Opioid toxicity

TERMINOLOGY

CLINICAL CLARIFICATION

- Opioid toxicity results in severe—sometimes fatal—effects that most commonly occur after overdose, which can be intentional or accidental [1]
- Primary toxic effect of opioid overdose is decreased rate and depth of respiration leading to pulmonary edema [1]
  - May result in death from hypoxia and respiratory arrest before pulmonary edema develops
- Effects on other organs include hypotension, bradycardia, and decreased body temperature [1]

CLASSIFICATION

- Toxicity caused by short-acting opioids, such as:
  - Morphine sulfate
  - Fentanyl
    - Fentanyl analogs
      - Carfentanyl is the most potent analog (100 times that of fentanyl) and is used as an anesthetic for large animals
      - Analogs with no licensed medical use include acetylfentanyl and butyrylfentanyl
  - Oxycodone
  - Hydrocodone
  - Codeine
  - Heroin
- Toxicity caused by longer-acting and delayed-release opioids, including:
  - Extended-release morphine sulfate
  - Methadone
  - Oxymorphone
- Toxicity caused by opioid receptor agonist-antagonist drugs, such as:
  - Agonist at one opioid receptor, antagonist at a different opioid receptor
    - Pentazocine
    - Butorphanol
    - Nalbuphine
    - Dezocine
  - Partial agonist at a single opioid receptor
    - Buprenorphine
    - Meptazinol

DIAGNOSIS

CLINICAL PRESENTATION

- History
  - History of nonprescribed opioid use or abuse [2]
    - Medical records may indicate previous use or abuse
    - Family or friends may confirm opioid use
    - Needles or other paraphernalia found near patient
  - History of prescribed opioid use [2]
    - Pills, pill bottles, or drug paraphernalia found near patient
  - Common symptoms even without any available history [2]
    - Apnea
    - Depressed consciousness
      - Can range from drowsiness to coma
- Physical examination
  - Common signs [3]
    - Depressed respiratory rate is the most specific sign
      - Respiratory rate of 12 breaths or fewer per minute, with stupor, is highly suggestive of acute opioid toxicity, especially when accompanied by miosis and/or depressed consciousness
    - Reduced size and reactivity of pupils
      - Pupil constriction to less than 2-mm diameter [4]
      - Not always present, particularly if opioids were ingested along with other substances
    - Hypotension, bradycardia, and hypothermia are usually present [3]

Published April 21, 2016; Updated May 31, 2019

- Other examination findings[3]
  - Skin
    - Evidence of fentanyl patches[1]
    - Needle track marks
      - Recent injection marks are small, red, inflamed, or surrounded by slight bruising
      - Old injection sites show pigmentation change and atrophied skin
  - Neurologic
    - Seizures often are associated with overdose of tramadol, propoxyphene, and meperidine, particularly if used concomitantly with medicines that lower seizure thresholds[1]
  - Mucous membrane[3]
    - Mucous membrane cyanosis is a late sign of hypoxia and hypotension
  - Pulmonary
    - Pulmonary edema in patients with apnea or severe bradypnea
      - Rales and frothy sputum are a late sign of severe opioid toxicity[1]
  - Cardiac
    - QTc prolongation may occur in some patients receiving methadone, increasing chance of developing a ventricular arrhythmia, particularly torsades de pointes[5]

