CREUF 2023

30 & 31 Mars 2023
MULHOUSE ● ALSACE

Opioids: from respiratory depression to the worldwide overdose epidemic

Bruno Mégarbane, MD, PhD

Department of Medical and Toxicological Critical Care, Lariboisière Hospital, INSERM UMRS-1144, Paris Cité University, Paris, France

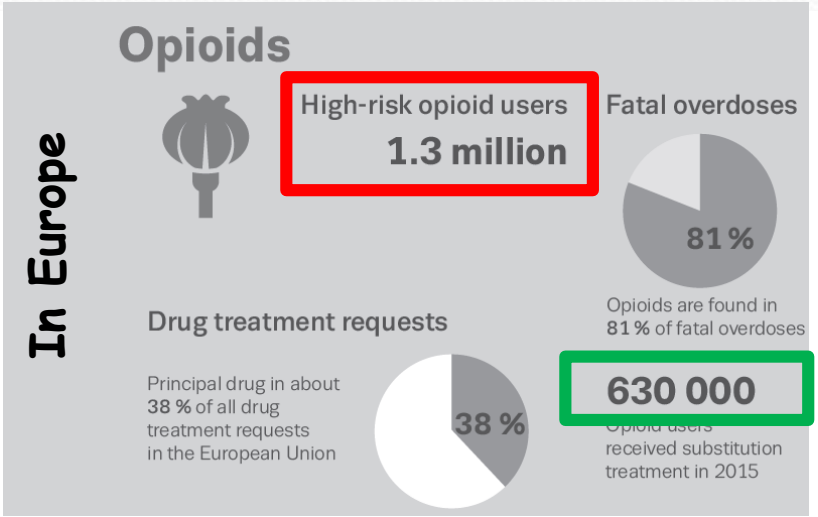
bruno.megarbane@lrb.aphp.fr

CREUF

Collège de réanimation des hôpitaux extra-universitaires de France

No conflict of interest to declare

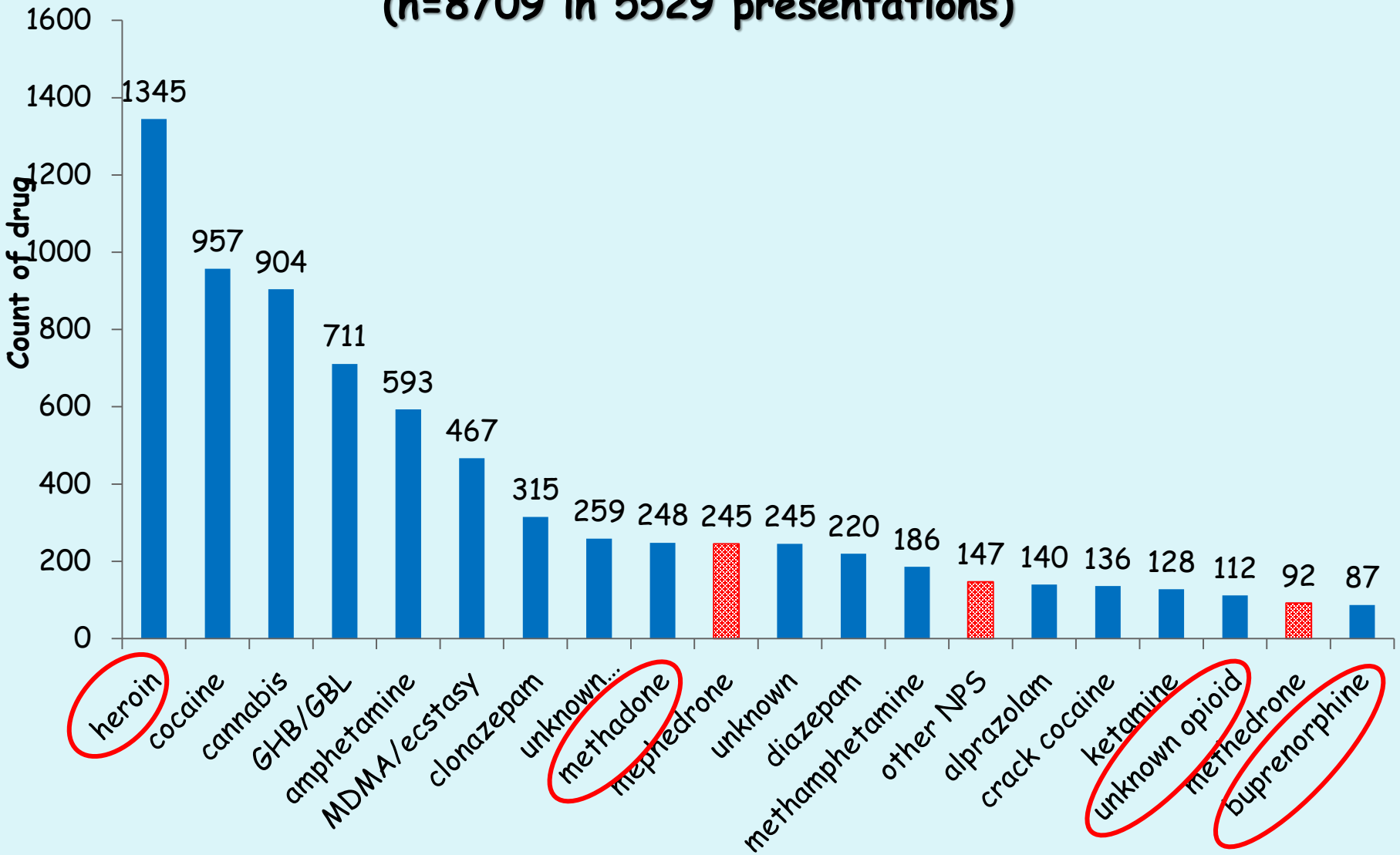
Opioids : the first cause of toxic death



Jones CM. JAMA 2013

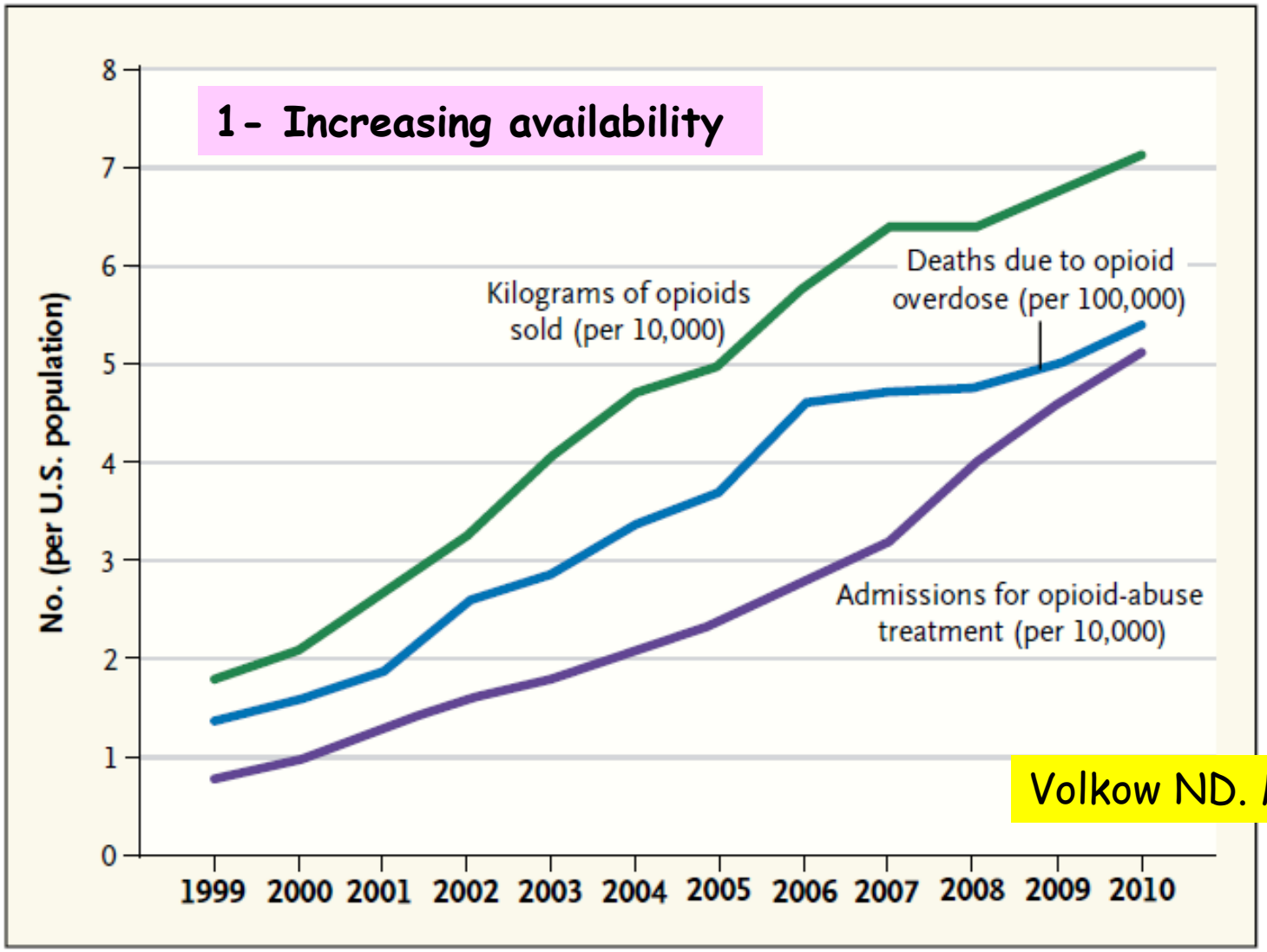
Top 20 most commonly reported drugs in the ED in Europe

