WHY ARE ANTIDEPRESSANTS STILL USED?

- Depression is common
- The morbidity and mortality is high
- Non-drug treatments are often unsatisfactory


POISONING WITH ANTIDEPRESSANTS

- Monoamine Oxidase Inhibitors
- Tricyclic Antidepressants (TCAs)
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Others
**MONOAMINE OXIDASE INHIBITORS (MAOIs)**

- First generation MAOIs
  - Phenelzine (*Nardil*)
  - Tranylcypromine
  - Isocarboxazid

- Reversible inhibitors (RIMAs)
  - Moclobemide (*Manerix*)

**MONOAMINE OXIDASE ENZYMES (MAOs)**

**FIRST GENERATION MONOAMINE OXIDASE INHIBITORS (MAOIs)**

- Tyramine
- Phenylephrine
- Norepinephrine
- Dopamine
- Serotonin (5HT)

**REVERSIBLE INHIBITORS OF MONOAMINE OXIDASE A (RIMAs)**

- Tyramine
- Phenylephrine
- Norepinephrine
- Dopamine
- Serotonin (5HT)

**MONOAMINE OXIDASE INHIBITOR (MAOI) POISONING**

- Clinical Features of poisoning (1)
  - Often latent period 6-12 hours, prolonged features
  - Agitation, restlessness,
  - Hallucinations, convulsions
  - Increased motor movements, nystagmus

**MONOAMINE OXIDASE INHIBITORS (MAOIs)**

- Clinical Features of poisoning (2)
  - Increased muscle tone, hypereflexia, myoclonus, pupillary dilatation
  - Hyperpyrexia, rhabdomyolysis, acute renal failure
  - Tachycardia, Hypertension, profuse sweating
MONOAMINE OXIDASE INHIBITORS (MAOIs)

- Management
  - Gastric decontamination (when appropriate)
  - Full supportive therapy
  - Cooling measures, diazepam and dantrolene
  - Beta blockers
  - Paralysis and ventilation

MOCLOBEMIDE

- Selective & reversible inhibitor of MOA type A (RIMA)
- Deaths have been reported in mixed overdoses involving moclobemide
- Fatal serotonin syndrome has occurred after overdoses of moclobemide taken with other serotonergic agents, (e.g. paroxetine, venlafaxine, citalopram or clomipramine)
- In one study 55% of patients co-ingesting moclobemide with a serotonergic agent developed serotonin toxicity (Isbister et al, 2003)
- Moclobemide prolongs the QT and QTc intervals in overdose and a 12-lead ECG should be done on all moclobemide self-poisonings (Downes et al 2005)
- Continuous cardiac monitoring can be considered in patients with a QTc > 500 ms or with known risks for QT prolongation


POISONING WITH ANTIDEPRESSANTS

- Monoamine oxidase inhibitors
  - Tricyclic antidepressants (TCAs)
  - Selective serotonin Reuptake Inhibitors (SSRIs)
  - Others

POISONING WITH ANTIDEPRESSANTS

- Tricyclic antidepressants (TCAs)
  - Dosulepin [Dothiepin] (Prothiaden)
  - Amitryptiline (Tryptizol)
  - Lofepramine (Gamanil)
  - Trazodone (Molipaxin)
  - Clomipramine (Anafranil)
  - Imipramine (Tofranil)
  - Mianserin (Bolvidon)

TRICYCLIC ANTIDEPRESSANT POISONING

- Clinical Features (Mild-moderate)
  - Dry Mouth
  - Dilated pupils
  - Sinus tachycardia
  - Urinary retention
  - Drowsiness
  - Hyporeflexia

TRICYCLIC ANTIDEPRESSANT POISONING

- Clinical Features (Severe)
  - Coma
  - Respiratory depression
  - Convulsions
  - Hypotension
  - Electrocardiographic changes
  - Arrhythmias
### TRICYCLIC ANTIDEPRESSANT POISONING

#### Conscious Pts.(%)
- Strabismus: 18
- Urine retention: 18
- Convulsions: 1
- Pulse 100-120: 37
- Arrhythmias: 0
- CNS toxicity: 10

