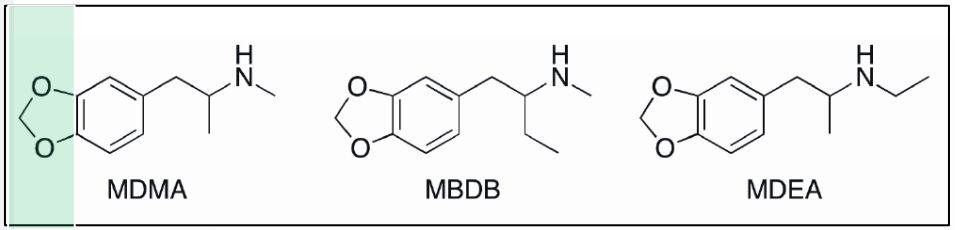
1

Synthetic cathinones

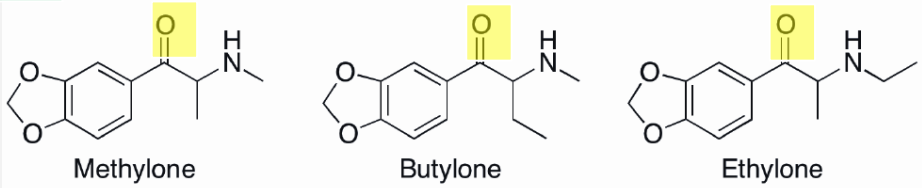
Cathinones: does structure predict activity?

Phenethylamine structure + β-keto group on the side-chain

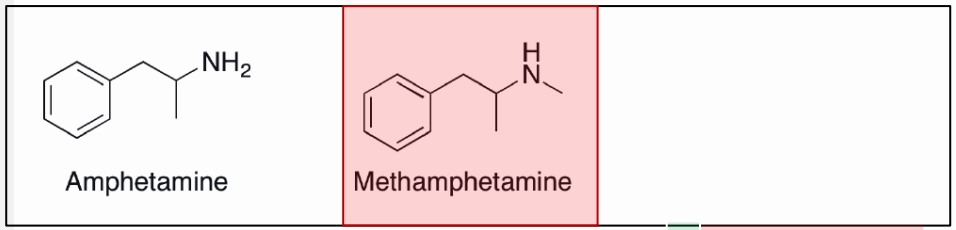
MDMA analogues



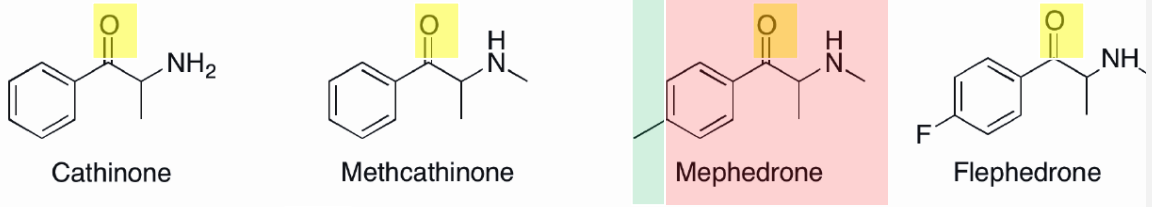
MDMA-like cathinones



Amphetamine analogues

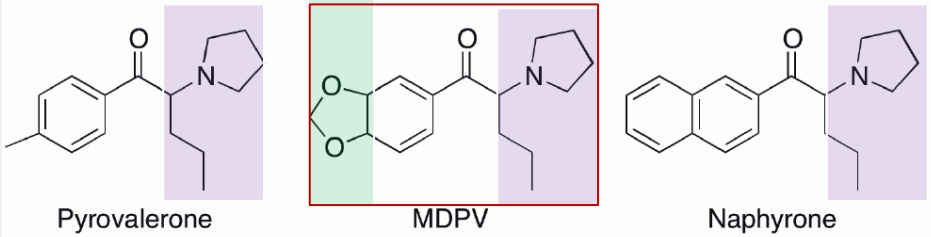


Amphetamine-like cathinones



Pyrovalerone cathinones

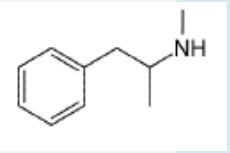
(+ Pyrrolidinil moiety)



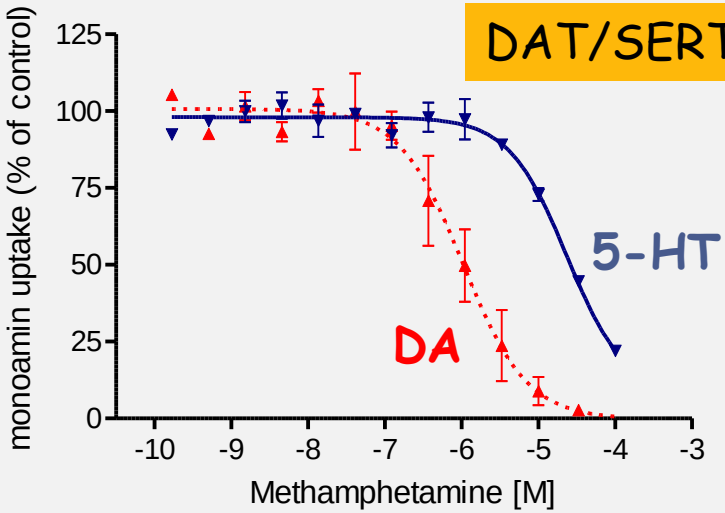
Pharmacology of stimulants and empathgens

Potency to inhibit NE, DA and 5-HT transport into transporter-transfected cells and their efflux from monoamine-preloaded cells

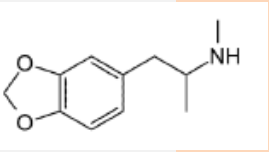
Methamphetamine



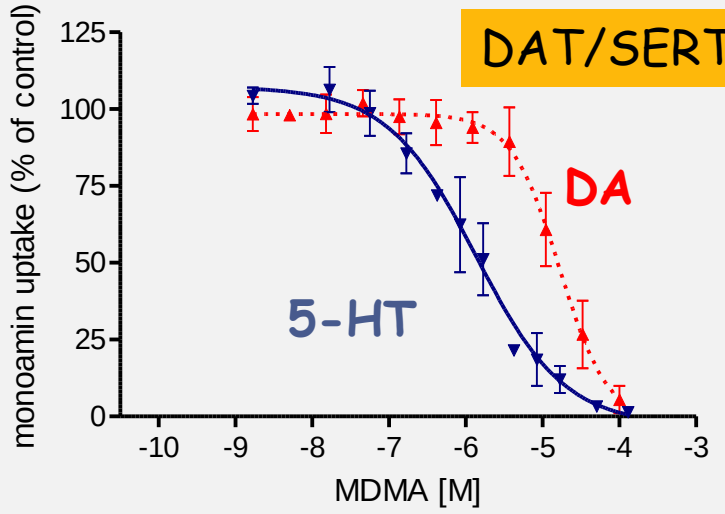
- dopaminergic
- stimulant
- highly addictive



MDMA (ecstasy)

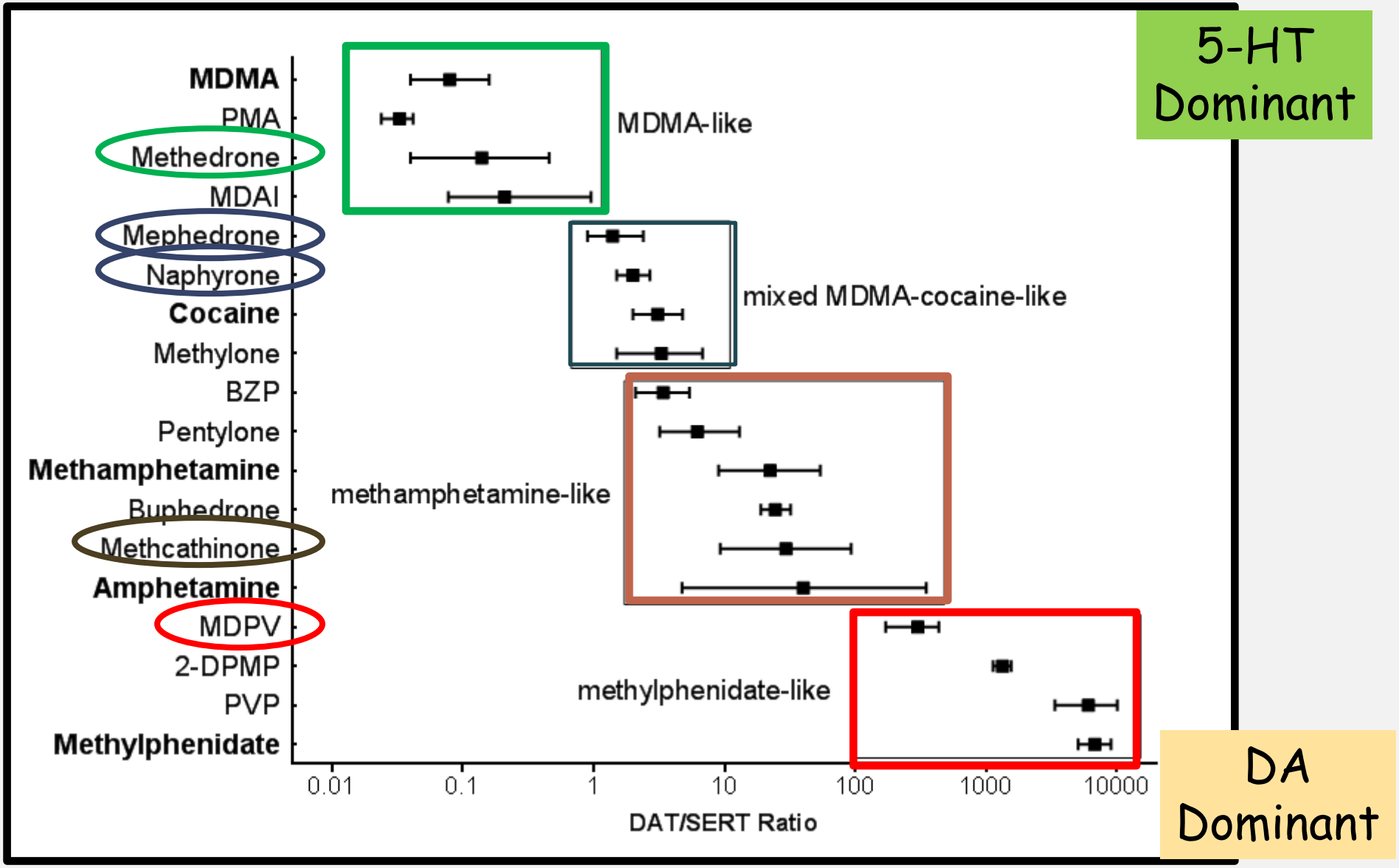


- serotonergic
- empathogen
- less stimulant
- less addictive



Simmler & Liechti. BMC Res Notes 2013

Classification of NPS according to DAT/SERT ratio



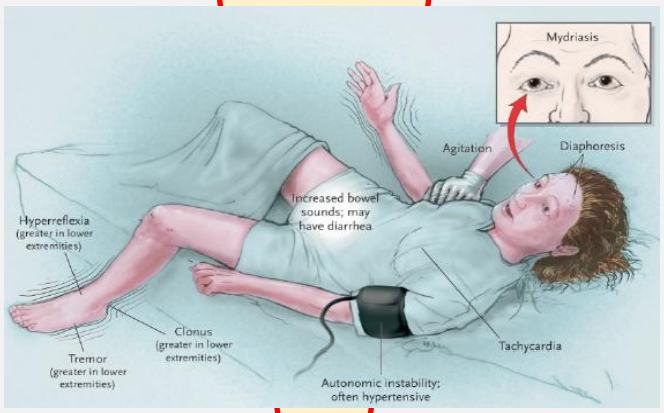
PCC report of cathinone toxicity

Adverse clinical effect	All cases	
	Number	%
Tachycardia	166	45.9
Agitation	142	39.2
Hypertension	76	21.0
Hallucinations	64	17.7
Confusion	47	13.0
Chest pain	26	7.2
Drowsiness	26	7.2
Fever	24	6.6
Electrolyte abnormality	20	5.5
Hyperventilation	19	5.2
Vomiting	19	5.2
CPK elevation	17	4.7
Diaphoresis	15	4.1
Hypotension	15	4.1
Rhabdomyolysis	13	3.6
Tremor	13	3.6
Dyspnea	12	3.3
Nausea	12	3.3
Creatinine	11	3.0
Headache	11	3.0
Mydriasis	11	3.0
Seizures	11	3.0
Total	362	

N= 236

Adrenergic signs

Encephalopathy signs

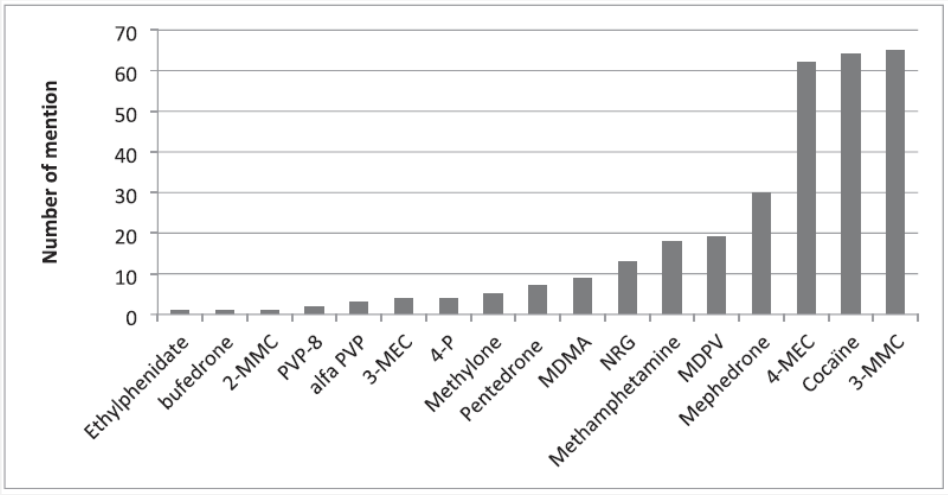


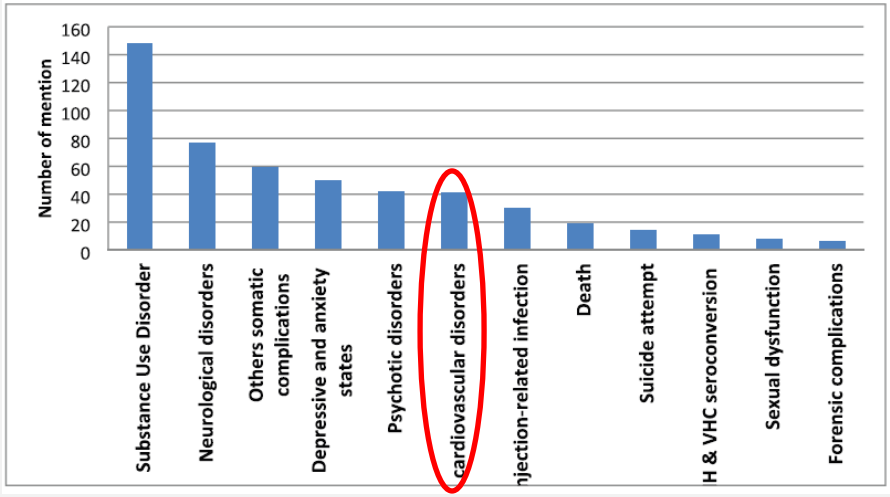
Serotoninergic signs

Organ dysfunction

Spiller HA. Clin Tox 2011

Chemsex practice in France: an update in addictovigilance data





Cases	Poly-drug use	Blood concentration (µg/L) Age	Mephedrone	4-MEC	Butylone	MDPV	3-MMC	(mg/L) GHB	Others
No. 1	Yes	54	1455		520			180	
No. 2	Yes	36	1	366		16			MXE, alcohol
No. 3	Yes	36	5	5594		628			MXE, alcohol, nordiazepam
No. 4	Yes	27		9830					Ethylchloride
No. 5	Yes	55						916	Zolpidem, alcohol
No. 6	Yes	55					5480		Poppers: MetHb 39%
No. 7	Yes	54	26				12		Mexedrone
No. 8	Yes	40	29	4950					

