Opioid overdose: mechanisms of toxicity and variability of presentation

Bruno Mégarbane, MD, PhD

Department of toxicological and medical critical care, Lariboisière Hospital, INSERM U705, Paris-Diderot University
Paris, France
bruno.megarbane@lrb.aphp.fr
Prescription opioids: first cause of toxic death in the US

National Center for Health Statistics, 2010

Jones CM. JAMA 2013
Trends in opioid abuse and mortality in the US

Dart RC. NEJM 2015
Trends in opioid & heroin use in Europe

**Opioids**

Adults (15–64)

1.3 million problem opioid users

Drug treatment requests

Principal drug in about 41% of all drug treatment requests in the European Union

41%

Treatment

700,000 opioid users received substitution treatment in 2013

Deaths

3.4% of all deaths of Europeans 15–39 years old are drug overdoses, opioids are found in 66% of fatal overdoses

EMCDDA, 2015
Regulation of ventilation

- Emotions and voluntary control
- CO₂
- O₂ and pH

Higher brain centers
Medullary chemoreceptors
Carotid and aortic chemoreceptors
Afferent sensory neurons

Central pattern generator

<table>
<thead>
<tr>
<th>Pons</th>
<th>Medulla oblongata</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dorsal respiratory group</td>
</tr>
</tbody>
</table>

- Somatic motorneurons (Inspiration)
- Somatic motorneurons (Expiration)

- Scalene and sternocleidomastoid muscles
- External intercostals
- Diaphragm
- Internal intercostals
- Abdominal muscles

Inspiration — Expiration
Opioid-related effects on ventilation

All \textit{\textmu}-receptor agonists cause a dose-dependent depression of respiration:
- Reduction in the brainstem sensitivity to CO$_2$
- Increase in the apneic threshold
- Decrease of the hypoxic drive to respiration
- Abolishment of carotid body chemoreception
- Depression of pontine & medullary centres involved in rhythmic respiration

- Characterized by dose-related, naloxone-reversible depression of the resting ventilation with a proportional reduction in Tidal volume, decreased PaO$_2$, and arterial pH along with increased PaCO$_2$.

- Usually attributed to interactions with mu2- and delta-OR, while kappa-OR seem not involved.
All opioids produce a similar toxidrome in excessive dosing.

SpO₂ and RR are surrogate indicators of ventilatory drive and provide limited information on the drug effects on ventilatory control.

\[ V_M \] and \( \text{PaCO}_2 \) are direct measures of ventilation but difficult to assess continuously.
Opioid-attributed death: the role of the dose?

Methadone-related deaths

Häkkinen M. *Forensic Sci Int* 2012

Buprenorphine-related deaths

Häkkinen M. *Eur J Clin Pharmacol* 2011
1- The pharmacokinetic / pharmacodynamic properties

Dahan A. Anesthesiology 2010
## Maintenance treatments

Oral long-acting opioid agonists used to avoid withdrawal and compulsive search for heroin and allow social and professional insertion of heroin addicts.

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD</strong></td>
<td>Full OR agonist</td>
<td>Partial OR agonist</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>oral</td>
<td>sublingual</td>
</tr>
<tr>
<td><strong>Daily dose</strong></td>
<td>Variable (5-120 mg)</td>
<td>8-16 mg</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>80%</td>
<td>75%</td>
</tr>
<tr>
<td><strong>Liver metabolism</strong></td>
<td>CYP 2B6, 2C19, 3A4, 2C9, 2D6</td>
<td>CYP 3A4</td>
</tr>
<tr>
<td><strong>Metabolite</strong></td>
<td>CDDP (inactive)</td>
<td>N-BUP (active)</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Urine &gt; feces</td>
<td>Feces &gt; urine</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>~25 h</td>
<td>~5 h</td>
</tr>
</tbody>
</table>
Onset and duration of action in therapeutic dosing and overdose of selected opioid analgesic agents

