Sedative/Hypnotic/Opioid Toxidromes

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- No financial disclosures

- All images are used solely for internal educational purposes

Paracelsus

All things are poisons, for there is nothing without poisonous qualities. It is only the dose which makes a thing poison.

AZ QUOTES

Toxicology is very complex!

- NEVER be afraid to look it up!
- Must think critically and understand why you are doing something and what the expected effect will be.

Primary treatment of most intoxications?

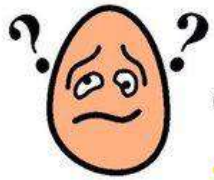
Supportive Care

TOXIDROMES

5 main toxidromes:

- Anticholinergic
- Cholinergic
- **Narcotic/Opioid**
- **Hypnotic/Sedative**
- Sympathomimetic

There are more toxidromes!

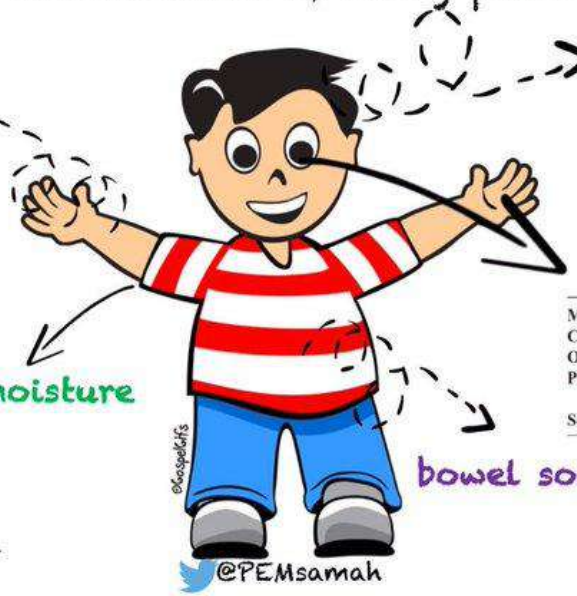


Toxidrome

Combination of the words "toxic" and "syndrome."

Toxidromes are groupings of physical signs that may help to suggest the drug class responsible for a poisoning.

The signs in the examination of every potentially poisoned patient:



pupil size and reactivity

Miosis (COPS)	Mydriasis (SAW)
Cholinergics, clonidine, carbamates	Sympathomimetics
Opiates, organophosphates,	Anticholinergics
Phenothiazines (antipsychotics), pilocarpine, pontine hemorrhage	Withdrawal
Sedative-hypnotics	

Toxicology

General Approach

INTOXICATIONS or DRUG OVERDOSES

↓

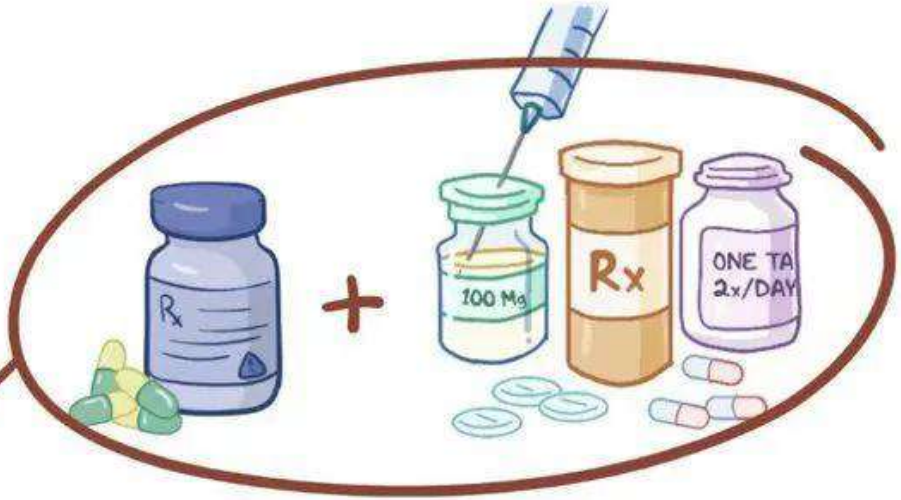
TOXIDROMES

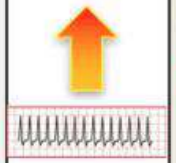
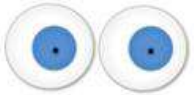
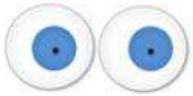
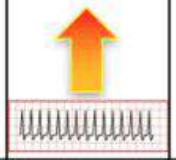
SYMPTOMS