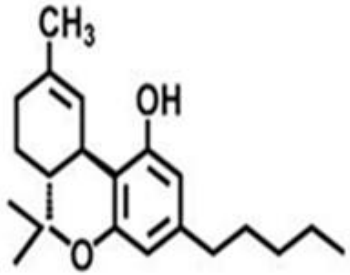
Batisse A. *Fundam Clin Pharmacol* 2021

2

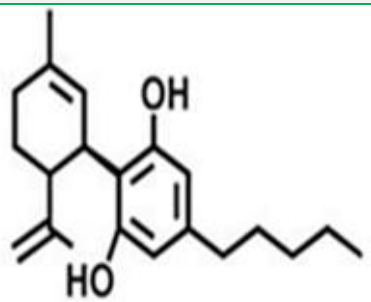
Synthetic cannabinoids

Synthetic cannabinoids: chemical structure

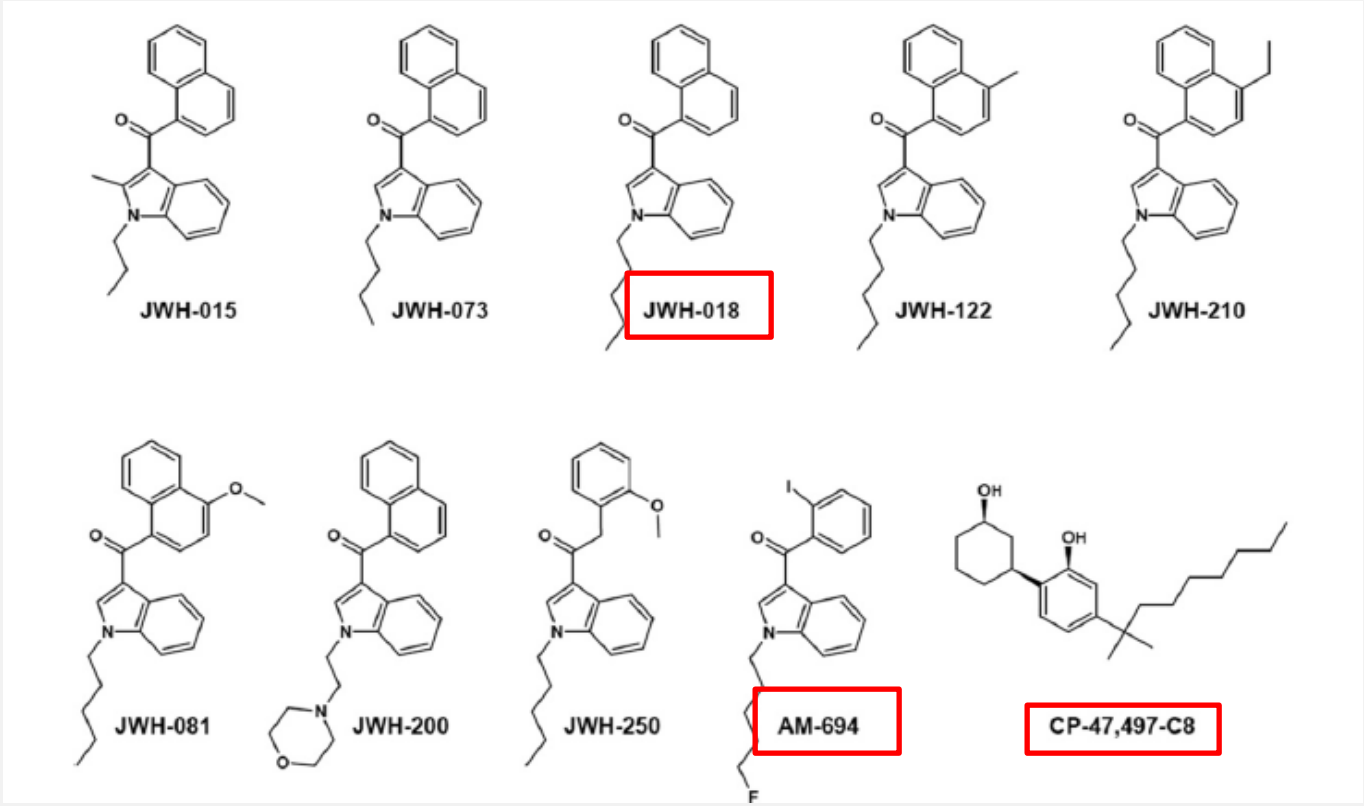
Used to obtain Δ9-THC-like psychological effects



Δ9-tetrahydrocannabinol (THC)



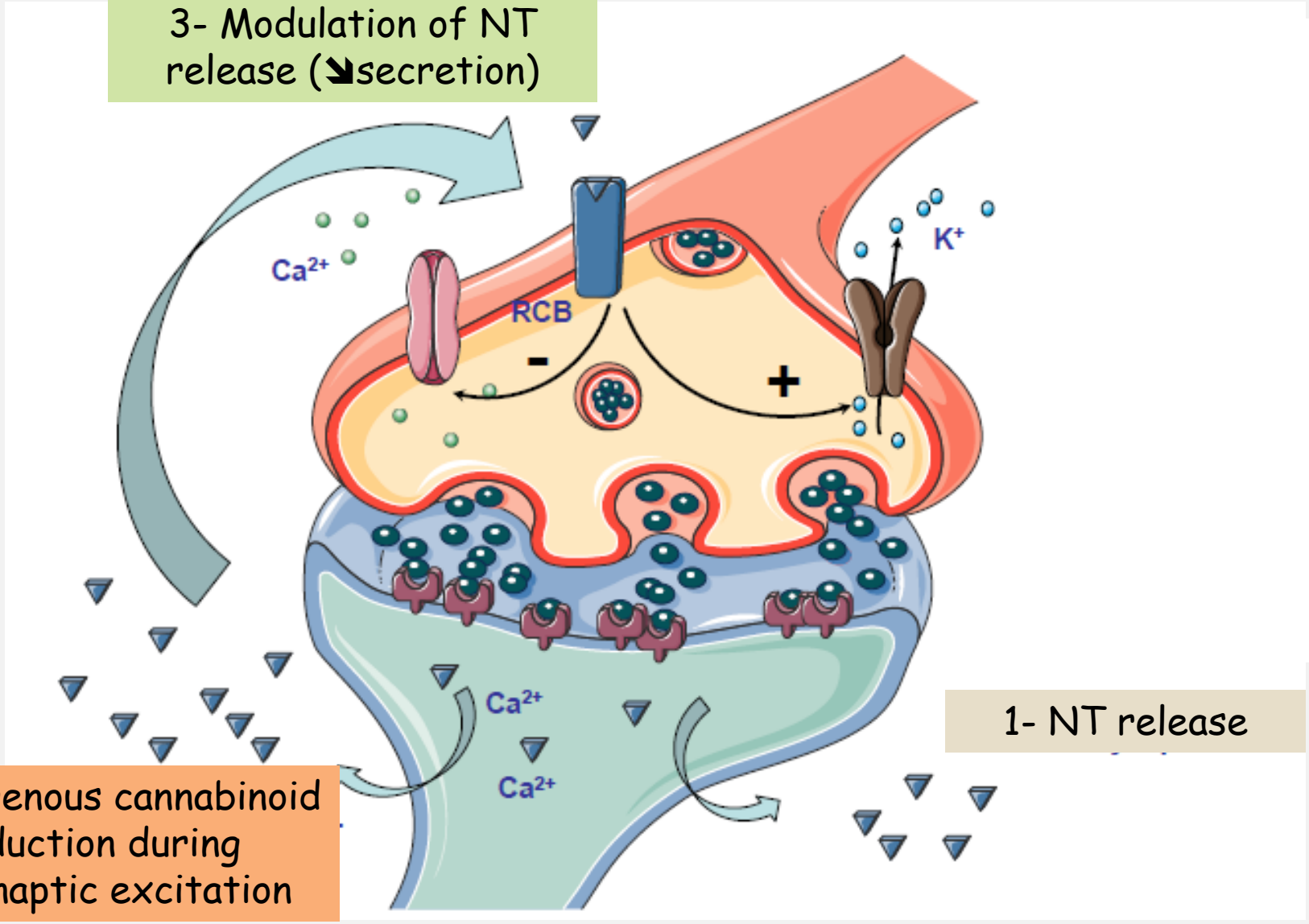
Cannabidiol (CBD)



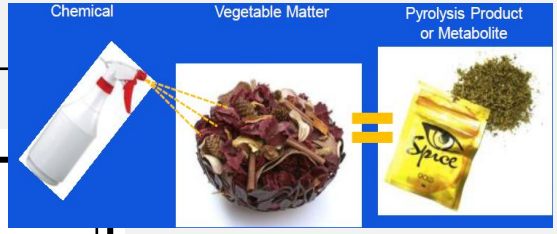
Computational melding of Δ9-THC chemical structure with aminoalkylindole (JWH series), indol (AM) and cyclohexylphenol (CP) derivates

The role of endogenous cannabinoids

= Retrograde messengers and synaptic modulators



Consequences of powerful cannabinoids



Substance	Ki (nM)	Affinity to CB1 receptors
THC	41 ± 2	1
XLR-11	24 ± 5	X 2
JWH-018	9 ± 5	X 5
JWH-073	8.9 ± 2	X 5
CP 47,497	2.2 ± 0.5	X 20
AM-2201	1	X 40
HU-210	0.06 ± 0.01	X 700

- Activity duration: up to24h (instead of4-6h)
- Incidence of symptoms x2-4
- Increased severity (5% in the ICU)
- Fatalities: 8 published cases

Synthetic cannabinoids related clinical toxicity

First generation:

Nausea/vomiting,

Occasional seizures

More recent generation:

Seizures,

Cardiotoxicity,

Sympathomimetic syndrome

Serotoninergic syndrome

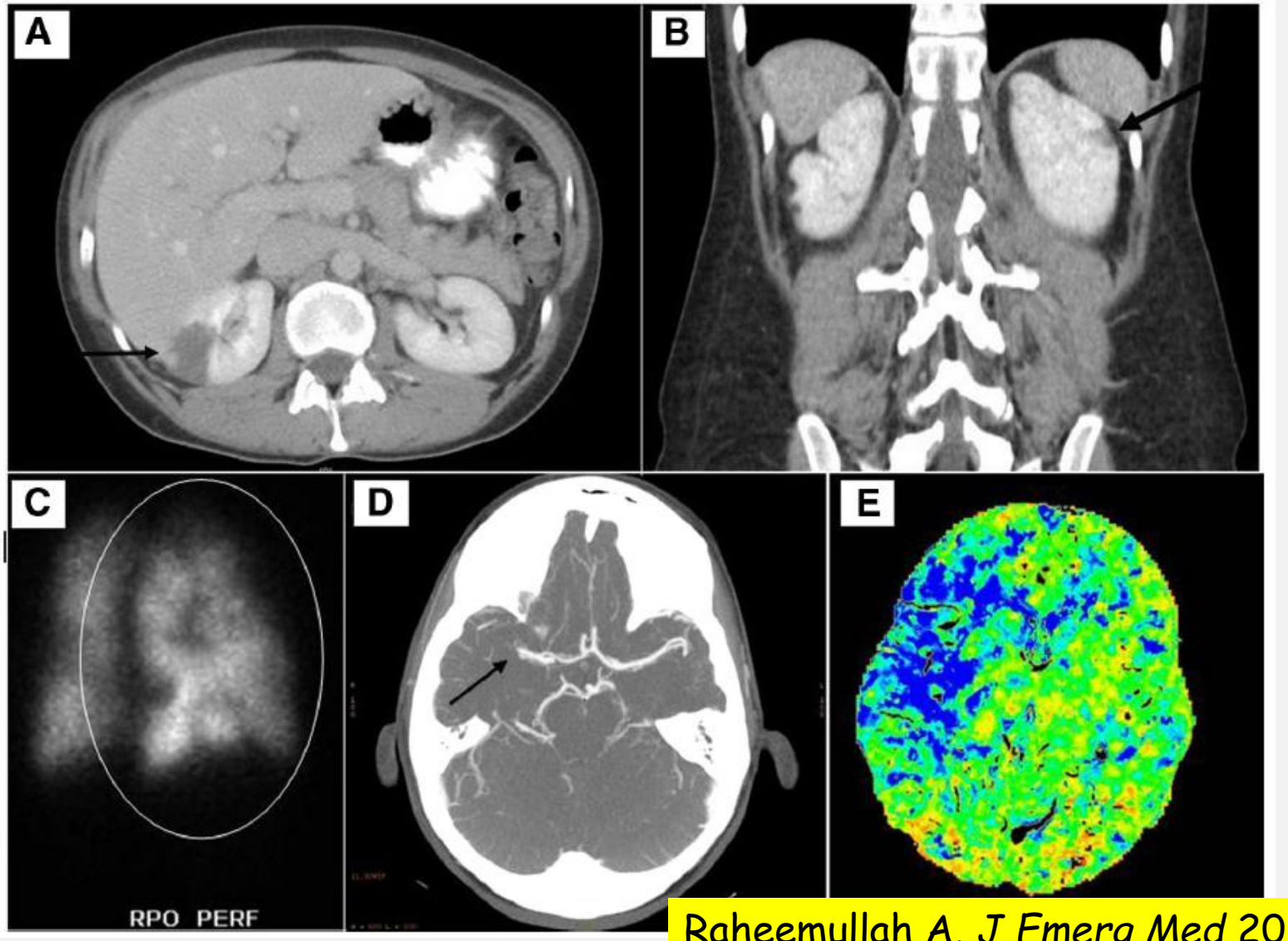
Cardiovascular events

Stroke

Nervous system	Restlessness/agitation	41
	Changes of perception/ hallucination	38
	Vertigo	24
	Anxiousness/panic attack	21
	Somnolence	17
	Initial unconsciousness for up to 60 minutes, followed by somnolence for several hours	17
	Confusion/disorientation	14
	Anaesthesia/paraesthesia	10
	Anterograde amnesia	7
	Acute psychosis[a]	3
	Generalized seizure with hypopnoic episode	3
	Aggressive behaviour	3
	Aphasia, mild	3
	Feeling hot	3
	Laugh attacks	3
Neuromuscular system	Muscle jerking/muscle cramps	7
	Muscle pain	7
	Myoclonia	3
	Shivering/shaking	14
Cardiovascular system	Tachycardia	76
	Bradycardia	3
	Other electrocardiographic changes[b]	14
	Hypertension	34
	Hypotension	7
	Syncope	3
	Dyspnoea	21
	Thoracic pain	10
Gastrointestinal system	Nausea/vomiting	28
	Dry mouth/globus sensation	14
	Excessive thirst	7
	Diarrhoea	7
Eyes	Mydriasis	38
	Conjunctival hyperaemia	14
Laboratory results	Hypokalaemia	28
	Elevation of creatine kinase	14
	Elevation of blood glucose	31

Hermanns-Clausen M. Addiction 2012

Repeated thrombosis after synthetic cannabinoid use



Raheemullah A. *J Emerg Med* 2016

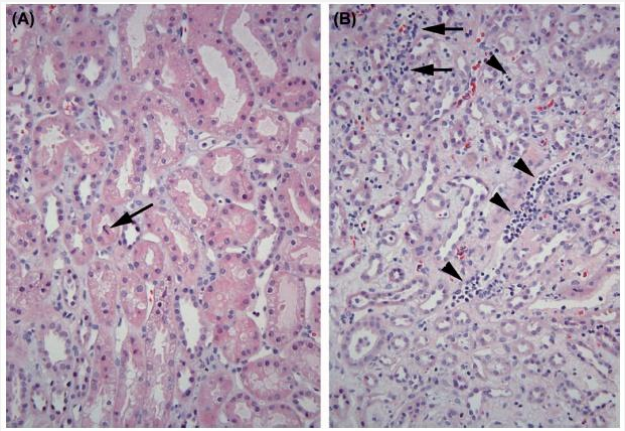
Cannabinoids-induced AKI

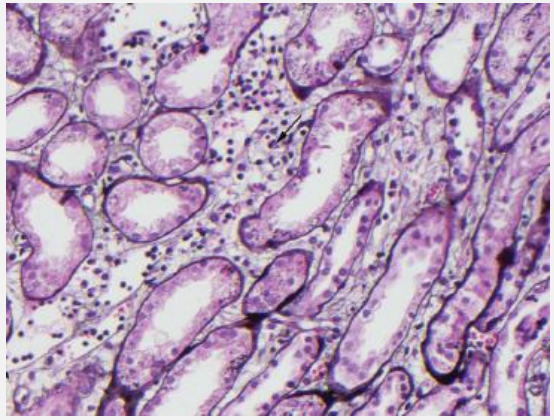
N=16; *Age*: 15 – 27 yrs

- Intense nausea and flank or abdominal pain

- Median peak creatinine: 6.6 mg/dL; proteinuria (N=8), casts (N=5), RBC in urine (N=8); increased cortical echogenicity (N=9/12)

Biopsy (N=8): tubular injury (N=6); interstitial nephritis (N=3)





Detection of **fluorinated SCB (XLR-11)** (N=4/6)

All patients were hospitalized; one required dialysis; none died

Tait RJ. *Clin Tox* 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

"Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York

Axel J. Adams, B.S., Samuel D. Banister, Ph.D., Lisandro Irizarry, M.D., Jordan Trecki, Ph.D., Michael Schwartz, M.D., M.P.H., and Roy Gerona, Ph.D.