#### Unconscious Pts.(%)
- Strabismus: 81
- Urine retention: 65
- Convulsions: 10
- Pulse >120: 13
- Arrhythmias: 12
- CNS toxicity: 35

### Electrocardiographic changes
- Prolonged PR, QRS and QT intervals (corrected QTc)
- Right axis deviation of the terminal 40 ms vector of the QRS complex in the frontal plane (T 40 ms axis)
- Brugada pattern (down-sloping ST segment elevation in leads V1-V3 in association with right bundle branch block)
- Non-specific ST segment and T wave changes
- Atrioventricular block
- Supraventricular and ventricular arrhythmias

PQRS duration >100 ms and a rightward T 40 ms axis predictors of cardiovascular toxicity but moderate sensitivity and specificity for predicting complications.

Thanacoody HK and Thomas SH. Tricyclic antidepressant poisoning: cardiovascular toxicity. Toxicol Rev. 2005; 24: 205-14

### Drug induced Brugada ECG pattern
- Left anterior fascicular block and incomplete right bundle branch block. Apart from the saddle back ST segment pattern without significant elevation in lead V2 (arrows), ST segment elevation or T wave abnormality is not seen in the right precordial leads.


### Treatment
- Gut decontamination
- Benefit gastric decontamination uncertain
- Consider activated charcoal (50 g for adults) by mouth or n.g. tube if patient presents within 1 hour of ingestion of more than 5 mg/kg, provided airway can be protected
- Second dose of charcoal (50 g) should be considered after 1-2 hours in patients with features of toxicity who are able to swallow, or who have been intubated.

27 patients
- 14 had TCA level > 1 mg/l
- 3 had cardiac arrest at early stage

Often during gastric emptying.

Bramble MG et al. Q J Med 1985: 56; 357-66
**TRICYCLIC ANTIDEPRESSANT POISONING**

- **Treatment**
  - **(Supportive)**
  - Treat hypotension
  - Treat Convulsions
  - Cardiopulmonary resuscitation

---

**TRICYCLIC ANTIDEPRESSANT POISONING**

- **Treatment**
  - **Treatment of hypotension**
  - Correct hypotension by raising foot of bed
  - In severe cases administration of colloid to expand intravascular volume required (central venous pressure monitoring may be required)
  - Alkalisation with sodium bicarbonate may correct hypotension.
  - If severe hypotension persists despite above measures and adequate filling pressures, consider use of inotropes with pure α agonist activity such as norepinephrine (Tran 1999)
  - Glucagon has been used to correct myocardial depression and hypotension (Sener 1995; Sensky 1999)
  - Glucagon 10 mg IV bolus may be given if patients are severely hypotensive.

---

**TRICYCLIC ANTIDEPRESSANT POISONING**

- **Treatment**
  - **Treatment of Convulsions**
  - Prophylactic anticonvulsants not shown to be effective
  - Control convulsions with IV diazepam or lorazepam
  - Give oxygen and correct acid base /metabolic disturb.
  - Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses
  - Phenytoin best avoided in tricyclic overdose (like TCAs it blocks sodium channels and may increase risk of cardiac arrhythmias)

---

**TRICYCLIC ANTIDEPRESSANT POISONING**

- **Prolonged resuscitation was successful in a patient after cardiac arrest due to imipramine poisoning**
- **TOXBASE:** After cardiac arrest, prolonged resuscitation may be successful and should be continued for at least 1 hour

---

**MODIFIED RELEASE TCAs**

- **MOLIPAXIN CR**
  - 150mg Roussel
  - 9.8 mm 3.9 mm

- **ANAFRANIL SR**
  - 75 mg Geigy
  - 8.1 mm 4.3 mm

- **LENTIZOL**
  - 50 mg Warner
  - 17.5 mm 6.0 mm 5.8 mm

**TRICYCLIC ANTIDEPRESSANT POISONING**

- **Treatment**
  - **Specific therapy**
    - Bicarbonate therapy
    - (Hyperventilation)
    - Antiarrhythmic therapy

