A GUIDE TO

deprescribing

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An Australian Government Initiative

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CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

ANTIEPILEPTIC DRUGS (AEDs)

KEY POINTS

Adults or children with epilepsy who have been free of seizures for at least two years may be able to stop their AEDs, although it has been suggested that a longer period (3-4 years) may be preferable in adults.[9] The period of seizure freedom in children can be considerably shorter than that in adults and depends on the epilepsy syndrome. This is particularly true for syndromes with a favourable outcome, such as Rolandic epilepsy and benign infantile epilepsies;[7] specialist advice is recommended.

Given that epilepsy is a constellation of various syndromes and sub-syndromes, each with a markedly different prognosis, a "one size fits all" approach is not feasible when contemplating AED withdrawal in patients with epilepsy in remission.[9]

The decision to continue or to stop AEDs in seizure-free patients should be individualised after proper assessment of risks and benefits, and consultation with a neurologist is often recommended.[8,9,24] Risk prediction tools exist.[22] It is paramount to discuss with patients whether the risk of seizure recurrence is worth the benefit of stopping the AED. Social aspects such as driving and employment, as well as emotional and personal factors, must be carefully considered along with any adverse effects and drug interactions.

Approximately 30-50% of patients will relapse on AED withdrawal, although the risk of seizure relapse can be as low as 15% in carefully selected patients.[9] Factors associated with a higher risk of recurrence following AED withdrawal include the presence of neurological deficit or mental retardation, structural abnormalities, abnormal EEG, focal epilepsy and adult age at onset of epilepsy.

Most relapses occur during the first year after withdrawal.[10] If seizures recur, most patients regain seizure control when treatment is resumed.

CONTEXT

This guide considers the discontinuation of antiepileptic drugs (AEDs) in patients with epilepsy, with a focus on adults relative to children. It also briefly addresses the prophylactic use of AEDs (e.g. following traumatic brain injury, neurosurgery or a stroke), where evidence is limited. The use of the gabapentinoid AEDs for other indications is covered by a separate deprescribing guide.

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits Reduced seizure frequency	**Increased Benefit** • Older age (>25 years) at onset of epilepsy • Drivers • Long duration of epilepsy / history of poor seizure control • Developmental delay or IQ <70 • Symptomatic (structural) epilepsy • History of myoclonic seizures • Neurological abnormalities on examination / MRI / CAT scan • Epileptiform abnormality on EEG	**Decreased Benefits** • Short duration of epilepsy and low number of seizures • Long seizure-free interval (years) • No epileptiform abnormality on EEG before withdrawal • Generalised tonic-clonic or absence seizures, with no history of focal seizures • Benign Rolandic epilepsy in children (almost always remits and AEDs can be successfully withdrawn in most patients) • One or low numbers of AEDs • Sub-therapeutic AED dosing
Main Harms CNS adverse effects	**Reduced Harms** • Use of low doses	**Increased Harms** • Children • Females of child-bearing age • Use of multiple medications (risk of interactions)

RECOMMENDED DEPRESCRIBING STRATEGY

Multiple factors, such as the number of AEDs, previous seizure frequency, seizure type and associated risk of injury, and the non-driving period, may influence the tapering period.[8] A slow taper (e.g. over 6 months) allows observation and helps to document the minimally effective doses in case the seizures recur. However, a slow taper prolongs the non-driving period.

A Cochrane systematic review that examined the evidence for the rate of withdrawal of AEDs (rapid or slow tapering) and its effect on seizure recurrence could not provide any reliable conclusions.[24] In the absence of definitive data, the decision needs to be individualised with a middle path approach of withdrawal over 3-6 months and one drug should be withdrawn at a time.[9,25]

The taper rate for benzodiazepines (especially clonazepam) and barbiturates should be particularly slow (may take up to 6 months or longer) because of the possibility of withdrawal symptoms and/or seizure recurrence.[5,25]

If seizures recur, the patient should start therapy again on the previous effective drug and dose. They can resume driving once there have been no seizures for four weeks.[8]

