# TRICYCLIC ANTIDEPRESSANTS POISONING IN PEDIATRICS

Nader Sadigh MD.

Ali Asghar Children's Hospital

# TRICYCLIC ANTIDEPRESSANTS

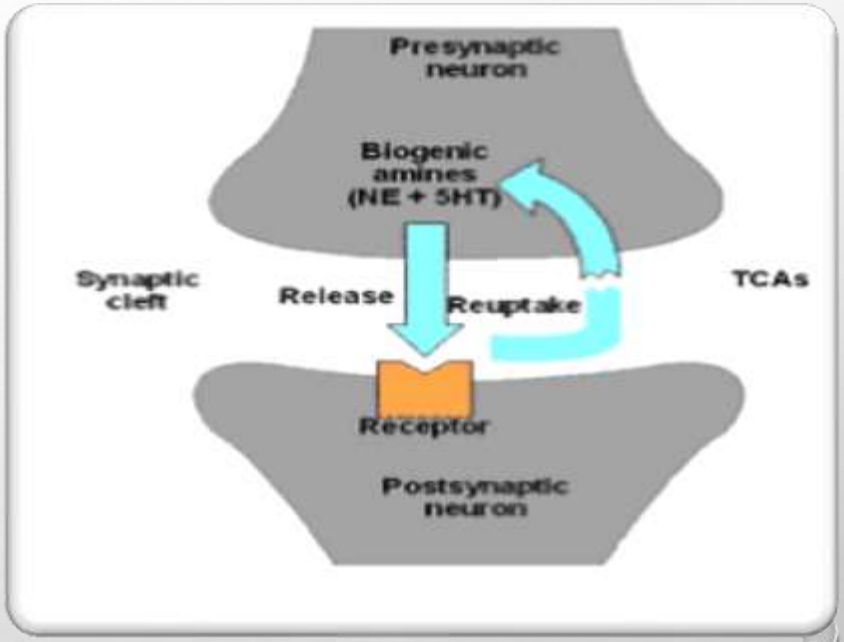
- AMITRIPTYLINE
- AMOXAPINE
- CLOMIPRAMINE
- DESIPRAMINE
- DOTHIEPIN
- DOXEPIN
- IMIPRAMINE
- LOFEPRAMINE
- NORTRIPTYLINE
- PROTRIPTYLINE
- TRIMIPRAMINE

# TRICYCLIC ANTIDEPRESSANTS

- TRICYCLIC ANTIDEPRESSANTS (TCA) ARE A CLASS OF MEDICATIONS TRADITIONALLY USED TO TREAT DEPRESSION
    - CURRENTLY BEING MORE WIDELY PRESCRIBED FOR PAIN SYNDROMES, PERIPHERAL NEUROPATHY, MIGRAINE PROPHYLAXIS, PANIC AND PHOBIC DISORDERS, AND OBSESSIVE-COMPULSIVE DISORDER
- TCA TOXICITY MAY BE FATAL
    - MORTALITY RATE OF ~15% (THOUGH HAS BEEN LOWER IN RECENT YEARS)
    - OVERDOSES ARE ON THE RISE GIVEN EXPANDING USE OF TCAS BEYOND DEPRESSION

