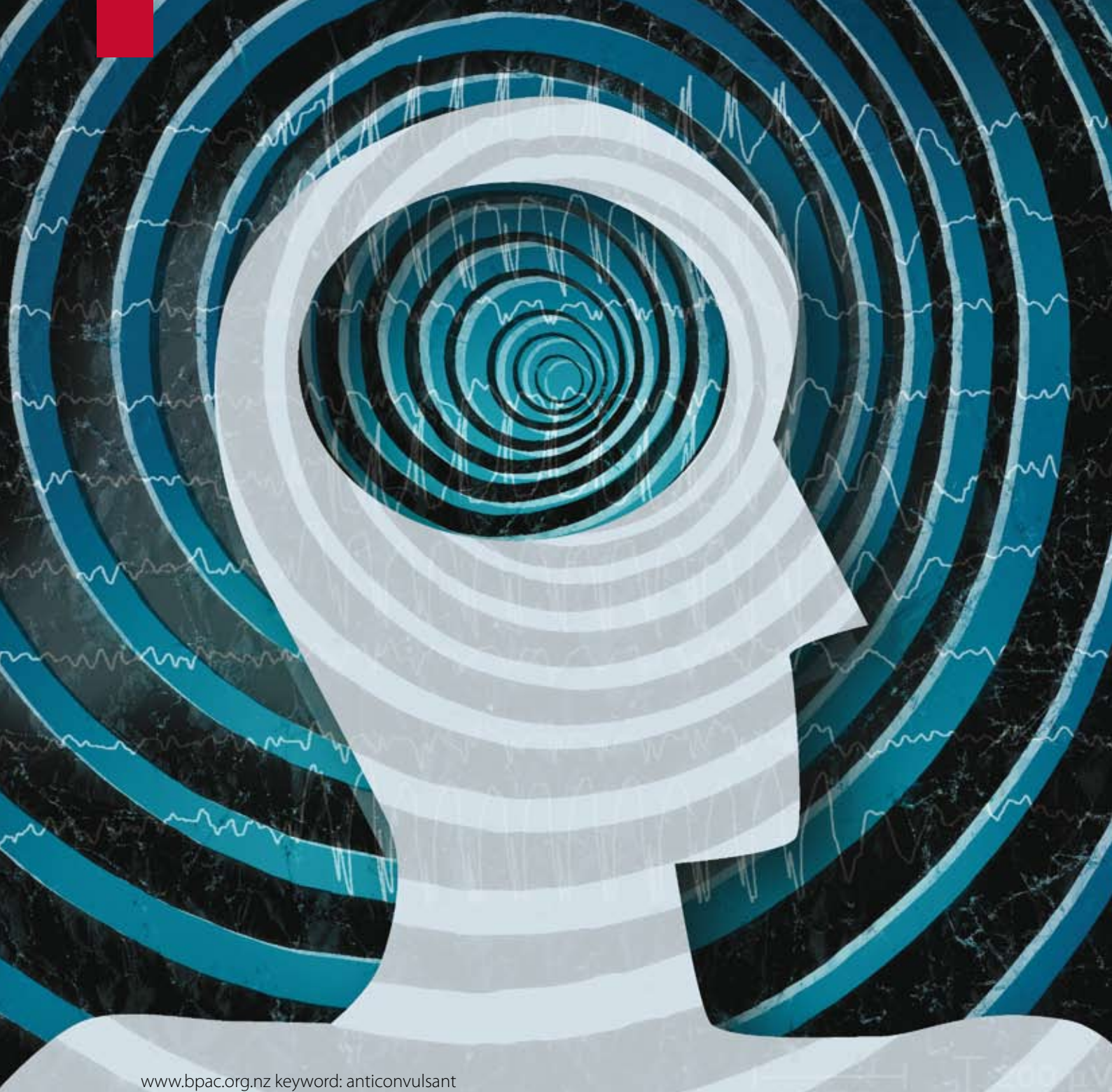

www.bpac.org.nz keyword: anticonvulsant

Prescribing issues associated with

anticonvulsant medications for EPILEPSY

Anticonvulsant medications are primarily used for the treatment of epilepsy, but may also have a place in the treatment of neuropathic pain, bipolar affective disorder and migraine prophylaxis.