CAUSES AND RISK FACTORS

- Causes
  - Overdose of opioid drugs[2]
    - Opioid drugs are substances that bind to 1 or more of the 4 opioid receptors (δ, κ, μ, and nociceptin receptors)
    - Toxicity is not necessarily dependent on dose of opioid used, but instead depends on individual tolerance at time of exposure
      - Tolerance may be dramatically different in patient subpopulations
    - More overdose deaths are due to prescription opioids than nonprescription forms[6]
      - Commonly prescribed opioids[7]
        - Hydrocodone
        - Oxycodone
        - Morphine
        - Codeine
        - Hydromorphone
        - Oxymorphone
        - Methadone
        - Fentanyl patch
        - Tapentadol
        - Diphenoxylate
        - Fentanyl
      - Commonly prescribed opioid receptor agonist/antagonist or partial-agonist drugs
        - Pentazocine
        - Butorphanol
        - Nalbuphine
        - Dezocine
        - Buprenorphine
        - Meptazinol
      - Most common nonprescription opioids
        - Heroin
        - Fentanyl (diverted or illicitly produced; typically added to heroin)
        - Carfentanyl (diverted from veterinary sources; typically added to heroin)
        - Loperamide (in supratherapeutic doses)
  - Overdose of buprenorphine usually does not cause lethal respiratory depression in adults unless administered intravenously or combined with another respiratory depressant, but lethal respiratory depression can occur in elderly or weak patients[8]
    - Death from buprenorphine in children results from respiratory depression, usually following unintentional exposure secondary to medication being stored in sight, accessed from a bag or purse, or not being stored in its original packaging[9]
  - Effects of toxic metabolites[10]
    - Normeperidine from meperidine: lowers seizure threshold and accumulates with repeated dosing

Published April 21, 2016; Updated May 31, 2019

  - Morphine-3-glucuronide from morphine: lowers seizure threshold and may be responsible for myoclonus and allodynia
- Risk factors and/or associations
  - Age
    - Higher incidence of opioid poisoning deaths in those aged 25 to 64 years, with highest incidence among those aged 45 to 54 years [11]
    - Advanced age is associated with reduced clearance of morphine, fentanyl, codeine, and oxymorphone, which increases risk of overdose (and requires more caution with prescribing) [10]
    - Children are more likely than adults to experience respiratory depression and death after unintentional exposure to agonist/antagonists such as buprenorphine [9, 12]
    - Children may be more sensitive to codeine dosing and can be accidentally overdosed owing to existence of rapid metabolizers of the prodrug codeine to the active drug morphine [13]
      - Avoid giving codeine to breastfeeding mothers
  - Sex
    - Incidence higher in men [2]
  - Ethnicity/race
    - Death rates in white populations are 4 times higher than in Hispanic or black populations [11]
  - Other risk factors/associations
    - Opioid toxicity is most highly associated with people who are prescribed high doses of opioid analgesics (over 100 mg of morphine or equivalent per day) [14]
    - Also associated with people who seek care from multiple physicians or receive early refills [2]
      - Risk of distribution to others
    - Prescription opioid death rates are highest in rural populations [2, 11]
    - Heroin death rates are highest in large central metropolitan areas [2]
    - Populations at greatest risk for opioid toxicity [2]
      - People with mental illness
      - People who report long-term medical use of opioids
      - People who report nonmedical use (ie, use without a prescription or medical need) of opioids in the past month
    - Hepatic impairment [10]
      - Especially important to consider when using oxycodone, morphine, or oxymorphone
      - Lower risk of toxicity with fentanyl and methadone
    - Renal impairment [10]
      - Particularly important when using morphine, hydromorphone, and other opioids with active metabolites
      - Less risk with fentanyl and methadone

DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
  - Primary diagnosis is based on: [15]
    - Classic symptoms of opioid overdose
      - Respiratory depression, often accompanied by central nervous system depression and miosis
    - Responsiveness to naloxone
- Laboratory
  - Urine toxicology tests [15]
    - Screen for acetaminophen levels
    - Do not rely on toxicology screens for the initial diagnosis or management of suspected opioid overdose
    - Positive screen for opioids does not confirm toxicity
    - Although positive toxicology results can indicate presence of opioids, negative results do not necessarily mean absence of opioids
      - Some opioids, such as fentanyl, may not be detectable using typical toxicology screening methods
- Imaging
  - Obtain chest radiographs in opioid-toxic patients with rales or hypoxia to evaluate for pulmonary edema or aspiration pneumonia
- Functional testing
  - Can use ECG to monitor bradycardia [15]
  - QTc prolongation may occur in some patients receiving methadone, increasing the chance of developing a ventricular arrhythmia, particularly torsades de pointes [5]
    - Doses above 100 mg daily produce a dose-dependent QTc prolongation
      - Regular monitoring of the QTc is recommended for patients receiving therapy who have baseline prolonged QT intervals greater than 501 milliseconds

