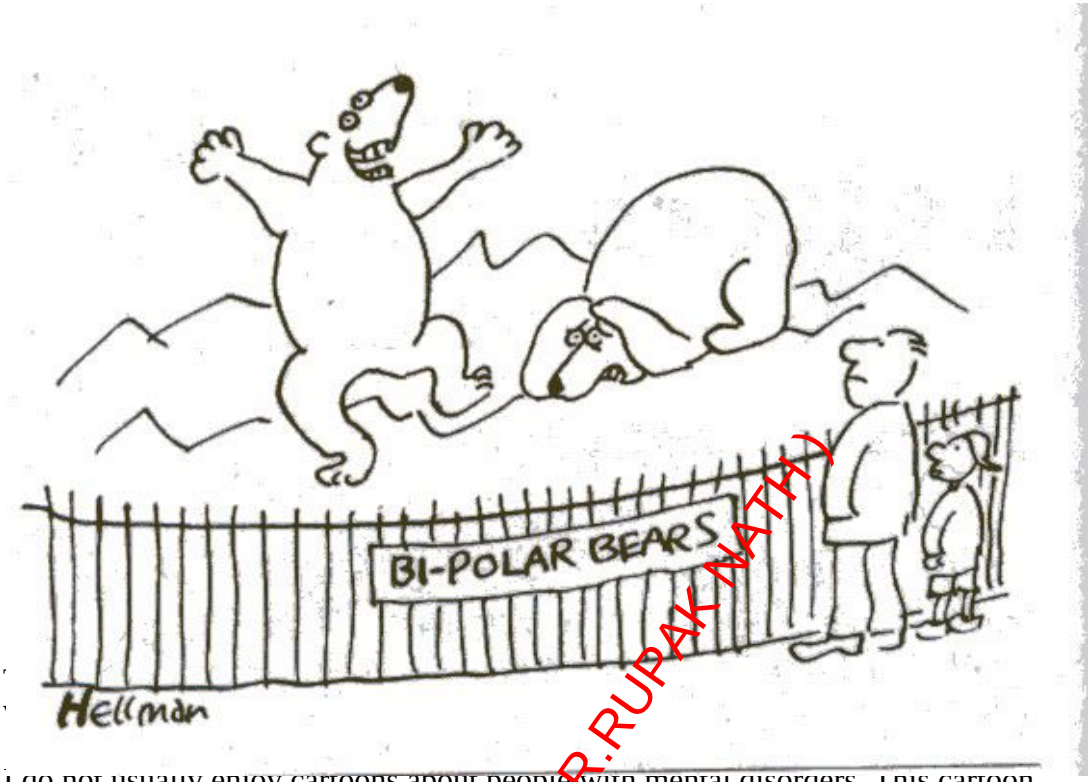
CHAPTER 18

MOOD STABIZERS



I do not usually enjoy cartoons about people with mental disorders. This cartoon supports the notion that what one is thinking about influences what one "sees". When I was first shown this cartoon, I was having difficulty with a patient with mania who was very disinhibited and doing himself a lot of social damage. I showed this to him and pointed out that he was the noisy one and the rest of us were like the other bear who had to cover his ears because of the noise. My "psychotic" patient pointed out, however, that the second bear was not covering his ears because of the noise, but was, in fact, very depressed. He was probably correct. The cartoon then lost some of its charm for me, but became a reminder that, as well as the manic patient, the doctor needs to avoid the trap of over-confidence.

DR.RUPNATH J(DR.RUPAK NATH)

Introduction

To this point, ideal mood stabilizers are like a Chinese dragons, none have been found. The ideal mood stabilizer would effectively treat both acute mania and depression, and provide prophylaxis against both (Calabrese and Rapport, 1999).

In general, we look to the current mood stabilizers more for prophylaxis than for acute treatment. While the mood stabilizers have a role in acute treatment, we have other treatment options in this phase (antipsychotics, antidepressants, ECT).

Putting the subject in context, lithium has been used as a mood stabilizer for half a century. It has efficacy at least equal to (if not greater than) the more recently introduced agents. Nevertheless, lithium is effective in only 50% of cases (Greil et al, 1997), and non-compliance due to side effects is a major issue. Progress in finding good mood stabilizers is long over-due.

