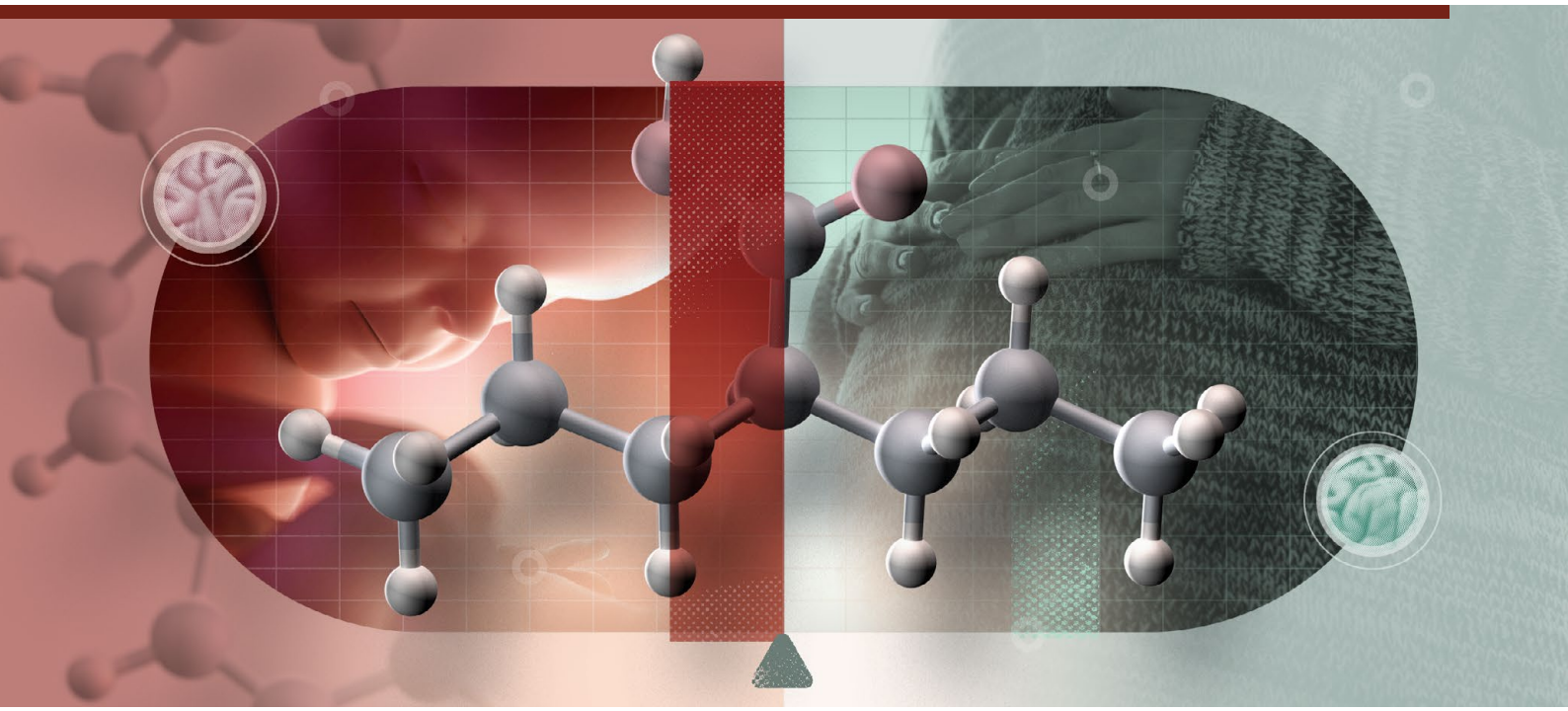


Balancing the benefits and risks of prescribing **antiepileptic medicines in women**

