the medicine cabinet: mood stabilisers part 2...

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As mentioned in the previous column, this is the continuation of the mood stabilisers information. These ones have even lesser evidence for use in treatment of mood problems in the intellectually disabled population but maybe used in those children who have intellectual disability and epilepsy. This reflects the relative lack of experience except in epilepsy.

Lamotrigine
Lamotrigine's discovery was serendipitous. One mechanism of action of phenytoin and phenobarbitone for epilepsy was due to effects on folate metabolism. This lead to development of a group of folate antagonists drugs called phenyltriazines of which lamotrigine is best known.

There have been both open label and placebo controlled trials to determine whether lamotrigine affects the irritability seen with autism. In one open label trial lamotrigine helped reduce both seizures and difficult behaviours in intractable epilepsy and autism. But in a blinded study there was no significant difference in children with or without epilepsy when given a placebo or lamotrigine (Robb 2010). Lamotrigine is used in child and adolescent psychiatry for the depressive symptomology associated with bipolar disorder type 1.

The most commonly reported adverse effects are infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhoea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia. Approximately 11.5% of paediatric patients receiving immediate-release lamotrigine as adjunctive therapy in clinical trials discontinued the drug because of an adverse effect; the adverse effects most frequently associated with discontinuance of lamotrigine therapy in these patients were rash (4.4% of patients), reaction aggravated (1.7% of patients), and ataxia (0.6% of patients) (AHFS accessed 3/4/12).

Besides the need for slow titration of dose to minimise the skin adverse effect of Steven Johnson syndrome (an allergic syndrome) other side effects reported at higher doses include hyperactivity and insomnia. There have also been reports of agitation, activation, irritability and insomnia as well as cognitive blunting.

Care should taken if adding lamotrigine to sodium valproate in the medication regime as valproate can raise the blood levels of lamotrigine by 200% and thus increased incidence of Stevens Johnson syndrome, the potential fatal skin reaction. Another important interaction is between lamotrigine and ethinyloestradiol which is found in many combination oral contraceptives. Ethinyloestradiol decreases the blood levels of lamotrigine such that during the sugar pill washout the dose of lamotrigine should be decreased to a third of the dose. (Wynn et al 2009)

Topiramate
Topiramate was discovered in 1979 by Bruce E Maryanoff and team for Ortho - McNeill Pharmaceuticals as an anticonvulsant. It is a sulfamate-substituted derivative of the monosaccharide D-fructose. (AHFS accessed 3/4/12).

Topiramate has multiple mechanisms of action including augmenting the GABA-A receptor, and acting a sodium channel blocker. It also inhibits carbonic anhydrase especially isoenzymes II and IV. Topiramate is also a glutamate receptor antagonist (especially AMPA/kainite subtype). It is also postulated topiramate may also inhibit protein kinase activity and possible serotonin activity on 5HT2C receptors.

Open label trial on n=5 with autism and severe behavioural difficulties together with sertraline and risperidone, n=2 showed much improvement when measuring behaviour of the CGI-I but the other three showed no improvement. Adverse effects were usually mild including sedation and weight loss (Robb 2010). Other notable adverse effects include cognitive problems especially in word-finding difficulties as well as mood problems and visual disturbance that causes persistence of images which is rare, benign but frightening. (Silberstein 2009)

Because of the bitter taste, immediate-release tablets of topiramate preferably should be swallowed intact and *not* broken or chewed but the capsules can be opened and sprinkled on food for those with swallowing difficulties. If the tablets are broken, they should be used immediately since stability of exposed drug beyond a brief period cannot be ensured; any unused portion should be discard (AHFS accessed 3/4/12).

Levetiracetam
Levetiracetam is an example of rational drug discovery. It is the alpha-ethyl analogue of the nootropic piracetam. It was discovered in 1992 while examining epileptic mice a compound was found to exhibit strong binding potential to an unknown receptors which were later identified as synaptic vesicle protein isoforms. Levetiracetam, a pyrrolidine derivative, is an anticonvulsant agent that is structurally unrelated to other currently available anticonvulsants (AHFS accessed 3/4/12).

An adjunctive antiepileptic, which is primarily used to treat complex partial seizures and primary generalised tonic-clonic seizures. It binds to the synaptic vesicle protein isoform (SV2A) in the brain, a unique mechanism of action compared to the other antiepilpetics. SV2A is involved in synaptic vesicle exocytosis (Silberstein, 2011).

> "There is significant evidence for the use of antiepileptics in treating epilepsy with comorbid intellectual disability..."

Levetiracetam has been studied in both open label and double blind placebo controlled trials. One open label trial n=10 showed improvement in irritability and aggression in autistic children over a 4 week period. A larger double blind placebo controlled study n= 20 showed no difference between placebo and drug on the Aberrant Behavior Checklist (ABC) with parent and teacher ratings. In fact some children reported adverse effects of agitation and aggression which is similar to findings in epilepsy and mental retardation studies with levetiracetam (Robb 2010).