Published April 21, 2016; Updated May 31, 2019

- QTc prolongation also may occur with loperamide toxicity[16]

DIFFERENTIAL DIAGNOSIS

- Most common
  - Clonidine and oxymetazoline toxicity (particularly in pediatric patients)
    - Both drugs are centrally acting α_1-blockers that cause depressed mental status, bradycardia, hypotension, and miosis
    - Partial response to naloxone is common
      - No easy or consistent way to differentiate from opioid toxicity
      - Urine test for these drugs is typically only available at reference laboratories
        - Results will not change patient management
    - Most children with clonidine or oxymetazoline toxicity will be treated as opioid toxic and vice versa
    - Nonresponse to naloxone is the best way to determine that the diagnosis is likely something other than opioid toxicity, but eliciting a response in patients with opioid toxicity may require large doses of naloxone
  - Acute subdural hematoma[15]
    - Common presentation is depressed mental status
    - CT scan results differentiate pure opioid toxicity from subdural hematoma
  - Other central nervous system depressant toxicity (eg, alcohol, barbiturate, benzodiazepine, cannabinoid)[17]
    - Cannot differentiate easily by symptoms alone
    - Differentiate by ineffectiveness of naloxone
      - Combined with quantitative alcohol serum levels, narrows diagnostic considerations
  - Meningitis and encephalitis
    - Both present with confusion and depressed mental status
      - Additional symptoms include headache, vomiting, and fever
    - Both do not respond to naloxone
    - Differentiate by using CT scan to reveal meningeal inflammation and using lumbar puncture to show evidence of infection
  - Hypoglycemia
    - Presents with confusion and depressed mental status
    - Differentiate using a bedside blood glucose test and response to glucose administration

TREATMENT

GOALS

- Reverse opioid toxicity
  - Treat with reversal agent
  - Secure airway
  - Restore respiratory status
  - Reverse central nervous system depression
- Avoid precipitating withdrawal

DISPOSITION

- Admission criteria
  - Admit children aged 3 years or younger who were exposed to opioids other than immediate-release formulations for 24-hour observation if ingestion of agents is suspected from history but cannot be confirmed[18]
  - Respiratory depression
    - Occurs after nonresponse to naloxone or during resedation after naloxone wears off and continued observation in the emergency department is unavailable
  - Criteria for ICU admission[19,1]
    - Patients whose toxicity is due to long-lasting and extended-release opioids
      - Long-lasting and extended-release opioids cause resedation after naloxone wears off
      - Require prolonged observation for respiratory depression and airway compromise
    - Patients who require a naloxone infusion
    - Patients who require orotracheal intubation
- Recommendations for specialist referral
  - Refer to medical toxicologist for specialty management of opioid toxicity
  - Refer to pain or addiction specialist to prevent recurrence and treat addiction

TREATMENT OPTIONS

- First priority is to restore respiration using a bag-valve mask until naloxone can be administered[1]

