

Pulmonary consequences of drug use

Bruno Mégarbane, MD, PhD

*Medical and Toxicological Critical Care Department Lariboisière
Hospital, Paris-Diderot University Paris - France*

bruno.megarbane@lrb.aphp.fr

Drug of abuse: a worldwide health concern

Proportion of users in the world
Amongst people age 15-64 worldwide

4,343m

All people
aged 15-64 in 2007

250m

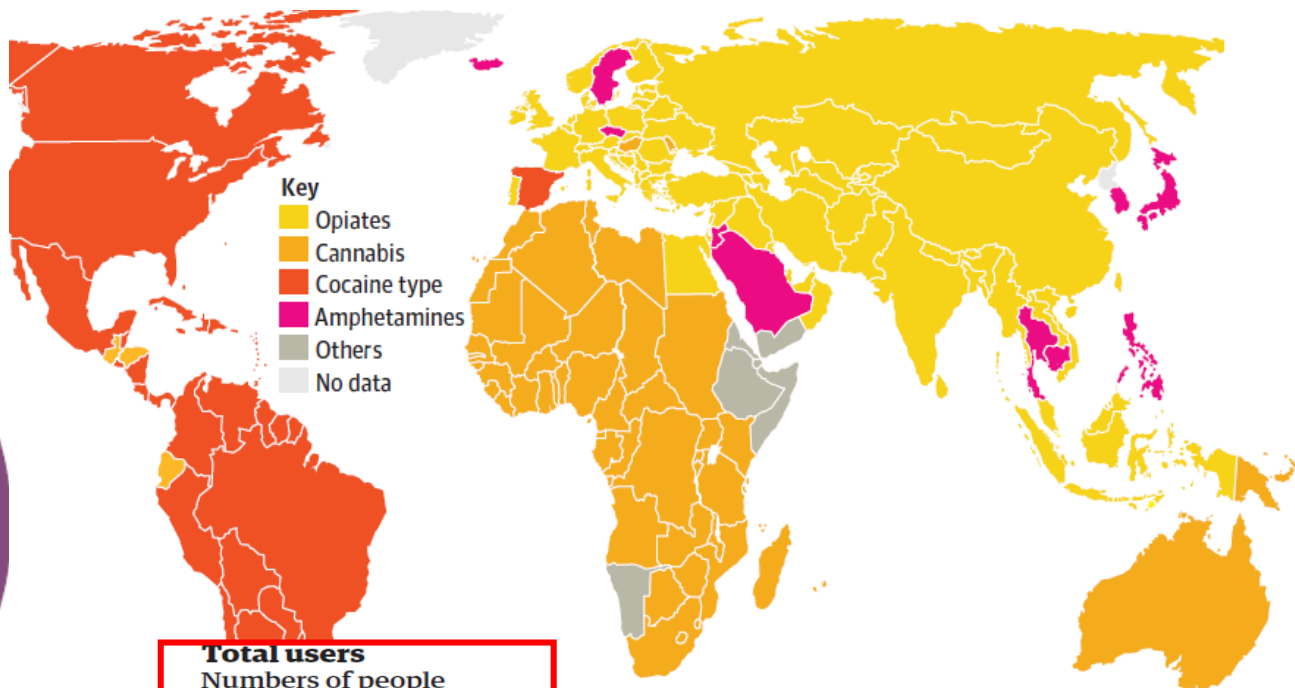
Number who have
used drugs once
in past year

38m

Problem drug users

21m

Number who inject drugs



Total users
Numbers of people

190m
Cannabis

50m

Amphetamines

23m

Ecstasy

21m

Opiates

20m

Cocaine

The particular situation of lung in drug abusers

- Lungs represent both a conduit into the systemic circulation and a barrier to the external environment
- Damage to lungs may occur from systemic as well as inhalational exposure to drugs of abuse
- Drug-related lung injuries may be acute /even life-threatening and sometimes result in chronic illness and sequelae
- Aspiration pneumonia related to CNS depression represents the most common respiratory complication
- Management is supportive and needs to stop the drug. Specific therapy (steroids) could be indicated. No antidote (except naloxone) is available

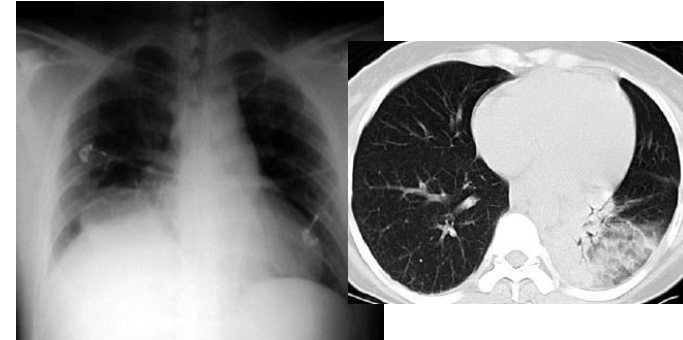
Non-specific drug-related lung injuries

- Resulting from:
- the route of drug self-administration
 - the drug contaminants
 - the abuser's vulnerability

Infections

The most common pulmonary complication from drug abuse

- Aspiration pneumonitis
- Community-acquired pneumonia
- Tuberculosis
- Septic embolism from endocarditis



Excessive bronchial reactivity

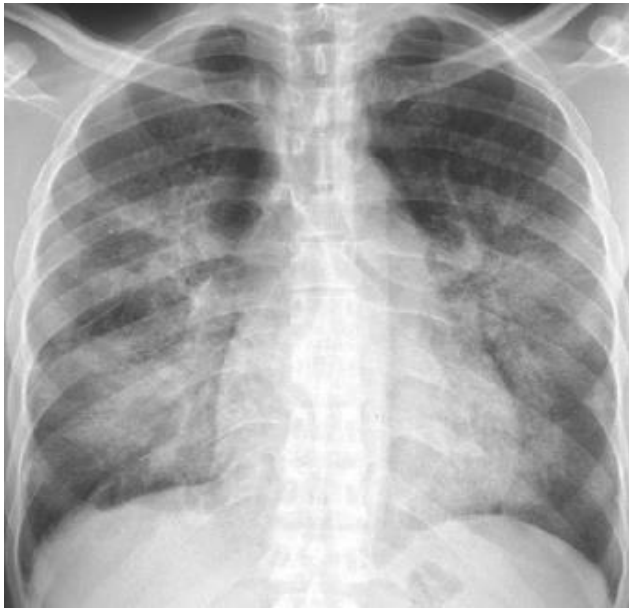
A common complication following drug inhalation

- In relation to nonspecific inflammatory mechanisms
- Resulting in activation of neutrophils
- Production of inflammatory mediators, oxidative stress

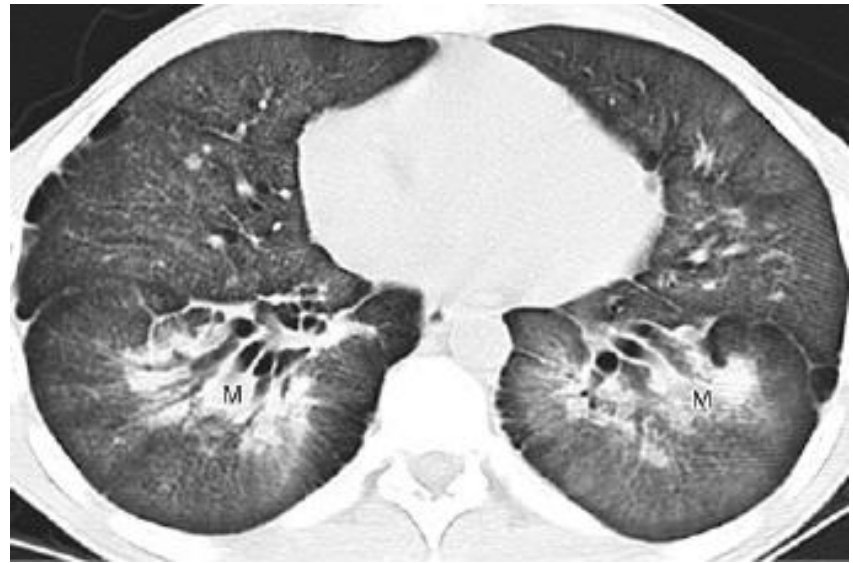
IV route

Tablet/contaminant IV injection

- Microcrystalline cellulose, povidone, talc, and cornstarch
- Repeated insults can lead to dyspnea, pulmonary hypertension, death
- Chest X-rays and CT: multinodular patterns
- Intravascular granulomata within the lungs



