

Bipolar Disorder

BASIC DEFINITIONS:

BIPOLAR I:

At least one **MANIC** or **MIXED** episode;
May also have history of hypomania or major depression; classic "manic depressive illness"

BIPOLAR II: "high-functioning" bipolar
MAJOR DEPRESSION with **HYPOMANIA**
NEVER had a Manic or Mixed episode; nor any schizoaffective or other psychotic disorder

HISTORY OF MANIA is a lot like history of PSYCHOSIS

3 or more of these symptoms; 4 symptoms if mood is irritable

- **FEELING HAPPY? EUPHORIC?**
- **Or... AGITATED? IRATE? WOUND UP?**
- **...Why?** This question asked to provoke a torrent of words
- **For how long?** usually rapid onset, over days.
- **Easily Distracted?** The mundane is abnormally important?
- **Been sleeping much?** Probably not. Much less rest required
- **Been spending much?** Massive debts form quickly
- **Been more talkative than usual?** Pressure of speech
- **Thoughts racing?** Subjective perception; "flight of ideas"
- **Increased goal-oriented activity?** Eg. Sport, sex...
- **Indulging in high-risk amusements?**
- **Got big plans?** Megalomaniacal schemes?
- **Got SPECIAL POWERS?** Reading thoughts? } **GRANDIOSITY**
- **Self-esteem inflated ridiculously?**
- **Delusions, are they?** **CHALLENGE THEM.** Are they mood-congruent, eg. delusions of grandiosity, or are they unrelated to the mood, eg. persecutory delusions?
- **DANGEROUS DELUSIONS?** Schedule- worthy?
- **Hallucinated, did we?** Just more psychotic features...

MIXED EPISODE?

- **Features of both mania and depression within the same episode**

OTHER IMPORTANT HISTORY:

- **Is this associated with seasonal change?** ...seasonal affective disorder?...
- **Drugs and Alcohol:** will almost certainly be using some substance or another while manic
- **Previous admissions to some sort of psychiatric unit:** 90% of patients will suffer a recurrence
- **Family history:** there is a strong genetic component: 80% for monozygotic twins.

MENTAL STATE EXAMINATION:

Appearance: may show evidence of **EXCESSIVE SELF CARE**
Too much make-up, too many layers of clothes etc..

Behaviour: Energetic, hyperactive

Speech: loud, rapid, pressured; jok

Mood: **ELEVATED** or **IRRITATED**

Affect labile if psychotic; amicable and joyous if elated

Thought Form distorted if psychotic

Thought Content may harbour delusions

Perceptual Disturbance ?... hallucinations?....

Insight will likely be limited; not always aware of condition

Judgement is most often quite impaired in mania, not so much in hypomania

Cognitive Testing might not be oriented if psychotic. Most often will show features of psychomotor agitation

First-degree relatives of people with BPI are approximately 7 times more likely to develop BPI than the general population.

CHARACTERISTICS OF Mania vs. Hypomania

How manic is manic enough for mania? DSM-IV:
Seems to be all about the **DURATION**, **FUNCTIONAL IMPAIRMENT** and the presence of **PSYCHOTIC FEATURES**

MANIA PROPER:

- at least 1 week
- Possibly psychotic
- severe impairment to social or occupational functioning

HYPOMANIA

- at least 4 days
- not at all psychotic
- little impairment to social or occupational functioning.

Only 10% of bipolar II patients ever have mania.
Recurrent mania is most often interspersed with recurrent depression.
Very few have only recurrent manic episodes.

RAPID CYCLING: "RAPID" means every 2 months
Or at least 4 times during any one year

CYCLOTHYMIA: periods, not episodes, of hypomania and depression. Subsyndromal mood swings, mild ones; mood swings either not influenced by stressful events or disproportionate to them
About 1/3rd of cyclothymics will develop bipolar disorder.

MAJOR FOCUS: PSYCHOTIC FEATURES and RISK TO SELF, OTHERS, REPUTATION or WELL-BEING; schedule them if they are about to spend all their money

Course of the condition: most bipolar patients have normal mood in between episodes. The "normality gap" narrows over the course of one's lifetime. Lifetime prevalence is 1%. Mean age of onset is late 20s.

