APPROACH TO COMA:

DESCRIBES AN ALTERED MENTAL STATUS WHERE THE PATIENT CANNOT BE ROUSED, IN A POTENTIALLY POISONED PATIENT, COMA MAY BE THE RESULT OF:

- Direct toxic effect on CNS:
  - Alcohols
  - Antipsychotics → amisulpride, chlorpromazine, clozapine, olanzapine, quetiapine
  - Anticonvulsants → valproate, carbamazepine, lamotrigine, tiagabine
  - Antidepressants → SSRI, TCA
  - Antihistamines
  - Baclofen
  - Beta blocker → esp propranolol
  - Centrally acting alpha-2 agonists → clonidine
  - Cholinergic agents →carbamates, donezipil, organophosphates
  - Hydrocarbons
  - Local anaesthetics
  - NSAIDs
  - Opioids
  - Sedative-hypnotic agents → benzos, GHB, bariturates, chloral hydrate
- Secondary effect → hypoxia, ↓BSL, ↓Na, ↓BP, seizures or cerebral oedema
- Alternative, non-toxicological causes → i.e. metabolic encephalopathy, trauma, meningoencephalitis, space-occupying lesion

WITH A FEW IMPORTANT EXCEPTIONS, MOST AGENTS THAT CAUSE TOXIC COMA PRODUCE RELATIVELY BENIGN AND TEMPORARY ALTERION IN MENTAL STATE THAT HAVE A GOOD PROGNOSIS WITH THOROUGH SUPPORTIVE CARE

MANAGEMENT:

- RESUSCITATION:
  - Establish airway and ventilation → immediate priority regardless of cause of coma → only exception is if hypoglycaemia detected or if there is a suspicion of opioid intoxication
  - Unlike trauma, there is no definitive measure of conscious state that predicts the need for intubation, and a patients' ability to protect their airway is poorly correlated with their GCS
- RISK ASSESSMENT:
  - Coma is usually a predictable response to poisoning where the agent and the dose are known
  - Toxic agents usually act on the CNS in a global and symmetrical fashion and any focal or unilateral neurological sign is highly suggestive of an alternative cause
- COMPLICATIONS OF COMA:
  - Pulmonary aspiration
  - Rhabdomyolysis
  - ARF
  - Compartment syndromes
  - Pressure areas

    - Hypoxic brain injury
- INVESTIGATIONS:
    - Aim is to detect toxic ingestions for which specific intervention is required:
        - ABG, anion gap and lactate → toxic alcohols
        - Drug levels → carbamazepine (MDAC), valproate (dialysis), toxic alcohol (dialysis)
    - Detect complications (CK, EUC, LFT, CXR)

APPROACH TO HYPOTENSION:

COMMON IN POISONED PATIENTS, IS USUALLY MILD AND SECONDARY TO PERIPHERAL VASODILATION. HOWEVER, POISONING SECONDARY TO CARDIOTROPIC MEDICATIONS IS FREQUENTLY ASSOCIATED WITH REFRACTORY HYPOTENSION AND MORTALITY IS MUCH HIGHER.

ALSO, HYPOTENSION NOT RESPONSIVE TO FLUID RESUSCITATION HERALDS A MUCH WORSE OUTCOME

AFTER ATTENTION TO AIRWAY AND VENTILATION:

- Check ECG, correct arrhythmia, consider specific antidotes (digoxin specific antibodies, calcium)
- Give 20mL/kg bolus:
    - Some toxidromes (iron, colchicine, theophylline or salicylates) require large volume resuscitation
    - In CCB overdose → liberal fluid resuscitation can lead to APO
- Consider atropine and pacing → rarely useful in toxic patients
- Commence inotropes (adrenaline and noradrenaline)
- Consider high-dose insulin
- Consider extraordinary manoeuvres → cardiopulmonary bypass

APPROACH TO SEIZURES:

TOXIC SEIZURES ARE USUALLY GENERALISED AND SELF-LIMITING AND EASILY CONTROLLED WITH BENZODIAZEPINES

MOST COMMON CAUSES OF TOXIC SEIZURES:

- Venlafaxine
- Bupropion
- Tramadol
- Amphetamines

IN CERTAIN POISONINGS, SEIZURES HERALD SEVERE INTOXICATION AND GRAVE PROGNOSIS UNLESS DEFINITIVE CARE IS RAPIDLY INSTITUTED:

- Chloroquine
- Propranolol
- Salicylates
- Theophylline
- TCA

SECONDARY HYPOXIA AND ACIDOSIS INCREASE THE SUSCEPTIBILITY FOR DYSRHYTHMIA AND SECONDARY RHABDOMYOLYSIS AND HYPERPYREXIA MAY LEAD TO DEHYDRATION, HYPERKALAEMIA AND RENAL FAILURE