Mood stabilizers are recommended in the treatment of primary bipolar disorders which are listed in DSM-IV as bipolar I disorder, bipolar II disorder, cyclothymia, and bipolar disorder not otherwise specified. The agents appear most effective in the first two listed disorders. They may also have a place in the acute treatment and prophylaxis of unipolar depression, although the evidence is less convincing. And, they are sometimes used in the management of impulsive behaviour (although, again, the evidence is not strong).

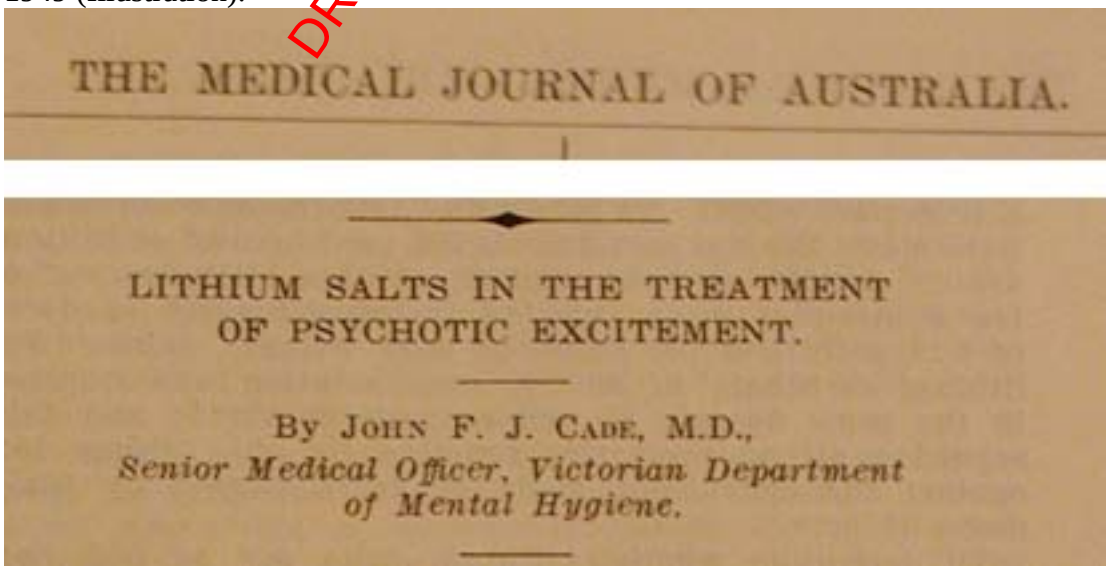
For a couple of decades, lithium was the only mood stabilizer available. Then certain anticonvulsants were found to have mood stabilizing capacity. Very recently, certain atypical antipsychotics began to be used in this way. This last group will be briefly mentioned here, with further details being available in Chapter 15 (Antipsychotic Drugs).

DR.RUPNATHJI(DR.RUPAK NATH)

LITHIUM

Lithium was discovered in 1817. Because lithium urate is highly soluble, lithium salts were used later that century for the treatment of gout. It was suggested that the beneficial effects obtained from the healing spas such as the waters at Lourdes may be because they contain higher than usual levels of lithium. But, recent analyses have not supported this romantic theory.