(n=8709 in 5529 presentations)



EuroDEN, Clin Tox 2015

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



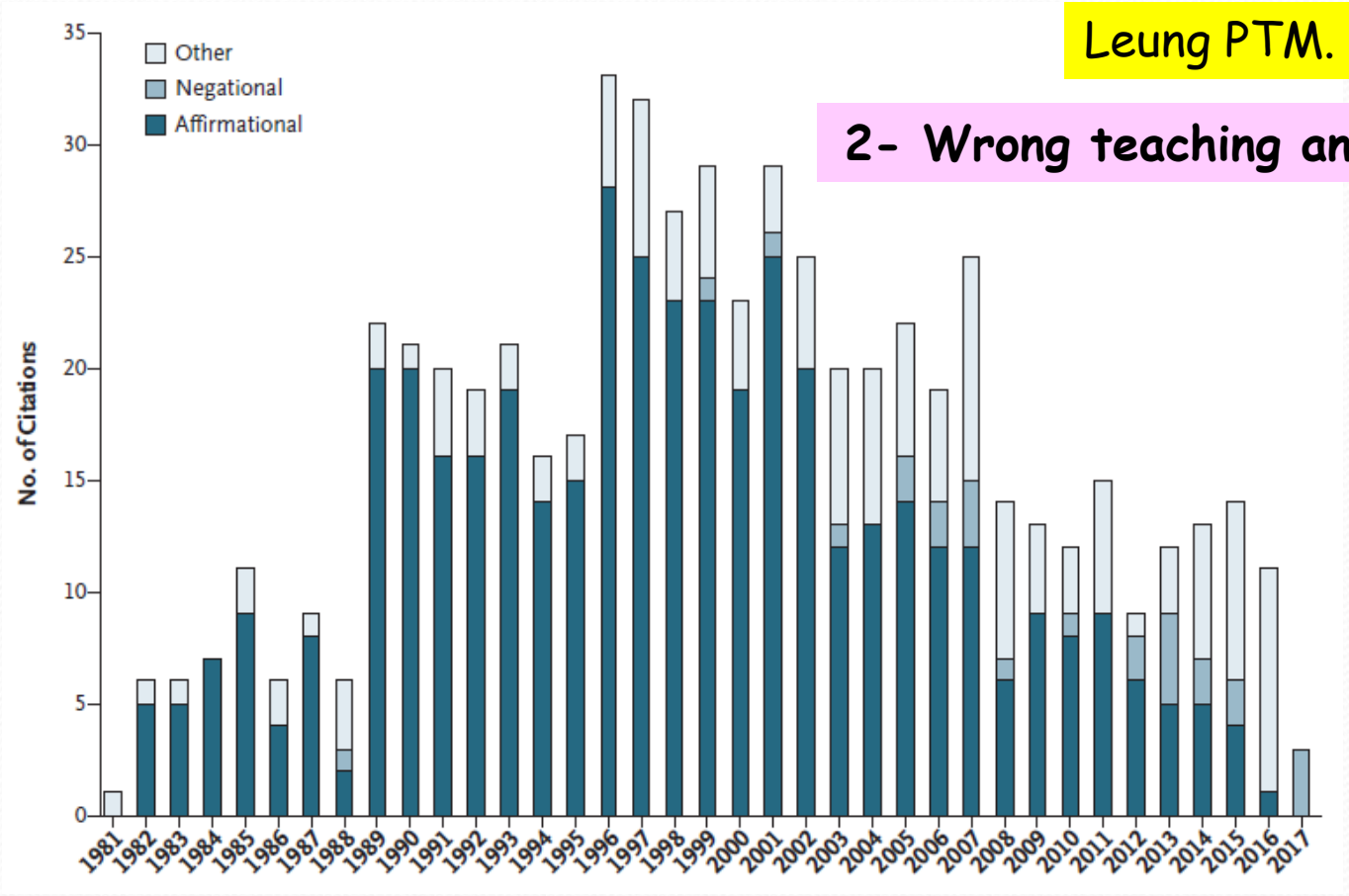
Volkow ND. *NEJM* 2014

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

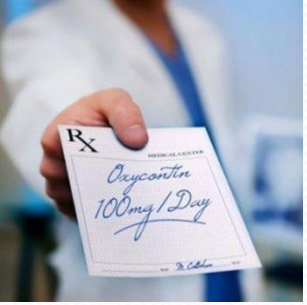
A 5-sentence letter published in the NEJM in 1980 was uncritically cited as evidence that addiction was rare with long-term opioid therapy [439/608 (72%)]

Leung PTM. NEJM 2017

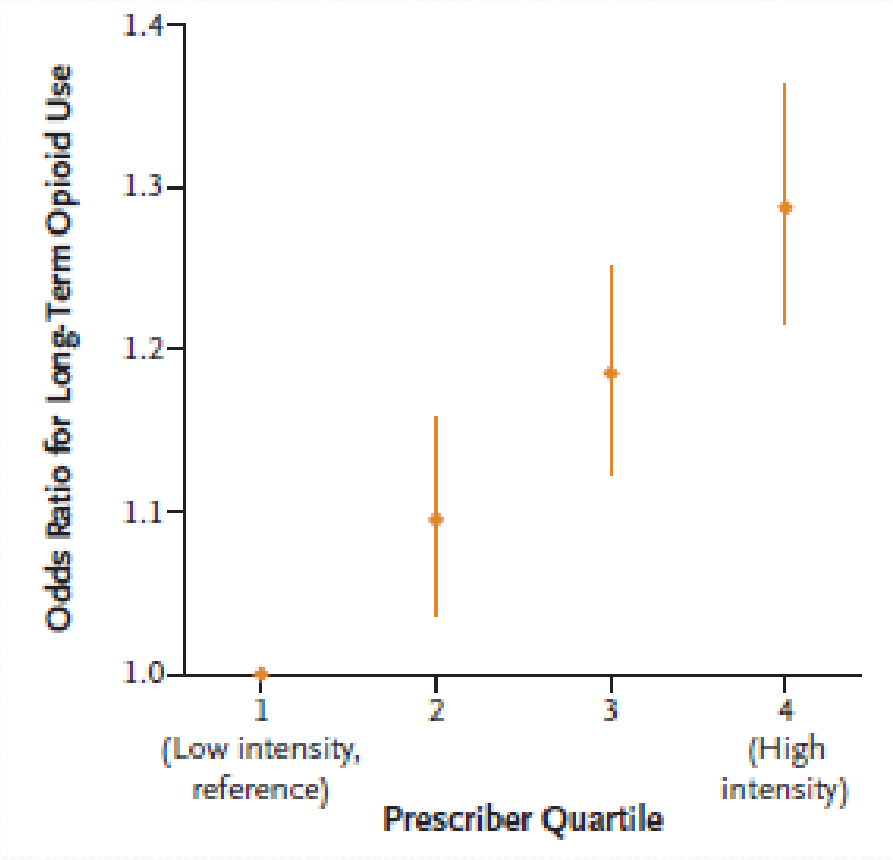
2- Wrong teaching and knowledge



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



Opioid-prescribing patterns of emergency physicians and risk of long-term use



- Rates of opioid prescribing varies widely between low-intensity and high-intensity prescribers (7.3% vs. 24.1%).

