Toxicology

Drug Overdose: Clinical Manifestations and Management

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Drug Overdose

- Drug overdose is a serious medical emergency that occurs when a person takes a toxic amount of a substance
- Overdose can lead to a wide range of symptoms and complications, often requiring immediate medical attention
- Understanding the clinical manifestations and appropriate management strategies for different drug overdoses is crucial for healthcare providers to effectively treat patients and minimize morbidity and mortality

Stimulants

- Stimulants are a class of drugs that increase the activity of the brain and the spinal cord. They are used for various purposes, such as enhancing alertness, attention, motivation, cognition, mood, and physical performance.
- Some examples of stimulants include:
  - Cocaine
  - Methamphetamines
  - Amphetamines

Stimulants

- Clinical Manifestations of Overdose:
  - Tachycardia: Rapid heart rate, often exceeding 100 beats per minute
  - Hypertension: Elevated blood pressure
  - Agitation: Restlessness, irritability, and hyperactivity
  - Hyperthermia: Elevated body temperature, sometimes leading to organ damage
  - Seizures: Abnormal electrical activity in the brain resulting in convulsions

Management Recommendations/Monitoring:

- ABCs (Airway, Breathing, Circulation): Ensure adequate oxygenation and ventilation, EKG
- Benzodiazepines for agitation: Drugs such as lorazepam or diazepam can help calm the patient
  - Helpful in reducing blood pressure and seizure management
  - Lorazepam, diazepam, midazolam (IV if possible)
- Cooling measures for hyperthermia: Use cooling blankets or ice packs to reduce body temperature
- Continuous cardiac monitoring: Monitor vital signs and cardiac rhythm closely for signs of arrhythmias
  - Nitroprusside or phentolamine for hypertension

Cocaine Overdose Management

- Cocaine induced MI
  - Avoid beta-blockers in cocaine OD
  - Aspirin 325 mg QD
  - Nitroglycerin 0.4 mg SL
  - Phentolamine
  - Sodium bicarbonate for QRS widening on EKG

Anticholinergics

- Drugs that block the action of Acetylcholine at both central and peripheral nervous system synapses. Acetylcholine is an excitatory neurotransmitter that plays a role in memory, learning, arousal and muscle action.
- Some examples of Anticholinergics include:
  - Tricyclic antidepressants(TCAs); Nortriptyline, Doxepin and Amitriptyline
  - First-gen antihistamines; Diphenhydramine and Doxylamine
  - Antipsychotic medication; Clozapine and Quetiapine

Anticholinergics

- Clinical Manifestations of Overdose:
  - Dry mouth: Decreased salivation leading to dryness in the mouth
  - Dilated pupils: Enlarged pupils due to inhibition of the parasympathetic nervous system
  - Urinary retention: Inability to urinate
  - Delirium: Acute confusion state characterized by altered consciousness and cognitive impairment
  - Hyperthermia
  - Hypotension, tachycardia, QRS widening on EKG

Management Recommendations/Monitoring:

- Supportive care: Maintain hydration (isotonic crystalloid bolus for hypotension) and monitor for complications such as hyperthermia
- Physostigmine for severe cases of delirium: A cholinesterase inhibitor that can reverse anticholinergic toxicity
  - May add lorazepam to manage agitation and seizures
  - Avoid antipsychotics for delirium in this situation (especially first generation) as many of them carry significant anticholinergic activity
- Continuous monitoring of vital signs: Monitor heart rate, blood pressure, and temperature regularly
- QRS widening (>100 ms) – consider sodium bicarbonate

Serotonergic Agents

- Serotonin agents are medications that affect serotonin levels in the brain and are used to treat various conditions such as depression, anxiety, and certain types of pain.
- Some examples of Serotonin Agents include;
  - Selective Serotonin Reuptake Inhibitors (SSRIs): Fluoxetine, Sertraline, Paroxetine, and Citalopram
  - Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs): Venlafaxine, Duloxetine and Desvenlafaxine
  - Tricyclic Antidepressants (TCAs): Amitriptyline, Imipramine, and Nortriptyline
  - Monoamine Oxidase Inhibitors (MAOIs): phenelzine and tranylcypromine

Serotonergic Agents

- Clinical Manifestations of Overdose:
  - Serotonin Syndrome:
    - Hyperthermia: Elevated body temperature
    - Agitation: Restlessness and increased activity
    - Diaphoresis: Profuse sweating
    - Tremors and hyperreflexia: Involuntary shaking movements

