# Medications for Neuropathic Pain

**B.C. Provincial Academic Detailing Service** **December 2018**

Current clinical practice guidelines addressing the management of neuropathic pain recommend antiepileptic medications (eg, gabapentin, pregabalin) and antidepressant medications (eg, amitriptyline, nortriptyline, duloxetine, venlafaxine) as first line pharmacotherapeutic choices.[1,2,3]

## Participants in this PAD education session will have the opportunity to discuss:

1. The evidence for antiepileptic and antidepressant medications for neuropathic pain as identified in Cochrane systematic reviews and regulatory reviews conducted by the US Food and Drug Administration (US FDA) and Health Canada
2. The available evidence for combining medications for neuropathic pain with attention to drug interactions
3. Drug information relevant to the prescribing and monitoring of specific medications for neuropathic pain

## Evidence for Practice

### Applicability

Antiepileptic and antidepressant medications recommended as first line choices by clinical practice guidelines for neuropathic pain have been tested in randomized controlled trials where the duration of follow up is typically 12 weeks or less.[2] The majority of trials enrolled participants with painful diabetic neuropathy or post herpetic neuralgia.[4-8]

### Efficacy

Cochrane systematic reviews of gabapentin, pregabalin and duloxetine estimate that approximately 3 to 4 people out of 10 achieve a substantial reduction in pain (50% or greater) with medication, versus 1 to 2 people receiving placebo.[5-7] The limited evidence for tricyclic antidepressants does not confidently support calculating a similar estimate.[9-12]

### Dose Response

For painful diabetic neuropathy and post herpetic neuralgia, regulatory reviews judge that titrating to doses of gabapentin > 1800 mg per day, pregabalin > 300 mg per day or duloxetine > 60 mg per day does not provide additional significant benefit.[13-23]

### Onset of Effect

In clinical trials of gabapentin, pregabalin and duloxetine, evidence of an effect (generally measured as a reduction in average pain scores) emerges by the first week.[13,14,16,18,19,21-24] The limited evidence for tricyclic antidepressants does not confidently support estimating onset of effect.[9-12]

### Combination Therapy

The available clinical trial evidence does not clearly inform which combinations of medications are safe and effective for neuropathic pain.[25] Recent observational studies identify that the co-prescription of gabapentin or pregabalin with an opioid is associated with an increased risk of opioid-related death that appears dose-related.[26,27]

## Medications for Neuropathic Pain: Evidence Brief using the Cochrane Library[1-25]

| Antiepileptic Medications | | | Antidepressant Medications | | |
|---|---|---|---|---|---|
| ■ gabapentin | 37 trials | 5914 participants | ■ duloxetine | 9 trials | 2776 participants |
| ■ pregabalin | 14 trials | 3680 participants | ■ venlafaxine | 6 trials | 460 participants |
| ■ carbamazepine | 10 trials | 480 participants | ■ amitriptyline | 17 trials | 1342 participants |
| ■ lacosamide | 5 trials | 1863 participants | ■ desipramine | 5 trials | 177 participants |
| ■ lamotrigine | 12 trials | 1511 participants | ■ nortriptyline | 6 trials | 310 participants |

**Other antiepileptic medications** ■ levetiracetam ■ oxcarbazepine ■ topiramate ■ valproic acid, divalproex sodium
**Other antidepressant medications** ■ imipramine
**Opioids** ■ hydromorphone ■ morphine ■ oxycodone ■ tramadol ■ transdermal fentanyl ■ methadone
**Other pharmacotherapies** ■ medical cannabinoids ■ acetaminophen with or without codeine ■ nonsteroidal anti-inflammatory drugs
**Combinations** ■ gabapentin or pregabalin + opioid ■ gabapentin or pregabalin + tricyclic antidepressant ■ tricyclic antidepressant + opioid

■ *high quality evidence* ➲ Cochrane reviewers are very confident that their evidence review identifies the likely therapeutic effect
■ *moderate or good quality evidence* ➲ Cochrane reviewers judge that their evidence review is a good indication of the likely therapeutic effect
■ *lacks clear evidence* ➲ Cochrane reviewers are not confident in the quality, quantity or consistency of the evidence for most outcomes
■ *limited or no therapeutic value* ➲ Cochrane reviewers judge that the available evidence indicates limited or no clinically relevant benefit