CHARACTERISTIC FINDINGS

→ CERTAIN SUBSTANCE or CLASS of SUBSTANCES

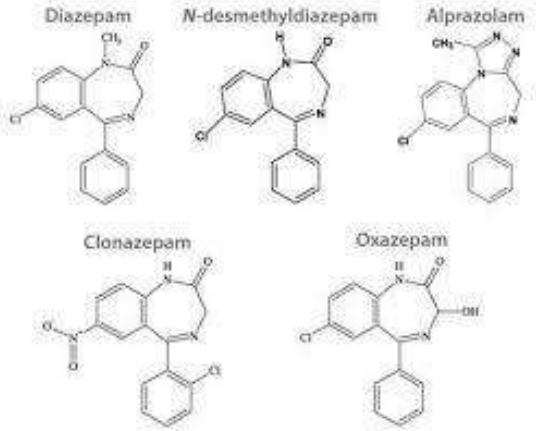
COMBINATION of FINDINGS



	HR & BP	Resp.	Temperature	Pupils	Bowel Sounds	Diaphoresis
Anticholinergic **Anticholinergics** –Atropine, scopolamine, glycopyrrolate benztropine, trihexyphenidyl **Antihistamines** – Chlorpheniramine, Cyproheptadine, Doxylamine, Hydroxyzine, Dimenhydrinate, Diphenhydramine, Meclizine Promethazine		No change 		Dilated 		
Cholinergic Organic Phosphorous Compounds: Carbamates • Arecholine, Pilocarpine, Urecholine (Betanechol), Carbachol, Choline, Metacholine, Mushrooms	No change 	No change 	No change 	Pinpoint 		
Opioid Morphine • Codeine • Tramadol • Heroin • Meperidine • Diphenoxylate • Hydromorphone • Fentanyl • Methadone • Propoxyphene • Pentazocine • DXM • Oxycodone • Hydrocodone				Pinpoint 		
Sympathomimetic Caffeine, cocaine, amphetamines, methamphetamines, Ritalin, LSD, Theophylline, MDMA				Dilated 		
Sedative-Hypnotic anti-anxiety agents, muscle relaxants, antiepileptics and preanesthetic medications –Barbituates –Benzodiazepines				No change 		

Toxidromes

TOXIDROME	CLINICAL FEATURES
Cholinergic	Vomiting, diarrhoea, excess salivation, lacrimation, urinary incontinence, miosis, bronchorrhoea, bronchospasm, bradycardia, muscle fasciculation, weakness
Anticholinergic	Tachycardia, hyperthermia, agitation, delirium, mydriasis, dry flushed skin, urinary retention
Cardiodepressant	Hypotension, bradycardia
Opioid	Deep sedation, miosis, respiratory depression
Salicylates	Rapid breathing, tinnitus, altered mental status, metabolic acidosis
Sedative-hypnotic	Coma with normal or depressed vital signs (moderate hypotension, bradycardia)
Sympathomimetic	Tachycardia, hypertension, hyperthermia, agitation, diaphoresis, mydriasis



Benzodiazepines

Benzodiazepines

What are benzodiazepines?

Benzodiazepines

- Sedative-hypnotic agents
- Used to treat anxiety, seizures, withdrawal states, insomnia, and drug-associated agitation
- Frequently combined with other medications for procedural sedation
- Widely prescribed

Benzodiazepine and nonbenzodiazepine hypnotic pharmacokinetics

Generic name	Trade name	Usual single adult dose (oral)	Oral peak (hours)	Half-life (hours) parent	Metabolite activity*	CYP3A4 interactions
Benzodiazepines						
Alprazolam	Xanax	0.25-0.5 mg	1-2	6-27	Inactive	Yes
Bromazepam¶	Lectopam	2-6 mg	1-2	8-20	Inactive	Limited
Chlordiazepoxide	Librium	5-25 mg	0.5-4	5-30	Active	Yes
Clobazam	Onfi	10-20 mg	0.5-4	36-42	Active (half-life 71-82 hours)	Limited (interacts via CYP2C19)
Clonazepam	Klonopin	0.25-0.5 mg	1-2	18-50	Inactive	Limited
Clorazepate	Tranxene	7.5-15 mg	1-2	Prodrug	Active	No
Diazepam	Valium	2-10 mg	0.5-1	20-50	Active	Limited
Estazolam	Prosom	0.5-2 mg	0.5-6	10-24	Inactive	Limited
Flunitrazepam¶	Rohypnol	0.5-2 mg	1-2	16-35	Active	Limited
Flurazepam	Dalmane	15-30 mg	0.5-1	2-4	Active	Limited
Lorazepam	Ativan	0.5-3 mg	2-4	10-20	Inactive	No
Midazolam	Versed	0.25 to 1 mg/kg maximum 20 mg (oral syrup for pediatric sedation)	1-2	1.5-3	Active	Yes
Oxazepam	Serax	10-30 mg	2-4	5-20	Inactive	No
Temazepam	Restoril	7.5-30 mg	1-2	3-19	Inactive	No
Triazolam	Halcion	0.125-0.25 mg	0.7-2	2-3	Inactive	Yes
Nonbenzodiazepine hypnotics						
Eszopiclone	Lunesta	1-3 mg	1	6-9	Active (less than parent)	Yes
Zaleplon	Sonata	5-15 mg	1	1	Inactive	Limited
Zolpidem	Ambien, Edluar, Zolpimist	5-10 mg	1-2	1.5-8.4	Inactive	Limited
Zopiclone¶	Immovane, Rhovane	3.75-7.5 mg	5-7	<2	Active (less than parent)	Yes
Other US FDA approved hypnotics						
Doxepin$^{\Delta}$	Silenor	3-6 mg	3.5	15	Active (half-life 31 hours)	Limited (interacts via CYP2D6)
Ramelteon	Rozerem	8 mg	0.5-1.5	1-2.6	Active (half-life 2-5 hours)	No
Suvorexant	Belsomra	10-20 mg	2	12	Inactive	Yes

Duration of action of compounds having active metabolite(s) is significantly greater than predicted by half-life of parent.

* Half-life of active metabolite(s) may exceed 50-100 hours.
¶ Not available in United States.
Δ Approach to diagnosis and management of overdose is reviewed separately. Refer to topic review of tricyclic antidepressant poisoning available in UpToDate.