Published April 21, 2016; Updated May 31, 2019

- Advanced airway intervention is rarely required unless there are coingestants or other illnesses or injuries
- Observe for and remove any fentanyl patches
- Drug treatment is the same regardless of causative opioid
  - Naloxone therapy is the standard treatment of opioid toxicity [1]
    - Empiric administration to unresponsive patients with suspected opioid overdose is recommended to reverse respiratory depression; however, only small doses may be required. Larger doses may precipitate withdrawal unnecessarily
    - Small doses also may be used for diagnostic purposes for patients with decreased level of consciousness of unknown cause
  - Naloxone prescriptions or access to OTC naloxone is an important treatment option for high-risk individuals
- Drug therapy
  - Naloxone [1]
    - Dose is empiric and depends on the amount of opioid the patient received or has taken
    - IV administration is most common and preferable method of delivery
      - IV naloxone continuous infusion is difficult and has several drawbacks
        - Difficult to titrate adequate dose to maintain adequate respiration while avoiding precipitating withdrawal
          - Recommended infusion strategy of hourly dose to match dose required to reverse apnea has not been validated
        - Relying on an IV infusion of drug to maintain ventilation
          - IV catheters can become kinked, be pulled out, or become otherwise dysfunctional
        - Patients still require ICU admission for monitoring
    - Use intramuscular, intranasal, or pulmonary administration when IV is not an option
    - Do not administer orally because it has high first-pass metabolism rate
    - Observation must last longer than the expected elimination time for naloxone. Minimum observation time for naloxone is 1 to 2 hours, but observe patient 4 to 6 hours in case there are coingestants [20, 21]
    - Toxic effects often reappear within 30 minutes of naloxone dosing, requiring further naloxone because it has a short half-life
    - Gradual titration of naloxone dose is preferred over isolated larger doses to avoid precipitating withdrawal
    - Opioids that require larger doses of naloxone [20]
      - Natural opium derivatives
        - Codeine
        - Methadone
      - Synthetic opiates
        - Diphenoxylate
        - Propoxyphene
      - Mixed opioid agonist-antagonists
        - Pentazocine
        - Butorphanol
        - Nalbuphine
      - Partial agonist
        - Buprenorphine
    - Intermittent IV, intramuscular, subcutaneous, or intraosseous dosage (standard syringe)
      - Naloxone Hydrochloride Solution for injection; Neonates: 0.1 mg/kg/dose IV/IM is recommended in clinical guidelines; may require repeated doses. FDA-approved labeling recommends 0.01 mg/kg/dose IV, IM, or subcutaneously initially; may repeat every 2 to 3 minutes.
      - Naloxone Hydrochloride Solution for injection; Infants and Children younger than 5 years or weighing 20 kg or less: 0.1 mg/kg/dose IV/IO (PALS recommendation); may require repeated doses. FDA-approved labeling recommends 0.01 mg/kg/dose IV, IM, or subcutaneously initially; may repeat every 2 to 3 minutes.
      - Naloxone Hydrochloride Solution for injection; Children and Adolescents 5 to 17 years or weighing more than 20 kg: 2 mg IV/IO (PALS recommendation); may require repeated doses. FDA-approved labeling recommends 0.01 mg/kg/dose IV, IM, or subcutaneously initially; may repeat every 2 to 3 minutes.
      - Naloxone Hydrochloride Solution for injection; Adults: 0.4 to 2 mg IV, IM, or subcutaneously, up to a total dose of 10 mg; doses may be repeated every 2 to 3 minutes PRN. In emergency settings, guidelines recommend 0.4 to 2 mg IV; alternatively, 0.4 to 0.8 mg may be given IM/subcutaneously if systemic perfusion is adequate.
        - High doses (5-10 mg) of naloxone have been required to reverse buprenorphine-induced respiratory depression; it may take up to 3 hours before maximum reversal is observed [22, 23]
          - Prompt consultation with a medical toxicologist is prudent