- Long-term opioid use is higher among patients treated by high-intensity prescribers than among patients treated by low-intensity prescribers (adjusted OR, 1.30 [1.23 to 1.37]; P<0.001)

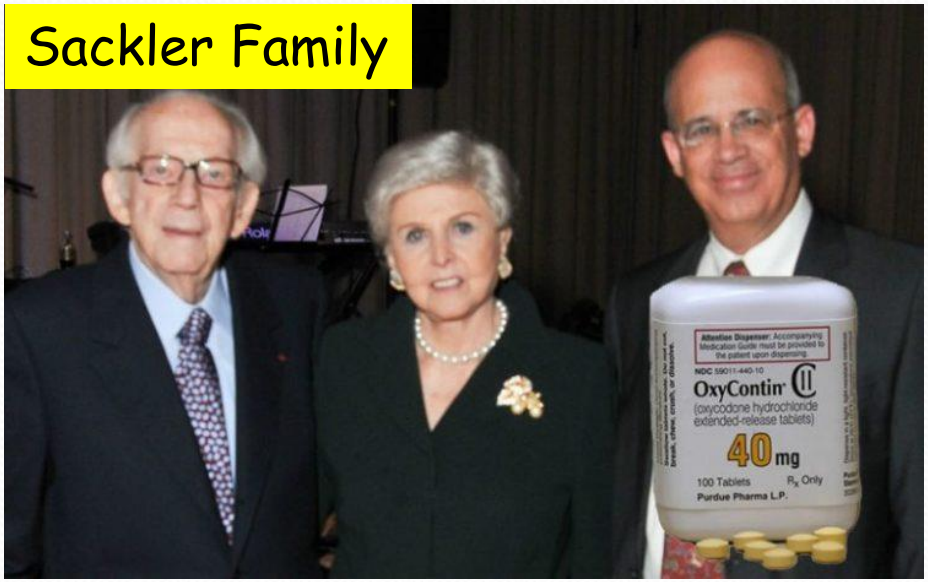
3- Inadequate prescriptions

Barnett ML. NEJM 2017

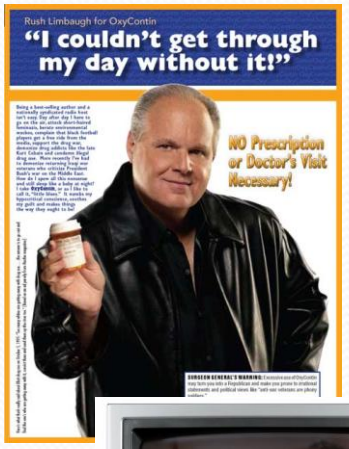
4- Guilty Big pharma

The role of Big Pharma: Accused of causing ½ million deaths

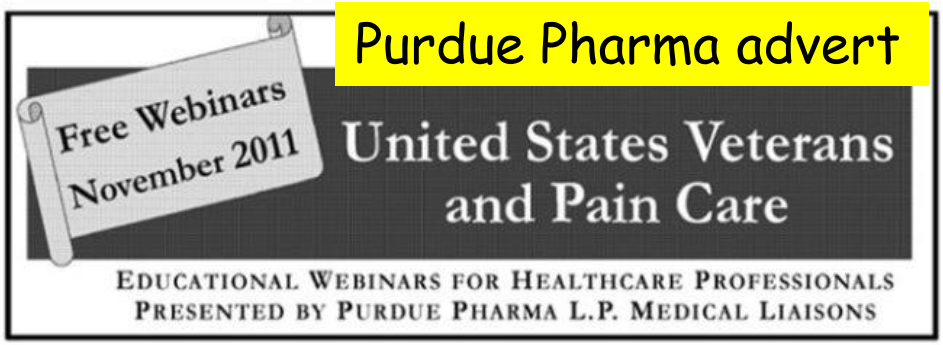
Sackler Family



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

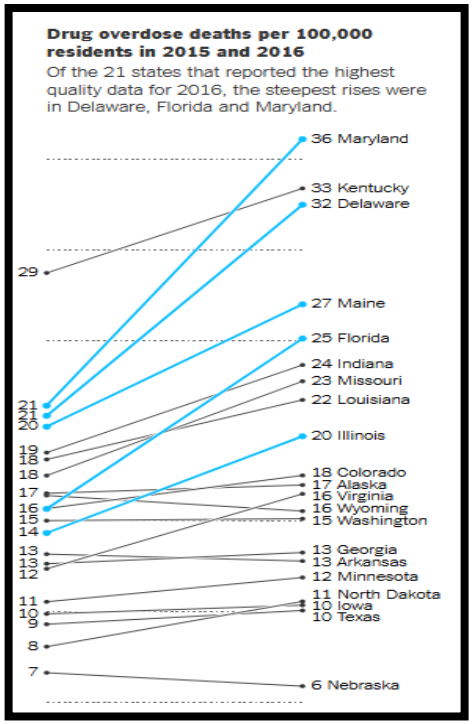


Purdue Pharma advert



Opioid-related deaths in the US (2000-2022)