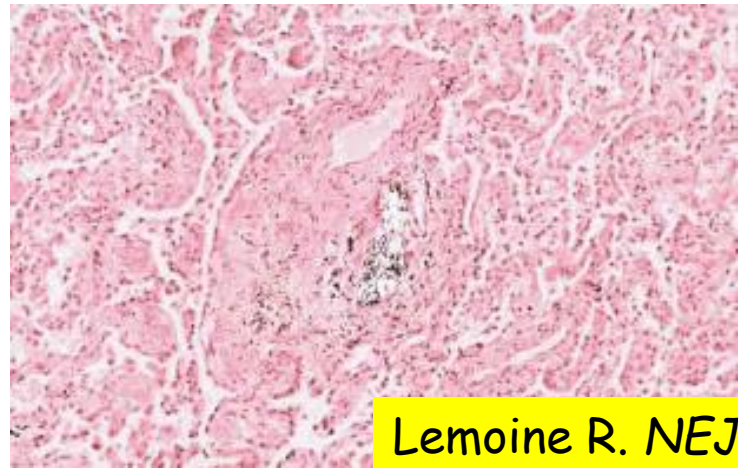
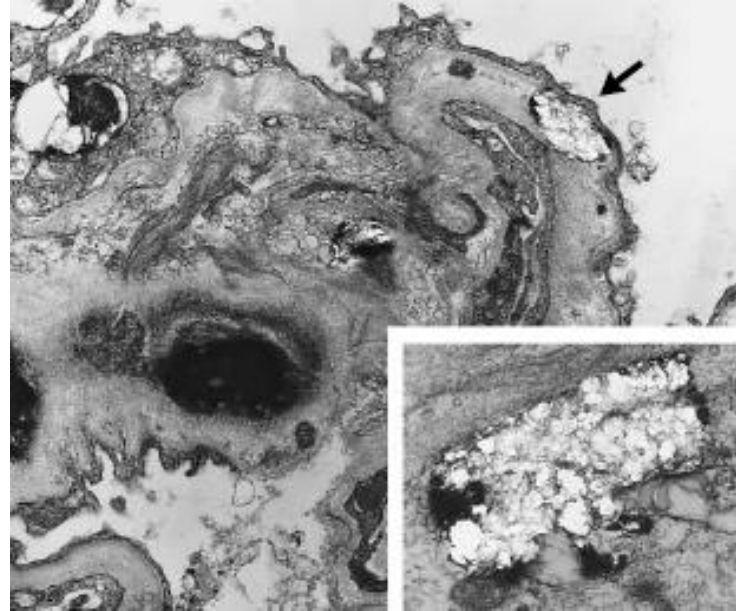
Fine nodular opacities and areas of coalescence



Tiny diffuse nodules and peribronchovascular conglomerate masses

IV route

Pulmonary granulomas in IV drug users

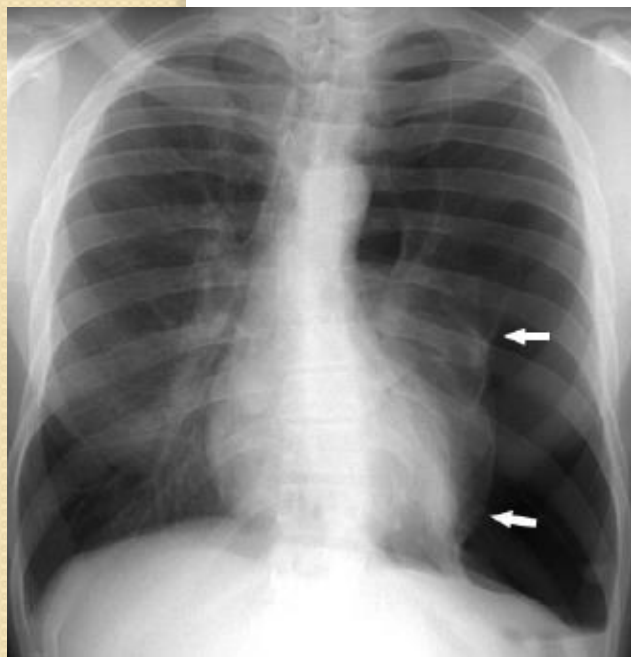


Lemoine R. NEJM 2000

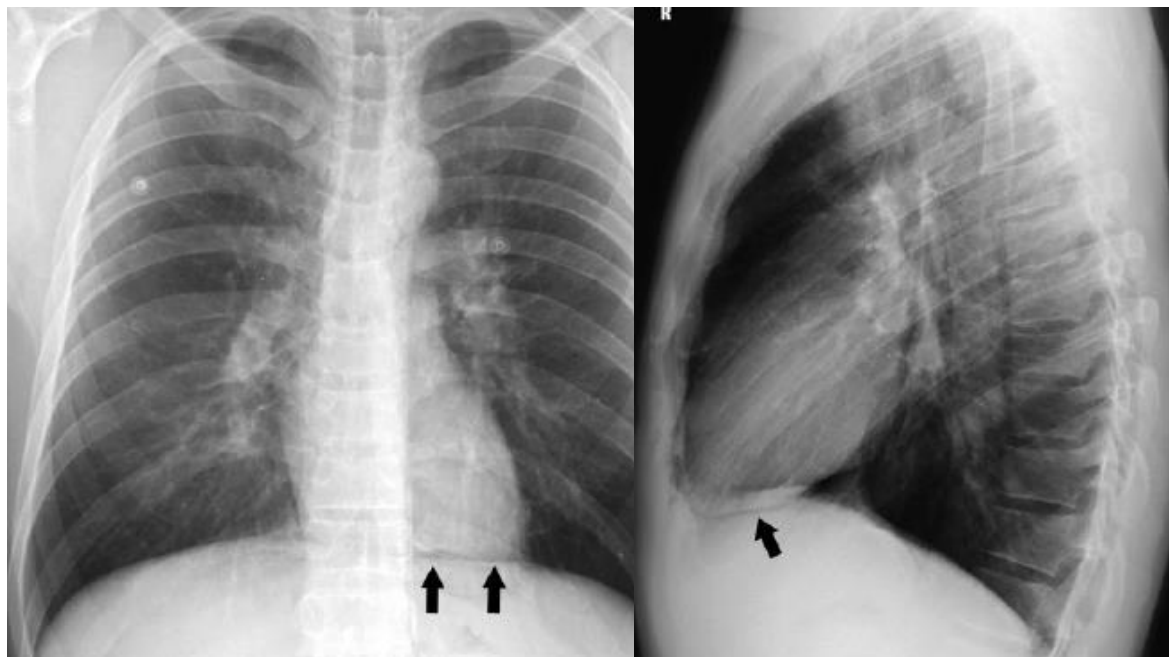
Inhalation route

Barotrauma

- Intensive Valsalva maneuver with breath holding
- In attempt to absorb the maximal possible drug amount



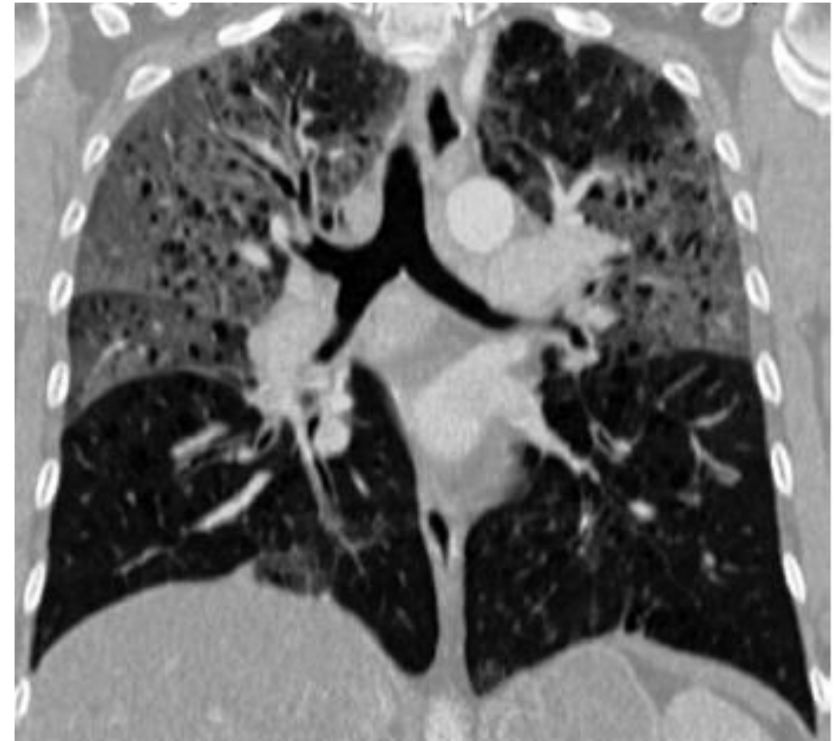
Spontaneous left PNO in a 33-yr-old crack smoker