Published April 21, 2016; Updated May 31, 2019

        - Giving bolus doses of naloxone, followed by an IV infusion (eg, 4 mg/hour) has been described to treat buprenorphine overdose [22]
    - Endotracheal dosage
        - Naloxone Hydrochloride Solution for injection; Infants and Children younger than 5 years or weighing 20 kg or less: Optimal ET dosage has not been determined; a dose of 2 to 3 times the IV dose has been recommended (equivalent to 0.2 to 0.3 mg/kg/dose ET).
        - Naloxone Hydrochloride Solution for injection; Children and Adolescents 5 to 17 years or weighing more than 20 kg: Optimal ET dosage has not been determined; a dose of 2 to 3 times the IV dose has been recommended (equivalent to 4 to 6 mg/dose ET).
        - Naloxone Hydrochloride Solution for injection; Adults: Optimal ET dosage has not been determined. In emergency settings, guidelines recommend 0.4 to 2 mg via ET tube.
    - Intranasal dosage (Narcan nasal spray)
        - Naloxone Hydrochloride Nasal spray, solution; Adults, Adolescents, Children, Infants, and Neonates: 1 spray (2 mg or 4 mg of naloxone) by intranasal administration. Seek immediate medical attention after administration of the first dose. May repeat dose in alternate nostrils every 2 to 3 minutes as needed; each device contains a single dose. Monitor closely until emergency medical personal arrive; continue to monitor pediatric patients for at least 24 hours.
    - Continuous IV or intraosseous infusion dosage
        - Naloxone Hydrochloride Solution for injection; Neonates, Infants, Children, and Adolescents: Limited data available. If repeated intermittent doses are required, calculate initial infusion rate based on effective intermittent dose; use two-thirds up to the full intermittent dose as initial hourly infusion rate (i.e., if a 0.02 mg/kg IV dose was effective, initiate infusion at 13 to 20 mcg/kg/hour [0.013 to 0.02 mg/kg/hour]). Titrate as needed. A continuous infusion rate of 2 to 160 mcg/kg/hour IV/IO has been suggested; however, most reports have utilized 24 to 44 mcg/kg/hour IV. When appropriate, wean in 25% increments while closely monitoring patient.
        - Naloxone Hydrochloride Solution for injection; Adults: Loading dose of 0.005 mg/kg IV followed by 0.0025 mg/kg/hour IV.
  - Naloxone can precipitate withdrawal symptoms, including: [24]
    - Anxiety, irritability, and restlessness
    - Patients can become violent and uncooperative
    - Goose flesh
    - Hot and cold sweats
    - Muscle, bone, and joint aches
    - Tremor
    - Nausea, vomiting, and diarrhea
    - Increased resting pulse rate
- Nondrug and supportive care
  - For apnea of fewer than 12 breaths per minute [1]
    - Provide ventilation with a bag-valve mask
    - Perform chin-lift and jaw-thrust maneuvers to diminish hypercapnia
  - Procedures
    - Orotracheal intubation [1]
        - General explanation
            - Insertion of a tube into the trachea to restore respiration
            - Safely ensures oxygenation and ventilation while providing protection against aspiration
        - Indication
            - To gain definitive control of the airway to restore respiration
- Special populations
  - Children
    - Overdose characterized by: [1]
        - Unexpectedly severe poisoning based on dose received
        - Prolonged toxic effects
    - Admit children aged 3 years or younger who were exposed to opioids other than immediate-release formulations for 24-hour observation if ingestion of agents is suspected from history but cannot be confirmed [18]
    - Children who ingest opioids may require larger doses of naloxone because they often ingest a higher dose than adults per kilogram of body weight [1]
  - Elderly people
    - Age-related changes in physiology and body composition may cause persistent intoxication [1]

Published April 21, 2016; Updated May 31, 2019

MONITORING

- For patients with opioid toxicity, it is ***mandatory*** to monitor respiratory adequacy and cardiovascular stability
  - Use pulse oximetry or end-tidal CO_2 to monitor respiration
  - Use periodic (every 15 minutes) blood pressure monitoring to assess for hypotension

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Respiratory depression and apnea
  - Apneic patients who receive naloxone frequently develop noncardiogenic pulmonary edema [1]
- Central nervous system depression with airway compromise
  - Vomiting can result in aspiration of gastric contents into the lungs
- Head trauma or brain injury due to falls related to loss of consciousness
- Multiple complications can occur secondary to prolonged hypotension, bradycardia, and hypothermia
- Death may occur in severe situations
  - Accidental overdose can occur when nonpharmaceutical agents contain unexpected substances such as fentanyl or its analogs