DIFFERENTIALS: Non-psychiatric causes of mania

Physiological:

- **SYSTEMIC LUPUS**
apparently can result in manic symptoms as a consequence of encephalitis
- **Neurosyphilis**
- **Multiple Sclerosis**
- **CNS neoplasm**
- **Wilson's disease**
- **Epilepsy**
- **HIV dementia**

Pharmacological

- **Antidepressants**
- **Thyroxine**
- **Amphetamines, cocaine**
- **MDMA**
- **Corticosteroids** (acutely)
- **Viral Hepatitis**

Just about any drugs, and any heavy metal poisoning can be the cause of depression

Endocrine:

- **Hyperthyroidism**
- **Hypothyroidism**
- **Phaeochromocytoma**
- **Cushing disease**

DIFFERENTIALS: different flavours of mania

- **First manic episode:** will probably recur (in 90%).
- **Hypomania** : "mania lite"
- **Recurrent Mania** : very rare to have just mania on its own.
- **Cyclothymic disorder** often disabling, but not severe enough to qualify for bipolar II
- **Manic Mood disorder due to a medical condition**
– eg. Endocrine abnormality
- **Substance-induced mood disorder** – In the first few days of corticosteroid therapy. Various drugs of abuse also cause mania-like behaviour and mental state features (as above); this may or may not go away with abstinence
- **Psychotic Mania** with delusions, emotional lability, thought form distortion and whatnot
- **MIXED EPISODE:** a state featuring both major depression AND mania !
- **Schizoaffective Disorder** a psychosis with mood disturbance (as opposed to bipolar mania mood disturbance with psychotic features)
- **Borderline Personality Disorder** sometimes has "highs" which approach hypomania
- **ADHD and/or Conduct disorder:** symptoms overlap with bipolar disorder, esp. in teens
- ALSO the ADHD and CD often co-exist with bipolar affective disorder.

Young and Klerman Classification: (1992)
Classification of Bipolar Disorder
Bipolar I - Mania and Major Depression
Bipolar II - Hypomania and Major Depression
Bipolar III - Cyclothymia
Bipolar IV – Antidepressant-induced hypomania... but is it truly a predisposition to bipolar bipolar
Bipolar V - Major Depression with a family history of bipolar disorder (most bipolar patients start out that way, with major depression for years)
Bipolar VI - Unipolar Mania (rare as hens teeth)

INVESTIGATIONS

- **FBC** is their depression the depression of anaemia?
- **ESR + ANA, ANCA, etc** ...raging lupus?
- **BSL** atypical antipsychotics can send you into diabetes via massive weight gain
- **EUC** Hyponatremia can cause depression; lithium can cause renal failure. Cardiotoxicity is worse with weird potassium levels.
- **Serum Calcium** **HYPERPARATHYROIDISM CAN CAUSE DEPRESSION(!)**
- **LFT** mood stabilisers can cause hepatitis; and most drugs are highly protein-bound.
- **ECG** Some TCAs are cardiotoxic; lithium can invert or flatten T waves. (this is reversible)
- **Urinary copper level** Wilson's disease is stupidly rare but you don't want to miss it
- **HIV serology** though HIV dementia should be obvious...
- **Syphilis serology** unlikely but embarrassing when ignored as a potential diagnosis
- **Serum Cortisol** may be elevated, but this is not of any except academic interest
- **Thyroid Function** Thyrotoxicosis....
- **CT of the BRAIN** largely for baseline
- **EEG** if ECT is indicated or for some reason being considered

MANAGEMENT of MANIA and MIXED STATES in the ACUTE PHASE

In the emergency department: remedy the immediate ills. Bleeding, burning, etc.

Risk to self or others? Severely disturbed? If they report that they are about to get into ridiculous debt, or if they appear ready to act dangerously in accordance with their delusions, **SCHEDULE THEM**; and they will only rarely threaten to sue.

APPROPRIATE RESTRAINTS whether chemical or physical, can be used.

