



Fast Facts Core Curriculum

Pain Miscellaneous Topics

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FAST FACTS AND CONCEPTS #49 GAPAPENTIN FOR NEUROPATHIC PAIN

Anita Kishore, Linda King MD, and David E Weissman MD

Introduction Gabapentin (Neurontin) has FDA indication to treat postherpetic neuralgia and partial onset seizures. Controlled clinical trials in diabetic neuropathy and postherpetic neuralgia show that gabapentin at 2400-3600 mg/day has a similar efficacy to tricyclic antidepressants and carbamazepine. Consistent, though less compelling clinical evidence supports its use for neuropathic cancer pain, pain associated with HIV infection, chronic back pain and others (readers wanting more in depth research findings are urged to consult Reference 1). Due to this emerging evidence, it is widely used for the treatment of neuropathic pain. The exact mechanism and site of action of gabapentin is unknown. Gabapentin is generally well-tolerated, easily titrated, has few drug interactions, and does not require laboratory monitoring. However, cost may be a limiting factor for some patients. Patients suitable for gabapentin should have a clear neuropathic pain syndrome, characterized by sharp, shooting, lancinating and/or burning pain, in a nerve root (radicular) or stocking/glove distribution. See *Fast Fact #289* for a comparison of gabapentin with pregabalin a similar neuropathic analgesic.

Adult Dosing Gabapentin is started at low doses (100 mg to 300 mg total daily) and increased by 100 – 300 mg every 1-3 days to effect. A typical schedule might be: day 1-2: 300 mg nightly; day 3-4: 300 mg twice daily; day 5-7: 600 mg twice daily; day 8 onwards: 600 mg three times a day. The usual effective total daily dose is 900-3600 mg, administered in three divided doses per day. Titration should proceed more slowly in elderly patients. If gabapentin is discontinued, it should be done over a minimum of a week to prevent withdrawal seizures.

Pediatric Use There is limited data available assessing its effectiveness in neuropathic pain in children. The American Pain Society recommends that gabapentin be considered for pediatric neuropathic pain especially when concurrent analgesics are found to be too sedating. Their recommended initial dose is 2 mg/kg/day with a usual dosage range of 8 to 35 mg/kg/day divided into 3 daily doses.

Dosing in Renal Failure Gabapentin doses must be reduced for patients with renal insufficiency.

- Creatinine Clearance (CrCl) 30-60 ml/min: maximum daily dose is 1400 mg, divided.
- CrCl 16-30 ml/min: maximum daily dose is 700 mg, given once daily.
- CrCl 15ml/min: maximum daily dose is 300 mg, once daily. Doses should decrease proportionally for CrCl less than 15 ml/min (e.g. 300 mg every other day for a CrCl of ~7.5 ml/min).
- For patients on hemodialysis a supplemental dose is usually given after dialysis (usually 100-300 mg).

Adverse Reactions Sedation, confusion, dizziness, and ataxia are the most common side effects, especially with rapid dose titration. Tolerance to these effects appears to develop within a few days if the dose is held at the highest tolerated dose until symptoms improve or stabilize.

Dosage Formulations Gabapentin is available in 100 mg, 300 mg, and 400 mg capsules, 600 mg and 800 mg tablets, and as a liquid (250mg/5mL).

Cost Gabapentin is more expensive than older agents used for neuropathic pain (tricyclic antidepressants and older anti-epileptic drugs such as carbamazepine). Generic gabapentin is available, although can cost ~\$100 for 90 600 mg tablets.

Other Palliative Care Uses of Gabapentin Small scale published trials have shown efficacy in the treatment of severe chronic hiccups, pruritus, postoperative pain, restless leg syndrome and hot flashes. Perhaps more compelling is its potential efficacy for chronic cough for which a randomized double-blind placebo controlled trial demonstrated significant improvement in cough-specific quality of life, cough frequency, and cough severity.

Summary Gabapentin is a safe and effective adjuvant analgesic for neuropathic pain. Physicians should become comfortable using and titrating gabapentin in patients with neuropathic pain syndromes.

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FAST FACTS AND CONCEPTS #85 EPIDURAL ANALGESIA

Debra Gordon RN and Mark Schroeder MD

Background Epidural analgesia with local anesthetics, opioids, and/or alpha-agonists can provide superior regional analgesia over conventional systemic routes (IV or PO). In contrast to drugs administered systemically, drugs administered in the epidural space are extremely potent since the drug is delivered close to the site of action (opioid and alpha receptors in the spinal dorsal horn or local anesthetic blockade of nerve roots). Because of this, systemic side effects such as nausea, sedation, and constipation, are minimized. In palliative care, epidural analgesia may be appropriate for patients with regional pain (e.g. pelvic pain from cervical cancer) and/or patients who do not tolerate or obtain relief from oral/parenteral drugs and non-drug therapies.

Indwelling Epidural Catheters In patients with refractory cancer pain, anesthesiologists typically place a more durable and longer lasting epidural catheter than the epidural catheters used for childbirth. These indwelling epidural catheters, are tunneled under the skin, directed away from the spine, and covered it with clear adhesive dressing to reduce infection. Indwelling epidural catheters can remain in place for weeks to months and can be utilized in the home setting; however, longer catheter durations are associated with higher risks of serious adverse effects such as a deep epidural infection. The best estimate is that one in 35 patients with an epidural catheter in place for 74 days for cancer pain can be expected to get a deep epidural infection and 1 in 500 may die of such complications. .