Pneumomediastinum in a 28-yr-old crack smoker with retrosternal chest pain

Inhalation route

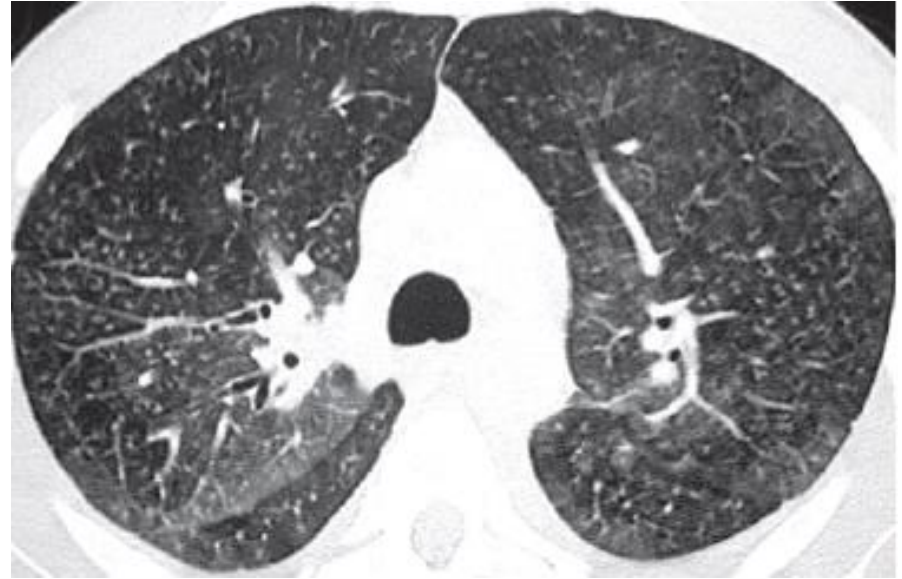
Valsalva maneuver effect on distribution of lung damage in heroin inhalation



Prowse SJ. *BJR* 2011

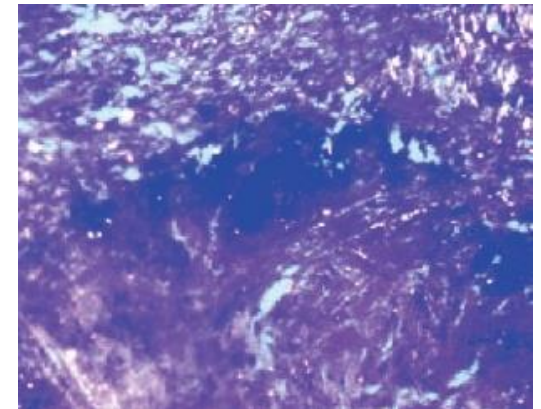
Repeated inhalation

Silicosis in crack cocaine smoker



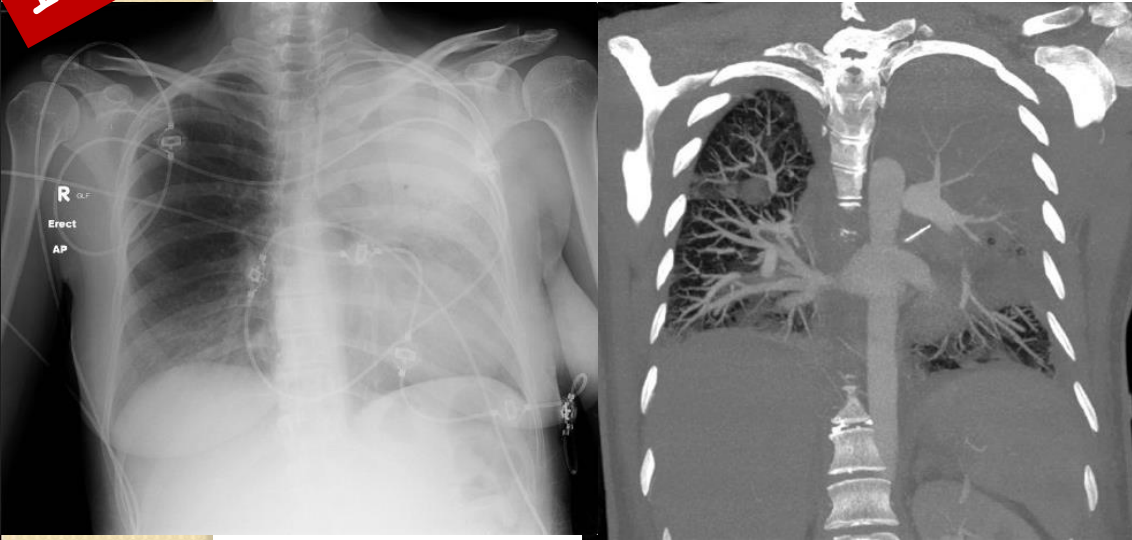
Diffuse bilateral reticulonodular opacities Centrilobular nodules & ground-glass opacities

