PALLIATIVE CARE NETWORK OF WISCONSIN

Non-Opioid Adjuvant Analgesics
Fast Facts and Concepts and CME Module

FAST FACTS AND CONCEPTS: CONTINUING MEDICAL EDUCATION MODULE
NON-OPIOID ADJUVANT ANALGESICS
Course Description and Learning Objectives

Course Description: Patients with serious illness are at risk for poorly-controlled pain which could severely impact their quality of life in their last months of life. In the setting of the opioid crisis, which has led to significant public health threats in the United States and other western countries, there has been a movement to better understand and utilize non-opioid analgesics. This trend also applies to palliative care and hospice patients. To prescribe non-opioid analgesics in a safe and effective manner, clinicians must be knowledgeable of the adjuvant analgesics available, their mechanism of action, the indications for their use, and safety considerations. In this module, users can attain 1.0 hours of CME credit after successful completion of all of the following tasks:

A. Content review of ten *Fast Facts and Concepts* covering the following topics:
    a. Lidocaine patch
    b. Ketamine
    c. Steroids for bone pain
    d. Antidepressants for neuropathic pain
    e. Tapentadol
    f. Antiepileptic drugs for neuropathic pain
    g. Pregabalin versus gabapentin
    h. Tramadol
    i. Oral versus intravenous acetaminophen
    j. Skeletal muscle relaxants
B. A score of 70% or higher on a 10 question quiz covering this content
C. Completion of a course evaluation

Learning Objectives: At the conclusion of this course, learners will:

1. List three non-opioid medications that can be utilized for neuropathic pain.
2. Describe starting doses and indications for three non-opioid adjuvant medications.
3. Highlight three safety considerations when prescribing non-opioid adjuvants.

FAST FACTS AND CONCEPTS #129
STEROIDS IN THE TREATMENT OF BONE PAIN
Elizabeth Weinstein and Robert Arnold MD

Background Corticosteroids are recommended as an adjuvant analgesic for cancer-related bone pain. The mechanism of action is likely related to decreasing tumor-related edema or inhibition of prostaglandin and leukotriene synthesis. This *Fast Fact* discusses the use of corticosteroids for painful bone metastases; see also *Fast Facts* #66, 67, and116 about palliative radiotherapy. Steroids have been shown to prevent pain flare associated with palliative radiation of bone metastases.

Dosing The ideal corticosteroid, dose, and duration of therapy for bone pain is unknown; current practice is derived from expert opinion and anecdotal case series. Dexamethasone is commonly used due to its lower mineralocorticoid effect and long half-life, which allows once-daily dosing. One randomized controlled trial demonstrated a decrease in pain scores in patients with cancer-related pain using oral methylprednisolone 16 mg PO twice a day. Other starting dosages reported in the literature include dexamethasone 4-8 mg PO daily or prednisone 20-30 mg PO 2-3 times per day.

Duration of Therapy The optimal duration of steroid therapy is unknown. If no benefit is seen within 5-7 days the drug should be discontinued. If beneficial, the drug should be tapered to the lowest effective dose or, if possible, discontinued to avoid long-term adverse effects.

Side Effects Side effects account for discontinuation of steroids in 5% of patients. Acute side effects include thrush (~30%), edema (20%), dyspepsia and peptic ulcer diseases, psychiatric symptoms (insomnia, delirium and anxiety), and glucose intolerance. Delayed side effects from long term use include adrenal suppression, moon facies/fat redistribution, increased susceptibility to infection, osteoporosis, skin fragility and impaired wound healing. A prospective review of 373 inpatients with advanced malignant disease demonstrated that the side effect profile of dexamethasone and prednisone are similar, although at equipotent doses dexamethasone causes slightly more thrush and psychiatric symptoms and less edema, weight gain and dyspepsia. The relationship between peptic ulcer disease and steroids is controversial; in one nested case-control study it appeared correlated with concurrent NSAID use and a cumulative dose greater than 1000 mg of prednisolone or 140 mg of dexamethasone. Case reports and prospective series suggest that psychiatric symptoms are most commonly seen in middle-aged women, are directly related to dosage, and usually resolve with dose reduction.

Summary Steroids are recommended for use in bone pain, but the choice of dose, duration and specific drug is largely empiric. Steroid toxicities are a concern; the duration of treatment should be minimized to reduce the risk of adverse events.