Drug interactions require consideration when withdrawing an AED, particularly those that influence the metabolism of other drugs. For example, hyperthyroidism could occur in a patient taking levothyroxine if an enzyme-inducing AED, such as carbamazepine, is stopped.[26]

BACKGROUND

Epilepsy is a chronic brain condition with many aetiologies and characterised by recurrent seizures with no discernible pattern. There are more than 70 million patients with diagnosed epilepsy worldwide. Oral antiepileptic drugs (AEDs) are the principal treatment in most patients and, as discussed further below, enable the majority of patients with epilepsy to achieve a sustained seizure-free status. For some patients with drug-resistant epilepsy whose seizures do not respond to AEDs, surgical treatment may eliminate seizures.[1]

There is continuing debate about whether, when and how to stop AEDs in patients with epilepsy in remission.[1-4] When a patient with epilepsy has not had a seizure for a long time, the only way to find out if drug therapy is still needed is to withdraw it.[5] It has been suggested that discontinuation of drug treatment in patients with long-term seizure freedom is not often discussed and that many patients may be living with an unnecessary drug burden.[6]

Making a decision to withdraw AEDs in patients with epilepsy requires a careful assessment of patient- and condition-related factors, patient preferences, and associated risks and benefits.[5,7-10] Although unnecessary continuation of AEDs can expose patients to adverse effects, a premature withdrawal with subsequent seizure recurrence may be distressing for the patient and bring significant personal consequences. The final decision needs to be individualised, but there are guidelines and tools which can assist in making an evidence-based decision.

The development of seizures is common with many neurosurgical conditions. AEDs are the primary treatment for decreasing seizure incidence in this setting and traditionally were used for extended periods of time despite their significant side effects. However, the necessity for prolonged treatment with AEDs in neurosurgical conditions has come into question, although the evidence is relatively limited.[11]

EFFICACY

AEDs are effective in stopping seizures in at least two-thirds of patients with newly-diagnosed epilepsy.[1,7,8,12] It has been suggested that the prognosis of epilepsy may be improving due to the expansion in the number of AEDs now available. The early response to treatment is a good guide to the long-term prognosis, although not inevitably so, and the longer an epilepsy is active, the poorer is the long-term outlook. The presence of neurodeficit is also associated with reduced likelihood of achieving seizure control.

Overall, about 25-30% of patients have a poor response to any drug therapy, and a subgroup will benefit from epilepsy surgery.

It is impossible to know in patients who are seizure-free for a long time whether the absence of seizures is due to suppression by their AED, or due to remission of the epilepsy. A decision to continue or to stop AED treatment requires an individualised harm-benefit assessment.[8]

TRAUMATIC BRAIN INJURY

Evidence suggests that levetiracetam and phenytoin are equally effective for the primary prevention of early seizures following traumatic brain injury.[11,13,14] The suggested duration of treatment is only 7 days, with no benefit in preventing late post-traumatic seizures. Discontinuation of prophylactic treatment is then recommended, although if the patient has undergone a surgical procedure an extended treatment duration may be warranted.[11] It appears that after a 2-year seizure free period on AED therapy it would be appropriate to consider therapy withdrawal. For patients who develop post-traumatic epilepsy with 2 or more seizure events, the duration of treatment is less clear.[11]

SUBARACHNOID HAEMORRHAGE

There is insufficient evidence to provide a definitive duration of AED treatment (or even if AEDs should be used prophylactically) in patients following subarachnoid haemorrhage.[11,15,16] If AEDs are started, early discontinuation after securing any vascular abnormality is likely safe and beneficial. AEDs should not be routinely continued after recovery from subarachnoid haemorrhage.[11]

BRAIN TUMOUR

Evidence on the timing and rate of AED withdrawal in the context of adult brain tumours is also limited but it appears that after 1-2 years of seizure freedom drug withdrawal may be appropriate.[11] Perioperative AED prophylaxis for brain tumour surgery provides a statistically significant reduction in early (within the first post-operative week) postoperative seizure risk .[17]