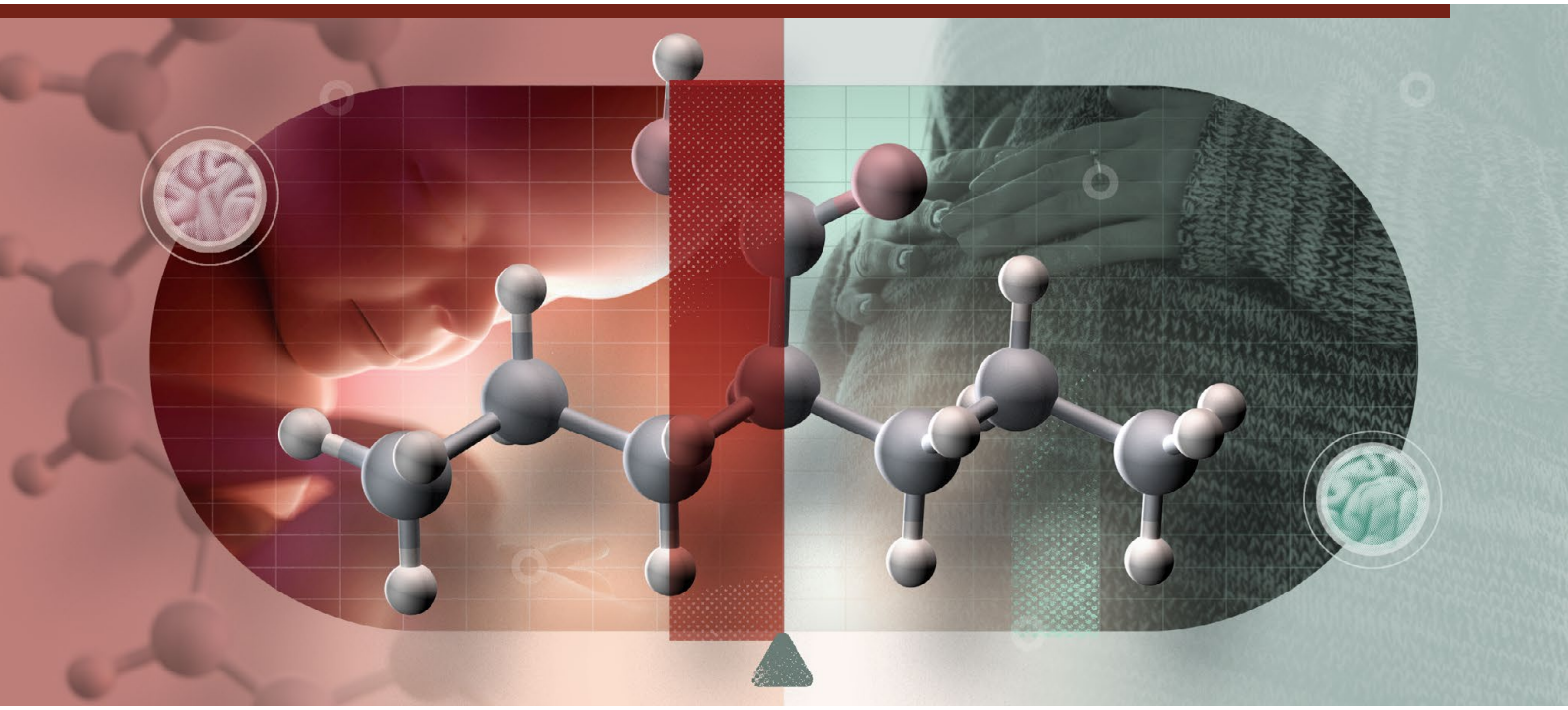
Antiepileptic medicines reduce the risk of seizures in people with epilepsy and are sometimes used as part of the management of people with mood disorders, neuropathic pain or migraine. The use of antiepileptic medicines, particularly sodium valproate, during pregnancy can result in harm to the fetus and cognitive and developmental issues in children. It is important that antiepileptic medicines are not withheld in women who require this treatment, but appropriate precautions need to be put in place to minimise the risk of harm.

Update 2022: New data suggests that topiramate is associated with an increased risk of neurodevelopmental disorders of the same magnitude, or higher, than sodium valproate.

