PSYCHIATRIC MEDICATIONS AND THEIR TOXIDROMES

AMISULPRIDE

OVERDOSE IS ASSOCIATED WITH QT PROLONGATION AND TORSADES DE POINTES

INGESTION OVER 4G SHOULD BE MONITORED FOR AT LEAST 16 HOURS

RISK ASSESSMENT:

- Small overdose (<8g) relatively benign
- Larger ingestions:
  - Bundle branch blocks
  - QT prolongation
  - Ventricular arrhythmia (including torsades)
  - Hypotension
  - Coma
- DOSE-RELATED:
  - 8-15G → ↑ sedation with cardiotoxicity (↓BP, QRS/QT prolongation, BBB)
  - >15g → significant risk of delayed coma and cardiotoxicity

TOXIC MECHANISM:

- Atypical antipsychotic
- Acts as D2/D3 antagonist with minimal affinity for serotonin, histamine or muscarinic receptor

TOXICOKINETICS:

- Two absorption peaks at 1 and 4 hours
- Large volume of distribution
- Elimination half life 12 hours

CLINICAL FEATURES:

- Asymptomatic initially but ECG manifestations usually apparent early
- Onset of coma, hypotension, BBB and torsades can be abrupt and occur at up to12 hours post-ingestion
- Key investigation is the ECG → QT or QRS prolongation
- Check for Ca, K and Mg abnormalities if ECG abnormal

MANAGEMENT:

- Early problems are coma and cardiac dysrhythmias
- Patient with established severe toxicity should be intubated with control of torsades with magnesium or chemical/electrical overdrive pacing
- Decontaminate with charcoal if presents within four hours
- No role for enhanced elimination

- If those who remain asymptomatic with a normal ECG at 16 hours → discharge

BUPROPION:

ANTIDEPRESSANT USED IN SUPPRESSION OF NICOTINE CRAVING → ONLY AVAILABLE IN CONTROLLED-RELEASE PREPARATION

HIGH RISK OF SEIZURES FOLLOWING OVERDOSE OF ANY AMOUNT

LIFE-THREATENING CARDIOTOXICITY WITH VERY HIGH DOSES

SUPPORTIVE CARE AND BENZODIAZEPINE SEDATION ENSURE GOOD OUTCOMES

RISK ASSESSMENT:
- High risk of seizures with ANY OVERDOSE → first seizure usually delayed 2-8 hours but can occur at 24 hours
- Risk of seizure ↑d if seizure threshold is lowered for another reason or if co-ingestion with other centrally acting sympathomimetic/serotonergic agents
- With doses>9g → risk of cardiotoxicity, instability and death
- 4.5g → 50% risk of seizures, usually within 8 hours
- >9g → seizures universal, risk of cardiotoxicity

TOXIC MECHANISM:
- Monocyclic antidepressant, ↑s levels of CNS excitatory neuroamines by inhibiting noradrenaline and dopamine reuptake
- Causes minimal serotonin reuptake inhibition and moderate anticholinergic effects
- Unknown mechanism as it relates to nicotine craving suppression

CLINICAL FEATURES:
- Develop progressively over 8 hours → ↑HR, ↑BP, tremors, GI disturbance followed by hallucination, altered mental state and seizures
- Cardiovascular manifestations after massive overdose and include shock, QRS widening, tachyarrhythmia → manifest within 6 hours

MANAGEMENT:
- Early intubation if massive overdose
- IV diazepam (5-10mg and repeated as necessary) for seizures
- Broad complex tachycardia → aggressively with intubation, hyperventilation and serum alkalinisation with **SODIUM BICARBONATE:**
    - Used as both an antidote and alkalinisng agent to manipulate drug distribution
    - Indications include:
        - Cardiotoxicity secondary to fast sodium channel blockade → TCA, bupropion, chloroquine, propranolol, Type 1a/1c antiarrhythmic