POST-STROKE

There is insufficient evidence to guide the routine use of AEDs for the primary and secondary prevention of seizures after stroke.[18] In accordance with standard management approaches, repeated unprovoked post-stroke seizures require treatment with AEDs, but there is no good evidence to inform which drug(s) should be used and for how long.[18]

ADVERSE EFFECTS

Up to 90% of patients experience adverse effects from AEDs.[3,8] These include dizziness, sedation, ataxia, weight changes, hepatic dysfunction, blood dyscrasias and cognitive and neuropsychiatric symptoms, which can negatively affect quality of life. Children are at particular risk of cognitive and behavioural AED-induced problems, and cumulative - even minor - effects of these drugs may permanently affect educational progress and eventual intellectual functioning.[10]

Valproate and several other AEDs are known to be teratogenic, with significant implications for women of child-bearing age who have epilepsy. Despite awareness of the risks associated with valproate having been recognised for several decades, it is reported that pregnant women continue to be exposed to this medication.[19]

The AEDs, particularly those that affect the hepatic cytochrome P450 enzyme system, are often implicated in drug interactions.

There are also concerns regarding bone health and an increased risk of fractures as a long-term complication with AEDs, in particular the enzyme-inducing agents such as phenytoin, carbamazepine, and phenobarbitone/primidone.

FACTORS TO CONSIDER

Any consideration of AED discontinuation should prompt review of the original diagnosis and evidence supporting this. Patients with an equivocal history of seizures, who never fulfilled the diagnostic criteria for epilepsy (e.g. acute isolated symptomatic seizures due to metabolic or electrolyte disturbances, or prophylactic use of an AED) or who had potentially inappropriate clinical indications (e.g. behavioural management in patients with dementia; "turns" that may have been cardiac or psychiatric in origin) should be re-evaluated to see if there is a compelling reason for continuing AED treatment.[8]

Many factors are associated with recurrent seizures after AED withdrawal. Epilepsy is a disorder with vast heterogeneity. The aetiology and clinical manifestations (and treatment) vary from patient to patient. The accurate prediction of the risk of recurrent seizures after AED withdrawal in seizure-free patients is challenging.[1] A large individual participant data meta-analysis identified independent predictors of seizure recurrence after AED therapy is withdrawn.[21] The authors of the analysis subsequently developed an online calculator (http://epilepsypredictiontools.info/), that includes variables such as EEG abnormalities, duration of remission and total number of seizures, to assist clinicians when counselling patients.[22] It calculates an individualised risk of seizures in the 2 and 5 years after AED withdrawal, and the chance to be seizure-free after 10 years. The calculator lacks information on some prognostic variables, such as aetiology, current seizure classification and magnetic resonance imaging abnormalities, and should not be used as a substitute for an individualised discussion of the full range of harms and benefits, but it helps substantially to guide tailored choices by the doctor and patient.[3,4,8]

