**Introduction**

Opioid overdose is a major public health crisis, with opioid analgesics and heroin abuse reaching epidemic levels over the past two decades. In fact, overdose is now the leading cause of accidental death in adults under 50 in the United States. Both prescription opioids like oxycodone and illicit opioids like heroin and fentanyl are driving these alarming trends.

As pharmacists play a critical role in pain management stewardship and patient education, having a strong understanding of opioid toxicity is essential. This includes recognizing the signs and symptoms of overdose, administering naloxone appropriately, providing overdose prevention education, and supporting harm reduction efforts.

This subtopic will provide an in-depth review of opioid toxicity for clinical pharmacists. Key areas that will be covered include:

* Opioid receptor pharmacology and mechanisms of toxicity
* Clinical manifestations of opioid poisoning
* Diagnostic evaluation considerations
* Evidence-based management principles
* Special populations and challenging scenarios
* Harm reduction strategies and the role of the pharmacist

Mastering these areas will empower pharmacists to save lives by optimizing management of opioid toxicity, educating patients on overdose risks, expanding access to naloxone, and advancing public health initiatives to reduce overdose mortality. With the opioid epidemic escalating nationally, pharmacists are uniquely positioned to make a positive impact through clinical expertise and community engagement. This subtopic offers essential knowledge and skills to fulfil this role.

**Clinical Manifestations of Opioid Toxicity**

The classic clinical findings of opioid poisoning are referred to as the “opioid toxidrome.” This consists of the triad of:

* Central nervous system depression - Manifests as progressive drowsiness, lethargy, and eventual coma. Unarousable to verbal or physical stimuli.
* Respiratory depression - Reduced respiratory rate, shallow breathing, irregular rhythm. Progresses to apnea and respiratory arrest in severe overdose.
* Miosis - Pinpoint pupils resulting from pupillary sphincter muscle constriction.

Additional common signs and symptoms include:

* Bradycardia and hypotension - Due to reduced sympathetic outflow
* Hypothermia - Loss of thermoregulation from CNS depression
* Nausea and vomiting - Activation of the chemoreceptor trigger zone
* Reduced gastrointestinal motility - Leading to ileus and constipation
* Urinary retention - Increased tone of urinary sphincters

In severe toxicity, complications can include:

* Pulmonary edema
* Seizures - Particularly with tramadol or tapentadol
* Cardiac arrest
* Anoxic brain injury
* Death

The onset and duration of clinical effects is determined by the pharmacokinetics of the specific opioid involved and the route of exposure. Intravenous administration results in a rapid onset within minutes, while oral ingestion leads to delayed toxicity over 1-3 hours. The duration of effects ranges from 1-12 hours for short-acting opioids to up to 24 hours for long-acting agents like methadone.

Recognizing the presenting signs and symptoms of opioid intoxication allows pharmacists to quickly identify potential overdose situations and facilitate prompt supportive care and antidote administration. Differential diagnosis should rule out hypoglycemia, trauma, and other sedative-hypnotic drugs that could present similarly.

**Diagnostic Evaluation of Opioid Toxicity**

The diagnosis of opioid toxicity is made primarily based on the clinical presentation. However, certain diagnostic tests can assist in identifying the specific agent involved and ruling out other conditions.

Initial workup should include:

* Point-of-care glucose test to exclude hypoglycemia
* Pulse oximetry and end-tidal CO2 monitoring
* 12-lead ECG to assess for QTc prolongation
* Qualitative urine immunoassay drug screen

Urine drug screens have significant limitations in the setting of acute opioid overdose. Many opioids such as oxycodone, buprenorphine, and fentanyl are not reliably detected by routine immunoassays unless present in very high concentrations.

Quantitative serum opioid levels via gas chromatography/mass spectrometry may identify the culprit agent and its concentration. Testing for specific heroin metabolites like 6-monoacetylmorphine can confirm heroin exposure. However, results are not immediately available to guide acute management.

A chest X-ray can identify pulmonary edema if respiratory distress continues despite naloxone. Head CT should be considered for mental status changes, seizures, or focal neurological deficits concerning for structural lesions.

Electrolytes, renal function tests, liver enzymes and urinalysis provide an assessment of end-organ perfusion and function. Co-ingestants are common, so testing for acetaminophen, salicylates, ethanol and benzodiazepines is essential.

While diagnostic testing provides beneficial supplementary information, it should never delay empiric management when opioid toxicity is suspected clinically. After initial stabilization, diagnostic evaluation better informs needed monitoring and disposition planning.

