All F'd Up and In Your Assignment:

Managing Acute Intoxication in the Emergency Department

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The speakers have no conflicts of interest to declare.

LEARNING OUTCOMES

1. *Describe selected toxidromes*
2. *Recall underlying pathophysiology*
3. *Describe appropriate interventions & treatment*

The Acutely Agitated and Intoxicated Patient

These patients have a *WIDE* differential, and the agitation may be secondary to a dangerous medical condition, including many significant threats to life[1]:

Table 1. Dangerous Causes of Agitation

System	Etiology
Metabolic/endocrine	Electrolyte abnormalities (e.g., sodium, calcium, magnesium, potassium, phosphate)
	Hypoglycemia
	Hyperglycemia (eg, DKA/HHNK)
	Hypoxia
	Hypercarbia
	Renal or liver failure
	Thyrotoxicosis
	Myxedema coma
	Nutritional deficiency (e.g., Wernicke's, vitamin B12 deficiency)
Infection	Sepsis
	Systemic infections
	Fever-related delirium
Neurologic	Head injury
	Stroke
	Intracranial mass
	Intracranial hemorrhage
	CNS infection (e.g., meningitis, encephalitis, abscess)
	Seizure
	Dementia
Toxicological	Anticholinergic intoxication
	Stimulant intoxication
	Steroid psychosis
	Antibiotic reaction
	Other drug reaction
	Carbon monoxide toxicity
	Alcohol intoxication or withdrawal
	Toxic alcohols
	Serotonin syndrome
	Neuroleptic malignant syndrome
Other conditions	Shock (e.g., hypovolemic, cardiogenic, distributive, obstructive)
	Burn
	Hypothermia
	Hyperthermia
Psychiatric	Psychosis
	Schizophrenia
	Paranoid delusions
	Personality disorder

Excited Delirium Syndrome (ExDS)

Elevated synaptic dopamine coupled with failed dopamine transported function leads to agitation, paranoia, and violent behaviors; CNS dopamine imbalance results in tachycardia, tachypnea, and hyperthermia, with the latter a "harbinger of death" in ExDS[2].

The clinical description of excited delirium includes reports of increasing excitement with wild agitation and violent, often destructive behavior that can last for hours to days. The forensic pathology descriptions suggest that the disorder can wax and wane in severity over time with rigidity or stupor alternating with excitement. These progress to increasing and possible fluctuations of fever and persistent autonomic instability with rapid and weak pulse and hypotension. Cocaine delirium shares clinical similarity to the acute onset of excitement, grandiosity, emotional lability, delusions, and insomnia associated with emergence of mania, and the disorientation and altered consciousness characteristic of delirium. Psychostimulant intoxication, drug withdrawal states, and undiagnosed mania and bipolar affective disorder are the most commonly reported antecedents[2].

Synthetic Cathinones aka "Bath Salts"

Synthetic drugs chemically related to cathinone, a psychostimulant found in the khat plant which provided psychostimulant and hallucinogenic effects similar to cocaine, 3,4-methylenedioxymethamphetamines (MDMA), methamphetamines, and amphetamines[3]. Brand names include Flakka, Cloud Nine, Lunar Wave, White Lightning, Bloom, Scarface, and Vanilla Sky[3].

Case studies[3] of cathinone intoxications describe symptoms such as tachycardia, hyperthermia, aggression, rhabdomyolysis, coagulopathy, anemia, acidosis, thrombocytopenia, anoxic brain injury, and cardiac arrest.

Acute Management

Prior to sedation, when safe to do so, begin with nonpharmacologic interventions[1]. Verbal de-escalation and attending to basic needs are a good starting point. Utilize the HALTTT questions (*"Are you Hungry Angry Lonely Tired Thirsty Toilet?")* as a basic framework.

