



PALLIATIVE CARE CASE OF THE MONTH

Anti-epileptic medicines for pain Management

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Case: Mr. RD is a 64 year-old gentleman with a history of metastatic lung cancer with metastases to the bone including the sacrum. He is seen in palliative care clinic for a several-month history of severe right lower extremity burning pain. Noting that RD's pain appeared to be neuropathic in nature, RD's primary care physician prescribed, in succession, duloxetine and then amitriptyline. Unfortunately, neither of these interventions decreased his pain. His oncologist prescribed a fentanyl patch and oxycodone 5-10mg as needed. RD reports that the opioid pain medications make him tired but do not relieve his pain. He wonders if there is anything else to try for his pain.

Discussion: Tri-cyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and anti-epileptic drugs (AEDs) are the mainstays of adjuvant therapy for neuropathic pain. This Case of the Month will focus on oral anti-epileptic neuropathic pain analgesics. 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. Gabapentin and pregabalin are considered first-line anti-epileptics for the treatment of neuropathic pain. 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. This NNT is more conservative than those previously published due to better definitions of efficacy outcomes and an increased number of participants and studies evaluated.

Adverse effects are frequent and include drowsiness, dizziness and edema. Typically, if the dose is increased slowly these side effects are tolerable (1). Gabapentin should be dose adjusted for renal dysfunction. It should be withdrawn gradually to avoid precipitating seizures (2). Pregabalin is effective in treating peripheral and central neuropathic pain. Given that both gabapentin and pregabalin are chemical analogs of GABA, they are not used simultaneously in clinical practice. There are no comparison studies of gabapentin versus pregabalin. Pregabalin's effectiveness increases as the dose approaches 600 mg/day. Based on a recent meta-analysis, 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).

Carbamazepine is effective in treating neuropathic pain, specifically trigeminal neuralgia, but is not considered first-line therapy due to its adverse effects. A 2011 meta-analysis focused on the use of carbamazepine for chronic neuropathic pain reported that carbamazepine reduced pain compared to placebo (NNT of 1.7, range 1.5-2.0). However, adverse events occur frequently: NNH = 2.6, range 2.1-3.5 (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.

Oxcarbazepine is an analogue of carbamazepine which is equally effective at treating trigeminal neuralgia as carbamazepine (5) but with fewer side effects (6). 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).

Personal details in the case published have been altered to protect patient privacy.

For palliative care consultations please contact the Palliative Care Program at PUH/MUH, 647-7243, beeper 8511, Shadyside Dept. of Medical Ethics and Palliative Care, beeper 412-647-7243 pager # 8513, Perioperative/ Trauma Pain 647-7243, beeper 7246, UPCI Cancer Pain Service, beeper 644-1724, Interventional Pain 784-4000, Magee Women's Hospital, beeper 412-647-7243 pager #: 8510, VA Palliative Care Program, 688-6178, beeper 296. Hillman Outpatient: 412-692-4724. For ethics consultations at UPMC Presbyterian-Montefiore and Children's page 958-3844. With comments about "Case of the Month" call Dr. Robert Arnold at (412) 692-4834.



(Discussion Continued)

Several small studies (n<60) showed benefit of the use of valproic acid (maximum of 1200 mg/day in divided doses) over placebo in the treatment of diabetic neuropathy (8). However, this data is not convincing. Other studies of valproic acid have failed to find an effect (9). Adverse effects include liver function test abnormalities, dizziness, drowsiness and nausea (2).

Topiramate was evaluated in a 2010 systematic review for the treatment of neuropathic pain. Of four randomized placebo-controlled trials, three were negative and one positive for the treatment of painful polyneuropathy. No studies were found to evaluate its efficacy in the treatment of post-herpetic neuralgia, peripheral nerve injury or central pain (9). Serious adverse events thought to be related to topiramate included convulsion and bradycardia plus syncope. Additional adverse effects include sedation, nausea, diarrhea and metabolic acidosis (2).

Summary: Neuropathic pain remains best treated with TCAs, SNRIs, and the AEDs gabapentin and pregabalin. For patients who are intolerant to or who experience pain unresponsive to those medications, one can consider therapy with other anti-epileptics. However, these agents are associated with more side effects and lower rates of efficacy.

Resolution of the case: RD was started on gabapentin and titrated up to a dose of 900mg three times a day with moderate pain relief. His opioids were tapered and discontinued.

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