Treatment with anticonvulsant medication is usually initiated after a history of two seizures, when further seizures are likely and when the benefit of treatment is anticipated to outweigh the adverse effects of medication. There is some evidence that initiating anticonvulsants after a single seizure may not result in improvement in the long term prognosis and may not reduce the risk of injury or mortality.[1,2]

Selection of an anticonvulsant is generally guided by the type of epileptic seizure, the risk of adverse effects and the presence of co-morbidities. Sodium valproate is used first line for generalised epilepsy syndromes. However, in women of child bearing potential, low dose lamotrigine (<200 mg/day) or carbamazepine are preferred because of the teratogenicity associated with sodium valproate (see page 11 for more information).[3] For patients with partial seizures, lamotrigine or carbamazepine are the preferred initial treatment choices.[4]

The goal of successful pharmacological treatment in epilepsy is the complete control of seizures. However for some people this may not be achievable without intolerable adverse effects.[5] Table 1 (over page) summarises the prescribing issues associated with common anticonvulsant medications.

Key concepts:

- Sodium valproate is used first line for generalised epilepsy syndromes except in women of child bearing potential
- For people with partial seizures and for women of child bearing potential lamotrigine or carbamazepine are the preferred initial treatment choices
- All anticonvulsant medications are associated with adverse effects which in rare circumstances can be potentially life-threatening
- An increased risk of anxiety, depression and suicidality has been associated with the use of anticonvulsants
- Some anticonvulsants, particularly phenytoin and carbamazepine, induce and increase the production of hepatic enzymes which can result in clinically significant drug interactions
- Routine therapeutic drug monitoring of anticonvulsants has limited clinical use

Table 1: Prescribing issues associated with common anticonvulsant medications[1, 6, 7, 8]

Multiple drug interactions and adverse effects may occur with all anticonvulsants. This table highlights the key areas of concern only. Seek further information if required.

Type of epilepsy	Adverse effects	Interactions	Monitoring	Notes
Sodium valproate				
All types of epilepsy First-line for generalised epilepsies	Common – weight gain, tremor, GI disturbance and hair loss (usually mild) Thrombocytopenia Hepatic failure Pancreatitis Other blood dyscrasias	Interacts with: ▪ Most other anticonvulsants, in general raising blood levels (particularly lamotrigine) ▪ TCAs ▪ Benzodiazepines ▪ Warfarin ▪ Aspirin (combination may result in easier bruising)	CBC, LFT, electrolytes at baseline, at three months and then annually Repeat tests if clinical suspicion of haematological or hepatic damage If warfarin commenced, check INR after 5–7 days (warfarin dose decrease may be required)	Avoid in women of childbearing potential Regarded as less sedating than other anticonvulsants
Carbamazepine				
Partial epilepsies (first-line), also in generalised or mixed epilepsies May worsen absence or myoclonic seizures	Common - nausea and vomiting, sedation, dizziness and ataxia Allergic rash (may be severe) Leucopenia Hyponatraemia (action not required if sodium stable above 125 mmol/L) Hepatotoxicity Other blood dyscrasias	Increased plasma concentration (increasing the risk of toxicity) if used with: ▪ Azole antifungals ▪ Macrolide antibiotics ▪ SSRIs e.g. fluoxetine Induces hepatic enzymes and reduces the effect of some medications including: ▪ Oestrogens and progestogens ▪ TCAs ▪ Warfarin ▪ Calcium channel blockers ▪ Statins	CBC, LFT, electrolytes at baseline Repeat tests if clinical suspicion of haematological or hepatic damage If warfarin commenced, check INR after 5–7 days (warfarin dose increase may be required)	Use slow release preparations Carbamazepine or lamotrigine are the anticonvulsant drugs of choice in pregnancy
Lamotrigine				
Most forms of epilepsy Alternate first-line for partial epilepsies	Common – allergic rash, headache, dizziness, blurred vision Serious allergic rash particularly: ▪ In children ▪ If dose increased rapidly ▪ If dose increased rapidly in combination with sodium valproate	Plasma concentration is increased by sodium valproate Plasma concentration is decreased by enzyme inducing anticonvulsants, oestrogens and progestogens	Not routinely indicated	Start low, go slow to avoid allergic rash Lamotrigine or carbamazepine are the anticonvulsant drugs of choice in pregnancy Avoid doses over 200 mg in women of childbearing potential