AK-47 24 Karat Gold Foil Wrapper containing herbal products, recovered from a patient involved in the outbreak (12 Jul 2016, Brooklyn, New York)

Fatalities attributed to synthetic cannabinoids

Type de spice (AM2201)

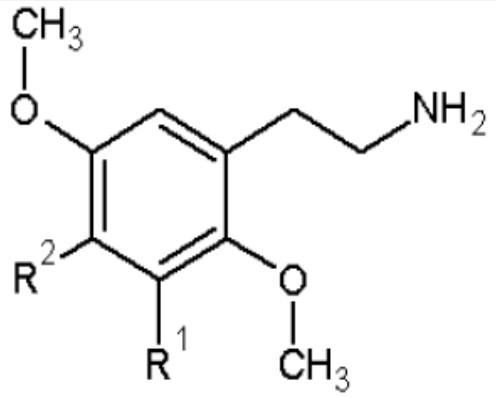
Auto-mutilations

Patton AL. *J Forensic Sci* 2013

3

Synthetic hallucinogens

Psychedelic phenetylamines



Name	R^1	R^2
2C-B	H	Br
2C-C*	H	Cl
2C-D*	H	CH_3
2C-E*	H	CH_2CH_3
2C-F	H	F
2C-G	CH_3	CH_3
2C-G-3	$(CH_2)_3$	
2C-G-4	$(CH_2)_4$	
2C-G-N	$(CH)_4$	
2C-H*	H	H
2C-I*	H	I
2C-N*	H	NO_2
2C-O	H	OCH_3
2C-O-4	H	$OCH(CH_3)_2$
2C-P*	H	$CH_2CH_2CH_3$

Name	R^1	R^2
2C-Se	H	$SeCH_3$
2C-T	H	SCH_3
2C-T-2*	H	SCH_2CH_3
2C-T-4*	H	$SCH(CH_3)_2$
2C-T-7	H	$S(CH_2)_2CH_3$
2C-T-8	H	$SCH_2CH(CH_2)_2$
2C-T-9	H	$SC(CH_3)_3$
2C-T-13	H	$S(CH_2)_2OCH_3$
2C-T-15	H	$SCH(CH_2)_2$
2C-T-17	H	$SCH(CH_3)CH_2CH_3$
2C-T-21	H	$S(CH_2)_2F$
2C-TFM	H	CF_3

NBOMe derivates

Wholesale Quantity Photographs

What Does it Look Like?

Retail Level Photographs

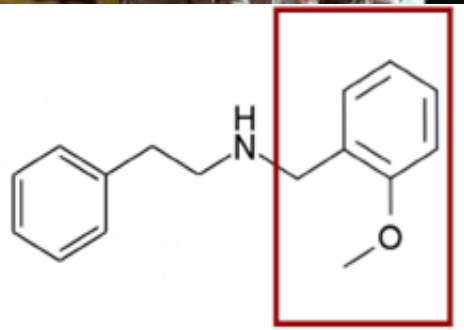
Commonly Sold on Small Pieces of Blotter Paper

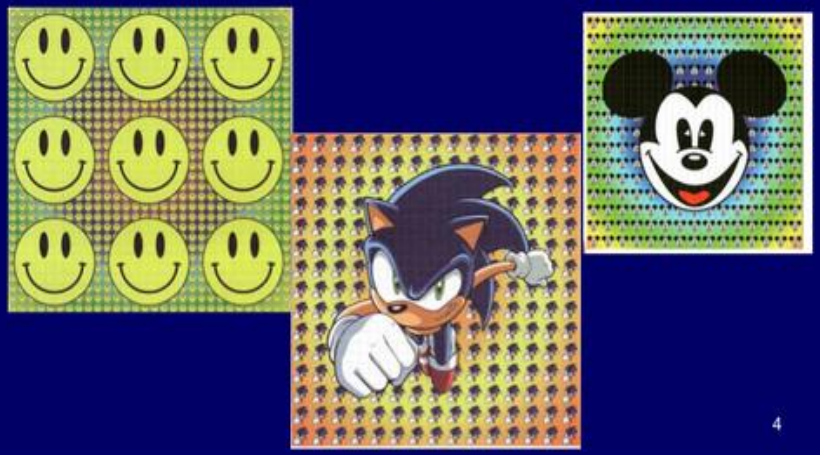
N-2-methoxybenzyl derivatives of the '*2C*-series' of phenethylamines

Extremely potent, active at µg level

Binding affinities at 5-HT2A receptors Ki 0.16–1.49nM

Typically detected in 'blotters'/tabs, sugar cubes



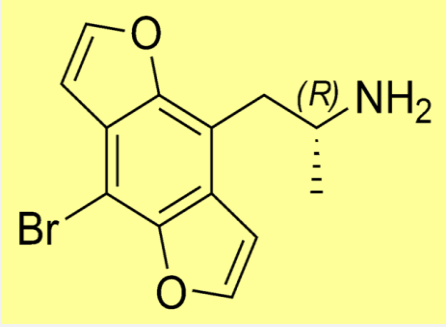


4

- Face appears flushed
- Confused and or combative
- Fast Heart Rate
- Sweating
- Pupils dilated
- Teeth grinding
- Possible seizures
- Unusual effects, pain, headaches, etc
- Numbing of mouth
- Bitter taste
- Powerful euphoric
- One time use can be deadly
- No known antidote

5

Bromo-dragonfly



Psychedelic hallucinogen drug belonging to the phenylethylamine family

300 time more powerful than mescaline and 1/5 time than LSD

Powerful 5-$HT_{2A,}$ agonist with α-agonist effects

Wood DM. *JMT* 2009

Methoxetamine toxicity

(High-affinity selective NMDA-R antagonist)

N=47

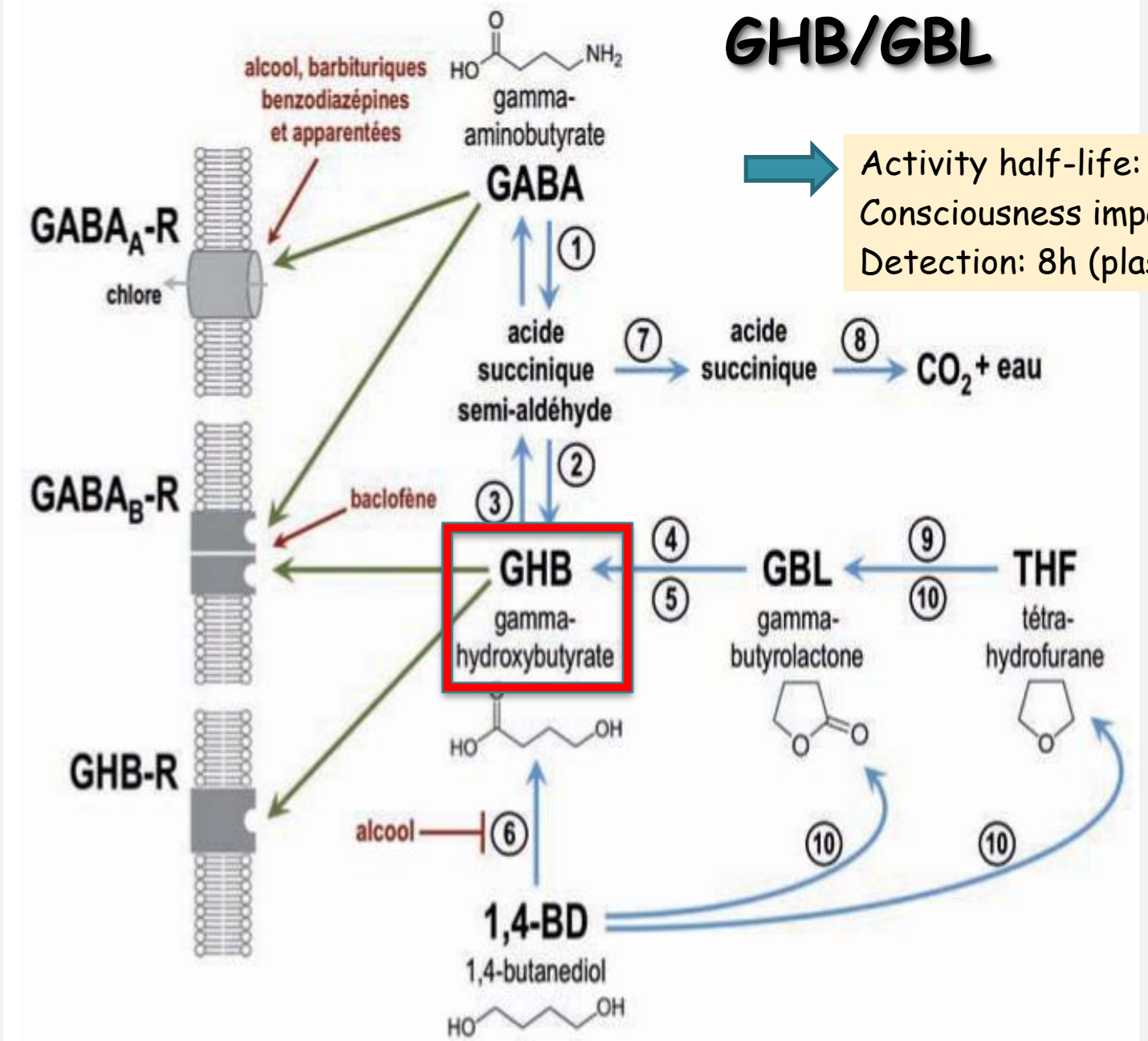
Feature group	Reported terms	Number of cases	% of total (95% CI)
Stimulant	Tachycardia, hypertension, mydriasis, palpitation, increased sweating	17	36 (24 to 50)
Acute mental health disturbance	Agitation, confusion, euphoria, aggression, hallucination, paranoia, hysteria, manic reaction, psychosis	20	43 (30 to 57)
Dissociative	Catatonia, dystonia, hypertonia, tetany	5	11 (5 to 23)
Cerebellar	Nystagmus, tremor	3	6 (2 to 17)
Reduced consciousness	Reduced conscious level, stupor, somnolence, coma	8	17 (9 to 30)
Seizures	Seizures	1	2.1 (0 to 11)

Hill SL. *Emerg Med J* 2014

4

GHB - GBL

GHB/GBL



Activity half-life: 1-3 h
Consciousness impairment <3h
Detection: 8h (plasma) et 12h (urine)

Endogenous GHB (blood < 5 µg/mL and urine < 10 µg/mL)

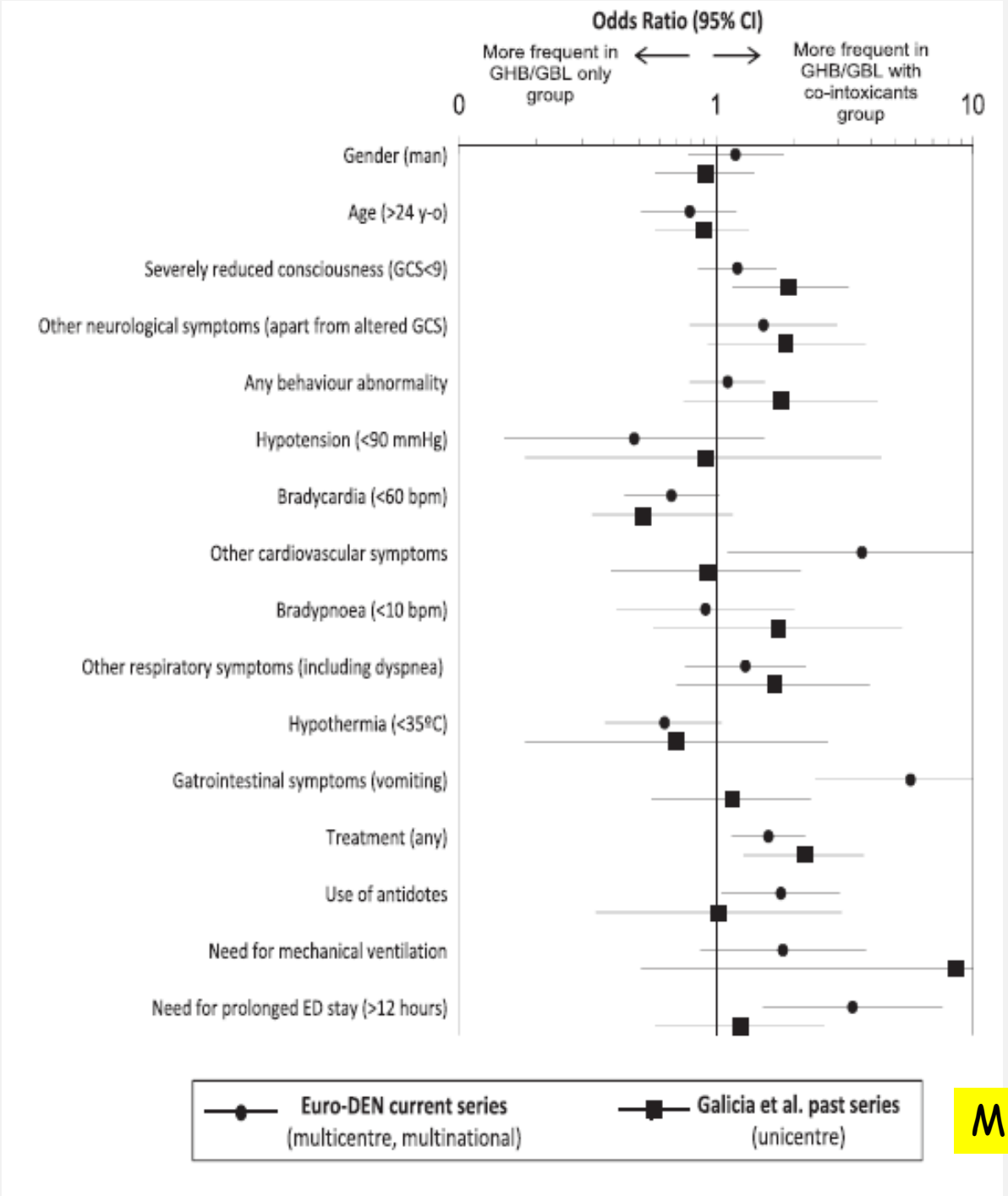
Toxicity attributed to GHB

- Dose- and concentration-effect relationships

Dose (mg/Kg)	Symptoms
10	Amnesia, myorelaxation, hypotonic, dizziness, myoclonus
20 - 30	Euphoria followed by sleepiness
30 - 50	Sedation, nausea/vomitig
50 - 100	Non-reactive coma (G-hole), respiratory depression, seizures, bradycardia, hypotension, nystagmus, myosis/mydriasis

- Tight therapeutic index
- Inter-individual variability
- Tolerance development if repeated use
- Aspiration, ↘K+, ↗ WBC, ↗CK, AVB
- Withdrawal: 1-6h, peak 24h, duration 14d