The 2022 Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) is a large observational study that included 4,494,926 children born between 1996 and 2007; 24,825 children were exposed to anti-epileptic medicines during gestation and of these, 16,170 were born to mothers with epilepsy. In children whose mothers had epilepsy but were not taking anti-epileptic medicines during pregnancy, there was a baseline eight-year cumulative incidence of 1.5% for autism spectrum disorder and 0.8% for intellectual disability. For children of mothers taking topiramate or valproate, the eight-year cumulative incidence for autism spectrum disorder and intellectual disability was 4.3% and 3.1%, and 2.7% and 2.4%, respectively. The use of topiramate was associated with an adjusted hazard ratio of 2.8 (95% CI, 1.4 - 5.7) for autism spectrum disorder and 3.5 (95% CI, 1.4 - 8.6) for intellectual disability. Higher doses of topiramate were associated with a further increased risk. These results suggest a strong association between the use of topiramate during pregnancy and neurodevelopmental disorders in the child.

Until now, there has been a lack of data to fully assess the magnitude of risk with topiramate compared to other anti-epileptics, but this new evidence suggests that topiramate poses a similar risk of neurodevelopmental adverse effects as sodium valproate (or potentially higher) therefore the same level of caution when considering use of topiramate in females of child-bearing potential should be applied.

Bjørk M-H, Zoega H, Leinonen MK, *et al*. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. JAMA Neurol 2022;79:672. doi:10.1001/jamaneurol.2022.1269.



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KEY PRACTICE POINTS:

- Antiepileptic medicines provide significant benefit to people with epilepsy, but they are associated with an increased risk of adverse effects during pregnancy; the risk of major congenital malformations is 4–7% compared to 2–3% in the general population, and the risk is greatest with sodium valproate, higher doses or concurrent use of multiple antiepileptic medicines
- Women of child-bearing age should be made aware of the potential risks of antiepileptic medicines, but also of the risk of seizures during pregnancy, i.e. if an appropriate antiepileptic medicine is not taken
- Two forms of effective contraception should be used by women who are taking an antiepileptic medicine; N.B. some hormonal contraceptives interact with enzyme-inducing antiepileptic medicines
- Pregnancy should be planned so an antiepileptic medicine regimen with the lowest risk for the individual woman, while balancing treatment efficacy, can be put in place
- If an antiepileptic medicine is being considered for a condition such as neuropathic pain or migraine prophylaxis, consider other suitable treatment options first in a woman of child-bearing age

Antiepileptic medicines are used in epilepsy, mood disorders and other conditions

Antiepileptic medicines, also known as anticonvulsants, are a first-line pharmacological treatment for seizure control in people with epilepsy. They are also an option for symptom management in some mood disorders, e.g. bipolar disorder, neuropathic pain and for migraine prophylaxis. The potential benefits of using antiepileptic medicines can vary widely depending on the indication and individual response to treatment. The risks, however, are the same; antiepileptic medicines are associated with an increased risk of teratogenic effects when used during pregnancy (see below).

It is recommended that antiepileptic medicines are only used when essential, and at the lowest effective dose. **Sodium valproate should not be initiated in women of child-bearing age for focal epilepsy, pain, headache or psychiatric illness** unless there are no other treatment options available and the benefits and risks have been considered.[1,2]

In epilepsy, the use of antiepileptic medicines is almost always essential, including during pregnancy.[3] Sodium valproate is

usually regarded as the most effective antiepileptic medicine for generalised epilepsy; however, due to its higher teratogenic risk (see later), levetiracetam or lamotrigine should be trialled first-line in women of child-bearing age – although sodium valproate may ultimately be required to achieve seizure control. Sodium valproate is not generally considered first line treatment for focal epilepsy – lamotrigine and carbamazepine are preferred, with levetiracetam a second line alternative.

