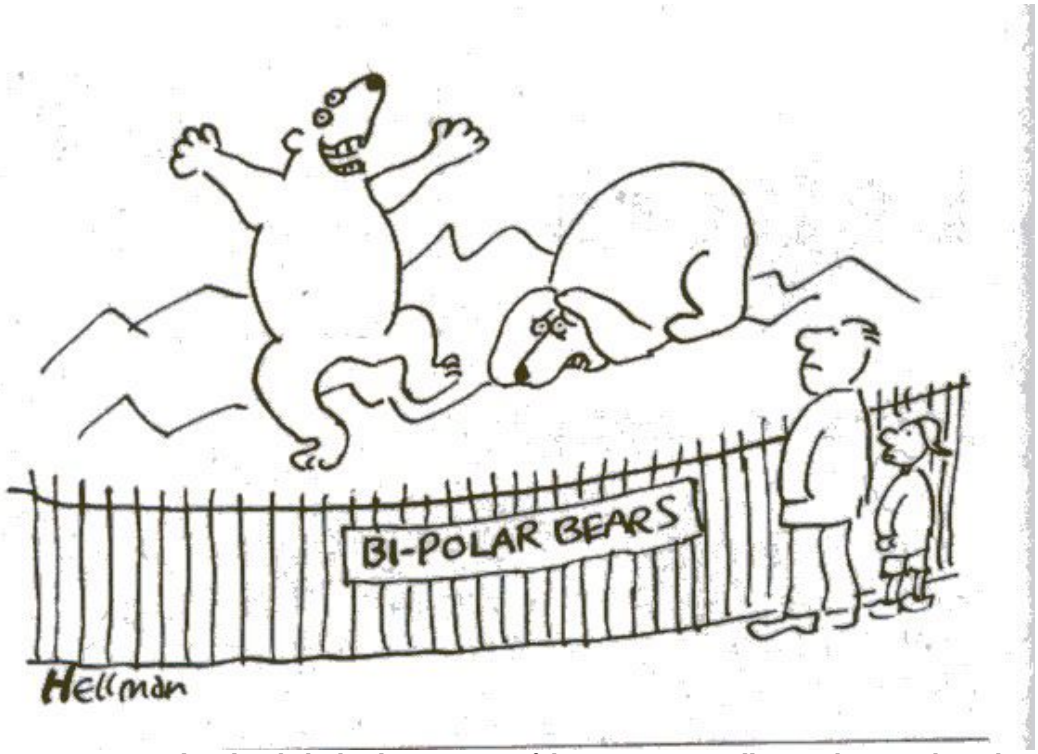
CHAPTER 18

MOOD STABILIZERS



This cartoon is reproduced with the kind permission of the artist Louis Hellman, whose work can be viewed at louishellman.co.uk.

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 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.

INTRODUCTION

'To this point, ideal mood stabilizers are like Chinese dragons, we know what they look like, but no-one has ever found one. The ideal mood stabilizer would effectively treat both acute mania and depression, and provide prophylaxis against both.' (Calabrese and Rapport, 1999).

For many decades the 'mood stabilizers' (agents which keep the mood in the normal range) were lithium and some anticonvulsants (agents which had no other application in the psychiatry). However, in the last decade or so many of the newer antipsychotics have also been classified as mood stabilizers.

In this Chapter only lithium and some of the anticonvulsants will be discussed. For details on the antipsychotics, the reader is referred to Chapter 15.

Mood stabilizers have two roles – the first is the suppression of acute mania – the second is prophylaxis, the suppression of descent into depressive episode or elevation into a manic episode.

Lithium efficacy is equal to (if not greater than) the more recently introduced agents (Gitlin and Frye, 2012; Prenning et al, 2013). Nevertheless, the available mood stabilizers including lithium, fail to prevent relapses in 40% of patients (Bouli et al, 2013), and non-compliance due to side effects is a major issue. Progress in finding good mood stabilizers is long over-due.