**Limitations of the evidence which preclude very confident conclusions about benefits and harms:**[1-25]

- trials were few in number or small in size (eg, fewer than 200 participants per treatment arm)
- short trial durations limit satisfactory assessment of efficacy and safety
- data on specific benefits (eg, numbers of people with a substantial reduction in pain) or harms (eg, serious adverse events) were not available from all trials
- incomplete accounting for participants' outcomes after they withdrew from the trial or discontinued treatment
- methods of blinding participants and personnel to treatment assignments were inadequately implemented or described
- manufacturer sponsorship of all or most of the identified trials

Carbamazepine Health Canada pain indication: symptomatic relief of pain of trigeminal neuralgia during exacerbation[26]

| Antiepileptic Medications | Starting Dose [Dosage Range] | Elimination Half-life | Approximate Monthly Cost [without fee or markup] | BC PharmaCare Coverage |
|---|---|---|---|---|
| **GABAPENTIN (Neurontin, generics)** 100, 300, 400 mg caps 600, 800 mg tabs | 300 mg once a day[1] [100 – 1800 mg per day][1] | 5-7 hours[1] | 100 mg: $1 \| 300 mg: $3 900 mg: $10 \| 1800 mg: $20 | Regular Coverage |

**Health Canada pain indications:** none[2] | dosages are those reported in the US prescribing information for the post herpetic neuralgia indication which recommends ➲ day 1: single 300 mg dose, day 2: 300 mg BID, day 3: 300 mg TID, titrated up to 1800 mg per day (divided TID) if needed[1]

**Drug Information Synopsis**

- **lower starting doses** suggested by the University of British Columbia's Therapeutics Initiative evidence review, and Canadian and Australian guidelines: gabapentin 100 mg per day[3-5]
- **maximum useful dose** US FDA review determines that doses greater than 1800 mg per day do not provide additional significant benefit[1,6]
  - target doses in clinical trials identified in the 2017 Cochrane systematic review ranged widely from 600 to 3600 mg per day | trials also varied by dose titration schedules and gabapentin formulations used[7]
  - bioavailability as doses increase, bioavailability decreases | 900 mg per day: 60% bioavailability | 3600 mg per day: 33% bioavailability[1]
- **renal elimination (lower maximum doses)**[1,2]
  CrCl 30-59 mL/min: maximum 1400 mg per day | CrCl 16-29 mL/min: maximum 700 mg per day
  CrCl 15 mL/min: maximum 300 mg per day | CrCl < 15 mL/min: reduce dose in proportion to CrCl
- **onset** reduction in pain (measured as mean pain scores) is evident in clinical trials by the first week[1,6]
- **most common adverse events** identified in US FDA review: *dose related* somnolence, *dose related* dizziness, peripheral edema[6]
- **respiratory depression** Health Canada 2016 safety review identified risk factors: respiratory or neurological disease, renal impairment, elderly, concomitant opioid use, concomitant central nervous system depressant use[2,8]
- **international utilization data** trends show increasing gabapentin and pregabalin prescribing, an increase in concomitant use with opioids and benzodiazepines, and indications of potential misuse and abuse[9-14]
- **withdrawal symptoms** agitation, confusion, insomnia, nausea, pain, sweating[1,2] | tapering tool: MedStopper ➲ medstopper.com
- **Canadian Agency for Drugs in Technology and Health (CADTH) 2018 review** found a lack of clear evidence to support gabapentin use in fibromyalgia and neuropathic pain conditions other than painful diabetic neuropathy and post herpetic neuralgia[15]
- **back pain** 2018 systematic review concludes that gabapentin and pregabalin do not reduce pain or disability in low back pain with or without radiating leg pain or in lumbar radicular pain[16]

