Toxidromes

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Toxidromes

- Toxidromes are combinations of specific signs and symptoms that reflect drug class effects on particular neuroreceptors.
- Management strategies are often determined by the toxidrome without concern for the specific agent that caused the signs and symptoms.

Examples

- Anticholinergic Toxidrome
- Cholinergic Toxidrome
- Sympathomimetic Toxidrome
- Opiate Toxidrome
- Hypnosedative Toxidrome
- Serotonin Syndrome
- Neuroleptic Malignant Syndrome

- The **anticholinergic** toxidrome is reflected by tachycardia, warm and dry skin, hypoactive bowel sounds, mydriasis, and urinary retention. A delirium occurs in more severe cases. This toxidrome is noted after overdosing on antihistamines, tricyclic antidepressants, and many antipsychotics.
- The **cholinergic** toxidrome includes diaphoresis, salivation, lacrimation, urination, defecation, miosis, and bradycardia. A severe exposure is lethal by bronchospasm and bronchorrhea.
- The **sympathomimetic** toxidrome involves tachycardia and mydriasis and may include delirium, but the skin is diaphoretic.
- The **opioid** toxidrome consists of pinpoint pupils, respiratory depression, and unresponsiveness.
- The **Sedative-hypnotics** are similar to opioids but without the pupillary changes.

What is Toxic Syndrome/Toxidrome and Why is Its Recognition Important?

- Toxic syndrome or toxidrome is a constellation of toxic effects comprising a set of clinical fingerprints for a group of toxic chemicals.

- Toxic syndrome or toxidrome recognition is important because it provides a tool for rapid detection of the suspected cause and can focus the differential diagnosis to consideration of only a few chemicals with similar toxic effects.

Anticholinergic Toxidrome

- Anticholinergic drugs have an affinity for the acetylcholine receptor and antagonize muscarinic/nicotinic receptors.

- The majority of blockade is at muscarinic receptors, but at high doses some blockade occurs at nicotinic receptors in the autonomic ganglia and at the motor end plates.

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- **Muscarinic receptors:**
  - M1: Central and enteric nervous systems
  - M2: Heart
  - M3: Smooth muscle
    - Increases exocrine gland secretion
    - Increases gut motility
    - Miosis via pupillary sphincter
    - Accommodation via ciliary muscles
    - Bronchoconstriction
    - Bladder constriction
- Therefore, muscarinic blockade will give the classic anticholinergic “dry as a bone, red as a beet, hot as a hare, mad as a hatter, blind as a bat”

Central effects:

- Agitated delirium (mad as a hatter) characterised by:
  - Fluctuating mental status
  - Confusion
  - Restlessness and fidgeting
  - Picking at objects in the air
  - Mumbling slurred speech
  - Disruptive behavior
- Tremor
- Myoclonus
- Coma
- Seizure (rare)

Peripheral effects:

- Mydriasis (blind as a bat)
- Tachycardia
- Dry mouth (dry as a bone)
- Dry skin
- Flushing (red as a beet)
- Hyperthermia (hot as a hare)
- Urinary retention
- Spares or absent bowel sounds

Sources:

- ATROPINE
- Antiepileptics (carbamazepine)
- Antihistamines
- Anti-Parkinson medications: Amantadine, benztropine
- Antipsychotics: Chlorpromazine, clozapine, olanzapine, droperidol, haloperidol, quetiapine
- Anti motion sickness agents: Scopolamine
- GI antispasmodics: e.g., hyoscyamine
- GU antispasmodics: e.g., oxybutynin, solifenacin
- Plant sources: Belladonna, Brugmansia (angel's trumpets), datura (Jimson Weed), Henbane (Stinking Nightshade), Mandrake
- Skeletal muscle relaxants: dantrolene
- SSRIs: Paroxetine
- TCAs: Amitriptyline, clomipramine, nortriptyline
- Topical eyedrops: cyclopentolate, homatropine, tropicamide

Diphenhydramine (Benadryl)

Signs & Symptoms

- Anticholinergic effects
- Tachycardia
- Mydriasis
- Dry mouth
- Agitation/Confusion/Hallucinations
- Severe
- Seizures
- Coma
- QRS widening, Torsades de Pointes

Treatment

- ✓ Maintain airway and respiratory function
- ✓ Supportive Care
- ✓ Benzodiazepines
- ✓ Agitation/Seizures
- ✓ Sodium Bicarbonate
- ✓ QRS widening/Dysrhythmias
- ✓ Antidotal – Physostigmine
- ✓ Acetylcholinestrase inhibitor
- ✓ Reversal of peripheral and central anticholinergic effects
- ✓ 0.5-2 mg slow IVP (> 5 minutes)
- ✓ Can repeat dose (lasts 15-30 minutes) in 20-30 minutes

Signs and symptoms

Signs and symptoms are variable. No particular pattern can accurately or reliably diagnose this toxidrome.