Boyer EW. NEJM 2012
2- The additional drug-specific mechanisms of toxicity

Tramadol overdose

<table>
<thead>
<tr>
<th>Effect</th>
<th># Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lethargy</td>
<td>26</td>
<td>30%</td>
</tr>
<tr>
<td>Agitation</td>
<td>9</td>
<td>10%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>9%</td>
</tr>
<tr>
<td>Seizures</td>
<td>7</td>
<td>8%</td>
</tr>
<tr>
<td>Coma</td>
<td>4</td>
<td>5%</td>
</tr>
<tr>
<td>Confusion</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>1</td>
<td>1%</td>
</tr>
</tbody>
</table>

N = 87

<table>
<thead>
<tr>
<th>Effect</th>
<th>Op</th>
<th>Ne</th>
<th>Se</th>
<th>Ac</th>
<th>Tr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Agitation</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Ataxia</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td>x</td>
<td>?</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Myoclonus</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Diaphoresis</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
Risk factors for seizures associated with tramadol overdose

- R 0.3 mm in aV_{R}(ECG)
- Mixed with benzodiazepines
- History of dependency
- Alleged tramadol dose
- Naloxone administration
- Respiratory rate
- Heart rate
- Tramadol only
- Mydriasis

Tashakori A. Clin Tox 2010

Ryani R. Clin Tox 2015

Taghaddosinejad F. JMT2011
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

- No appreciable concentrations of norfentanyl detected (42%) and <1 ng/ml (52%)
- Absence of correlation between elevated fentanyl and rises in norfentanyl concentrations
- In several cases, strikingly high fentanyl with no norfentanyl detected

Lack of measurable norfentanyl in half of the cases suggests a very rapid death, consistent with acute chest rigidity. An alternate explanation could be a dose-related rapid onset of respiratory arrest. However, deaths occurred with low fentanyl in the therapeutic range (1-2 ng/ml) in apparent non-naive opiate abusers.

Burns G. Clin Tox 2016
3- The role of tolerance and abstinence

The hypothetic model of tolerance to intoxicating and lethal effects of opioids following repeated administrations

White JM. *Addiction* 1999
In 18/28 heroin fatalities, opioids were absent in the most recent hair segment, suggesting reduced tolerance to opioids.

However, blood morphine levels were similar to those found in the 10 subjects that showed continuous opioid use.

Hair and blood analysis disclosed an extensive use of additional drugs.

Druid H. Forensic Sci Int 2007
Case report -

- Normal pregnancy and delivery
- Post-delivery pain:
  - Codeine 120 mg/day
  - Acetaminophen 500 mg/day
- D7: lethargy, difficulty in breastfeeding
- D13: neonate sudden death
- Postmortem findings:
  - No hereditary disease
  - Blood morphine: 70 µg/L (N: 10-12)
  - Serum acetaminophen: 5.9 µg/L
- Mother genotyping:
  - heterozygote CYP 2D6*2x2 (ultrarapid)
  - UGT 2B7*2 (ultrarapid)

Koren G. Lancet 2007
Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication

<table>
<thead>
<tr>
<th></th>
<th>surgery</th>
<th>PACU</th>
<th>ward</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg Tramadol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ng/ml Tramadol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ng/ml O-Desmethyltramadol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hours</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg Tramadol Loading Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg Tramadol via PCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS at movement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS at rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−)-Tramadol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)-Tramadol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−)-O-DT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)-O-DT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sedation Score: 1 1 1 2 3 3 3 5
SaO₂ %: 97 98 97 95 90 92
BP mmHg: 150/90 125/90 119/88
Heart rate (min): 76 71 77 73 70
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)
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.