Birefringent particles representing free silica



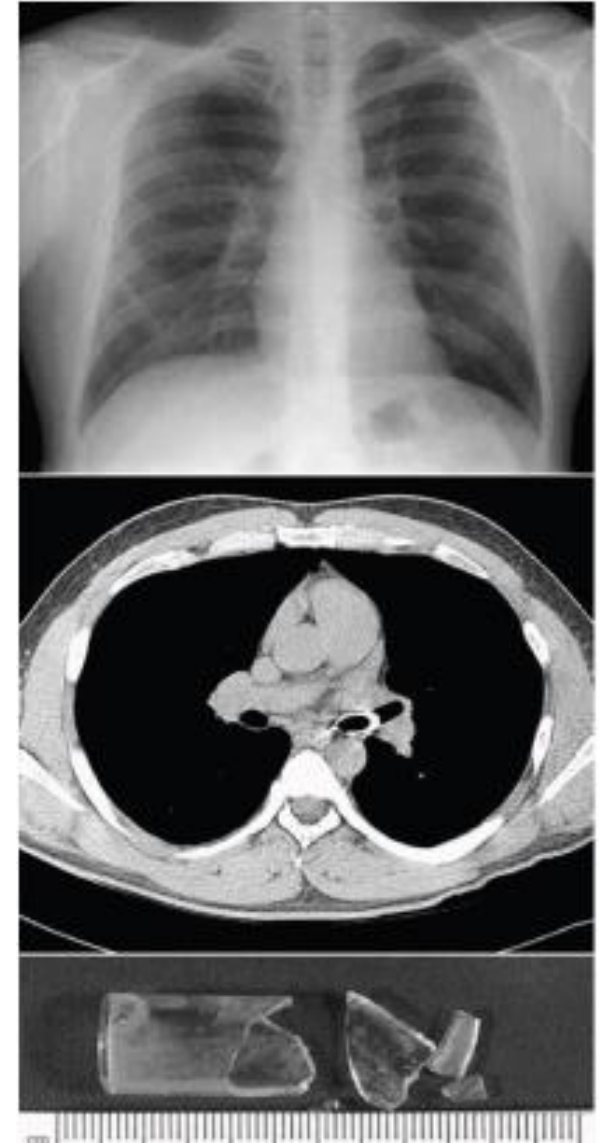
Inhalation route

Foreign body aspiration pneumonia in IV drug user



Bhaskar B. *Saudi J Anaesth* 2012

Crack pipe aspiration

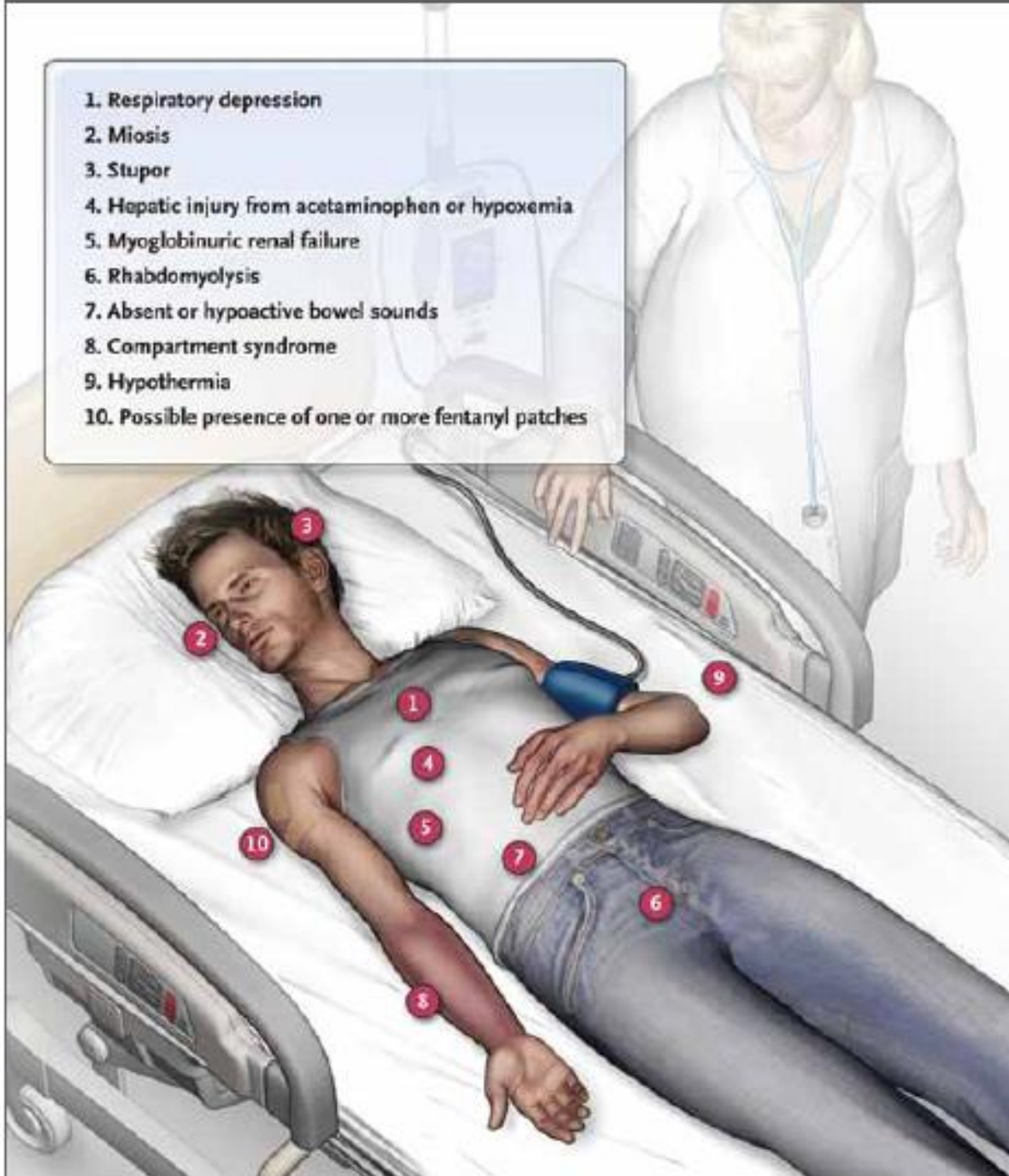


Kovitz KL. *Respiration* 2004

Specific drug-related lung injuries

Direct or indirect toxicological mechanism

1. Respiratory depression
2. Miosis
3. Stupor
4. Hepatic injury from acetaminophen or hypoxemia
5. Myoglobinuric renal failure
6. Rhabdomyolysis
7. Absent or hypoactive bowel sounds
8. Compartment syndrome
9. Hypothermia
10. Possible presence of one or more fentanyl patches



1

Opioid overdose

All opioids produce a similar toxidrome in excessive dosing;



Supportive care

One antidote:
Naloxone

however, pattern of opioid abuse is various and changing

Boyer EW. NEJM 2012

The unusual presentations of opioid overdose

Non cardiogenic pulmonary edema

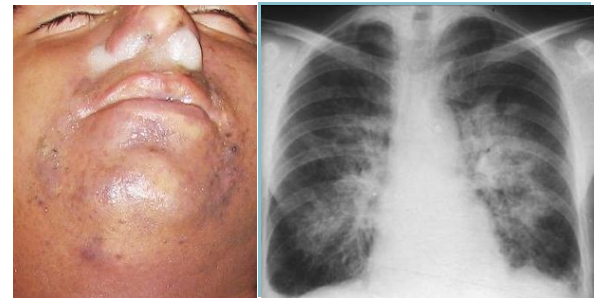
Forensic findings

- Pink foam in the airways
- Swollen heavy lungs
- Exsudative siderophage infiltration
- Typically: >3h after exposure



Clinical findings in poisoning

- Rare complication with decreasing incidence
- Immediate or 4h after exposure
- Mechanical ventilation (33%)
- X-rays: typical bilateral (75%), unilateral edema (15%), localized lesions (7%)
- Mechanisms:
 - 1- Valsalva maneuver against a closed glottis
 - 2- Severe hypoxemic alveolar injury
 - 3- Anaphylactoid reaction
 - 4- Naloxone-induced heart stunning



2

"Crack Lung"

Acute syndrome after the inhalation of (free base) cocaine

Presentation: Fever, hypoxemia, hemoptysis, respiratory failure

Pulmonary findings

- Pulmonary edema
- Diffuse alveolar hemorrhage
- Eosinophil pulmonary infiltrations
- Nonspecific interstitial pneumonia
- Bronchiolitis obliterans with organizing pneumonia (BOOP)
- Barotrauma, asthma

Long term complications

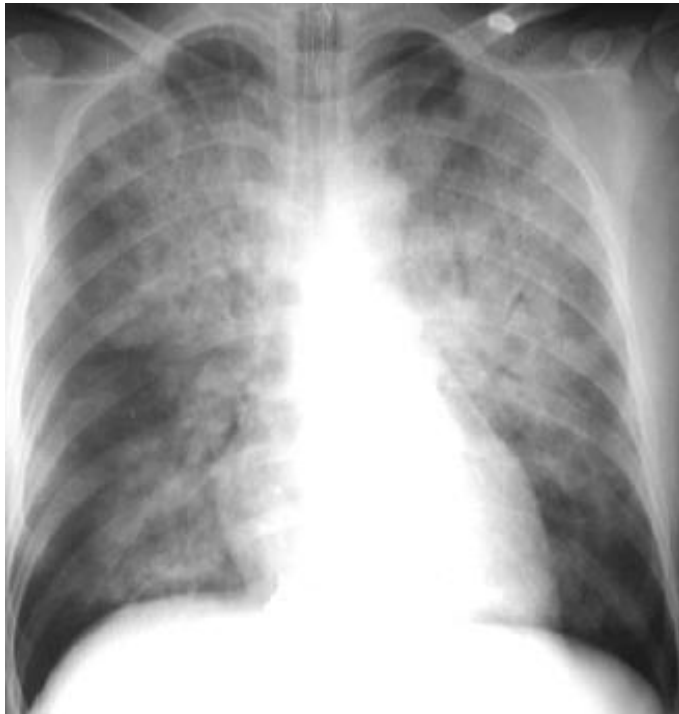
Pathophysiology

- High temperature of volatilized drug ($>700^{\circ}\text{C}$)
- Non-volatilized impurities
- Profound local vasoconstriction
- Macrophage activation
- Basal cell hyperplasia and ciliary dysfunction



Cocaine-induced cardiogenic pulmonary edema

36-yr-old cocaine abuser woman who presented with shortness of breath and chest pain after smoking crack



Extensive bilateral heterogeneous central and parahilar opacities



Bilateral heterogeneous opacities

Crack lung

Cocaine-induced pulmonary edema: outcome



Presentation
Bilateral opacities



Day 2
Complete clearing

Gotway MB. *Radiographics* 2002

Cocaine-related eosinophilic lung disease



Bilateral opacities with peripheral distribution



Extensive bilateral ground-glass opacities and airspace consolidation.

Restrepo CS. *Radiographics* 2007

Cocaine-related pulmonary fibrosis

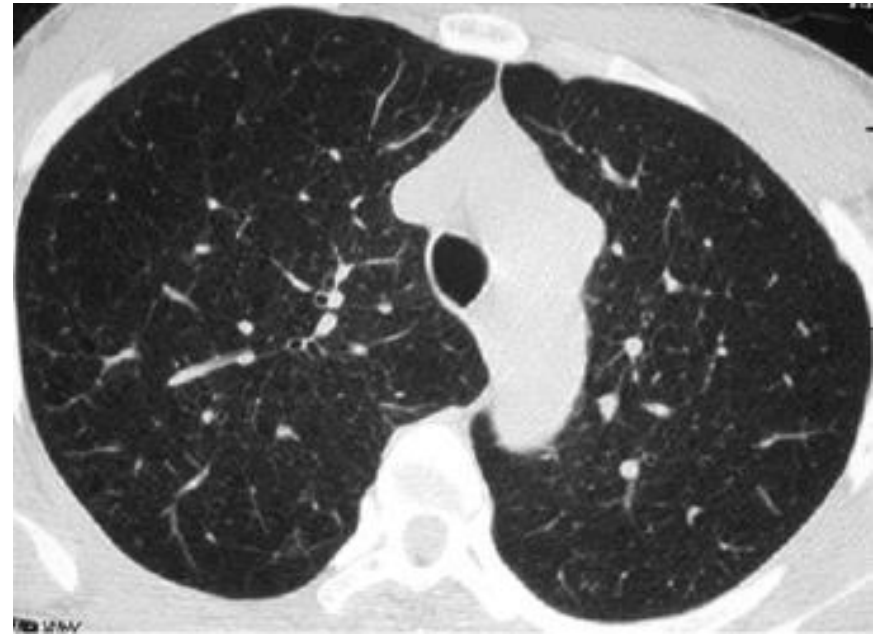
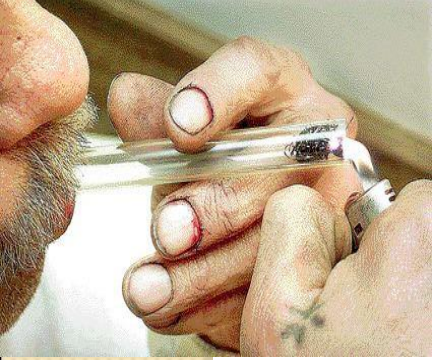
38-yr-old woman with a long history of crack cocaine smoking



Bilateral, predominantly anterior reticular opacities and honeycombing with some ground-glass appearance in the inferior lobes

Cocaine smoking-related emphysema

36-yr-old woman with a history of heavy crack abuse



Diffuse advanced emphysema

Hyperinflation and signs of pulmonary hypertension with predominant hyperlucency in the upper regions

Cocaine-related pulmonary hypertension

43-yr-old man with a history of cocaine abuse



Prominence of the pulmonary arteries



Dilatation of the main pulmonary arteries



3

Marijuana pulmonary toxicity

- Irritating effects (like cigarettes)
- Loosely packed, unfiltered and hotter smoke
- More deep inhalation, longer retain of smoke (4x cigarette)