Adverse neuropsychiatric effects reported during levetiracetam treatment are classified into 3 categories: somnolence and fatigue, coordination difficulties, and behavioural abnormalities

Gabapentin
Gabapentin was discovered in Japan over 40 years ago and then sold onto the pharmaceutical company Warner-Lambert which conducted studies using low dose gabapentin as add-on therapy in

epilepsy management. Warner-Lambert was later acquired by Pfizer and now is available in generic form.

Gabapentin is a structural analogue of the neurotransmitter GABA and hence works at the GABA receptors to have an inhibitory effect but also reduces the amount of excitatory neurotransmitter glutamate. Gabapentin has relaxing anti-anxiety and anticonvulsant effects and is also used in chronic pain therapy.

There has been some preliminary data in use of gabapentin for behavioural problems associated with intellectual disability but the early studies have not been replicated.

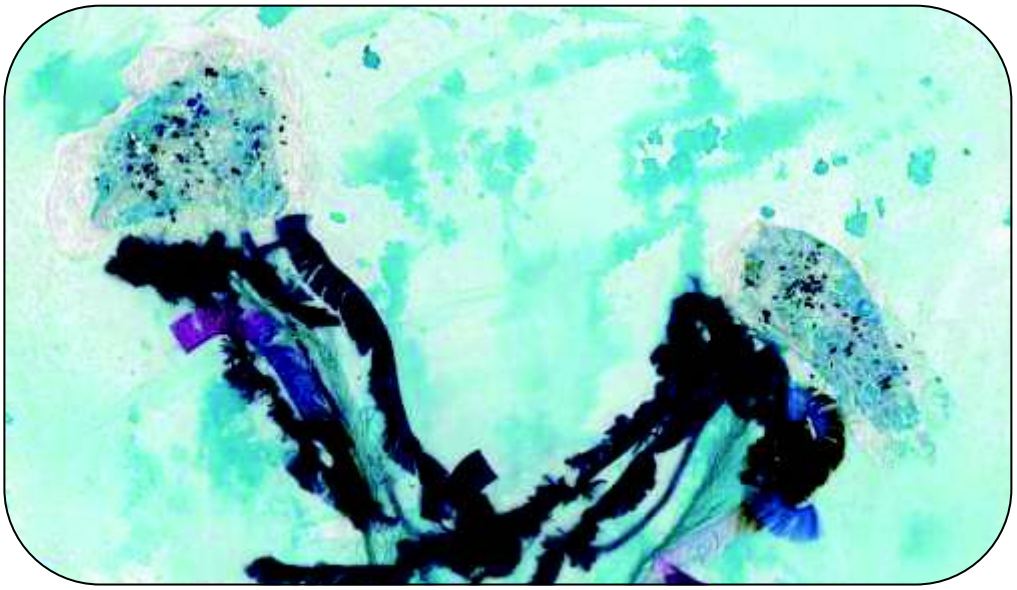
Adverse effects include sedation, dizziness, fatigue, and ataxia as well as weight gain, nausea constipation and dry mouth. There have also been reports of blurred vision.

Other anticonvulsants
These include phenytoin, phenobarbitone, primidone, benzodiazepines such as clonazepam, clobazam and diazepam, as well as the newer antiepileptics such as lacosamide, vigabatrin, rufinasmide, and tiagibine have not shown promise in early case studies when trialled for behavioural problems but this is not to say that in time there might not be positive studies.

Common adverse effects
All these medications are known to put on weight except for topiramate and levetiracetam and can be sedating. Several of these medications also have significant dermatological adverse effects which can have significant bearing on the patient.

Most antiepileptics cause GI disturbances such as nausea and vomiting, gastric distress, dysphagia, loss of taste, constipation, diarrhoea, and anorexia with or without weight loss. The severity of adverse GI reactions may be minimized by administering the drugs with water or food. The succinimide derivatives such as ethosuximide (only one available in Australia) frequently cause hiccups (AHFS accessed 3/4/12).

All anticonvulsants can produce drowsiness, and for this reason patients should be cautioned that these drugs may impair their ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery,



driving a motor vehicle). .(AHFS accessed 3/4/12)

Vigabatrin causes retinal atrophy and visual defects which can be permanent so should be monitored.

Drug	Behavioural Effects	Cognitive Effects
Clonazepam	Irritability, aggression, hyperactivity, disobedience, antisocial activities	
Phenobarbital	Hyperactivity, fussiness, lethargy, disturbed sleep, irritability, disobedience, stubbornness, depressive symptoms	Deficits on neuropsychologic tests, impaired short-term memory and memory concentration tasks
Phenytoin	Unsteadiness, involuntary movements, tiredness, alteration of emotional state	Deficits on neuropsychologic tests; impaired attention, problem solving, and visuomotor tasks

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

Conclusion
Although when prescribing antiepileptic's for behavioural interventions there is poor evidence, there is significant evidence for the use of antiepileptics in treating epilepsy with comorbid intellectual disability. Care should also be taken when administering psychometric testing with children and adolescents on some of these medications as they can adversely affect their cognitive functions as well as their ability to even read the questions.

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