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

Nielsen MK. *Forensic Sci Int* 2015
BZD use during buprenorphine treatment for opioid dependence: safety outcome

<table>
<thead>
<tr>
<th>Type of ED visit</th>
<th>Proportions</th>
<th>ORs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BZD Rx</td>
<td>No BZD Rx</td>
</tr>
<tr>
<td>Overdose</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>0.26</td>
<td>0.09</td>
</tr>
<tr>
<td>Psychiatric visit</td>
<td>0.21</td>
<td>0.12</td>
</tr>
<tr>
<td>Medical visit (e.g. infection)</td>
<td>0.38</td>
<td>0.29</td>
</tr>
</tbody>
</table>

No effect of BZD prescriptions on opioid overdose; however, BZD prescription was associated with more frequent ED visits and accidental injuries, especially among females.

Schuman-Olivier Z. Drug Alcohol Dep 2012
Naloxone: pharmacology properties

- Pure opioid antagonist at mu (high affinity), kappa, and delta receptors
- No agonist properties
- High first-pass metabolism (poor oral bioavailability)
- 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)
Bell-shaped naloxone reversal of opioid-induced respiratory depression

Van Dorp E. *Anesthesiology* 2006
## Comparison of heroin, methadone and BUP overdoses

<table>
<thead>
<tr>
<th></th>
<th>Heroin (N = 26)</th>
<th>Buprenorphine (N = 39)</th>
<th>Methadone (N = 19)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide</td>
<td>12%</td>
<td>18%</td>
<td>58%</td>
<td>0.0007</td>
</tr>
<tr>
<td>Co-ingestions</td>
<td>73%</td>
<td>95%</td>
<td>89%</td>
<td>0.04</td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td>5 [3 - 9]</td>
<td>7 [4 - 10]</td>
<td>4 [3 - 10]</td>
<td>0.1</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>10 [6 - 13]</td>
<td>12 [8 - 15]</td>
<td>10 [6 - 13]</td>
<td>0.4</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>82 [64 - 95]</td>
<td>94 [87 - 98]</td>
<td>91 [82 - 97]</td>
<td>0.05</td>
</tr>
<tr>
<td>pH</td>
<td>7.29 [7.17-7.34]</td>
<td>7.35 [7.24-7.38]</td>
<td>7.33 [7.23-7.42]</td>
<td>0.07</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>51 [45 - 55]</td>
<td>50 [45 - 66]</td>
<td>50 [36 - 57]</td>
<td>0.7</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>46%</td>
<td>41%</td>
<td>47%</td>
<td>0.6</td>
</tr>
<tr>
<td>Response to naloxone</td>
<td>81%</td>
<td>0%</td>
<td>71%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Response to flumazenil</td>
<td>0%</td>
<td>87%</td>
<td>60%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Mégarbane B. JSAT 2010
Usefulness of naloxone to treat tramadol poisoning

<table>
<thead>
<tr>
<th>Complication</th>
<th>Patients who did not receive naloxone</th>
<th>Patients who received naloxone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration pneumonia</td>
<td>2 (2.4)</td>
<td>2 (10.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>Need to intubation</td>
<td>8 (9.4)</td>
<td>6 (31.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3 (3/6)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Tashakori A. *Clin Tox* 2010
Empirical adaptation of naloxone dosage in a case of methadone poisoning
Preventing opioid overdose deaths with take-home naloxone

Narcan is packaged with a medicine vial, syringe barrel, and a nasal atomizer.

- Place the assembled Narcan atomizer in one nostril.
- Press firmly on the base of the glass vial, spraying half of the Narcan dose deep into the nasal cavity.
- Do the same in the other nostril.

<table>
<thead>
<tr>
<th>Number of programs of naloxone distribution</th>
<th>Number of naloxone vials distributed over one year</th>
<th>Number of program participants</th>
<th>Number of reported opioid overdose reversals</th>
</tr>
</thead>
<tbody>
<tr>
<td>188</td>
<td>38 860</td>
<td>53 032</td>
<td>10 171</td>
</tr>
</tbody>
</table>

CDC. MMWR Morb Mortal Wkly Rep 2012
The unusual presentations of opioid overdose

**Forensic findings**

- **Foam cone**
  - Relatively common finding in opioid deaths though not diagnostic
  - Suggests exsudative etiology