~ 64,000 deaths / year



Fentanyl

Heroin

Prescription analgesics

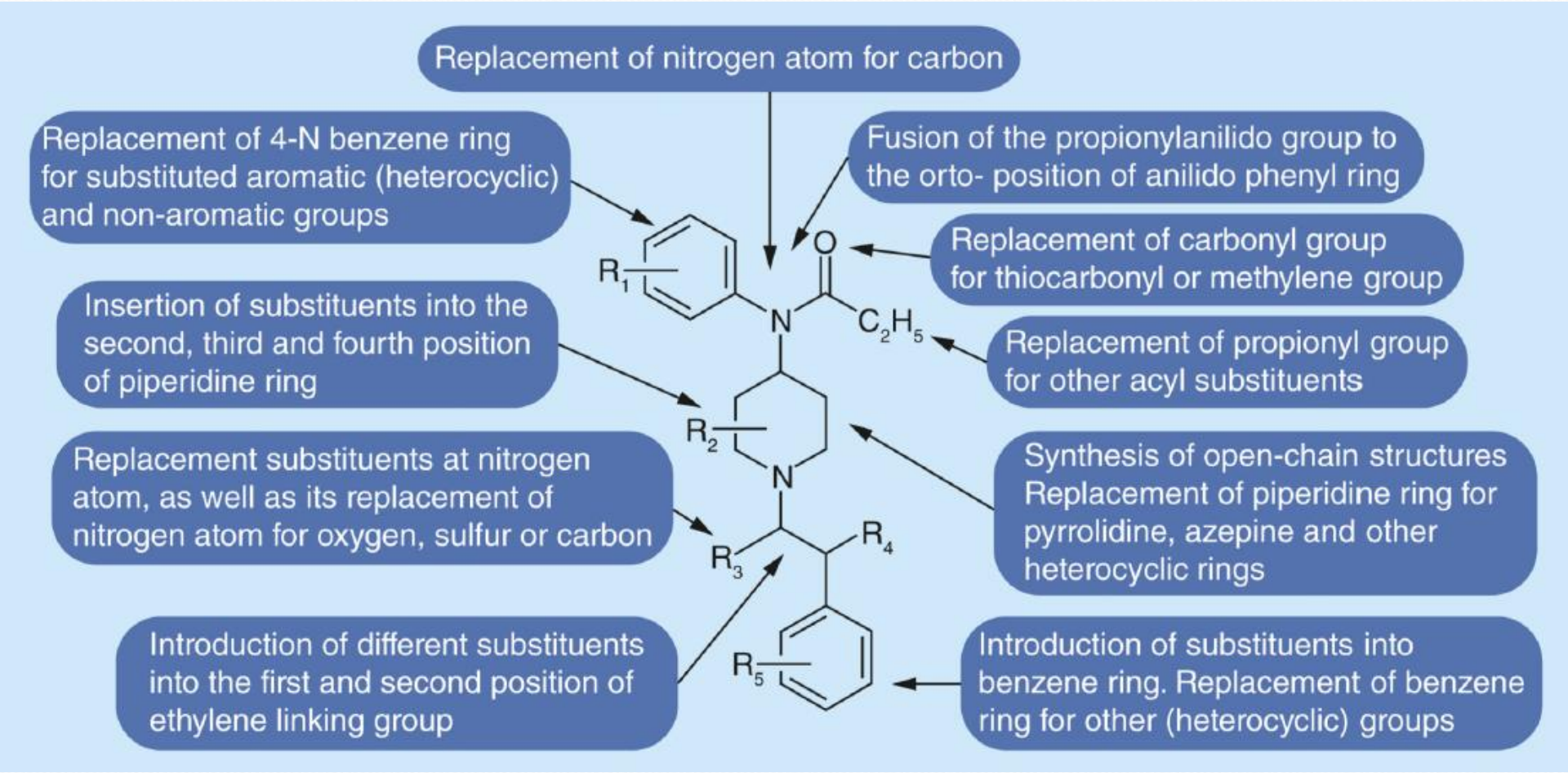
Cocaine

Methamph

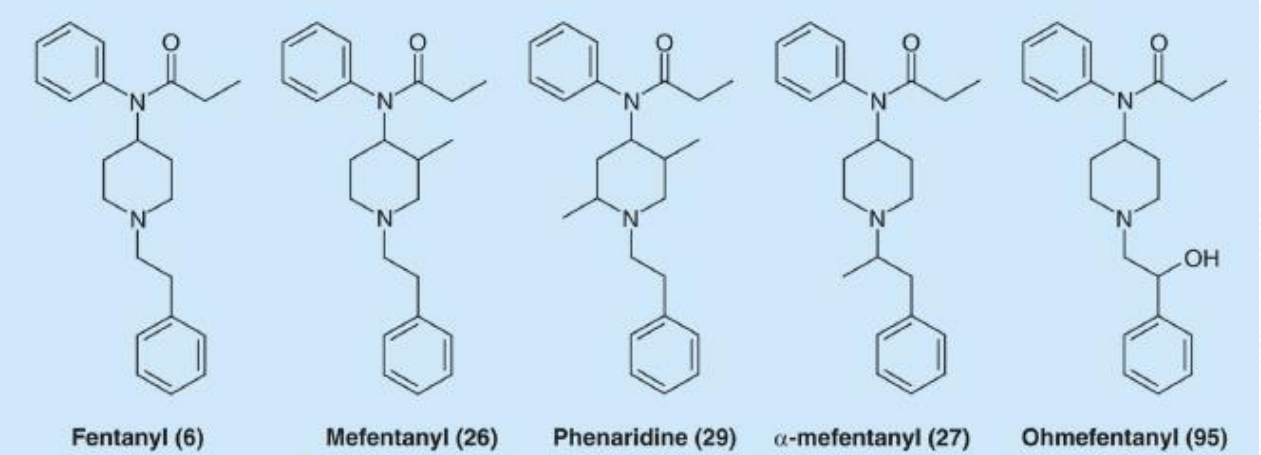
Methadone

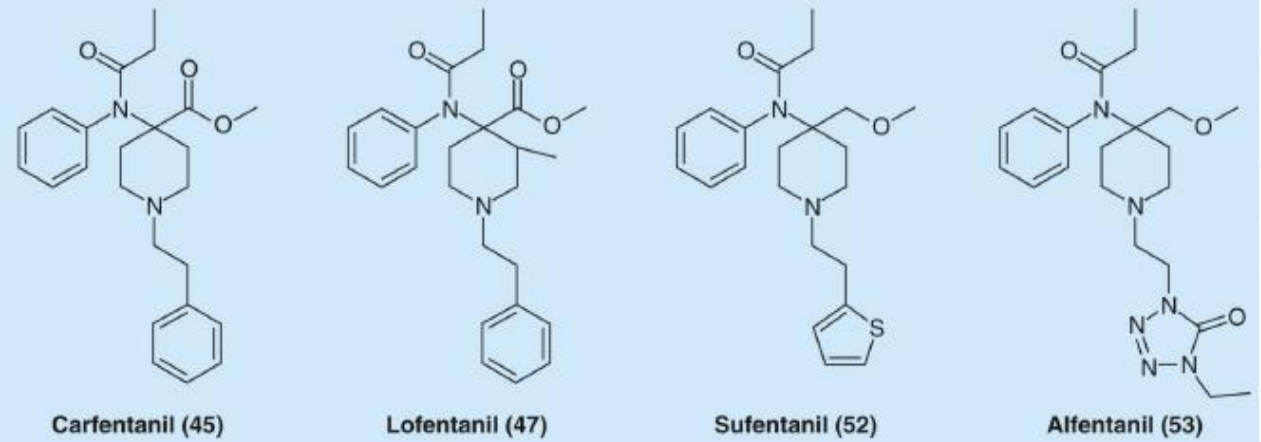
New York Times 2017

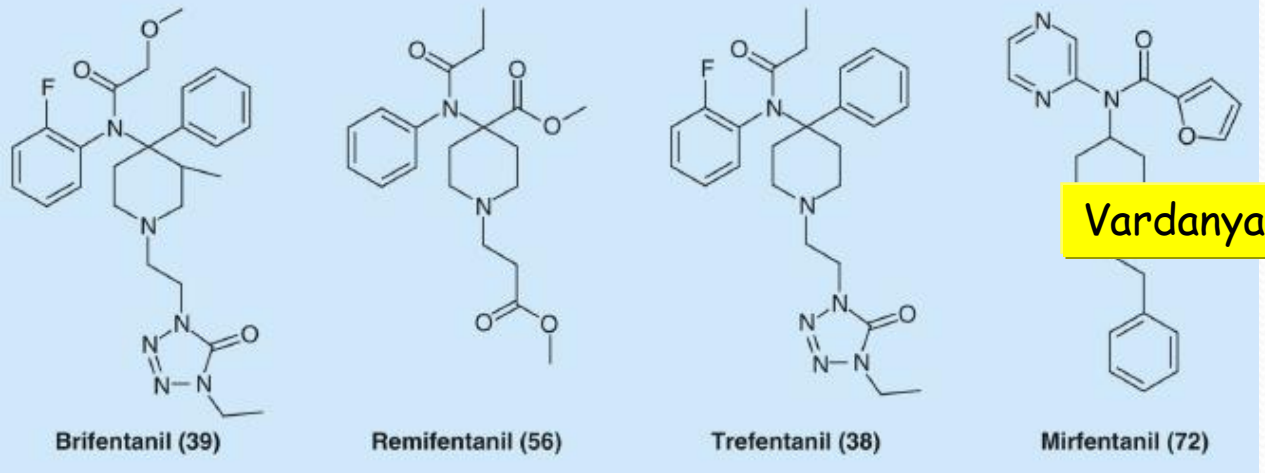
Chemistry of fentanyl derivatives



Fentanyl derivatives







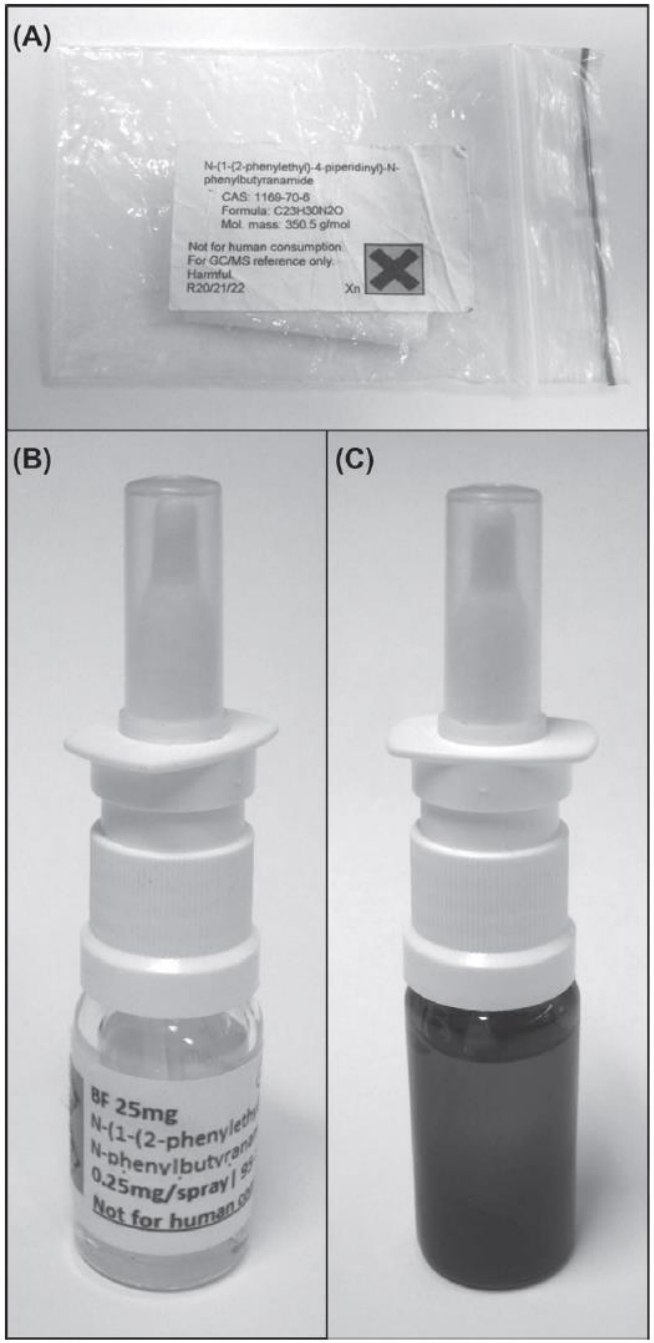
Potent structural analogues of fentanyl, originally synthesized as pharmaceuticals candidates became drugs of abuse

Vardanyan RS. *Future Med Chem* 2014

srlf
SOCIÉTÉ DE RÉANIMATION DE LANGUE FRANÇAISE

Presentation of illicitly produced designer fentanyls

25 mg butyrfentanyl labeled bottles, each spray yields 0.25 mg and the content is sufficient for 95-105 puffs.



The usual presentation of opioid overdose

All opioids produce a similar toxidrome in excessive dosing.