- Differential Dx:
  - Encephalitis
  - Hypoglycaemia
  - Hyponatraemia
  - NMS
  - Neurotrauma
  - Sepsis
  - Serotonin syndrome
  - Subarachnoid haemorrhage
  - Wernicke’s encephalopathy

Management:

- Avoid treating agitation with anticholinergic drugs (e.g., droperidol, haloperidol)
- **Antidote: Physostigmine**
  - Reversible acetylcholinesterase inhibitor
  - Indications:
    - ✓ Agitated delirium not controlled by benzodiazepine sedation
    - ✓ Isolated anticholinergic poisoning
  - Contraindications:
    - ✓ Bradyarrhythmias
    - ✓ Intraventricular block (QRS >100ms)
    - ✓ AV block
    - ✓ Bronchospasm
  - Duration of action shorter than delirium, however repeat doses may not be required

Cholinergic Toxidrome

- Result of increased acetylcholine activity at both central and peripheral nicotinic and muscarinic receptors.

- Can arise from either:
  - Cholinesterase inhibitors (e.g., organophosphate and carbamates)
  - Cholinomimetics – have direct agonist action at muscarinic or nicotinic sites (e.g., pilocarpine, muscarine)

Signs and symptoms

Central nervous system:

- Agitation
- Central resp depression
- Coma
- Confusion
- Lethargy
- Seizures

Neuromuscular:

- Fasciculation
- Muscle weakness

Parasympathetic muscarinic effects:

- Abdo. cramps
- Bradycardia
- Bronchoconstriction
- Bronchorrhoea
- Diarrhoea
- Lacrimation
- Miosis
- Salivation
- Urinary incontinence
- Vomiting

Sympathetic nicotinic effects:

- Hypertension
- Mydriasis
- Sweating
- Tachycardia

Sources:

- **Acetylcholinesterase inhibitors:**
  - Organophosphates
  - Carbamate insecticides
  - Chemical warfare nerve agents (e.g., sarin)
  - Agents used in dementia: Donepezil, galantamine, rivastigmine, tacrine
  - Agents used in myasthenia gravis: edrophonium, neostigmine, physostigmine, pyridostigmine
- **Acetylcholine agonists:**
  - Muscarinic agents: Acetylcholine, carbachol, pilocarpine
  - Nicotinic agents: Nicotine
  - Mushrooms (muscarine)

Differential diagnosis

- Causes of weakness (myasthenia gravis, botulism)
- Cardiotropic intoxication resulting in bradycardia and vomiting (digoxin, β-blockers, CCBs)
- Gastroenteritis and abdominal emergencies
- Mushroom ingestion
- Respiratory disorders (asthma)
- Salicylate intoxication
- Serotonin syndrome
- Sympathomimetic syndrome
- Theophylline intoxication

Management

- **Atropine:** If signs of muscarinic excess. Keep giving it until drying of secretions is achieved
- Seizure control with benzos
- Decontamination
- **Organophosphate/carbamate/ nerve agent poisoning: Pralidoxime.**
  - Initial bolus: 2g pralidoxime in 100ml 0.9% NaCl over 15 minutes
  - Infusion: 500mg/hr (6g in 500ml 0.9% NaCl at 42ml/hr)