Short-term exposure:

Bronchodilation, reduction in breathlessness

Long-term smoking:

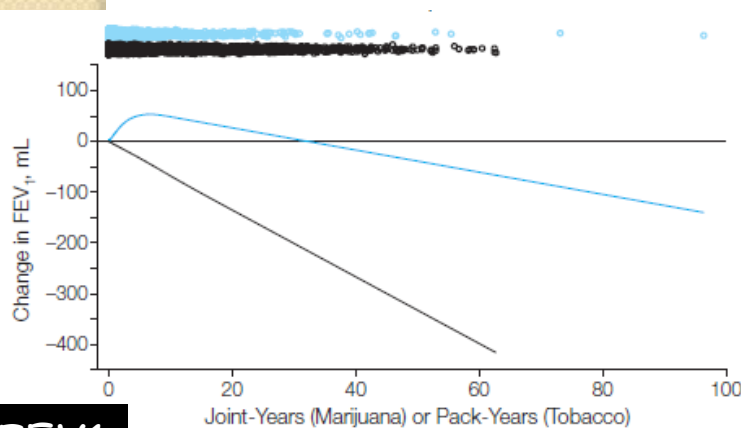
Symptoms suggestive of obstructive lung

Chronic cough and sputum production

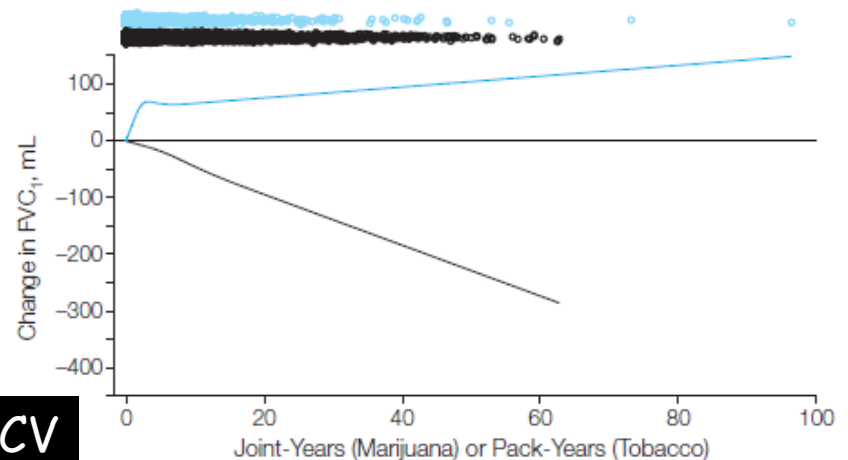
Association between marijuana exposure and pulmonary function over 20 years

In contrast to tobacco exposure, association between marijuana exposure and pulmonary function is nonlinear ($p < 0.001$):

- At low levels of exposure: Forced expiratory volume in the 1st second of expiration (FEV₁) increases by 13 mL/joint-year (95% CI, 6.4-20; $p < 0.001$) and Forced vital capacity (FVC) by 20 mL/joint-year (95% CI, 12-27; $p < 0.001$)
- At higher levels of exposure: these associations level or reverse.



FEV₁



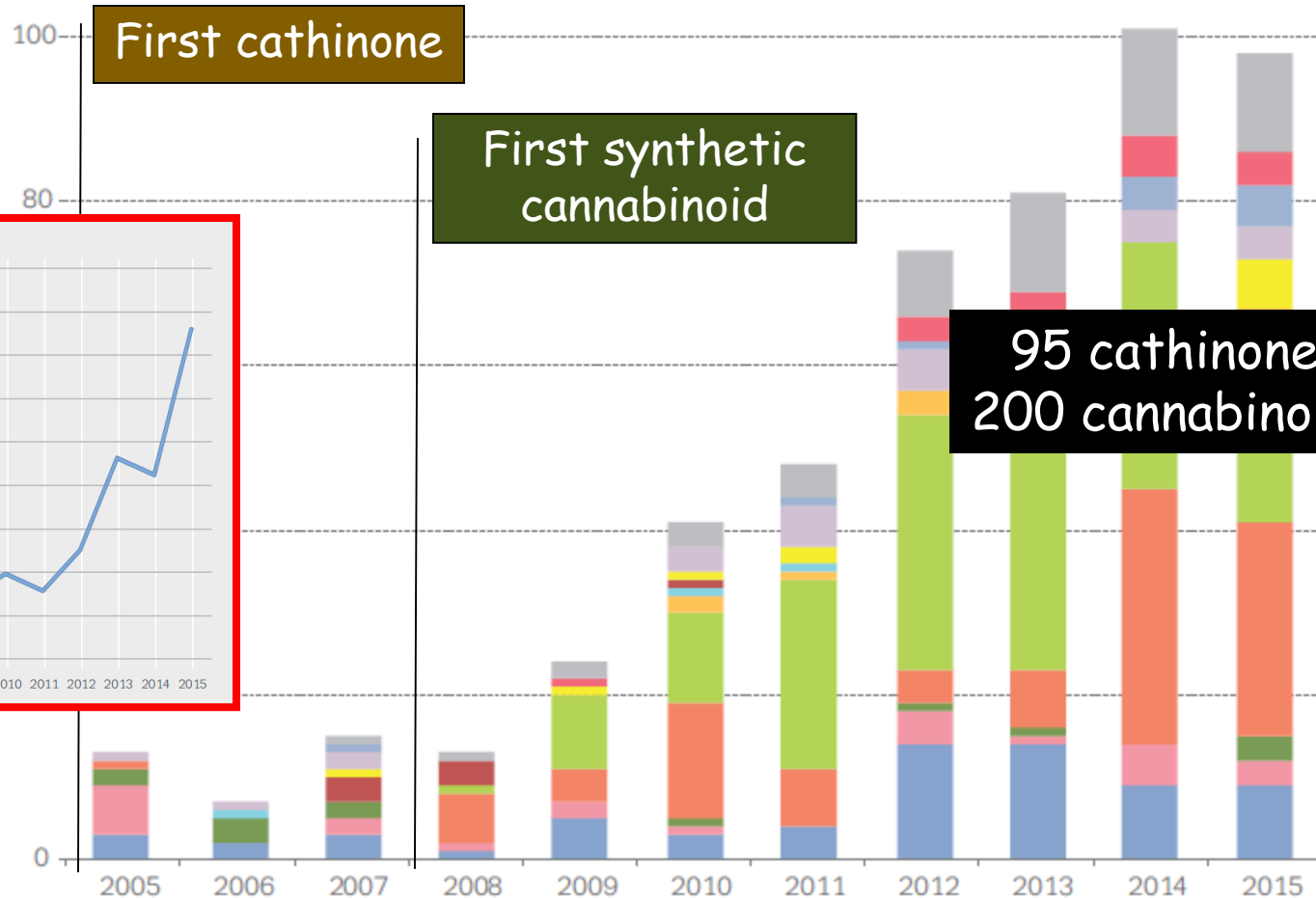
FVC

Pletcher MJ. JAMA 2012



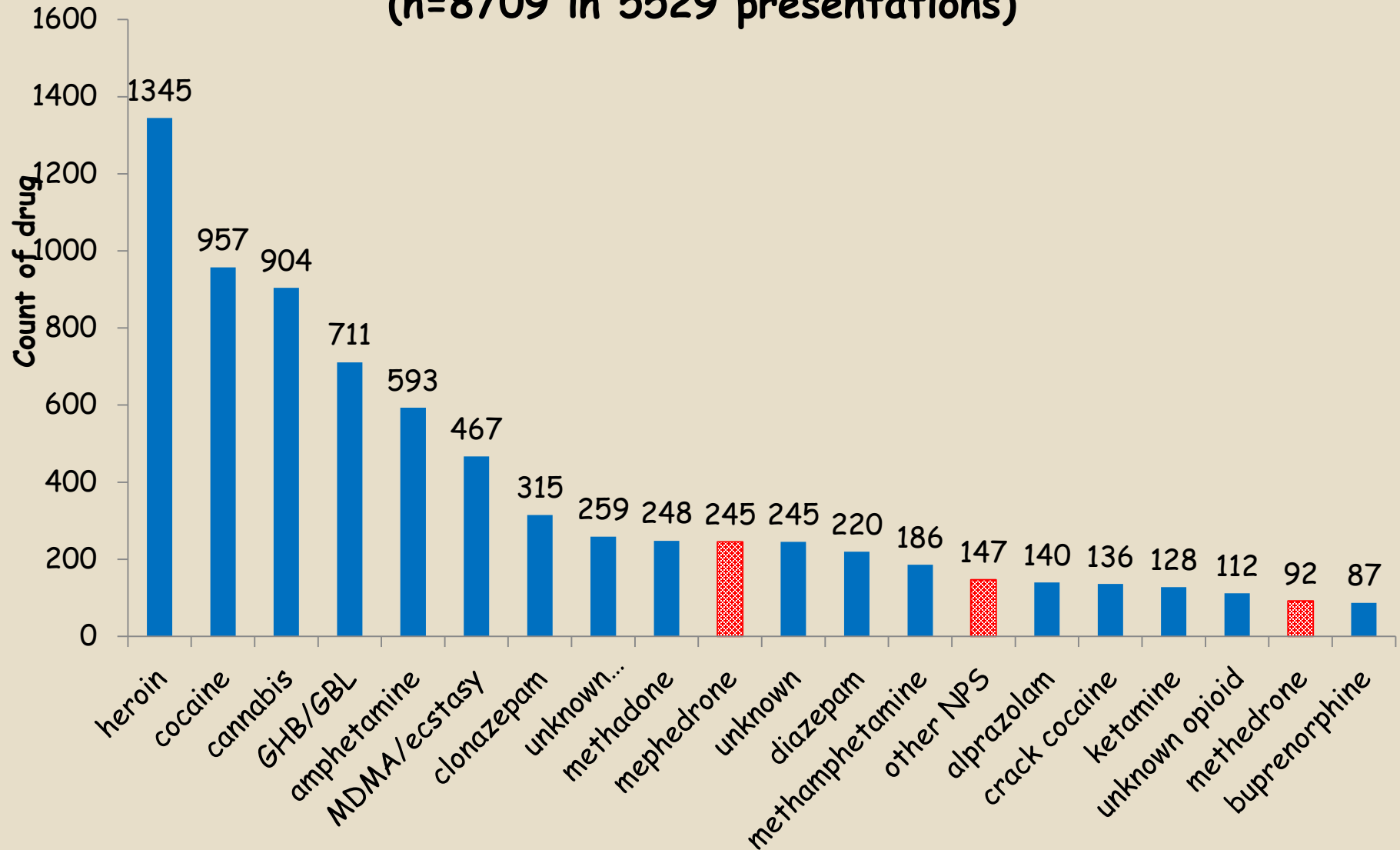
NPS notified to the EU Early Warning System