SpO_2 and RR are surrogate indicators of ventilatory drive but provide limited information on drug-related effects on ventilatory control

$PaCO_2$ and V_M are direct measures of ventilation but difficult to assess continuously

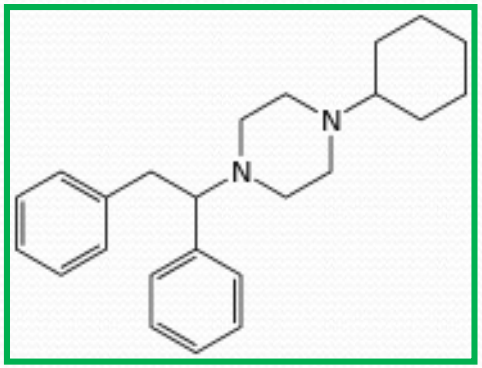
Intoxications involving acrylfentanyl – the Swedish STRIDA project –

Clinical features at any time during admission	All cases ($N = 11$)
CNS depression (RLS $\geq$2, GCS $\leq$14, not graded)	10
Tachycardia (BPM $\geq$100)	10
Miotic pupils	8
Respiratory depression (RR $\leq$10, SO_2 $\leq$90%)	8
Hypertension (systolic blood pressure $\geq$140 mmHg)	5
Unconsciousness (RLS $\geq$4, GCS $\leq$5)	6
Renal insufficiency (P-creatinine $\geq$100 µmol/L)	3
Apnea	3
Agitation	2

Efficiency of naloxone when used

Helander A. *Clin Tox* 2017

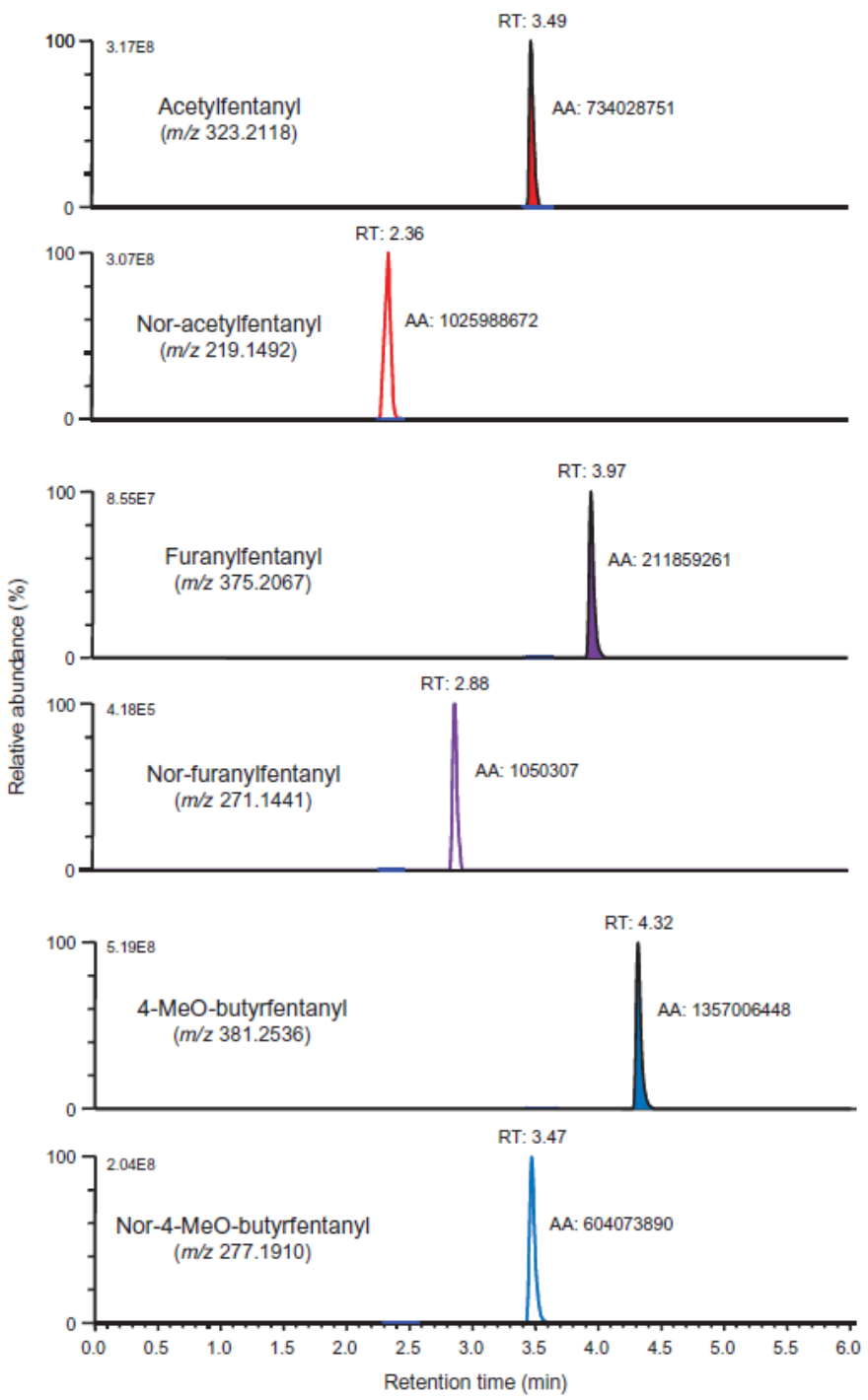
Acute skin and hair symptoms followed by severe, delayed eye complications in subjects using the synthetic opioid MT-45



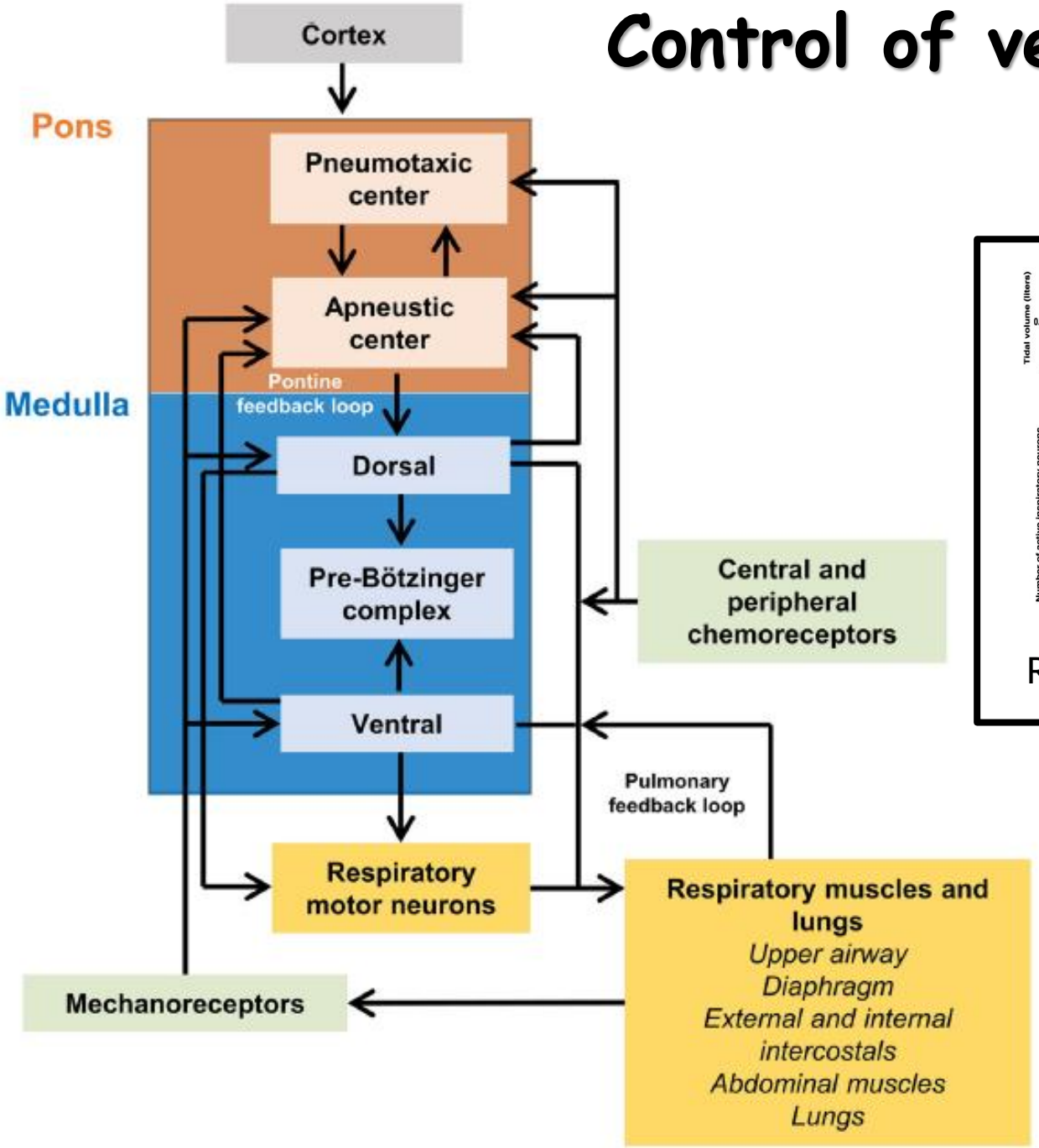
Widespread folliculitis and dermatitis

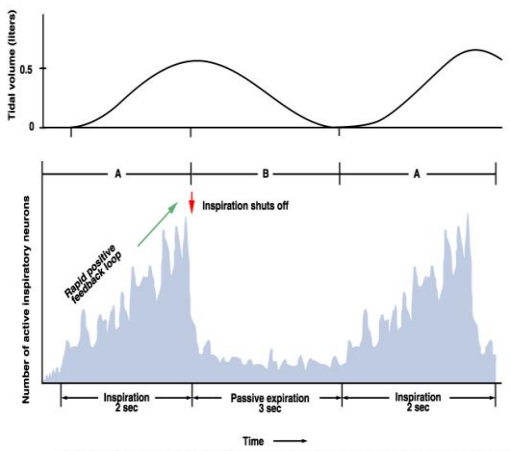
Helander A. *Br J Dermatol* 2016

Identification by analytical techniques combining liquid chromatography + mass spectrometry (LC–HRMS, LC–MS/MS, LC–HRMS/MS)