| **Gabapentin for Painful Diabetic Neuropathy** *2017 Cochrane systematic review*[7] | | discontinuation due to adverse event | NNH 30 |
|---|---|---|---|
| NNT 6 ●●●●●● | substantial reduction in pain (reduction from baseline ≥ 50%) | any adverse event | NNH 8 |
| NNT 5 ●●●●● | much or very much improved (patient's impression of change) | dizziness | NNH 8 |
| **Gabapentin for Post Herpetic Neuralgia** *2017 Cochrane systematic review*[7] | | ataxia | NNH 9 |
| NNT 7 ●●●●●●● | substantial reduction in pain (reduction from baseline ≥ 50%) | somnolence | NNH 11 |
| NNT 10 ●●●●●●●●●● | much or very much improved (patient's impression of change) | peripheral edema | NNH 20 |

*NNT number needed to treat; ● responder; ● non responder; NNH number needed to harm; estimates derived from pooled gabapentin doses & formulations*

| Antiepileptic Medications | Starting Dose [Dosage Range] | Elimination Half-life | Approximate Monthly Cost [without fee or markup] | BC PharmaCare Coverage |
|---|---|---|---|---|
| **PREGABALIN (Lyrica, generics)**<br>25, 50, 75, 150, 200, 225, 300 mg caps | 75 mg BID or 50 mg TID[1]<br>[25 – 600 mg per day][1] | 6 hours[1] | 75 mg BID: $20<br>150 mg BID: $25 | No Regular Coverage<br>Palliative Care Coverage |

**Health Canada pain indications:** diabetic peripheral neuropathy, post herpetic neuralgia, spinal cord injury, fibromyalgia[1]

**Drug Information Synopsis**

- **lower starting doses** suggested by Canadian and Australian guidelines: pregabalin 25 or 75 mg per day[2,3]
- **maximum useful dose** Health Canada and the US FDA determine that doses greater than 300 mg per day do not provide additional significant benefit relative to the increased risk of adverse events[1,4-7]
- **renal elimination (lower maximum doses)**[1]
  - CrCl 30-60 mL/min: maximum 300 mg per day
  - CrCl 15-30 mL/min: maximum 150 mg per day
  - CrCl < 15 mL/min: maximum 75 mg per day
- **onset** reduction in pain (measured as mean pain scores) is evident in clinical trials within the first week[1,4,5,7]
- **most common adverse events** identified by US FDA and Health Canada reviews: *dose related* somnolence, dizziness, peripheral edema, ataxia, confusion, blurred vision, dry mouth, constipation, dyspepsia, weight gain[1,4-7]
- **ophthalmologic** *dose related* abnormal vision**,** blurred vision, diplopia[1,4,5,7]
- **heart failure** 2016 American Heart Association scientific statement: pregabalin may exacerbate underlying heart failure[8]
  - 2016 Ontario cohort study of adults aged ≥ 66 found no difference in heart failure risk between pregabalin and gabapentin[9]
- **international utilization data** trends show increasing gabapentin and pregabalin prescribing, an increase in concomitant use with opioids and benzodiazepines, and indications of potential misuse and abuse[10-15] | pregabalin is a controlled substance in the United States due to euphorigenic properties[4,5,16]
- **withdrawal symptoms** insomnia, nausea, headache, anxiety, hyperhidrosis, diarrhea[1,7] | tapering tool: MedStopper ➲ medstopper.com
- **back pain** 2018 systematic review concludes that gabapentin and pregabalin do not reduce pain or disability in low back pain with or without radiating leg pain or in lumbar radicular pain[17]

| **Pregabalin for Painful Diabetic Neuropathy** *2009 Cochrane systematic review*[18] | | discontinuation due to adverse event | NNH 16 |
|---|---|---|---|
| NNT 8 ●●●●●●●● | substantial reduction in pain (reduction from baseline ≥ 50%) | any adverse event | NNH 7 |
| NNT 6 ●●●●●● | much or very much improved (patient's impression of change) | dizziness | NNH 6 |
| | | somnolence | NNH 8 |
| **Pregabalin for Post Herpetic Neuralgia** *2009 Cochrane systematic review*[18] | | discontinuation due to adverse event | NNH 10 |
| NNT 5 ●●●●● | substantial reduction in pain (reduction from baseline ≥ 50%) | any adverse event | NNH 7 |
| NNT 6 ●●●●●● | much or very much improved (patient's impression of change) | dizziness | NNH 5 |
| | | somnolence | NNH 8 |