If other means of de-escalation are not effective, pursue pharmacologic interventions[1]:

Table 4. Medications for the Treatment of the Agitated Patient

Type of Medication	Available Routes and Doses
Haloperidol	p.o./i.m./i.v.: 5 mg (maximum: 20 mg over 24 h)
Risperidone	p.o.: 2 mg (maximum: 6 mg over 24 h)
Olanzapine	p.o./i.m./i.v.: 5–10 mg (maximum: 20 mg over 24 h)
Ziprasidone	i.m.: 10–20 mg (Maximum: 40 mg over 24 h)
Aripiprazole	i.m.: 9.75 mg (Maximum: 30 mg over 24 h)
Lorazepam	p.o./i.m./i.v.: 2 mg
Midazolam	p.o./i.m./i.v.: 2 mg
Ketamine	i.m.: 4–6 mg/kg; i.v.: 1–2 mg/kg

p.o. = per os (orally); i.m. = intramuscular; i.v. = intravascular.

Haloperidol is a first-generation antipsychotic (FGA) which has a mean onset of sedation of 25-28 minutes, and a mean total sedation time of 84-126 minutes[1]. Second generation (atypical) antipsychotics (SGA) such as olanzapine, ziprasidone, risperidone have increasing literature for use. These agents work at D2 receptors (similar to FGAs), but also target 5-HT2A, histamine, norepinephrine, and alpha-2 receptors[1].

Ketamine has support of use in the acutely agitated patient. It targets a variety of receptors, has an onset of sedation of 5 minutes, and duration of effect of 5-30 minutes[1].

The goal of pharmacologic intervention is to provide a safe environment for the patient and staff to rapidly assess and support ABCDs and initiate appropriate diagnostics to guide further treatment. Ketamine is unlikely to resolve the underlying processes causing agitation and in this context it is used to gain rapid control of violent patients so that safe medical evaluation can proceed and treatment of the underlying cause can commence[4].

To the extreme of this idea is that with the presupposition of ExDS and its associated mortality, consider of performing rapid sequence induction (RSI) for intubation. Numerous reports (aka anecdotes) abound of the use of IM succinylcholine to obtain control of acutely agitated patients where other less invasive means have failed. As of this writing, none have been located in published literature. There is ample discussion of IM succinylcholine in the context of pediatric anesthesia, but it is a [WARNING] large step to extrapolate that data to the acutely ill ExDS population, so extreme caution is advised.

With that Warning: there are numerous accounts and anecdotes that have been relayed of IM succinylcholine 4mg/kg IM followed by endotracheal intubation, IV sedation, and ongoing management. The risks of this approach cannot be over-emphasized, as there is no turning back once the onset of paralysis is achieved. Practitioners MUST be agile in all means of airway securement including rescue methods (CICO), immediate vascular access (IV or IO), and hemodynamic support.

Making the Case for Dantrolene

Neuroleptic malignant syndrome (NMS) is a potentially fatal condition presenting in 0.002-3% of patients taking antipsychotic drug therapy that is characterized by hyperthermia, labile blood pressures, tachycardia, altered mental status, and muscle rigidity[5]. Diagnosis of NMS relies on history and symptomology. As acutely altered patients rarely provide a comprehensive history on presentation, recognizing the potential for NMS in an acutely altered patient is paramount, with the presence of muscular rigidity further driving a presumptive diagnosis. Further objective data supporting this diagnosis are metabolic acidosis, myoglobinuria, elevated creatinine and BUN, and ECG changes such as prolonged PR, QRS, and QT intervals along with ST and T-wave abnormalities[5].

