PHARMACOLOGICAL MANAGEMENT OF MANIA

Bipolar Disorder

Mania: Is characterized by 1 week of;

- **Elevated, Expansive, Irritable Mood +3 (4):**
- **Inflated self-esteem or Grandiosity**
- **Decreased need for sleep (rested with <3hrs)**
- **Talkative**
- **Flight of ideas, racing thoughts**
- **Distractibility**
- **Increased goal-directed activity / psychomotor agitation.**
- **Increased pleasurable activity with painful consequence (spending, sex, investments)**

Bipolar Disorder

- Depressive episode: 2 weeks of(5 symptoms)
- Depressed (Irritable in children)
- Anhedonia
- Decrease or increase in appetite
- Decrease or increase in sleep
- Psychomotor agitation /retardation
- Fatigue / decreased energy
- worthlessness / guilt
- Decreased concentration / indecisive
- suicidal ideation

Bipolar Disorder

- **BP-I: Mania (with/without Depression)**

  (M or M-D)
- **BP-II: Major Depression and hypomania(D-m)**
- **Cyclothymia: Hypomania and depressive symptoms (m-d)**

- **Mixed episode: M + D (same time)**
- **Rapid cycling: 4 or more episodes / year**

Bipolar disorder

- **The treatment of bipolar disorder may be divided into three overlapping phases**
  - **Acute manic episode**
  - **Depressive episode**
  - **Prophylactic treatment**

- **The main treatment for a manic episode being mood stabilisers.**

Mood Stabilisers

- **Lithium**

- **Anticonvulsants**
  - **Valproic Acid**
  - **Carbamazepine**
  - **New Anticonvulsants**
    - **Lamotrigine**
    - **Topiramate**
    - **Gabapentin**

- **Antipsychotics**

Lithium

- Effective mood stabiliser.
- Discontinued relapse near 100%
- Therapeutic Levels: 0.6-1.5 mEq/ml

  0.3-0.8 in elderly

  Same levels for prophylaxis

  Narrow therapeutic index

Pharmacological properties

- mechanism unclear
- appears to reduce the neurotransmitter-induced activation of second messenger systems
- the effect may be via G proteins

Lithium

- **Pharmacokinetics**
  - rapidly absorbed from the gut
  - absorption is complete in 6-8 hours
  - Cmax serum after immediate release preparation = 1.5 – 2 hours
  - Cmax serum after MR preparation = 4 – 4.5 hours
  - Bio-availability = 100%
  - volume of distribution = 0.7-0.9 L/kg
  - Half-life between 14 and 30 hours
  - Time to steady state is between 5 and 7 days
  - Moves out of cells more rapidly than sodium
  - a third is excreted within 12 hours

Lithium

- Excreted by the kidney, with 80% reabsorbed in the proximal renal tubules.
- Dehydration causes plasma levels to increase.
- Because lithium is transported in competition with sodium, more is reabsorbed when sodium concentrations fall.

Lithium

- **Neurological side effects**
  - **fine tremor**
  - **weakness**
  - **dysarthria**
  - **ataxia**
  - **impaired memory**
  - **seizures (rare)**
  - **neurotoxicity with neuroleptics or CARBAMAZEPIN**

Lithium

- **Effects on Renal/ Fluid balance**
  - **Increased urine output with decreased urine-concentrating ability (10 % of patients).**
  - **Thirst**
  - **Diabetes insipidus (rare) - distal tubule becomes resistant to influence of ADH, possibly due to blockage of ADH-sensitive adenylate cyclase.**
  - **Reports of tubular damage in patients on prolonged treatment.**

Lithium

- **Gastrointestinal side effects**
  - **altered taste (commonly metallic taste)**
  - **anorexia**
  - **nausea**
  - **diarrhea**
  - **weight gain (esp. in women)**

Lithium

- **Endocrine**
  - **Thyroid gland enlargement occurs in 5% - shrinks if THYROXINE is given and returns to normal 1-2 months after LITHIUM is stopped**
  - **Hypothyroidism occurs in 3-4 %.**

- **Haematological- leucocytosis**

- **Dermatological**
  - **acne**
  - **exacerbation of psoriasis**
  - **alopecia**

Lithium

- **Toxicity**
- **Early plasma levels 1.5-2 mEq/L** ; anorexia, vomiting, diarrhoea, coarse tremor, ataxia, dysarthria, confusion, sleepiness
- **Later plasma levels > 2 mEq/L** ; impaired consciousness, neurological signs:(nystagmus , muscle twitching, hyperreflexia, convulsions)
- **Severe overdose** ; toxic psychosis, convulsions, syncope, oliguria, circulatory failure, coma and death occur at higher levels

Lithium

- **Contraindications;**
  - thyroid disease
  - hypopituitarism
  - Addison's disease
  - pregnancy - LITHIUM crosses the placenta, increased incidence of birth defects (esp. cardiac abnormalities). LITHIUM is secreted in breast milk
  - caution in compromised renal function

Lithium

- **Interactions •**
  - **increased LITHIUM levels with:**
    - **NSAIDs (except ASPIRIN)**
    - **METRONIDAZOLE**
    - **Antihypertensives (ACE-inhibitors and METHYLDOPA)**
    - **Salt deficiency**
  - **Increased potentiation of antipsychotics in producing EPS (esp. HALOPERIDOL)**
  - **Continuation of LITHIUM therapy with ECT may lead to neurotoxicity**
  - **LITHIUM increases brain 5-HT levels, and in combination with SSRIs has led to neurotoxicity (myoclonus, seizures, hyperthermia)**