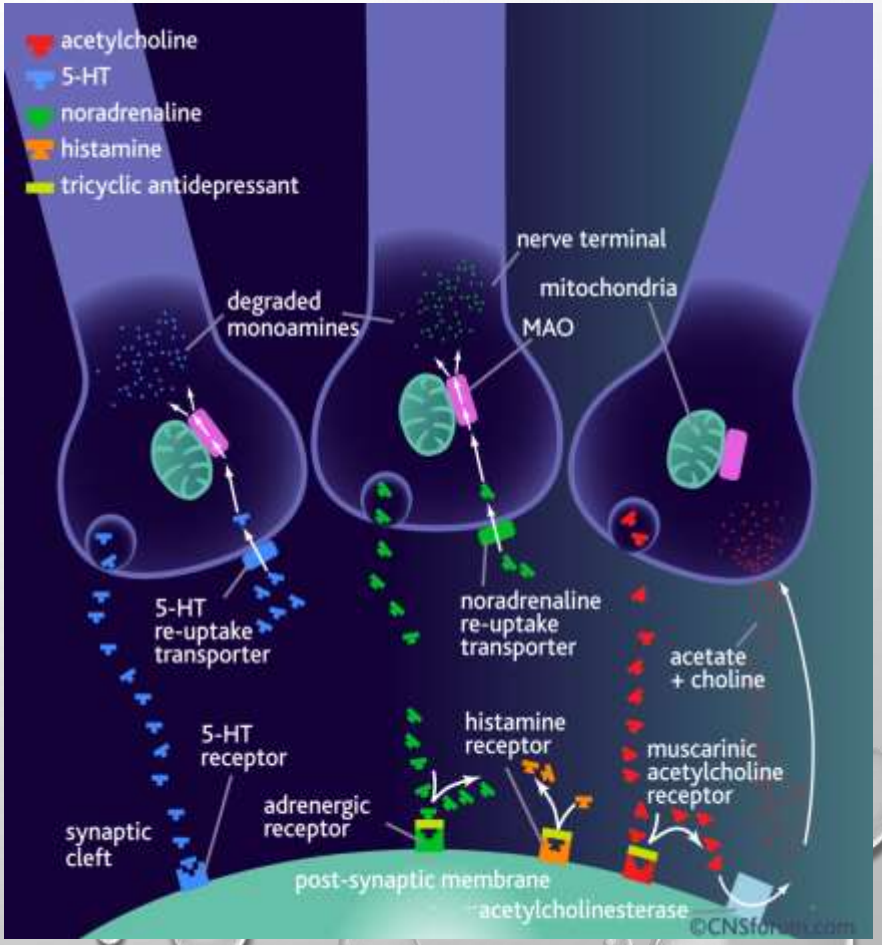
# TRICYCLIC ANTIDEPRESSANTS MECHANISM

- BLOCKING REUPTAKE OF NORADRENALINE AND SEROTONIN
- THESE EFFECTS ARE PROBABLY UNIMPORTANT IN OVERDOSE EXCEPT IN COMBINED OVERDOSE WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