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



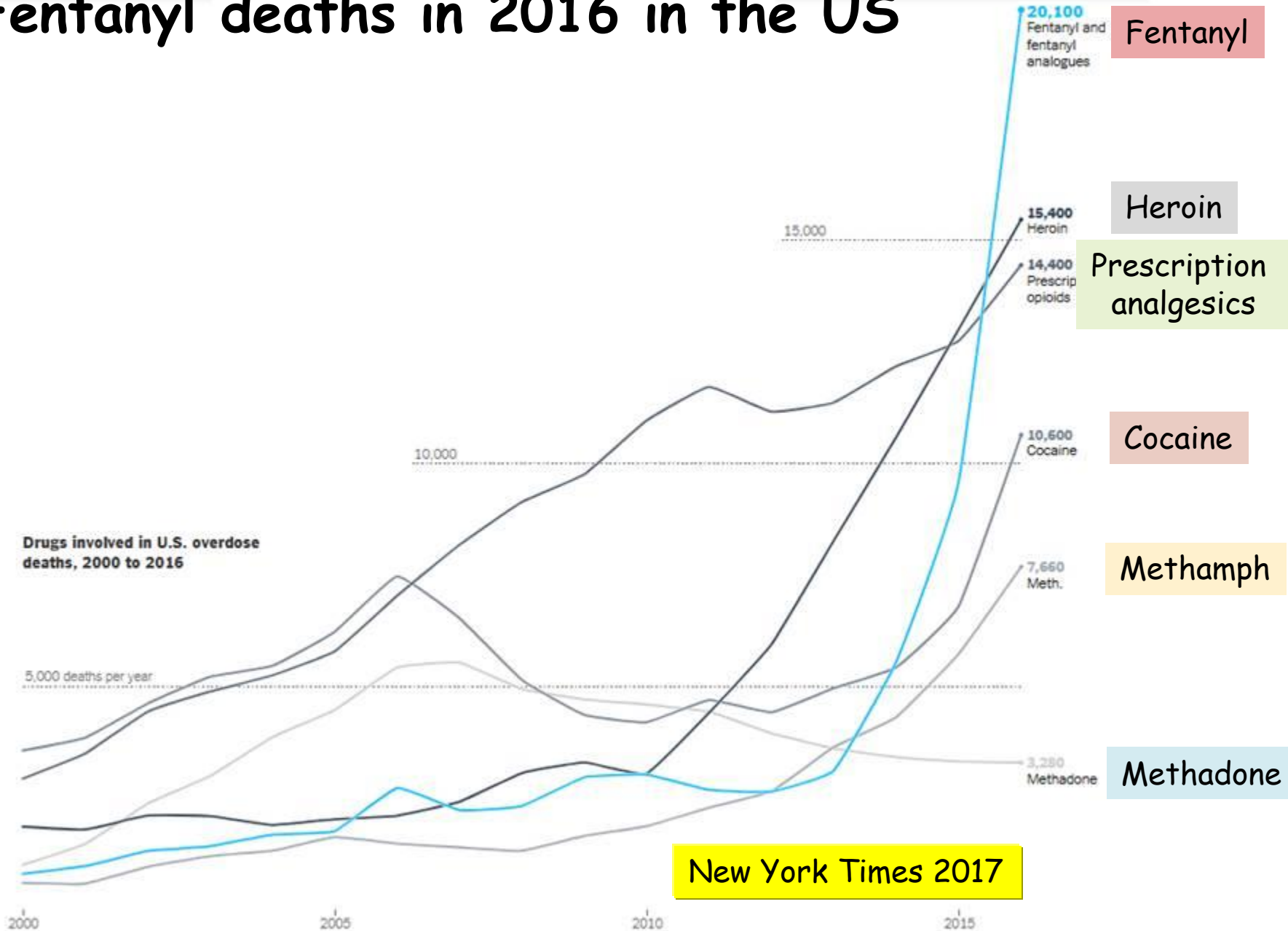
Top 20 most commonly reported drugs in the ED in Europe

(n=8709 in 5529 presentations)



EuroDEN, unpublished data

Fentanyl deaths in 2016 in the US



PCC report of cathinone toxicity

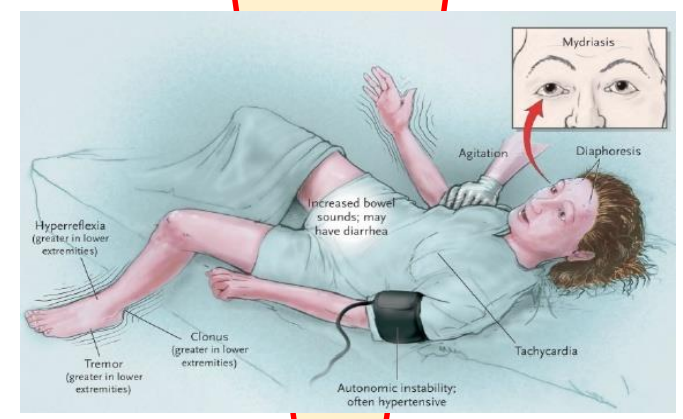


N= 236

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	

Adrenergic symptoms/signs

Encephalopathy features



Serotonergic signs

Organ dysfunction

Synthetic cannabinoids related clinical toxicity

First generation:

nausea/vomiting,
occasional seizures

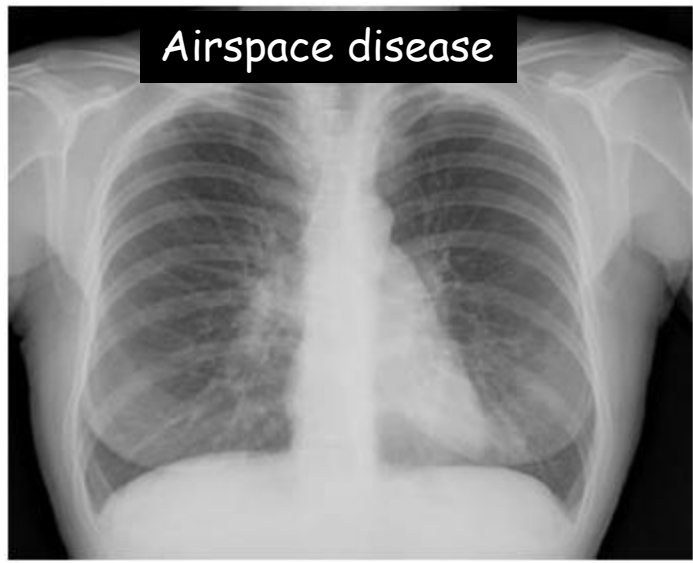
More recent generation:

seizures,
cardiotoxicity,
sympathomimetic syndrome
serotonergic syndrome
Cardiovascular events
Stroke