Lithium

- **Drug Monitoring**
  - **Blood samples taken 12 hours post dose**
  - **Serum levels of 1.0- 1.5mEq/L in mania are generally effective. (1,800mg/day)**
- **Aim for 0.4 – 0.8 during maintenance phase. This is achieved by a daily dose of 900 to 1,200mg.**
- **Closer monitoring required with rapid-cycling patients**
- **Regularly check blood levels every 3 months. Thyroid and renal function every 6 months**

Carbamazepine

- **Pharmacological Properties**
  - **GABA agonist**
  - **Blocks neuronal sodium channels and also affects calcium channels**
  - **Facilitates some aspects of brain 5-HT function**

Carbamazepine

Pharmacokinetics

- Slowly, but completely absorbed
- Peak plasma levels reached 2 to 8 hrs after a single dose
- Steady state levels are reached after 2 to 4 days on steady dose.
- Extensively metabolized, with at least one metabolite being active
- Half-life average is 26 hours (range 18 to 54 hours)
- With chronic administration half-life decreases to average of 12hours.
- At the start of therapy, CARBAMAZEPINE induces its own catabolic enzymes

Carbamazepine

- **Side effects**
  - Drowsiness
  - Dizziness
  - Ataxia
  - Diplopia
  - Nausea
  - Headache
  - Rash (5 %), Stevens-Johnson
  - Neuroteratogenic

Carbamazepine

- Elevation of liver enzymes
- Agranulocytosis - rare (1 in 10,000 - 1 in 125,000), patients should be warned about fever and infection. Monitor FBC fortnightly for first 2 months
- Leucopenia- usually in the first few weeks of treatment
- SIADH
- Disturbances in cardiac conduction

Carbamazepine

Interactions

- **Increased metabolism of TCAs, BZDs, HALOPERIDOL, Oral contraceptives, THRYROXINE, WARFARIN, anticonvulsants.**
- **Carbamazepine levels increased by : SSRIs, ERYTHROMYCIN, ISONIAZID, some MAOIs,**
- **Decreased effect of other Ca2+ channel blockers: FELODIPINE , NICARDIPINE.**
- **Neurotoxicity with LITHIUM**

Carbamazepine

USE/Dose

- **Baseline: Medical Hx, CBC+diff, LFT, Renal, TFT,**
- **Start low:**
- **100-400 mg/day,**
- **Increase by 100-200 mg every several days, repeat CBC, LFT**
- **clinical monitoring effective**

Sodium Valproate

- **Pharmacological properties**
  - mechanism unclear
  - Increased:
    - GABA release
    - GABA-B receptor density
    - neuronal responsiveness to GABA
    - potassium conductance
  - Reduced:
    - GABA breakdown
    - GABA turnover
    - sodium influx

Sodium Valproate

- **Pharmacokinetics**
  - **Rapidly absorbed ; completely absorbed in 1 to 2 hours. Peak concentrations 4 to 5 hours after oral dose.**
  - **Widely and rapidly distributed**
  - **Half-life of 8-18 hours**
  - **Metabolized in the liver - many metabolites are active**

Sodium Valproate

- **Two third of patients with acute mania respond to Valproate.**
- **Response mostly noted within 1 to 4 days after achieving valproate serum concentrations ranging from 50 to 150 micrograms/ml.**
- **For treatment of acute mania, an oral loading dose can be given at 20 to 30mg/kg a day.**
- **Most patients attain therapeutic plasma concentration on a dosage between 1,200 and 1,500mg a day.**

Sodium Valproate

Side effects

- **Gastrointestinal**: Nausea, vomiting, diarrhoea, weight gain
- **CNS**: Tremor, sedation, ataxia, dysarthria
- **Hematological**: Thrombocytopenia, inhibition of platelet aggregation
- Acute pancreatitis (rare)
- Elevation in hepatic transaminases, several reports of fatal hepatic toxicity

NOTE: VALPROATE must be stopped if vomiting, anorexia, jaundice, or sudden drowsiness occur

Sodium Valproate

- **Interactions**
  - Potentiates the effects of central sedatives
  - Increases side-effects of other anticoagulants
  - Increases plasma levels of: Benzodiazepines, barbiturates, PHENYTOIN.
  - Increased tremor with LITHIUM
  - Increases effects of: WARFARIN,ASPIRIN.
  - VALPROATE levels increased by: AMITRIPTYLINE, FLUOXETINE.
  - VALPROATE levels decreased by CARBAMAZEPINE
  - **Contraindications**: pre-existing liver disease, pregnant or nursing mothers

Lamotrigine

- **Seems to be more effective in treating depressive episodes of bipolar**
- **Used less than other anticonvulsants for Bipolar Disorder**

M.O.A

- **Voltage- gated sodium channel agonist**
- **Inhibits the release of glutamate**

Lamotrigine

Side Effects

- Benign rash (10%)
- Sedation
- Blurred vision
- Dizziness
- Ataxia
- Headache
- Tremor
- Insomnia
- Poor coordination
- Fatigue
- Nausea and vomiting
- Can cause flu like symptoms in some people

Lamotrigine

Dose:

- **Monotherapy 100- 200 mg/day**
- **Halved if used with other medication**
- **Monitor for rash**

Pharmacokinetics

- **Elimination half life 33 hours**
- **Higher if used concurrently with other anticonvulsant medication**
- **Metabolized through the liver**

Lamotrigine

Drug interaction:

- **Depressive effects may be increased by other CNS depressants**

Atypical Antipsychotics

- **Increasing use of antipsychotic medication in the management of bipolar mood disorders.**
- **Evidence shows that atypical antipsychotics are effective in the treatment of manic symptoms either alone or in combination with the traditional mood stabilisers.**
- **All SDAs are FDA approved for treatment of acute mania.**
- **Olanzapine, Risperidone, Quetiapine, Ziprasidone and Aripripazole, Clozapine.**