Type of epilepsy	Adverse effects	Interactions	Monitoring	Notes
Phenytoin				
Most forms of epilepsy May worsen absence or myoclonic seizures	Common - headache, tiredness, nausea, dizziness, drowsiness and insomnia Allergic rash (may be severe) Hirsutism, coarsening of facial features, acne and gingival hyperplasia Hepatotoxicity Blood dyscrasias	Induces hepatic enzymes and reduces the effect of some medications including: ▪ Oestrogens and progestogens ▪ TCAs ▪ Warfarin ▪ Calcium channel blockers ▪ Statins	CBC, LFT, electrolytes at baseline, at three months and then annually Repeat tests if clinical suspicion of haematological or hepatic damage If warfarin commenced, check INR after 5–7 days (warfarin dose increase may be required)	Therapeutic drug monitoring is useful due to non-linear pharmacokinetics e.g. when adjusting dose or adding additional medications with potential for interaction No longer widely used (narrow therapeutic index, long term toxicity)
Gabapentin				
Partial and secondarily generalised tonic-clonic seizures May worsen absence or myoclonic seizures	Common – dizziness, tiredness and nausea Weight gain, peripheral oedema Allergic rash (may be severe)	No clinically important drug interactions	Not routinely indicated	More widely used for neuropathic pain than epilepsy
Topiramate				
Generalised seizures Partial epilepsy	Common – ataxia, confusion, dizziness, tiredness Weight loss Acute angle closure glaucoma Kidney stones Cognitive impairment (up to 15%) particularly if used with sodium valproate	Can decrease serum concentration of digoxin and oral contraceptives by about 30%	Not routinely indicated	Often used as adjunctive therapy Patients should be advised to have adequate fluid intake

Notes:

Phenobarbitone and **primidone** are effective in most forms of epilepsy except absence seizures. However they are no longer widely used due to multiple adverse effects particularly on the CNS and respiratory system. Their use is associated with tolerance, dependence and in elderly people, with falls, osteoporosis and fractures. Primidone can be effective for essential tremor.

Ethosuximide is only effective for absence seizures. It may worsen generalised tonic clonic seizures. It is not widely used.

Vigabatrin is used in treatment of epilepsy (via special authority) that is not well controlled with other anticonvulsants. It may worsen absence or myoclonic seizures. Its use has been limited by the risk of concentric irreversible visual field defects, which are seen in 30–40% of patients.[9] These defects are usually initially asymptomatic and begin with bilateral nasal field loss. Refer for baseline visual field testing by perimetry with follow up tests every six months.[10]

Levetiracetam is only available by specialist application to the Special Access Panel. It is effective as adjunctive treatment of partial onset seizures with or without secondary generalisation.

Pregabalin is effective in the treatment of partial seizures with or without secondary generalisation. It is indicated in New Zealand as adjunctive therapy for patients with this type of epilepsy and also for neuropathic pain, however it is not subsidised.

Oxcarbazepine is not subsidised in New Zealand and therefore not widely used.

Adverse effects of anticonvulsant medication

All anticonvulsant medications are associated with adverse effects which may significantly impact on quality of life, contribute to non-compliance and in rare circumstances be potentially life-threatening.

Common dose related adverse effects

Initiation of anticonvulsants is associated with a number of very common dose related adverse effects including:

- Sedation, tiredness, dizziness, ataxia, tremor, slurred speech, confusion, decreased coordination
- Dry mouth, nausea, diarrhoea, GI disturbance

Typically these effects are of mild to moderate severity, are dose related and resolve within the first few weeks of treatment.