Medications The epidural solution typically contains a local anesthetic such as bupivacaine along with an opioids such as fentanyl and morphine. Clonidine is sometimes utilized when neuropathic pain is present. If the patient is getting a low dose of the anesthetic, lower leg movement and function is often preserved; at higher doses, however, patients may lose ambulation. Drugs administered epidurally are distributed by three main pathways:

- Diffusion through the dura into the CSF, then to the spinal cord or nerve roots.
- Vascular uptake by the vessels in the epidural space into systemic circulation.
- Uptake by the fat in the epidural space; creating a drug depot from which the drug can eventually enter the CSF or the systemic circulation.

Patient Controlled Epidural Analgesia (PCEA) Epidural analgesia can be administered by intermittent boluses (by a clinician or by patient controlled epidural analgesia using an appropriate pump); continuous infusion; or a combination of both. PCEA is used to supplement a basal rate, to allow a patient to manage breakthrough pain in order to meet their individual analgesic requirements. Like IV PCA, PCEA can provide more timely pain relief, more control for the patient, and convenience for both the patient and nurse to reduce the time required to obtain and administer required supplemental boluses. Unlike IV PCA, the lockout interval of PCEA varies widely based on the lipid solubility of the opioid administered, from 10 minutes with fentanyl to 60-90 minutes when morphine is used. If local anesthetic is used, the lockout interval should be at least 15 minutes to allow for peak effect of the supplemental local anesthetic dose.

Management Due to the proximity of drug delivery to its site of action, frequent assessment of pain relief, side effects, and signs or symptoms of technical complications (catheter dislodgement, epidural hematoma or abscess, pump malfunction, etc.) are necessary. This should be done every hour for the first 24 hours, then every 4 hours. Assess and document on the pain management flowsheet:

- Patient's pain rating using patient-specific pain scale (e.g. 0-10), both at rest and with activity.
- Level of sedation & respiratory rate, *preferably by the same nurse during each shift.*
- Side effects: pruritis, nausea, urinary retention, orthostatic hypotension, motor block.
- Sign of catheter insertion site infection or epidural abscess such as back pain, tenderness, erythema, swelling, drainage, fever, malaise, neck stiffness, progressive numbness, or motor block.
- Changes in sensory/motor function that may indicate an epidural hematoma including unexplained back pain, leg pain, bowel or bladder dysfunction, motor block.

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FAST FACTS AND CONCEPTS #117 PEDIATRIC PAIN ASSESSMENT SCALES

Gena Walker and Robert Arnold MD

Background Neonates and infants do experience pain. In fact, research has shown that neonates may experience as much pain as older children and long-term consequences from exposure to repeated painful stimuli. Untreated pain leads to increased sensitivity to subsequent stimuli. Assessing pain in neonates and young children requires use of age appropriate scales. There is no empirical evidence demonstrating the superiority of one assessment tool, but research suggests that the same scale(s) should be used within an institution.

Behavioral Observational Scales: The primary method of pain assessment for infants, children less than 3 yrs old, and developmentally disabled patients. Validated tools include:

- **CRIES:** Assesses Crying, Oxygen requirement, Increased vital signs, facial Expression, Sleep. An observer provides a score of 0-2 for each parameter based on changes from baseline. For example, a grimace, the facial expression most often associated with pain, gains a score of 1 but if associated with a grunt will be scored a 2. The scale is useful for neonatal postoperative pain.
- **NIPS:** Neonatal/Infants Pain Scale has been used mostly in infants less than 1 yr of age. Facial expression, cry, breathing pattern, arms, legs, and state of arousal are observed for 1 minute intervals before, during, and after a procedure and a numeric score is assigned to each. A score >3 indicates pain. An example is available at: http://www.anes.ucla.edu/pain/assessment_tool-nips.htm.
- **FLACC:** Face, Legs, Activity, Crying, Consolability scale has been validated from 2 mo to 7 years. FLACC uses 0-10 scoring. An example is available at: http://www.anes.ucla.edu/pain/assessment_tool-flacc.htm.
- **CHEOPS:** Children's Hospital of Eastern Ontario Scale. Intended for children 1-7 yrs old. Assesses cry, facial expression, verbalization, torso movement, if child touches affected site, and position of legs. A score ≥ 4 signifies pain. An example is available at: http://www.anes.ucla.edu/pain/assessment_tool-cheops.htm.

Self report: Children 3 years of age and older can rank their pain using one of several validated scales including:

- **Wong-Baker Faces scale:** 6 cartoon faces showing increasing degrees of distress. Face 0 signifies "no hurt" and face 5 the "worst hurt you can imagine." The child chooses the face that best describes pain at the time of assessment. An example is available at: <http://www1.us.elsevierhealth.com/FACES/>.
- **Bieri-Modified:** 6 cartoon faces starting from a neutral state and progressing to tears/crying. Scored 0-10 by the child. Used for children >3 years.
- **Visual analogue scale:** Uses a 10 cm line with one end marked as no pain and the opposite end marked as the worst pain. The child is asked to make a mark on that line that is then measured in cm from the no pain end.