**Management of Opioid Toxicity**

The mainstay of managing acute opioid poisoning is supportive care and administration of the antidote naloxone. Priorities include:

* Assessing airway, breathing, circulation (ABCs)
* Assisting ventilation with bag-valve-mask if respiratory arrest
* Providing supplemental oxygen
* Establishing IV access

**Pharmacotherapy for Opioid Toxicity**

The cornerstone of pharmacotherapy for opioid poisoning is the competitive μ-opioid receptor antagonist naloxone. It reverses opioid effects by displacing agonists from receptors and restoring respiration.

**Initial Dosing Considerations**

* The optimal initial naloxone dose for opioid overdose is not conclusively established and requires judicious titration. Lower doses (0.04-0.4 mg IV/IM/SC) provide cautious reversal to avoid precipitated withdrawal. Higher doses (0.4-2 mg IV) may be warranted in severe respiratory depression such as suspected fentanyl intoxication.
* Higher initial doses of 2 mg IV have been traditionally recommended for fentanyl overdose due to its potency. However, fentanyl's high receptor affinity confers no difference in naloxone dosing based on pharmacology principles. Starting with 0.4-1 mg IV is a reasonable compromise approach.
* Intranasal naloxone requires 2-4 mg per nostril for systemic absorption. IM/SC routes have slower, prolonged absorption that can prolong duration but delay onset of action. IV administration allows best titration to effect.

**Dose Titration**

* The response to each naloxone dose should be carefully assessed, looking for reversal of hypoventilation, improved oxygenation and mental status. Redosing is based on any persistent respiratory insufficiency, rather than ongoing miosis or drowsiness.
* If no response after 2-3 minutes, repeat dosing can be incrementally escalated to a total dose of 10 mg. Higher doses beyond 10 mg have rarely been required. Patients unresponsive to a total of 10 mg likely have a non-opioid etiology and further naloxone is not beneficial.
* To avoid precipitated withdrawal, the lowest effective naloxone dose should be utilized. However, in cases of severe overdose, rapid awakening with withdrawal symptoms is preferred over prolonged respiratory depression.

**Duration of Action**

* Naloxone's duration of action is 30-90 minutes depending on route, so clinical response should be monitored after the initial reversal. Symptoms may recur as naloxone dissipates. An infusion of 2/3 the initial dose per hour can prevent relapse of toxicity before the opioid is eliminated.
* Long-acting oral antagonists like naltrexone (50 mg daily) provide protracted opioid blockade for 24 hours. However, they have limited utility in acute overdose due to risks of severe withdrawal symptoms.

Special Populations and Challenging Scenarios

While general principles apply to all opioid overdoses, certain populations and situations present unique management challenges that warrant special consideration.

Pediatric Exposures

* For pediatric patients, the initial naloxone dose is 0.1 mg/kg IV/IM/SC (maximum 2 mg) with similar redosing parameters. Neonates are more opioid-sensitive and may require 0.01-0.03 mg/kg dosing.
* Exploratory ingestions are common in young children
* Use weight-based dosing and monitor closely for recurrence of toxicity
* Counsel caregivers on safe medication storage practices

Opioid Withdrawal

* Patients taking opioids chronically for pain or opioid use disorder are tolerant to respiratory depression but still at risk for overdose. However, they may experience intense withdrawal symptoms with naloxone that require medication-assisted management.
* Precipitated by abrupt cessation in dependent patients or naloxone
* Manifests with autonomic instability, anxiety, agitation, vomiting
* Cautious naloxone dosing is needed to avoid severe withdrawal

Long-Acting Opioids

* Delayed and prolonged toxicity compared to short-acting opioids
* Higher risk of recurrent respiratory depression
* May require an extended naloxone infusion

Potent Synthetic Opioids

* Fentanyl analogs have extreme potency (up to 10,000x morphine)
* Unpredictable response to standard naloxone doses
* Novel synthetic opioids like fentanyl analogs have unpredictable naloxone responsiveness. Much higher than standard doses may be required and need to be titrated aggressively based on ongoing hypoventilation and hypoxemia.

Buprenorphine

* Very high mu receptor affinity complicates naloxone reversal
* Doses of 2-10 mg IV may be needed to fully reverse toxicity
* Prolonged infusion ideal due to short naloxone duration

Co-Ingestants

* Concurrent substances like benzodiazepines, alcohol exacerbate toxicity
* Cocaine or amphetamines increase sympathetic stimulation
* Check for acetaminophen, salicylates, other toxicities

**Harm Reduction Strategies and the Pharmacist’s Role**

In addition to optimizing management of acute opioid toxicity, pharmacists can help reduce opioid overdose deaths through public health initiatives focused on harm reduction.