Sympathomimetic Toxidrome

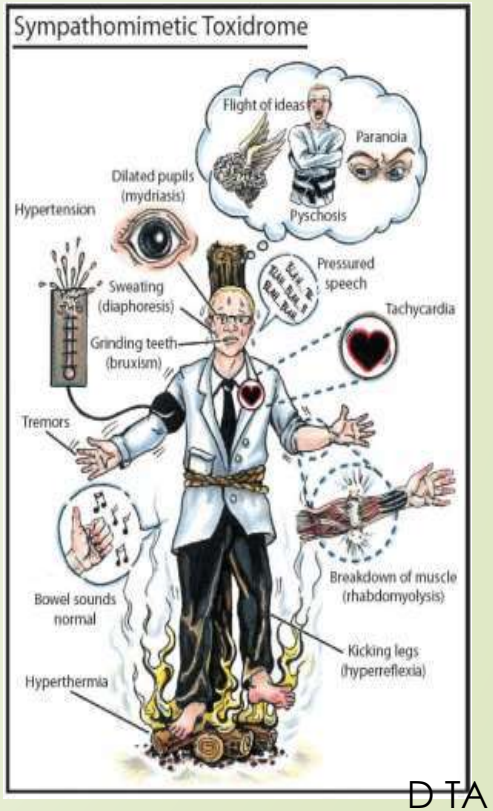
- **Sympathomimetics:** drugs that have an activating effect on the sympathetic nervous system through the direct or indirect effect on catecholamines.
  - **Direct acting:** alpha-agonists, dopaminergic agents
  - **Indirect acting** agents: cause increased catecholamine release, inhibition of enzymatic breakdown, or delayed reuptake (e.g., pseudoephedrine, amphetamines, cocaine).
  - Cocaine can affect dopamine

Signs & Symptoms

- Tachycardia
- Hypertension
- Hyperthermia
- Hyperreflexia
- Mydriasis
- Diaphoresis
- Normal bowel sounds

Other associated Sx

- Pressured speech
- Flight of ideas
- Paranoia
- Tremors
- Chest pain
- Rhabdomyolysis



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Treatment:

- **Hypertension and tachycardia:**
  - Titrated benzos first
  - Phentolamine 1mg IV repeated every 5 minutes
  - Titrated vasodilator infusion
  - NEVER give β-blockers (can lead to unopposed alpha stimulation and vasoconstriction)
- **Seizures:** IV diazepam (second line: barbiturates)
- **Agitation:** Benzos (second line: droperidol, olanzapine)
- **Hyperthermia**
  - >38.5: continuous core temp monitoring, benzo sedation, fluid
  - >39.5: rapid external cooling. May need paralysis, intubation, ventilation.
- **Hyponatraemia**: If profound (<120mmol) + altered mental state/seizures, give hypertonic saline
  - 3% NaCl 4ml/kg over 30 mins. Keep repeating to maintain Na >120mmol)

Opiate Toxidrome

- Due to narcotics and narcotic derivatives, binding to opiate receptors in CNS and bowel.
- **Classical presentation:**
  - CNS depression
  - Respiratory depression
  - Miosis
- **Other/complications**
  - Tachycardia (response to hypoxia, hypercarbia)
  - Decreased bowel sounds
  - Peripheral vasodilation with hypothermia, hypotension
  - Resp. depression and subsequent coma can be fatal

Special cases:

✓ **Dextropropoxyphene (Darvon):** 20mg/kg may cause CNS depression, seizures, cardiac dysrhythmias (fast Na channel blocking effect)

✓ **Pethidine:** Repeated therapeutic doses associated with seizures

- Implicated in serotonin syndrome

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Management

- **Sodium bicarbonate** if dextropropoxyphene poisoning leading to ventricular arrhythmias

- **Naloxone** for CNS depression: Competitive opioid antagonist at mu, kappa, and delta receptors

  - **Treatment dose:**
    - Initial bolus 100 microg IV (or 400 microg IM/subcut.)
    - Then give repeated 100 microg boluses every 30-60 seconds until adequate spontaneous respiration
    - If necessary, infusion:
    - 2/3 of the initial dose required to wake the patient up, per hour.

HypnosedativeToxidrome

- Hypnosedatives: Modulate activity of GABA neutrotrasmitter complex

- Include:
  - Benzodiazepines
  - Barbiturates
  - Zolpidem, zopliclone
  - Baclofen
  - Gamma-hydroxybutyrate (GHB)
  - Chloral hydrate
  - Paraldehyde

Signs & Symptoms

- Respiratory depression
- Bradycardia
- Hypotension
- Poor coordination
- Slurred speech
- Ataxia
- Lethargy
- Disinhibition
- Decreased muscle tone
- Nystagmus
- Neurological depression
- Stupor
- Coma

Treatment: supportive therapy

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Serotonin Syndrome

- Clinical manifestation of excessive stimulation of serotonin receptors in the CNS
- Life threatening toxicity rare following single SSRI ingestion.
- Is more common with combo of MAOI and SSRIs.