Parent or Caregiver Report:

- **INRS:** Individualized Numeric Rating Scale. This is a validated pain assessment tool for nonverbal children with intellectual disability. Essentially, it is an adaptation of the numeric rating scale that incorporates the parents' and/or caregiver's descriptions of the child's past and current responses to pain. Once described, the responses are then stratified on a scale from 0 to 10.

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FAST FACTS AND CONCEPTS #148
THE LIDOCAINE PATCH**Drew A Rosielle MD**

Background The Lidocaine Patch 5% is a topical analgesic developed to treat peripherally generated neuropathic pain. It is approved in the US for treating post-herpetic neuralgia (PHN). This *Fast Fact* reviews its mechanism of action, research data, and dosage information.

Mechanism of Action The lidocaine patch is believed to provide analgesia by reducing aberrant firing of sodium channels on damaged pain fibers directly under the patch. Less than 5% of the lidocaine is absorbed, an insufficient dose to cause systemic effects or local anesthesia (patients do not feel numb under the patch) (1,2). It was initially expected that only superficial pain qualities would be affected by the patch; however there is evidence that non-superficial qualities of pain (e.g. “dull” or “deep” pain) are also diminished by the patch (3,4). Nociceptive pain generation (such as sensitivity to pinprick, or hot or cold painful stimuli) is not affected. Tachyphylaxis has not been formally investigated; case reports have indicated some individuals have used the patch successfully for over a decade.

Research Data Most of the research using the lidocaine patch, and all of the randomized, placebo-controlled trials, have been in neuropathic pain syndromes. It has shown modest (10-20 mm decrease in pain on the 100 mm visual analog scale) but significant efficacy in PHN in randomized, placebo-controlled trials (1). Several controlled, blinded studies evaluating the efficacy of the patch for acute pain syndromes (surgical/incisional pain, acute rib fractures) have not shown the patch to be superior to placebo for these syndromes (5,6,7). Due to its ease of use and lack of toxicity or drug interactions, it is being used much more widely than PHN. Multiple case-reports, open-label studies, and unpublished anecdotal reports have found the patch efficacious for a range of neuropathic conditions (e.g. diabetic neuropathy, post-surgical neuralgia), chronic low back pain, osteoarthritis, bony metastases, vertebral compression fractures, and on open decubitus ulcer beds (8,9). **Note:** this latter practice is directly warned against by the manufacturer and there are no published data as to the patch’s safety when used on open wounds. Great caution is necessary in interpreting results of non-blinded, non-controlled clinical reports due to the high likelihood of a placebo effect (10).

Administration/Toxicity The lidocaine patch comes as a 10x14 cm adhesive patch containing 700 mg of lidocaine. A box of 30 patches costs approximately \$300 USD (priced August 2015 at www.drugs.com). One to three patches, or only a portion of a patch, can be placed directly over painful areas. Due to concerns about systemic lidocaine toxicity, up to a maximum of 3 patches applied simultaneously for 12 hours a day has been approved. Onset of analgesia is within a few hours and patients should be able to determine whether the patch is helpful within a week. Some patients find that pain worsens when the patch is off for 12 hours or if it is left on for more than 18 hours, therefore extended dosing has been investigated. Several pharmacokinetic studies have shown that systemic lidocaine levels remain well within the safe range with doses of up to 4 patches on for 24 hours (11). Adverse reactions are rare, mild, and mostly topical (rash). The patch is contraindicated in advanced liver failure due to decreased clearance of lidocaine.

Summary The lidocaine patch 5% is an expensive, safe, and modestly effective topical analgesic for post-herpetic neuralgia. It has not been proven to be effective for other pain syndromes, and clinicians should strongly consider reports of its efficacy to be related to placebo mechanisms.

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FAST FACTS AND CONCEPTS #187
NON-TRICYCLIC ANTIDEPRESSANTS FOR NEUROPATHIC PAIN

Pippa Hawley B.Med, FRCPC

Background Tricyclic antidepressants (TCAs) have long been recognized as effective agents for neuropathic pain. Due to their sedating and anticholinergic side effects there has been much interest in newer antidepressant agents with different side effect profiles. This *Fast Fact* reviews the use of non-tricyclic antidepressants for neuropathic pain.

Pharmacology Serotonin (5HT) and norepinephrine (NE) mediate descending inhibition of ascending pain pathways in the brain and spinal cord. Experience has suggested that newer antidepressants which enhance NE action are more effective analgesics than many older antidepressants which predominantly enhance 5HT action. TCAs are thought to cause analgesia by NE and 5HT reuptake inhibition; they also have other pharmacologic properties that may contribute to analgesia such as reducing sympathetic activity, NMDA-receptor antagonism, anticholinergic activity, and sodium-channel blockade. Non-tricyclic antidepressants seem to be less efficacious for neuropathic pain (see below): this may in part be because of their 'cleaner' pharmacodynamic profiles.