Adverse effect	CBZ	CLB	ETS	GBP	LCM	LEV	LTG	PGN	PER	PHB	PHT	TGB	TPM	VPA	VGB	ZNS
EARLY ONSET ADVERSE EVENTS																
Somnolence	-	🔴	🟡	🟡	🟡	🟡	🟡	🟡	-	🔴	-	🔴	🔴	-	🟡	🔴
Dizziness	-	🔴	🟡	🟡	🟡	🟡	🟡	-	-	-	🔴	🔴	🔴	-	🟡	🟡
Seizure aggravation	🟡	🟡	-	🟡	-	-	-	🟡	-	-	🟡	🟡	-	-	🔴	-
Gastrointestinal	🟡	-	🔴	🟢	-	🟢	-	-	-	-	-	-	-	🟡	-	🟡
Hypersensitivity (SJS/TEN)	🟡	-	🟡	-	-	-	🟡	-	-	🟡	🟡	-	🟡	-	-	🟡
Rash	🟡	-	-	-	-	-	🟡	-	-	-	🟡	-	-	-	-	-
LATE ONSET ADVERSE EVENTS																
Encephalopathy	-	-	-	-	-	-	-	-	-	-	🟡	-	-	🟡	🔴	-
Depression	-	-	🟡	-	-	-	-	-	-	🟡	🟡	🟡	-	-	🟡	-
Behavioural problems	-	-	-	-	-	🟡	-	-	🟡	🔴	🟡	🟡	🔴	-	🔴	🟡
Psychotic episodes	🟢	-	🔴	-	-	🟢	-	-	-	🟢	🟢	🟢	🟢	🟢	🔴	-
Blood cell disorders	🔴	-	🟡	-	-	-	-	-	-	🟡	🟡	-	-	🔴	-	-
Pancreatitis	-	-	-	🟢	-	-	-	-	-	-	-	-	-	🟡	-	-
Liver failure	-	-	-	-	-	-	-	-	-	-	-	-	-	🟡	-	-
Nephrolithiasis	-	-	-	-	-	-	-	-	-	-	-	-	🟢	-	-	🟡
Osteoporosis	🟢	-	-	-	-	-	-	-	-	🟡	🟡	-	-	🟢	-	-
Hyponatremia	🟢	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight gain	🟡	-	-	🟡	-	-	-	🔴	-	-	-	-	-	🟡	🟡	-
Weight loss	-	-	-	-	-	-	-	-	-	-	-	-	🟡	-	-	🟡
Cognition impaired	🟡	🟡	-	-	-	-	-	-	-	🔴	🟡	-	🟡	-	-	🟡
Teratogenicity	-	-	-	-	-	-	-	-	-	-	-	-	🟡	🔴	-	-
Retinal dysfunction	-	-	-	-	-	-	-	-	-	-	-	-	-	🔴	-	-

Key: – No increase 🟢 Low risk 🟡 Medium risk 🔴 High risk

Overview of adverse effects of individual AEDs[20]

CLB=clobazam; CBZ=carbamazepine; ETS=ethosuximide; GBP=gabapentin; LEV=levetiracetam; LCM=lacosamide; LTG=lamotrigine; PGN=pregabalin; PER=perampanel; PHB=phenobarbital; PHT=phenytoin; TPM=topiramate; VPA=valproate; VGB=vigabatrin; ZNS=zonisamide; SJS/TEN=Stevens-Johnson syndrome or toxic epidermal necrolysis.

However, no factor or model can exactly predict the risk of seizure recurrence in an individual and hence each patient needs to be assessed and counselled on an individual basis, with consideration of patient preferences.[1,9] For instance, as the patient must stop driving during dose reduction and for 3 months after the last dose, many patients choose to continue therapy indefinitely.[8]

Even if the clinician achieved perfect risk prediction, relapse risk alone is insufficient to inform clinical decision-making. An example where existing literature is nearly silent is that not all relapses are equal. The patient with prior generalised convulsions may prefer a more conservative approach than the patient with prior exclusively brief focal onset aware seizures.[3]

IN FAVOUR OF DEPRESCRIBING

Where AED adverse effects are present and reducing quality of life.

Women of childbearing age can avoid concern about the potential teratogenicity of AEDs upon their withdrawal, although switching can substantially reduce the risk. Sodium valproate has the highest risk of major congenital malformations. Other drugs are considered safer, with lamotrigine and levetiracetam having the lowest risk. For newer AEDs the risk of harm is still unknown.[8]

There is the potential to avoid drug interactions with AEDs. For instance, carbamazepine and phenytoin induce hepatic cytochrome P450 enzyme systems and can reduce the efficacy of oral contraceptive pills.

