the medicine cabinet: mood stabilisers...

Mood Stabilisers – helping with the ups and downs: Part 1

Judy Longworth
Senior Clinical Pharmacist
The Children's Hospital at Westmead

Mood stabilisers help with control of the highs and lows of mood. Sometimes they are used to elevate the low mood or reduce the exuberance of the high mood sometimes exhibited as agitation or impulsivity. Beyondblue describes them as medications that keep one's moods on an even keel without the highs and lows. Types of mood stabilisers include carbamazepine, lithium carbonate, and sodium valproate and these will be discussed in part I with lamotrigine and some more other antiepileptics discussed in part II. Sometimes antipsychotics are also used as adjuvant therapies for the mood stabilisers in controlling mood but these will not be discussed here.

In recent years, there have been many clinical trials of atypical antipsychotics being used as mood stabilisers in both adults and adolescents. But there is lack of high level evidence for the antiepileptics in either mental health population or those with developmental disability atypical antipsychotics in the management of behaviour problems in either the adult or child and adolescent population with developmental disabilities. Although there is evidence for use of antiepileptics in the autistic population with comorbid epilepsy, there is little evidence for use as mood stabilisers in this population. Although there is a long clinical history of successful use in this population.

What are the medications?
Mood stabilisers include lithium and some of the drugs that are antiepileptic medications. These antiepileptic medications include primarily sodium valproate, carbamazepine, and lamotrigine. But other antiepileptics have also been trialled with varying success in mood regulation such as gabapentin, topiramate, levetiracetam and zonisamide and these will be mentioned in part II.

What do they do?
These medications affect the GABA/glutamate system as well as the ion channels but lithium only affects the ion channels. Although the pathophysiology of abnormal unstable moods is not known, it may be linked to abnormal neuronal activity with increased ionic flow through ion channels in an electric storm, which is analogous to ictal states such as seizure. (Stahl, 2002) Theoretically, mood stabilisers that normalise the flux of ions would reduce the mania and prevent mood instability.

What are they?
Lithium
An essential salt found worldwide and therapeutically discovered by John Cade in1949 in Melbourne after discovering that guinea pigs after using lithium urate which appeared conscious but immobile as if in a state of lethargy. From these observations he thought he could use lithium carbonate in manic excitation and agitation. (Thuillier, 1999). Although forgotten it was taken up again by Mogen Schou in 1955 who advocated giving adequate doses to achieve good blood levels but again the work went largely unnoticed until by 1975 there was three thousand reports of lithium extraordinary capacity to be both curative and preventative for mood disorders (Thuiller, 1999).

The distinctive mechanism of action of lithium has not be been replicated by the pharmaceutical industry and due the toxic nature or narrow therapeutic index of lithium it needs regular blood monitoring (Stahl 2002). Lithium can also be toxic to the kidneys, heart and thyroid as well as nervous system, another reason for close monitoring not just of lithium levels but also how these organs are functioning such as measuring thyroid hormone levels and calcium levels..

Lithium is an ion whose mechanism of action is not certain, although it is hypothesised to interact with the second messenger systems to result in a stabilisation of neuronal ion flow. It is possible in mania or even seizures that the ion channels are excessively opened thus not being regulated by the second messenger system consisting of a neurotransmitter such as serotonin in normal neuronal ion flow. (Stahl, 2002)

Lithium has been used successfully in children and adolescents for bipolar disorder, chronic aggressive conduct disorders, and periodic mood and behaviour disorders and pervasive developmental disorders eg autism. Nausea, vomiting and diarrhoea as well as weight gain are recognised adverse effects. Some of these are eased over the long term but a change to the slow-release dosage preparation can also be helpful. There are also skin effects such as acne and aggravation of psoriasis as well as dryness and thinning of the hair which could be associated with hypothyroidism associated with lithium therapy. Other common adverse effects include tremor, polyuria, myoclonus, and EPS have been reported. Recent reports have shown there are no significant increased risks of congenital malformations.

Lithium is also shown to have reduced suicide rates in bipolar disorder. This effect may be due to reduced dysphoria, anger, aggression and impulsivity. All these characteristics are valuable in the pervasive developmental disability population who are able to cope with blood tests.

Sodium Valproate (overseas preparations contain valproic acid or divalproex a combination of valproic acid and valproate)

"When any psychometric testing is being done it is important to take into account medication and its effect on the student's functioning...."

Valproate increases serotoninergic activity by blocking the voltage-dependent sodium and calcium channels. Originally used as anticonvulsant or antiepileptic but now licensed for the treatment of acute mania in Australia. Valproate was also discovered serendipitously by Pierre Emymard in 1962 while doing studies on rats and rabbits testing an antiepileptic effect.

Valproate is now widely used as an antiepileptic in both adults and children as well as licensed for treatment of mania associated with bipolar disorder. There have been a number of clinical trials about use of valproate for aggression in pervasive developmental disorders.