*NNT number needed to treat; ● responder; ● non responder; NNH number needed to harm; estimates are for pregabalin 300 mg per day*

| Antidepressant Medications | Starting Dose [Dosage Range] | Elimination Half-life | Approximate Monthly Cost [without fee or markup] | BC PharmaCare Coverage |
|---|---|---|---|---|
| **DULOXETINE (Cymbalta, generics)**<br>30, 60 mg delayed release caps | 60 mg once a day[1]<br>[30 – 120 mg once a day][1] | 12 hours[2] | 30 mg: $15<br>60 mg: $30 | Limited Coverage<br>Palliative Care Coverage |

**Health Canada pain indications:** diabetic peripheral neuropathy, fibromyalgia, chronic low back pain, osteoarthritis of the knee[1]
**Health Canada contraindications include:** hepatic impairment (case reports of hepatic injury), CrCl < 30 mL/min, uncontrolled glaucoma[1]

**Drug Information Synopsis**

- **lower starting dose** suggested by Canadian and Australian guidelines: duloxetine 30 mg once a day[3,4]
- **maximum useful dose** Health Canada and the US FDA determine that doses greater than 60 mg per day do not provide additional significant benefit but do increase the risk of adverse events[1,2,5,6]
- **onset** reduction in pain (measured as mean pain scores) is evident in clinical trials within the first week[1,2,5]
- **most common adverse events** identified by US FDA and Health Canada reviews: *dose related* nausea (taking with food may reduce initial nausea), dry mouth, constipation, anorexia, somnolence, dizziness, asthenia, fatigue, insomnia, hyperhidrosis[1,2,5,6]
- **urinary retention, urinary hesitancy** reports involving hospitalization, catheterization in some cases[1,2]
  - not approved as a treatment for stress urinary incontinence by Health Canada or the US FDA[7]
- **orthostatic hypotension, syncope** *dose related*
  - risk factors: concomitant antihypertensives, Cytochrome P450 1A2 inhibitors[2,5]
- **Beers Criteria** 2015 American Geriatric Society List of Potentially Inappropriate Medication Use in Older Adults | use with caution due to risk of syndrome of inappropriate antidiuretic hormone secretion or hyponatremia (monitor sodium when initiating or changing doses)[8]
  - hyponatremia risk factors: older adults, diuretics, volume depletion[1,2]
- **withdrawal symptoms** dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis, vertigo, somnolence, myalgia[1,2] | tapering tool: MedStopper ➲ medstopper.com
- **enteric coating** must be swallowed whole without chewing, crushing or opening capsule[1]
  - enteric coated pellets protect against degradation in acidic environment to naphthol, which can cause abdominal pain, cramping, nausea, vomiting and other severe systemic effects[9] | caution advised in conditions that may slow gastric emptying (eg, gastroparesis)[1,2,5]

| **Duloxetine for Painful Diabetic Neuropathy** *2014 Cochrane systematic review*[10] | | | |
|---|---|---|---|
| NNT 5 ●●●●● | substantial reduction in pain (reduction from baseline ≥ 50%) | discontinuation due to adverse event | NNH 18 |
| | | any adverse event | NNH 12 |
| | | nausea | NNH 7 |
| | | dry mouth | NNH 14 |
| | | somnolence | NNH 15 |
| | | dizziness | NNH 22 |

*NNT number needed to treat; ● responder; ● non responder; NNH number needed to harm; estimates are for duloxetine 60 mg per day*
*NNT 'much or very much improved (patient's global impression of change)' not reported*