Resources

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FAST FACTS AND CONCEPTS #132
KETAMINE USE IN PALLIATIVE CARE
Eric Prommer MD

Ketamine is FDA approved as a rapid-acting IV dissociative general anesthetic. There has been increased interest in its off-label use for pain control, administered via various routes. This *Fast Fact* reviews the use of ketamine in palliative care primarily for analgesia.

Mechanism of Action The N-methyl-D-aspartate/glutamate receptor (NMDA) is a calcium channel closely involved in the development of central (dorsal horn) sensitization. This channel has a role in opioid-resistant pain, neuropathic pain, allodynia, and hyperalgesia. Ketamine enters and blocks the open channel at a phencyclidine site, thereby inhibiting the excitatory effects of glutamate and aspartate. Ketamine also interacts with nicotinic, muscarinic, and opioid receptors. Pre-clinical data suggests it may also have anti-inflammatory effects.

Pharmacology As an anesthetic, ketamine is given IV or IM. For pain, the parenteral solution can be delivered at much lower doses by oral, intranasal, transdermal, rectal, and subcutaneous routes. Onset of analgesia is 15-30 minutes; duration of action is 15 minutes to 2 hours, possibly longer orally. A greater portion of ketamine is metabolized to a breakdown product with less affinity for NMDA receptors (norketamine) when taken orally versus IV. It is not yet clear if this reduces the analgesic properties of oral ketamine in a clinically significant way. Ketamine is physically stable when mixed with morphine, low-dose dexamethasone, haloperidol, and metoclopramide. Drugs that interact with CYP34A may affect its metabolism (e.g. azole antifungals, macrolides, HIV protease inhibitors, and cyclosporine).

Side Effects Undesirable effects of high dose ketamine used for general anesthesia (1-2 mg/kg IV or 6.5-13 mg/kg IM) include psychotomimetic phenomena (dysphoria, blunted affect, psychomotor retardation, nightmares, hallucinations), excessive salivation, and tachycardia. Co-administration with either lorazepam or haloperidol is a common empiric practice to minimize the potential for psychotomimetic side effects. Side effects at the lower doses used for pain are dose dependent, with dissociative feelings ("spaced out"), nausea, sedation, delirium, and hallucinations reported more frequently with IV administration. There is increasing concern about the potential for neuropsychiatric, urinary, and hepatobiliary toxicity with long term exposure to ketamine. In particular, delusions, memory impairment, dysuria, and abnormal liver functional tests have been associated with therapeutic analgesic doses of just 2 weeks duration. Ketamine can enhance its own metabolism via hepatic induction. This likely contributes to the rapid and dangerous tolerance to desired euphoric feelings among abusers.

Analgesic Effectiveness There is an absence of large controlled trials supporting ketamine as an analgesic for cancer or neuropathic pain. While there is a large body of case reports, retrospective surveys, and uncontrolled trials suggesting that ketamine effectively relieves cancer and non-cancer pain from neuropathy, ischemia, bone metastasis, or mucositis, smaller controlled trials have had mixed results. If used as an analgesic, a short term, "burst" treatment (e.g. appropriate ketamine dosing given over 2-4 days) should be considered, as evidence suggests the analgesic effects of "burst" treatment can extend several weeks.

Analgesic Effectiveness in Children Literature on the pediatric use of ketamine as an analgesic is scarce. In a case series, 8 of 11 children with cancer pain had opioid sparing effects as well as subjective improvements in pain and alertness with an IV ketamine infusion dosed at 0.1 to 1 mg/kg/hour. No significant psychotropic side effects were noted, but all patients had lorazepam co-administered

Other Potential Palliative Uses of Ketamine

- Single use of IV ketamine (typically 2.5 to 5 mg prn) often in combination with morphine or midazolam has been described for peri-operative use, dressing changes, and orthopedic emergencies.
- Topical ketamine as an oral rinse has been described to treat mucositis, and as a gel for neuropathy.

- Ketamine has antidepressant effects in depressed patients perhaps even within hours after one dose. However, its use for depression is experimental and should be restricted to controlled trials.

Titration Schedule There are no studies comparing various titration or dosing schedules, nor routes of administration. Usual initial analgesic oral dose in adults is 10-25 mg TID to QID with titration in steps of 10-25 mg. The maximum reported oral dose is 200 mg QID. A common initial IV dose in adults is 50-100 mg/day, with titration at increments of 25-50 mg/day, and a usual effective dose of 100-300 mg/day. Careful monitoring of blood pressure, heart rate, and psychotomimetic effects should occur. Drowsiness may ensue when patients are on background opioids. Consequently, some clinicians empirically reduce opioid doses by 25-50% when starting IV ketamine.