Adverse effects may be minimised by:[5]

- Choosing a slow release formulation when practical to avoid rapid rises in serum concentration
- Starting with a low dose and slowly increasing at one or two week intervals
- Using monotherapy if possible

Allergic rash is common with phenytoin, carbamazepine and lamotrigine. Gradual introduction of carbamazepine and lamotrigine is thought to significantly reduce the incidence of this. In general if a rash develops the medication should be withdrawn as allergic rashes have the potential to progress to severe skin and systemic reactions.

Mild haematological reactions can occur, e.g., leucopenia with carbamazepine and thrombocytopenia with sodium valproate. These changes are usually transitory, dose related and require no intervention, however in rare cases they may be life threatening.[11,12]

Potentially life-threatening adverse effects

Rare, life-threatening adverse effects with anticonvulsants include:[11,12]

- Skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis
- Systemic reactions e.g. hypersensitivity resulting in multi-organ failure
- Haematological reactions including thrombocytopenia, aplastic anaemia, agranulocytosis and leucopenia
- Hepatic failure

Routine monitoring has not been shown to be of value in identifying these conditions. Instead patients should be advised of the risks and asked to report any warning signs such as rash, fever, bruising and other signs of infection such as sore throat.

Abrupt withdrawal of any anticonvulsant medication has the potential to precipitate seizures or status epilepticus. Before an anticonvulsant medication is stopped e.g. because of a serious adverse effect, an additional anticonvulsant should first be added that can quickly obtain therapeutic levels. Consultation with a specialist is recommended.

Anticonvulsants and suicidality

An increased risk of anxiety, depression and suicidality has been associated with the use of anticonvulsants. It is recommended that all patients taking anticonvulsants for any indication are routinely assessed for symptoms of these conditions. This recommendation is based on a recent FDA meta-analysis of clinical trials involving 11 anticonvulsant drugs, reporting that patients taking these drugs had twice the risk of suicidal thoughts and behaviours than those patients taking a placebo (0.43% compared to 0.22%).[13]

See BPJ 14, June 2008 “Anticonvulsants associated with suicidality”.

Anticonvulsants and osteoporosis

Anticonvulsant medications (particularly phenytoin, sodium valproate, carbamazepine, primidone and phenobarbitone) are associated with a reduction in bone mineral density and an increased fracture risk.[14, 15]

Many guidelines recommend that all patients taking any anticonvulsant medication should be offered lifestyle and dietary advice to reduce the risk of osteoporosis.[14, 16] Vitamin D supplementation should be considered for patients who have additional risk factors for osteoporosis.[17]

See BPJ 17, October 2008 "Prevention of osteoporosis".

Dose adjustments

Dose adjustments may be required for patients with impaired hepatic function

Most anticonvulsant medications are metabolised by the liver. If hepatic function is impaired, lower doses may be required to avoid elevated serum drug levels. Gabapentin, pregabalin, levetiracetam and vigabatrin are excreted without metabolism by the liver and should not require dose adjustment in patients with impaired hepatic function.

Dose adjustments may be required for patients with impaired renal function

A reduction in renal excretion of some anticonvulsants and/or their active metabolites may result in an increase in adverse effects or toxicity and doses may need to be reduced.

Dose adjustment in elderly people

In many elderly people, changes in renal or hepatic function and altered pharmacodynamic response may increase the likelihood of adverse effects. Therefore lower doses of anticonvulsants may be required.

Enzyme induction

Some anticonvulsants, particularly phenytoin and carbamazepine induce and increase the production of hepatic enzymes. This can result in clinically significant drug interactions by increasing the metabolism of some co-administered drugs e.g. oral contraceptives, warfarin, calcium channel blockers and many antipsychotic and antidepressant drugs.

Enzyme induction can be associated with an increase in gamma-glutamyl transferase (GGT). An isolated increase in GGT (up to 1.5 – 2 times upper limit of normal) is not usually of concern unless it is associated with increases in transaminases which may signal hepatotoxicity, requiring further investigation. Alcohol use can increase the GGT level further.

