Pharmaceutical Benefits Scheme restrictions on anti-epileptic drug prescribing promote unsafe and outdated practice

The PBS urgently needs to update anti-epileptic drug prescribing restrictions that put patients and prescribers at risk

In May 2018, the European Medicines Agency banned the prescription of valproate to women of childbearing age for use in migraine and bipolar disorder unless they are enrolled in a special pregnancy prevention program. Its use in epilepsy is banned unless there is no other effective treatment available.[1] This follows numerous reports of a substantially increased, dose-related risk of fetal malformations (in particular neural tube defects including spina bifida) in babies born to mothers exposed to valproate during pregnancy.[2,3] In addition, newer longitudinal studies showed a substantial negative effect on multiple cognitive domains in children exposed to valproate in utero.[4] On average, their intelligence quotient at 6 years of age is reduced by 7 to 10 points compared with children exposed to other anti-epileptic drugs (AEDs).[4] Manufacturers and national pharmaceutical regulators first warned of the risk of severe congenital malformations in the 1990s and, in practice, most epileptologists worldwide have avoided prescribing valproate to pregnant women ever since.[5] This was made possible by the licensing of two new drugs that are highly effective in genetic generalised epilepsies but without the risk of neural tube defects or likely neurocognitive effects: lamotrigine (first licensed in 1994) and levetiracetam (first licensed in 1999). To avoid common adverse effects of valproate, such as weight gain, metabolic syndrome, hair loss and gastrointestinal disturbance, epileptologists have since also reduced prescribing valproate to women without childbearing potential and to men. The only exception most epileptologists would accept for prescribing valproate during pregnancy is in women with genetic generalised epilepsy in whom seizure control is not achieved with levetiracetam, lamotrigine or topiramate, often in combination therapy. Usually, such women do respond to small doses of valproate in combination with lamotrigine or levetiracetam. As the valproate-induced fetal malformations are dose-dependent, the risk of fetal malformations is balanced with the risk of uncontrolled generalised tonic–clonic seizures during pregnancy.

The Australian Government Pharmaceutical Benefits Scheme (PBS), which subsidises pharmaceuticals for public patients, severely restricts the choice of AEDs that can be prescribed first line. In 2019, only nine AEDs can be prescribed without restrictions. These include the first effective drugs used to treat epilepsy: phenobarbital (1912), phenytoin (1938), primidone (1954) and carbamazepine (1974), and drugs that are only used in specific epilepsy syndromes such as sulthiame (for self-limited epilepsy with centrotemporal spikes in childhood) and ethosuximide (for childhood absence epilepsy), both licensed in the 1960s. Valproate, first licensed in 1978, was the last AED to be listed on the PBS without restriction. The other two non-restricted AEDs are benzodiazepines, which are usually not used as monotherapy to treat epilepsy.

Since 1978, numerous new AEDs with similar efficacy to the old AEDs but improved side effect profiles and safety[6,7] have been marketed. Most of these are listed on the PBS but with varying degrees of prescribing restrictions. The most common restriction requires that the condition "must have failed to be controlled satisfactorily by other anti-epileptic drugs", which in fact renders these AEDs second line drugs in Australia.

New AEDs include levetiracetam and lamotrigine, which are recommended for first line use in new-onset focal epilepsies in the 2018 American Academy of Neurology clinical guidelines, co-developed with the American Epilepsy Society,[8] the 2018 United Kingdom National Institute for Health and Care Excellence guidance,[9] and the 2017 German Society for Neurology guidelines,[10] which are also endorsed by the Swiss and Austrian Neurological Societies (Box). In addition, the United States and UK guidelines recommend oxcarbazepine to be used first line for focal epilepsies.[8,9]

For generalised epilepsies, the German guidelines recommend lamotrigine and levetiracetam as first line therapy, and the UK guideline recommends lamotrigine and topiramate. Topiramate is no longer recommended for first line use in the US and German guidelines because it carries an increased risk of congenital malformations in babies exposed in utero. The teratogenicity of topiramate is lower than that of valproate but still significant.[11]

All three international guidelines recommend ethosuximide and valproate as first line AEDs for childhood absence epilepsies, with valproate limited for use in girls before they reach childbearing age.

Except for childhood absence epilepsy, the new guidelines do not cover childhood epilepsies adequately and the UK guidance on treating childhood epilepsies is controversial. Specific childhood epilepsy syndromes such as infantile spasms, Lennox–Gastaut and Dravet syndromes and self-limited epilepsy with centrotemporal spikes and other idiopathic focal epilepsies require targeted therapeutic approaches best coordinated by paediatric epileptologists.