Valproate has a number of adverse effects such as sedation, tremor, cognitive problems, and hyperammonemia leading to delirium and tremor and these may be caused sodium and calcium channel effects or GABA effects. Valproate associated liver toxicity is associated with nausea, jaundice and anorexia. Other rarer reported adverse effects include sedation, tremor, dizziness, diplopia (double vision) blurred vision, cognitive problems. Nausea, vomiting, abdominal pain, diarrhoea, anorexia and constipation are more common but problematic weight gain, periph-

eral oedema, bronchitis, pharyngitis, alopecia and carnitine depletion is less common.

Another important aspect of sodium valproate is its effect on organogenesis and thus its action as a teratogen. This can be helped with careful planning as well as addition of folate supplements.

Carbamazepine

GABA modulator (www.psychotropics.dk) licensed for treatment of epilepsy since 1974 (USA) and trigeminal neuralgia. In the USA it is also licensed for use in bipolar 1 disorder as well as acute mania.

Chemically related to the tricyclic antidepressants (Goodman and Gilman, 2011), like phenytoin, carbamazepine limits the repetitive firing of action potentials evoked by a sustained depolarization experimentally in mouse spinal cord or cortical neurons. Carbamazepine is absorbed slowly and erratically after oral administration. Peak concentrations in plasma usually are observed 4-8 hours after oral ingestion, but may be delayed by as much as 24 hours, especially following the administration of a large dose. The drug distributes rapidly into all tissues. Approximately 75% of carbamazepine binds to plasma proteins, and concentrations in the cerebrospinal fluid appear to correspond to the concentration of free drug in plasma.

Carbamazepine induces the P450 cytochrome (CYP) 2C, CYP3A, and uridine 5 diphosphate glucuronosyltransferase (UGT) liver enzymes, thus enhancing the metabolism of other drugs degraded by these enzymes. Of particular importance in this regard are oral contraceptives, which are also metabolized by CYP3A4.

There is no simple relationship between the dose of carbamazepine and concentrations of the drug in plasma. Therapeutic concentrations are reported to be 6-12 microg/ml, although considerable variation occurs. Side effects referable to the CNS are frequent at concentrations above 9 microg/ml. However the patient's response is the best measure of therapeutic limitation.

Carbamazepine patients have reported low white blood cell counts with increased infections or bruising at the beginning of therapy, this can be monitored by careful watching for any new infections or general feeling of unwell. Liver enzymes need to be monitored where practical with patients taking valproate, topiramate and carbamazepine.

Although used in child and adolescent psychiatry both for its affect in controlling moods and irritability, there is little evidence published for it is use in this population (Haessler 2010) but is licensed for use in adults who are unresponsive to lithium in the Great Britain.

Other important factors

When any psychometric testing is being done it is important to take into account medication and its effect on the student's functioning.

Drug	Behavioural Effects	Cognitive Effects
Carbamazepine	Difficulty sleeping, agitation, irritability, emotional lability	Impaired task performance
Valproic acid	Drowsiness (especially when used in combination with barbiturates)	Minimal adverse effects on psychosocial tests

Adverse Behavioural and Cognitive Effects Associated with Anticonvulsants. (AHFS 2012 accessed 3/4/12)

The antiepileptics have metabolic and immune effects with valproate having notably weight gain and somnolence as well as transient nausea to vomiting and increased appetite has been noted. Increased weight gain is also associated with lithium as well as gastrointestinal symptoms including nausea, vomiting and diarrhoea. Other adverse effects are polyuria, polydipsia and enuresis. Benign rash can occur in 5-20% patients taking antiepileptics but the incidence of the severe Steven Johnson syndrome is more 1 in 3000. (Amaladoss et al 2010)

Conclusion

These medications have their place in the doctor's pharmacopeia but with all medications they have their limitations and are not quick fix agents to fix a long standing problem but are powerful agents that can help pay a part the management of mood and other affective disorders.

References

1. www.beyondblue.org.au (accessed 5/1/12)
2. Stahl SM. Essential Psychopharmacology of Antipsychotics and Mood Stabilisers. 2002 Cambridge UP Cambridge UK.
3. Thullier J Ten Years that changed the face of mental illness. 1999 Martin Dunitz London
4. Goodman and Gilman 12th ed 2011 accessed through ACCESS Medicine (through CIAP 8/3/12)
5. www.psychotropics.dk (accessed 8/3/12)
6. Taylor D, Paton C and Kapur S. The Maudsley Prescribing Guidelines in Psychiatry 11th ed 2012 Wiley Blackwell
7. AHFS 2012 online (accessed through CIAP 3/4/12)
8. Amaladoss A, Roberts N, Amaladoss F. Evidence for use of mood stabilisers and anticonvulsants in the treatment of non-affective disorders in children and adolescents. Clin Neuropharm 2010: 33(6) 303-11
9. Haessler F, Reis O. Pharmacotherapy of disruptive behavior in mentally retarded subjects: a review of the current literature. Developmental Disabilities Research Reviews 2010 16: 265-72

For further information the following websites may be of help

Beyond blue
www.beyondblue.com.au
Black Dog
www.blackdog.com.au
Reach Out
www.au.reachout.com
National Prescribing Service
www.nps.org.au