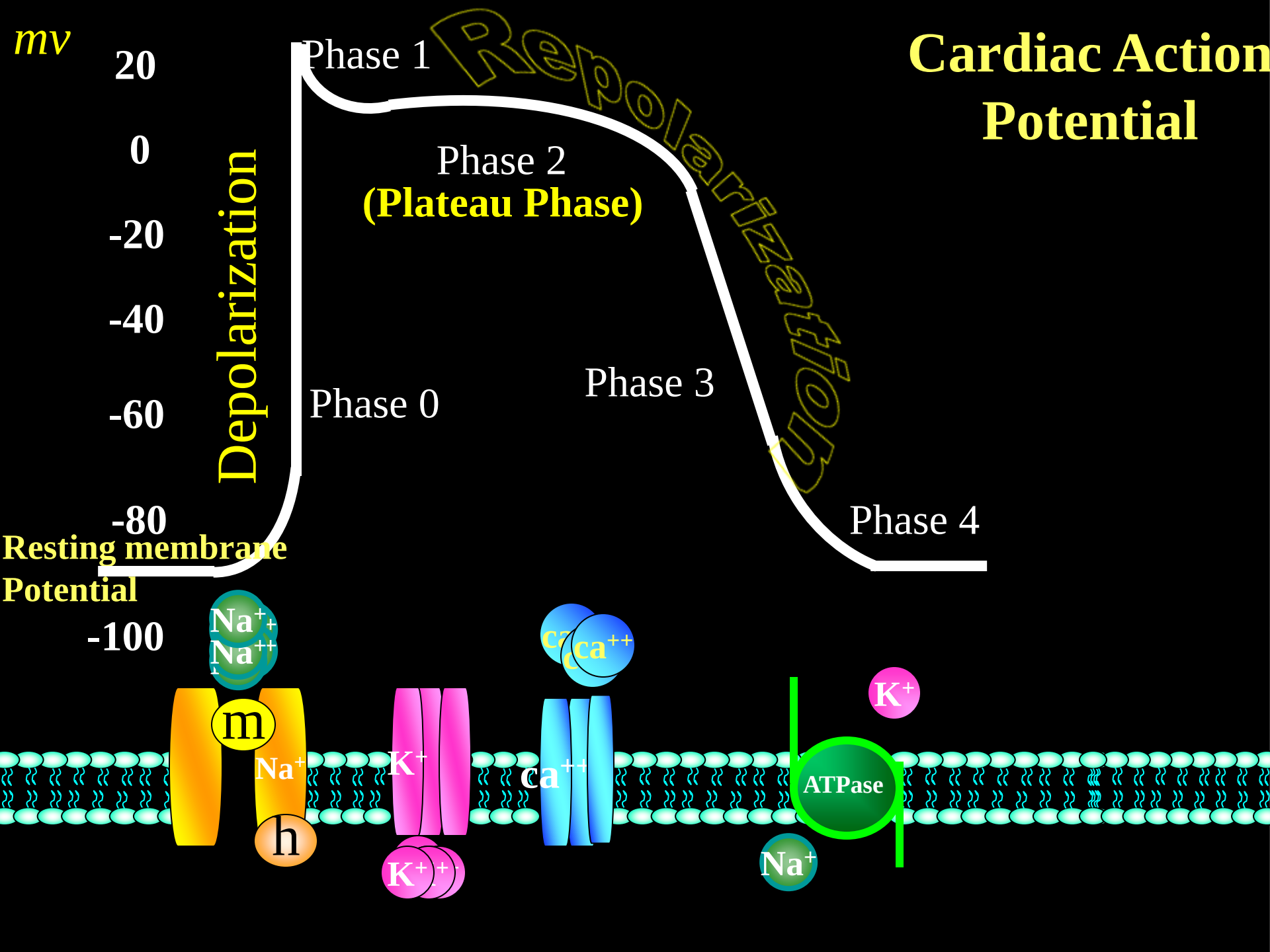


# TRICYCLIC ANTIDEPRESSANTS
## MECHANISM

- THE DRUGS ARE PHARMACOLOGICALLY "DIRTY" AND BIND TO MANY OTHER RECEPTORS:
  - INCLUDING HISTAMINE(H1 & H2) (SEDATION)
  - ALPHA 1 & 2 (VASODILATATION)
  - GABA-A (SEIZURES )
  - MUSCARINIC RECEPTORS (ANTICHOLINERGIC EFFECTS )

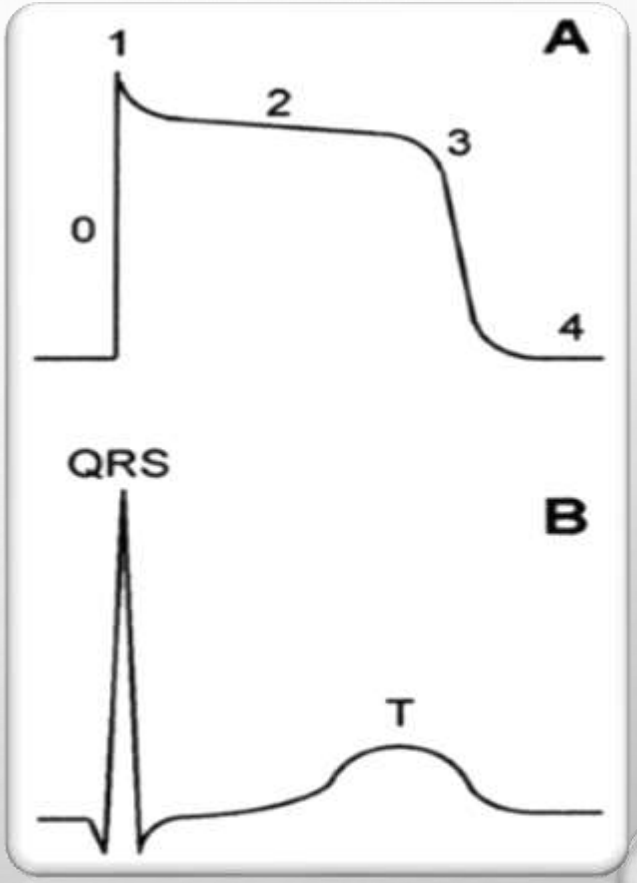


# Cardiac Action Potential



# TRICYCLIC ANTIDEPRESSANTS
## MECHANISM

- THE DURATION OF PHASE 0 IN THE HEART AS A WHOLE IS MEASURED INDIRECTLY AS THE DURATION OF THE *QRS COMPLEX* ON THE ECG.
- THUS, BLOCKADE OF THE NA+ CHANNEL CAN BE INDIRECTLY MEASURED BY ESTIMATING QRS WIDTH.
- THE MOST COMMON ABNORMALITY IS SINUS TACHYCARDIA.