- **Therapy of Arrhythmias (1)**
  - 12 lead ECG and assess QRS duration
  - QRS duration of > 120 ms may indicate cardiotoxicity
  - QRS duration of > 160 ms suggests severe cardiotoxicity with very high risk of arrhythmia
  - Seek urgent senior medical attention and consider immediate administration of bicarbonate

- **Therapy of Arrhythmias (2)**
  - Correct metabolic acidosis using iv sodium bicarbonate (CAUTION: if given by a peripheral venous line, irritant to veins and can cause skin necrosis in cases of extravasation)
  - 1.26% sodium bicarbonate alternative for patients who are haemodynamically stable
  - Even in absence of acidosis, consider alkalisation with iv sodium bicarbonate (50 mL 8.4%) in patients with:
    - QRS duration > 120 msec
    - arrhythmias
    - hypotension resistant to fluid resuscitation
  - Further doses of sodium bicarbonate may be given cautiously depending on clinical response, to achieve arterial pH 7.5-7.55 (Hoffman et al 1993) but care needed as alkalosis to pH>7.65 is potentially fatal.
  - Resist temptation to treat arrhythmias with drugs; best treated by correction of hypoxia and acidosis

- **Therapy of Arrhythmias (3)**
  - Resist temptation to treat arrhythmias with drugs. Best treated by correction hypoxia/acidosis
  - Magnesium sulphate and lidocaine may be used for VT/VF.
  - Class Ia (e.g. quinidine, disopyramide, procainamide) and class Ic antiarrhythmic drugs (e.g. flecainide, propafenone) contraindicated as they may worsen sodium channel blockade and exacerbate arrhythmias.
  - Class II agents (beta-blockers) may also induce hypotension

- **Therapy of Arrhythmias (4)**
  - Prolongation of QRS and QTc may be associated with risk TdeP
  - TdeP may be treated with magnesium sulphate 8-10 mmol iv over 30-120 seconds, repeated twice at intervals of 5-15 minutes if necessary
  - Hypoxia, electrolyte abnormalities and acid base disturbance should be corrected (NB These rapid infusion rates of magnesium (which are needed if the patient is having frequent or continuous torsade) usually cause flushing)
  - Alternatively, or if these measures fail, TdeP may be abolished by increasing underlying heart rate e.g. by atrial or ventricular pacing or by isoprenaline (isoproterenol) infusion to achieve heart rate 90-110 beats/minute
  - TdeP usually not helped by antiarrhythmic drugs. Those which prolong the QT interval (e.g. amiodarone, quinidine) make it worse (use only after specialist advice)

**TORSADES DE POINTES (TdeP)**

Torsades de Points  Torsades des Pontes
Torsades de Points  Torsades des Pontes
Torsades de Points  Torsades de Ponte
Torsades des Points  Torsades de Point
Torsades des Points  Torsades des Ponte
Torsades des Points  Torsades des Pontes
TRICYCLIC ANTIDEPRESSANT POISONING

- Treatment
  - Enhancement of Elimination?
  - NO (sadly)
  - Forced diuresis, haemodialysis and haemoperfusion of no value due to large volumes of distribution of TCAs
  - ANTIDOTES?
  - Extremely large amounts required and at present the use of Fab fragments limited by cost and possibility of renal toxic effects

POISONING WITH ANTIDEPRESSANTS

- Monoamine Oxidase Inhibitors
- Tricyclic Antidepressants (TCAs)
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Others

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

- Clinical Features of poisoning (mild-moderate)
  - Often minimal
  - May be latent period,
  - GIT- nausea, vomiting, abdominal pain
  - CNS- Agitation, tremor, dizziness, sweating,
  - CVS- sinus tachycardia, hypertension

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

- Clinical Features of poisoning (severe)
  - May be latent period
  - GIT- severe nausea, vomiting, abdominal pain
  - CNS- drowsiness, coma, convulsions
  - CVS- bradycardia, hypertension, junctional rhythm

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

- Treatment
  - Supportive therapy
  - Gastric decontamination
  - Treat complications

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

- Clinical Features of poisoning (severe)
  - SEROTONIN SYNDROME
  - has been reported following overdose of SSRIs alone or in combination with other serotinergic drugs.
    - Alteration of mental status
    - Neuromuscular hyperactivity
    - Autonomic instability.
**SEROTONIN SYNDROME**