Table 1. Diagnostic criteria via Diagnostic and Statistical Manual of Mental Disorders (DSM-5),[5] Levenson,[4] and Caroff and Mann.[6]

Source	Presentation features	Diagnostic criteria
Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[5]	•Exposure to dopamine antagonist within 72 hours prior to symptom development •Hyperthermia (>100.4°F or >38°C on at least two occasions) •Generalized rigidity •Creatine kinase elevation (at least four times upper limit of normal) •Changes in mental status •Autonomic instability (tachycardia, diaphoresis, blood pressure elevation or fluctuation, urinary incontinence, pallor)	Presence of these cardinal features are suggestive of diagnosis
	Major: •Fever •Rigidity •Elevated creatine phosphokinase concentration Minor: •Tachycardia •Abnormal arterial pressure •Tachypnea •Altered consciousness •Diaphoresis •Leukocytosis	Presence of all three major, or two major and four minor features
Caroff, Mann 1936	Major: •Treatment of neuroleptics within seven days of onset (2-4 weeks for depot) •Hyperthermia •Muscle rigidity •Exclusion of other drug-induced, systemic, or neuropsychiatric illnesses Minor: •Change in mental status •Tachycardia, hypertension or hypotension, tachypnea or silorrhea •Tremors •Incontinence •Creatine phosphokinase elevation or myoglobinuria, leukocytosis, metabolic acidosis	Presence of all four major items and five minor features

NMS Treatment Pathway[5]

1. Stop causative agent
2. Support ABCs
3. Benzodiazepines (lorazepam 1-2mg IM/IV every 4-6 hours or diazepam 10mg IV every 8 hours)
4. Dantrolene 1-2.5 mg/kg IV, repeat to maximum of 10mg/kg/day
5. Consider further medical management

Summary: K-ABC(D)

K: Obtain rapid control of acute agitation, consider ketamine 4-6mg/kg IM.

A: Maintain a patent airway, utilize RSI and intubation as clinically indicated

B: Support ventilation with FiO2 as clinically indicated

C: Support vascular volume with crystalloids as clinically indicated

(D): Consider dantrolene 1-2.5mg/kg IV when clinically indicated

Cocaine Intoxication

Cocaine is a naturally occurring highly addictive stimulant produced from the coca plant. It can be injected, snorted or smoked.

Cocaine acts an indirect sympathomimetic agent[6] and inhibits the reuptake of serotonin, dopamine, norepinephrine and epinephrine and is dose dependent. Higher doses leads to increased clinical manifestations.

Central Nervous System:

Dopamine and serotonin are responsible for the feel good sensation with increased sense of well being, confidence and euphoria at lower doses[7]. At higher doses, agitation is common.

Risks:

- Stroke risk increases by 7 times after cocaine use[8]. This is likely secondary to hypertension and vasoconstriction.
- Hyperthermia caused by increased heat production, peripheral vasoconstriction preventing heat from being dissipated and decreased ability to sense increased body temperature[9].

Cardiovascular System:

These stem from increased availability of norepinephrine & epinephrine. Manifestations can include: tachycardia, hypertension, vasoconstriction, increased myocardial oxygen demand , enhanced platelet aggregation and coronary vasospasm[6,10,11]. Chest pain can be a common symptom and is often what brings these patients to seek medical attention.

Risks:

- MI due to platelet aggregation, increased myocardial oxygen demand and coronary vasospasm. This put the cocaine user at a 24 times greater risk for MI during the first 60 minutes[12]. Typical STEMI treatment should be given regardless of cocaine use including fibrinolytic therapy or percutaneous intervention[10].

Treatment:

ABCs always, if the patient requires intubation, avoid succinylcholine as it can prolong paralysis and the effects of cocaine[6].

Otherwise, treatment utilizing **DAN**:

D: Diazepam 5 to 10mg IV every 3 to 5 minutes[6]. Benzodiazepines enhance the effect of GABA (gamma-aminobutyric acid) which helps to counteract epinephrine and norepinephrine[10].

A: Aspirin 325mg PO to decrease platelet aggregation[12] and decrease potential for thrombus formation.

N: Nitroglycerin 0.4mg SL and assess need for continuous nitroglycerin infusion to mediate hypertension[6,12].

Discharge of cocaine intoxication patients depends upon their clinical improvement. Any evidence of end organ damage should be followed with hospital admission[6].