PHENYTOIN IS NOT INDICATED FOR THE MANAGEMENT OF TOXIC SEIZURES

TOXICOLOGICAL CAUSES OF SEIZURES:

- **ANTICONVULSANTS → carbamazepine, topiramate, tiagabine**
- **ANTIDEPRESSANTS →** TCA, venlafaxine, bupropion, citalopram
- **ANTIARRHYTHMICS →** quinidine
- **ANTIHISTAMINES**
- **ANTIMALARIALS →** Chloroquine, hydroxychloroquine, quinine
- **ANTIPSYCHOTICS →** butyrophenones, phenothiazines, atypicals (inc olanzapine, quetiapine)
- **ISONIAZID**
- **HYPOGLYCAEMIC AGENTS →** insulin, sulfonylureas
- **LOCAL ANAESTHETIC AGENTS →** lignocaine
- **NSAIDS →** MEFENAMIC ACID
- **PROPRANOLOL**
- **SALICYLATES**
- **SYMPATHOMIMETICS →** amphetamines and derivatives, cocaine
- **THEOPHYLLINE**
- **WITHDRAWAL SYNDROMES →** alcohol, barbiturates, benzodiazepines

TREATMENT OPTIONS:

- **Benzodiazepines are first line, followed by barbiturates (phenobarbitone 10-20mg/kg up to 300mg or thiopentone 3-5mg/kg if ventilated**

- **PYRIDOXINE is third line agent in seizures secondary to isoniazid**

APPROACH TO DELIRIUM AND AGITATION:

CHARACTERISED BY (DSM IV CRITERIA):

- Altered conscious state with impaired attention
- Decreased cognition manifested by disorientation, memory deficit, abnormal speech
- Acute onset and fluctuating course (distinct from dementia)
- Evidence of an associated medical condition

DUTY OF CARE → the delirious patient is not competent to make decisions about their own welfare and thus we have a duty of care to protect them from serious harm or death

TOXICOLOGICAL CAUSES OF AGITATION AND DELIRIUM:

- ALCOHOL (and withdrawal)
- ANTICHOLINERGIC SYNDROME
- ANTIDEPRESSANTS → venlafaxine, bupropion, MAO-I
- ATYPICAL ANTIPSYCHOTICS
- BENZODIAZEPINE (and withdrawal)
- HALLUCINOGENIC AGENTS → ketamine, PCP
- NEUROLEPTIC MALIGNANT SYNDROME
- SALICYLATES
- SEROTONIN SYNDROME
- SYMPATHOMIMETIC SYNDROME
- THEOPHYLLINE

CONTRIBUTORY CONDITIONS THAT MIMIC OR WORSEN AGITATION:

- Acid-base disturbance
- Behavioural disturbance
- CNS infection
- Dementia
- Electrolyte disturbance (↓Na)
- Endocrine emergency (thyroid storm)
- Hypoglycaemia
- Hypoxia
- Organ failure (hepatic encephalopathy)
- Psychosis
- Seizures
- Stroke
- Trauma (ICH)
- Withdrawal

MANAGEMENT:

- Delirium is usually a predictable response to poisoning where the agents and dose are known

- Important to consider important complications of delirium → aspiration, DVT/PE, dehydration/related electrolyte anomalies, hypoventilation/hypoxia, hyperthermia, rhabdomyolysis, injury to self/others
- Consider toxidromes where specific interventions are necessary:
    - Anticholinergic agents → physostigmine
    - NMS → bromocriptine
    - Serotonin syndrome → paralysis and ventilation, cyproheptadine
    - Salicylates → urinary alkalinisation, haemodialysis
    - Theophylline → MDAC, dialysis
- Manage the patient in a calm environment, with one-to-one nursing
- Temporary physical restraints only while awaiting pharmacological sedation:
    - IV benzos as first line
    - Antipsychotics (haloperidol, droperidol are effective but have EPSE and anticholinergic effects), olanzapine has calming effect without major sedation or EPSE

APPROACH TO SEROTONIN SYNDROME:

THE CLINICAL MANIFESTATION OF EXCESSIVE STIMULATION OF SEROTONIN RECEPTORS IN THE CNS.