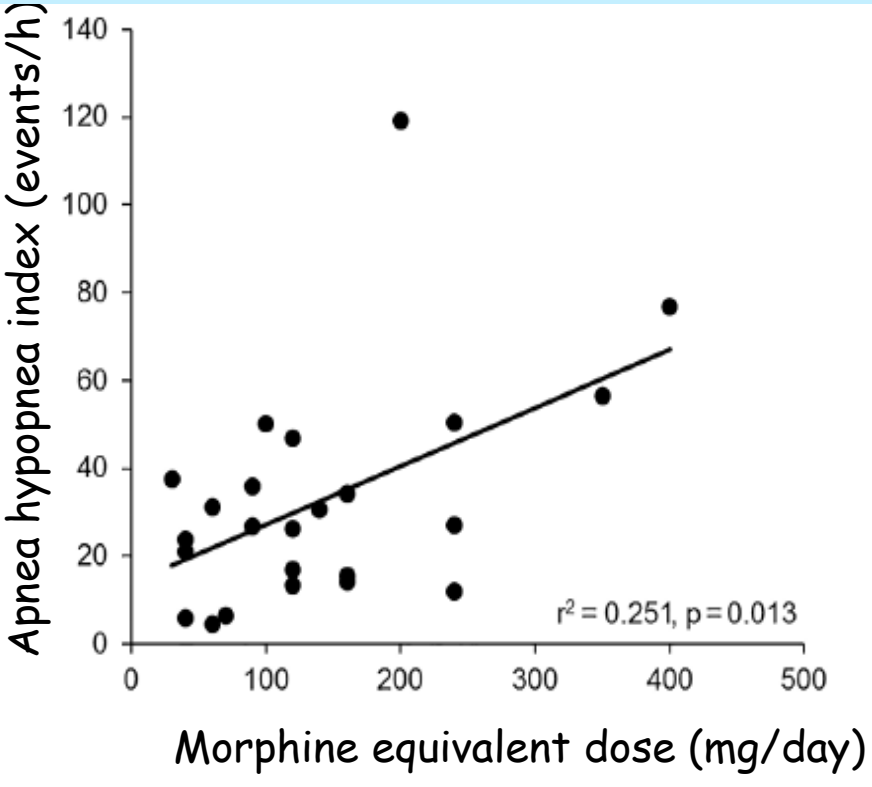
Control of ventilation





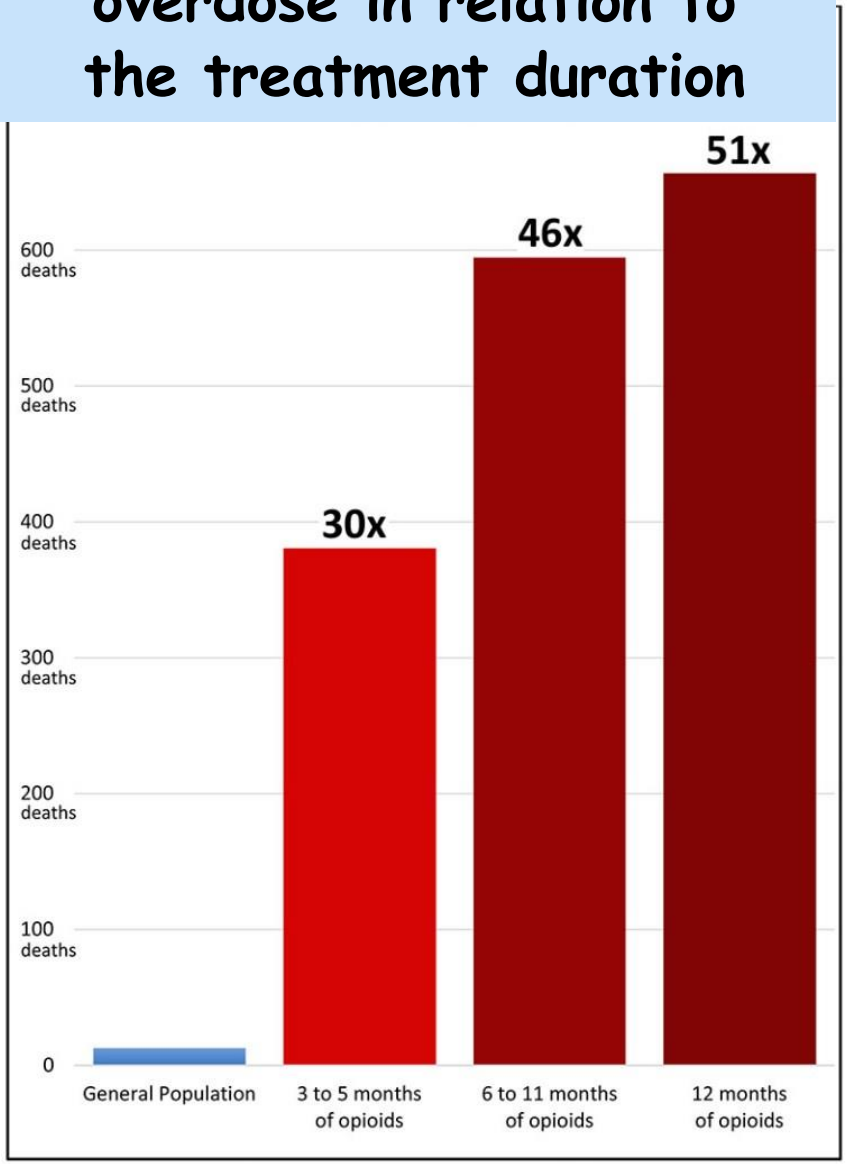
Recorded from DRG neurons

Sleep disordered breathing and chronic respiratory failure in patients with chronic pain on long-term opioid therapy



Rose AR. *J Clin Sleep Med* 2014

Risk of death from opioid overdose in relation to the treatment duration



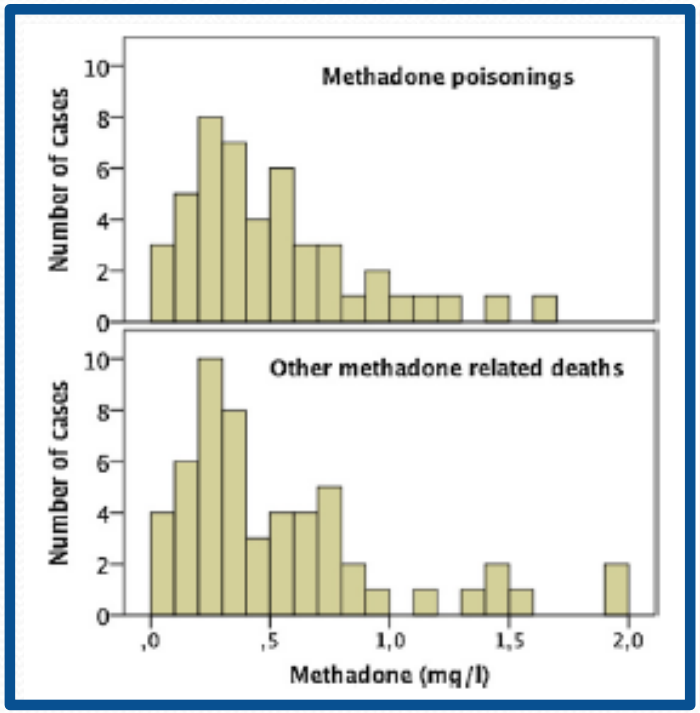
AGO graph from Massachusetts Department of Public Health data