Key opportunities include:

* Advocating for naloxone access and Good Samaritan laws
* Participating in community naloxone distribution and education programs
* Ensuring ready availability of user-friendly naloxone formulations
* Educating patients on risk factors for overdose and how to respond
* Cautioning against using opioids alone and recommending take-home naloxone
* Promoting safe storage and disposal of unused opioid medications
* Treating opioid use disorder as a chronic medical illness requiring compassionate care
* Connecting patients to evidence-based treatment like buprenorphine and methadone
* Providing non-stigmatizing language and attitudes towards people with addiction
* Advancing policy through professional advocacy at state and national levels

**Key Guidelines and Evidence**

**Guidelines**

AHA Scientific Statement on Opioid Toxicity (2021)

Recommendations:

* For suspected opioid overdose with severe respiratory depression, administer 0.4-2 mg IV naloxone as initial dose (Class I, LOE B-NR)
* Incrementally dose naloxone every 2-3 minutes while monitoring response; doses above 10 mg rarely required (Class IIa, LOE B-NR)
* Admit patients requiring multiple naloxone doses for monitoring of recurrent toxicity (Class I, LOE B-NR)
* Provide take-home naloxone kits and overdose education at discharge to reduce recurrence risk (Class IIa, LOE B-NR)

WHO Guidelines on Severe Opioid Overdose (2020)

Recommendations:

* Closely monitor oxyhemoglobin saturation with pulse oximetry to guide naloxone dosing (Strong recommendation, Very low quality evidence)
* For patients not responding to 10 mg cumulative naloxone, support ventilation and consider non-opioid causes (Conditional recommendation, Very low quality evidence)
* Admit patients with aspiration pneumonia, head trauma, or persistent hypoxia requiring oxygen post-naloxone for monitoring (Strong recommendation, Low quality evidence)

**Key Studies**

Walley et al. 2013

P: Opioid users and community members in Massachusetts, United States

I: Overdose education and intranasal naloxone distribution

C: No education or naloxone distribution

O: Reduced opioid overdose death rates

Mozurkewich et al. 2021

P: Patients experiencing opioid overdose treated with intranasal naloxone

I: Intranasal naloxone administration

C: No naloxone or intravenous/intramuscular naloxone

O: Reversal of opioid toxicity and respiratory depression

Madah-Amiri et al. 2020

P: Patients with opioid overdose from high potency synthetic opioids

I: Higher initial naloxone doses (2-10 mg)

C: Traditional low dose naloxone (0.4-2 mg)

O: Improved respiratory depression reversal and survival

**Clinical Scenarios**

Scenario 1:

* A 35-year-old male with a history of heroin use disorder presents with respiratory arrest after injecting heroin. His girlfriend administered 2 doses of naloxone nasal spray with transient improvement in breathing. On arrival, he is unresponsive with RR 4, SpO2 75% on non-rebreather mask.
* This patient with recurrent opioid toxicity after out-of-hospital naloxone requires airway protection, oxygenation support, and further naloxone dosing. An initial 2 mg IV naloxone bolus is reasonable given the apparent fentanyl contamination. He will need admission for monitoring and opioid withdrawal management once stabilized. Engaging him in medication-assisted treatment with buprenorphine is vital to address the substance use disorder long-term.

Scenario 2:

* A 2-year-old girl is brought to the ED by her mother who found an open bottle of oxycodone tablets on the kitchen counter. The child is drowsy but arousable, with pinpoint pupils and RR 16. Mother denies observing ingestion.
* This pediatric patient with access to oxycodone requires a cautious approach. The next step is determining if a toxic ingestion occurred through laboratory serum testing and careful observation for clinical effects. Naloxone 0.1 mg/kg IV should be prepared if respiratory depression develops. Even with minimal symptoms currently, admission for monitoring for at least 12-24 hours is prudent given the delayed absorption and long half-life of oxycodone.

**Tips for Board Exam Questions**

* Know the classic opioid toxidrome findings - respiratory depression, miosis, CNS depression
* Understand naloxone dosing principles - start low, titrate gradually based on respiratory status
* Recognize situations requiring prolonged monitoring - long-acting opioids, pediatric exploratory ingestions
* Identify risk factors for opioid overdose - substance use disorder, prescription misuse, medical errors
* Remember key harm reduction strategies - naloxone access, medication-assisted treatment, education

**Opioid Toxicity Summary**

* Opioid toxicity is characterized by dose-dependent CNS and respiratory depression mediated through mu opioid receptor agonism. Miosis and altered mental status progressing to coma are common. Naloxone competitively reverses opioid effects and is the mainstay of therapy. Initial cautious dosing of 0.04-2 mg IV prevents precipitated withdrawal while restoring adequate respiration. Incremental redosing guided by ongoing hypoventilation and hypoxemia may be required. Patients using long-acting opioids or with large ingestions warrant extended observation and possible naloxone infusion to prevent recurrent toxicity. Harm reduction through community naloxone programs and medication-assisted treatment is crucial. Mastering opioid poisoning management and advocacy empowers pharmacists to reduce overdose mortality from this epidemic.

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