OCCURS WHEN EXCESS SEROTONIN ACCUMULATES DUE TO A NUMBER OF MECHANISMS:

- Inhibition of serotonin metabolism (MAO-I)
- Prevention of serotonin reuptake (SSRI)
- Increased intake of serotonin precursors (tryptophan)

CLINICAL FEATURES:

- Characterised by the TRIAD OF MENTAL STATUS CHANGES, AUTONOMIC STIMULATION, NEUROMUSCULAR EXCITATION
- MENTAL STATE CHANGES:
  - Apprehension
  - Anxiety
  - AGITATION, PSYCHOMOTOR ACCELERATION, DELIRIUM
  - Confusion
- AUTONOMIC STIMULATION:
  - DIARRHOEA
  - Flushing
  - HYPERTENSION
  - Hyperthermia
  - MYDRIASIS
  - SWEATING
  - TACHYCARDIA
- NEUROMUSCULAR EXCITATION:
  - CLONUS (esp ocular and ankle)
  - HYPERREFLEXIA
  - HYPERTONIA (LL >UL)
  - MYOCLONUS
  - Rigidity
  - Tremor
- Continuous clinical spectrum
- FULMINANT SYNDROME:
  - Life-threatening syndrome characterised by generalised rigidity, autonomic instability, marked mental status changes and hyperthermia
  - Without prompt intervention → rhabdomyolysis, renal failure, DIC and DEATH
- Symptoms are usually of rapid onset and resolves within 24-48 hours
  - Usually develops within 8 hours of deliberate poisoning and frequently after patient presents

DIAGNOSIS:

- A clinical diagnosis
- Requires history of ingestion of one or more serotonergically-active agents (or a change in their dose) plus index of suspicion in presence of characteristic clinical features

- ALGORITHM
- MAY DEVELOP IN FOLLOWING SETTINGS:
    - Introduction or increase in dose of serotonergic agent
    - Change in therapy from one agent to another without adequate WASHOUT
    - Drug interaction (or interaction with illicit drug, herbal preparation)
    - Deliberate self-poisoning
- AGENTS IMPLICATED:
    - ANALGESICS/ANTITUSSIVES:
        - Dextromethorphan, fentanyl, pethidine, TRAMADOL
    - ANTIDEPRESSANTS → TCA
    - Drugs of abuse → MDMA, amphetamines
    - Herbal preparations → ST JOHN'S WORT
    - Lithium
    - MAO-I → moclobemide, phenelzine
    - SSRI, SNRI
    - Tryptophan

MANAGEMENT:

- **RESUSCITATION →** if there is coma, recurrent seizures, hyperthermia or severe rigidity, proceed to RSI and intubation. This will prevent furter muscle-generated heat production
- **Titrated benzodiazepines usually adequate to treat hypertension and tachycardia → IF REFRACTORY, CONSIDER SHORT-ACTING VASODILATOR (GTN, NITROPRUSSIDE)**
- **ANTIDOTES:**
    - The efficacy of serotonin antagonists has not been established in clinical trials
    - CYPROHEPTADINE:
        - Given orally or via NG (8mg q8h for 24 hours)
        - Alternatives are chlorpromazine, olanzapine
        - Antagonists only useful in mild-moderate serotonin syndrome, refractory to benzodiazepine administration → NOT IN SEVERE CASES WHICH CAN ONLY BE MANAGED BY TIMELY INTUBATION AND PARALYSIS WITH ACTIVE COOLING

APPROACH TO ANTICHOLINERGIC SYNDROME:

ARISES DUE TO COMPETITIVE INHIBITION OF CENTRAL AND PERIPHERAL ACETYLCHOLINE MUSCARINIC RECEPTORS AND IS POTENTIALLY LIFE-THREATENING

BEST CHARACTERISED AS AN AGITATED DELIRIUM ASSOCIATED WITH VARIABLE SIGNS OF PERIPHERAL MUSCARINIC BLOCKADE

CLINICAL FEATURES:

CENTRAL:

- Agitated delirium (MAD AS A HATTER) → fluctuating mental state, confusion, restlessness, visual hallucination, picking at objects in the air, slurred speech
- Tremor
- Myoclonus
- Coma and seizures (rare)

PERIPHERAL:

- Mydriasis
- Tachycardia
- Dry mouth
- Dry skin (DRY AS A BONE)
- Flushing (RED AS A BEET)
- Hyperthermia (HOT AS HADES)
- Sparse or absent bowel sounds
- Urinary retention

Diagnosis is clinical in the presence of a history of ingestion of a known anticholinergic agent:

- ANTIPARKINSONIAN DRUGS → amantadine, benztropine
- ANTIHISTAMINES → chlorpheniramine, cyproheptadine, dimenhydrinate, diphenhydramine, doxylamine, pheniramine, promethazine
- ANTIDEPRESSANTS → TCA
- ANTIPSYCHOTICS → butyrophenones, phenothiazines, atypical agents
- ANTICONVULSANTS → carbamazepine
- MOTION SICKNESS AGENTS → hyoscine, scopolamine, meclizine
- ANTI-MUSCARINIC AGENTS → atropine, glycopyrrolate
- TOPICAL OPHTHALMOLOGICAL AGENTS → cyclopentolate, tropicamide, homatropine
- URINARY ANTISPASMODIC AGENTS → oxybutynin