Benzodiazepines

- **Very low toxicity** to be expected
- Excellent prognosis is expected with supportive care of CNS depression
- Classic presentation of BZD overdose a patient with **CNS depression with normal vital signs**
- Respiratory compromise is uncommon with oral BZD overdose but risk increases if co-ingestants (eg. ethanol)

Benzodiazepines

- **<u>Consider co-ingestions! Very common!</u>**

Benzodiazepines

What do you do with a patient who presents to the ER with a benzodiazepine overdose?

Primary treatment of most intoxications?

Supportive Care

Benzodiazepines: Treatment

- **ABC**: protect airway if GCS <8 and not expected to improve

Benzodiazepines: Treatment

- ABC: protect airway if GCS <8 and not expected to improve
- **DEFG: Don’t Ever Forget Glucose** for ANY patient with altered mental status

Benzodiazepines: Management

- ABC: protect airway if GCS <8 and not expected to improve
- **DEFG: Don’t Ever Forget Glucose**
- ECG
- IV fluids
- Pregnancy test in women of childbearing age
- Ethanol + paracetamol + aspirin levels

Benzodiazepines: Management

- ABC: protect airway if GCS <8 and not expected to improve

- **DEFG: Don’t Ever Forget Glucose**

- ECG
- IV fluids
- Pregnancy test in women of childbearing age
- Ethanol + paracetamol + aspirin levels

- Full history
- Full clinical exam

Benzodiazepines: Management

- ABC: protect airway if GCS <8 and not expected to improve

- **DEFG: Don’t Ever Forget Glucose**

- ECG
- IV fluids
- (Pregnancy test in women of childbearing age)
- (Ethanol + paracetamol + aspirin levels)

- Full history
- Full clinical exam

- **Signs of trauma? Other causes of decreased level of consciousness?**

Benzodiazepines

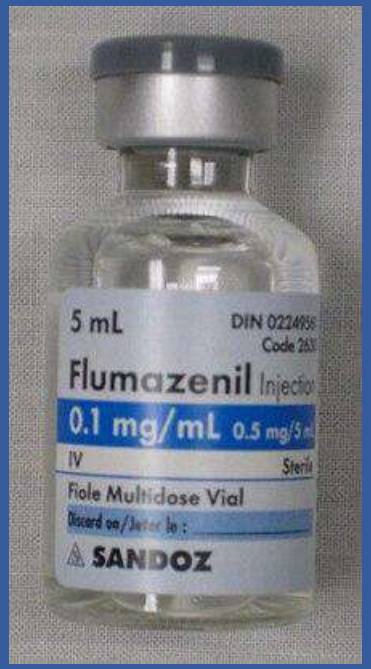
- Activated charcoal can be considered but is often ***not recommended*** due to early onset of sedation and excellent outcomes with good supportive care
- Exceptions might be very early and large ingestions and toxic co-ingestions
- Absolutely no indication for gastric lavage.

Benzodiazepines

- There is an antidote.
- Do you know what it is?

Benzodiazepine Antidote:

Flumazenil



Benzodiazepines

Flumazenil:

Nonspecific competitive antagonist of the BZD receptor.

Should NOT be routinely used

Short-acting: effect of the flumazenil will wear off before the effect of many benzodiazepines

Benzodiazepines

Risks of Flumazenil?

Benzodiazepines – risks of flumazenil

- Triggering a seizure if the patient is a chronic benzodiazepine user

- Triggering a toxidrome or a seizure if mixed ingestion

Benzodiazepines

Indications for Flumazenil?

Benzodiazepines

Indications for Flumazenil?

- Reversal of conscious sedation (i.e. Iatrogenic over sedation)
- Accidental paediatric ingestion
- Diagnostic tool to avoid further investigation
- Management of airway and breathing when resources are not available to safely intubate and ventilate the patient

Benzodiazepines dosing

- **<u>Flumazenil:</u>**

- Initial dose: 0.2 mg IV

- Can be repeated: 0.2-0.5 mg over 30 seconds repeated at 1-minute intervals

- Maximum total cumulative dose: 3 mg

- (In the event of resedation, repeat doses may be given at 20-minute intervals if needed, at 0.5 mg per minute to a maximum of 1 mg total dose and 3 mg in 1 hour.)

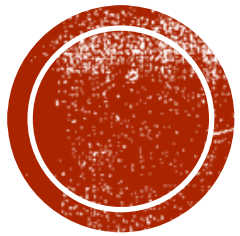
Benzodiazepine Withdrawal

Table 1. Symptoms of Benzodiazepine Withdrawal

Psychologic	Neurologic	Physiologic
Anxiety	Seizures	Tachycardia
Depression	Delirium Tremens	Elevated Blood Pressure
Insomnia	Ataxia	Diaphoresis
Depersonalization	Parasthesias[8]	Flu-Like Symptoms[5,8]
Panic Attacks	Perceptual Distortion	Muscle Stiffness
Agitation	Visual Disturbances	Headaches
Acute Psychosis	Memory/Other Cognitive Impairment	GI: Nausea/Vomiting/Diarrhea
Irritability	Weakness	Hyperpyrexia
Delirium	Tremors	Shortness of Breath
Agoraphobia[8]	Hypersensitivity	Dysphagia[8]

Benzodiazepines: Management

- **Good supportive care** usually leads to good outcomes.
- Once acute overdose has been dealt with, remember **social and psychiatric** evaluation and risk assessment.