In bipolar disorder, lithium, olanzapine, quetiapine and fluoxetine are typically first-line options, along with non-pharmacological interventions. If patients do not respond sufficiently to these medicines, sodium valproate or lamotrigine may be trialled.[4]

In neuropathic pain, tricyclic antidepressants, gabapentin or pregabalin are considered equally effective first-line pharmacological treatment options. Topical capsaicin cream can be used for localised pain. Carbamazepine is the first-line treatment for trigeminal neuralgia.[5]

In migraine, people who are unable to effectively control symptoms during acute attacks may consider using prophylactic medicines. Typically, prophylactic treatment is only required for a short time period. Beta-blockers (nadolol or metoprolol) are first-line options, amitriptyline is an alternative. Nortriptyline, venlafaxine or propranolol (not if using rizatriptan) can also be trialled. Topiramate or sodium valproate are "last resort" options if all other treatments are ineffective.[6]

For further information, see
- Bipolar disorder: **www.bpac.org.nz/BPJ/2014/July/bipolar.aspx**
- Neuropathic pain: **www.bpac.org.nz/BPJ/2016/May/pain.aspx**
- Migraine: **www.bpac.org.nz/2017/headache.aspx**

Antiepileptic medicines have adverse effects on fetal development

The use of antiepileptic medicines during pregnancy is associated with an increased risk of congenital malformations, lower intelligence quotient (IQ) scores and higher need for educational intervention in the affected children.[1] The combination of these adverse effects has been referred to as Fetal Anti-Convulsant Syndrome (FACS).[1]

In pregnancies where a woman has taken an antiepileptic medicine, rates of major congenital malformations are 4–7% compared to 2–3% in the general population.[1] However, rates vary according to the antiepileptic medicine(s) used and dose. Most of the available data on teratogenicity comes from females taking antiepileptic medicines for epilepsy, but the risks are thought to be similar when used for other conditions, such as bipolar disorder.[7]

There is no evidence that antiepileptic medicines are associated with specific malformations. Major and minor congenital malformations* may affect almost any body system, including cardiac, renal, urinary, gastrointestinal, skeletal and neural tube defects, and facial dysmorphisms.[8]

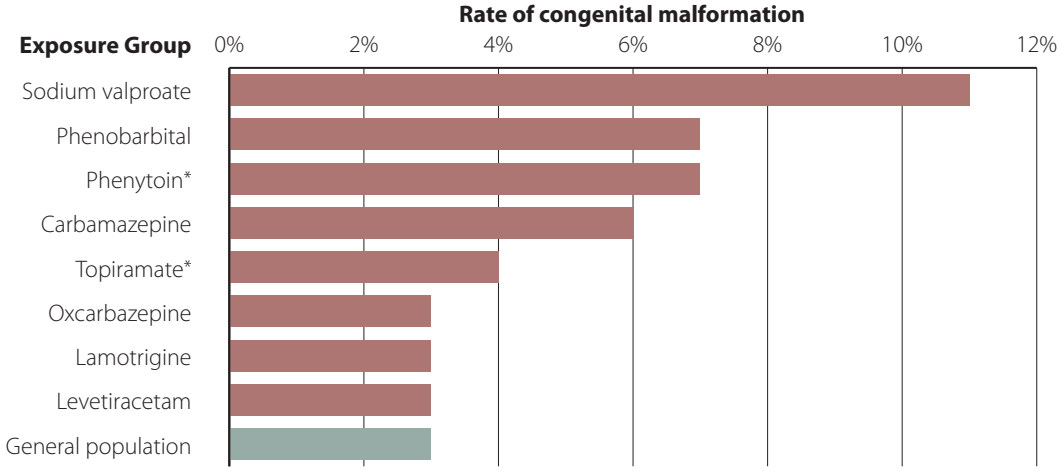


Figure 1: Rates of major congenital malformations associated with antiepileptic medicine use[1, 8] N.B. this data does not include neurodevelopmental adverse effects in affected children.

* Data on risks associated with phenytoin or topiramate use are based on limited numbers of pregnancies

The use of antiepileptic medicines during pregnancy may also increase the risk of obstetric complications such as spontaneous abortion or a child being born small for gestational age.[9–11]

* Major congenital malformations are those that have significant medical, social or cosmetic consequences, such as atrial or ventricular septal defects, dysplastic hip or hypospadias. Minor congenital malformations are defined as a structural anomaly or dysmorphic feature which does not require surgical intervention or treatment, such as epicanthal folds, hypertelorism (widely spaced eyes), microstomia (small mouth), or a broad or flat nose.[8, 12]

Sodium valproate is associated with the highest risk

The risk of congenital malformations is highest with the use of sodium valproate, where approximately 10–11% of pregnancies are affected, followed by phenobarbital, phenytoin and carbamazepine (Figure 1).[1, 8] Available data do not provide sufficient information to estimate risk for all available antiepileptic medicines, such as topiramate, lacosamide, gabapentin or pregabalin.[13] Low rates of congenital malformations have been reported for lamotrigine and levetiracetam.[1, 8] However, this does not necessarily mean that there is no risk from using these medicines during pregnancy.