- **Pulmonary edema**
  - Swollen, heavy lungs
  - Variegated, hemorrhagic surface
  - Aspiration common, alveolar hemorrhages
  - Siderophage infiltration
  - Death typically >3 hrs after last drug use

Dinis-Oliveira RJ. *Tox Mech Meth* 2012

Siegel H. *Hum Pathol* 1972

Todorović MS. *Vojnosanit Pregl* 2011
149 patients with heroin overdose between 1968 and 1970
48% had pulmonary edema
Overall death rate: 8.7% (18.3% in patients with pulmonary edema)

135 patients received nalorphine
19 responded with agitation, of whom 11 developed pulmonary edema and 7 died

All patients who died had pulmonary edema

Duberstein JL. Am J Med 1971
Opioid-induced pulmonary edema

- 27 patients (85% M; 34 years) during 53-month period
  20 patients (74%) hypoxic on ED arrival
  6 patients (22%) symptoms within the first hour

- 9 patients (33%) required mechanical ventilation
  All intubated patients but one were extubated within 24 h.

- 18 patients (66%) required supplemental oxygen alone
  Hypoxia resolved spontaneously within 24 h (74%) or 48 h (22%)

- 20 patients (74%) with classical radiograph findings of bilateral fluffy infiltrates but unilateral edema (15%) and more localized disease (7%)

Infrequent complication of heroin overdose with decreased incidence
Clinically apparent either immediately or within 4 h of the overdose

Sporer KA. Chest 2001
Mechanisms of opioid-induced pulmonary edema (1)

1- Valsalva maneuver against a closed glottis (Müller maneuver)
   → Negative intrathoracic pressure
   → Transudative pulmonary edema
Rapid development and dissipation after revision of underlying condition

2- Severe hypoxemic myocardial dysfunction
   → Transudative pulmonary edema
   → Echocardiography cardiac dysfunction

3- Pneumocyte hypoxia
   → Damage to the alveolar integrity
   → Edema fluid often with the same protein levels as serum
However, no such edema in other psychotropic drug-induced ALI

Clemmenson C. Dan Med Bull 1963
Duberstein JL. Am J Med 1971
Katz S. Am Rev Respir Dis 1972
Mechanisms of opioid-induced pulmonary edema (2)

4- Anaphylaxis/anaphylactoid
→ Tryptase in heroin overdose and anaphylaxis > trauma deaths
→ Tryptase increases after IV but not inhalation heroin in volunteers (minimal changes; pharmaceutical heroin)

However, lung tissues from heroin vs sudden cardiovascular deaths: no difference in IgE positive cells, alveolar staining for collagen or laminin

Fineschi V. Forensic Sci Int 2001
Rook EJ. Drug Alcohol Depend 2006
Dettmeyer R. Forensic Sci Int 2000
Naloxone-induced pulmonary edema

- Autopsy finding before naloxone existed
- Confounding factors?

Acute precipitated opioid withdrawal associated with massive sympathetic response
Myocardial stunning due to catecholamine excess

- Hydrostatic pressure-related
- Transudate
- Typically resolves rapidly
- Preventable by starting naloxone dose at 0.04 mg

Boyer EW. NEJM 2012
Aspiration pneumonia

Foreign body aspiration

Bhaskar B. Saudi J Anaesth 2012
Valsalva maneuver effect on distribution of lung damage in heroin inhalation

Prowse SJ. BJR 2011
Conclusions

- Opioid overdose represents a challenging health concern worldwide.

- The toxidrom is typical but variability in features and dose/severity relationships is related to the involved molecule, the development of tolerance, the co-ingestion of psychotropic drugs and the genetic/non-genetic individual vulnerability.

- Management is based on supportive care (oxygen and mechanical ventilation). Naloxone is the first-line antidote to reverse CNS depression.

- Preventing opioid overdose deaths is mandatory and could be achieved by maintenance treatments and take-home naloxone.