PROGNOSIS

- Recurrence is likely in patients with opioid abuse history [2]
- In 1 study, approximately 1% of patients with nonfatal opioid overdoses went on to have fatal overdoses within 1 year [25]
- Mortality rate is 5.1 per 100,000 with opioid analgesics [26]

SCREENING AND PREVENTION

SCREENING

PREVENTION

- Provider education and implementation of prescription drug monitoring programs assist in avoiding the following: [27, 28]
  - Inappropriate prescription of opioid analgesics
  - Chronic prescription of opioids for acute pain
  - Prescription of high-dose opioid analgesics
- Use prescription and insurance data to screen and reduce opioid prescription for: [28, 27]
  - Patients seeking care from multiple physicians
  - Patients obtaining early refills
    - At risk for providing opioids to others
- Increase availability of opioid-dependence treatment, especially office-based medication-assisted treatment with buprenorphine/naloxone [27, 28]
- To decrease risk of opioid toxicity death, distribute naloxone and promote education about its use in communities where opioid toxicity is likely [27, 28]
- Provide naloxone to patients receiving chronic opioid therapy, particularly those requiring higher doses, and train patient and family members how to administer intranasally when overdose is suspected [29, 27, 28]
- Refer opioid abusing or dependent patients to Narcotics Anonymous or similar support programs [27, 28]
  - Inpatient and outpatient rehabilitation counseling is an important aspect of prevention

SYNOPSIS

KEY POINTS

- Opioid toxicity results in severe—sometimes fatal—effects that most commonly occur after overdose, which can be intentional or accidental
- Opioid toxicity causes respiratory depression, generally accompanied by depressed consciousness and miosis
  - Diagnosis is made based on these 3 primary symptoms, which may not always present together, paired with a positive response to naloxone
- Opioid toxicity is often coupled with ingestion of other substances, such as acetaminophen or ethanol
- Restore respiration using a bag-valve mask until naloxone can be administered
- IV naloxone, a competitive opioid antagonist, is the gold standard reversal agent
- Continuously observe patients receiving naloxone because it has a short half-life
  - Observation must last longer than the expected elimination time for naloxone. Minimum observation time for naloxone is 1 to 2 hours, but observe patient 4 to 6 hours in case there are coingestants
- Naloxone, although necessary, can cause withdrawal symptoms, which can be stressful to patients and caregivers; cautious titration to desired effect (reversal of respiratory suppression) is recommended
- Recurrence is likely in patients with opioid use disorder history

Published April 21, 2016; Updated May 31, 2019

URGENT ACTION

- First priority is to restore respiration
- If symptoms are present, begin treating with naloxone to reverse opioid toxicity; do not wait for drug screen or immunoassay results to confirm diagnosis
- Admit to ICU if patient is intoxicated by long-lasting opioids, has recurrent respiratory depression, requires naloxone infusion, or requires intubation

PITFALLS

- Naloxone can precipitate opioid withdrawal and is titrated for best effect
- Do not attribute altered mental status to opioid toxicity solely based on positive drug screen results; the screen is qualitative not quantitative
  - May present along with head trauma, which can hinder restoration of consciousness