        - Prevention of redistribution of drugs to the CNS (severe salicylate poisoning)
        - Immediate correction of profound life-threatening metabolic acidosis → cyanide, toxic alcohols, isoniazid
        - Enhanced elimination by urinary alkalinisation → salicylate, phenobarbitone
        - ↑d urinary solubility → methotrexate, drug-induced rhabdomyolysis
    - Contraindicated in:
        - APO, hypokalaemia, alkalosis of any cause, CCF (poorly controlled), renal failure, severe hypernatraemia (sodium load)
    - MECHANISM OF ACTION OF SODIUM BICARBONATE:
        - Elevation of serum pH → improves fast sodium channel function (maximal at 7.5-7.55) → added sodium load has added but separate positive effect.
            - ↑pH also alters drug disgtribution as it can reduce the proportion of the drug in the un-ionised form
            - ↑pH for immediate correction of life-threatening acidosis
        - Alkalinisation of urine → ION-TRAPPING AND ENHANCED URINARY ELIMINATION, thus unable to be re-absorbed
            - Urinary alkaline pH promotes water solubility of some drugs preventing tubular precipitation
    - ADMINISTRATION OF SODIUM BICARBONATE:
        - In cardiac arrest → repeated boluses of 2mmol/kg until stability achieved
        - Serum alkalinisation →consider with ventricular arrhythmia, hyptension, wide QRS → 100mmol bicarbonate in 1L at 250mL/h. Better to do this with hyperventilation
        - Urinary alkalinisation → correct hypokalaemia if present then give 1-2mmol/kg of NaHCO3 with 20mmol KCl to maintain normokalaemia
- DECONTAMINATION → GENERALLY DO NOT PERFORM UNLESS INTUBATED DUE TO HIGH RISK OF SEIZURES

CLOZAPINE:

DELIBERATE OVERDOSE IS UNUSUAL AS THIS IS CLOSELY CONTROLLED

CARE IS SUPPORTIVE

RISK ASSESSMENT:

- Clear dose response is NOT defined, but most poisonings are benign
- Coma uncommon and more likely in patients naïve to clozapine
- Children taking more than 2.5mg/kg may have delayed EPSE

TOXIC MECHANISM:

- It is a tricyclic dibenzodiazepine ATYPICAL ANTIPSCHOTIC
- Antagonist at mesolimbic D1/D2 receptors, 5HT receptors and peripheral ALPHA-1 receptors
- It is also a potent antagonist at M1, H1 and GABA receptors

TOXICOKINETICS:

- Significant first pass effect
- Highly protein bound

CLINICAL FEATURES:

- Onset of intoxication is rapid
- Lethargy, confusion, sedation, ↑HR and ortostatic hypotension are common
- Anticholinergic effects often occur
- Hypersalivation is characteristic
- Seizures in 5-10%
- EPSE more common in kids
- Resolves within 24 hours

MANAGEMENT:

- Basic resuscitative measures ensure good outcome in majority
- No role for decontamination as it is rapidly absorbed and has benign course

LITHIUM (ACUTE AND CHRONIC POISONING)

ACUTE LITHIUM OVERDOSE PRODUCES GI UPSET PREDOMINANTLY → IF ADEQUATE URINARY LITHIUM EXCRETION IS MAINTAINED, THEN THE NEUROTOXICITY OBSERVED WITH CHRONIC POISONING SHOULD NOT OCCUR

ACUTE OVERDOSE:

- Acute ingestion 25g causes GI symptoms, but so long as dehydration is avoided, renal function is preserved and sodium does not become depleted, neurotoxicity should not follow → these conditions significantly impair urinary lithium excretion and thus lithium is redistributed to tissue compartments, including CNS
- TOXIC MECHANISM:
  - Lithium carbonate is a direct irritant to the GIT
  - Once absorbed, lithium substitures for Na and K → modulate intracellular second messengers
- TOXICOKINETICS:
  - Almost exclusively eliminated by the kidney, being dependent on GFR, which is reduced in water or sodium-depleted states
- CLINICAL FEATURES OF ACUTE OD:
  - Nausea, vomiting, abdominal pain and diarrhoea are characteristic
  - Neurological symptoms, if they develop, ARE DELAYED → reflecting slow redistribution into the CNS, first sign is TREMOR
- Those who present late with severe GI symptoms may require fluid resuscitation and sodium repletion
  - Maintain urine output at 1mL/kg/hour
  - Elimination of lithium can be enhanced with haemodialysis in the patient→ should not be required in the patient with normal renal function→ reserved for patients with established renal failure and those with established neurotoxicity
- COMA IN THE CONTEXT OF ACUTE SELF-POISONING IS **NEVER** DUE TO LITHIUM → ALWAYS LOOK FOR A CO-INGESTANT