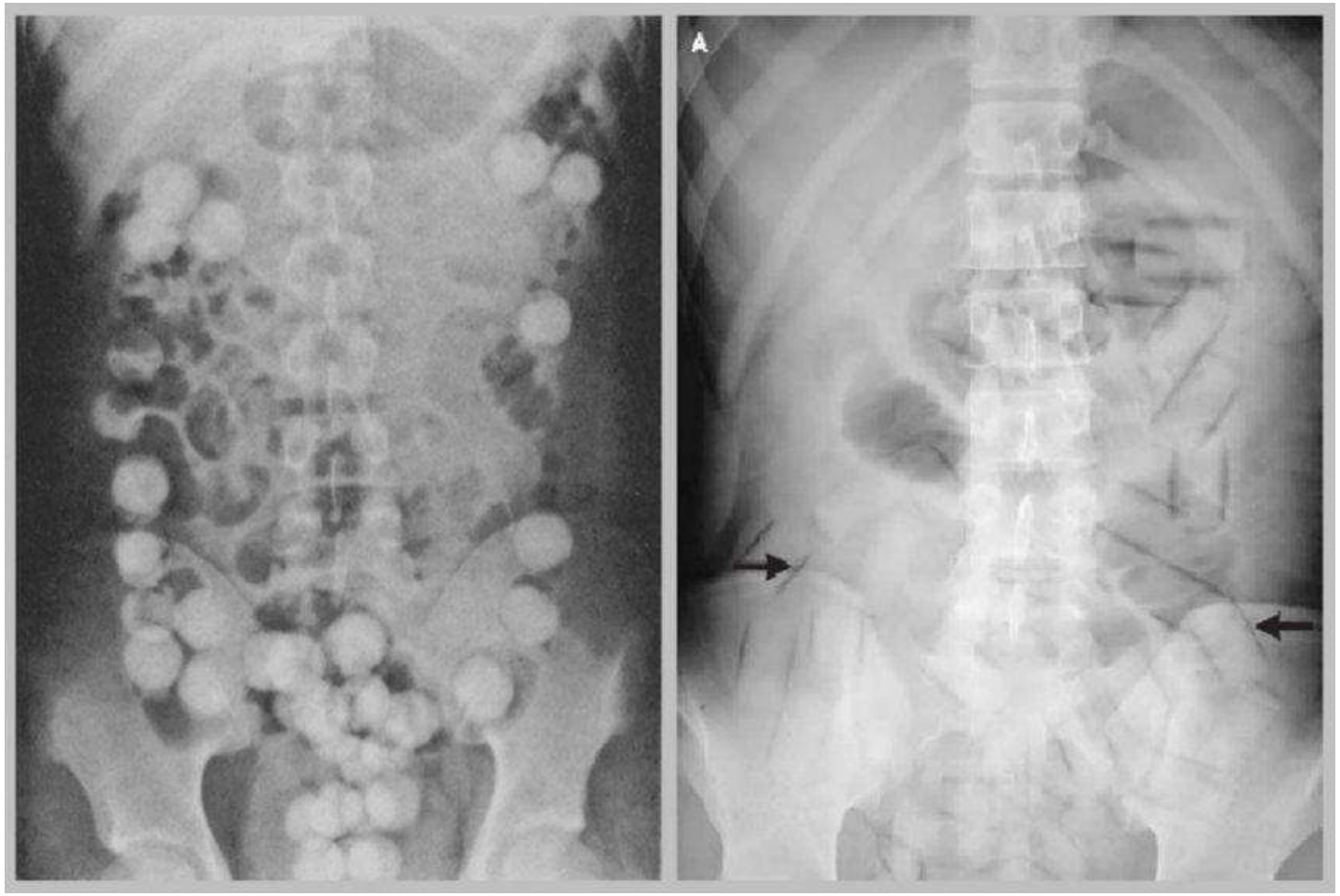
OPIOID TOXICITY

OPIOIDS: FIRST FIVE MINUTES

- ABCs
- Vital signs
- Oxygen
- Continuous pulse oximetry
- Ensure adequate ventilation

BODY PACKING

- Technique for illegal drug transport
- Systemically ingest many individually wrapped packets of drug
- Internal rupture of packet results in massive accidental overdose
- May cause intestinal obstruction



https://www.researchgate.net/publication/344203294_Demography_and_Mortality_of_Body_Packers_an_Extended_Experience_from_a_Referral_Center/figures?lo=1&utm_source=google&utm_medium=organic

BODY STUFFING

- Rapid ingestion or ‘stuffing’ of packets orally, rectally, vaginally
- To hide drug stash
- Usually total amount in body less than packing
- Higher risk for packet rupture and accidental overdose

Figure 1. Recovered packets filled with opioids in different sizes and shapes (blue arrow: leaked packet)

https://globemcc.com/articles/a-fatal-case-of-opioid-body-packer-syndrome-presented-with-seizures/doi/globecc.galenos.2023.70783

SIGNS AND SYMPTOMS

- Look
  - Excessive somnolence?
  - Pupils constricted, sluggish?
  - Slow, shallow respirations?
- Listen
  - Quiet bowel sounds?
  - Bradycardia? Hypotension?
- Feel
  - May be hypothermic
  - If febrile, infection due to injection use?
  - Rectal and vaginal exams if possible packing/stuffing