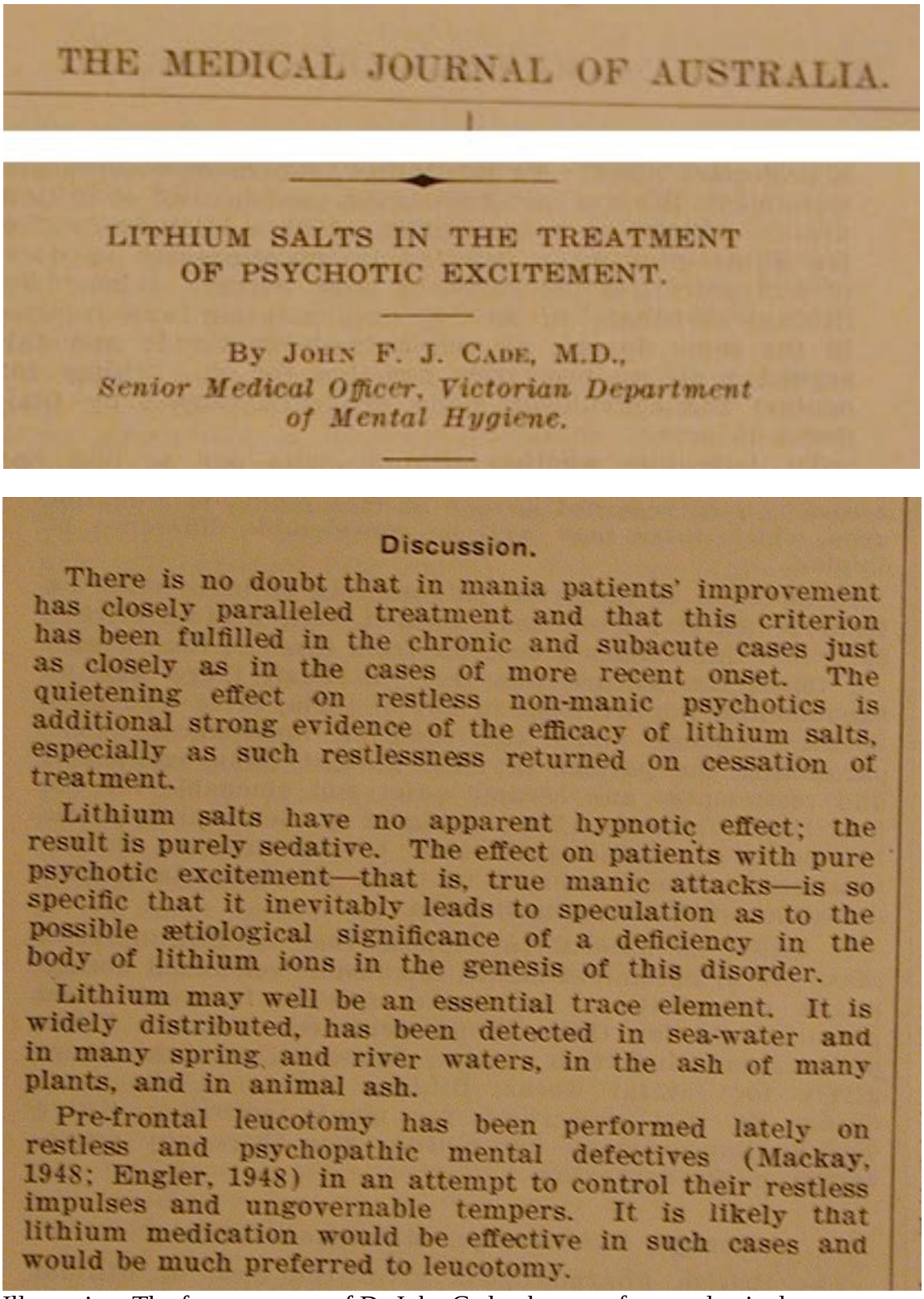
Mood stabilizers are recommended in the treatment of 'Bipolar and Related Disorders', listed in DSM-5 as bipolar I disorder, bipolar II disorder, cyclothymic disorder. These agents appear most effective in the first two listed disorders. They may also have a place in the acute treatment and prophylaxis 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).

Most of the studies of the management of bipolar disorder examine 'monotherapy' (treatment with a single agent). This is good science. However, as lithium and most other mood stabilizers have only a modest effect in acute mania, and limited efficacy in many prophylactic cases, in the real world, combinations of medications are given, based on 'clinical judgement' rather than research (Pfennig et al, 2013).

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 have been 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.



THE MEDICAL JOURNAL OF AUSTRALIA.

LITHIUM SALTS IN THE TREATMENT OF PSYCHOTIC EXCITEMENT.

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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.

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 naturally occurring substances, 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 in clinical psychiatry 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 unclear. 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. For a recent review see Can et al (2014).

As mentioned in the Introduction, lithium (and the other mood stabilizers) fail to prevent relapses in 40% of patients (Bouli et al, 2013), and non-compliance is a problem.

Nevertheless, in 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 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 effective 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)

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.
- 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.

- It has long been known that lithium irreversibly decreases the glomerular filtration rate – however, this slight decrease does not move kidney function into the pathological range. However, a recent study of people who have taken lithium for 30 years suggests there is a risk of glomerular failure (Bocchetta et al, 2013).
- 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.

Uncommon

- 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. 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. This is 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).