Shep LJ. *Clin Tox* 2012



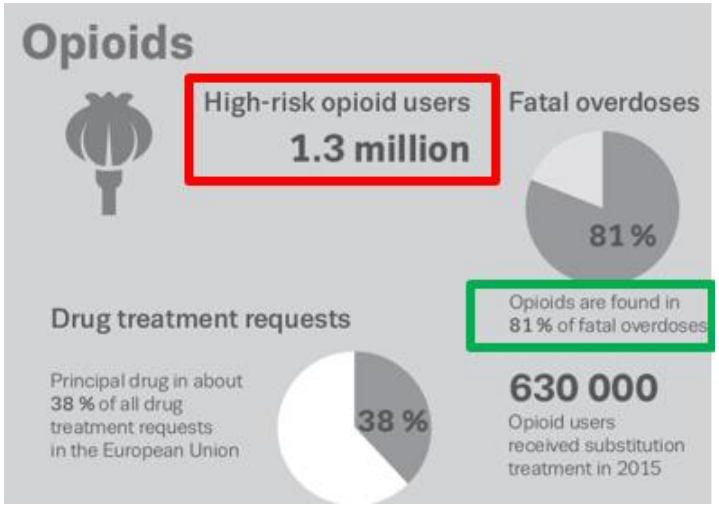
Mixed GHB/GBL poisonings

Miro O. *Tox Lett* 2017

5

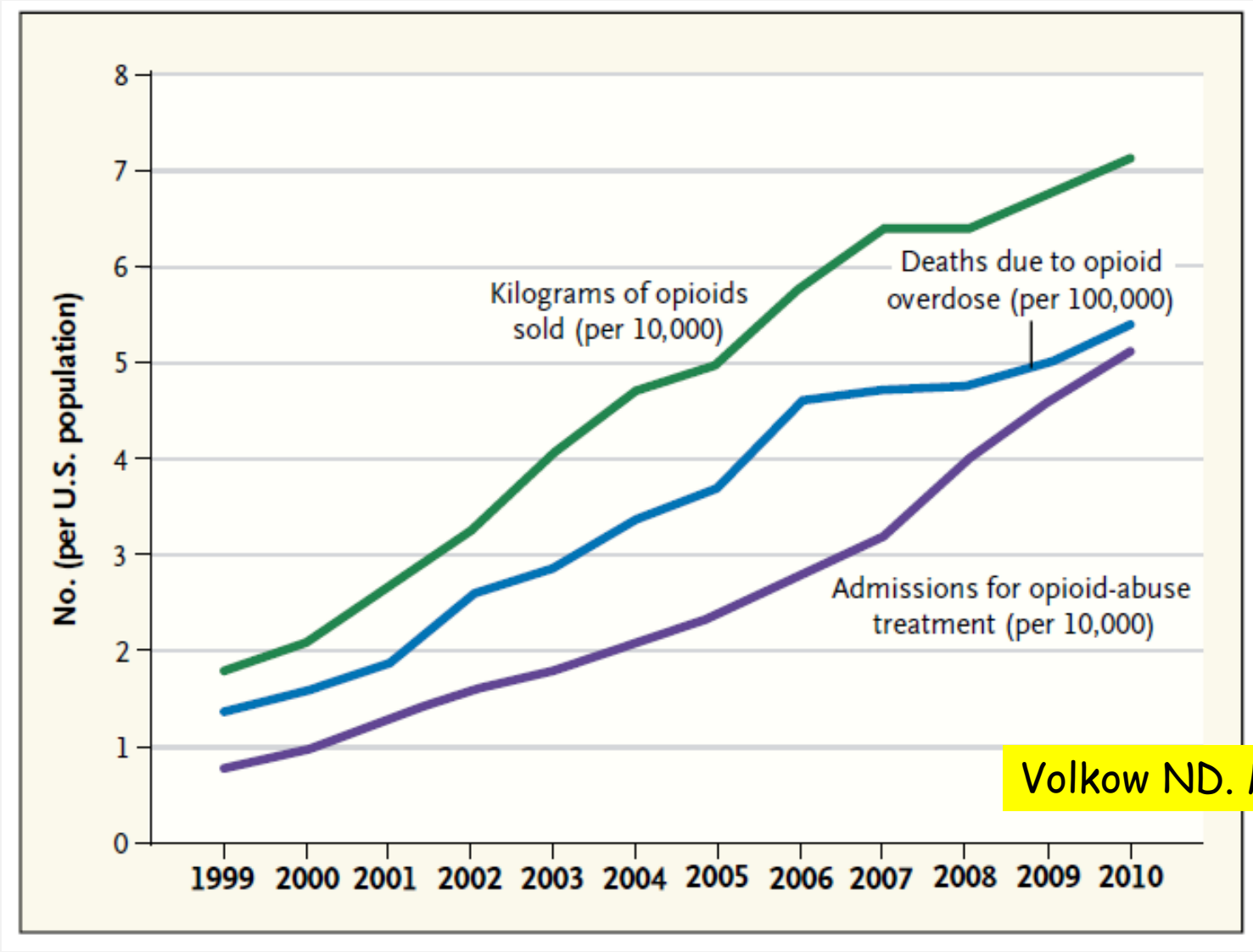
New opioids

Prescription opioids : first cause of toxic death in the US



Jones CM. JAMA 2013

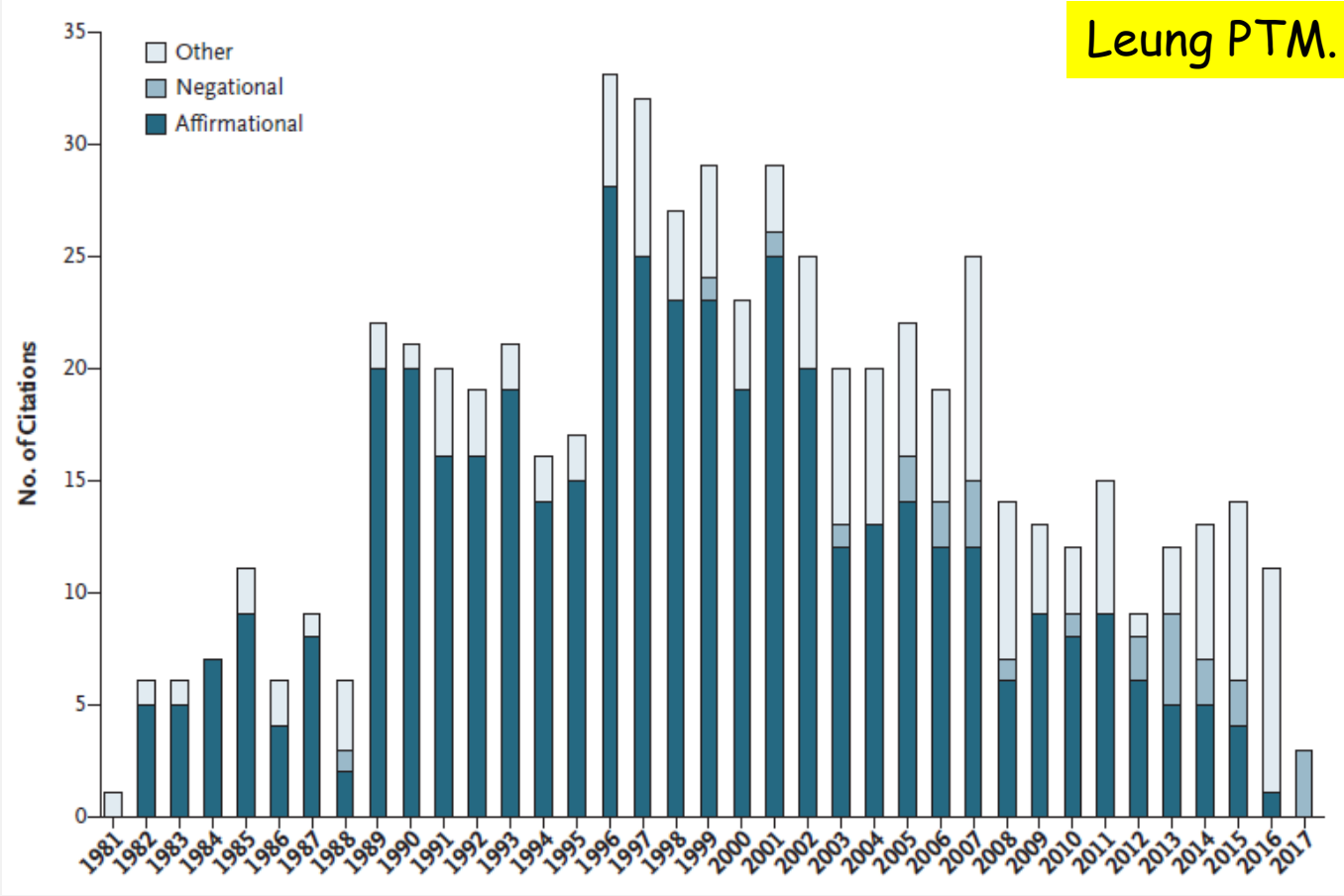
The US Opioid-Overdose Epidemic
Opioid sales, admissions for opioid-abuse treatment and deaths due to opioid overdose, 1999–2010



Volkow ND. *NEJM* 2014

A 1980 NEJM letter on the risk of opioid addiction when prescribed for chronic pain

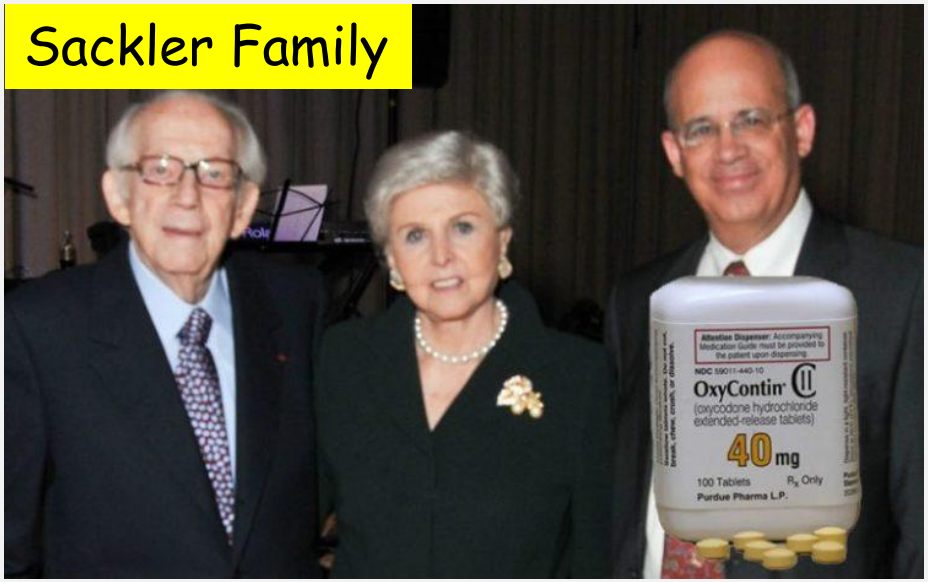
A 5-sentence letter published in the NEJM in 1980 was uncritically cited as evidence that addiction was rare with long-term opioid therapy [439/608 (72%)]



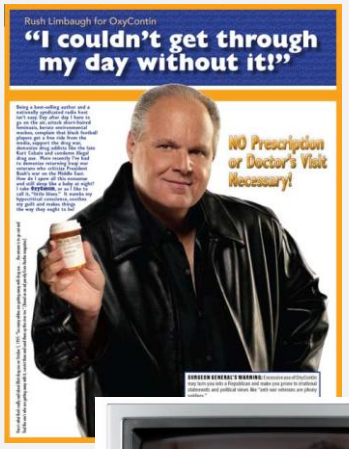
Porter J, Jick H. Addiction rare in patients treated with narcotics. NEJM 1980;302:123

The role of pharmaceutical compagnies: Accusation for half a million deaths

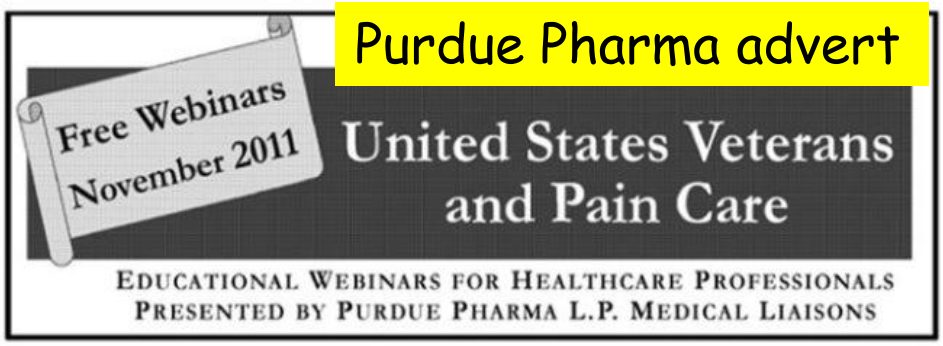
Sackler Family



The 19th wealthiest family in the US with a fortune of $13 billion in 2016



Purdue Pharma advert



The epidemic of opioid overdose deaths in the US

120K- 120,000 people died in 2023 from opioid overdose

1M - 1 million people died from opioid overdose since 1999

10M - 10 million people misuse opioids in a year

72% - Opioids are a factor in 7 out of 10 overdose deaths

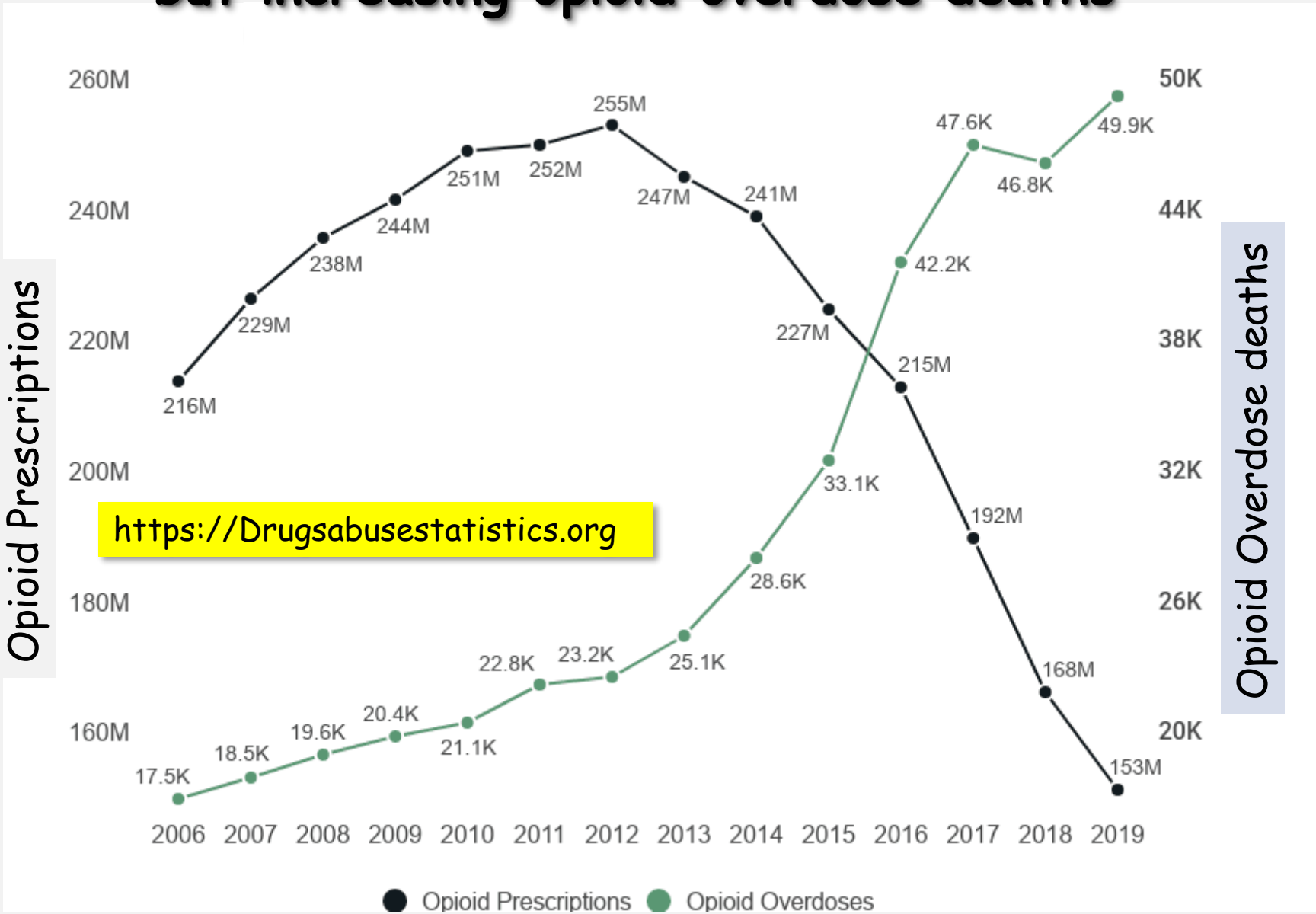
Wave 1
Prescription opioids

Wave 2
Heroin

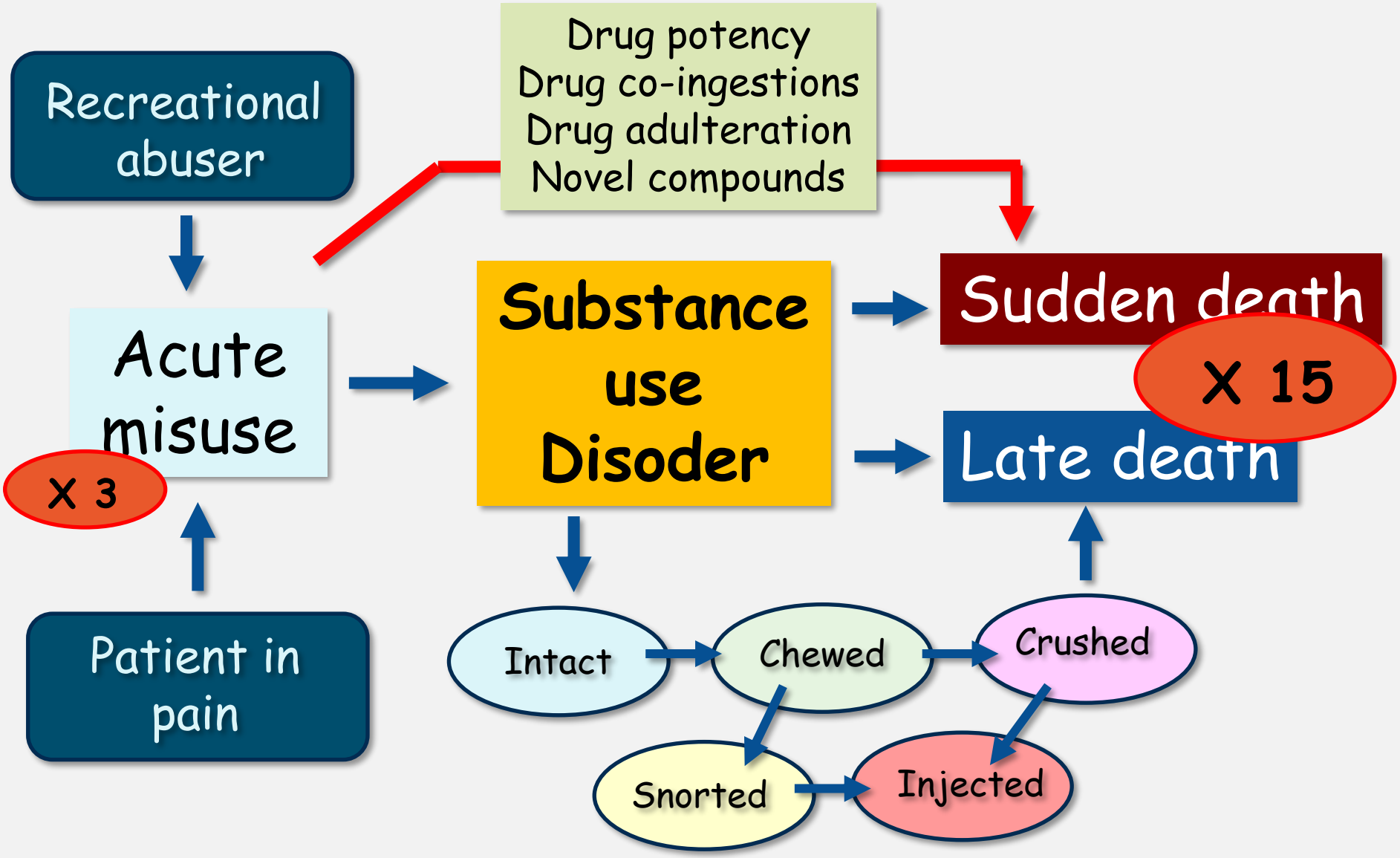
Wave 3
Fentanyl

Wave 4
Fentanyl + stimulants

The US Paradox: decreasing opioid prescription but increasing opioid overdose deaths