Management and Monitoring

- Discontinuation of serotonergic agents: Stop all medications that increase serotonin levels
- Supportive care: Provide hydration, oxygen, and temperature regulation
- For very high temperature, (>41.1 Celsius) treat immediately with sedation, paralysis, and intubation
- Benzodiazepines for sedation, agitation and/or seizures: Manage symptoms of agitation with sedatives (lorazepam IV)
  - Cyproheptadine as an alternative for non-responders
- Continuous monitoring for complications: Monitor vital signs and neurological status closely for deterioration
- EKG for QTc prolongation risk

Hallucinogens

- Hallucinogens are a class of drugs that cause hallucinations, alterations in perception, and profound changes in thought processes and emotions.
- Some examples of hallucinogens include;
  - LSD (Lysergic Acid Diethylamide)
  - Psilocybin (Magic Mushrooms)
  - DMT (Dimethyltryptamine)
  - PCP (Phencyclidine)

Hallucinogens

- Clinical Manifestations of Overdose:
  - Hallucinations: Perceptual distortions or false sensory experiences
  - Anxiety: Feelings of fear or apprehension
  - Psychosis: Loss of contact with reality, including delusions and hallucinations
  - Tachycardia: Rapid heart rate
  - Hypertension: Elevated blood pressure

Management and Monitoring

- Supportive care in a calm environment: Provide reassurance and a safe environment
- Benzodiazepines for severe agitation or psychosis: Manage symptoms with sedatives to promote relaxation
  - Antipsychotics may used in conjunction if necessary
- Continuous monitoring for potential complications: Monitor vital signs and mental status regularly to detect any worsening of symptoms

Opioids

- Opioids are natural, semisynthetic and synthetic products that mimic the natural substance obtained from the opium poppy plant that are usually used to reduce moderate to severe pain.
- Some examples of Opioids are;
  - Oxycodone
  - Hydrocodone
  - Fentanyl
  - Morphine
  - Heroin
  - Codeine

Opioids

- Clinical Manifestations of Overdose:
  - Respiratory depression: Slow or shallow breathing, cyanosis
  - CNS depression: Sedation, confusion, coma
  - Pinpoint pupils: Constricted pupils (miosis)
  - Hypotension: Low blood pressure
  - Bradycardia: Slow heart rate

Management and Monitoring

- ABCs (Airway, Breathing, Circulation): Ensure airway patency, administer oxygen if needed (<90% saturations)
- Naloxone administration: Reversal agent for opioid overdose, titrate to effect
- Supportive care: Monitor vital signs, provide respiratory support if necessary
- Consideration of long-acting opioid antagonists (e.g., naltrexone) for sustained reversal
- EKG is more critical for methadone and loperamide (QTC prolongation risk)

Benzodiazepines

- Benzodiazepines (benzos) and Z-drugs (non-benzodiazepine hypnotics) are central nervous system depressants commonly prescribed for conditions such as anxiety, insomnia, and certain seizure disorders.
- Some examples include;
  - Benzodiazepines: Alprazolam , Clonazepam, Diazepam, Lorazepam, Midazolam, Temazepam, Flunitrazepam
  - Z-drugs (non-benzodiazepine): Zolpidem, Zaleplon, Eszopiclone

Benzodiazepines

- Clinical Manifestations of Overdose:
  - CNS depression: Sedation, confusion, coma
  - Respiratory depression: Slow or shallow breathing
  - Hypotension: Low blood pressure
  - Bradycardia: Slow heart rate
  - Hyporeflexia: Decreased or absent reflexes

Management and Medication

- ABCs (Airway, Breathing, Circulation): Ensure airway patency, administer oxygen if needed
- Flumazenil administration: Reversal agent for benzodiazepine overdose, use with caution due to potential for seizures
  - Use is controversial
- Supportive care: Monitor vital signs, provide respiratory support if necessary

Flumazenil Use

- Contraindications
  - Given to patients with altered mental status with unclear diagnosis
  - Altered mental status with suspected seizure
  - History of seizures (controversial)
    - Some experts may give lower dosages
  - Co-ingestion of seizure promoting drug (Bupropion, TCA)
  - Using benzo for seizures