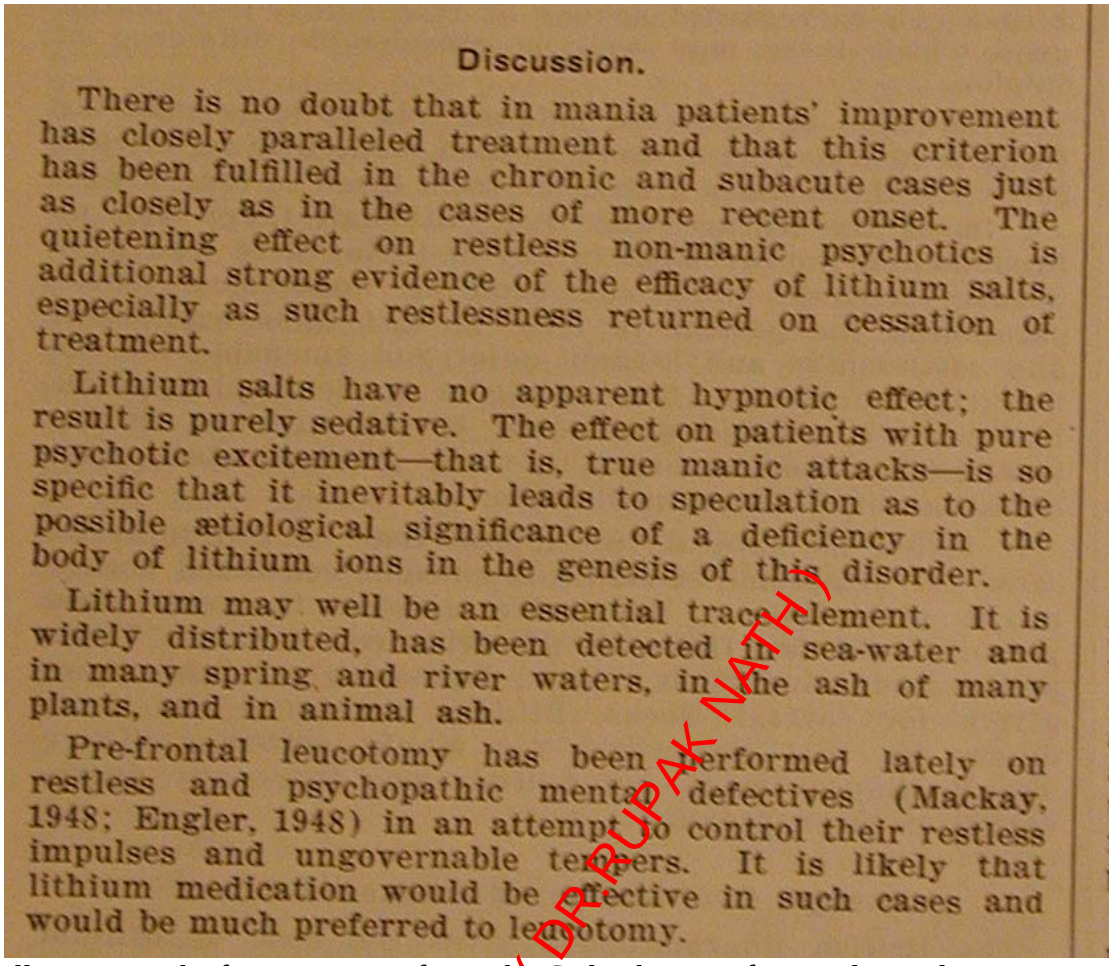
In the 1940's, John Cade, an Australian psychiatrist was studying the effect of lithium urate on the renal function of guinea pigs. Coincidentally, he observed the substance had a calming effect. Subsequently, he used lithium salts in the treatment of acute mania in humans, and published his observations in the Medical Journal of Australia, 1949 (Illustration).



THE MEDICAL JOURNAL OF AUSTRALIA.

LITHIUM SALTS IN THE TREATMENT OF PSYCHOTIC EXCITEMENT.

By JOHN F. J. CADE, M.D.,
Senior Medical Officer, Victorian Department of Mental Hygiene.



Discussion.

There is no doubt that in mania patients' improvement has closely paralleled treatment and that this criterion has been fulfilled in the chronic and subacute cases just as closely as in the cases of more recent onset. The quietening effect on restless non-manic psychotics is additional strong evidence of the efficacy of lithium salts, especially as such restlessness returned on cessation of treatment.

Lithium salts have no apparent hypnotic effect; the result is purely sedative. The effect on patients with pure psychotic excitement—that is, true manic attacks—is so specific that it inevitably leads to speculation as to the possible ætiological significance of a deficiency in the body of lithium ions in the genesis of this disorder.

Lithium may well be an essential trace element. It is widely distributed, has been detected in sea-water and in many spring and river waters, in the ash of many plants, and in animal ash.

Pre-frontal leucotomy has been performed lately on restless and psychopathic mental defectives (Mackay, 1948; Engler, 1948) in an attempt to control their restless impulses and ungovernable tempers. It is likely that lithium medication would be effective in such cases and would be much preferred to leucotomy.

Illustration. The famous paper of Dr John Cade: the most frequently cited paper ever published in the Medical Journal of Australia.