- **HALOPERIDOL 10mg and MIDAZOLAM 10mg**
- **CHLORPROMAZINE is an alternative**

In the Acute Psychiatric Inpatients Unit:

- **SEVERE, DISABLING behavioural disturbance?**
This calls for ECT, and soon. Rapid immediate improvement is needed before a meaningful history can be extracted and proper long-term treatment can be negotiated. In some cases this need justifies the use of dramatic measures like ECT.
- **Is it MANIA or MIXED MANIA? First line therapy is different**
 - MANIA = LITHIUM
 - MIXED EPISODE: = VALPROATE or CARBAMAZEPINE
- **Mood-Incongruent Psychosis?**
 - MANIA = Benzodiazepine (maybe) + Atypical Antipsychotic
 - MIXED EPISODE: = Atypical Antipsychotic alone
- **Mood-congruent psychosis, or not psychotic?**
 - MANIA AND MIXED EPISODE: = Benzo + Atypical
- **None of that is working?**
 - EITHER: try another mood stabilizer,
 - OR: try two mood stabilizers simultaneously
 - Do NOT combine divalproate together with carbamazepine, yet
- **Still not working?**
 - EITHER: try THREE simultaneous mood stabilizers,
 - OR: add RISPERIDONE
 - Risperidone not doing anything? Switch to **CLOZAPINE**
- **STILL NOT WORKING?**
Time for measures largely held to be experimental;
 - EITHER: Calcium Channel Blocker (eg. Verapamil),
 - OR: add LAMOTRIGINE to one or two mood stabilisers
 - OR: add GABAPENTIN to one or two mood stabilisers
- **ACTUALLY GETTING WORSE??**
 - ECT is the most dangerous and thus most reluctant measure

MANAGEMENT of RAPID CYCLING in the ACUTE PHASE

Most often this is a known bipolar patient with recent onset of rapid cycling.

1) **DO NOT abruptly change the medications.**

2) **Stabilize sleep, manage substances (eg. caffeine, nicotine)Then:**

- Start **VALPROATE**.
- If symptoms persist, add **LITHIUM or CARBAMAZEPINE** .
- **All three mood stabilizers** if that doesn't work.
- **ECT = last resort**

MANAGEMENT of BIPOLAR DEPRESSION in the ACUTE PHASE

Emergency department management is no different from major depression.

Due to delay in the effect of antidepressants, their effects will not be useful in ED.

To have control, one may resort to OLD-SCHOOL ANTIPSYCHOTICS and MIDAZOLAM

In the Acute Psychiatric Inpatient Unit:

- Severely disabling behavioural disturbance?

- ECT first, ask questions later

- for some reason UNMEDICATED?

- Commence Lithium: especially if not psychotic or suicidal

- Already on Lithium or another mood stabilizer?

- Play with the dose

- Dose already too high, or lithium not working?

- MILD depression: try psychotherapies; if not useful, then drugs.

of course, best to still keep them on the existing medication, especially if they have been compliant.

- SEVERE depression: stack more drugs;

NO TRICYCLICS, EVER!

Good chance of flipping into hypomania or rapid cycling

- mood stabilizer + antidepressant
- mood stabilizer + another mood stabilizer
- mood stabilizer + Lamotrigine
- mood stabilizer + Gabapentin

- PSYCHOTIC FEATURES?

- mood stabilizer + Risperidone
- mood stabilizer + Risperidone + Antidepressant
- TWO mood stabilizers

Risperidone seems the drug of choice, but if it does not work, consider other antipsychotic agents

- Nothing working? Try options with uncertain risk/benefit relationships

- Electroconvulsive Therapy
- THREE mood stabilizers at once
- Change the antipsychotic to **CLOZAPINE**

MANAGEMENT of BIPOLAR DISORDER soon after the ACUTE PHASE

The arbitrary "acute phase" usually lasts 2 to 10 weeks. The end of this phase is marked by euthymia and the resolution of psychotic features. Now, you can

- Educate the patients, the friends and the family.
- Use whatever mood stabilizer seems to be working
- If there is no more psychosis, discontinue antipsychotic over 2-3 weeks
- If there is no more sleep disturbance, discontinue benzos over 2-3 weeks
- Discontinue antidepressant over 6 to 12 weeks

This arbitrary "early continuation phase" which follows the acute phase lasts 6 to 12 weeks.