In addition to the PBS restriction as a second line drug, the PBS listing of levetiracetam only allows

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Recommended first line anti-epileptic drugs in national clinical guidelines in the United Kingdom, Germany, the United States and Australia[8–10,13]

	UK	Germany*	US	Australia
Focal epilepsies	Lamotrigine	Lamotrigine	Lamotrigine	Carbamazepine
	Levetiracetam	Levetiracetam	Levetiracetam	
	Carbamazepine		Zonisamide	
	Oxcarbazepine		Oxcarbazepine	
	Valproate†		Gabapentin	
Generalised or unknown onset epilepsies	Lamotrigine	Lamotrigine		Valproate†
	Topiramate†	Levetiracetam		Levetiracetam‡
Childhood absence epilepsy	Ethosuximide	Ethosuximide	Ethosuximide	Ethosuximide
	Valproate†		Valproate†	Valproate†

* Also endorsed by the Swiss and Austrian Neurological Societies. † Not recommended for use in women of childbearing age. ‡ Recommended first line for women of childbearing age who can fall pregnant, but patients need to pay privately for this prescription as Pharmaceutical Benefits Scheme restrictions do not allow subsidy for this indication. ◆

its use in focal epilepsies. This is surprising as the Pharmaceutical Benefits Advisory Committee (PBAC), the official body that makes all recommendations concerning PBS listings to the Australian Minister of Health, decided in 2008 to extend the PBS listing of levetiracetam to generalised epilepsies.[12] It seems that the Department of Health administration never implemented this decision and the reasons for this have not been made public. As generic preparations are now available for levetiracetam and lamotrigine, considerations of cost to the PBS should no longer be an obstacle to lifting the current restrictions on these two AEDs.

Other newer AEDs such as zonisamide, oxcarbazepine, gabapentin, vigabatrin and tiagabine also fall into this second line AED category.

The three latest drugs listed on the PBS for third line use include perampanel, lacosamide and brivaracetam. These have varying restrictions but all three can only be used as add-on drugs after at least one first line AED and at least two second line AEDs have failed and, for all three, the initial prescription must be issued by a neurologist.

What do PBS prescription restrictions mean for prescribing doctors?

The April 2019 version of the Australian electronic Therapeutic Guidelines, a prescribing tool used by many doctors and the only available Australian guidelines on treating epilepsy, still recommend treating focal epilepsies first line with carbamazepine and generalised or unknown onset epilepsies with valproate or levetiracetam in women who do not have reliable contraception,[13] a recommendation that directly follows from the outdated PBS restrictions. Unfortunately, both these recommendations are not in line with current US or European guidelines. Only the UK guidance still recommends the prescription of carbamazepine for first line use in focal epilepsies. Carbamazepine has been dropped from the US and European guidelines as a first line AED because of its unfavourable side effect profile compared with levetiracetam and lamotrigine.

Carbamazepine is also known to aggravate seizure frequency and intensity in many genetic or idiopathic generalised syndromes.[14] Therefore, it is much safer to use a first line AED such as levetiracetam or lamotrigine that is effective for both focal and generalised epilepsies and that does not carry the risk of aggravating the condition, considering that many patients with epilepsy are misclassified at the onset of their disease, in particular when they are first seen by non-epileptologists. The only caveat is for juvenile myoclonic epilepsy where in rare cases an aggravation of myoclonic seizures is seen with lamotrigine.[15] However, in most patients with juvenile myoclonic epilepsy, lamotrigine achieves excellent seizure control with few side effects.

Another issue is that many seizure patients have associated conditions that must be considered when prescribing AEDs. The best example is old age when carbamazepine, valproate and phenytoin are in general avoided because of a higher sensitivity of older patients to the adverse effects of these drugs on cognitive and cerebellar function, causing memory deficits, tremor and gait ataxia. More serious side effects such as carbamazepine-induced hyponatraemia, valproate encephalopathy or fatal phenytoin-induced cardiac arrhythmias also need to be considered.

In our opinion, the European Medicines Agency decision might have medico-legal consequences for Australian prescribers even if the European restrictions on valproate are not legally implemented in Australia. In June 2018, the Therapeutic Goods Administration Advisory Committee on Medicines[16] recommended to:

- avoid use of valproate in women of childbearing age for all non-seizure indications;
- for seizure indications, consider alternatives if they exist; and
- always use the lowest effective dose.

These recommendations cannot be implemented in daily prescribing practice unless the PBS restrictions on the use of levetiracetam and lamotrigine as second line drugs are lifted and levetiracetam is also made available to patients with generalised or unknown onset epilepsies as already recommended by the PBAC.

In practice, most epileptologists ignore the PBS restrictions and follow the internationally recommended prescribing guidelines. This puts the practitioner at risk of legal and financial sanctions. Australian doctors treating patients with epilepsy are therefore stuck between the proverbial rock and hard place.

Conclusions

The Australian Department of Health needs to urgently review the current PBS restrictions on AED prescribing. This will allow safe patient care and end the legal and ethical dilemma that doctors currently face when prescribing AEDs. Doctors should not be forced to choose between safe patient care and complying with outdated government regulation.

The first priority for this review is to lift the PBS restrictions on levetiracetam and lamotrigine. Given that both drugs are now available as generic medications, this should not have a significant budget impact for the PBS.

The second priority is to review the restrictions on other well tolerated and effective second and third line AEDs such as zonisamide, oxcarbazepine, lacosamide and perampanel. Cost considerations will be the major obstacle for the latter, but usually the Department of Health manages to negotiate acceptable price levels with manufacturers once the PBAC recommends changes to the PBS listing.

This long-awaited PBS update would finally allow Australian doctors to prescribe AEDs in line with international best practice without imposing a financial burden on patients or contravening PBS regulations.

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