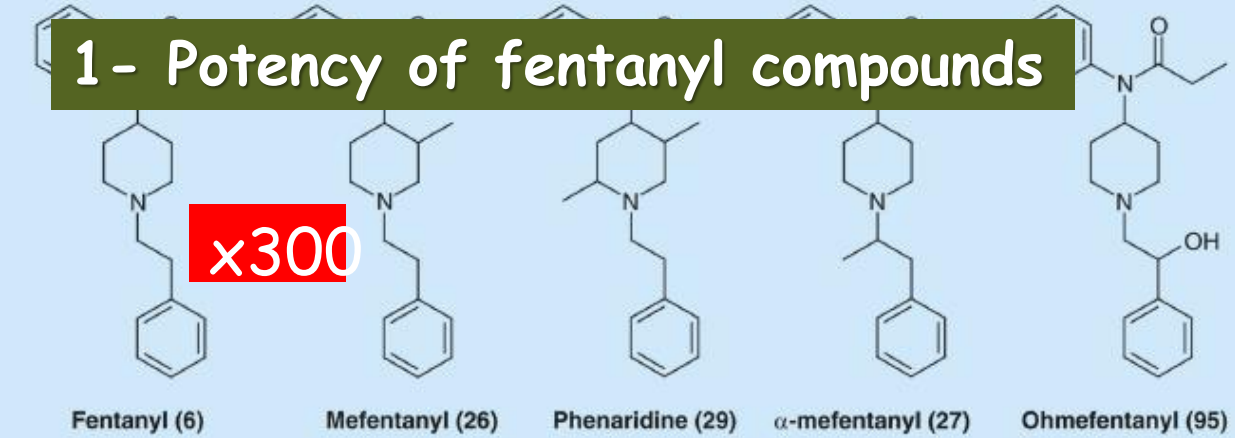


The traditional view of opioid abuse
- the downward spiral -

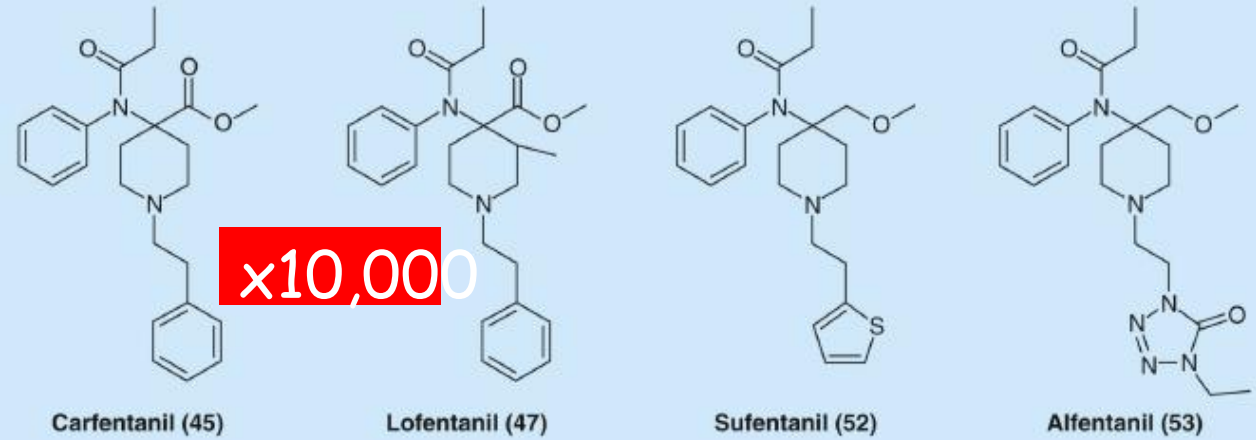


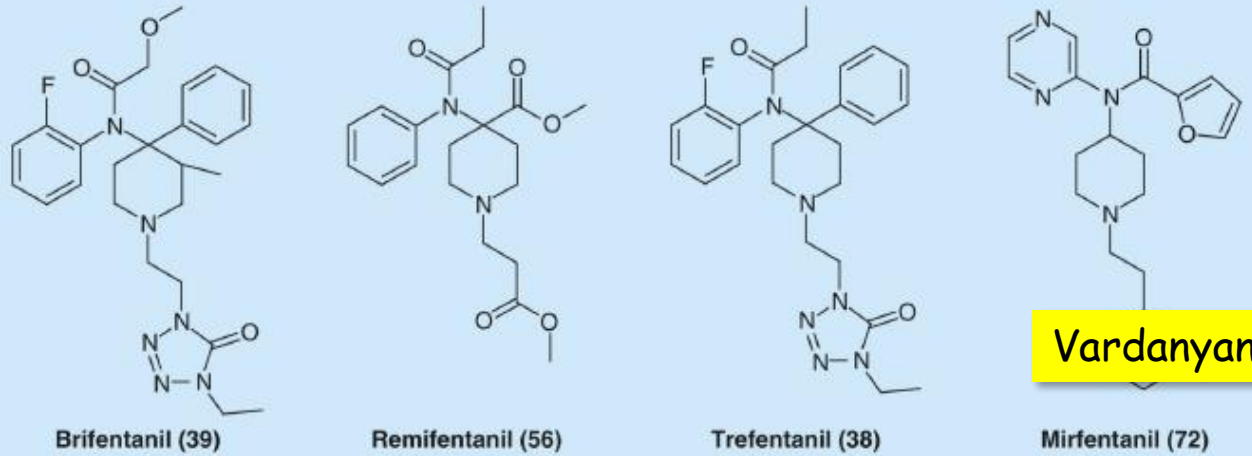
1- Potency of fentanyl compounds

x300



x10,000





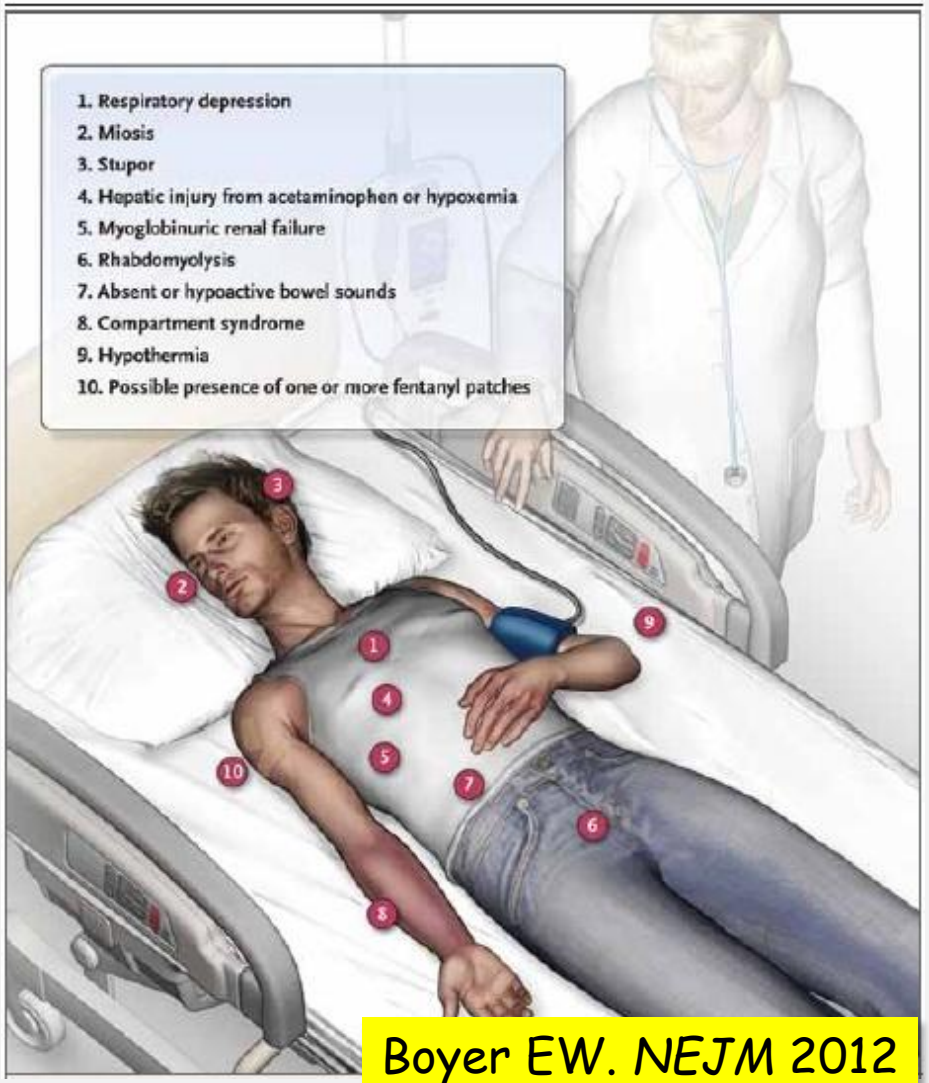
Fentanyl derivatives

Potent structural analogues of fentanyl, originally synthesized as pharmaceuticals candidates became drugs of abuse

Vardanyan RS. *Future Med Chem* 2014

Presentations of fentanyl overdose

↑ Usual CNS depression



Boyer EW. *NEJM* 2012

↑ Wooden chest wall syndrome

- With fentanyl in operating room
- Mechanical ventilation (100%)
- Reversibility using naloxone?
- Death with fentanyl at therapeutic dose range in non-naive opiate users
- Frequent lack of measurable norfentanyl despite high fentanyl
- **<u>Mechanisms</u>**:

Activation of NA cœrulospinal (fentanyl) or 5HT pathways (oxycodone)

Burns G. Clin Tox 2016

The role of counterfeit and falsified drugs

- 20 M **fake prescription pills seized** in 2022
(> last 2 yrs combined)

The most counterfeit pill = **oxycodone 30mg**
(M30s, Mexican Blues, Blues, M-Boxes)

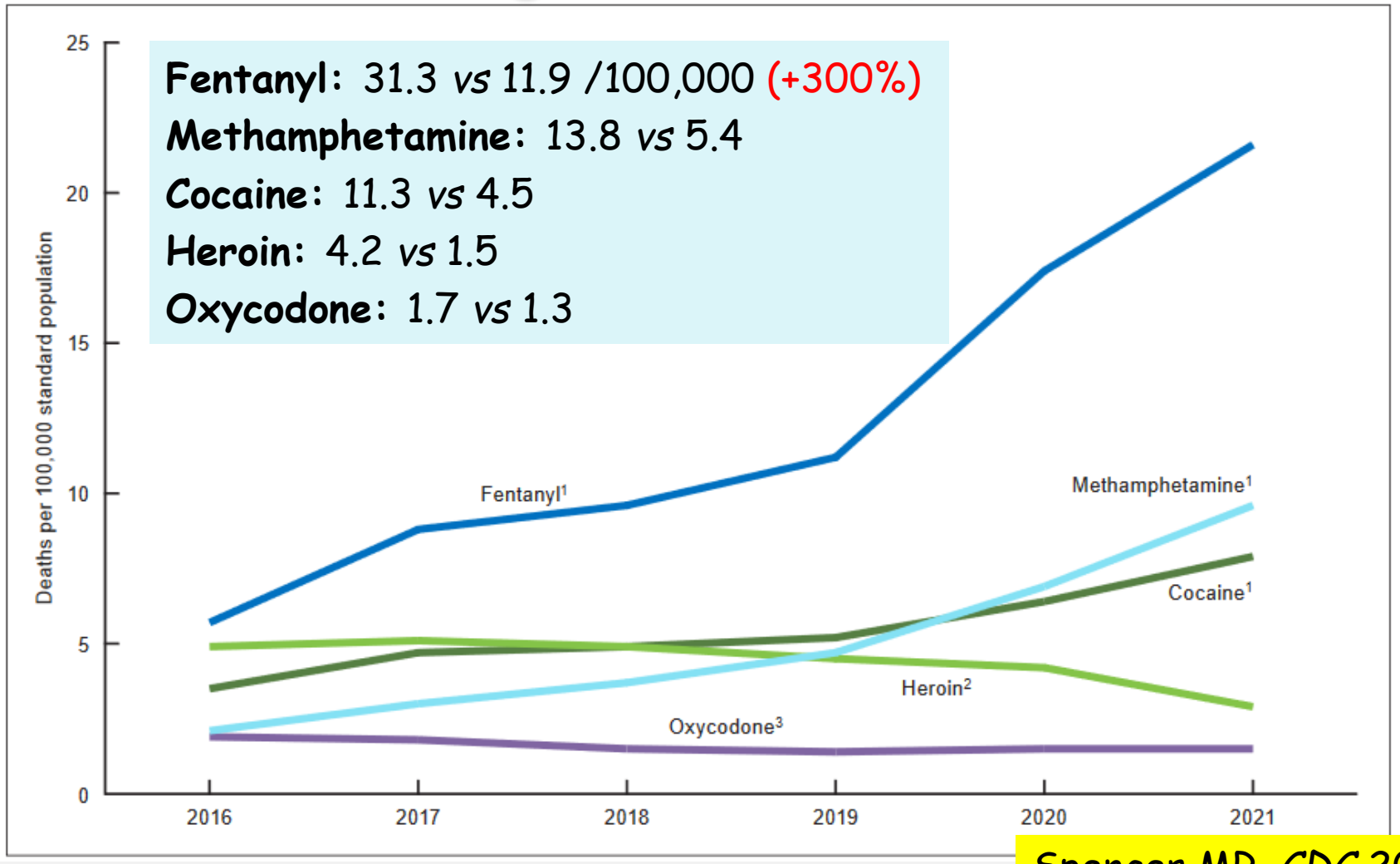
People think they are purchasing legitimate prescription medications; however, pills often contain lethal amounts of illicit drugs
(4/10 with a lethal fentanyl dose)

- Seizure of 78 M **fentanyl-lace fake pills** and 12,000 pounds of **fentanyl powder** in 2023
= equivalent to 377 M deadly doses

- Rainbow fentanyl = "brightly-colored" fentanyl used to target young Americans

2- Impact of multidrug (including stimulant drug) use

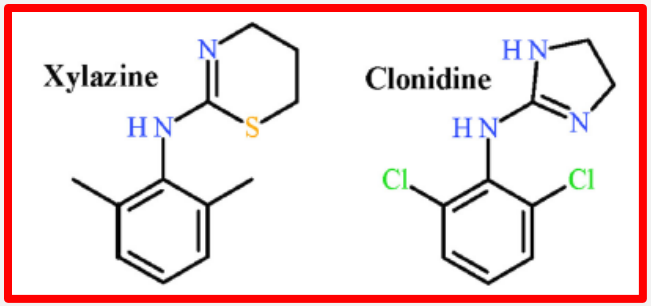
Age-adjusted drug overdose death reates by selected drugs in the US (2016–2021)