Multiple medicines are associated with higher risk

A meta-analysis reported a rate of congenital malformations of 17% when more than one antiepileptic medicine was taken during pregnancy.[13]

Higher doses are associated with higher risk

Higher doses are associated with higher rates of congenital malformations for a number of antiepileptic medicines, including sodium valproate, carbamazepine, lamotrigine and phenobarbital.[8] For example, congenital malformations occur in approximately 6% of pregnancies when less than 650 mg/day of sodium valproate is taken, compared to over 25% of pregnancies when more than 1450 mg/day is taken.[14] Typical maintenance doses of sodium valproate for the treatment of epilepsy are 1000–2000 mg, daily.[15]

Sodium valproate is also associated with neurodevelopmental effects

Exposure to sodium valproate during pregnancy can have adverse outcomes on a child's intelligence and educational achievement. Children who are exposed to sodium valproate during pregnancy have on average IQ scores 8–11 points lower and inferior language skills compared to children who are not exposed, and may have increased risks of autism spectrum disorder and attention deficit hyperactivity disorder.[1, 16, 17] There are currently less data available regarding the neurodevelopmental effects of antiepileptic medicines other than sodium valproate. However, reduced intelligence and lower educational achievement has been reported in children exposed to multiple antiepileptic medicines taken concurrently during pregnancy.[13, 17]

Discussing the risks of antiepileptic medicines

Although antiepileptic medicines are often initiated in secondary care, or prescribed on the recommendation of a clinician in secondary care, dispensing data show that the majority of prescriptions are subsequently written by a general practitioner.[18] Clinicians in primary care are therefore well-placed to discuss the potential benefits and adverse effects of antiepileptic medicines with patients.

Women of child-bearing age who are prescribed an antiepileptic medicine (or being considered for treatment) should be:[19]

- Informed of the risks of seizures during pregnancy
- Informed of the potential teratogenic effects of antiepileptic medicines
- Involved in discussions regarding lower risk or alternative treatment options, if clinically appropriate
- Provided with appropriate contraception
- Encouraged to plan a pregnancy in advance

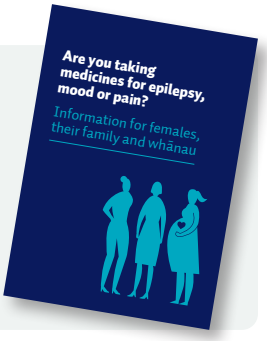
Start discussions about benefits and risks early

Women of childbearing age, and their caregivers if appropriate (e.g. if the patient is a child), need to be well-informed about the risks associated with antiepileptic medicine use during pregnancy and the need for contraception, before they initiate these medicines and before they become sexually active. Clinicians should revisit these issues with young patients as they mature.

Balance the risk: It is also important to discuss the risks associated with not taking antiepileptic medicines and the need for patients to keep taking their medicines if they become pregnant. Reassure patients and caregivers that despite increases in risk, the majority of children exposed to sodium valproate or other antiepileptic medicines do not have congenital malformations.[3]

Patients, caregivers and clinicians can take away different impressions of what is discussed during a clinical encounter. Check the understanding of the conversation at the end of the consultation.