Clinical Evidence Most randomized controlled trials of non-tricyclic antidepressants for pain have been for diabetic peripheral neuropathy or post-herpetic neuralgia. There have been a few well controlled studies in the treatment and prevention of chemotherapy induced peripheral neuropathy (CIPN) but limited good data in other neuropathic conditions.

- **Selective Serotonin Reuptake Inhibitors (SSRIs):** *Fluoxetine* is not effective for neuropathic pain. *Paroxetine* and *citalopram* have shown only mild benefit for HIV-related and diabetic neuropathy in small studies. Other SSRIs have not been evaluated.
- **Serotonin Norepinephrine Reuptake Inhibitors (SNRIs):**
 - *Venlafaxine*: Low doses of are predominantly serotonergic, but higher doses add substantial noradrenergic effects. Doses of 150-225 mg/day appear to have mild to moderate analgesic effect (30-50% reduction in pain) with a number needed-to-treat (NNT) of 4.6 in painful diabetic neuropathy (only one out of every 4-5 patients treated will benefit). In contrast, TCAs have shown a NNT of 2-3. Pilot data, in addition to one randomized controlled trial, support the use of extended release venlafaxine in preventing the onset of CIPN if given at doses of 25 mg to 75 mg a day one hour prior to chemotherapy infusion as well as 11 days after. One head-to-head trial showed venlafaxine 225 mg/day had the same tolerability as 150 mg/day of imipramine (a TCA), but venlafaxine was less effective for pain. Side-effects of venlafaxine include nausea, sedation, headache and dizziness. The usual starting dose is 37.5 mg daily, increasing weekly in 37.5 mg increments. Use of venlafaxine for analgesia is not FDA approved; a 75 mg tab costs approximately \$3.70 (average US wholesale price).
 - *Duloxetine*: has been shown to have a mild to moderate analgesic effect in industry-sponsored trials in diabetic peripheral neuropathy (NNT 5.2). In addition, a randomized controlled trial showed relatively small but significant neuropathic pain relief compared with placebo. Onset of analgesia is at about 1 week, with maximum effect at about 4 weeks. A dose of 60 mg a day has been best studied for both diabetic peripheral neuropathy and CIPN; 60 mg BID may lead to increased analgesia but at the expense of an increased risk of nausea, sedation, constipation, sweating, and insomnia. *Duloxetine* has an FDA indication for use in diabetic peripheral neuropathic pain in the USA. A 60 mg tab costs approximately \$3.50.
- **Other Antidepressants** *Bupropion* is a dopamine and norepinephrine reuptake inhibitor with mild analgesic effect according to one study involving 41 patients with a mix of neuropathic pain syndromes. *Mirtazapine* has a complicated pharmacology with unknown analgesic effects.

Summary There are relatively well defined and preferred therapies for neuropathic pain including newer generation anticonvulsants (such as gabapentin), TCAs, and opioids in select patients. In patients with ongoing pain despite treatment with these agents, or who are intolerant to them, venlafaxine or duloxetine may be helpful. There are no comparative studies between non-tricyclics for neuropathic pain, thus an agent should be selected based on its side-effect profile, cost, and familiarity with use.

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FAST FACTS AND CONCEPTS #271 ANTI-EPILEPTIC DRUGS FOR PAIN

Seth Hepner and René Claxton MD

Introduction Tri-cyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and anti-epileptic drugs (AEDs) are the mainstays of adjuvant therapy for neuropathic pain. This *Fast Fact* reviews the evidence for the use of AEDs in the treatment of neuropathic pain. For a more in-depth look at gabapentin, pregabalin, and antidepressants for neuropathic pain see *Fast Facts* #49, 187, 288, and 299. Due to lack of head-to-head data, evidence is presented as numbers needed to treat (NNT) and numbers needed to harm (NNH). For instance, an NNT of 5 for 50% pain reduction means for every 5 patients treated with a drug, only 1 of them would achieve a 50% reduction in pain. All data presented and doses mentioned are for adults and based on investigations of patients with chronic pain. Given the paucity of research about the use of adjuvants for pain management in patients with life-limiting illnesses, many clinicians empirically extrapolate available data to palliative care patients.

Gabapentin is effective in treating central and peripheral neuropathic pain. According to a 2011 Cochrane review of the effect of gabapentin on chronic neuropathic conditions (including post-herpetic neuralgia, painful diabetic neuropathy, mixed neuropathic pain), the NNT is 5.8 (4.8-7.2) to achieve at least moderate benefit. Adverse effects are frequent, usually tolerable and include drowsiness, dizziness and edema (1). Gabapentin should be dose adjusted for renal dysfunction. It should be withdrawn gradually to avoid precipitating seizures. Maximum dose is 3,600 mg/day (2).

Pregabalin is effective in treating peripheral and central neuropathic pain. Its effectiveness increases as the dose approaches 600 mg/day. At a dose of 600 mg/day, the NNT to decrease pain by 50% for the following conditions is: 3.9 (range 3.1-5.1) for post-herpetic neuralgia; 5.0 (range 4.0-6.6) for diabetic neuropathy; and 5.6 (range 3.5-14) for central neuropathic pain. There was no difference in incidence of side effects among participants taking pregabalin vs placebo and no indication of a dose response to side-effects (3). Dosing starts at 150 mg/day in divided doses either twice or three times daily (2).