DR.RUPNATH JI(DR.RUPAK NATH)

In the first half of the 20th century, lithium salts were considered harmless and were used by physicians to lower blood pressure (by competing with sodium in the kidney). Serum levels were not monitored and a number of patients died. Thus, lithium salts were abandoned as hypotensive agents, and gained a reputation as highly dangerous substances.

As a naturally occurring substance, lithium salts could not be patented. There was, therefore, no financial incentive for a drug company to promote the lithium treatment of mania, and acceptance was slow. The US Food and Drug Administration did not approve this use of lithium until 1970.

The mechanism of action of lithium on the CNS remains a matter of discussion. Lithium ions interact with the transport of cations across the neuron membrane, resulting in a smaller resting voltage gradient. This has been interpreted as evidence that lithium makes the neuron "less excitable" and less liable to discharge. There is evidence lithium modulates glutamate release, and the actions of the enzymes inositol monophosphate and glycogen synthase kinase-3 (Bachmann et al, 2005). Animal studies show lithium is neuroprotective, protecting neurones against glutamate induced excitotoxicity (Chuang, 2005) and promotes neurogenesis and neurite growth (Chen & Manji, 2006). Regulation of gene expression is proposed.

20% of people with bipolar disorder will remain symptom free as long as they continue to take lithium. In a large proportion of the remainder who continue to take lithium (there is a high discontinuation rate) there will be a reduction in the frequency and severity of relapses.

Psychiatric uses

- Prophylaxis of mania
- Prophylaxis of depressive episodes (both bipolar and unipolar)
- Prophylaxis in schizoaffective disorder (usually in combination with an antipsychotic)
- Treatment of acute mania (lithium is usually not sufficient as the sole agent and is usually supported by an antipsychotic). Best for euphoric mania – may not be good for rapid cycling and mixed episodes
- In acute treatment resistant depression, as augmentation of antidepressants.
- Prophylaxis in impulse control disorders (the evidence is not strong)

DR RUPAK TIWARI (DR. RUPAK NATH)

Side-effects

<u>Common</u>

- Nausea and diarrhoea. These often settle after a few weeks. These may be lessened in the early stages by taking small doses four times per day, and moving to twice daily doses at a later stage.
- Metallic taste in the mouth.
- Increased thirst and drinking more fluid than previously. This depends on a number of factors. Importantly, lithium may block the effect of antidiuretic function on the kidneys, leading to the passing of excessive urine.
- Weight gain. This may depend on a number of factors. Lithium may slightly reduce the metabolic rate. It is important to point out to patients that they will probably be drinking more, and they should consume calorie free drinks, such as water, rather than soft-drinks or sweetened tea/coffee.
- Tremor. Propranolol is usually helpful.

<u>Uncommon</u>

- Complaints of slowing of thinking/ tiredness/lack of energy. In assessing these complaints, be alert to the possibility that patients may have come to accept mania/hypomania as “normal”. Also, be alert for signs of developing depression.
- Impairment of creativity. This may be related to the above complaint, and the same alerts apply. However, there is good evidence that some highly creative individuals (particularly painters, writers and musicians) refuse lithium due to perceived impairment of creativity. This raises the interesting point that hypomania may contribute to the creative output of the world. If two individuals are of equal talent, training and experience, and one is mildly hypomanic (not needing hospitalization) he/she is going to have more energy, sleep less, have more thoughts and take more risks than the other. This should

not be read as support for the naïve notion that madness and genius are opposite sides of the same coin.
- Hypothyroidism. Lithium may substitute for iodine and interfere with the production of thyroid hormone. If lithium has been beneficial, add thyroxine. If lithium has been of no or little benefit, consider ceasing (the hypothyroidism is reversible) and commencing another mood stabilizer.
- Acne and psoriasis may be made worse
- Diabetes insipidus is an extreme form of interference with the action of antidiuretic hormone (mentioned above). Endocrinology consultation is appropriate. This condition corrects with the cessation of lithium therapy.
- Disturbance of diabetes control may be a complication of lithium therapy, and adjustment of insulin dosage may be indicated.

Lithium Toxicity

Toxicity occurs at high serum levels. In extreme cases, convulsions, acute renal failure, coma and death may result. These are rare, but the patient and family need to be aware of danger signs.