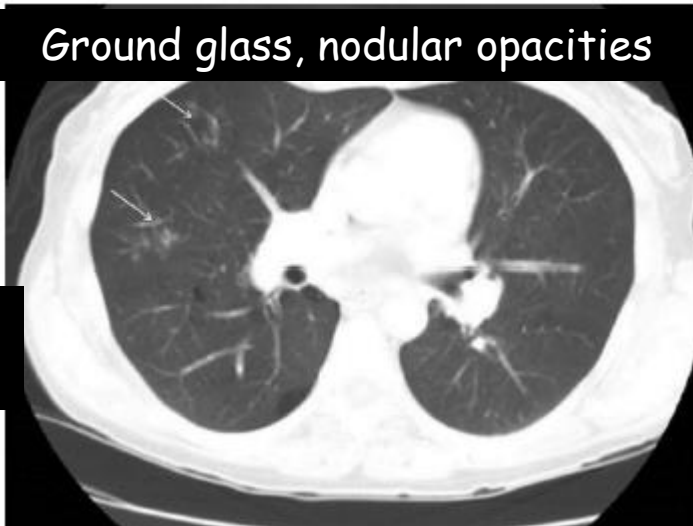
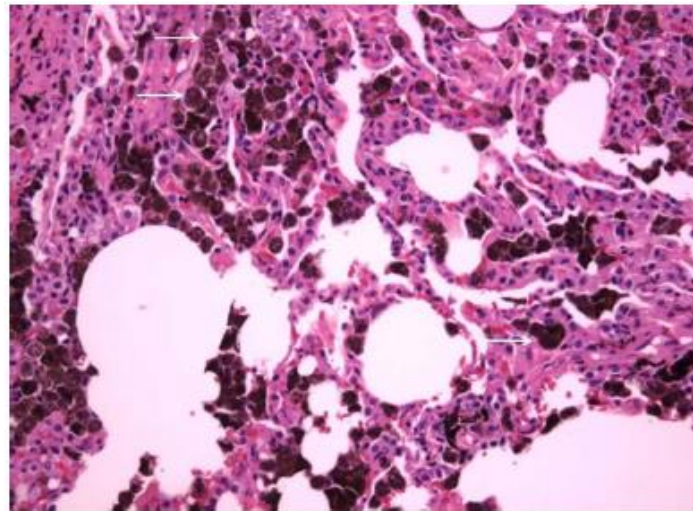
Nervous system	Restlessness/agitation	41
	Changes of perception/ hallucination	38
	Vertigo	24
	Anxiousness/panic attack	21
	Somnolence	17
	Initial unconsciousness for up to 60 minutes, followed by somnolence for several hours	17
	Confusion/disorientation	14
	Anaesthesia/paraesthesia	10
	Anterograde amnesia	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
Gastrointestinal system	Dyspnoea	21
	Thoracic pain	10
	Nausea/vomiting	28
	Dry mouth/globus sensation	14
	Excessive thirst	7
Eyes	Diarrhoea	7
	Mydriasis	38
	Conjunctival hyperaemia	14
Laboratory results	Hypokalaemia	28
	Elevation of creatine kinase	14
	Elevation of blood glucose	31

Synthetic cannabinoids as a cause for black carbonaceous BAL

Chronic cannabinoid user, fever, productive yellow sputum, bilateral rhonchi and wheezes



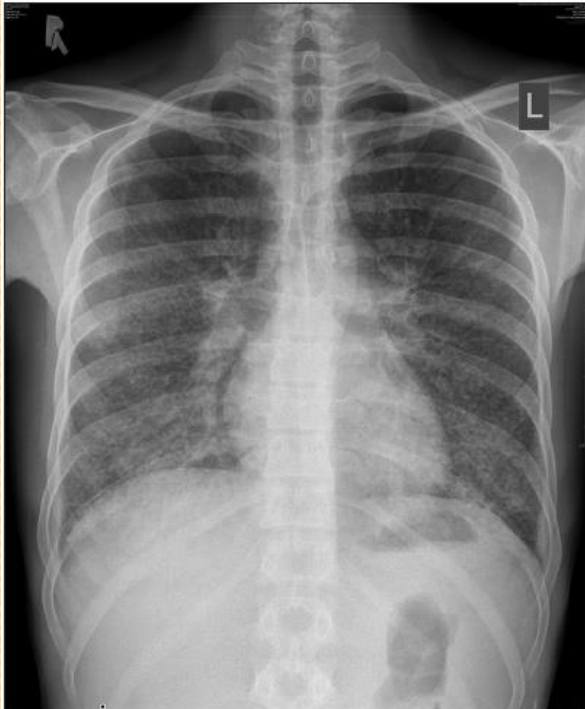
Browning-dark pigmented Mph
type II pneumocyte hypertrophy
Minimal fibrosis



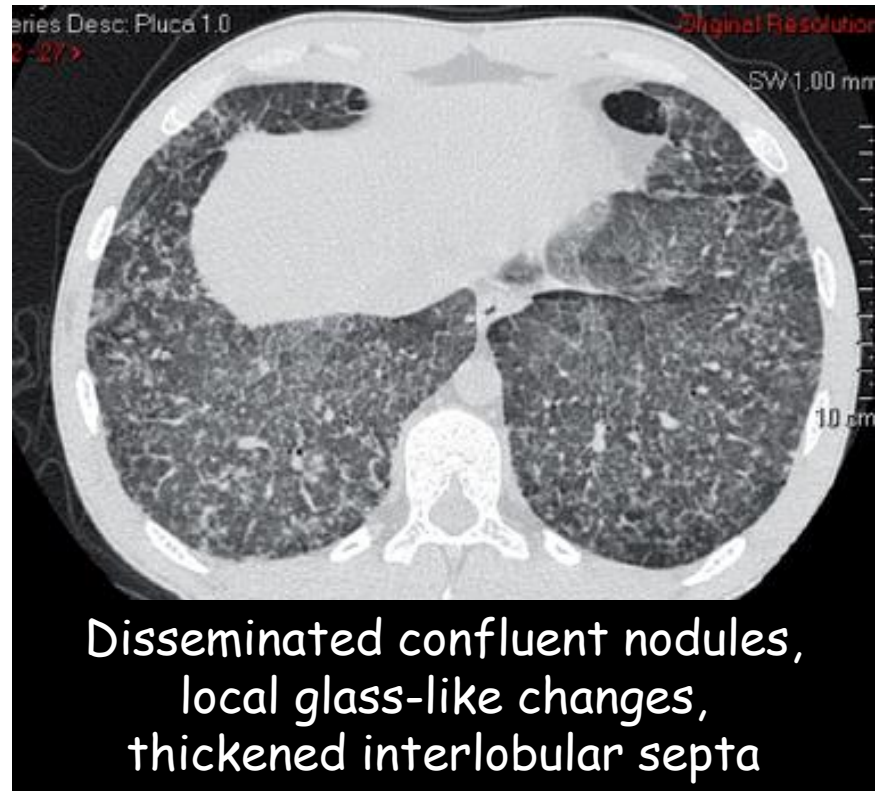
Dark soot-coloured fluid
(inhaled impurities)

Toxic Lung Injury in a Patient Addicted to "Legal Highs"

Smoker of artificial hashish for 6 months tachypnea, cyanosis, SpO₂ 70%, increased catarrh (lasting for 6 months) and cough (lasting 4 months)



Diffuse confluent interstitial

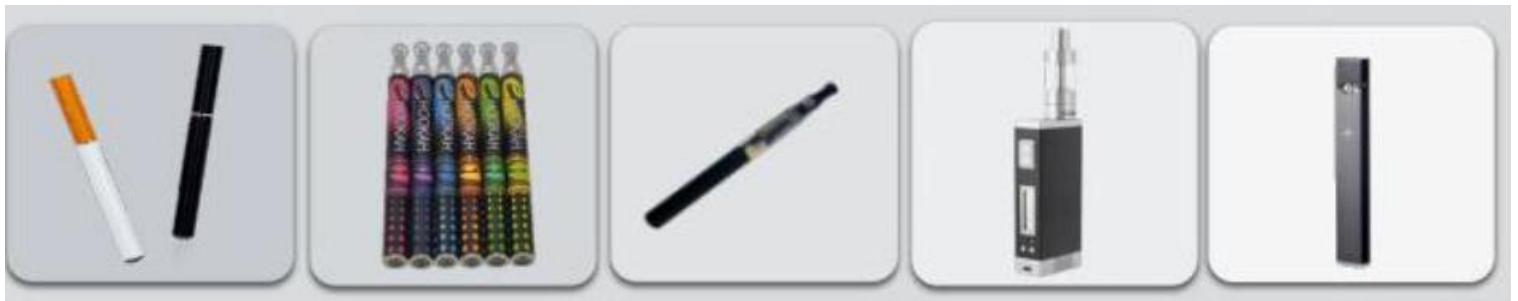


Disseminated confluent nodules,
local glass-like changes,
thickened interlobular septa

Histopathology: organizing pneumonia with lipid bodies in the organizing lesions, most likely caused by inhaling irritants



E-cigarette and vaping attributed lung injury



E-cigarette products: liquids, cartridges, pods

E-cigarette liquid can contain

- Nicotine
- Flavorings
- Propylene glycol and vegetable glycerin used in varying proportions as carriers
- Cannabinoids: Δ -9-tetrahydrocannabinol (THC), cannabidiol (CBD), butane hash oil (BHO)
- Other substances: Heavy metals (e.g., lead, nickel, tin), volatile organic compounds, ultrafine particles, cancer-causing chemicals

E-cigarette liquid types

- Commercial refillable e-liquid
- Commercial non-refillable e-liquid
- Homemade or street sources



CDC Confirmed Case Definition (September 18, 2019)