# TRICYCLIC ANTIDEPRESSANTS
## MECHANISM

- OTHER CARDIAC CHANNEL EFFECTS INCLUDE REVERSIBLE INHIBITION OF THE OUTWARD POTASSIUM CHANNELS RESPONSIBLE FOR REPOLARISATION GIVING A MECHANISM FOR QT PROLONGATION AND ARRHYTHMIA GENERATION

- TCAS DEMONSTRATE A *DOSE DEPENDENT* DIRECT ***DEPRESSANT*** EFFECT ON **MYOCARDIAL CONTRACTILITY** THAT IS INDEPENDENT OF IMPAIRED CONDUCTION
  - ALTER MITOCHONDRIAL FUNCTION AND UNCOUPLE OXIDATIVE PHOSPHORYLATION

# TRICYCLIC ANTIDEPRESSANTS
## KINETICS

- HIGHLY LIPID SOLUBLE WEAK BASES
  - RAPIDLY ABSORBED
    - ANTICHOLINERGIC EFFECTS MAY PROLONG ABSORPTION
- HIGH VOLUME OF DISTRIBUTION
  - DEATH AND TOXICITY MAINLY BEFORE REDISTRIBUTION (TOXIC COMPARTMENT) (HEART, BRAIN)
- PROTEIN BINDING > 95%
  - MAY SATURATE INCREASING FREE FRACTION
  - PH DEPENDENT
    - TOXICITY INCREASE WITH ACIDOSIS
    - PROLONGED CLINICAL COURSE
    - ALKALINISATION CAUSES SIGNIFICANT DECREASE IN THE PERCENTAGE OF FREE AMITRIPTYLINE; WITH A DROP OF 20% WHEN PH RISES FROM 7.0-7.4 AND 42% OVER A PH RANGE OF 7.4-7.8.
- $P_{450}$ HEPATIC METABOLISM
  - SATURABLE: LONG ELIMINATION HALF LIFE
  - ACTIVE METABOLITES

# TRICYCLIC ANTIDEPRESSANTS CLINICAL EFFECTS

- SYMPTOMS AND SIGNS AT PRESENTATION DEPEND UPON THE DOSE AND THE TIME SINCE INGESTION.

- PATIENTS WHO ARE ASYMPTOMATIC AT THREE HOURS POST INGESTION OF NORMAL RELEASE MEDICATION DO **NOT NORMALLY DEVELOP MAJOR TOXICITY**

| CYCLIC ANTIDEPRESSANT TOXIDROME | |
|---|---|
| S | Shock/Seizure |
| A | Altered mental status |
| L | Long QRS |
| T | Terminal R Wave in AVR |

| ANTICHOLINERGIC TOXIDROME | |
|---|---|
| RED AS A BEET | Cutaneous vasodilation (flushing) |
| DRY AS A BONE | Dry mouth |
| HOT AS A HARE | Anhidrotic hyperthermia |
| BLIND AS A BAT | Nonreactive mydriasis |
| MAD AS HATTER | Altered mental status: Agitation to coma |
| FULL AS A FLASK | Urinary retention and palpable bladder. |
| OTHER | Tachycardia, Decreased or absent bowel sounds |