Alcohol

- Alcohol overdose, also known as alcohol poisoning, can occur when a person consumes a large amount of alcohol in a short period of time. Any alcoholic beverage, including beer, wine, and spirits, can lead to overdose if consumed excessively.
- Examples of alcoholic beverages;
  - Hard Liquor/Spirits
  - High-Alcohol Craft Beers
  - Fortified Wines (Higher alcohol content wines)

Alcohol

- Clinical Manifestations of Overdose:
  - CNS depression: Sedation, confusion, coma
  - Respiratory depression: Slow or shallow breathing
  - Hypotension: Low blood pressure
  - Hypothermia: Low body temperature
  - Hypoglycemia: Low blood sugar levels

Management and Monitoring

- ABCs (Airway, Breathing, Circulation): Ensure airway patency, administer oxygen if needed
- Supportive care: Monitor vital signs, provide respiratory support if necessary
- Lavage and Activated Charcoal not effective (alcohol is absorbed quickly)
- Fluid resuscitation: Address dehydration and electrolyte imbalances
  - Isotonic crystalloid
- Consideration of glucose supplementation: Correct hypoglycemia if present
- Thiamine administration: Prevent Wernicke's encephalopathy in chronic alcoholics
  - Give IV in comatose patients

Marijuana

- Marijuana, also known as cannabis, is generally considered to have a low risk of overdose compared to many other substances. However, consuming extremely high doses of THC (tetrahydrocannabinol), the psychoactive compound in marijuana, can lead to adverse effects.
- Some forms of marijuana products;
  - Marijuana-infused edibles; Cookies, brownies, candies, and beverages
  - Cannabis concentrates, Hash oil, wax, shatter, or dabs
  - Synthetic cannabinoids: Synthetic marijuana or spice

Marijuana

- Clinical Manifestations of Overdose:
  - CNS effects: Euphoria, relaxation, altered perception of time
  - Psychomotor impairment: Decreased coordination, impaired judgment
  - Cardiovascular effects: Tachycardia, orthostatic hypotension
  - Respiratory effects: Bronchodilation, coughing
  - Psychiatric effects: Anxiety, paranoia, psychosis (rare)

Management and Monitoring

- Supportive care: Reassurance and observation in a calm environment (dim lights, reduce stimulation)
- Symptomatic treatment: Address symptoms such as anxiety or nausea if present
  - Benzo for anxiety if supportive care measures aren’t effective
- Monitoring for complications: Assess for any adverse reactions or exacerbation of psychiatric conditions
- Education: Provide counseling on the risks of marijuana use and potential interactions with other substances

OTC Analgesics

- Overdosing on over-the-counter (OTC) analgesics, such as acetaminophen (APAP) and nonsteroidal anti-inflammatory drugs (NSAIDs), can have serious consequences.
- Here are some examples:
  - Acetaminophen: can lead to liver damage, liver failure, and even death if not treated promptly. maximum daily limit is typically 4 grams for adults
  - NSAIDs: can cause gastrointestinal bleeding, kidney damage, and cardiovascular problems

Acetaminophen

- Clinical Manifestations of Overdose:
  - Early symptoms: Nausea, vomiting, diaphoresis
  - Later symptoms: Right upper quadrant pain, hepatic tenderness
  - Laboratory findings: Elevated liver enzymes, coagulopathy
  - Fulminant hepatic failure: Jaundice, encephalopathy, renal failure

APAP Management and Monitoring

- Activated charcoal administration:
  - Consider in cases of significant overdose within 4 hours of ingestion
  - Reduces absorption of acetaminophen from the gastrointestinal tract
- Early administration of N-acetylcysteine (NAC) if possible
  - NAC replenishes hepatic glutathione, preventing or reversing hepatotoxicity
  - Oral or intravenous NAC regimens are available depending on the severity of the overdose

Acetylcysteine Indications

- Acetaminophen serum concentration above the treatment line (see next slide – Rumack Matthew Monogram)
- Serum acetaminophen concentration is unavailable or will not return within 8 hours of time of ingestion and suspected ingestion of >150 mg/kg (7.5 g total dose regardless of weight) of acetaminophen
- Reliable history with previous ingestions causing use of acetylcysteine or causing higher concentrations or elevated LFTs
- History of liver injury with acetaminophen
- Unreliable history, elevated acetaminophen concentration