Early signs
- Nausea
- Vomiting
- Diarrhoea
- Unsteady gait
- Mental confusion

Severe signs
- 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. It is associated with an increased risk of neural tube defects, perinatal complications and tricuspid valve deformity. 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. Lithium is recommended over other mood stabilizers in pregnancy (Gentile, 2012; Deiana et al, 2014).

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. Maintenance will require lower doses, around 1g/d.

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. Thyroid and renal function checked twice yearly.

Low doses are required by the elderly and those with renal impairment.

CARBAMAZEPINE

Carbamazepine has a structure similar to the TCA, imipramine. It was initially developed as an antidepressant, in the 1950s, but was found to be useful and marketed as a treatment of epilepsy and neuropathic pain. Over recent decades 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. Recent work suggests the modulation of prefrontal dysfunction (Schneider et al, 2014).

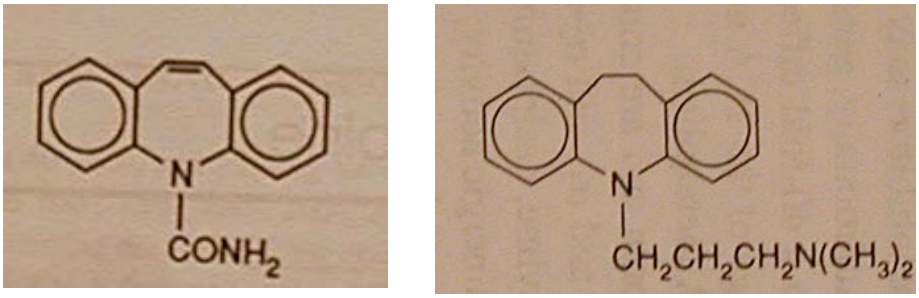

Illustration. Tricyclic structure of carbamazepine (left) resembles that of imipramine (right).

In the treatment of acute mania, 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). However, carbamazepine remains less commonly used in mania than lithium and sodium valproate, in part because of side-effects.

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.

<u>Haematological</u>
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.

<u>Hepatic</u>
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.

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. Risk to the unborn is greater than with carbamazepine than lithium (Gentile, 2012).

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.

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 both acute mania and long term maintenance, sodium valproate is as effective as lithium and carbamazepine (Macritchie et al, 2004; Cipriani et al, 2013). 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), with generally fewer side effects.

The mode of action is uncertain; as with 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

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 reported, and the overall risk may be as high as 11% (Ernst and Goldberg, 2002). Gentile (2012) states risk to the unborn is unacceptable.

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).

LAMOTRIGINE

Lamotrigine is the most recent anticonvulsant to be found to have mood stabilizing effects. It appears (in contrast to the other mood stabilizers) to be more effective in preventing relapse into depression than relapse into mania (Calabrese et al, 2003; Gitlin and Frye 2012). However, it also has some 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, and may be associated with multi-organ failure.

Recent work suggests that the therapeutic response to lamotrigine is dependent on plasma concentration (Kagawa et al, 2014).

Commence with caution: 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

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. The metabolic syndrome remains a concern.

Quetiapine

Quetiapine has a favourable side-effect profile; sedation and weight gain being the main problems.

Quetiapine as a monotherapy or as an adjunct to other agents is recommended by most guidelines as a first-line choice in both acute and maintenance therapy for bipolar depression (Suttaijt et al, 2014) and acute and maintenance therapy for mania.

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 been approved by the FDA as a bipolar maintenance treatment. Aripiprazole plus another mood stabilizer is a popular contemporary combination (Malempati, 2015).

Side effects include akathisia, somnolence and constipation. Severe weight gain is not often encountered.

Risperidone and ziprasidone

These agents are both effective in the treatment of acute mania. Both are associated with side effects such as dry mouth, downiness, and dizziness. Both share some risk of hyperglycaemia and diabetes. Possible side effect include akathisia and other acute extrapyramidal symptoms. Risperidone, in particular, is associated with hyperprolactinemia. Ziprasidone, in particular, is associated with prolongation of the QTc interval.

COMBINATION THERAPY

A combination of an anticonvulsant and an atypical antipsychotic is more effective in mood stabilization than mono-therapy (Ogawa et al, 2014).

MOOD STABILIZERS AND THE IMMUNE SYSTEM

Throughout psychiatry there is great interest in the immune system.

“These drugs might influence cytokine production by modulating ion channels and γ-aminobutyric acid (GABA) receptors of immune cells” (Himmerich et al, 2013).

MOOD STABILIZERS, GENETICS AND EPIGENETICS

The interaction of mood stabilizers and genetics is being discussed (Can et al, 2014)

Throughout psychiatry there is also a great interest in epigenetics. Asai et al (2013) found a profound effect of lithium on DNA methylation, in distinction from the anticonvulsants – but this is work at a very early stage.
For a review which includes the mood stabilizers, see Seo et al (2014).

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