Causative agents:

- **Analgesics and antitussives** – dextromethorphan, fentanyl, pethidine, tramadol
- **Antidepressants**
  - SSRIs
  - TCAs
  - MAOIs
- **Drugs of abuse** – amphetamines
- **Herbal preparations** (St John's Wort)
- **Tryptophan, lithium**

Signs & Symptoms:

1. Autonomic stimulation: diarrhoea, flushing, hyperthermia, mydriasis, sweating, tachycardia
2. Neuromuscular excitation: clonus, hyperreflexia, increased tone, myoclonus, rigidity, tremor
3. Mental state changes: anxiety, agitation, psychomotor acceleration, delirium, confusion

Differential Diagnosis:

- ✓ **NMS** (has a slower onset, development of acute parkinsonism with bradykinesia and lead-pipe rigidity, and an absence of neuromuscular excitation)
- ✓ **Anticholinergic toxidrome**
- ✓ **Malignant hyperthermia:**

  Does not produce neuromuscular excitation and requires a history of volatile anaesthetic exposure.

Management

- Supportive care
- May need intubation + ventilation +/- paralysis if coma, recurrent seizures, hyperthermia >39.5C
- Antidote: cyproheptadine 8mg (serotonin antagonist).
  - ✓ Not indicated in severe SS
  - ✓ May be useful in mild serotonin syndrome refractory to benzodiazepines.
- Requires ICU admission if severe.
- Sx likely resolve with complete recovery within 24- 48 hours.

Neuroleptic Malignant Syndrome

- Rare and potentially lethal, due to the use of neuroleptic medications.
- Controversial aetiology, may be due to deficiency/blockade of dopaminergic neurotransmission in nigrostriatal, mesolimbic, and hypothalamic-pituitary pathways.
- Suspect if the patient presents with the toxidrome and has a history of ingestion of one or more neuroleptic agents.

Clinical features:

- **Central nervous system:**
  Confusion, delirium, stupor, coma
- **Autonomic instability:**
  Hyperthermia, tachycardia, hypertension, respiratory irregularities, cardiac dysrhythmias
- **Neuromuscular:**
  - Lead-pipe rigidity
  - Generalised bradykinesia or akinesia
  - Dystonia and abnormal postures
  - Abnormal involuntary movements
  - Incontinence

Management:

- Supportive
- May need intubation + paralysis if temperature >39.5
- Use specific agents like bromocriptine (dopamine agonist) in moderate or severe cases
- Dantrolene – severe muscle rigidity

Condition	Obs	Pupils	Skin	Bowel sounds	Neuromuscular tone	Reflexes	Mental status
Anticholinergic	Tachycardia Hyperthermia	Mydriasis	Hot, dry, red	Sparse or absent	Normal	Normal	Agitated delirium
Cholinergic	Muscarinic: Bradycardia Nicotinic: Tachycardia and hypotension	Miosis	Diaphoretic	Hyperactive	Fasciculations Muscle weakness	Normal	Agitation, confusion Coma, seizures
Opiate toxicity	Tachycardia Bradypnoea Hypotension Hypothermia	Miosis	Peripheral vasodilation May be hypothermic, cool	Decreased	Normal	Normal	CNS depression. Coma
Hypnosedative	Bradycardia Bradypnoea Hypotension Hypothermia	Nystagmus	Normal	Normal	Decreased muscle tone Ataxia	Normal	Slurred speech, stupor, disinhibition, CNS depression, coma
Sympathomimetic	Tachycardia Tachypnoea Hypertension Hyperthermia	Mydriasis	Diaphoresis	Normal	Neuromuscular excitation, tremor	Hyperreflexia	Agitation, pressured speech, flight of ideas, paranoia
Serotonin syndrome	Tachycardia Tachypnoea Hypertension Hyperthermia	Mydriasis	Diaphoresis	Hyperactive	Increased, especially lower limbs	Hyperreflexia and clonus	Agitation progressing to coma
Neuroleptic malignant syndrome	Tachycardia Hypertension Tachypnoea Hyperthermia	Mydriasis or normal	Sweaty but pale	Normal	Lead-pipe rigidity	Bradyreflexia	Mutism, staring, bradykinesia, coma