Toxicity can occur with intentional or unintentional overdose. The most common cause is unintentional dehydration, which occurs with excessive exercise in hot weather, urinary tract infection, kidney disease, concomitant diarrhoea and vomiting, and drugs reducing renal clearance of lithium (predominantly thiazide diuretics, and anti-inflammatory drugs, including non-steroidal anti-inflammatories).

DR.RUPNATHJI(DR.RUPAK NATH)

<u>Early signs</u>
- Nausea
- Vomiting
- Diarrhoea
- Unsteady gait
- Mental confusion

<u>Severe signs</u>
- Marked tremor
- Slurred speech
- Ataxia
- Delirium/coma
- Abdominal pain
- Renal failure

Management includes immediate cessation of lithium, determination of blood level (interpreted with knowledge of the time of last ingestion) and medical review.

Lithium passes into the foetal circulation. In rare cases, tricuspid valve deformity has been reported. The thyroid function of the newborn may be temporarily impaired. Lithium passes into the breast milk, and bottle feeding is recommended (Llewellyn and Stowe, 1998). In spite of the slight danger to the foetus, mothers with severe bipolar disorder may elect to continue lithium therapy.

Preliminary work-up

Lithium may impact on thyroid (hypothyroidism) and renal function (nephrogenic diabetes insipidus; rarely nephritis) and the ECG (benign, reversible depression of the T wave). It is necessary to have baseline thyroid and renal function estimates and ECG.

Assess the reproductive plans of females.

Dose and monitoring

The appropriate dose is determined by the serum lithium concentration. In the acute situation, strive for 0.6-1.2 mmol/L. For prophylaxis, strive for 0.6-0.8 mmol/L. Serum levels are high shortly after ingestion and then fall. The therapeutic range is standardized at 12 hours after the last dose. The usual method is to draw blood before the morning dose. For acute treatment 500-2000 mg/day will be needed, given in divided doses, 2-4 times per day. Lower doses are required by the elderly and those with renal impairment.

In the first instance, levels are checked at 5-7 day intervals (to ensure a steady state has been achieved), and adjustments may be required on a weekly basis for 2-3 weeks. Thereafter, if there is no further change in dose, levels should be measured 4 times per year.

DR.RUPNATHJI(DR.RUPAKNATH)

CARBAMAZEPINE

Carbamazepine has a structure similar to the TCA imipramine (Illustration). It was initially developed as an antidepressant, in the 1950s, but was not marketed for that purpose. It was found to be useful and marketed as a treatment of epilepsy and neuropathic pain. Over the last 30 years carbamazepine has been used in psychiatric disorders. The mode of action is uncertain; the blockade of sodium channels with reduction of membrane excitability may play a role.

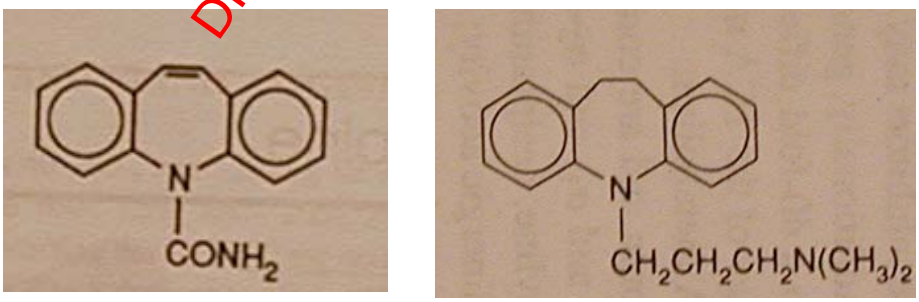


Illustration. Tricyclic structure of carbamazepine (left) resembles that of imipramine (right).

In the treatment of acute mania, carbamazepine is as effective as lithium and haloperidol. In a meta-analysis of carbamazepine versus lithium, relapse occurred in 55% of patients taking carbamazepine and 60% of those taking lithium, but there was no significant difference (Davis et al, 1999).

Psychiatric uses

- Acute mania (usually in combination with an antipsychotic)
- Prophylaxis in bipolar disorder – particularly where there is "rapid cycling", failed response to lithium, inability to tolerate side-effects of other mood stabilizers, and a "mixed affective state".
- Schizoaffective disorder
- Depressive phase of bipolar disorder.