Patient information about antiepileptic medicines is available from: **www.acc.co.nz/assets/provider/antiepileptic-medicine-females-family.pdf**



Prescribe appropriate contraception

It is essential that women of childbearing age who are taking an antiepileptic medicine are also taking appropriate contraception. The risks of congenital malformations associated with antiepileptic medicine use during pregnancy are highest in the first trimester, before many people realise they are pregnant.[1]

Ideally, women taking an antiepileptic medicine should be prescribed two forms of recommended contraception, i.e. one of the options in Table 1 plus condoms, taking into account the potential for medicines interactions with enzyme-inducing antiepileptic medicines (Table 2).[1, 20] If women are prescribed an oral contraceptive, ensure they know what to do if a dose is missed (especially important if taking progesterone-only pills) or if vomiting or diarrhoea occurs.

Long-acting reversible contraceptives are the most effective form of contraception. This includes intrauterine devices and progestogen implants (if not using an enzyme-inducing antiepileptic medicine), with less than 1% of women experiencing pregnancy after one year of use (Table 1).[21, 22]

Medroxyprogesterone acetate injections, progesterone-only or combined hormonal pills have low rates of failure in circumstances of perfect use, however, with typical use 6-9% of women experience an unintended pregnancy after one year.[21, 22]

Patient information leaflets covering various contraceptive options are available from: **www.nzf.org.nz/nzf_70421**

Contraceptive options for women taking enzyme-inducing antiepileptic medicines

The use of combined hormonal contraceptives or progesterone-only pills or implants is not recommended within 28 days of taking an enzyme-inducing antiepileptic medicine (Table 2).[13] Some clinicians may be familiar with the practice of using a high-dose hormonal contraceptive, e.g. 50 micrograms of ethinylestradiol, in patients taking an enzyme-inducing antiepileptic medicine with the purpose of counteracting the change in hepatic metabolism.[23] However, the contraceptive effectiveness of this method has not been studied.[13] A wider variety of contraceptive options are now available, making it easier to avoid this combination of medicines. For patients taking lamotrigine, the use of combined hormonal contraceptives is not recommended as these medicines reduce circulating levels of lamotrigine and can lead to an increase in seizures.[13]

Table 1: Preferred contraceptive methods in females taking antiepileptic medicines.[13, 20]

Contraceptive method: use one recommended option plus condoms	**% of women experiencing pregnancy after one year of typical use** [21,22]	**Antiepileptic medicine**	
		Enzyme-inducing†, e.g. carbamazepine, phenytoin	**Non-enzyme inducing**†**,** e.g. sodium valproate, lamotrigine, levetiracetam
Intrauterine device (levonorgestrel or copper)	< 1%	✓	✓
Progesterone-only implant	< 1%	Not recommended*	✓
Medroxyprogesterone acetate injections	6%	✓	✓
Combined hormonal oral pill or vaginal ring	9%	Not recommended*	✓ (except for lamotrigine)**
Progesterone-only pill§	9%	Not recommended*	✓
Condom	18%	✓	✓
If emergency contraception is required:		Copper IUD recommended Alternative: 3 mg levonorgestrel (2 tablets)	Standard emergency contraceptive options, i.e. 1.5 mg levonorgestrel or copper IUD

* Not recommended due to a decrease in contraceptive efficacy

** Not recommended if taking lamotrigine due to a decrease in antiepileptic efficacy

† See Table 2

§ Subsidised progesterone only pills need to be taken within a three hour window to ensure contraceptive effectiveness

Emergency contraception options

A copper IUD is recommended for emergency contraception for women taking enzyme-inducing antiepileptic medicines.[13, 20] Alternatively, levonorgestrel 3 mg (two tablets) can be prescribed, however, this is an unapproved dose and the effectiveness of this option has not been adequately studied.[15, 20]

Standard emergency contraceptive options can be used for patients taking other antiepileptic medicines.[20]

Some patients experience nausea after taking an oral levonorgestrel emergency contraceptive; if vomiting occurs within three hours a repeat dose is recommended.[20]

Plan before a pregnancy

For women with epilepsy, planning prior to pregnancy is especially important to manage the combined risks of pregnancy, their epilepsy and the antiepileptic medicines used to control seizures. Approximately one-third of women with epilepsy have an increased frequency of seizures during pregnancy.[13] Seizures during pregnancy are a serious complication and carry mortality risks for both the mother and unborn child, including changes in fetal heart rate, reduced birth weight, pre-term birth and pregnancy loss.[3, 26] Uncontrolled seizures are also a risk factor for sudden unexpected death in epilepsy (SUDEP).[13]

