

Neuropathic pain in pregnancy: gabapentinoids & antiepileptic drugs

When treating neuropathic pain in a woman who is pregnant, the use of gabapentinoids (e.g. gabapentin) or an antiepileptic drug (AED) (e.g. levetiracetam, lamotrigine) is a last line option. This is due to the limited availability of data for safe use during pregnancy. Other options should be trialled first. These include: non-pharmacological therapies (e.g. physical therapy), topical agents (e.g. lidocaine, capsaicin), tricyclic antidepressants (e.g. amitriptyline), or serotonin and noradrenaline reuptake inhibitors (e.g. venlafaxine). The gabapentinoids have similar efficacy to tricyclic antidepressants and of the AEDs, carbamazepine has evidence for treating trigeminal neuralgia.

Safety in pregnancy

Data from pregnancy registries in epilepsy have found that there is a higher rate of major congenital malformations in infants exposed to AEDs (4-7%) compared to the general population (2-3%).⁽¹⁾ Risk factors include higher daily doses and therapy with more than one AED. The risk of congenital malformations (e.g. neural tube, cardiac, craniofacial and skeletal defects) is greatest with valproate and lowest with levetiracetam, lamotrigine and gabapentin. However, the newer agents have less data available to assess their risk in pregnancy.^(1,2) There is also the possibility of long-term impairment of neurodevelopment in children exposed to AEDs *in utero*.⁽³⁾

Table: Safety of gabapentinoids and AEDs in pregnancy and efficacy in neuropathic pain

Antiepileptic drug	Safety in pregnancy	Efficacy in neuropathic pain
Gabapentin	Major congenital malformations: 1.47%* (95% CI 0.26-3.64) Based on data from three studies (n=190) The available data does not identify an increased risk of congenital malformations. ⁽⁴⁾ Small for gestational age and neurologic abnormalities have been reported in exposed infants e.g. failure to gaze up (sunsetting). ⁽⁵⁾	There is reasonably good evidence of efficacy for gabapentin and pregabalin in diabetic neuropathy and post herpetic neuralgia. These effects are modest, with numbers needed to treat (NNTs) ranging from 4-14 for ≥50% pain intensity reduction over baseline. ⁽⁶⁾
Pregabalin	Lack of human data prevents risk assessment. ⁽⁵⁾ Animal reproduction data suggest moderate risk. ⁽⁵⁾ Use gabapentin.	
Levetiracetam	Major congenital malformations: 1.77%* (95% CI 0.98-2.79) Based on data from three studies (n=817)	Effectiveness not established. (7,8)
Lamotrigine	Major congenital malformations: 2.31%* (95% CI 1.87-2.78) Based on data from seven studies (n=4195)	Effectiveness not established. (7,9)
Topiramate	Major congenital malformations: 4.28%* (95% CI 2.65-6.29) Based on data from three studies (n=473) First trimester use increases the risk of oral clefts. A cohort study found the risk ratio for oral clefts at doses ≤100 mg was 1.64 (95% CI 0.53–5.07) and for doses >100 mg it was 5.16 (95% CI 1.94–13.73). ⁽¹⁰⁾	Effectiveness not established. ⁽⁶⁾
Carbamazepine	Major congenital malformations: 4.93%* (95% CI 3.84-6.16) Based on data from 30 studies (n=4666)	Effective in trigeminal neuralgia. ⁽¹¹⁾
Valproate	Major congenital malformations: 10.93%* (95% CI 8.9-13.13) Based on data from 26 studies (n=2565) Risk outweighs benefit for pain indications. Do not use.	Effectiveness not established. ⁽⁶⁾

*Prevalence of major malformations (any type) calculated from a systematic review of 50 studies that compared pregnancy exposure with AED monotherapy, to the children of women without epilepsy or women who had epilepsy but who were not treating it with an AED.⁽²⁾
Major congenital malformations are any structural abnormalities of the body or organs present from birth (e.g. skeletal, orofacial, cardiac malformations).

General considerations when prescribing gabapentinoids or AEDs for neuropathic pain in pregnancy

- Weigh the potential harms against the benefits. The benefit may outweigh the harm when treating epilepsy but may not when treating neuropathic pain.
- Avoid first trimester exposure.
- Use the lowest possible dose. Higher doses are associated with higher pregnancy risk. The dose used in epilepsy may be higher than the dose required to manage pain.
- Consider the possibility of neonatal abstinence syndrome if used near term.
- Folic acid 0.8 mg daily should be taken 1-3 months before conception and during the first trimester. When the risk of neural tube defects is high, folic acid 5 mg is recommended until term (e.g. carbamazepine).⁽¹²⁾

References

1. ACC: Supporting treatment safety [Internet]. [cited 2018 Apr 6]. Available from: <https://www.acc.co.nz/for-providers/treatment-safety/>
2. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. In: The Cochrane Library [Internet]. John Wiley & Sons, Ltd; 2016 [cited 2018 Apr 6]. Available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD010224.pub2/full>
3. Martindale: The Complete Drug Reference [Internet]. London: The Royal Pharmaceutical Society of Great Britain; [cited 2018 Jun 8]. Available from: <https://www.medicinescomplete.com/mc/martindale/current/>
4. USE OF GABAPENTIN IN PREGNANCY [Internet]. [cited 2018 Apr 6]. Available from: <http://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-GABAPENTIN-IN-PREGNANCY/>
5. Briggs GG, Freeman RK, Towers CV, Forinash AB. Drugs in pregnancy and lactation [Internet]. 11th ed. Philadelphia (PA): Wolters Kluwer (US); 2017 [cited 2018 Jun 8]. Available from: <https://wolterskluwer.vitalsource.com/#/>
6. Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice AS, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. In: The Cochrane Library [Internet]. John Wiley & Sons, Ltd; 2013 [cited 2018 Apr 6]. Available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD010567.pub2/full>
7. IBM Micromedex® [Internet]. Greenwood Village (CO): Truven Health Analytics (US); [cited 2018 Jun 28]. Available from: <http://www.micromedexsolutions.com/micromedex2/librarian>
8. Wiffen PJ, Derry S, Moore RA, Lunn MP. Levetiracetam for neuropathic pain in adults. In: The Cochrane Library [Internet]. John Wiley & Sons, Ltd; 2014 [cited 2018 Apr 6]. Available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD010943.pub2/full>
9. Wiffen PJ, Derry S, Moore RA. Lamotrigine for chronic neuropathic pain and fibromyalgia in adults. In: The Cochrane Library [Internet]. John Wiley & Sons, Ltd; 2013 [cited 2018 Apr 6]. Available from: <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD006044.pub4/full>
10. Hernandez-Diaz S, Huybrechts KF, Desai RJ, Cohen JM, Mogun H, Pennell PB, et al. Topiramate use early in pregnancy and the risk of oral clefts: A pregnancy cohort study. *Neurology*. 2018 Jan 23;90(4):e342–51.
11. Haanpää ML, Gourlay GK, Kent JL, Miaskowski C, Raja SN, Schmader KE, et al. Treatment Considerations for Patients With Neuropathic Pain and Other Medical Comorbidities. *Mayo Clin Proc*. 2010 Mar;85(3 Suppl):S15–25.
12. UpToDate® [Internet]. Hudson (OH): Wolters Kluwer Clinical Drug Information Inc. (US); [cited 2018 Jun 28]. Available from: <http://www.uptodate.com/>