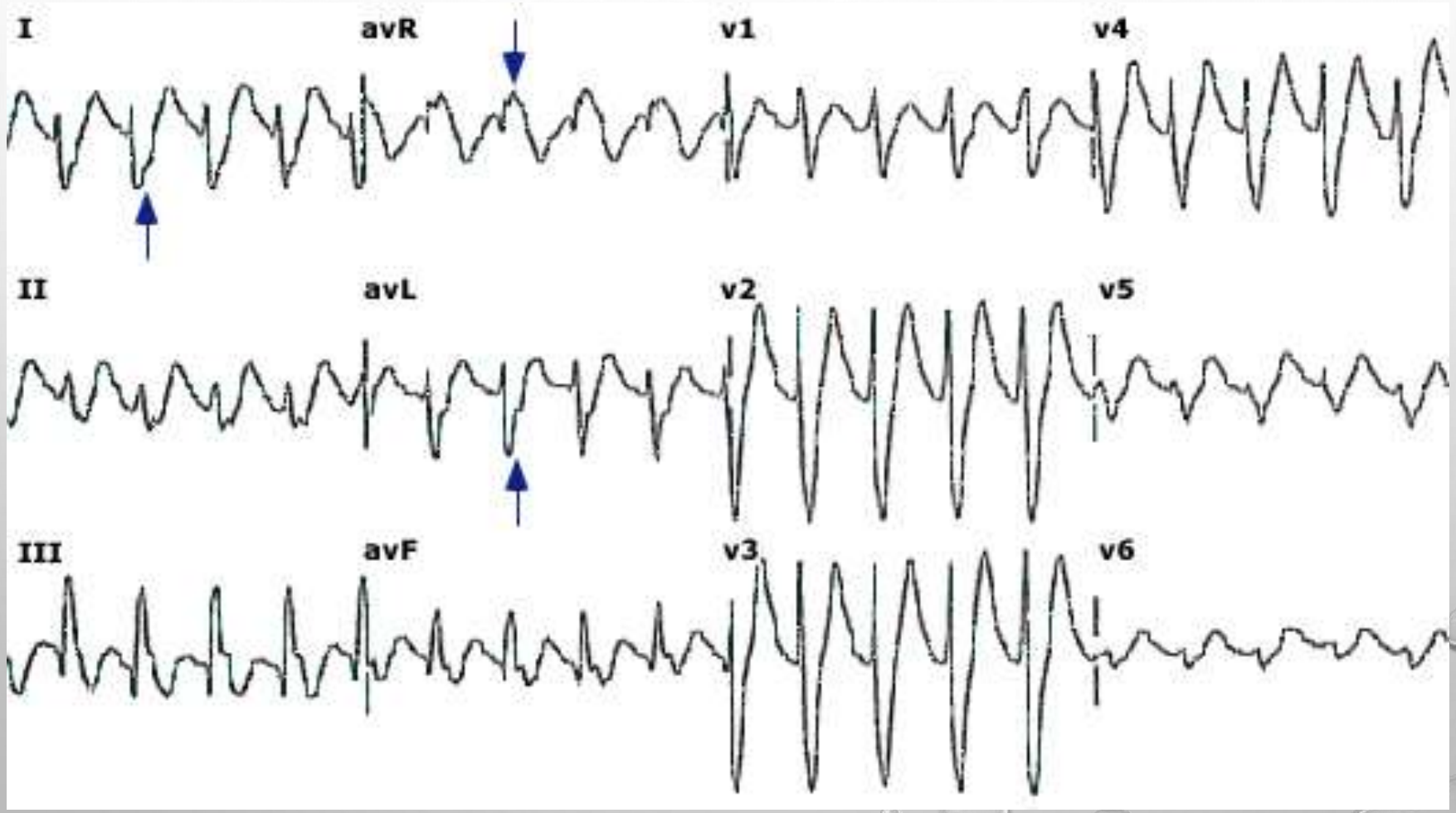
# TRICYCLIC ANTIDEPRESSANTS CLINICAL EFFECTS

- IN ACUTE TCA OVERDOSE THERE A THREE MAJOR TOXIC SYNDROMES. THESE ARE
  - ANTICHOLINERGIC EFFECTS
  - CARDIAC TOXICITY
  - CNS TOXICITY (SEDATION AND SEIZURES)

- DEATH IN TCA OVERDOSE IS USUALLY DUE TO CNS AND CARDIOTOXIC EFFECTS.