OPIOIDS: FIRST FIVE MINUTES

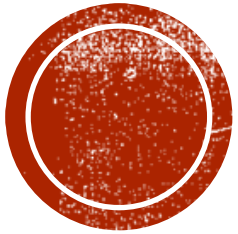
- ABCs
- Vital signs
- Oxygen
- Continuous pulse oximetry
- Ensure adequate ventilation

SEROTONIN SYNDROME

- Opioids may contribute to serotonin syndrome
- Pethidine, dextromethorphan particularly high risk
- Caution in combining serotonergic agents
- Serotonin syndrome marked by agitation, myoclonus, hyperthermia, seizure, shock. **High mortality.**

PETHIDINE TOXICITY

- Also called meperidine
- Neurotoxic metabolite
- High dosages lower seizure threshold
- High risk for drug interactions
  - MAOI interaction
  - Serotonin syndrome



INVESTIGATIONS

Opioid toxicity

INVESTIGATIONS

- A clinical diagnosis

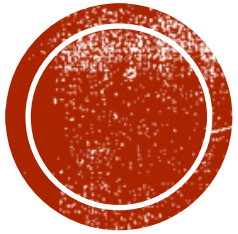
- No need for routine lab screening in uncomplicated opiate intoxication

- Investigations indicated if diagnosis is in question or if other complications (trauma, aspiration injury) are associated with patient presentation

IMAGING

- Chest x-ray
  - If inhalational injury or other possible aetiologies hypoxia

- Abdominal x-ray
  - If suspect possible body packing



MANAGEMENT

Opioid toxicity

MANAGEMENT

Goals of acute management

- Support and protect the altered patient while acutely intoxicated
  - Ensure adequate ventilation
  - Prevent aspiration

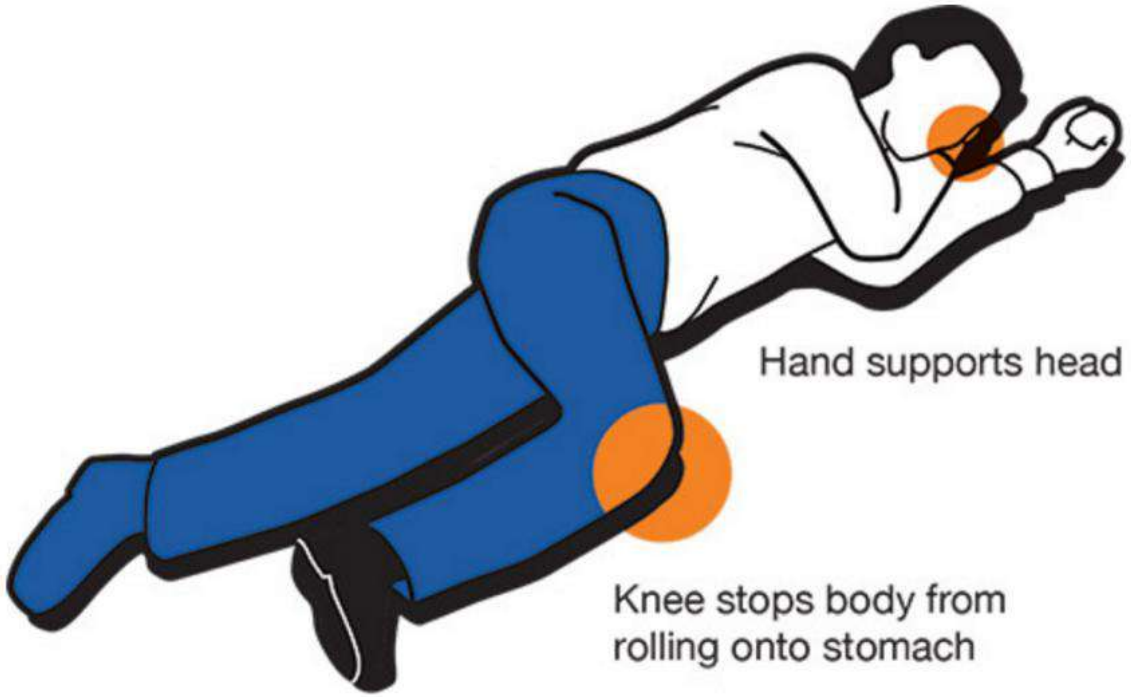
- Search for and treat conditions or injuries "hidden" by altered mental status

MANAGEMENT

- Protect airway
  - Elevate head of bed to 30°
  - Recovery position
- Monitor for adequate ventilation
  - Continuous pulse oximetry
- (Activated charcoal only if life-threatening co-ingestions in alert patient with no risk airway compromise)

The Recovery Position

Keep the Airway Clear



Stay with person. If you must leave them alone at any point, or if they are unconscious, put them in this position to keep airway clear and prevent choking.

NALOXONE

- A potent opioid antagonist

- Temporarily reverses opioid effects
  - Duration of action naloxone ~1 hour
  - Duration of action of opiates many hours
  - Respiratory suppression will recur after naloxone given → monitor closely!

NALOXONE

- A potent opioid antagonist

- Temporarily reverses opioid effects
  - **Duration of action naloxone ~1 hour**
  - **Duration of action of opiates many hours**
  - Respiratory suppression will recur after naloxone given → monitor closely!