APAP Management and Monitoring

- Supportive care: Monitor liver function tests, provide symptomatic treatment for nausea and vomiting
- Consultation with toxicology or hepatology services for severe cases
- Consideration of liver transplantation in cases of fulminant hepatic failure

NSAIDs

- Clinical Manifestations of Overdose:
  - Gastrointestinal effects: Nausea, vomiting, abdominal pain, gastrointestinal bleeding
  - Renal effects: Acute kidney injury, electrolyte abnormalities, metabolic acidosis
  - Cardiovascular effects: Hypertension (hypotension reported in severe overdose), heart failure, myocardial infarction (rare)

Management and Monitoring

- Activated charcoal within 2 hours of ingestion
- Symptomatic treatment: Address gastrointestinal symptoms, maintain hydration
- Monitoring for renal impairment: Check serum creatinine and electrolytes
- Supportive care: Monitor blood pressure and cardiovascular status

Aspirin

- Activated charcoal
- Avoid sedatives if possible (opioids/benzos) may worsen metabolic acidosis
- Volume replacement
- Use sodium bicarbonate to alkalinize
  - Remember MUDPILES (elevated anion-gap metabolic acidosis – S = Salicylates/Aspirin)

Substance Abuse

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Alcohol

Signs of Alcohol Abuse

- Higher tolerance
- Blackouts
- Concerns from friends/family
- Legal or financial issues
- Liver disease
- Signs of intoxication
  - Slurred speech, poor gait, confusion, vomiting, euphoria, disinhibition

Alcohol Addiction

- Loss of control
- Lack of other interests
- Withdrawal symptoms
  - Sweating, shaking, anxiety, DT’s
- Guilt
- Worry
- Change in relationships

Nutritional Deficiency

- Alcoholics often will have nutritional deficiencies
  - B12 deficiency
  - Thiamine
  - Folic acid
- Wernicke's Encephalopathy
  - Neurological disorder that can cause delirium
  - Typically due to lack of dietary thiamine

Alcohol Withdrawal

- Withdrawal symptoms when abstaining
  - Withdrawal symptoms include sweating, shakiness, GI upset, tremor
  - Severe withdrawal may include seizures, hallucinations and delirium tremens
- Delirium tremens
  - Most severe problem with withdrawal
  - Confusion, hallucinations, hypertension, sweating, tachycardia, agitation
  - Can be life threatening
  - DT typically begins 48-96 hours after last drink

Acute Withdrawal

- Severity of withdrawal scale
  - Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) – scored up to 67; higher score, the more likely patients need medication for withdrawal
  - >20 severe withdrawal
  - >8 consider pharmacotherapy
- Withdrawal seizures/DT's
  - Benzodiazepine – lorazepam, diazepam
  - Long-acting may provide more stable concentrations (i.e. diazepam, chlordiazepoxide)

Chronic Management

- Craving/Pleasure reduction
  - Naltrexone (Vivitrol, ReVia)
    - Mechanism of Action: Blocks mu receptors, not completely understood how, but it helps reduce reward sensation from drinking
    - May be given while patient is still drinking
    - Be careful in patients who are also on opioids as this medication will precipitate opioid withdrawal
    - GI side effects
    - Possible increase in LFT's, avoid if significantly elevated LFTs (3x upper limit of normal) or in liver failure which can be more likely in this patient population
    - Oral option given once daily or long acting injectable option is given every 4 weeks

Chronic Management

- Acamprosate (Campral)
  - Mechanism of Action: Not well understood, but reduces withdrawal symptoms
  - Recommended to be started after patient has been abstaining from alcohol
  - Improves abstinence
  - Contraindicated in CrCl less than 30 mls/min
  - Diarrhea is predominant side effect
  - Frequent dosing/adherence may be an issue with this patient population (TID)
  - Alternative to naltrexone as first-line therapy
- Disulfiram (Antabuse)
  - Mechanism of Action: Disulfiram inhibits complete metabolism of alcohol resulting in the disulfiram reaction
  - Disulfiram reaction: Dysphoric, headache, flushing, and GI symptoms when alcohol is ingested (negative feedback)
  - Need to take the medication for it to work
    - May not be a great option for patients who are unreliable or who are unsupervised

Smoking Cessation

Smoking Cessation

- First line Agents
  - Varenicline
    - Preferred by ATS
  - Nicotine replacement
  - Bupropion
- 2nd Line Agents
  - TCA's
  - Clonidine
- Counseling