Carbamazepine is effective for neuropathic pain, specifically trigeminal neuralgia, but is not considered first-line therapy due to its adverse effects. A meta-analysis reported that carbamazepine reduced chronic neuropathic pain compared to placebo with NNT of 1.7. However, adverse events occur frequently: NNH = 2.6 (4). Common side effects include leukocytosis, thrombocytopenia, dizziness, drowsiness, ataxia, nausea/vomiting and blurred vision. Additionally, there is a risk of agranulocytosis, aplastic anemia, and Stevens Johnson syndrome. Laboratory tests (BUN, complete blood count, sodium, liver function tests, urinalysis) and serum drug levels should be checked at baseline and during treatment. Dosing starts at 100-200 mg twice a day and is titrated by 200 mg/day every 3 – 5 days until pain relief is achieved. Maximum dose is 1,200 mg/day (2).

Oxcarbazepine is an analogue of carbamazepine which is equally effective at treating trigeminal neuralgia (5) but with fewer side effects (6). Oxcarbazepine can be started at 300 mg twice a day and titrated up by 300 mg/day every 3 days to therapeutic effect. Maximum dose is 2,400 mg/day (2).

Valproic acid was evaluated in a 2011 meta-analysis for the treatment of neuropathic pain. There were insufficient data for reliable pooled analysis, and the authors recommend against its use as first line therapy (7). Several small studies (n<60) showed benefit (maximum of 1200 mg/day in divided doses) over placebo in the treatment of diabetic neuropathy (8). However, studies of valproic acid have failed to find an effect (9). Adverse effects include liver function test abnormalities, dizziness, drowsiness and nausea. Maximum dose is 60 mg/kg/day (2).

Topiramate has not demonstrated convincing efficacy for painful diabetic neuropathy. In three studies totaling more than 1200 participants, topiramate did not show a statistically significant effect (9). A subsequent randomized controlled trial of 317 patients with diabetic neuropathy showed a benefit over placebo with a NNT of 6.9. Serious adverse events include convulsion,

bradycardia, and syncope (10). Additional adverse effects include sedation, nausea, diarrhea and metabolic acidosis (2). Dosing starts at 50 mg/day and can be titrated up to 400 mg/day (10).

Lacosamide has weak evidence supporting its use. In a randomized, placebo controlled study, patients treated with lacosamide (100-400 mg/day) for diabetic neuropathy showed a decrease in baseline pain by 2 or more points on an 11-point scale compared to controls, NNT 10.9. Side effects were similar (12). Subsequent trials have failed to show similar effects except for a subgroup analysis of 400 mg/day (9). Dosing starts at 50 mg twice daily. Abrupt discontinuation can precipitate seizures (2).

Using other AEDs including phenytoin and levetiracetam is not supported by clinical research. Although, a single small study (n=92) demonstrated benefit for lamotrigine in treating painful HIV-related neuropathy at doses of 200-400 mg daily (12, 9, 13).

Summary TCAs, SNRIs, and the AEDs gabapentin and pregabalin are the best adjuvant analgesics for neuropathic pain. For patients who are intolerant to or who have pain refractory to the above medications, one can consider therapy with carbamazepine, oxcarbazepine, valproic acid, topiramate or lacosamide, keeping in mind they are associated with more side effects and lower rates of efficacy.

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**FAST FACTS AND CONCEPTS #272
POSTHERPETIC NEURALGIA**

Shannon Ryan-Cebula MD and Hunter Groninger MD

Background Postherpetic neuralgia (PHN) is a syndrome of zoster-associated pain persisting more than 3 months after resolution of an initial herpes zoster (HZ) rash ('shingles').

Epidemiology Inconsistencies in diagnosis and data collection make the incidence of HZ and PHN difficult to estimate (1,2). PHN develops rarely in those under 50 years. However, it occurs in 20% of persons 60 to 65 with HZ and its incidence rises to 30% in persons over 80 years old (1,2). Risk factors for PHN include severe acute shingles-related pain, rash severity (i.e., more than 50 lesions), increasing age, and immunocompromised status (3,4).

Pathophysiology In acute HZ, reactivation of the virus from the dorsal root ganglia of spinal or cranial nerves causes inflammation and damage to the affected nerve tissue, resulting in acute pain. Subsequently, primary afferent neurons responding to the acute neuronal damage of zoster reactivation can cause sensitization of the nociceptive dorsal horn neurons, resulting in a prolonged exaggerated response to non-noxious stimuli (1). This central sensitization is thought to be a key mechanism in the development and maintenance of the pain of PHN.

Natural History Most HZ patients experience resolution of the rash and acute HZ pain within two months (1). For those who develop PHN, prolonged severe disabling symptoms rarely remain beyond 6 months (5). A small subset may experience irreversible damage to skin and sensory abnormalities that can result in ongoing pain for years (2). For all patients with acute HZ and/or PHN, physical and emotional quality-of-life can be affected (6-8).