MAINTENANCE MANAGEMENT of BIPOLAR DISORDER

- **ONLY Discontinue medication if side-effects are not tolerated.**

Must continue psychotherapy and monitor symptoms closely.

IF the disorder is strongly genetic, or episode was very severe, or episodes recurrent:

PHARMACOTHERAPY CONTINUES INDEFINITELY

Otherwise, continue drugs for no less than 6 months, and taper over 3 months.

Always better to go slow.

MOOD STABILISERS

Lithium Carbonate is the first drug of choice for both acute and prophylactic management of bipolar disorder. However 30% of bipolar patients will not respond to lithium. Seems slightly better for bipolar mania than bipolar depression. Not bad for schizoaffective disorder and severe cyclothymia. Can sometimes improve the effect of antidepressants in major depression. Can sometimes improve the effects of antipsychotics in schizophrenia. May be helpful in borderline personality disorder. Nobody is entirely sure how it works. May act by blocking inositol-1-phosphatase in neurons with subsequent interruption of the phosphatidylinositol second messenger system.

HALF LIFE is 20 hrs.

RENALLY EXCRETED: renal failure will lead to toxicity, effect is inversely proportional to creatinine clearance.

Always given in divided doses during the day. Bi-daily or tri-daily.

Therapeutic effect may take 4-6 weeks.

True prophylactic effect may take more than 2 months.

PRE-LITHIUM WORK UP: looking for contraindications

- **ECG** looking for heart disease: lithium can alter conduction
- **EUC** looking for renal disease and hyponatremia
- **TFT** looking for hypothyroidism

STOP DIURETICS! Lithium + diuretics = paradoxical antidiuretic effect.

MONITORING LITHIUM: tests are useful after 5 days have passed since the dose change.

Take the sample 12 hrs since last dose!

Usually taken in the morning before the morning dose

MONITOR LITHIUM WEEKLY for the first 8 weeks;

FORTNIGHTLY for the next 8 weeks

MONTHLY for 8 months

Every 3-4 months thereafter

Check thyroid function regularly

NO LACTATING OR CHILD-BEARING ON LITHIUM!

Cause Ebstein's anomaly of the foetal heart, and foetal thyroid weirdness.

THERAPEUTIC LEVELS:

0.8-1.6 mmol/L

Long term maintenance:

0.5-0.8 mEq/L.

DO NOT EXCEED 2mmol/L.

Lethal dose around 4 mol/L

SIDE EFFECTS:

Having just started lithium, you may suffer:

Due to rapid rise in serum lithium levels; these will improve as the levels stabilize

- **Nausea**
- **Diarrhoea**
- **Vertigo**
- **Muscle weakness**
- **Cognitive impairment:** "fuzzy thinking", a strange dazed feeling

Side effects at the maintenance dose

These are not indications to reduce dose

- **Fine tremor of the hands** treated with propranolol
- **Fatigue**
- **Thirst** } lithium-induced Diabetes Insipidus;
- **Polyuria** } treated with Amiloride
- **constipation or diarrhoea**
- **epigastric discomfort**
- **metallic taste,**
- **oedema** which responds to spironolactone ←
- **hypermagnesaemia** But... spironolactone causes an unpredictable increase in lithium levels
- **hypercalcaemia**
- **Hypothyroidism**
- **T-wave flattening and inversion**
- **WEIGHT GAIN AND HAIR LOSS!**
- **Acne and Psoriasis may get worse.**

MANAGEMENT OF TOXICITY:

No specific antidote; monitor levels every 6 hours and use osmotic diuresis (eg. mannitol or urea infusion). Also you may try alkalinising the urine.

SIGNS OF TOXICITY:

- **Increasing anorexia**
- **diarrhoea and vomiting**
- **muscle weakness**
- **lack of coordination,**
- **drowsiness**
- **lethargy**
- **giddiness**
- **ataxia, dysarthria**
- **blurred vision**
- **coarse tremor,**
- **muscle twitching.**

ANTICONVULSANTS as MOOD STABILISERS

Carbamazepine seems more effective for rapid cycling than lithium.