CHRONIC POISONING:

- Will develop in patients on long-term lithium therapy who develop impaired renal excretion of lithium for any reason
- RISK ASSESSMENT:
  - Consider in any patient on lithium who presents with neurological signs or symptoms
  - Significant obtundation or seizure activity carries a risk of permanent neurological sequelae
  - Serum concentrations of lithium correlate poorly with degree of toxicity
- CLINICAL FEATURES:
  - PRINCIPALLY NEUROLOGICAL
  - GRADING SYSTEM → **HANSEN AND AMIDSEN:**
    - Grade 1 → tremor, hyperreflexia, agitation, ataxia, weakness

        - Grade 2 → stupor, rigidity, hypertonia, hypotension
        - Grade 3→ coma, convulsions, myoclonus
    - Clinical features also include features of precipitating illness
    - Most common causes of impaired lithium excretion:
        - Renal dysfunction
        - Diabetes insipidus (can be associated with lithium treatment)
        - Sodium depletion
        - Dehydration
        - Drug interactions (NSAIDs, ACE-I, SSRI, thiazides, topiramate)
- INVESTIGATIONS:
    - Lithium level is essential to confirm the diagnosis, but its absolute value correlates poorly with degree of severity
    - EUC
    - Thyroid function → people on lithium develop hypothyroidism
- MANAGEMENT:
    - Acute resuscitation is unlikely to be needed except in the case of coma/seizures
    - Careful attention to correcting water/sodium deficits and restoring renal function are crucial to maximize lithium excretion
    - CONSIDER HAEMODIALYSIS IN THE PATIENT WITH NEUROLOGICAL IMPAIRMENT AND A LITHIUM LEVEL 2.5MMOL/L

MIRTAZAPINE:

USUALLY FOLLOWS A BENIGN COURSE

MILD CNS DEPRESSION AND TACHYCARDIA MOST COMMONLY

CARE IS SUPPORTIVE

RISK ASSESSMENT:

- Relatively minor toxidrome, even after large ingestions
- In kids, accidental ingestions up to 100mg without serious adverse consequence

TOXIC MECHANISM:

- Centrally acting alpha-2 antagonist that enhances release of serotonin and noradrenaline

CLINICAL FEATURES:

- If symptoms occur, it is within four hours
- Mild tachycardia, drowsiness, confusion and miosis occur
- Care is supportive
- Consider alternative diagnosis in patient with seizures, coma or haemodynamic instability

MONOAMINE OXIDASE INHIBITORS:

IRREVERSIBLE, NON-SELECTIVE AGENTS → PHENELZINE, TRANYLCYPROMINE

REVERSIBLE MAO-A → MOCLOBEMIDE

OVERDOSE OF THE IRREVERSIBLE NON-SELECTIVE MAO-I ARE ASSOCIATED WITH POTENTIALLY LETHAL SEROTONIN TOXICITY IN OVERDOSE. NEWER REVERSIBLE AND SELECTIVE AGENTS HAVE A MORE BENIGN COURSE UNLESS CO-INGESTED WITH OTHER SEROTONERGIC AGENTS

RISK ASSESSMENT:

- Overdose on moclobemide alone causes minor symptoms only
  - Mild serotonin toxicity in <5%
  - QTc prolongation but no reported torsades
  - BEWARE CO-INGESTION WITH OTHER SEROTONERGIC AGENTS, irrespective of dose
- Overdose on PHENELZINE/TRANYLCYPROMINE associated with DOSE-DEPENDENT, POTENTIALLY LETHAL SEROTONIN SYNDROME

TOXIC MECHANISM:

- They inhibit MAO A and B
  - MAO-A metabolises serotonin, noradrenaline and dopamine → if irreversible, requires new enzyme synthesis over days to re-establish enzymatic function

TOXICOKINETICS:

- Significant first-pass effect → phenelzine and tranylcypromine have active metabolites

CLINICAL FEATURES:

- MOCLOBEMIDE alone is benign → beware co-ingestion and risk of severe serotonin toxicity
- PHENELZINE OR TRANYLCYPROMINE → usually asymptomatic for the first 6-12 hours
  - Onset of toxicity heralded by restlessness, agitation, tachycardia, clonus/hyperreflexia, involuntary movements
  - Followed by rapid decline in conscious state
  - Muscle rigidity develops → respiratory compromise, hypoxia/respiratory acidosis, hyperthermia and rhabdomyolysis
  - Autonomic instability → lability in blood pressure
  - DIC and multi-organ dysfunction may ensue
- TYRAMINE REACTION → HYPERTENSIVE CRISIS AFTER INGESTION OF FOOD CONTAINING TYRAMINE → ICH, rhabdo, ARF, DIC may follow

MANAGEMENT:

- Hypertension and tachycardia usually controlled with titrated IV benzodiazepines
- Severe hypertension may require parenteral vasodilator therapy → nitroprusside, GTN, alpha-antagonists
    - NO BETA-BLOCKERS → unopposed alpha agonism
- HYPERTHERMIA RESULTING FROM MAO-I toxicity requires aggressive therapy (risk of multi-organ failure above 39.5)
- Consider decontamination in those who present within 2 hours of phenelzine or tranylcypromine OD

OLANZAPINE:

ASSOCIATED WITH SEDATION, DELIRIUM AND COMA IN ASCENDING DOSES

SUPPORTIVE CARE ENSURES GOOD OUTCOME

RISK ASSESSMENT:

- Predictable dose-dependent clinical features
- EPSE are uncommon → >300mg ↑g sedation progressing to coma likely to require intubation, and hypotension secdonary to peripheral alpha blockade

TOXIC MECHANISM:

- Antagonist at D2, 5HT-2, H1 and M1 as well as peripheral alpha receptors
- Large first pass effect after oral dosing

CLINICAL FEATURES:

- Sedation, ataxia, miosis, orthostatic hypotension and tachycardia are common
- Fluctuating mental status with intermittent agitated delirium occurs
    - Lasts <24 hours
    - Seizures, EPSE, QTc prolongation are rare
- Coma can occur following large ingestions and last 18-24 hours
- GENERAL SUPPORTIVE CARE, PARTICULARLY OF COMA AND DELIRIUM LEADS TO GOOD OUTCOMES

PHENOTHIAZINES AND BUTYROPHENONES:

Phenothiazines = chlorpromazine, prochlorperazine, thioridazine (no longer sold due to high rates of ventricular arrhythmia).

Butyrophenones = haloperidol, droperidol

THESE NEUROLEPTIC AGENTS CAUSE CNS DEPRESSION, ORTHOSTATIC HYPOTENSION AND ANTICHOLINERGIC EFFECTS IN OVERDOSE.

RISK ASSESSMENT:

- Dose dependent CNS depression, tachycardia, hypotension and anticholinergic effects
- Chlorpromazine causes coma with ingestions >5g
- Cardiac dysrhythmias and seizures are very uncommon (esp now that thioridazine is off the market)

TOXIC MECHANISM:

- Phenothiazines are antagonists at central D2 receptors, but their adverse effect profile is mediated by their antagonist actions at other sites (H1, GABAa, M1, α-1 and α-2 and 5HT). Butyrophenones are a separate class, but with similar mechanism of action.
- Cardiac toxicity is mediated by sodium and potassium blocking effects

TOXICOKINETICS:

- Absorption is slow and erratic following overdose
- Large volume of distribution with lipid solubility
- Extensive first pass metabolism

CLINICAL FEATURES:

- Occurs with 2-4 hours
- Sedation, ataxia, orthostatic hypotension and tachycardia are common
- Agitated delirium may last up to 24 hours
- Urinary retention common
- Coma following large ingestions of chlorpromazine and may last 18-48 hours
- Seizures and EPSE are uncommon

MANAGEMENT:

- General supportive care usually ensures a good outcome
- Activated charcoal is NOT indicated for patients without coma
- Hypotension is usually secondary to peripheral vasodilation and responds with to fluid resuscitation

QUETIAPINE:

SECOND-GENERATION ATYPICAL ANTIPSYCHOTIC → SELF-POISONING IS ASSOCIATED WITH SEDATION, DELIRIUM, COMA, TACHYCARDIA AND HYPOTENSION

CURRENTLY A LEADING CAUSE OF TOXIC COMA REQUIRING I.C.U. ADMISSION

RISK ASSESSMENT:

- Predictable, dose-dependent CNS depression with brisk tachycardia
- Mild hypotension → may be profound with massive overdose
- QT prolonged but no reports of torsades
- Co-ingestion with other CNS depressants ↑s risk of coma
- 3g appears to be the threshold dose, above which there is an ↑g risk of CNS depression, coma and hypotension. Delirium and seizures may occur

TOXIC MECHANISM:

- Antagonist at mesolimbic D2, 5HT-2a, H1, M1 and peripheral α-1 receptors (hence hypotension)

TOXICOKINETICS:

- Metabolised to an active metabolite

CLINICAL FEATURES:

- Onset within 2-4 hours and may last up to 72 hours
- Sedation and sinus tachycardia (>120) are common
- Coma lasts 18-48 hours
- Seizures in <5%
- Hypotension
- QT prolongation rare and no reports of torsades

MANAGEMENT:

- No specific investigations. If ECG normal at 4 hours → no further monitoring unless intubated
- Resuscitation along standard lines
- Fluid resuscitate if hypotensive and if no response → NORADRENALINE. Adrenaline infusion may paradozically exacerbate the hypotension, perhaps due to β-2 mediated vasodilation.
- Benzodiazepines titrated to response for agitated delirium
- Onset of sedation/coma is rapid and outcome is good with thorough supportive care, hence no role for decontamination
- Kids should be observed after ingestions 100mg. Advise parents that EPSE may ensue over coming 3 days

RISPERIDONE:

MILD SEDATION, TACHYCARDIA AND ORTHOSTATIC HYPOENSION

SUPPORTIVE CARE ENSURES A GOOD OUTCOME

RISK ASSESSMENT:

- Dose-effect profile not well defined
- Mild features are typical → sedation, tachycardia and orthostatic hypotension
- In kids, >1mg will lead to lethargy, EPSE as well as above

TOXIC MECHANISM:

- Antagonist at mesolimbic D2, 5HT-2A, α-2 and peripheral α-1 receptors
- Compared with other antipsychotic agents in its class, it has much lower affinity for H1 and M1 receptors

TOXICOKINETICS:

- Renal impairment prolongs half-life
- Hepatic metabolism produces active metabolite

CLINICAL FEATURES:

- Onset is within 4 hours
- Lethargy, confusion, sedation (mild) and tachycardia are common
- Miosis and mydriasis are reported
- EPSE may be seen
- QT ↑ is reported but no torsades
- Anticholinergic features are rate
- Resolves within 24 hours

MANAGEMENT:

- Resuscitation along standard lines → ensures good outcome
- No role for decontamination or enhanced elimination
- Patients who are well, not sedated and have normal ECG at 4 hours may be medically cleared
- Coma, seizures or significant alterion in vital signs prompt consideration of alternative diagnosis

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI):

DELIBERATE SELF-POISONING IS COMMON AND USUALLY BENIGN

SEROTONIN TOXICITY DEVELOPS IN A SMALL MINORITY

CITALOPRAM AND ESCITALOPRAM ARE UNIQUE IN THEIR ABILITY TO PRODUCE QT-PROLONGATION

RISK ASSESSMENT:

- Overdose is usually benign, regardless of dose
- Mild serotonin toxicity in less than 20% and lasts <12 hours
- Seizures in <4% and more likely with citalopram
- If >600mg citalopram ingested, QT prolongation likely, but torsade only rarely
- Co-ingestion of other serotonergic agents, tramadol, or SNRI greatly ↑s risk of severe serotonin syndrome

TOXIC MECHANISM:

- Enhance central serotonergic neurotransmission by inhibiting serotonin reuptake

TOXICOKINETICS:

- SSRI rapidly absorbed following oral administration
- Hepatic metabolism to less active and water-soluble metabolites

CLINICAL FEATURES:

- Many patients remain asymptomatic
- Minor symptoms within four hours and resolve by 12
- Mild serotonin syndrome in <20% → anxiety, tremor, tachycardia, mydriasis
- Severe serotonin syndrome does not develop unless there is co-ingestion of another serotonergic agent
- Seizures are uncommon and are most strongly associated with citalopram (<2%) → benzodiazepine control
- QT prolongation following citalopram OD, dose-dependent (12% >500ms in one case-series)

MANAGEMENT:

- Resuscitation along standard lines
- Manage as for serotonin syndrome (see earlier discussion)
- ↑g anxiety, sweating, tremor, tachycardia and mydriasis herald the onset of seizures → prophylactic benzodiazepine administration
- Activated charcoal is not indicated unless warranted by co-ingestants → consider if >600mg citalopram ingested within the last four hours (and patient awake/cooperative)

TRICYCLIC ANTIDEPRESSANTS (TCA):

REMAINS A MAJOR CAUSE OF MORBIDITY AND MORTALITY

DELIBERATE SELF-POISONING MAY LEAD TO RAPID ONSET OF CNS AND CARDIOVASCULAR TOXICITY

PROMPT INTUBATION, HYPERVENTILATION AND SODIUM BICARBONATE AT FIRST EVIDENCE OF SEVERE TOXICITY ARE LIFE-SAVING

RISK ASSESSMENT:

- Ingestion of 10mg/kg life-threatening → onset of severe toxicity usually within 2 hours of ingestion
- Seizures and myoclonus more common with DOXEPIN
- At >30mg/kg, severe toxicity with pH dependent cardiotoxicity and coma expected to last 24 hours
- Any ingestion 10mg/kg in toddlers is life threatening

TOXIC MECHANISM:

- TCA are noradrenaline and serotonin reuptake inhibitors and GABAa blocking agents
- Myocardial toxicity is chiefly due to blockade of inactivated fast sodium channels
- Other toxic effects are mediated by M1 and H1 antagonism
- Inhibiton of post-synaptic α-1 adrenergic receptors
- TCAs also cause reversible inhibition of potassium channels and direct myocardial depression unrelated to conduction defects

TOXICOKINETICS:

- Peak levels within 2 hours
- Highly protein bound with large volume of distribution
- Hepatic metabolism to active metabolites with some enterohepatic recirculation

CLINICAL FEATURES:

- Severe toxicity is characterised by rapid deterioration in clinical status within 1-2 hours of ingestion → patients may present alert only to rapidly develop coma, seizures, hypotension and cardiac dysrhythmia
- CNS features:
    - Sedation and coma usually precede CV signs
    - Seizures
    - Anticholinergic delirium (obscured by coma)
- CARDIOVASCULAR:
    - Sinus tachycardia with mild hypertension
    - Hypotension due to α-blocking effects and impaired contractility

    - Broad-complex tachydysrhythmia (broad complex bradyarrhythmia occurs pre-arrest)
- ANTI-CHOLINERGIC EFFECTS:
    - May be delayed and prolonged
    - Agitation, restlessness
    - Mydriasis
    - Warm, flushed skin
    - Urinary retention and ileus
    - Myoclonic jerks

INVESTIGATIONS:

- ECG ARE VITAL IN THE MANAGEMENT AND DIAGNOSIS OF TCA INTOXICATION
- ECG FEATURES INCLUDE:
    - PR/QRS prolongation
    - Large terminal R-wave in aVR
    - ↑'d R/S ration (>0.7) in aVR
    - QT prolongation secondary to potassium channel blockade
    - QRS widening reflects degree of fast sodium channel blockade
        - >100ms predictive of seizures
        - >160ms predictive of ventricular tachycardia