NALOXONE

- Dose response related to dose of opiate
  - May cause withdrawal syndrome in chronic opioid users
    - Vomiting
    - Wheezing
    - Agitation, anger, physical violence toward healthcare provider
  - Give small doses serially
  - Goal is to improved respiration, not normal consciousness

NALOXONE DOSING

- Naloxone 0.4 - 2mg IV/IM to start
  - If no improvement, repeat dose at 2-3 minutes
  - Continue in intervals up to a maximum of 10 mg
  - Children 0.01mg/kg IV/IM to start
  - If no improvement, may increase dose to 0.1mg/kg at 2-3 minute intervals

- Large overdoses may require infusion
  - Naloxone 0.004mg/ml IV continuous infusion, titrate dose to response
  - Dilute naloxone 2mg in 500mL NS or D5W

PULMONARY COMPLICATIONS

- Symptomatic management
- Supportive care
  - Continuous pulse oximetry to monitor
  - Mask oxygen for hypoxia
  - Consider noninvasive positive pressure ventilation, if patient able to protect airway
  - Intubation and ventilatory support if severely depressed respiratory status and naloxone not available

INGESTED PACKETS

- Asymptomatic packers
  - Confirm bowel sounds
  - Administer polyethylene glycol (PEG) electrolyte solution orally 2 L/hr until packets passed and stools watery and clear

CRITICAL DOCUMENTATION AND DISPOSITION

Opioid toxicity

CRITICAL DOCUMENTATION

- Specific agent ingested
- Any co-ingestions
- Prior opioid use, frequency of use
- Vital signs
- Therapies given and patient response

DISPOSITION

- Observe asymptomatic patients for 6-12 hours after time of ingestion

- Discharge
  - Normal mental status, normal respiratory status, and naloxone not needed in last four hours

- Admit
  - Repeat naloxone doses required
  - Aggressive airway support required
  - Neurological sequelae


V
Vanadium
Cr
Chrom
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Mangan
Eisen
Kobalt
Nb
Mo
Molybdän
Tc
Technetium
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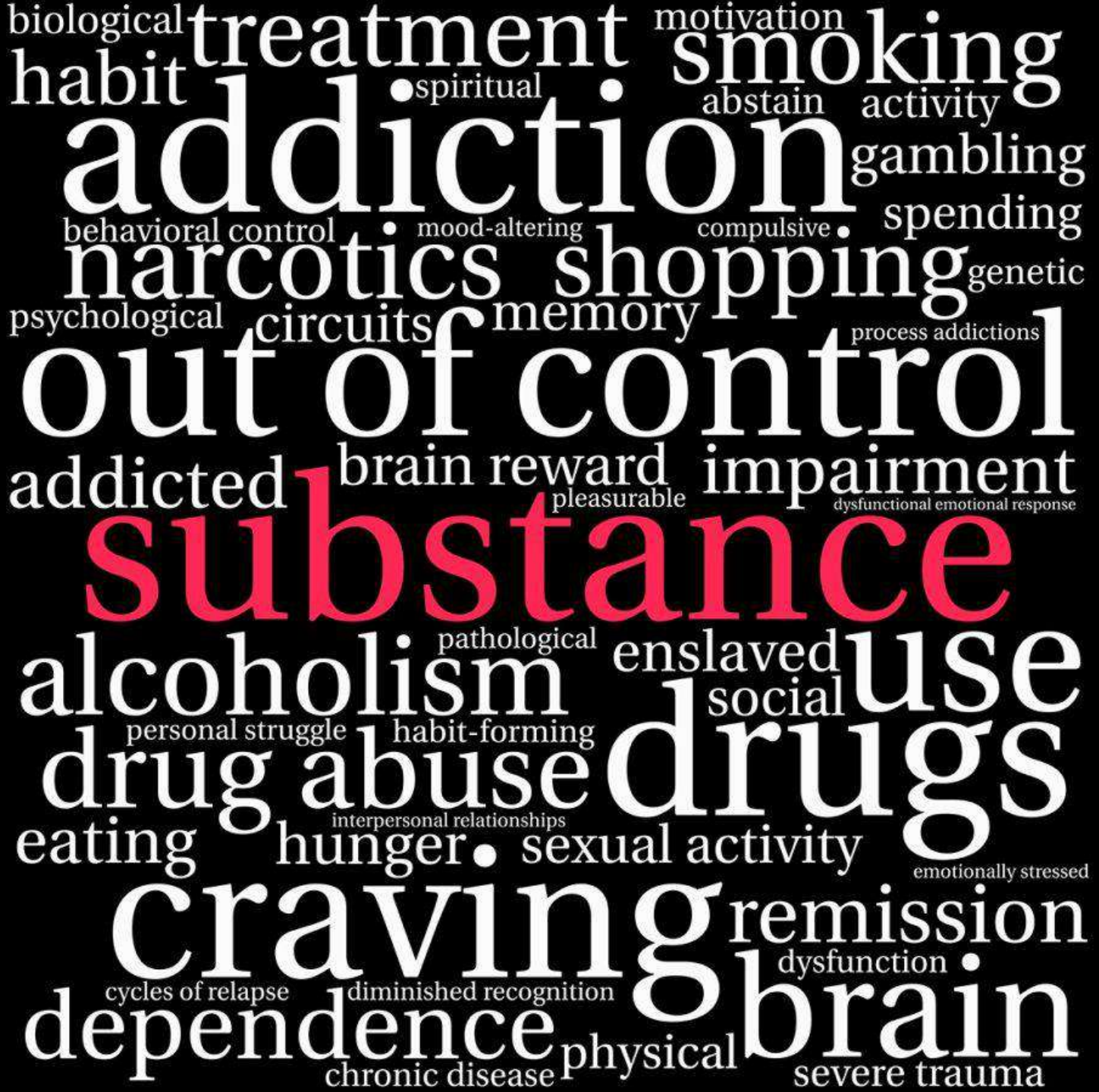
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out of control
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impairment
pleasurable
dysfunctional emotional response
substance
alcoholism
pathological
enslaved
use
social
personal struggle
habit-forming
drug abuse
drugs
interpersonal relationships
eating
hunger
sexual activity
emotionally stressed
craving
remission
dysfunction
cycles of relapse
diminished recognition
dependence
brain
physical
chronic disease
severe trauma