Prevention In adults over 60 years old, live vaccination against the zoster virus reduces overall incidence of HZ by 50% and PHN by two-thirds. It is contraindicated in patients with immune deficiencies (primary or acquired such as patients with leukemia), including patients taking immunosuppressants or high dose corticosteroids (9). Initiating antiviral drugs within 72 hours of rash onset reduces acute and chronic pain associated with HZ. There is no clear benefit to initiation after this window (10-12). Best available evidence does not support the routine use of glucocorticoids in preventing PHN (10).

Pain management strategies PHN is a quintessential neuropathic pain syndrome and the approach to treatment is similar to other neuropathic syndromes. Recent guidelines cite strong evidence for using tricyclic antidepressants (TCAs), gabapentinoids (gabapentin, pregabalin), opioids, lidocaine 5% patch, and capsaicin 8% patch to manage PHN (13,14). (See *Fast Facts* #49, 148, 255, and 271.) Strong evidence also supports combined therapy of gabapentin plus opioids or TCAs (14). Second-line therapies include topical salicylate and topical capsaicin 0.075% cream. Epidural steroid injections and acupuncture are likely no better than placebo (14). While serotonin norepinephrine reuptake inhibitors such as duloxetine are commonly used for neuropathic syndromes (see *Fast Fact* #187), there are currently no published trials regarding their use for PHN.

Cost There is limited literature regarding cost effectiveness among commonly used agents. The following table provides current information regarding starting dose, effective dose, and cost (15).

| Drug | Starting dose (cost in USD/ month) | Typical effective dose (cost/month) |
|---------------------------|------------------------------------|-------------------------------------|
| Gabapentin 300 mg capsule | 900 mg/day (\$19) | 1800 mg/day (\$99) |
| Pregabalin 50 mg capsule | 150 mg/day (\$180) | 450 mg/day (\$180) |

| | | |
|-----------------------------|------------------------------|--------------------------|
| Desipramine 25 mg tablet | 25 mg/day (\$38) | 100 mg/day (\$99) |
| Nortriptyline 50 mg capsule | 50 mg/day (\$20) | 75 mg/day (\$20) |
| Lidocaine 5% patch | 1 patch per 12 hours (\$217) | 1 patch/12 hours (\$217) |
| Capsaicin 8% patch | 1 patch per 90 days (\$265) | 1 patch/ 90 days (\$265) |

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**FAST FACTS AND CONCEPTS #288
PREGABALIN IN PALLIATIVE CARE**

Jennifer Pruskowski PharmD and Robert M Arnold MD

Background Pregabalin (Lyrica®) is a second generation antiepileptic drug that was developed after gabapentin (See *Fast Fact* #049). This *Fast Fact* will review pregabalin and its role in palliative care. A comparison between pregabalin and gabapentin is also available (See *Fast Fact* #289).

Pharmacology Pregabalin binds to the alpha-2 (α -2 δ) subunit of voltage-gated calcium channels in the CNS, subsequently inhibiting the release of excitatory neurotransmitters. Its oral bioavailability is $\geq 90\%$ and can be taken with or without food. Peak plasma concentrations occur within 1.5 hours. Pregabalin does not bind to plasma proteins, undergoes negligible metabolism, and does not affect the major CYP450 enzymes in humans. It is unlikely to have significant drug interactions (1,2).

Dosing Starting dose for pregabalin is 150 mg/day in two to three divided doses, and may be increased to 300 mg/day within 1 week. Maximum daily dose is 450 mg/day and 600 mg/day (in divided doses) for fibromyalgia and other neuropathic pain disorders, respectively.

Dosing in Renal Impairment and Failure Pregabalin must be adjusted for patients with a CrCl < 60 mL/min, as it is approximately 90% renally eliminated (2).

| CrCl (mL/min) | Total Daily Dose of Pregabalin (mg/day). Columns represent typical 'step-up' doses | | | | Dose Regimen |
|---|---|-------|---------|-----|-------------------|
| | 150 | 300 | 450 | 600 | |
| ≥ 60 | 150 | 300 | 450 | 600 | BID or TID |
| 30-60 | 75 | 150 | 225 | 300 | BID or TID |
| 15-30 | 25-50 | 75 | 100-150 | 150 | Once daily or BID |
| < 15 | 25 | 25-50 | 50-75 | 75 | Once daily |
| Supplementary Dosage Following Hemodialysis:* Patients on the 25 mg once daily regimen: 25 or 50 mg Patients on the 25–50 mg once daily regimen: 50 or 75 mg Patients on the 50–75 mg once daily regimen: 75 or 100 mg Patients on the 75 mg once daily regimen: 100 or 150 mg | | | | | |

Adverse Drug Reactions and Cautions Dizziness is the most commonly reported side effect, followed by somnolence which is the most frequent reason for discontinuation. Other side effects are dose-dependent and reversible -- dry mouth, angioedema, peripheral edema, blurred vision, weight gain, and difficulty with concentration/attention (3).