Also good for schizoaffective disorder and cyclothymia. Particularly helpful in controlling extreme impulsive or aggressive behaviour.

Mechanism of psychiatric useful effects is unknown.

Metabolised by the liver, and it will induce its own enzymes so serum levels fall over time.

Anticonvulsants take about 3 weeks to reach full psychiatric effect.

PRE-CARBAMAZEPINE WORK-UP:

Causes SPINA BIFIDA

- **ECG** looking for heart disease:
- **LFT** because that's the metabolising organ

MONITORED JUST LIKE LITHIUM

SIDE EFFECTS:

- Nausea
- Vomiting
- Diarrhoea or Constipation
- Loss of appetite
- Sedation
- Dizziness
- Ataxia
- Confusion
- Rash and pruritis
- Stevens-Johnson Syndrome
- Hepatitis
- Urinary retention
- AV conduction defects
- Agranulocytosis (in 0.005% of patients)

A minimum 14-day washout should elapse before beginning an MAOI due to the molecular similarity between tricyclic antidepressants and carbamazepine.

Signs of toxicity include:

- Confusion
- stupor,
- motor restlessness
- ataxia
- mydriasis
- muscle twitching
- tremor
- athetoid movement,
- nystagmus,
- abnormal reflexes,
- oliguria
- nausea and vomiting.

Sodium Valproate is the first drug of choice for rapid cycling bipolar disorder.

Valproate causes decreased GABA metabolism with secondary increased CNS GABA concentrations. Valproate may also impact signal transduction through actions on protein kinase C. It is unknown if these mechanisms are involved in the treatment of psychiatric disorders

The average half-life is 8-10 hours, making bi-daily or tri-daily dosing necessary.

METABOLISM has little to do with CYP450, mainly glucouronidation and mitochondrial beta-oxidation

Causes SPINA BIFIDA and various other neural tube defects

Valproate is highly protein bound and, at higher concentrations, this system becomes saturated and there is more unbound drug available. This actually enhances the metabolism of the drug and lowers the serum concentration.

Serum valproate levels can be obtained at 3 days after a change of dose

Serum levels should be drawn 12 hours after the previous dose and are usually done in the morning before the AM dose.

SIDE EFFECTS:

- sedation dizziness
- nausea and vomiting
- Pancreatitis usually occurs early in treatment.
- Hepatitis
- Thrombocytopenia
- Tremor
- Ataxia
- Headache
- Insomnia
- Agitation
- Weight gain
- Alopecia
- maculopapular rash.

Overdose:
SOMNOLESCENCE
HEART BLOCK
COMA

Gabapentin is good for bipolar disorder, but not good enough to be a monotherapy.

MECHANISM: chemically related to the neurotransmitter GABA, but it does not act on GABA receptors. It is not converted into GABA and does not effect GABA metabolism or reuptake. The mechanism of its effect in psychiatric disorders is unknown.

Renally excreted, half-life of 5-7 hrs. No need to monitor serum levels (we don't know what the therapeutic window is, so it matters very little).

SIDE EFFECTS:

- fatigue
- somnolence
- ataxia
- nausea and vomiting
- dizziness
- weight gain or loss
- edema
- Hypertension
- Change in appetite
- Dyspepsia
- Flatulence
- Gingivitis
- Easy bruising
- Arthralgia
- Nystagmus
- tremor
- diplopia
- blurred vision
- Anxiety
- Irritability
- hostility
- agitation
- depression

Gabapentin has reduced absorption with antacids, and it should be taken at least 2 hours after antacid administration.

Lamotrigine seems effective as an adjunctive therapy OR a monotherapy.

The mechanism of action is unknown. It may have an effect on sodium channels that modulate release of glutamate and aspartate. It also has a weak inhibitory effect on 5-HT receptors. Hepatic metabolism, half-life of 25 hours.

SIDE EFFECTS:

- Dizziness
- Sedation
- Headache
- Diplopia
- Ataxia
- decreased coordination
- Stevens-Johnson (most likely to occur in the first 4-6 weeks.)
- Weight gain.
- Nausea and vomiting.
- Agitation
- irritability
- anxiety
- depression
- mania.