**Limited coverage**: Special Authority Criteria available from: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/special-authority

| Antidepressant Medications | Starting Dose [Dosage Range] | Elimination Half-life | Approximate Monthly Cost [without fee or markup] | BC PharmaCare Coverage |
|---|---|---|---|---|
| **AMITRIPTYLINE (Elavil, generics)**<br>10, 25, 50, 75, 100 mg tabs | 10 – 25 mg once a day[1]<br>[10 – 150 mg per day][1] | 30 hours[2] | 10 mg: $1<br>25 mg: $3 | Regular Coverage |
| **NORTRIPTYLINE (Aventyl)**<br>10, 25 mg caps | 10 – 25 mg once a day[3]<br>[10 – 100 mg per day][3] | 30 hours[2] | 10 mg: $10<br>25 mg: $15 | Regular Coverage |

**Health Canada pain indications:** none[4,5] | dosages are those reported in Cochrane systematic reviews[1,3]
**Health Canada contraindications include:** severe hepatic impairment, acute myocardial infarction, acute heart failure[4,5]

**Drug Information Synopsis**

- **Cochrane systematic reviews** available evidence precludes confident assessment of tricyclic antidepressant therapeutic effects[1,3,6,7]
- **dose response** 2015 systematic review could not define a relationship between dose and therapeutic effect[8]
- **genetic metabolic variability** range of poor to ultrarapid metabolizers
  - Cytochrome P450 2D6 polymorphism: amitriptyline, nortriptyline | Cytochrome P450 2C19 polymorphism: amitriptyline[4,5,9,10]
- **peripheral, central, cardiovascular adverse effects** include dry mouth, vision disturbance, constipation, urinary retention, increased intraocular pressure, sedation, cognitive impairment, delirium, psychomotor slowing, orthostatic hypotension, tachycardia[4,5]
  - absolute risk for specific adverse events are not quantified in systematic reviews[1,3,6,7]
  - 2009 nortriptyline trial reported dry mouth as the most common adverse event, affecting approximately 60% of participants[11]
- **Beers Criteria** 2015 American Geriatric Society List of Potentially Inappropriate Medication Use in Older Adults: avoid due to anticholinergic, sedating, orthostatic hypotension adverse effects; use with caution due to risk of syndrome of inappropriate antidiuretic hormone secretion or hyponatremia (monitor sodium when initiating or changing doses)[12]
- **relative safety** 1996 systematic review did not identify a difference in adverse events between tricyclic antidepressants but direct comparative evidence is limited[13]
  - nortriptyline is a principal metabolite of amitriptyline[4,9,10]
- **dementia** observational studies identify a relationship between higher cumulative anticholinergic medication exposure and dementia[14,15]
- **heart failure** 2016 American Heart Association scientific statement: tricyclic antidepressants may exacerbate underlying heart failure secondary to negative inotrope, proarrhythmic properties[16]
- **QTc interval prolongation** Torsades de pointes risk under certain conditions: bradycardia, hypokalemia, hypomagnesemia, excessive dose, impaired drug elimination, use with other medications known to prolong QTc interval | avoid in congenital long QT syndrome[17,18]
- **overdose** cardiovascular, central nervous system, anticholinergic effects[4,5]
  - British Columbia Drug & Poison Information Centre (BC DPIC) 24-Hour Poison Information Line ➲ *1-800-567-8911*
- **withdrawal symptoms** nausea, headache, malaise, irritability, restlessness, sleep disturbance[4,5] | tapering tool: MedStopper ➲ medstopper.com
- **insomnia** Cochrane systematic review did not identify supportive clinical trial evidence for amitriptyline or nortriptyline as treatments for insomnia[19]