There may also be the desire to feel 'cured', with a sense of well-being and resulting improved quality of life, and to avoid the inconvenience and stigma of taking drugs daily.[8,9]

AGAINST DEPRESCRIBING

There is a lack of high-quality data to guide clinical practice. The available literature has its limitations, with most studies being relatively small observational studies with short follow-up periods.[9]

Overall, when compared with staying on AEDs, it seems that AED withdrawal increases the risk of seizures by two-fold, on average, which can be reduced by the careful selection of patients.[9,10] However, after 2 years of AED withdrawal, the risk of seizure recurrence in patients who have undergone AED withdrawal appears to be same as that of those who continue on AED therapy.[9,10] Clinicians might fear inability to regain seizure control in case of post-withdrawal relapse, but a previous failed AED withdrawal attempt does not predict future long-term control.[3,21] The possibility of inducing refractory epilepsy with AED withdrawal appears to be very low (perhaps 1-5%) in an individual who was previously well-controlled on AED therapy.[9]

The AED weaning period may be associated with significant anxiety. This can be regarding seizure recurrence, restricted social activities and a possible impact on employment and driving.[8] Seizure recurrence can have devastating physical, psychological and social consequences.[4,8] These may include injury, loss of self-esteem, stigma around seizures, unemployment and the inability to drive. The loss of driving privileges, even temporarily, may be the sole reason a patient decides against stopping AEDs.[8] In Australia patients must stop driving while being weaned off AEDs and for an additional 3 months after the last dose. If there is seizure recurrence, patients may resume driving if the previously effective treatment is reinstituted and there have been no seizures for 4 weeks.[8]

There may be alternatives to AED withdrawal for the patient to consider such as dose reduction or change of AED to address adverse effects, drug interactions or teratogenicity. Some patients may only need clarification and reassurance regarding the safety profile of their AED.[8]

There may be theoretical concerns about an increased risk of precipitating sudden unexpected death in epilepsy (SUDEP) if a patient is not taking AEDs.[3,23] However, seizure freedom was correlated with a 27-fold decreased odds of SUDEP[23] and most patients remain seizure-free after AED withdrawal, so the risk of SUDEP in these individuals seems to be low.[3]

Patients with a significant risk of seizure recurrence should not discontinue AEDs, even after a long period of seizure freedom.[8] They include patients with juvenile myoclonic epilepsy or focal epilepsy with a structural aetiology, who only have a small chance of successful AED withdrawal.

FACTORS THAT MAY MODIFY BENEFIT OF ANTIEPILEPTIC DRUGS

Possible Increase in Benefit of AEDs

Older age (>25 years) at onset of epilepsy

Drivers

Presence of comorbidities that may also benefit from some AEDs (e.g. bipolar disorder, migraine prophylaxis)

Long duration of epilepsy and/or history of poor seizure control

Developmental delay or IQ <70

Symptomatic (structural) epilepsy

History of myoclonic seizures

Neurological abnormalities on examination

Epileptiform abnormality on EEG

Abnormalities on magnetic resonance imaging or computed tomography

Recurrence after past attempts to withdraw all antiepileptic therapy

Possible Decrease in Benefit of AEDs

Short duration of epilepsy and low number of seizures

Long seizure-free interval (years)

No epileptiform abnormality on EEG before withdrawal

Generalised tonic-clonic or absence seizures, with no history of focal seizures

Benign Rolandic epilepsy in children (almost always remits and AEDs can be successfully withdrawn in most patients)

Sub-therapeutic AED dosing

FACTORS THAT MAY MODIFY HARM OF ANTIEPILEPTIC DRUGS

Possible Increase in Harm of AEDs

Children

Females of child-bearing age

Use of multiple medications (risk of interactions, overlapping adverse effects)

Possible Decrease in Harm of AEDs

Minimal number of AEDs

Appropriate dosage modification and plasma level monitoring (if applicable) of AEDs

Use of "newer" AEDs with less adverse effects and drug interactions

DISCONTINUATION SYNDROMES

Slow discontinuation of AEDs should be encouraged, and the duration of the tapering period should be tailored to the patient's needs and preference.[7,8] There appears to be no increased risk of status epilepticus or death following planned AED withdrawal.[9]

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