- Uganda is number one in Africa for alcohol use per person
- 5.9% of deaths globally are attributable to alcohol use

Scope of substance use disorders

- Unhealthy use of alcohol
- Use of illicit drugs
- Nonmedical use of prescription drugs

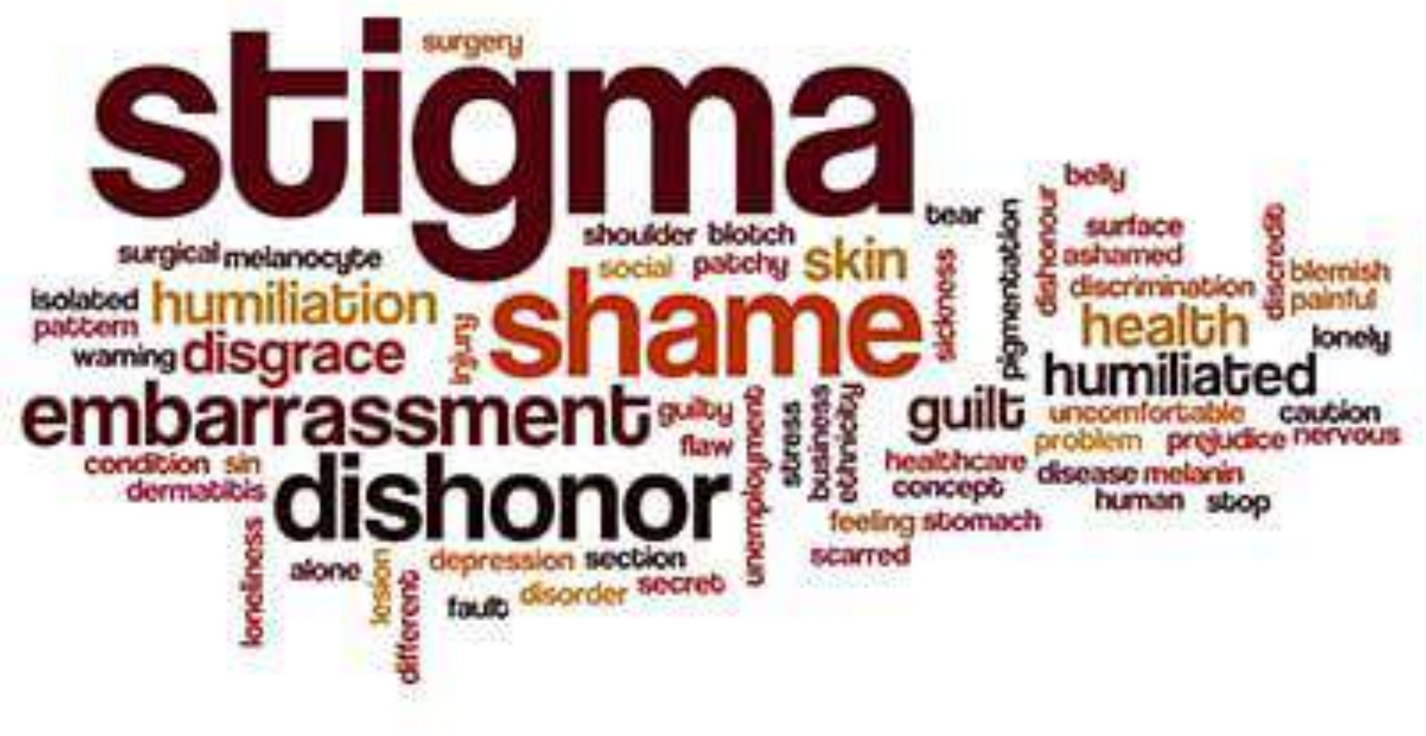
- Like asthma, diabetes, hypertension and other chronic diseases…

- Like asthma, diabetes, hypertension and other chronic diseases…

- Substance use has
  - Genetic component
  - Difficult adherence to medications
  - Loss to follow up
  - Exacerbations
  - Repeat visits to ED
  - Hospital admissions

Substance use disorder

a chronic, relapsing medical condition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disease melanin
human
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feeling stomach
scarred
loneliness
alone
lesion
different
depression section
fault
disorder
secret

Don’t label your patient!!