Using an e-cigarette ("vaping") in 90 days prior to symptom onset

AND

Pulmonary infiltrate (opacities on X-ray or ground-glass opacities on CT)

AND

Absence of pulmonary infection on initial work-up. **Minimum criteria** are

A negative respiratory viral panel *and*

A negative influenza PCR or rapid test;

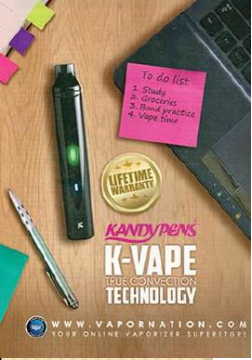
AND

All other clinically-indicated respiratory testing (e.g., urine Antigen for *S pneumoniae* and *Legionella*, sputum culture if productive cough, BAL culture if done, blood culture, HIV-related opportunistic respiratory infections if appropriate) are negative

AND

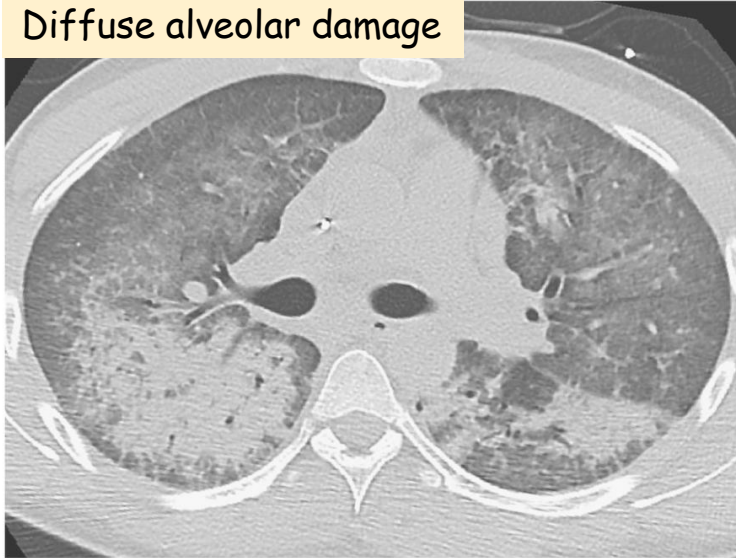
No evidence of alternative plausible diagnoses

Layden J. NEJM 2019

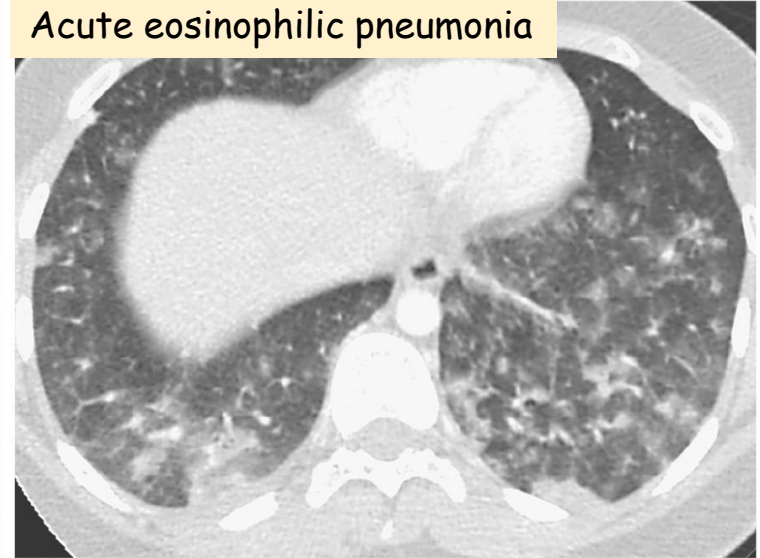


Imaging of vaping-associated lung disease

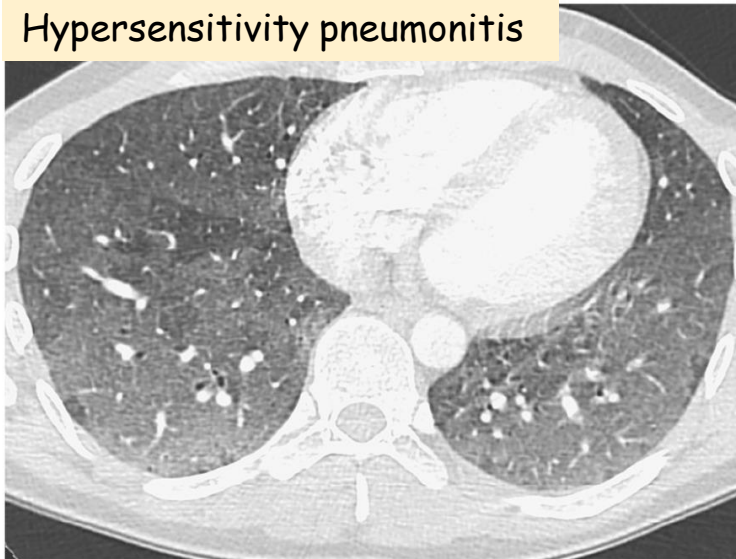
Diffuse alveolar damage



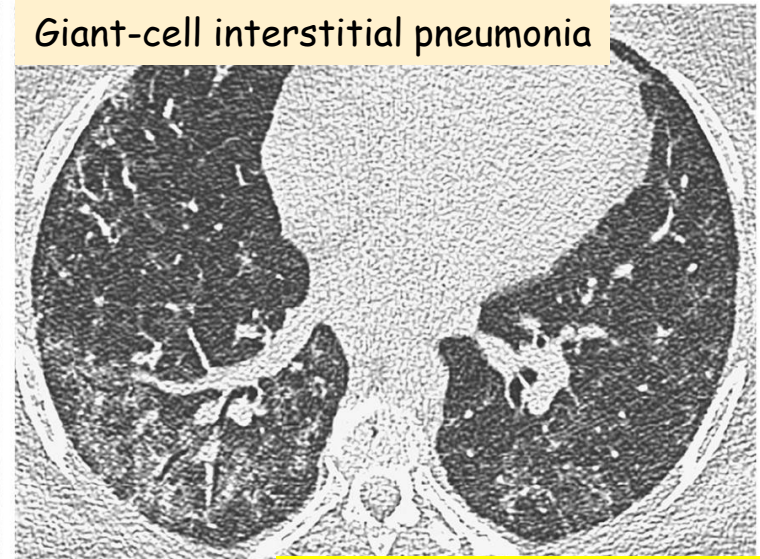
Acute eosinophilic pneumonia



Hypersensitivity pneumonitis



Giant-cell interstitial pneumonia



Spectrum of clinical and pathologic diagnoses

Acute lung injury and adult respiratory distress syndrome (ARDS)

Diffuse alveolar damage

Lipoid pneumonia

Acute necrotizing pneumonitis

Organizing pneumonia with lipid-laden macrophages

Non-specific inflammation

Hypersensitivity pneumonitis

Eosinophilic pneumonia

→ lipid-staining (e.g., Oil Red O, Sudan Black) on fresh tissues and bronchoalveolar lavage fluid

Outcomes

- Gradual onset of various symptoms over days to weeks

Respiratory (cough, chest pain, shortness of breath)

Gastrointestinal (abdominal pain, nausea, vomiting, diarrhea)

Systemic symptoms (fatigue, fever, weight loss)

GI symptoms sometimes precede respiratory symptoms

- Acute hypoxemic respiratory failure requiring $O_2 \pm$ ventilatory support (mechanical ventilation or ECMO)

- Patients who did not respond to antibiotics alone tended to respond to systemic corticosteroids

- Most patients were young and healthy pre-illness

- Some patients who did not recover to pre-illness pulmonary function at time of discharge, demonstrated improvement during post-hospitalization

- Some patients had reduced post-hospitalization pulmonary function

- Some patients died in the hospital

EVALI cases and deaths reported to CDC

48 EVALI deaths

Median age: 52 years (17-75)

Outbreak may have peaked around September 15

2,291 hospitalized EVALI cases

67% male

Median age: 24 years (13-77); 78% <35 years

Complete information on substances used in e-cigarette in the three months prior to symptom onset (N= 1,782)

80% use THC-containing products (35% exclusive use)

54% use nicotine-containing products (13% exclusive use)

12% use CBD-containing products (1% exclusive use)

40% use both THC- and nicotine-containing product use

5% no use THC-, nicotine-, or CBD-containing product use

The most commonly reported product brand included Dank vapes (56%), TKO (15%), Smart Cart (13%), and Rove (12%).

Regional difference in THC-containing product use were noted.

Conclusions

- Opioids rarely produce pulmonary edema. Mechanisms are multifactor. Naloxone likely represents a negligible risk for lung toxicity
- Cocaine can produce acute lung toxicity by indirect (cardiogenic edema) or direct effects (crack lung)
- Despite larger use, rare studies have investigated marijuana-related effects on lung: If not massive, it may be good (bronchodilatation) ! However, delayed risks of cancer and immunocompromise are worrying!
- Data regarding respiratory toxicity of the NPS are limited.
- The recent EVALI cases and deaths question the e-cigarette safety