Spencer MR. *CDC* 2023

3- Increasing fentanyl adulteration with xylazine

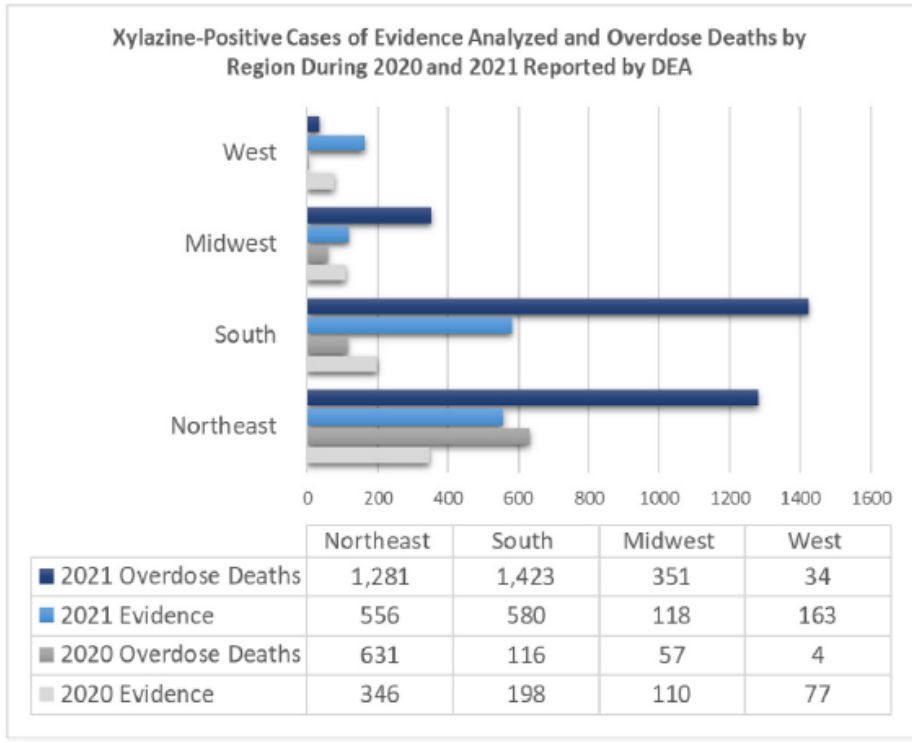
The "zombie drug" apocalypse



Veterinary drug, centrally acting α2 adrenergic R agonist ➔ sedation & muscle relaxation + necrotic skin AE

Clinical Effect, n (%)	Total Exposures (N = 76)	Exposures Without Other Substances (N = 48)
Drowsiness/lethargy	36 (47.4)	21 (43.8)
Bradycardia	15 (19.7)	13 (27.1)
Hypotension	8 (10.5)	5 (10.4)
Hypertension	7 (9.2)	4 (8.3)
Puncture/wound	6 (7.9)	4 (8.3)
Slurred speech	6 (7.9)	3 (6.3)
Coma	5 (6.6)	1 (2.1)
Ocular irritation/pain	5 (6.6)	4 (8.3)
Respiratory depression	4 (5.3)	1 (2.1)

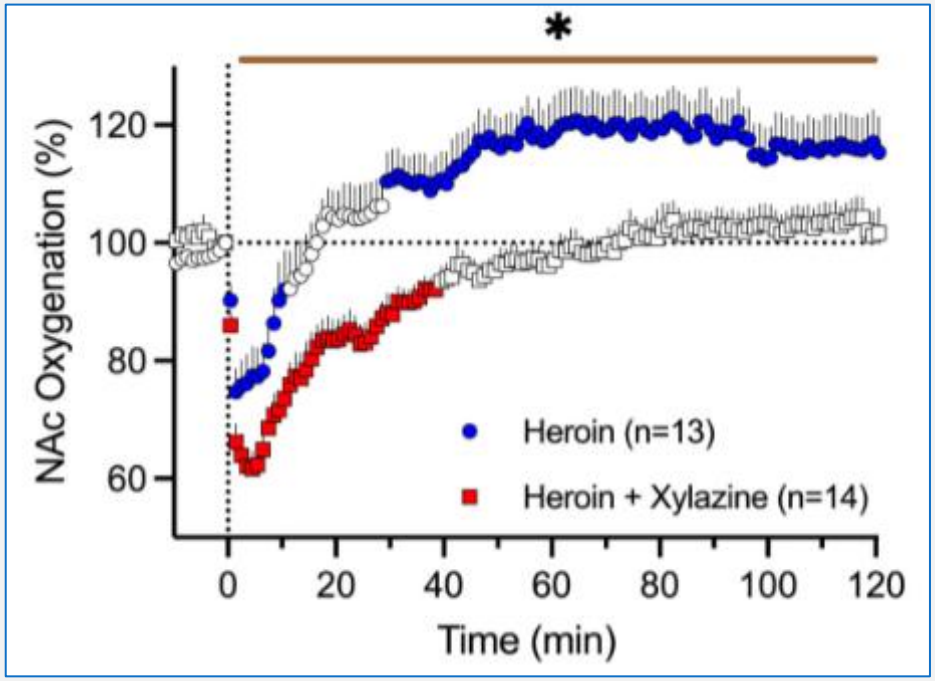
Forrester M. *J Emerg Med* 2016

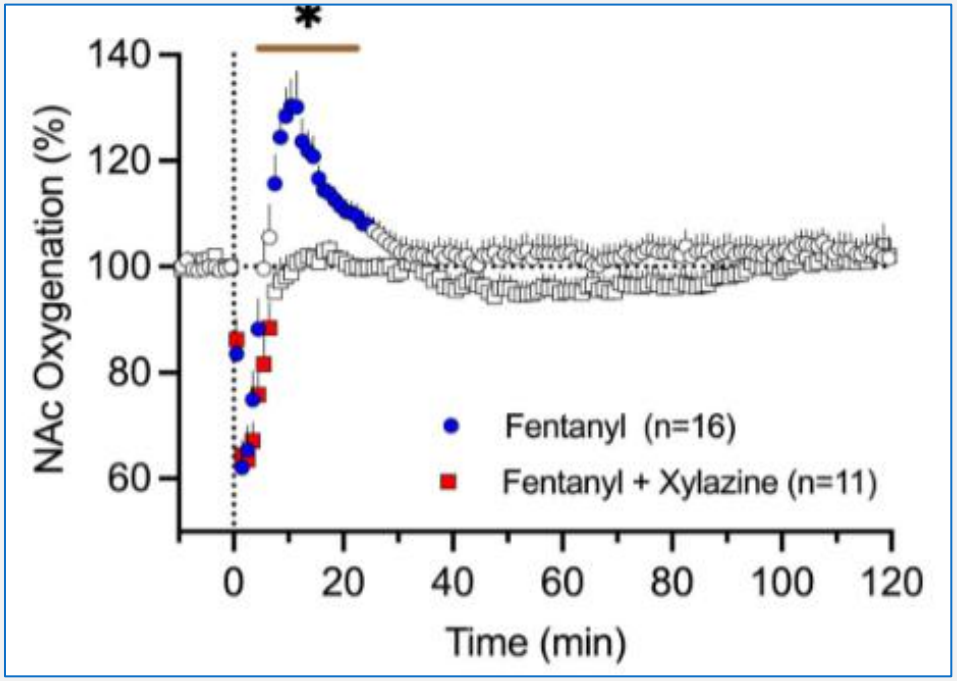


	Northeast	South	Midwest	West
2021 Overdose Deaths	1,281	1,423	351	34
2021 Evidence	556	580	118	163
2020 Overdose Deaths	631	116	57	4
2020 Evidence	346	198	110	77

Silva Torres LA. *J Forensic Leg Med* 2024

Does xylazine worsen opioid-related neurorespiratory depression?



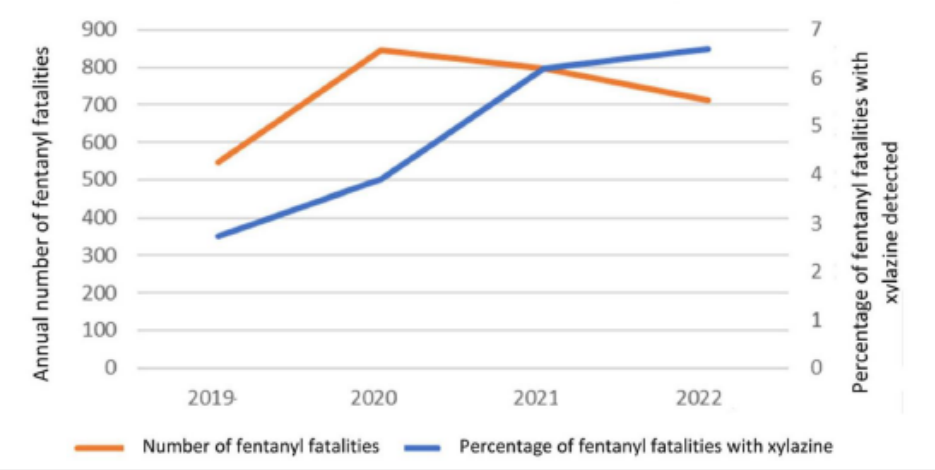


Xylazine/heroin potentiates initial O_2 decrease, deleting the hyperoxic portion of the biphasic response ==> more robust and prolonged brain hypoxia

Xylazine/fentanyl eliminates hyperoxic phase of response + prolongs brain hypoxia ==> attenuation of compensatory mechanisms to counteract brain hypoxia

Choi S. Psychopharmacology 2023

Relationship of blood xylazine and fentanyl concentrations in fatalities



Postmortem fentanyl concentrations were greater in cases with xylazine detected than those without xylazine.

It is unclear why patients who were exposed to xylazine tolerated higher opioid doses prior to dying

Hypothesis: xylazine may act to competitively antagonize some degree of MOR binding by opioids

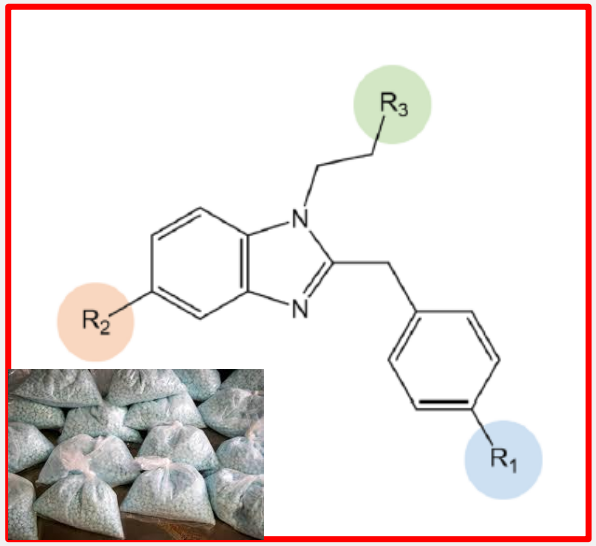
Table 2. Postmortem xylazine and fentanyl concentrations.

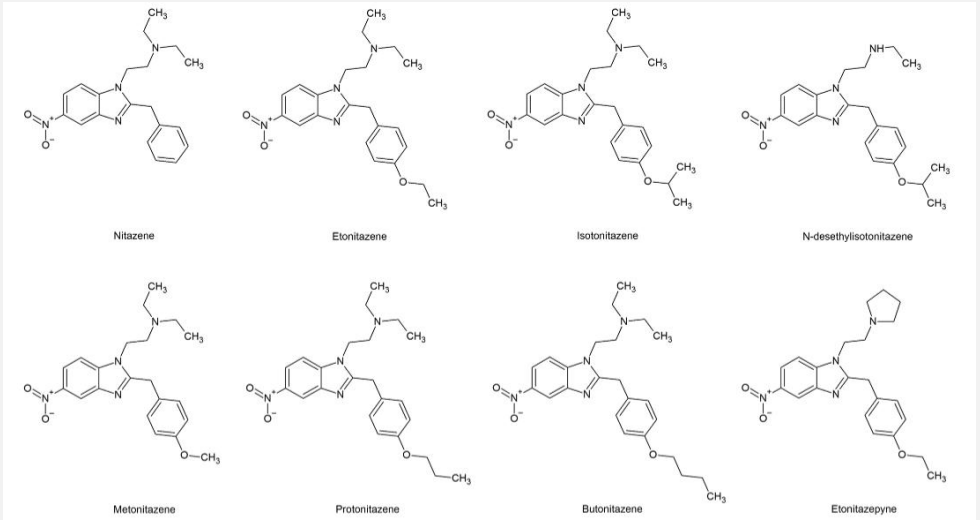
Drug	Median with quartiles (μg/L)	Range (μg/L)
All xylazine concentrations	21.0 (8.8, 44.0)	3.3–2,755
Fentanyl concentrations, all fatalities	10.0 (5.7, 18.0)	0.3–1,349
Fentanyl concentrations, without xylazine	10.0 (5.6, 18.0)	0.3–1,331
Fentanyl concentrations, with xylazine	17.0 (7.9, 27.0)	1.2–1,349

Hays HL. *Clin Tox* 2024

4- Emergence of non-fentanyl synthetic opioids

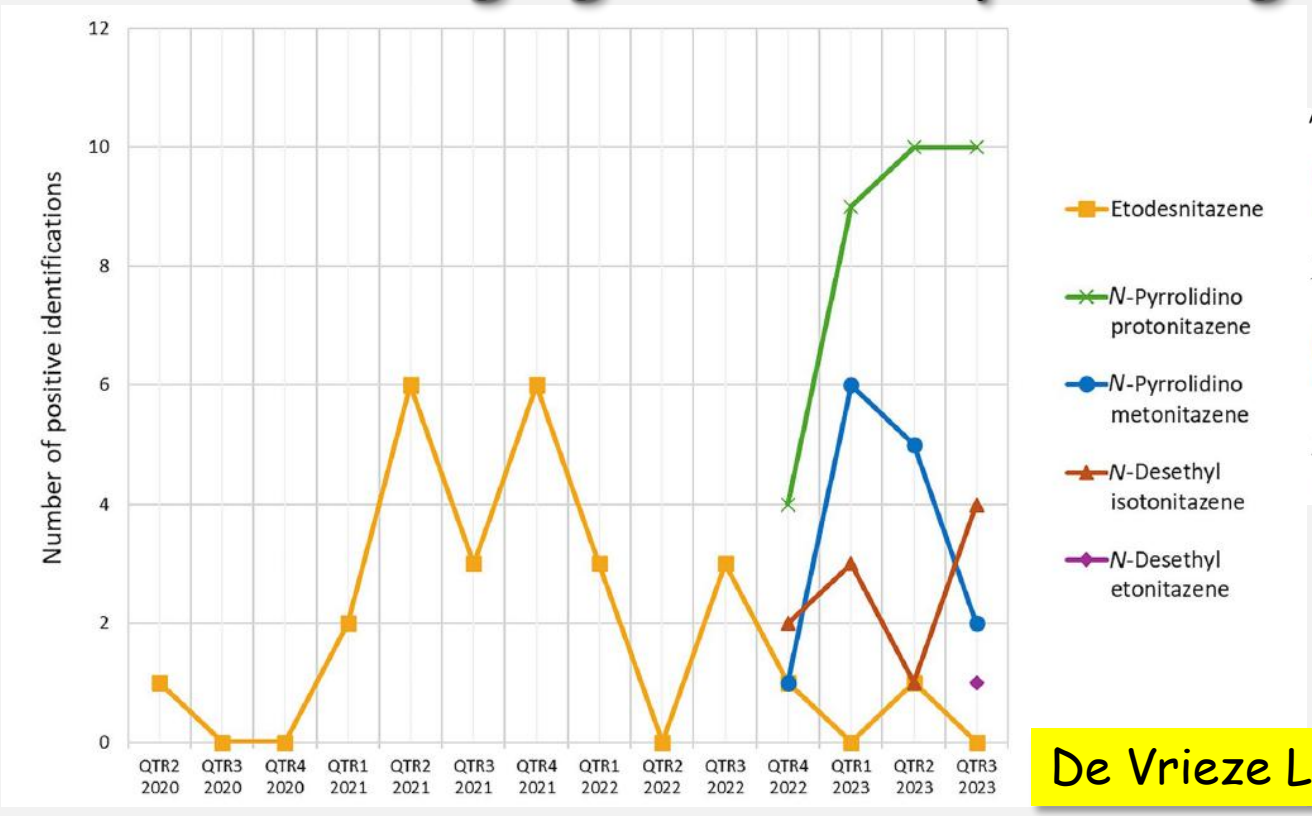
2-Benzylbenzimidazoles (nitazenes)