- Alcoholic or **person with alcohol use disorder**
- Diabetic or **person with diabetes**
- Thyroid disease or **person with thyroid disorder**
- Cancer patient or **person with cancer**
- Drug addict or **person with addiction**

Brief negotiated interview

1. Establish rapport
2. Provide feedback
3. Enhance motivation
4. Negotiate a plan of action

BNI Steps	Dialogue/Procedures
1. Raise subject	Hello, I am _____. Would you mind taking a few minutes to talk with me about your alcohol use? <<PAUSE and LISTEN>>
2. Provide feedback	
• Review screen	From what I understand you are drinking [insert screening data]… We know that drinking above certain levels can cause problems, such as [insert facts]…I am concerned about your drinking.
• Make connection	What connection (if any) do you see between your drinking and this ED visit? *If pt sees connection:* reiterate what pt has said *If pt does not see connection:* make one using facts
• Show NIAAA guidelines and norms	These are what we consider the upper limits of low risk drinking for your age and sex. By low risk we mean that you would be less likely to experience illness or injury if you stayed within these guidelines.
3. Enhance motivation	
• Readiness to change	[Show readiness ruler] On a scale from 1–10, how ready are you to change any aspect of your drinking?
• Develop discrepancy	*If patient says:* *≥2 ask* Why did you choose that number and not a lower one?
• Explore pros and cons	*<2 or resistance ask pros and cons* Help me to understand what you enjoy about drinking? <<PAUSE AND LISTEN>> Now tell me what you enjoy less about drinking. <<PAUSE AND LISTEN>>
• Use reflective listening	On the one hand you said, <<RESTATE PROS>> On the other hand you said, <<RESTATE CONS>> So tell me, where does this leave you?
4. Negotiate and advise	
• Negotiate goal	What's the next step?
• Give advice	What do you think you can do to stay within the safe drinking guidelines? If you can stay within these limits you will be less likely to experience [further] illness or injury related to alcohol use.
• Summarize	This is what I've heard you say…Here is a drinking agreement I would like you to fill out, reinforcing your new drinking goals. This is really an agreement between you and yourself. Provide drinking agreement [pt keeps 1 copy]
• Provide handouts and suggest PC f/u	Suggest Primary Care f/u to discuss drinking level/pattern
• Thank patient	Thank patient for his/her time

FIGURE 292-2. Screening, brief intervention, and referral to treatment algorithm as taught in the standardized ED curriculum. BNI = brief negotiated interview; f/u = follow-up; NIAAA = National Institute on Alcohol Abuse and Alcoholism; PC = primary care; pt = patient. [Reproduced with permission from D'Onofrio G, Pantalon MV, Degutis LC, Fiellin DA, O'connor PG: Development and implementation of an emergency practitioner-performed brief intervention for hazardous and harmful drinkers in the emergency department. *Acad Emerg Med* 12: 249, 2005. Copyright John Wiley & Sons.]

- You may be what your patient has been looking for:

  a sympathetic ear

Thank you!!

Serotonin syndrome: Rapid overview of emergency management

To obtain emergency consultation with a medical toxicologist, in the United States, call 1-800-222-1222 for the nearest regional poison control center. Contact information for poison control centers around the world is available at the WHO website and in the UpToDate topic on regional poison control centers (society guideline links).

Clinical and laboratory features

The Hunter Criteria for SS are fulfilled if the patient has taken a serotonergic agent and has one of the following:

- Spontaneous clonus
- Inducible clonus and agitation or diaphoresis
- Ocular clonus and agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia
- Temperature above 38°C and ocular clonus or inducible clonus

SS is a clinical diagnosis; no laboratory test can confirm the diagnosis. SS can manifest a wide range of clinical symptoms from mild tremor to life-threatening hyperthermia and shock.

Examination findings can include: hyperthermia, agitation, ocular clonus, tremor, akathisia, deep tendon hyperreflexia, inducible or spontaneous clonus, muscle rigidity, dilated pupils, dry mucus membranes, increased bowel sounds, flushed skin, and diaphoresis. Neuromuscular findings are typically more pronounced in the lower extremities.

The following tests may be helpful in severe cases of SS to narrow the differential and to monitor potential complications:

- Complete blood count, basic electrolytes, creatinine, and blood urea nitrogen
- Creatine phosphokinase, hepatic transaminases, coagulation studies
- Blood culture, urinalysis, urine culture
- Chest radiograph
- Head computed tomography, lumbar puncture

Differential diagnosis

Neuroleptic malignant syndrome

Anticholinergic toxicity

Malignant hyperthermia

Sympathomimetic toxicity

Meningitis or encephalitis

Sedative-hypnotic (eg, alcohol, benzodiazepine, clonidine, baclofen) withdrawal

Thyroid storm

Acute extrapyramidal syndromes (eg, dystonic reaction)

Treatment

Discontinue serotonergic agents.

Sedate using benzodiazepines (eg, lorazepam 1 to 2 mg IV per dose; 0.02 to 0.04 mg/kg per dose in children): goal is to eliminate agitation, neuromuscular abnormalities (eg, tremor, clonus), and elevations in heart rate and blood pressure; titrate dose to effect.

Provide: oxygen (maintain SpO_2 ≥94); IV fluids; continuous cardiac monitoring.

Anticipate complications; in severe SS vital signs can fluctuate widely and rapidly.

If benzodiazepines and supportive care fail to improve agitation and abnormal vital signs, give cyproheptadine (12 mg orally or by orogastric tube for initial adult dose; pediatric doses included in main text).

Treat patients with temperature >41.1°C with immediate sedation, paralysis, and endotracheal intubation; treat hyperthermia with standard measures; avoid antipyretics such as acetaminophen.

IV: intravenous; SS: serotonin syndrome.