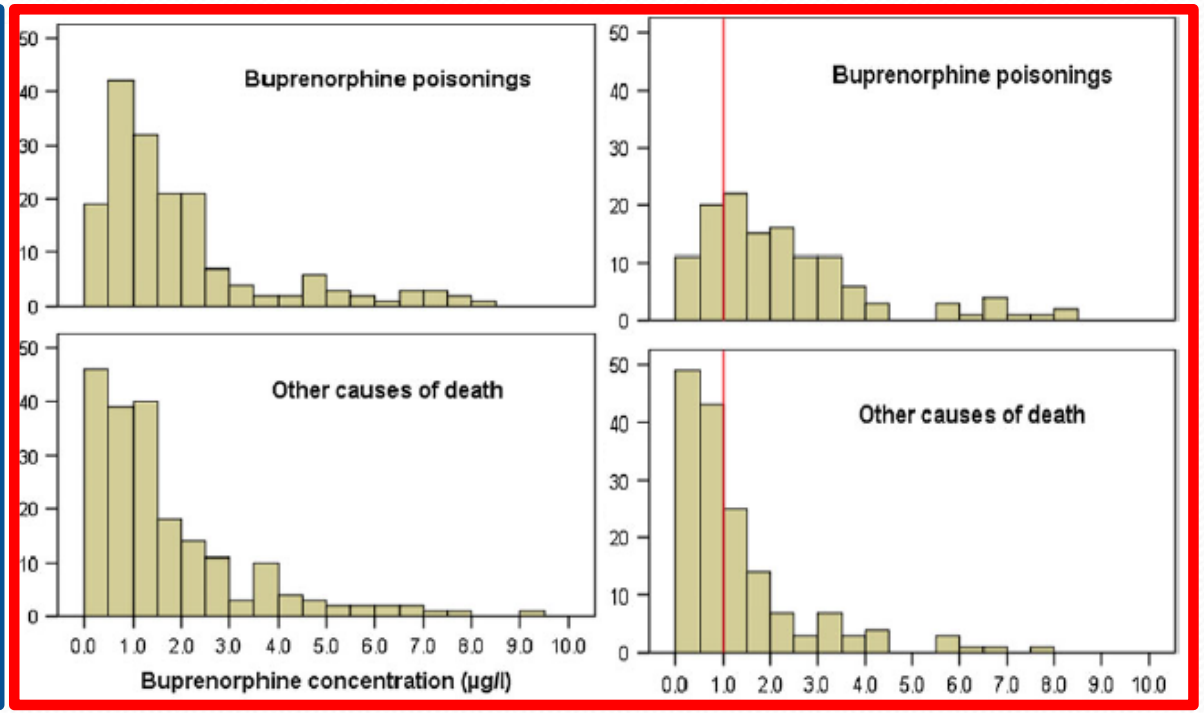
Risk factors for severe respiratory depression from prescription opioid overdose

Prescription opioid	*SRD rate (%)*	*RR (descending)*	*95% CI*
Tapentadol	2/2 (100)	27.0	3.9–185
Fentanyl	5/6 (83.3)	22.5	3.2–159
Oxymorphone	2/3 (66.7)	18.0	2.2–144
Methadone	59/116 (50.9)	13.7	2.0–95
Hydromorphone	4/9 (44.4)	12.0	1.5–94
Morphine	5/12 (41.7)	11.3	1.5–86
Oxycodone	40/124 (32.3)	8.7	1.3–60
Hydrocodone	9/31 (29.0)	7.8	1.0–58
Buprenorphine	2/7 (28.6)	7.7	0.8–73
Tramadol	3/12 (25.0)	6.8	0.8–58
Codeine	1/27 (3.7)	1.0 (ref)	–

Fox LM. *Addiction* 2018

Opioid-attributed death: role of the dose?





Methadone-related deaths

Buprenorphine-related deaths

Häkkinen M. *Forensic Sci Int* 2012

Häkkinen M. *Eur J Clin Pharmacol* 2011

Could chest wall rigidity be a factor in the rapid death from illicit fentanyl abuse?

(N= 48)

Acute chest wall rigidity is a well-recognized complication

1- Deaths occurred with fentanyl in the therapeutic range (1–2 ng/ml) in apparent non-naive opiate abusers

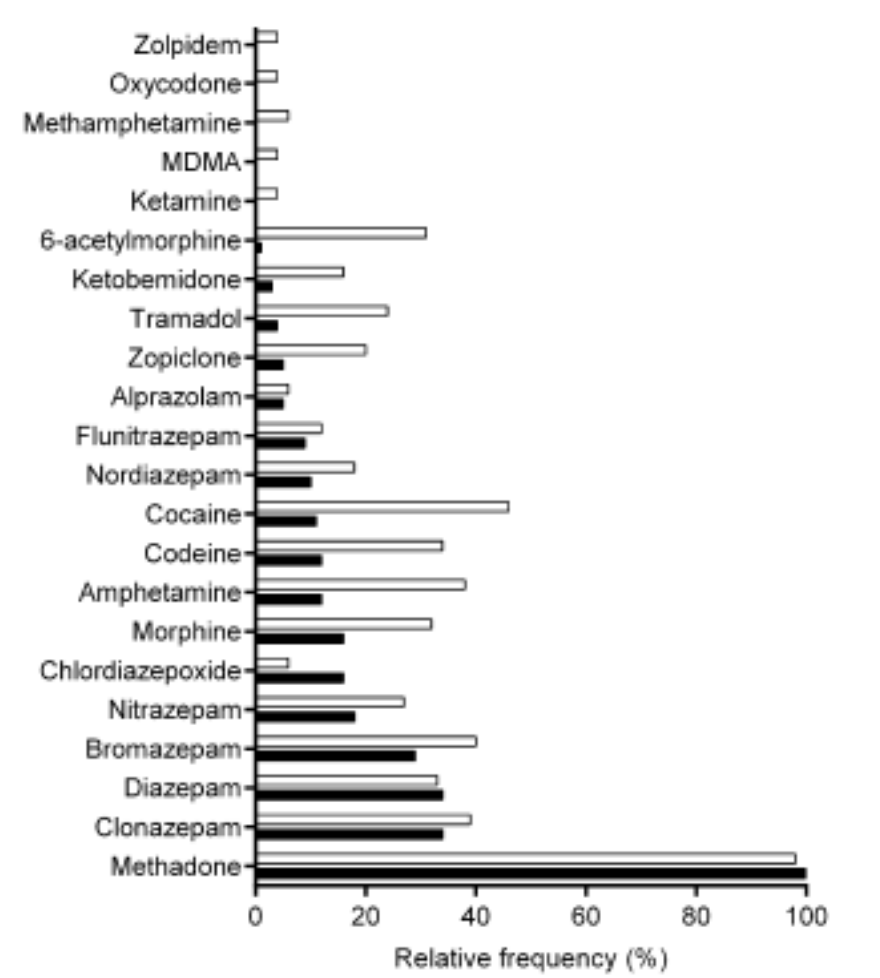
↪ questioning the onset of dose-dependent respiratory arrest as mechanism of death

2- Lack of measurable norfentanyl in half of the cases despite high fentanyl
- No correlation between elevated fentanyl and rises in norfentanyl

↪ suggesting a very rapid death, consistent with acute chest rigidity

Burns *G. Clin Tox* 2016

Drug-drug interactions



Abundance of hypnotics and drugs of abuse in blood (black) and proximal hair segments (white) in 99 methadone-related fatalities.

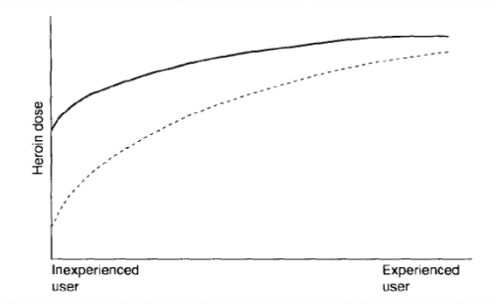
Based on segmental hair analysis, continuous exposure of methadone suggested that reduced tolerance of methadone is not a critical factor among methadone-related fatalities.

In contrast, a high abundance of co-ingested CNS depressants suggested that adverse effects from drug-drug interactions are more important risk factors for fatal outcome