Varenicline

- Mechanism of Action: Partial nicotine agonist which mildly stimulates nicotine receptors
- 12 week course which may be doubled to 24 weeks as necessary and tolerated for some patients
- Patients can still smoke while using this medication for the first week
  - Extended smoking duration added to labeling (can taper down over time, don’t just have to quit after the first week)
- Notorious adverse effect of vivid dreams
- Possible risk of psych changes
- Insomnia
- Nausea/vomiting

Nicotine Replacement Products

- Mechanism of Action: Replacement of nicotine to reduce withdrawal symptoms and ease cravings
- Patches
  - 3 doses; 21, 14, and 7 mg
  - Start with 21 mg for patients using 10 or more cigarettes per day
  - 14 mg patch for those using less than 10 cigarettes per day
  - Not intended for PRN use
  - Remove patch at night if patient experiences vivid dreams or sleep disturbances
- Gum
  - 4 mg and 2 mg dosages; use the 4 mg dose if the patient has their first cigarette within 30 minutes of awakening
  - Max 24 pieces per day

Nicotine Replacement Products

- Lozenge
  - Similar dosing to gum
  - Max 20 lozenges per day
- Nasal Spray
  - 2 sprays (1 in each nostril) considered one dose and is 1 mg of nicotine
  - Maximum of 40 doses per day (80 individual sprays)
- *Vaping is not considered a nicotine replacement product
- Smoking is generally discouraged while using NRT
  - Adjust dosing of NRT

Bupropion

- Activating
- Increases the risk of seizures (avoid use in patients with seizure history, alcohol abuse, and eating disorder history)
- Can be used for corresponding depression
- CYP2D6 inhibition
- May be used with NRT
- 150 mg BID target but once daily does have some proven efficacy

Alternatives

- Clonidine
  - Antihypertensive
  - Avoid in elderly
- Nortriptyline
  - Highly anticholinergic
  - Avoid in elderly

Opioids

Signs of Opioid Overdose

- Respiratory depression
  - Snoring like noise
  - Benzodiazepines and other sedatives enhance risk
- Unconsciousness
- Pinpoint pupils
- No bowel sounds
- Response to naloxone

Opioid Overdose Management

- Naloxone
  - Opioid antagonist
  - Reverses effects of prescription narcotic medications such as hydrocodone, hydromorphone, oxycodone, etc. as well as heroin
  - Can be administered IV/IM/SC and intranasal
  - Several states have “Good Samaritan” laws providing immunity to those who assist someone having an opioid overdose

Signs of Opioid Withdrawal

- Withdrawal when stopping use
  - Nausea
  - Sweating
  - Anxiety
  - Insomnia
  - Chills
  - Irritability

Drugs to Manage Opioid Withdrawal Symptoms

- Withdrawal
  - Clonidine
  - Diphenhydramine
  - Trazodone
  - Simple analgesics
  - Loperamide

Opioid Use Disorder

- All combined with psychotherapy
- Buprenorphine/naloxone (Suboxone)
  - Combination of a partial mu agonist and an opioid antagonist
  - Prevents reward, euphoria from other opioid agonists
  - Naloxone is included in the formulation to reduce abuse potential (reduce risk of injecting/snorting)
  - Will precipitate opioid withdrawal, but partial opioid agonist of buprenorphine may help blunt the severity of withdrawal symptoms
  - Can be started prior to full withdrawal
  - Schedule 3 controlled substance
  - Lower risk of respiratory depression compared to full agonist therapy with methadone

Opioid Use Disorder

- Naltrexone (Vivitrol, ReVia)
  - Mu antagonist – blocks the effect of opioid agonists
  - Needs to be taken regularly which may be challenging in some situations
  - Long acting injectable medication may improve adherence concerns (Vivitrol)
  - Precipitates withdrawal so shouldn’t be started for maintenance therapy until withdrawal is finished
  - Does not cause dependence compared to methadone/Suboxone so should not cause withdrawal symptoms when discontinued

Opioid Use Disorder

- Methadone
  - Very long half life
  - Prevents other opioids from binding to mu receptor so patients may not get as much euphoria from shorter acting opioids like heroin
  - Full agonist
    - Will cause sedation and other opioid like effects
  - Will prevent withdrawal as you are giving an opioid agonist
  - QTc drug interactions
  - Requires special dispensing from an opioid treatment program