| **EKG CHANGES** | |
|---|---|
| INTERVALS AND PATTERNS | ARRHYTHMIAS |
| ↑ PR interval, ↑ QTc | Sinus tachycardia |
| ↑ QRS (terminal 40 msec prolongation) | Sinus tachycardia w/aberrancy (↑QRS) |
| ↑ QRS > 100 msec in Lead II | Atrioventricular Blocks |
| Brugada Pattern: RBBB, down sloping ST elevation in $V_{1-3}$ | Ventricular ectopy |
| | Ventricular tachycardia |
| AVR: R wave > 3mm. R/S > 0.7 | Ventricular fibrillation |
| I, AVL: Deep slurred S wave | Asystole |

# CARDIAC EFFECTS



# PREDICTORS OF ADVERSE EVENTS:

- QRS > 100 MS IS PREDICTIVE OF SEIZURES
- QRS > 160 MS IS PREDICTIVE OF VENTRICULAR ARRHYTHMIAS (E.G. VT)

# CARDIAC EFFECTS

- **ARRHYTHMIAS**

  THE MOST COMMON ARRHYTHMIA IS ***SINUS TACHYCARDIA*** WHICH IS DUE TO ANTICHOLINERGIC ACTIVITY AND/OR INHIBITION OF NOREPINEPHRINE UPTAKE BY TRICYCLIC ANTIDEPRESSANTS.

- **HYPOTENSION**:

THE BLOOD PRESSURE MAY BE *ELEVATED* IN THE *EARLY STAGES* AFTER OVERDOSE, PRESUMABLY DUE TO THE INHIBITION OF NOREPINEPHRINE UPTAKE.

- ✓ HYPOVOLAEMIA,
- ✓ DECREASED PERIPHERAL RESISTANCE DUE TO ALPHA-ADRENERGIC BLOCKADE
- ✓ IMPAIRED MYOCARDIAL CONTRACTILITY AND CARDIAC OUTPUT

# CENTRAL NERVOUS SYSTEM EFFECTS

- PATIENTS WILL OFTEN HAVE A RAPID ONSET OF DECREASING LEVEL OF CONSCIOUSNESS AND COMA BECAUSE OF A VERY **RAPID ABSORPTION** OF THE DRUG
- PATIENTS SHOULD BE ASSESSED ON ADMISSION TO SEE IF THEY ARE HYPERREFLEXIC OR HAVE MYOCLONIC JERKS OR ANY EVIDENCE OF SEIZURE ACTIVITY
- A NUMBER OF TCAS (DOTHIEPIN, DESIPRAMINE, AND AMOXAPINE) CAUSE SEIZURES MORE FREQUENTLY. THUS, THEY MAY CAUSE SEIZURE AT LOWER DRUG INGESTIONS
- CONVULSIONS MAY LEAD TO **HAEMODYNAMIC COMPROMISE**.

# TREATMENT

- **SUPPORTIVE**
  - ABC
  - ECG MONITORING
- **GI DECONTAMINATION**
  - IF PATIENTS ARE ALERT AND CO-OPERATIVE AND HAVE INGESTED > 5 MG/KG, **CHARCOAL** MAY BE ADMINISTERED ORALLY
  - IF THE PATIENT IS **UNCONSCIOUS** AND REQUIRES **INTUBATION** TO PROTECT THE AIRWAY INSERT AN **OROGASTRIC TUBE**, ASPIRATE STOMACH CONTENTS THEN GIVE **ACTIVATED CHARCOAL**

# TREATMENT OF SPECIFIC COMPLICATIONS

- **SEIZURES**
  - ➔ DIAZEPAM 5-20 MG IV
  - ➔ PHENOBARBITONE 15-18 MG/KG IV
  - ➔ PHENYTOIN SHOULD BE AVOIDED ( SODIUM-CHANNEL BLOCKING)
- **ANTICHOLINERGIC DELIRIUM**
  - ➔ MILD DELIRIUM CAN OFTEN BE MANAGED WITH REASSURANCE PLUS OR MINUS BENZODIAZEPINES
  - ➔ NEUROLEPTICS SHOULD BE AVOIDED (MOST OF WHICH HAVE SIGNIFICANT ANTICHOLINERGIC ACTIVITY)