Other enzyme inducing anticonvulsants include phenobarbitone and primidone. Topiramate and oxcarbazepine are inducers at high dose but at lower doses have some inhibiting properties.[6] Sodium valproate is an inhibitor of specific isoenzymes and typically increases the concentrations of other anticonvulsants, particularly lamotrigine and the active metabolite of carbamazepine. Doses of lamotrigine should be halved while taking sodium valproate.

Routine therapeutic drug monitoring of anticonvulsants has limited clinical usefulness (except phenytoin)

Therapeutic drug monitoring (TDM) has traditionally been used to guide treatment decisions for patients with epilepsy.[7, 18] However, there have been no randomised studies that demonstrate that TDM has a positive impact on clinical outcomes in patients with epilepsy.[7] It is now recognised that the usefulness of routine TDM has been overemphasised and that optimal treatment should rely primarily on a careful assessment of the patient's clinical state.[7, 19]

Despite this, TDM may be of benefit in some circumstances for some patients, because of the pharmacokinetic

variability of anticonvulsant medications and the often unpredictable nature of epilepsy.[7] However, a clinical decision should usually not be made based on the serum concentration alone.

TDM may be beneficial in the following specific clinical situations;[7]

- When pharmacokinetics (and consequently, dose requirement) alter, e.g. in children, in elderly people, in pregnancy, in people with co-morbidities or when a drug interaction is suspected
- When increasing the dose of an anticonvulsant with non-linear pharmacokinetics e.g. phenytoin (see sidebar)
- If seizures persist despite an apparently adequate dosage
- If toxicity is suspected or when it is difficult to assess this clinically, e.g. in children or people with mental disability

The importance of steady state

If TDM is to be clinically useful and comparable, samples should be taken after steady state has been reached and should be collected at the same time of day e.g. usually just prior to the next dose. The time to reach steady state varies widely for anticonvulsants and additionally there are diurnal fluctuations in the serum concentrations of drugs which have short elimination half lives (e.g. carbamazepine. sodium valproate).

For further information see Best Tests, July 2009, "Practical considerations for therapeutic drug monitoring".

Phenytoin and non-linear pharmacokinetics

Most drugs used in clinical practice exhibit linear pharmacokinetics. That is, they have a constant half-life and, at steady state, the dose rate is directly proportional to the plasma concentration. In linear pharmacokinetics, if the dose is doubled the resultant plasma concentration is doubled. Phenytoin, however, exhibits non-linear pharmacokinetics as its metabolism becomes saturated at plasma concentrations associated with therapeutic use. Increases in phenytoin dose should be made cautiously in small increments to avoid toxicity, e.g. a dose increase of 30 mg. After each dose increase, monitor clinical effect and plasma concentration.

Special issues in the management of epilepsy

Females with epilepsy

For women of child bearing potential with epilepsy, the main concerns are adequate contraception and when pregnancy is planned, safety during pregnancy and labour. GPs can be actively involved in helping educate women with epilepsy about the pros and cons of treatment with anticonvulsants and provide advice on contraception and pre-conception care.

Anticonvulsants and contraception

Several anticonvulsants, in particular carbamazepine and phenytoin, increase the metabolism of oestrogen and progestogen and therefore reduce the effectiveness of the combined oral contraceptive (COC). Topiramate and lamotrigine may also reduce the effectiveness of the COC to a lesser extent. Sodium valproate does not affect oestrogen metabolism.

It is recommended that women taking enzyme inducing anticonvulsants who require contraception, be prescribed a COC containing at least 50 µg of oestrogen. Mid cycle bleeding can be an indication that the oestrogen dose is inadequate. In this situation the options are to advise that:[16]

- The oestrogen dose can be increased by taking two 30 µg pills per day (and in some cases up to two 50 µg pills per day)

and/or

- The COC can be taken continuously for three months with a four day break between cycles

and/or

- A barrier form of contraception be used concurrently

or

- An alternative method of contraception may be more appropriate.