MANAGEMENT:

- Acute TCA is potentially life-threatening with early threats being coma, respiratory acidosis, seizures, dysrhythmia and arrest
- Close monitory mandatory for six hours post-ingestion
- At onset of CNS depression, prompt intubation and hyperventilation are indicated
- VENTRICULAR DYSRHYTHMIA:
    - DEFIBRILLATION UNLIKELY TO BE EFFECTIVE
    - Administer sodium bicarbonate 100mmol (2mmol/kg) every 1-2 minutes until restoration of perfusing rhythm
    - Lignocaine (1.5mg/kg) is third-line therapy when pH >7.5
    - Type-1a anti-arrhythmic (procainamide), amiodarone and beta-blockers are CONTRAINDICATED
- HYPOTENSION:
    - IV crystalloid, sodium bicarbonate, adrenaline/noradrenaline
- SEIZURES → benzodiazepine
- Intubated patients are hyperventilated to pH7.5-7.55
- ACTIVATED CHARCOAL AFTER AIRWAY SECURED IN INGESTIONS >10mg/kg
- SODIUM BICARBONATE IS CONSIDERED AN ANTIDOTE IN THIS CIRCUMSTANCE
- DO NOT STOP RESUSCITATION EFFORTS UNTIL THE PATIENT HAS BEEN INTUBATED AND TREATED WITH BICARB TO A pH of 7.50-7.55
    - Reports of good neurological outcome after prolonged CPR
- Onset of coma may be abrupt and herald precipitous decline

- Intubation, hyperventilation and bicarbonate when administered promptly in patients who arrive alive or shortly post-arrest is normally sufficient to ensure survival

VENLAFAXINE AND DESVENLAFAXINE:

POTENT SEELCTIVE SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS

VENLAFAXINE OVERDOSE IS POTENTIALLY LIFE-THREATENING AND FREQUENTLY CAUSES SEIZURES OR CARDIOVASCULAR TOXICITY IN VERY LARGE INGESTIONS

LESS EXPERIENCE WITH DESVENLAFAXINE, BUT IT IS EXPECTED TO BE SIMILAR TO VENLAFAXINE

RISK ASSESSMENT:

- 14% have seizures but incidence is dose dependent (>4.5g, the risk approaches 100%)
- >7G predicts hypotension and cardiac dysrhythmias
- High risk of serotonin syndrome if other serotonergic agents are co-ingested, irrespective of dose

TOXIC MECHANISM:

- Both are potent serotonin and noradrenaline reuptake inhibitors (SNRI)
- Also exhibit rate-dependent sodium channel blocking activity
- Weak dopamine reuptake activity and no M1, H1 or α-1 adrenergic receptors

TOXICOKINETICS:

- Venlafaxine is well absorbed but has extensive first pass metabolism (desvenlafaxine has far less first-pass effect)

CLINICAL FEATURES:

- Onset of significant clinical features may be delayed up to 6-12 hours following overdose
- Dysphoria, anxiety, mydriasis, sweating, tremor, clonus, tachycardia and hypertension → heralds onset of seizures
- Seizures are generalised, short duration and terminated with benzos
- **COMA NOT A FEATURE OF VENLAFAXINE OVERDOSE**
- Severe serotonin syndrome develops only where there is co-ingestion of other serotonergically active drugs
- Rhabdomyolysis is reported infrequently
- Minor QRS/QT prolongation may occur but is unlikely to be associated with dysrhythmia, except in massive overdose

MANAGEMENT:

- Early intervention required with SEIZURES AND BROAD-COMPLEX TACHYDYSRHYTHMIAS
    - Seizures → benzos
    - Broad-complex dysrhythmia → sodium bicarbonate

- ↑g agitation, tachycardia and tremor herald onset of seizures → prophylactic benzos
- Management of severe serotonin syndrome as outlined previously
- Activated charcoal in those who present within 2 hours after >4.5g overdose → if >7g → give 50g activated charcoal post-intubation