# BICARBONATE

BOTH **SODIUM LOADING** AND **ALKALINISATION** HAVE BEEN SHOW TO BE EFFECTIVE IN REVERSING TCA INDUCED CONDUCTION DEFECTS AND HYPOTENSION

SODIUM BICARBONATE IS THE ***DRUG OF CHOICE*** FOR THE TREATMENT OF VENTRICULAR DYSRHYTHMIAS AND/OR HYPOTENSION DUE TO TCA POISONING

# MANAGEMENT

- IF THE **QRS IS PROLONGED**, THIS IS USUALLY DUE TO Na CHANNEL BLOCKADE, AND SODIUM BICARBONATE 1 TO 2 MEQ/KG SHOULD BE ADMINISTERED AS A BOLUS.
- IF **QTc PROLONGATION** IS NOTED, ELECTROLYTE CONCENTRATIONS SHOULD BE OPTIMIZED WITH SPECIAL ATTENTION TO Mg, K, Ca
- **SEIZURES** ARE OFTEN SHORT-LIVED AND OFTEN SELF-LIMITED, BUT TREATMENT WITH BENZODIAZEPINES MAY BE NECESSARY.
- HYPOTENSION IS FREQUENTLY RESPONSIVE TO INTRAVENOUS FLUID RESUSCITATION.
  SEIZURES AND CARDIOVASCULAR TOXICITY SHOULD NOT BE TREATED WITH PHYSOSTIGMINE AS THIS CAN LEAD TO CARDIOVASCULAR COLLAPSE AND SUDDEN DEATH.
- WHILE NOT FULLY STUDIED IN CHILDREN, A QRS DURATION GREATER THAN 100 ms IS ASSOCIATED WITH SEIZURES, A QRS > 160 MS WITH DYSRHYTHMIAS, AND A TALL R WAVE (>3 MM) IN AVR WITH SEIZURES AND DYSRHYTHMIAS.
- WHEN CONFRONTED WITH A QRS >120 MS, 1TO 2 MEq/Kg BOLUSES OF SODIUM BICARBONATE SHOULD BE ADMINISTERED. IF ADDITIONAL EPISODES OF QRS WIDENING OCCUR, MORE BICARBONATE BOLUSES CAN BE GIVEN.

| THERAPY OVERVIEW | |
|---|---|
| GI Decontamination<br>(intact airway/intubated) | Gastric lavage within 1 hour of ingestion<br>Activated charcoal: 1 gm/kg within 2 h |
| ET Intubation | Mild hyperventilation |
| Sinus tachycardia with<br>QRS > 100 msec | $NaHCO_3$:1-2 meq/kg IV bolus<br>Repeat Q30 min, Consider infusion<br>Target serum pH 7.5-7.55 |
| Ventricular tachycardia | $NaHCO_3$: 1-2 meq/kg IV bolus<br>Lidocaine bolus: 1 mg/kg slow IV<br>Lidocaine infusion: 20-50 mcg/kg/min |
| Torsades | $MgSO_4$:20-50 mg/kg (max 2 gm) IV bolus over 2 m<br>Overdrive pacing |
| Hypotension | Fluid resuscitation<br>$NaHCO_3$: 1-2 meq/kg IV bolus<br>Norepinephrine or Phenylephrine infusion |
| Seizures | Benzodiazepines: Lorazepam<br>Barbiturates: Phenobarbital<br>Propofol or Midazolam infusion<br>NO Phenytoin: Worsens sodium channel blockade<br>Paralysis, general anesthesia with EEG monitoring |

# DISPOSITION

- UNINTENTIONAL INGESTIONS THAT REMAIN ASYMPTOMATIC AND WITH A NORMAL EKG MAY BE SAFELY DISCHARGE AFTER 6 HOURS WITH POISON CONTROL CENTER CONSULTATION.
- THOSE WITH SIGNIFICANT MANIFESTATIONS REQUIRING ALKALINIZATION SHOULD BE ADMITTED TO AN INTENSIVE CARE UNIT AND ALKALINIZATION CONTINUED FOR 12-24 HOURS AFTER THE QRS WITH NORMALIZES.
- ALL INTENTIONAL OVERDOSES SHOULD BE EVALUATED BY PSYCHIATRY.