The use of enzyme inducing anticonvulsant medications (e.g. carbamazepine, phenytoin) may also reduce the effectiveness of the progesterone only pill (POP). The POP therefore is not recommended for women who are taking anticonvulsants.

Barrier methods, depot medroxyprogesterone acetate (DMPA, Depo-Provera), standard intrauterine contraceptive devices (IUCD) and the levonorgestrel intrauterine system (Mirena) are effective and may be suitable choices.[20] However, because both DMPA and some anticonvulsants are associated with weight gain and lower bone mineral density with long term use, DMPA may not be a first line choice in some women.[20,21] If DMPA is used, it is recommended that the interval between injections is shortened to ten weeks.[11]

If emergency contraception is required for women taking enzyme inducing anticonvulsants, it is usually recommended that twice the normal dose of the progesterone-only emergency contraceptive pill should be taken.[16, 21] An IUCD fitted within five days of unprotected intercourse could be offered as an alternative.[20]

Pre-conception care

As many anticonvulsants are associated with an increased risk of neural tube defects, it is recommended that all women of child bearing potential who are taking anticonvulsants take folic acid 5 mg/day.[11,22] Once pregnant, folic acid (5 mg daily) should be continued for the first trimester.

Women with epilepsy who are planning a pregnancy should be referred for specialist advice. The combined input of both a neurologist and an obstetrician is usually required.

Anticonvulsants and pregnancy

Carbamazepine, or lamotrigine in doses under 200 mg/day, when used as monotherapy, are the anticonvulsant drugs of choice in pregnancy.[23, 24]

The use of the majority of anticonvulsant medications increases the risk of teratogenicity. The risk of major congenital malformation in the general population is approximately 2–3% compared to 4–7% in women taking anticonvulsant medications.[22] The risk is higher for the older anticonvulsant medications (especially sodium valproate) when combination therapy is required or when anticonvulsants are taken at higher doses.[22, 23]

The type of congenital malformation varies with the type of anticonvulsant medication, e.g., sodium valproate is associated with neural tube, craniofacial, skeletal, cardiovascular and urogenital defects. Exposure of the foetus to sodium valproate may also be associated with development delay and cause cognitive impairment.[25]

In some women, anticonvulsant treatment can be safely withdrawn before pregnancy, although this should be confirmed by a specialist. If tonic clonic seizures are likely to occur during pregnancy then an anticonvulsant should be continued because these seizures are likely to be harmful to both mother and foetus.

The challenge is to strike a balance between the risk of uncontrolled seizures and the risk of teratogenicity. Ideally, use a single anticonvulsant at the lowest possible dose to maintain seizure control.

Anticonvulsants and breast feeding – guidelines advise that most women taking anticonvulsants can breast feed safely.[16]

Limited alcohol is usually acceptable

Alcohol is a CNS depressant and lowers seizure threshold. Although a very small amount of alcohol can be enough to trigger a seizure in some people with epilepsy, the majority can safely consume a limited amount of alcohol. Excess consumption of alcohol, binge drinking or acute withdrawal from alcohol can induce seizures, even in a patient with no history of epilepsy.

A small to modest intake (one to two drinks per occasion, totalling no more than three to six drinks per week) is suggested as a safe upper level of alcohol intake. This amount has been shown not to alter serum concentrations of anticonvulsants and not to increase the frequency of seizures.[26]

Best practice tip: It is safer to advise patients that some alcohol is allowed while on anticonvulsant medication, rather than risk a situation where patients do not take their medication when they drink.

Epilepsy and driving

Any person who has a seizure, irrespective of cause, should receive advice about driving.

Patients who have had a single seizure, without a diagnosis of epilepsy, are subject to the same driving restrictions as patients with a formal diagnosis of epilepsy.

A patient with epilepsy controlled by treatment may still be able to hold a licence to drive a private motor vehicle. However, a diagnosis of epilepsy for a driver of a commercial vehicle will result in the permanent loss of this class of licence, in most circumstances.

A medical practitioner is required to notify the Director of Land Transport Safety if they are aware that a patient with uncontrolled seizures continues to drive. This should be discussed with the patient first who should be offered the opportunity to seek a second opinion if required.