DIFFERENTIAL DIAGNOSIS:

- Encephalitis
- Hypoglycaemia
- Hyponatraemia
- Ictal phenomenon

- NMS
- Neurotrauma
- Sepsis
- Serotonin syndrome
- SAH
- Wernicke's encephalopathy

MANAGEMENT:

- Attention to basics of resuscitation
- Once established, the duration of delirium is difficult to predict
- Prevent complications → injury (self/others), dehydration, hyperthermia, rhabdomyolysis, pre-renal failure, pulmonary aspiration/atelectasis
- Treat agitation with diazepam
- PHYSOSTIGMINE is a centrally acting acetylcholinesterase inhibitor that may be used to reverse anticholinergic delirium in selected patients

APPROACH TO THE CHOLINERGIC SYNDROME:

A RESULT OF INCREASED ACETYLCHOLINE ACTIVITY BOTH CENTRALLY AND PERIPHERALLY AND IS POTENTIALLY LETHAL

ARISES FROM EITHER ACETYLCHOLINESTERASE ENZYME INHIBITION OR DIRECT AGONIST ACTION

MOST CASES OF CLINICALLY SIGNIFICANT POISONING ARE DUE TO ORGANOPHOSPHATE OR CARBAMATE PESTICIDES

CLINICAL FEATURES:

- Classically, the patient in cholinergic crisis has COPIOUS SECRETIONS, VOMITING, DIARRHOEA AND ALTERED MENTAL STATUS
    - Fasciculation and muscle weakness may be prominent
- Death is due to respiratory failure from excessive respiratory secretions and weakness of ventilatory muscles
- CNS → agitation, central respiratory depression, coma, confusion, lethargy, seizures
- Neuromuscular → fasciculation, muscle weakness
- Parasympathetic muscarinic effects ("DUMBBELS"):
    - Diarrhoea
    - Urinary symptoms
    - Miosis
    - Bronchorrhoea
    - Bronchospasm
    - Emesis
    - Lacrimation
    - Salivation
- Sympathetic nicotinic effects:
    - Hypertension
    - Mydriasis
    - Sweating
    - Tachycardia
- Complications include:
    - Rapid onset of respiratory failure
    - Seizures
    - Dehydration
    - Medium and long-term neurological sequelae of organophosphates

MANAGEMENT:

- Efforts to decontaminate the patient or use sophisticated personal protective equipment should NOT delay resuscitation efforts
- Early control of pulmonary secretions and administration of oxygen is key to survival
- Administer atropine if there are any objective signs of muscarinic excess → cough, dyspnoea, respiratory failure, vomiting, diarrhoea, salivation, lacrimation or bradycardia → if improvement not rapid → RSI and intubation

- PRALIDOXIME administered for nicotinic effects

APPROACH TO NEUROLEPTIC MALIGNANT SYNDROME:

A RARE BUT POTENTIALLY LETHAL SYNDROME COMPLICATING THE USE OF NEUROLEPTIC MEDICATIONS (OCCURS IN 0.02-0.5% OF PATIENTS TAKING THESE MEDICATIONS)

CHARACTERISED BY NEUROMUSCULAR RIGIDITY, ALTERED MENTAL STATUS AND AUTONOMIC INSTABILITY

AETIOLOGY IS UNCLEAR

CLINICAL FEATURES (DSM IV):

- Development of severe muscle rigidity and elevated temperature associated with antipsychotic use
- ≥2 of the following:
  - Diaphoresis
  - HT
  - Tachycardia
  - Incontinence
  - Dysphagia
  - Mutism
  - Tremor
  - Altered level of consciousness
  - Leucocytosis
  - Laboratory evidence of muscle injury (↑CK)
- Symptoms from first two are NOT due to another substance or condition
- Symptoms in first two are NOT accounted for by a mental disorder (e.g. mood disorder with catatonia)

CT, LP, MRI are all normal

Hepatic and renal dysfunction, metabolic acidosis, ↓Ca, ↓Mg all occur

MANAGEMENT:

- RSI AND intubation if hyperthermia or severe rigidity compromising ventilation
- Avoid any agents with dopamine antagonist effects
- Benzos are controversial as they may play a role in aetiology
- BROMOCRIPTINE indicated if there is autonomic instability
- Role of dantrolene and ECT controversial
- Prevention of complications:
  - Respiratory failure
  - Dehydration
  - Renal failure
  - Multiorgan failure
  - Thromboembolism
  - Recurrence on re-challenge in 30-50%
- Supportive care paramount