Nielsen MK. *Forensic Sci Int* 2015

The role of tolerance and abstinence

Tolerance theory



Tolerance

↓

Dose increase

↓

Death

White JM. *Addiction* 1999

Abstinence theory

Abstinence

↓

Tolerance decrease

↓

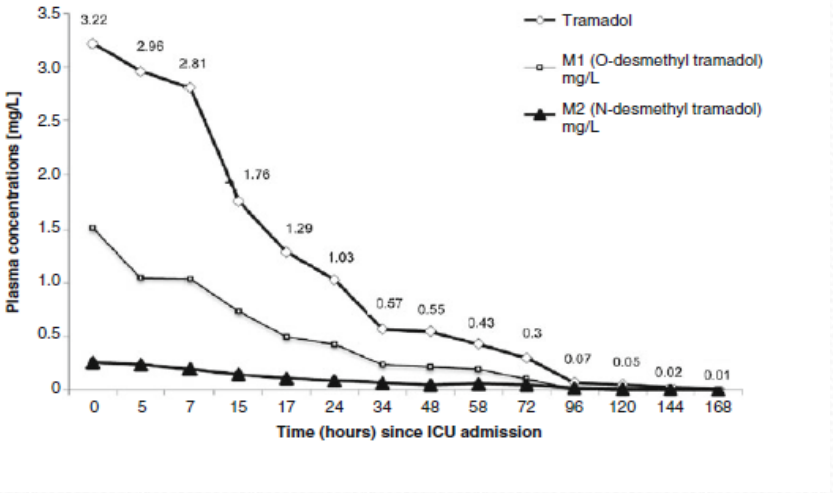
Re-consumption

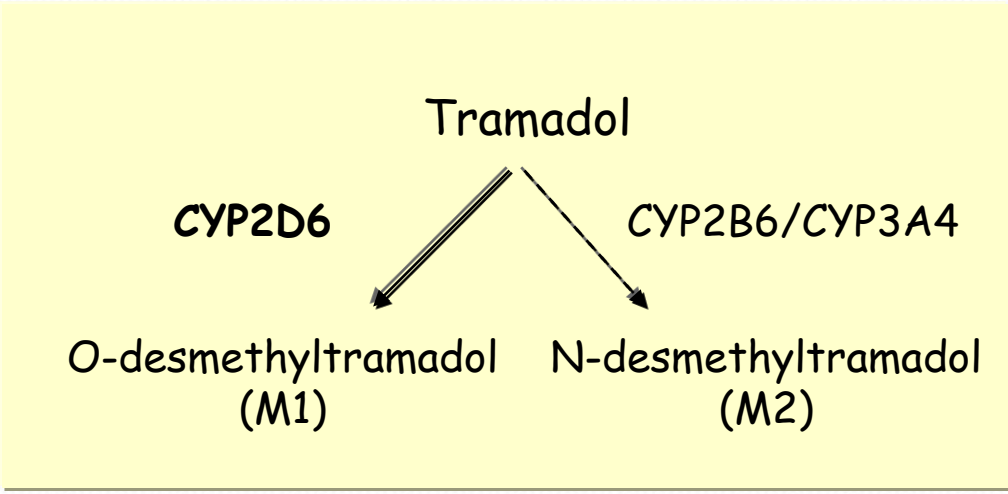
↓

Death

Druid H. *Forensic Sci Int* 2007

Vulnerability related to gene polymorphism: Near-fatal tramadol cardiotoxicity in a CYP2D6 ultrarapid metabolizer





- Ultrarapid metabolizer phenotype suggested by tramadol/M1 metabolic ratio
- Heterozygous for duplicated wt allele predictive of CYP2D6 ultrarapid metabolizer phenotype

+ Ketoconazole at inhibitory concentration of CYP3A/CYPB6 (200 ng/ml)

Elkalioubie A. *Eur J Clin Pharmacol* 2011

Naloxone: pharmacology properties

- Pure opioid antagonist at mu (high affinity), kappa, and delta receptors
- No agonist properties
- High first-pass metabolism (poor oral bioavialability)
- Short-plasma half-life 50 min
- Duration of action: 1-4 h
- Administered IV, IM, SC, IN

Widely used to reverse opioid toxicity

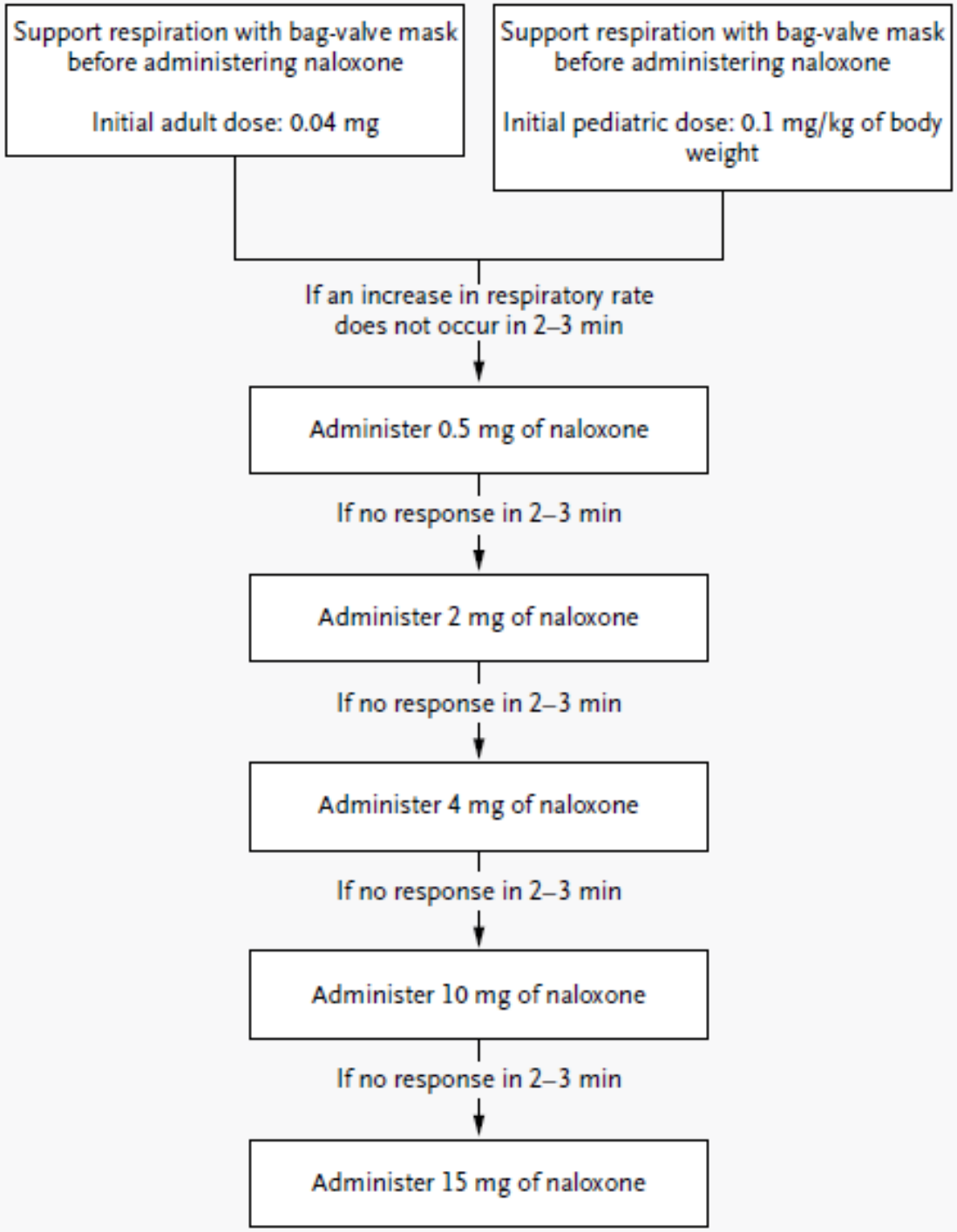
Dose-dependent reversal of opioid agonist effects

High dose may precipitate acute opioid withdrawal syndrome

Naloxone Dosing

Total dose = 32 mg naloxone
(i.e., 80 vials at 0.4 mg)

Boyer EW. *NEJM* 2012



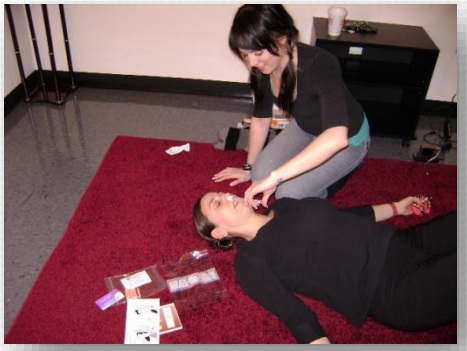
Comparison of heroin, methadone and BUP overdoses

	Heroin (N = 26)	Buprenorphine (N = 39)	Methadone (N = 19)	*p*
Suicide	12%	18%	58%	**0.0007**
Co-ingestions	73%	95%	89%	**0.04**
Glasgow Coma Score	5 [3 - 9]	7 [4 - 10]	4 [3 - 10]	0.1
Respiratory rate	10 [6 - 13]	12 [8 - 15]	10 [6 - 13]	0.4
SpO_2 (%)	82 [64 - 95]	94 [87 - 98]	91 [82 - 97]	**0.05**
pH	7.29 [7.17-7.34]	7.35 [7.24-7.38]	7.33 [7.23-7.42]	0.07
$PaCO_2$ (mmHg)	51 [45 - 55]	50 [45 - 66]	50 [36 - 57]	0.7
Mechanical ventilation	46%	41%	47%	0.6
Response to naloxone	81%	0%	71%	**<0.0001**
Response to flumazenil	0%	87%	60%	**0.02**

Mégarbane B. *JSAT* 2010

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

Conclusions

- Opioid overdose represents a challenging health concern worldwide

- **Toxicity** = CNS depression leading to asphyxic death

- **The reasons for the epidemic crisis:**
  1- Increased availability with inadequate prescriptions
  2- High risk of dependence and tolerance development
  3- Genetic/non-genetic individual vulnerability
  4- Emergence of the opioid NPS

- **Preventing opioid overdose deaths** is mandatory and could be achieved by maintenance treatments and take-home naloxone. New strategies based on preclinical findings and therefore with more uncertain timelines are under development.