Full information can be found in "Medical aspects of fitness to drive – A Guide for Medical Practitioners" which is available online at: **www.landtransport.govt.nz/licensing/docs/medical-aspects.pdf**

This guide has recently been updated and there have been some minor changes to the section on epilepsy.

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References

1. Wiebe S, Tellez-Zenteno JF, Shapiro M. Management of a first seizure. An evidence-based approach to the first seizure. Epilepsia 2008;49(suppl 1):50-7.
2. Elger CE, Schmidt D. Modern management of epilepsy: A practical approach. Epilepsy Behav 2008;12:501-39.
3. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet 2007;369:1016-26.
4. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet 2007;369:1000-15.
5. Schmidt D. Drug Treatment of epilepsy: Options and limitations. Epilepsy Behav 2009;15:56-65.
6. Stein MA, Kanner AM. Management of newly diagnosed epilepsy. A practical guide to monotherapy. Drugs 2009;69(2):199-222.
7. Patsalos PN, Berry DJ, Bourgeois BFD. Antiepileptic drugs – best practice guidelines for therapeutic drug monitoring: A position paper by the subcommission of therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008;49(7):1239-76.
8. Medsafe. Medicine data sheets. Available from www.medsafe.govt.nz (Accessed October 2009).
9. Hitiris N, Brodie MJ. Modern antiepileptic drugs: guidelines and beyond. Curr Opin Neurol 2006;19:175-80.
10. Willmore LJ, Abelson MB, Ben-Menachem, et al. Vigabatrin:2008 Update. Epilepsia 2009:50(2);163-73.
11. Iorio M L, Moretti U, Colcera S, et al. Use and safety profile of antiepileptic drugs in Italy. Eur J Clin Pharmacol 2007;63:409-15.
12. Arroyo S, de la Morena A. Life-threatening adverse events of antiepileptic drugs. Epilepsy Res 2001:47:155-74.
13. Hesdorffer DC, Kanner AM. The FDA alert on suicidality and antiepileptic drugs: Fire or false alarm? Epilepsia 2009;50(5):978-86.
14. Clinical Knowledge Summaries (CKS). Epilepsy. CKS Clinical topic. Available from www.cks.nhs.uk (Accessed October 2009).
15. Vestergaard P. Epilepsy, osteoporosis and fracture risk – a meta-analysis. Acta Neurol Scand 2005;112:277-86.
16. National Institute for Clinical Excellence (NICE). The diagnosis and management of the epilepsies in adults and children in primary and secondary care. NHS, UK 2004. Available from www.nice.org.uk (accessed October 2009).
17. Medicines and Healthcare products Regulatory Agency (MHRA). Antiepileptics: adverse effects on bone. Drug safety advice 2009:2(9). Available from www.mhra.gov.uk (accessed October 2009).
18. Anderson GD. Pharmacokinetic, pharmacodynamic and pharmacogenetic targeted therapy of antiepileptic drugs. Ther Drug Monit 2008;30(2):173-80.
19. Berkovic SF. Treatment with anti-epileptic drugs. Aust Fam Phys 2005;34(12):1017-20.
20. Crawford PM. Managing epilepsy in women of childbearing age. Drug Safety 2009;32(4):293-307.
21. Schwenkhagen AM, Stodieck SRG. Which contraception for women with epilepsy? Seizure 2008;17:145-50.
22. Kluger BM, Meador KJ. Teratogenicity of antiepileptic medications. Semin Neurol 2008:28(3);328-35.
23. Meador KJ, Penovich P, Baker, GA et al. Antiepileptic drug use in women of childbearing age. Epilepsy Behav 2009;15:339-43.
24. Tomson T, Battino. Teratogenic effects of antiepileptic drugs. Seizure 2008;17:166-71.
25. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004;75:1575-83.
26. Gordon E, Devinsky O. Alcohol and Marijuana: Effects on epilepsy and use by patients with epilepsy. Epilepsia 2001:42(10);1266-72.