Tricyclic Antidepressant (TCA) Overdose

Features consistent with sodium-channel blockade

Interventricular conduction delay — QRS > 100 ms in lead II

Right axis deviation of the terminal QRS:

Terminal R wave > 3 mm in aVR

R/S ratio > 0.7 in aVR

Patients with tricyclic overdose will also usually demonstrate **sinus tachycardia** secondary to muscarinic (M1) receptor blockade.

In overdose, the tricyclics produce rapid onset (within 1-2 hours) of:

Sedation and coma

Seizures
Hypotension
Tachycardia
Broad complex dysrhythmias
Anticholinergic syndrome
Tricyclics mediate their **cardiotoxic effects** via blockade of myocardial fast sodium channels (QRS prolongation, tall R wave in aVR), inhibition of potassium channels (QTc prolongation) and direct myocardial depression.
Other toxic effects are produced by blockade at muscarinic (M1), histamine (H1) and α_1-adenergic receptors. **The degree of QRS broadening on the ECG is correlated with adverse events:**
QRS > 100 ms is predictive of seizures
QRS > 160 ms is predictive of ventricular arrhythmias (e.g. VT)

(Source: https://litfl.com/tricyclic-overdose-sodium-channel-blocker-toxicity/)

The most common arrhythmia to occur due to TCA toxicity is sinus tachycardia and this is due to the anticholinergic properties of TCAs and the inhibition of NE. Hypotension occurs due to a reduction in myocardial contraction and reduced systemic vascular resistance due to the alpha-adrenergic blockade[13].

Acute Management[14]
QRS widening is the standard for determining toxicity.
The exact mechanism by which NaHCO3 acts to reverse Na channel blockade is not fully understood.
Some studies point to the increase in sodium concentration, other research favor alterations in pH.
Administration guidelines vary, but a general guideline is:
Administer Sodium Bicarbonate 8.4% 1-2 mEq/kg bolus to obtain a serum pH of 7.45-7.55, followed by an infusion of 150mEq in 1L D5W to maintain that pH (150mL/hr)

Intravenous Lipid Emulsion (ILE) Therapy[15]
Intravenous lipid emulsion (ILE) is emerging as a promising therapy for severe toxicity from lipophilic drugs.
Dosing recommendations remained to be largely based on its original indication for local anesthetic systemic toxicity (LAST)

Dosing Guidelines:
Intralipid 20% 1.5-4.5 mL/kg bolus followed by infusion at 0.25mL/kg/min

The Web site http://www. lipidrescue.org/ provides a wealth of information about the use of ILE for drug toxicity.
Currently, no standard of care exists dictating when lipids should be used to treat overdoses. Treatment is entirely based on the discretion of the clinician. Theoretically, the ideal patients for lipid therapy are those with severe hemodynamic compromise not responding to conventional methods of resuscitation[16].

2% Lidocaine[13]

If Sodium Bicarb fails to stabilize, consider other antiarrhythmic medications.
Lidocaine (Class Ib) acts as a sodium channel blocker, but does NOT depress the initial phase of depolarization in healthy cardiac tissue.
Furhter, it dissociates quicker from sodium channels than TCAs.
It is thought that by rapidly binding to sodium channels lidocaine directly displaces the slower depolarizing TCAs, leaving more channels unbound, and therefore facilitating cardiac conduction.

Summary: ABC-BLT

(ABCs, Bicarbonate, Lipid, Lidocaine Treatment)
A: Maintain a patent airway, utilize RSI and intubation as clinically indicated
B: Support ventilation with FiO2 as clinically indicated
C: Support vascular volume with crystalloids as clinically indicated
B: Sodium bicarbonate 1-2 mEq/kg bolus to obtain a serum pH of 7.45-7.55, followed by an infusion of 150mEq in 1L D5W to maintain that pH (150mL/hr)
L: Intralipid 20% 1.5-4.5 mL/kg bolus followed by infusion at 0.25mL/kg/min
L: Lidocaine 05-1.5mg/kg

Cannabinoid Hyperemesis

Cannabinoid Hyperemesis is a cyclical vomiting syndrome without other organic causes in the setting of cannabis use[17]. Typically, these patients have a history of frequent cannabis use for over a year at least weekly[18,19].