Research Data Pregabalin is FDA indicated for several non-cancer pain syndromes including: diabetic peripheral neuropathy, post-herpetic neuralgia, fibromyalgia, and neuropathic pain associated with spinal cord injury, as well as an adjunctive therapy for adult patients with partial onset seizures. The number needed to treat for a 50% reduction in diabetic neuropathic pain is 4 when pregabalin is dosed at 600 mg/day (4). There is limited information for its use in cancer-related neuropathic pain (5). In a double-blind, placebo-controlled, randomized trial in patients with neuropathic cancer pain, pregabalin was compared to gabapentin, amitriptyline and placebo; VAS scores were significantly lower in the pregabalin group, and there were clinically significant

morphine sparing effects of pregabalin (6). One randomized, controlled trial suggests low-dose pregabalin (25-50 mg/day) as an effective adjuvant for cancer related bone pain (7).

Cost Pregabalin comes in a 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg oral capsules, and 20 mg/mL oral solution. It is not available as a generic formulation. Pregabalin is approximately eight to ten times more costly than amitriptyline, and three times more costly than venlafaxine ER and gabapentin.

Summary Pregabalin is a relatively expensive medication that may have a role in management of neuropathic pain associated with in cancer, several non-cancer syndromes, and as an adjuvant to opioids for painful bone metastases.

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FAST FACTS AND CONCEPTS #289 A COMPARISON OF PREGABALIN AND GABAPENTIN IN PALLIATIVE CARE

Jennifer Pruskowski PharmD and Robert M Arnold MD

Background Gabapentin (Neurontin®) and pregabalin (Lyrica®) share a similar mechanism of action; however the compounds differ in their pharmacokinetic and pharmacodynamic characteristics. See *Fast Fact #049* for more information regarding gabapentin and *Fast Fact #299* for pregabalin. This *Fast Fact* will compare and contrast these two agents.

Pharmacokinetic Profile Comparison The major pharmacokinetic difference between gabapentin and pregabalin is their absorption from the GI tract. The absolute bioavailability of gabapentin drops from 60-33% as the dosage increases from 900-3600mg/day(1), while pregabalin remains $\geq 90\%$ irrespective of dosage. This suggests that dose escalations of gabapentin are accompanied by a therapeutic ceiling effect, although this has not been proven in studies. Neither medication binds to plasma proteins, both undergo negligible metabolism, and both are renally excreted with terminal half-lives of 5-6 hours. Overall, literature suggests that pregabalin has a small pharmacokinetic advantage over gabapentin, although there is little evidence-based literature to support its clinical superiority in patient care (2).

Pharmacodynamic Profile Comparison The onset of pregabalin is approximately 25 minutes, compared to 1-3 hours for gabapentin. Equally important, pregabalin can be more rapidly titrated to an effective dose range than gabapentin (1-2 days for pregabalin versus approximately 9 days for gabapentin) (3).

Other Differences Research suggests a target dose of at least 900-1,800mg/day (in divided doses) of gabapentin to maintain analgesia for persistent pain (4), although doses as high as 6,000mg/day have been taken for cancer pain (5). With pregabalin, it appears analgesia can be achieved and maintained at any dose (6). The side effects of both drugs are dose dependent, reversible, and relatively similar in nature (e.g., dizziness and somnolence). There is no significant difference in the number of drug interactions. Gabapentin is not a controlled substance, while pregabalin is designated as a Schedule V drug.

Use in Palliative Care Gabapentin is FDA-approved for post-herpetic neuralgia, and adjunctive therapy in the treatment of partial onset of seizures, while pregabalin is approved for diabetic peripheral neuropathy, post-herpetic neuralgia, fibromyalgia, and neuropathic pain associated with spinal cord injury, as well as an adjunctive therapy for adult patients with partial onset seizures. Research suggests the number need to treat (NNT; i.e. the number of patients needed to be treated in order for one patient to benefit) in diabetic neuropathy for pregabalin is 4 (for a 50% reduction at 600 mg/day); while gabapentin had only a small effect on pain reduction (therefore the NNT was not reported) (7). Although gabapentin is frequently given to patients with chemotherapy-induced peripheral neuropathy, few controlled trials have been conducted and investigations have shown conflicting results. There has been only one study comparing the efficacy of gabapentin and pregabalin in neuropathic cancer pain. In this double-blind, randomized, placebo-controlled trial, patients were given amitriptyline, gabapentin, pregabalin, or placebo. There were statistically lower VAS scores in the pregabalin group when compared to the others. The authors also noted a statistically and clinically significant morphine-sparing effect of pregabalin as well (8). This single, mid-quality trial has not been replicated

Cost Pregabalin is approximately three times more expensive than gabapentin, which is available as a generic.

Summary Pregabalin has some pharmacokinetic advantages over gabapentin, but is much more costly. There are no clear data demonstrating improved clinical outcomes of one agent over

the other.

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FAST FACTS AND CONCEPTS #363 OPIOIDS FOR NEUROPATHIC PAIN

Linda Huang PharmD, Dilafruz Khakimova PharmD, Jennifer Pruskowski PharmD

Background Neuropathic pain is caused by damage of the somatosensory nervous system leading to abnormal neural excitability (1). Patients often describe it as ‘burning’, ‘tingling’ or ‘shooting’ down a nerve distribution, and some may experience allodynia where they feel pain from non-painful stimuli like air or light touch on skin. Approximately 10% of the general population has neuropathic pain (2). The role of opioids for neuropathic pain is controversial and examined in this Fast Fact.