Side-effects

Only about 5% of patients cease carbamazepine due to side effects. More common during the initiation phase, they often subside over time. They include dizziness, dry mouth, dyspepsia, ataxia, sedation, nausea/vomiting and diplopia. Weight gain is less common than with many other agents.

Haematological
Carbamazepine has been associated with suppression of the white blood cells (which is considered clinically unimportant) and rarely, with potentially fatal, severe blood dyscrasias, including agranulocytosis, pancytopenia, and aplastic anaemia

Hepatic
Carbamazepine has been associated with benign elevations of hepatic transaminases and rarely, with potentially fatal non-dose-related idiosyncratic hepatic failure.

Cardiovascular
Carbamazepine slows intracardiac conduction, and is relatively contraindicated in heart block

Dermatological
Rashes (benign) occur in 5-15% of patients. However, exfoliative dermatitis, Stephen-Johnson syndrome, and toxic epidermal necrosis have been reported. In view of the potentially fatal outcome, the recommendation is that carbamazepine be discontinued if rash occurs. Hair loss (reversible on discontinuation of carbamazepine).

Endocrine
Carbamazepine can exert antidiuretic effects, resulting in clinically insignificant hyponatremia in up to 40% of patients

Drug interactions
Drug interactions require caution. Carbamazepine may increase the metabolism of psychotropic drugs (valproate, lamotrigine, atypical antipsychotics, and anxiolytics), and general medical drugs (analgesics, antibiotics, and steroids).
Other drugs (cytochrome P450 3A4 inhibitors) can inhibit carbamazepine metabolism, potentially leading to carbamazepine toxicity.

Toxicity

Overdose can be fatal: atrioventricular block, coma, seizure and respiratory depression. Early signs include nystagmus, tremor, ophthalmoplegia, and myoclonus.

DR.RUPNATHJI(DR.RUPAK NATH)

Use during pregnancy is associated with a 1% incidence of spina bifida. Craniofacial defects and developmental delay have been reported. Carbamazepine passes into the breast milk, but this appears to be of little clinical importance. The baby should be monitored for jaundice, sedation and weight gain.

Preliminary work-up

A preliminary ECG is recommended. In view of the risk of blood dyscrasias and hepatic failure, a full blood count and liver function test is wise before treatment is commenced. These are often repeated every 2 weeks for the first few months, and then every 3-6 months. However, as the reactions are rare and idiosyncratic, it is unlikely that a routine screening strategy will be reduce risk.

Assess the reproductive plans of females.

Carbamazepine can decrease the blood concentration of other medications including the oral contraceptive. If there is evidence of breakthrough bleeding, another form of birth control should be considered.

Dose and monitoring

The starting dose is 100-200 mg/day, and increased over 1-2 weeks. This slow start reduces the risk of side-effects (including rash). The dose/blood level should be checked after a few weeks, because the drug induces metabolizing liver enzymes which may cause a reduction the blood level, after a stable initial period. The effective dose is usually in the range of 600-1200 mg/day.

The optimal therapeutic carbamazepine plasma concentration for mood stabilization is yet to be established. Some psychiatrists use the levels recommended for epilepsy prophylaxis (17-50 micromol/L). Others increase the dose until side-effects intervene, and then reduce the dose such that the side-effects are tolerable.

DR.RUPNATHJI(DR.RUPAK NATH)

SODIUM VALPROATE

Sodium valproate was initially marketed as an anti-convulsant. Following the success of carbamazepine as a mood stabilizer, sodium valproate was found to be effective in this regard. It is now the most widely used mood stabilizer, in part at least, because of a superior side-effect profile.

In both acute mania and long term maintenance, sodium valproate is as effective as lithium and carbamazepine (Macritchie et al, 2004). It may be superior to lithium in the treatment of rapid cycling and mixed mania. In comparison to lithium, sodium valproate treatment provides comparable medical costs, clinical and quality of life outcomes (Revicki et al, 2005).

The mode of action is uncertain; as with the other mood stabilizers; there is blocking of sodium channels. In addition, there is potentiation of gamma aminobutyric acid (GABA) and effects on intracellular protein regulation. Animal studies show sodium

valproate is neuroprotective, protecting neurones against glutamate induced excitotoxicity (Chuang, 2005) and promotes neurogenesis and neurite growth (Chen & Manji, 2006).