Three Phases[17]*:*

Prodromal Phase:
Early morning nausea, fear of vomiting and normal eating patterns exist in this phase which can last for months or years. Patients may increase cannabis use during this phase to help relieve nausea.
Hyperemetic Phase:
Intense periods of nausea and vomiting, up to 5 times per hour which may potentially be debilitating. Patients may have significant weight loss during this phase. Compulsive habits of warm bathing for symptom relief is also present in most patients. Clinically, patients appear dehydrated but otherwise hemodynamically stable. Patients often present for treatment during this phase.
Recovery Phase:
Occurs with complete cessation of cannabis use with total resolution of symptoms within 12 hours to 3 weeks. This includes normal eating patterns, regular bathing habits and weight gain.

Treatment:

-Complete cessation of cannabis is the only standard treatment[19].
-Admission if necessary for symptomatic management including IV hydration.
-Haldol 5mg IM may be helpful, while not fully understood it may be related to the blocking of dopamine[18].
-Proton pump inhibitors are used frequently to help alleviate symptoms of gastritis[17].
-Weight monitoring can be helpful to ensure adequate caloric intake and hydration status[17].

Accidental Pediatric Marijuana Ingestion

With the increasing legalization of marijuana, emergency departments have seen an increase in visits due to unintentional exposure to marijuana[20]. Any pediatric patient that is presenting with altered mental status or an onset of lethargy or ataxia, accidental ingestion should be considered[21].

The risk of accidental exposure especially with edible products as they often have attractive packaging[22] and appear to be candy or sweets.

Signs and Symptoms[23,24]:
-Drowsiness and lethargy
-Ataxia, dizziness
-Tachycardia
-Respiratory depression or apnea

Treatment is supportive in nature[24].
Maintain ABCs, provide airway management if needed, ensure euglycemia. Length of stay is dependent upon amount ingested and severity of symptoms[25].

Diagnosis of marijuana ingestion can be difficult especially in the setting of delay in seeking care and parental involvement. A urine drug screen can help to confirm the diagnosis[24].

As with all cases involving pediatrics, consider your state laws in regards to reporting to social services or child protective services[23,24].

Naloxone-Induced Non-Cardiogenic Pulmonary Edema (NCPE)

The first known case of pulmonary edema after [naloxone] administration was published by JW Flacke et al. in 1977[26]. (Anesthesiology 1977;47[4]:376.)

Naloxone is an opiate antagonist, and is used for reversal of opioid effects. The adverse reactions of this drug include hypertension, ventricular arrhythmias, cardiac arrest, seizures, and rarely, pulmonary edema. Naloxone-induced non-cardiogenic pulmonary edema (NCPE) has been scarcely reported in literature, and in order to recognize this complication, naloxone should be administered cautiously with closer observation of patients undergoing opioid detoxification[27].

Naloxone is a competitive mu-opioid-receptor antagonist that reverses the effects of opioid intoxication. Naloxone-induced NCPE is suggested to occur at a rate ranging from 0.2 to 3.6% in patients. The pulmonary edema is likely caused by an adrenergic response from a large increase in centrally mediated catecholamines following naloxone administration. When naloxone is given to a patient, a catecholamine-mediated response is elicited. The effect of catecholamines results in hypertension, tachycardia, and diaphoresis[27].

It is well established in emergency medicine that recreational over- dose on opiates is often deadly, usually before prehospital care is initiated. Severe cardiopulmonary complications from

naloxone are rare, but **fear of complications should never preclude the use of naloxone** in suspected overdose, even in the prehospital setting by bystanders and first responders. It would be meaningful for first responder personnel to be aware of the potential complications of naloxone, and to have a plan to activate the proper emergency services in the event of an arrest or severe dyspnea[26].

Questions are welcome!!!

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