SELECTED REFERENCES

1 Boyer EW: Management of opioid analgesic overdose. N Engl J Med. 367(2):146-55, 2012
2 Centers for Disease Control and Prevention (CDC): CDC grand rounds: prescription drug overdoses - a U.S. epidemic. MMWR Morb Mortal Wkly Rep. 61(1):10-3, 2012
3 Fareed A et al: Illicit opioid intoxication: diagnosis and treatment. Subst Abuse. 5:17-25, 2011
4 Weinhold LL et al: Opioid miosis: effects of lighting intensity and monocular and binocular exposure. Drug Alcohol Depend. 31(2):177-81, 1993
5 Alinejad S et al: A systematic review of the cardiotoxicity of methadone. EXCLI J. 14:577-600, 2015
6 Warner M et al: Drugs most frequently involved in drug overdose deaths: United States, 2010-2014. Natl Vital Stat Rep. 65(10):1-15, 2016
7 Dunn KM et al: Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med. 152(2):85-92, 2010
8 Häkkinen M et al: Parenteral buprenorphine-naloxone abuse is a major cause of fatal buprenorphine-related poisoning. Forensic Sci Int. 232(1-3):11-5, 2013
9 Lavonas EJ et al: Root causes, clinical effects, and outcomes of unintentional exposures to buprenorphine by young children. J Pediatr. 163(5):1377-83.e1-3, 2013
10 Smith HS: Opioid metabolism. Mayo Clin Proc. 84(7):613-24, 2009
11 Chen LH et al: Drug-poisoning deaths involving opioid analgesics: United States, 1999-2011. NCHS Data Brief. 1-8, 2014
12 Pedapati EV et al: Toddlers requiring pediatric intensive care unit admission following at-home exposure to buprenorphine/naloxone. Pediatr Crit Care Med. 12(2):e102-7, 2011
13 Andrzejowski P et al: Codeine in paediatrics: pharmacology, prescribing and controversies. Arch Dis Child Educ Pract Ed. 101(3):148-51, 2016
14 WHO: Information sheet on opioid overdose. WHO website. Published November 2014. Accessed May 22, 2019. http://www.who.int/substance_abuse/information-sheet/en/
15 Williams R et al: Emergency diagnosis of opioid intoxication. Lab Med. 31(6):334-42, 2000
16 Miller H et al: Loperamide misuse and abuse. J Am Pharm Assoc (2003). 57(2S):S45-S50, 2017
17 Erickson TB et al: The approach to the patient with an unknown overdose. Emerg Med Clin North Am. 25(2):249-81; abstract vii, 2007
18 Boyer EW et al: Methadone and buprenorphine toxicity in children. Am J Addict. 19(1):89-95, 2010
19 Nelsen JL et al: Management considerations following overdoses of modified-release morphine preparations. World J Emerg Med. 1(1):75-6, 2010
20 Bickell WH et al: Life-threatening opioid toxicity. In: Dellinger RP, ed: The Substance Abuser: Problems in Critical Care. Philadelphia, PA: Lippincott; 1987:106
21 Clarke SF et al: Naloxone in opioid poisoning: walking the tightrope. Emerg Med J. 22(9):612-6, 2005
22 van Dorp E et al: Naloxone reversal of buprenorphine-induced respiratory depression. Anesthesiology. 105(1):51-7, 2006
23 Gal TJ: Naloxone reversal of buprenorphine-induced respiratory depression. Clin Pharmacol Ther. 45(1):66-71, 1989
24 Berna C et al: Tapering long-term opioid therapy in chronic noncancer pain: evidence and recommendations for everyday practice. Mayo Clin Proc. 90(6):828-42, 2015
25 Olfson M et al: Risks of fatal opioid overdose during the first year following nonfatal overdose. Drug Alcohol Depend. 190:112-9, 2018
26 QuickStats: Rates of deaths from drug poisoning and drug poisoning involving opioid analgesics -- United States, 1999–2013. CDC website. Published January 16, 2015. Accessed May 22, 2019. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6401a10.htm
27 Centers for Disease Control and Prevention (CDC): Community-based opioid overdose prevention programs providing naloxone - United States, 2010. MMWR Morb Mortal Wkly Rep. 61(6):101-5, 2012
28 Beletsky L et al: Prevention of fatal opioid overdose. JAMA. 308(18):1863-4, 2012
29 American Heart Association: CPR and EEC Guidelines: Summary of Key Issues and Major Changes. AHA website. Accessed May 22, 2019. https://eccguidelines.heart.org/index.php/circulation/cpr-ecc-guidelines-2/part-10-special-circumstances-of-resuscitation/highlights-introduction/highlights/

Published April 21, 2016; Updated May 31, 2019