Why Try Opioids for Neuropathic Pain? Opioids are broad-spectrum analgesics. While there are numerous non-opioid adjuvant medications and analgesic-based interventions available to patients with neuropathic pain, these interventions have their own associated risks and side-effects. Besides, many who are nearing end-of-life from a progressive illness may already be on opioids. These patients may have trouble swallowing oral medications and they often have renal dysfunction, limiting their ability to tolerate many non-opioid adjuvants. Only a minority of patients with neuropathic pain experience a clinical benefit from one analgesic intervention and require multi-modal therapies (3). Therefore, the clinical question of dose-escalating or initiating an opioid vs adding a non-opioid adjuvant arises frequently.

Opioids vs Non-Opioids for Neuropathic Pain Large systematic reviews and meta-analyses have examined opioids as a class for neuropathic pain of any etiology. Although these studies have led to disparate conclusions (3-8), a Cochrane review and a 2015 meta-analysis suggest that “strong opioids” (i.e. oxycodone, methadone, and morphine) at doses ranging from 15-240 mg oral morphine equivalents (OMEs) reduce neuropathic pain by at least 33% from baseline (3,4). These “strong opioids” were found to have a number-needed-to-treat (NNT) of 4.3 after 4-12 weeks of treatment and a number-needed-to-harm (NNH) of 11.7. For comparison, meta-analyses noted an NNT of 3.6 for tri-cyclic antidepressants or TCAs (such as amitriptyline or nortriptyline), 6.4 for serotonin-norepinephrine reuptake inhibitors or SNRIs (such as duloxetine or venlafaxine), 7.2 for gabapentin, 7.7 pregabalin, and 8.7 for capsaicin for neuropathic pain. The NNH is 13.4 for TCAs, 11.8 for SNRIs, 25.6 for gabapentin, 13.9 for pregabalin, and 8.7 for capsaicin (see Fast Facts #49, #187, #197, #271, #288, & #289) (4). Constipation, somnolence, delirium, dizziness, and dry mouth are the most commonly reported adverse effects of opioids. Maximum effectiveness was associated with 180 mg OMEs/day, with no additional benefit for higher doses (3,4). While TCAs, SNRIs, gabapentin, or pregabalin are considered by many experts to be first-line analgesics for neuropathic pain, opioids are often considered as second or third-line agents for many patients or as a co-analgesic when prompt pain relief during titration of a first-line medication is required (4). There is little published evidence on NSAIDs and acetaminophen for neuropathic pain, though commonly prescribed (9,10).

Clinical Evidence for Individual Opioids Although oxycodone, morphine, and methadone are the most studied opioids for neuropathic pain, there are no well-designed studies to compare the safety or efficacy of any one specific opioid over another.

- **Hydromorphone:** One randomized study explored its efficacy but with a high risk of bias and incomplete outcomes data (11). Hence, there is insufficient evidence to support or refute its role for neuropathic pain.
- **Fentanyl:** There is insufficient evidence to support fentanyl for neuropathic pain, based on one randomized study of 258 participants at patch doses of 12-50 mcg/hr for 12 weeks (12).
- **Methadone:** Randomized control trials have shown some efficacy but it is unclear if methadone offers any additional neuropathic pain control over other opioids (8,13) (see Fast Fact #171).

- **Tramadol and Tapentadol:** Tramadol at doses of 100-400 mg/day has achieved 30% neuropathic pain relief compared with placebo in study periods of 4-6 weeks, with NNT of 3.8 and NNH of 8.3 (14) (see Fast Fact #290). Tapentadol, a similar analgesic, has also improved neuropathic pain at doses of 100-500 mg/day in 8-12-week study periods (15-18).
- **Buprenorphine:** experts cite its kappa receptor antagonism as a theoretical advantage for alleviating neuropathic pain over other opioids, but no well-controlled trials have yet confirmed this. It is considered a partial opioid agonist, as such it may be less associated with delirium and constipation. It can be a reasonable agent for opioid-naïve patients being initiated on an opioid. However, rotating patients to buprenorphine from other opioids be complicated and is best done by only experienced clinicians (see Fast Fact # 268) (19).
- **Other:** There is no supporting evidence nor clinical rationale for the targeted selection of codeine, hydrocodone, or oxycodone for neuropathic pain (20,21). Although not a true opioid agonist, dextromethorphan has been associated with significant neuropathic pain relief, especially for diabetic neuropathy, at doses of 120-920 mg/day for up to 3 months in duration (8). A high prevalence of intolerable side effects (drowsiness and dizziness especially) limits its use, however.

Conclusion While opioids are not first-line agents for most patients with neuropathic pain, meta-analyses suggest they have efficacy when prescribed as monotherapy or part of a multi-modal regimen for patients with refractory, function-impairing neuropathies, especially when prognosis is short. A ceiling effect has been observed when opioids are prescribed for neuropathic pain and the benefit of increasing the opioid dose for beyond 180-240 mg/day should be pursued only on an individual patient basis.

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