Women with epilepsy should be encouraged to discuss pregnancy plans at least six to twelve months in advance so that treatment can be altered as necessary to establish good seizure control with a medicine regimen which has the lowest possible risk of harm to the fetus.[1, 3] Pregnancy planning in women with epilepsy results in improved seizure control during pregnancy, fewer pregnancies exposed to sodium valproate and fewer changes in antiepileptic medicine regimen during pregnancy.[27] Obstetric care is necessary for women with epilepsy who become pregnant. Planning prior to pregnancy is also important for women regularly taking antiepileptic medicines for indications other than epilepsy.

If pregnancy occurs without prior planning, urgent referral to or discussion with the patient's neurologist or psychiatrist, and an obstetrician is recommended; ideally within 48 hours of the pregnancy being confirmed.[1] Advise patients not to stop taking their medicines of their own accord as this may cause frequent and prolonged seizures which places their unborn child and themselves at risk.

A higher folic acid dose is recommended for females taking antiepileptic medicines

Folic acid supplementation is recommended from a minimum of four weeks before to at least 12 weeks after conception to reduce the risk of neural tube defects. A higher than usual dose of folic acid (5 mg per day) is recommended for females taking antiepileptic medicines.[28] Folic acid supplementation reduces the background risk of spontaneous neural tube defects, however, it does not reduce the teratogenic effects of antiepileptic medicines.[1, 13]

Further resources

The Accident Compensation Corporation (ACC), Ministry of Health, Health Quality & Safety Commission and Foetal Anti-Convulsant Syndrome New Zealand have developed booklets for healthcare professionals and patients regarding the risks associated with the use of antiepileptic medicines

Table 2: Antiepileptic medicines and their effects on hepatic enzymes[20, 24, 25]

Enzyme-inducing antiepileptic medicines	Non-enzyme-inducing antiepileptic medicines
■ Carbamazepine	■ Clobazam
■ Oxcarbazepine	■ Clonazepam
■ Phenobarbital	■ Ethosuximide
■ Phenytoin	■ Gabapentin
■ Primidone	■ Lacosamide
■ Rufinamide	■ Lamotrigine
■ Topiramate	■ Levetiracetam
	■ Pregabalin
	■ Retigabine
	■ Sodium valproate
	■ Vigabatrin

to aid discussions with patients about how to mitigate these risks. PDFs of these booklets can be downloaded from the web addresses below, or contact **treatmentinjury@acc.co.nz** to order printed copies.

- Information for healthcare professionals: **www.acc.co.nz/assets/provider/antiepileptic-medicine-females-healthcare-providers.pdf**
- Information for patients: **www.acc.co.nz/assets/provider/antiepileptic-medicine-females-family.pdf**

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N.B. Expert reviewers are not responsible for the final content of the article.

References:

1. Accident Compensation Corporation (ACC). Benefits and risks of taking antiepileptic medicine for females. Information for healthcare professionals. 2017. Available from: www.acc.co.nz/assets/provider/antileptic-medicine-females-healthcare-providers.pdf (Accessed Oct, 2018).
2. Medicines and Healthcare Products Regulatory Agency (MHRA). Valproate medicines (Epilim, Depakote): contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met. 2018. Available from: www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-contraindicated-in-women-and-girls-of-childbearing-potential-unless-conditions-of-pregnancy-prevention-programme-are-met (Accessed Oct, 2018).
3. National Institutes for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. 2018. Available from: www.nice.org.uk/guidance/cg137 (Accessed Oct, 2018).
4. National Institute for Health Care Excellence (NICE). Bipolar disorder: assessment and management. 2018. Available from: www.nice.org.uk/guidance/cg185 (Accessed Oct, 2018).
5. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17:1113-e88. doi:10.1111/j.1468-1331.2010.02999.x
6. British Association for the Study of Headache (BASH). Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type headache, cluster headache, medication-overuse headache. 2010. Available from: www.bash.org.uk/wp-content/uploads/2012/07/10102-BASH-Guidelines-update-2_v5-1-indd.pdf (Accessed Oct, 2018).
7. Jazayeri D, Graham J, Hitchcock A, et al. Outcomes of pregnancies in women taking antiepileptic drugs for non-epilepsy indications. Seizure 2018;56:111–4. doi:10.1016/j.seizure.2018.02.009
8. Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol 2018;17:530–8. doi:10.1016/S1474-4422(18)30107-8
9. Richards N, Reith D, Stitely M, et al. Antiepileptic drug exposure in pregnancy and pregnancy outcome from national drug usage data. BMC Pregnancy Childbirth 2018;18:84. doi:10.1186/s12884-018-1728-y
10. Kilic D, Pedersen H, Kjaersgaard MIS, et al. Birth outcomes after prenatal exposure to antiepileptic drugs - a population-based study. Epilepsia 2014;55:1714–21. doi:10.1111/epi.12758
11. Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet 2015;386:1845–52. doi:10.1016/S0140-6736(15)00045-8
12. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev 2016;11:CD010224. doi:10.1002/14651858.CD010224.pub2
13. Royal College of Obstetricians & Gynaecologists. Epilepsy in pregnancy (green-top guideline No.68). Royal College of Obstetricians & Gynaecologists 2016. Available from: www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg68/ (Accessed Oct, 2018).
14. Pennell PB. Prescribing antiepileptic drugs to women of reproductive age. Lancet Neurol 2018;17:485–6. doi:10.1016/S1474-4422(18)30154-6
15. New Zealand Formulary (NZF). NZF v76. 2018. Available from: www.nzf.org.nz (Accessed Oct, 2018)
16. Haskey C, Galbally M. Mood stabilizers in pregnancy and child developmental outcomes: a systematic review. Aust N Z J Psychiatry 2017;51:1087–97. doi:10.1177/0004867417726175
17. Lacey AS, Pickrell WO, Thomas RH, et al. Educational attainment of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2018;89:736–40. doi:10.1136/jnnp-2017-317515
18. Ministry of Health. Pharmaceutical Claims Collection. 2018.
19. Angus-Leppan H, Liu RSN. Weighing the risks of valproate in women who could become pregnant. BMJ 2018;361:k1596.
20. Faculty of Sexual and Reproductive Healthcare. Clinical Effectiveness Unit Clinical Guidance: Drug interactions with hormonal contraception. 2017. Available from: www.fsrh.org/standards-and-guidance/current-clinical-guidance/drug-interactions/ (Accessed Oct, 2018).
21. World Health Organisation (WHO). Selected practice recommendations for contraceptive use. Third edition. 2016. Available from: www.who.int/reproductivehealth/publications/family_planning/SPR-3/en/ (Accessed Oct, 2018).
22. Faculty of Sexual and Reproductive Healthcare. Progestogen-only implants. 2014. Available from: www.fsrh.org/standards-and-guidance/documents/cec-ceu-guidance-implants-feb-2014/ (Accessed Oct, 2018).
23. Reimers A. Contraception for women with epilepsy: counseling, choices, and concerns. Open Access J Contracept 2016;7:69–76. doi:10.2147/OAJC.S85541
24. Reimers A, Brodtkorb E, Sabers A. Interactions between hormonal contraception and antiepileptic drugs: Clinical and mechanistic considerations. Seizure 2015;28:66–70. doi:10.1016/j.seizure.2015.03.006
25. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol 2006;61:246–55. doi:10.1111/j.1365-2125.2005.02529.x
26. Sveberg L, Svalheim S, Taubøll E. The impact of seizures on pregnancy and delivery. Seizure 2015;28:35–8. doi:10.1016/j.seizure.2015.02.020
27. Abe K, Hamada H, Yamada T, et al. Impact of planning of pregnancy in women with epilepsy on seizure control during pregnancy and on maternal and neonatal outcomes. Seizure 2014;23:112–6. doi:10.1016/j.seizure.2013.10.003
28. Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Vitamin and mineral supplementation and pregnancy. 2015. Available from: www.ranzcog.edu.au/Statements-Guidelines/ (Accessed Oct, 2018).

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