- **Alteration of mental status**
  - Occur in 40% of patients and may range from agitation, confusion, delirium, and hallucinations to drowsiness and coma

- **Neuromuscular features**
  - Occur in around 50% and include profound shivering, tremor, teeth grinding, myoclonus and hyperreflexia

- **Autonomic instability**
  - Occurs in around 50% and includes tachycardia, fever, hypertension/hypotension, flushing, diarrhoea and vomiting

---

**SEROTONIN SYNDROME**

- **TREATMENT (1)**
  - Monitor urea, electrolytes, and creatine kinase. Send urine for myoglobin analysis
  - Commence intravenous fluids to correct hypotension and to replace insensible fluid loss if temperature raised
  - Fitting should be controlled with benzo’s such as diazepam. Myoclonic jerking said to be helped by clonazepam
  - In serious cases: propranolol may help reduce autonomic dysregulatory effects, but role controversial

---

**SEROTONIN SYNDROME**

- **TREATMENT (2)**
  - Cyproheptadine has been used
  - Cooled IV fluid to replace insensible losses and correct hyperthermia
  - Tepid sponging and use of fans
  - Dantrolene may be of benefit if above measure fail to reduce temperature and evidence of muscle rigidity
  - If all measures fail consider paralysing and ventilating patient for management of malignant hyperthermia

---

**SEROTONIN SYNDROME**

- **TREATMENT (3)**
  - If the CK is raised or rhabdomyolysis suspected, volume replacement and urine alkalinization may be helpful in preventing or reducing the severity of rhabdomyolysis-induced renal failure
  - Give volume replacement and 225 mmol of 8.4% sodium bicarbonate over two hours to increase urine pH to >7
  - Haemodialysis or haemofiltration may be required for acute renal failure or severe hyperkalaemia

---

**POISONING WITH ANTIDEPRESSANTS**

- Monoamine oxidase inhibitors
- Tricyclic antidepressants (TCAs)
- Selective serotonin Reuptake Inhibitors (SSRIs)
- Other antidepressants

**POISONING WITH ANTIDEPRESSANTS**

- Other antidepressants
  - Venlafaxine (Efexor)
  - Nefazodone (Dutonin)
  - Tryptophan (optimax)
  - Mirtazapine (Zispin)
  - Citalopram
VENLAFAXINE

- Drowsiness, sinus tachycardia, hypotension or hypertension, convulsions, sweating and dizziness
- Coma, prolongation of the QT and QRS duration and ventricular arrhythmias
- Rise in plasma creatine kinase and rhabdomyolysis possible (Pascale et al. 2005)
- Effects may be enhanced by simultaneous ingestion of other drugs acting on monoamine mechanisms [e.g. other antidepressants, monoamine oxidase inhibitors, lithium (Adam-Manes et al. 2006) and ecstasy]
- Risk of serotonin syndrome (alone or in combination)

CITALOPRAM

- Nausea, vomiting, sweating, tachycardia, drowsiness, coma, dystonia, convulsions, hyperventilation and hyperpyrexia
- Rarely features of the "serotonin syndrome" may occur in severe poisoning.
- Nodal rhythm, prolonged QT intervals and wide QRS complexes
- "Prolonged bradycardia with severe hypotension and syncope have been reported" (Rothenhausler et al 2000)
- "Associated with QTc prolongation. Consider cardiac monitoring with large ingestions and patients with associated cardiac disease" (Isbister et al 2004)

DEATHS ASSOCIATED WITH ANTIDEPRESSANT POISONING 1989-1994

- Twenty-three deaths were recorded, 15 associated with dothiepin, 4 with amitryptyline, 2 with imipramine, 1 with amitriptyline and imipramine and 1 with amoxapine
- All the deaths occurred before admission to the unit, indicating that preventive strategies are more likely to have an impact on mortality than improvements in treatment.

POISONING WITH ANTIDEPRESSANTS

- Monoamine Oxidase Inhibitors
- Tricyclic Antidepressants (TCAs)
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Others

"An ounce of prevention is worth a pound of cure.”
Henry de Bracton c.1240