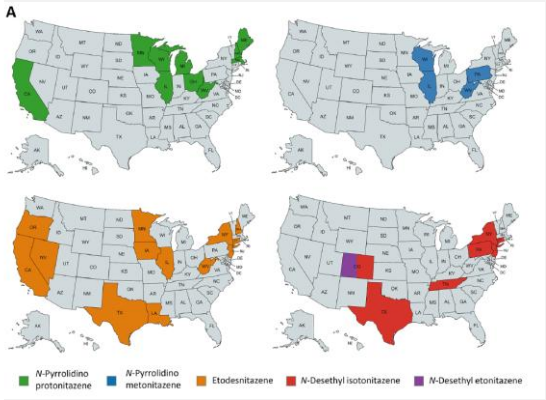




De Vrieze LM. *Arch Toxicol* 2024

The emerging nitazene poisonings in the US

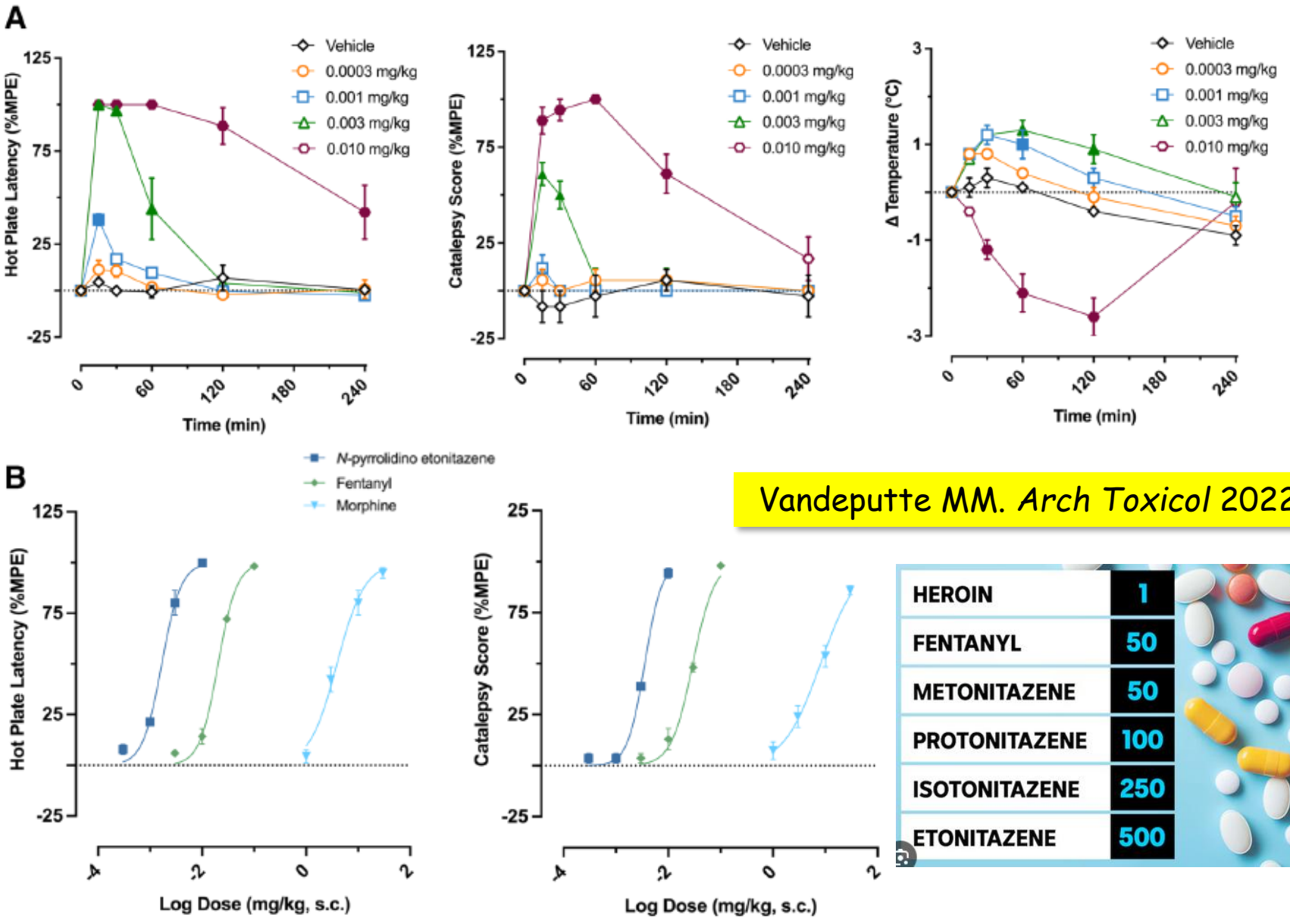




De Vrieze LM. *Arch Toxicol* 2024

Compound of interest	*N* Qualitative	*N* Quantitative	Mean (±SD) (ng/mL)	Median (ng/mL)	Range (ng/mL)
Etodesnitazene	26	15	25 ± 36	4	0.1–120
N-Pyrrolidino protonitazene	39	26	8 ± 17	1.2	0.3–55
N-Pyrrolidino metonitazene	15	11	3 ± 7	0.47	0.2–26
N-Desethyl isotonitazene	16	9	4 ± 2	3.4	0.82–8.3

Pharmacological evaluation of etonitazepyne (2)



Vandeputte MM. *Arch Toxicol* 2022

HEROIN	1
FENTANYL	50
METONITAZENE	50
PROTONITAZENE	100
ISOTONITAZENE	250
ETONITAZENE	500

Naloxone in novel potent opioid vs fentanyl overdose

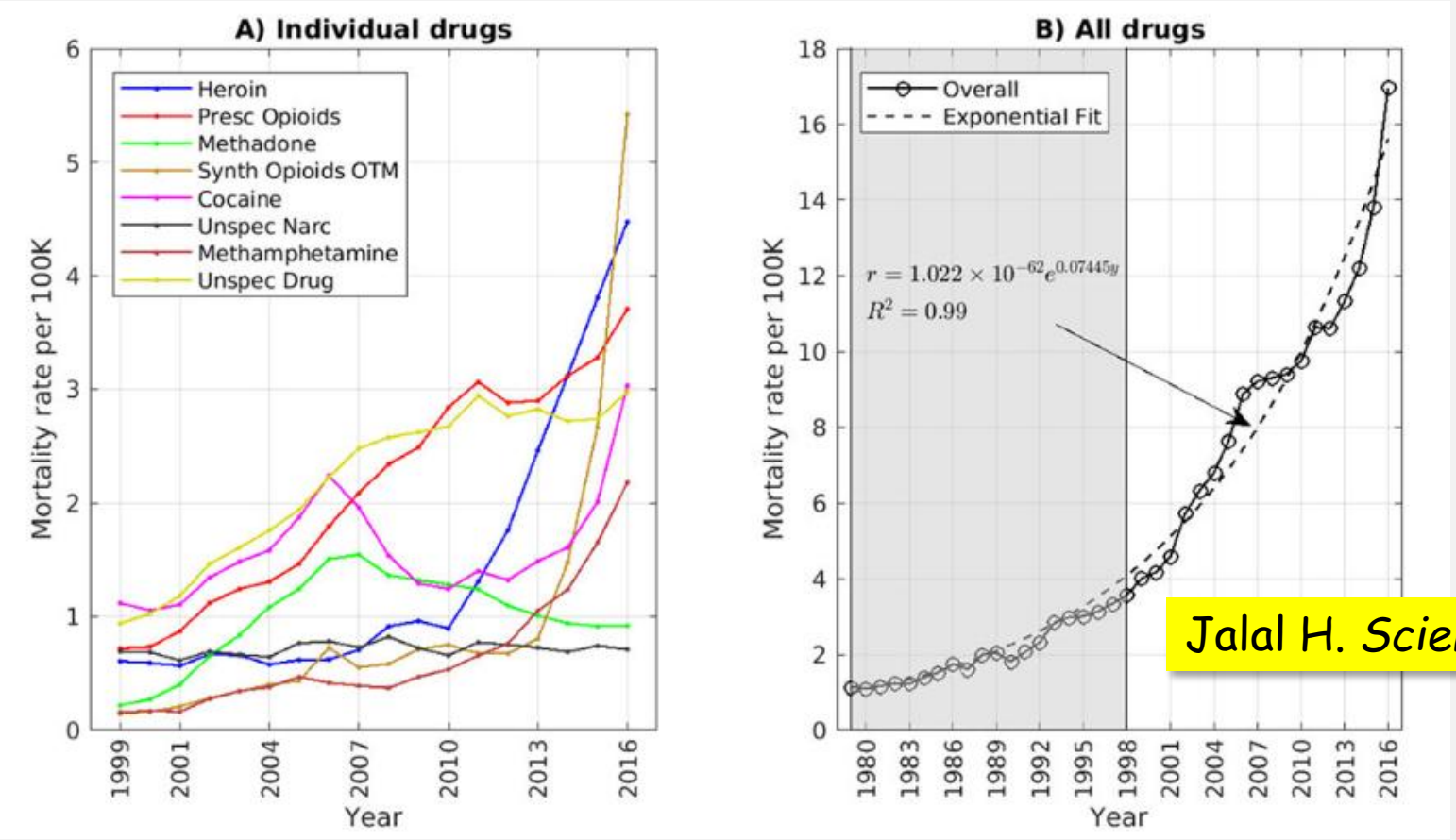
Of 537 opioid overdose with complete laboratory testing data, 11 (2%) positive for only fentanyl and 9 (1.7%) positive for NPOs (brorphine, isotonitazene, metonitazene, or N-piperidinyl etonitazene).

Higher naloxone boluses in-hospital (1.33 [1.50] *vs.* 0.36 [0.92], P=0.02)
Metonitazene overdose associated with cardiac arrest (2/2 patients, 100%) and more naloxone doses (3 (0) naloxone doses).

In this cohort ED study, in-hospital naloxone dosing was high in patients who tested positive for NOPs compared to fentanyl alone.

Amaducci A. *Psychopharmacology* 2023

Long-term perspective: real wave or alternative phenomenon?



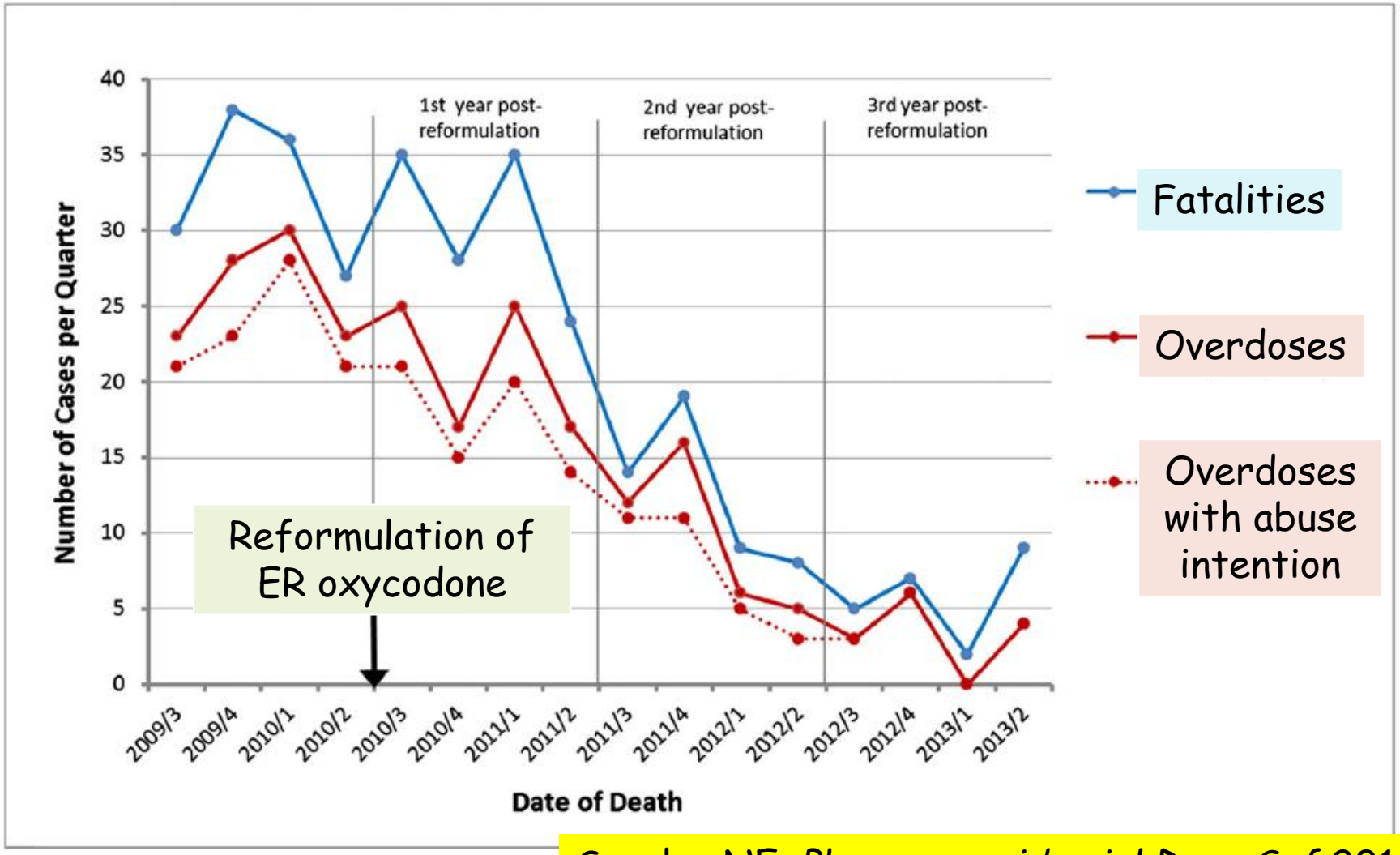
Jalal H. *Science* 2018

Multiple distinctive sub-epidemics of different drugs (primarily prescription opioids, heroin, methadone, synthetic opioids, cocaine, and methamphetamine), each with its own specific demographic and geographic characteristics

==> 38-yr smooth exponential curve of US annual accidental drug poisoning deaths

Role of regulation

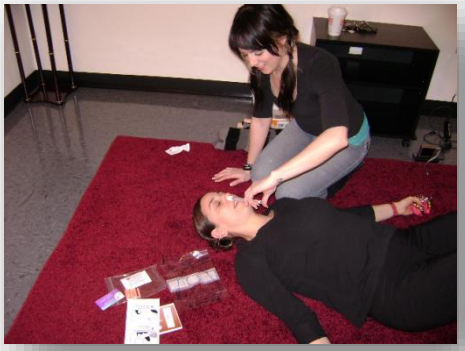
Reduction in deaths following the introduction of extended-release oxycodone with an abuse-deterrent formulation in the US



Sessler NE. *Pharmacoepidemiol Drug Saf* 2014

Preventing opioid overdose deaths with take-home naloxone

- Death from opioid overdose occurs frequently at home, 1-3 h after exposure and often in the presence of bystanders (80%)
- BCLS by bystanders are generally not sufficient



Number of programs of naloxone distribution	Number of naloxone vials distributed over one year	Number of program participants	Number of reported opioid overdose reversals
136	140 053	152 283	26 463

Wheeler E. *MMWR Morb Mortal Wkly Rep* 2015

Worrying signals with synthetic opioids in Europe

In the US

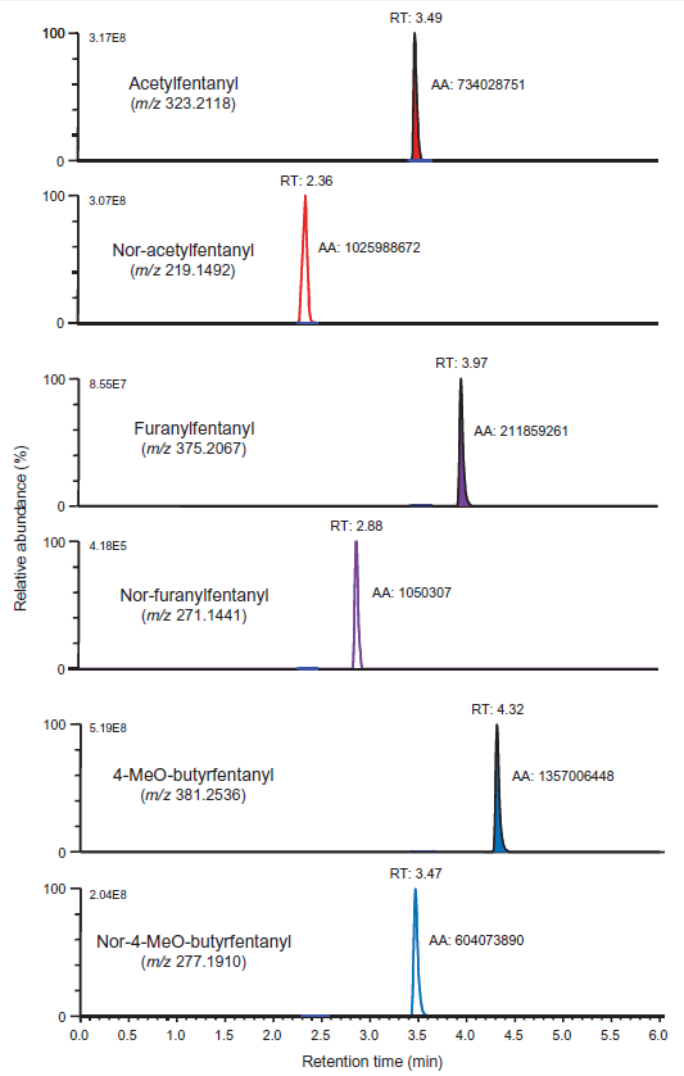
- 101 000 fatal overdoses in 2024, ↓ 10% from previous year
- Federal laws facilitating addiction treatment,↑ availability of naloxone
- ↓ fentanyl supply & concentration in seized pills (abandon of Mexico's Sinaloa)
- Theory of depletion of susceptible (tolerance and learning of dose measuring)
- Xylazine: soporific effect; switch to snorting/smoking or throwing away adulterated drugs

In Europe:

- Opioids associated with ¾ of toxic deaths and heroin with the greatest share
- Aging heroin-using population, prominently increasing use of stimulants
- Fentanyl diversion from therapeutic use + illicit manufacturing in Baltic Countries
- ↑ synthetic opioid demand, shortage in heroin since Taliban's ↓in poppy cultivation
- 50% opioid overdose in Estonia related to nitazenes
- Synthetic opioids + cheap street BZDs as a driver of trends in mortality

Griffiths, PN. *Addiction* 2024

Analytical techniques (LC-HRMS, LC-MS/MS, LC-HRMS/MS)



Take home message

1- NPS toxicity as mainly amphetamine-like
2- Possible life-threatening presentation and organ failure
3- Importance of analytical identification
4- Supportive care (except naloxone)

Agitation
Confusion
Seizures
Adrenergic Sd
Serotoninergic Sd
Organ failure

+

Recreational context

+

Negativity of the usual tox screening (opiates, cocaine, amphetamine, THC)

=

- Suspect NPS intoxication
- Call the Poison Center
- Send a blood sample to a specialized Tox lab

Strategy of management of toxic cardiovascular failure

Diagnosis of shock

↓

Determination of the mechanism of shock

↓

Definition of the optimal treatment

↓

Diagnosis of the refractoriness of shock

Conventional supportive treatments in ICU

- **Intubation and mechanical ventilation :**
  - Severe arrhythmias and associated collapse
  - Coma, convulsions, respiratory failure
- **Treatment of collapse/shock**
  - Fluids + adequate catecholamines
- **Treatment of torsade-de-pointes**
  - Defibrillation, $MgSO_4$, titrated isoproterenol, cardiac pacing
  - Correction of electrolyte imbalance (K^+, Mg^{2+})
- **Treatment of monomorphic ventricular tachycardia**
  - Defibrillation, $MgSO_4$, lidocaine infusion
- **Cardiac pacing**
  - High degree AV block with preserved inotropism

Recommendations for the management of life-threatening betablocker poisonings

Beta-blockers

Dobutamine 5-20 µg/kg/min
Isoprenaline 1-5 mg/h (Sotalol)

↓

Glucagon 2-5 mg IV bolus
2-10 mg/h continuous infusion
Or
Insulin 1 IU/kg IV bolus
1 IU/kg/h continuous infusion

↓

Epinephrine 0.5-10 mg/h

± **Cardiac Pacing**

COR	LOE	Recommendations
1	B-NR	1. We recommend that high-dose insulin be administered for hypotension due to β-blocker poisoning refractory to or in conjunction with vasopressor therapy.
1	C-LD	2. We recommend that vasopressors be administered for hypotension due to β-blocker poisoning.
2a	C-LD	3. It is reasonable to use a bolus of glucagon, followed by a continuous infusion, for bradycardia or hypotension due to β-blocker poisoning.
2a	C-LD	4. It is reasonable to utilize extracorporeal life support techniques such as VA-ECMO for life-threatening β-blocker poisoning with cardiogenic shock refractory to pharmacological interventions.
2b	C-LD	5. It may be reasonable to administer atropine for β-blocker–induced bradycardia.
2b	C-LD	6. It may be reasonable to attempt electrical pacing for β-blocker–induced bradycardia.
2b	C-LD	7. It may be reasonable to use hemodialysis for life-threatening atenolol or sotalol poisoning.
3: No Benefit	C-LD	8. Intravenous lipid emulsion therapy is not likely to be beneficial for life-threatening β-blocker poisoning.

Lavonas EJ. *Circulation* 2023

Recommendations for the management of life-threatening calcium-channel blocker poisonings

Calcium channel blockers

Calcium chloride 1 g IV bolus /15 min
4 doses, 20-50 mg/kg/h infusion

⬇

Insulin 1 IU/kg IV bolus
1-10 IU/kg/h continuous infusion

⬇

Epinephrine 0.5-10 mg/h
Norepinephrine 0.5-10 mg/h

⬇

Methylene blue 2 mg/kg bolus
1 mg/kg/h infusion

COR	LOE	Recommendations
1	B-NR	1. We recommend administering vasopressors for hypotension from calcium channel blocker (CCB) poisoning.
1	B-NR	2. We recommend administering high-dose insulin for hypotension due to CCB poisoning.
2a	C-LD	3. It is reasonable to administer calcium for CCB poisoning.
2a	C-LD	4. It is reasonable to administer atropine for hemodynamically significant bradycardia from CCB poisoning.
2a	C-LD	5. It is reasonable to utilize extracorporeal life support techniques such as VA-ECMO for cardiogenic shock due to CCB poisoning that is refractory to pharmacological interventions.
2b	C-LD	6. It might be reasonable to attempt electrical pacing for CCB poisoning with refractory bradycardia.
2b	C-LD	7. The usefulness of a glucagon bolus and infusion for CCB poisoning is uncertain.
2b	C-LD	8. The usefulness of administering methylene blue for refractory vasodilatory shock due to CCB poisoning is uncertain.
3:No Benefit	C-LD	9. The routine use of intravenous lipid emulsion (ILE) therapy for CCB poisoning is not recommended.

Lavonas EJ. *Circulation* 2023

Recommendations for the management of life-threatening sodium-channel blocker poisonings

Sodium channel blockers

Sodium bicarbonates 8.4%
250 ml to be repeated 3 times
+ 2g KCl / 250 ml
(cocaine: **Lidocaine** IV)

↓

Epinephrine 0.5-10 mg/h
Norepinephrine 0.5-10 mg/h

COR	LOE	Recommendations
1	B-NR	1. We recommend using sodium bicarbonate to treat life-threatening cardiotoxicity from tricyclic and/or tetracyclic antidepressant poisoning.
2a	C-LD	2. It is reasonable to use sodium bicarbonate to treat life-threatening cardiotoxicity caused by poisoning from sodium channel blockers other than tricyclic or tetracyclic antidepressants.
2a	C-LD	3. It is reasonable to use extracorporeal life support, such as VA-ECMO, to treat refractory cardiogenic shock from sodium channel blocker poisoning.
2b	C-LD	4. It may be reasonable to use Vaughan-Williams class Ib antidysrhythmics (eg, lidocaine) to treat life-threatening cardiotoxicity from class Ia or Ic sodium channel blockers.
2b	C-LD	5. It may be reasonable to use intravenous lipid emulsion to treat life-threatening sodium channel blocker poisoning refractory to other treatment modalities.

Lavonas EJ. *Circulation* 2023

Recommendations for the management of life-threatening cocaine & local anesthetic poisonings

Cocaine Poisoning

COR	LOE	Recommendation
1	C-LD	1. We recommend rapid external cooling for life-threatening hyperthermia from cocaine poisoning.
2a	C-LD	2. It is reasonable to administer sodium bicarbonate for wide-complex tachycardia or cardiac arrest from cocaine poisoning.
2a	C-LD	3. It is reasonable to administer lidocaine for wide-complex tachycardia from cocaine poisoning.
2a	C-LD	4. It is reasonable to administer vasodilators (eg, nitrates, phentolamine, calcium channel blockers) for patients with cocaine-induced coronary vasospasm or hypertensive emergencies.

Local anesthetic Poisoning

COR	LOE	Recommendations
1	C-LD	1. We recommend the administration of intravenous lipid emulsion for local anesthetic poisoning.
1	C-LD	2. We recommend the use of benzodiazepines to treat seizures associated with local anesthetic systemic toxicity.
2a	C-LD	3. It is reasonable to administer sodium bicarbonate for life-threatening wide-complex tachycardia associated with local anesthetic toxicity.
2a	C-EO	4. It is reasonable to administer atropine for life-threatening bradycardia associated with local anesthetic systemic toxicity.
2a	C-EO	5. It is reasonable to utilize extracorporeal life support techniques such as VA-ECMO in local anesthetic toxicity with refractory cardiogenic shock.

Lavonas EJ. *Circulation* 2023

Recommendations for the management of life-threatening cardiac glycoside poisonings

Cardioglycosides

Atropine 0.5-1 mg to be repeated

⬇

Anti-digoxin Fab fragments
Semi-molar or molar dose
(if not available: ventricular pacing)

COR	LOE	Recommendations
1	B-NR	1. We recommend administration of digoxin-specific antibody fragments (digoxin-Fab) for digoxin or digitoxin poisoning.
2a	C-LD	2. It is reasonable to administer digoxin-Fab for poisoning due to *Bufo* toad venom and yellow oleander.
2b	C-LD	3. It may be reasonable to administer digoxin-Fab to treat poisoning from cardiac glycosides other than digoxin, digitoxin, *Bufo* toad venom, and yellow oleander.
2b	C-LD	4. It may be reasonable to administer atropine for bradydysrhythmias caused by digoxin and other cardiac glycoside poisoning.
2b	C-LD	5. It may be reasonable to attempt electrical pacing to treat bradydysrhythmias from digoxin and other cardiac glycoside poisoning.
2b	C-LD	6. It may be reasonable to administer lidocaine, phenytoin, or bretylium to treat ventricular dysrhythmias caused by digitalis and other cardiac glycoside poisoning until digoxin-Fab can be administered.
3: No Benefit	B-NR	7. We do not recommend the use of hemodialysis, hemofiltration, hemoperfusion, or plasmapheresis to treat digoxin poisoning.

Lavonas EJ. *Circulation* 2023

Lipid emulsion to treat cardiotoxicant drug-related toxicity

To treat severe anesthetics side-effects in the OR as well as membrane-stabilizing agent or calcium-channel blocker poisonings.

Dose regimen: 1.5 ml/kg IV bolus then 0.25 ml/kg/min infusion

Mechanisms:

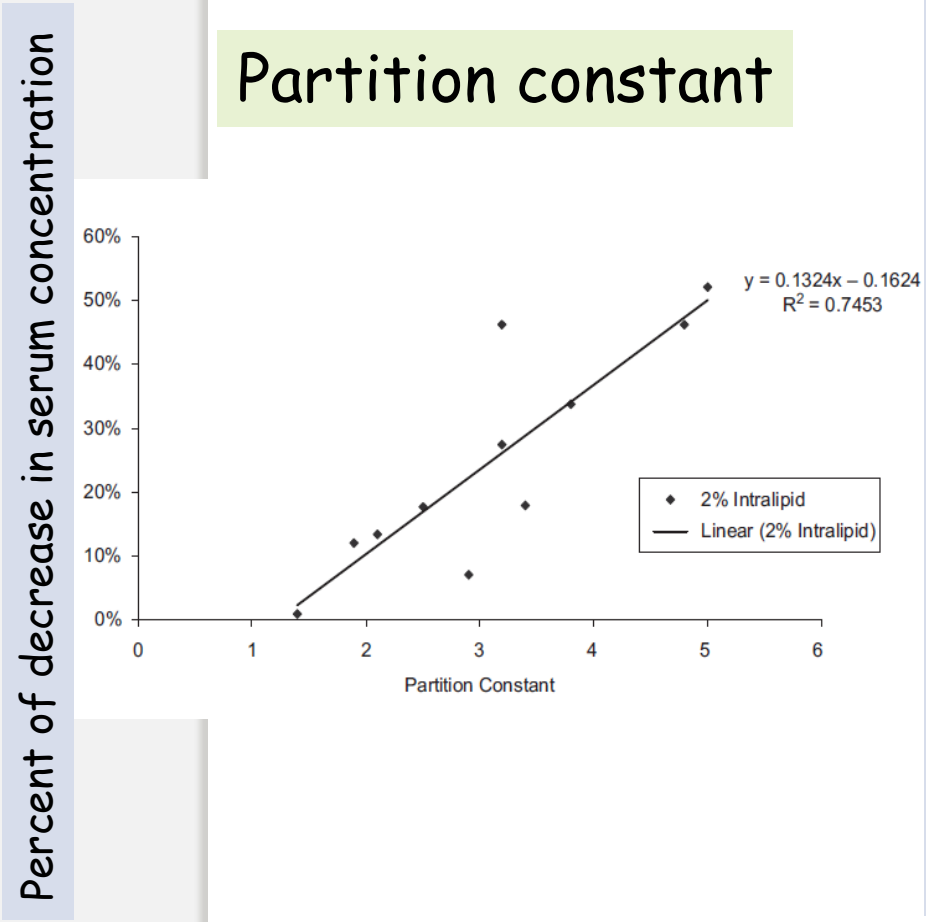
- Lipid sink / sponge: alteration of tissue distribution
- Modulator of myocardial energy, overcoming the inhibition of fatty acid-dependent metabolism
- Activator of myocardial Ca^{2+} channel increasing Ca^{2+} current
- Other toxin-specific mechanisms?

Sirianni AJ. *Ann Emerg Med* 2008
Finn SD. *Anesthesia* 2009
Weinberg GL. *Anesthesiology* 2009

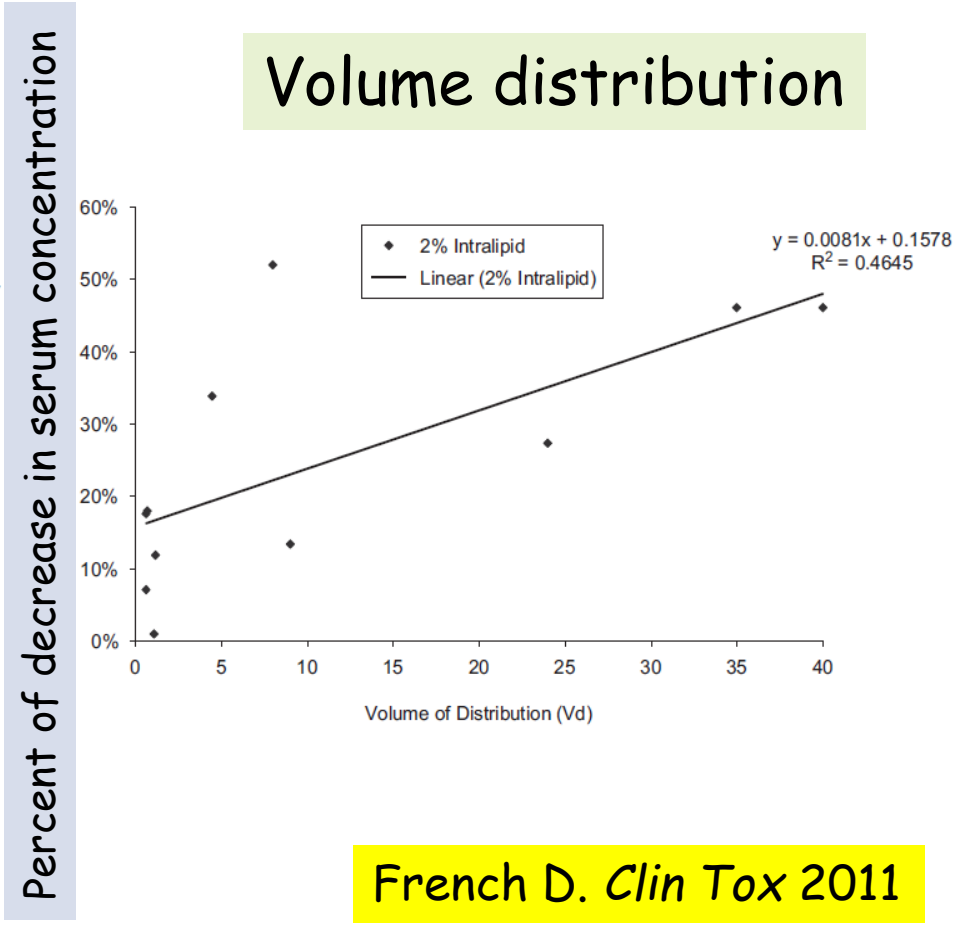
Partition constant and volume of distribution as predictors of ILE efficacy for toxicological emergencies

Serum drug concentration decrease plotted against the partition constant and the volume of distribution of eleven drugs with 20% Intralipid® added to the sample

Partition constant



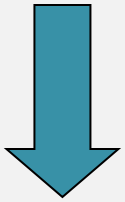
Volume distribution



French D. *Clin Tox* 2011

ECMO indications in acute poisonings

Which patients to treat with ECLS ?



Numerous risks

Too late : To result in anoxic brain injury or multiorgan failure

Undiscriminated use: to treat patients who would spontaneously have had favorable outcome with pharmacological treatments

Definition of refractory cardiac failure in sodium-channel blocker poisonings

N = 137

Hypotension Systolic BP ≤ 90 mmHg) despite :

Adequate fluids ≥ 1,000 ml

+ 8.4% sodium bicarbonate ≥ 375 ml

+ epinephrine ≥ 3 mg/h (glucagon ≥ 5 mg/h if b-blocker)

Respiratory failure : PaO_2/FiO_2 ≤ 150 mmHg with MV + sedation

+

Renal failure : urine output ≤ 20 ml/h ou creatinine ≥ 120 µM (M) ou 90 µM (F)

The cardiac origin is supported by echocardiography (surface shortening fraction < 30%) or right catheterism (cardiac index ≤ 2.5 l/min/m^2 + pulmonary artery occlusion pressure ≥ 18 mmHg)