## Medications for Neuropathic Pain: Giving Attention to Drug Interactions

| | |
|---|---|
| **Gabapentin**[1-4] | |
| Opioids | ▪ potentiates risk of respiratory depression, sedation, syncope, death<br>▪ 2017 Ontario case-control study:[4] increase in risk of opioid-related death when gabapentin is co-prescribed with an opioid: adjusted odds ratio (aOR) 1.49 (95%CI 1.18, 1.88) \| dose-response ➲ gabapentin < 900 mg per day: aOR 1.32 (95%CI 0.89, 1.97), gabapentin 900-1799 mg per day: aOR 1.56 (95%CI 1.06, 2.28), gabapentin ≥ 1800 mg per day: aOR 1.58 (95%CI 1.09, 2.27) |
| Aluminum or Magnesium Antacids | ▪ decreased absorption of gabapentin; separate administration by 2 hours |
| **Pregabalin**[1,5-7] | |
| Opioids | ▪ potentiates risk of respiratory depression, sedation, reduced gastrointestinal function (eg, constipation, obstruction)<br>▪ 2018 Ontario case-control study:[7] increase in risk of opioid-related death when pregabalin is co-prescribed with an opioid: aOR 1.68 (95%CI 1.19, 2.36) \| dose-response ➲ pregabalin ≤ 300 mg per day: aOR 1.52 (95%CI 1.04, 2.22), pregabalin > 300 mg per day: aOR 2.51 (95%CI 1.24, 5.06) |
| Thiazolidinediones | ▪ potentiates risk of edema, weight gain ➲ eg, pioglitazone, rosiglitazone |
| **Duloxetine**[1,8-12] | |
| Cytochrome P450 1A2 Inhibitors | ▪ altered metabolism of duloxetine ➲ eg, ciprofloxacin, fluvoxamine [contraindicated] |
| Cytochrome P450 2D6 Inhibitors | ▪ altered metabolism of duloxetine ➲ eg, bupropion, fluoxetine, paroxetine |
| Cytochrome P450 2D6 Substrates | ▪ altered metabolism of other medications by duloxetine ➲ eg, amitriptyline, nortriptyline, codeine, tramadol, tamoxifen, carvedilol, metoprolol |
| Monoamine Oxidase Inhibitors | ▪ serotonin toxicity ➲ eg, MAOI antidepressants, linezolid, methylene blue [contraindicated] |
| Serotonin Modulators | ▪ serotonin toxicity ➲ eg, other serotoninergic antidepressants, tramadol |
| Anticoagulants, Antiplatelets, NSAIDs | ▪ possible potentiated bleeding risk |
| **Amitriptyline, Nortriptyline**[1,10,11,13-16] | |
| Cytochrome P450 2D6 Inhibitors | ▪ altered metabolism of amitriptyline, nortriptyline ➲ eg, bupropion, duloxetine, fluoxetine, paroxetine |
| Monoamine Oxidase Inhibitors | ▪ serotonin toxicity ➲ eg, MAOI antidepressants, linezolid, methylene blue [contraindicated] |
| Serotonin Modulators | ▪ serotonin toxicity ➲ eg, other serotoninergic antidepressants, tramadol |
| Drugs known to prolong QTc interval | ▪ QTc interval prolongation, Torsades de pointes: QT Drug Lists Credible Meds ➲ crediblemeds.org |
| Anticholinergic Medications | ▪ additive anticholinergic effects ➲ eg, cyclobenzaprine, urinary incontinence medications, antihistamines, inhaled anticholinergic bronchodilators |
| Alpha 2 Agonists | ▪ diminished antihypertensive effect ➲ eg, clonidine, methyldopa |
| Cytochrome P450 Drug Interaction Table Indiana University ➲ http://medicine.iupui.edu/clinpharm/ddis/ | |

# Medications for Neuropathic Pain

**B.C. Provincial Academic Detailing Service** **December 2018**

## Evidence to Practice

- Do set ***realistic expectations with clear goals of therapy*** in advance of the medication trial[1]
- Do aim to make a decision regarding the success of the medication trial by ***weeks 2 to 4***[2]
- Do discuss ***discontinuing ineffective medications*** before trialing another
- Do consider the relationship between ***medication dose, renal function, and drug interactions*** with ***efficacy and safety***
- Do ***revisit*** whether ongoing medication is useful or harmful

**Reference list is available upon request.**

Drug Costs are from McKesson Canada and are approximate without markup or professional fee:
https://mckesson.ca/pharmaclik

BC PharmaCare Formulary Search:
https://pharmacareformularysearch.gov.bc.ca/

*Materials are designed to be used in conjunction with an academic detailing session provided by a PAD pharmacist.*

*For more information, or to schedule an academic detailing session, please contact:*

**BC Provincial Academic Detailing Service**
**Phone: 604 660-2101**
**Fax: 604 660-2108**
**Email: PAD@gov.bc.ca**
**Web: www.bcpad.ca**