Psychiatric uses

- Acute management of mania
- Prophylactic management of mania
- Schizoaffective disorder
- Management of bipolar depression (No controlled studies)

Side-effects

Common

- Nausea
- Vomiting
- Abdominal pain
- Diarrhoea
- Tremor
- Somnolence
- Dizziness
- Weight gain
- Hair loss (reversible on discontinuation of valproate)

Rare but potentially fatal (idiosyncratic)

- Acute haemorrhagic pancreatitis
- Agranulocytosis
- Liver failure
- Polycystic ovarian syndrome

DR.RUPNATHJI(DR.RUPAK NATH)

Toxicity

Toxicity occurs with overdose and may take the form of heart block, coma, and death. Haemodialysis may be necessary to eliminate the drug.

Sodium valproate is associated with a 1% risk of neural tube defects, such as spina bifida when taken during the first trimester of pregnancy. Other congenital malformations have been recently reported, and the overall risk may be as high as 11% (Ernst and Goldberg, 2002).

Sodium valproate passes into the breast milk at less than 10% of the serum concentration. The effects on the nursing child are uncertain, but the risk is considered to be very low.

Drug interactions

Amitriptyline (TCA) and fluoxetine (SSRI) may increase valproate concentration, possibly by inhibiting valproate metabolism.

Aspirin may elevate the free fraction of valproate, by displacing from protein-binding sites, thereby increasing the effects on the central nervous system.

Valproate can displace diazepam, carbamazepine and warfarin, thereby increasing the activity of these drugs.

Dosage and monitoring

Blood count, liver function tests, and if appropriate, pregnancy testing.

The starting dose is 250-1000 mg per day, in two divided doses. Dose can be increased every 2-3 days, depending on response and tolerance. In acute mania, oral loading of 20mg/kg can be given on the first day, to achieve rapid therapeutic levels. Patients who are not acutely manic may have difficulty tolerating this load. The usual therapeutic concentration is 50-150 micrograms/mL (blood drawn 12 hours after the last dose).

DR RUPNATH J(DR.RUPAK NATH)

LAMOTRIGINE

Lamotrigine is the most recent anticonvulsant to be discovered as having a mood stabilizing effects. It appears that lamotrigine (in contrast to the other mood stabilizers) appears more effective in preventing relapse into depression than relapse into mania (Calabrese et al, 2003). However, also has effective mania prevention action.

Lamotrigine is a first line drug in the treatment of bipolar depression.

This agent is generally well tolerated. Weight gain is not a major problem. The most common adverse event is headache. A rash occurs in up to 6% of patients, and is a cause of discontinuation. A serious rash with mortality occurs in up to 0.1% of patients – may be associated with multi-organ failure.

Commence at 25 mg/day for 2 weeks, at week 3 increase to 50 mg/day, at week 5, increase to 100 mg per day at week 6, 200 mg/day (maximum dose).

ATYPICAL ANTIPSYCHOTICS AS MOOD STABILIZERS

As mentioned above, further details are available in Chapter 15. For as long as they have been available, the antipsychotics have been used to calm patients with acute mania. However, in recent times, many of the atypical antipsychotics have been used as mood stabilizers.

Olanzapine

Olanzapine is widely used in the treatment of acute mania. It has been shown effective as a bipolar maintenance treatment (Tohen et al, 2005).

Olanzapine is associated with significant weight gain (in most studies >50% of patients gain more than 5lb) and sedation. These are the main causes of discontinuation. Other issues are increased risk of diabetes and hyperlipidemia.

Aripiprazole

Aripiprazole is effective in acute mania. It has recently been approved by the FDA as a bipolar maintenance treatment (Marcus et al, 2004).

Side effects include akathisia, somnolence and constipation. Weight gain is not often encountered. There may be a risk of hyperlipidemia and diabetes, but the evidence is not yet convincing.

Risperidone, quetiapine and ziprasidone

These agents are all effective in the treatment of acute mania. All are associated with side effects such as dry mouth, downiness, and dizziness. All share some risk of hyperglycaemia and diabetes. Risperidone and ziprasidone are more likely to cause akathisia and other acute extrapyramidal side effects. Risperidone, in particular, is associated with hyperprolactinemia. Ziprasidone, in particular, is associated with prolongation of the QTc interval.

DR.RUPAK NATH)

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DR.RUPNATHJI(DR.RUPAK NATH)