Summary The current collection of evidence is likely insufficient to fully assess the potential benefits versus harms of ketamine as an analgesic. A short course of low-dose ketamine (at sub-anesthetic doses) can be considered in the palliative care setting with the following notes of caution:

- Ketamine should be reserved for pain refractory to opioids and other standard analgesics due to its potential for neuropsychiatric, urinary tract, and hepatobiliary toxicity.
- If urinary symptoms occur in the absence of an infection, clinicians likely should stop the ketamine.
- Analgesic use should be limited to palliative care and/or pain specialists.
- In patients with a prognosis more than a few weeks, attempts to withdraw ketamine at least 2-3 weeks after initiation should be made in earnest.

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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 additional 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 for the treatment of CIPN. 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** *Buproprion* 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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recommended in the product labeling. Accordingly, the official prescribing information should be consulted before any such product is used.

FAST FACTS AND CONCEPTS #228
TAPENTADOL

Rohtesh S Mehta MD, MPH and Robert M Arnold MD

Background Tapentadol is an oral analgesic, approved by the FDA in 2009 for the management of moderate to severe acute pain in adults. This *Fast Fact* reviews its pharmacology and use.

Pharmacology

- Tapentadol is a centrally-acting, synthetic, oral mu-opioid receptor agonist which also inhibits norepinephrine and serotonin reuptake within the CNS. It is structurally and pharmacologically similar to tramadol (see *Fast Fact* #290 for more information on tramadol).
- Oral bioavailability ranges from 32% to 42%, with a half-life of 4 ½ hours.
- The drug is metabolized in the liver (97% by Phase-2 conjugation) and excreted in the urine.
- Tapentadol has no known pharmacologically active metabolites, no relevant CYP interactions, and no drug-drug interactions through cytochrome induction or inhibition (1).
- There are no dosing adjustments required in mild-to-moderate renal or hepatic impairment (Child class A or B); it has not been studied in patients with severe hepatic impairment (Child class C).

Research Data The FDA approval was based on industry-coordinated, randomized controlled studies conducted in patients with osteoarthritis and after bunionectomy. In these studies 50 mg doses of tapentadol was shown to be non-inferior to 10 mg of oxycodone immediate-release in the treatment of pain, but the incidence of nausea, vomiting, dizziness, and constipation was significantly lower (2,3). In another single-dose study involving patients undergoing molar extraction, tapentadol 200 mg demonstrated improved analgesia but higher sedation than 60 mg of oral morphine (4). Total daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been tested, nor has tapentadol been studied in children. Tapentadol has not been tested in a randomized, controlled fashion for cancer pain nor in palliative care settings; however, prospective observational studies showed it to be well tolerated and effective for opioid naïve (doses 100 mg per day) and opioid tolerant patients (doses 350 to 450 mg per day) with moderate to severe cancer pain (5,6). There are not enough data to comment on whether the drug has a ceiling effect, nor its long-term safety and efficacy (the longest study is a 1 year safety study). It has not been comparatively studied against tramadol.

Side Effects and Cautions Tapentadol's side effect profile is generally similar to opioids: nausea, vomiting, constipation, addiction, respiratory depression, pruritus, dizziness and drowsiness. A pooled analysis of randomized controlled trials suggest that gastro-intestinal side effects are likely milder than other opioids (7). As with tramadol, there is a theoretical increased risk of seizures, as well as serotonin syndrome if given with other serotonergic agents (e.g. antidepressants, drugs with monamine oxidase inhibitory effects). Abuse and addiction are possible as with any opioid agonist. An abstinence syndrome has not yet been described; in one study drug tapering was not required after 90 days of treatment (2).

Dosing and Cost Tapentadol is available as 50, 75 and 100 mg immediate-release tablets and 50, 100, 150, 200, and 250 mg extended release tablets. The initial dose is 50-100 mg every 4 hours (although a second dose can be given one hour after the initial dose). The average wholesale pricing for tapentadol is approximately $5 to $7 per immediate release tab and $5 to $15 per extended release tablet. For comparison, tramadol costs $0.07/tab (50 mg), oxycodone costs $0.70 (15 mg tab), and morphine costs $0.18 (15 mg tab).

Summary Tapentadol is a novel analgesic, with a 50 mg dose similar in efficacy to 10 mg of oxycodone. Currently its only clearly defined benefit over established opioids is its gentler GI side effect

profile. Its cost, potential ceiling effect, safety concerns with drug interactions, and uncertainty about long-term efficacy and safety limit its current application.

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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 carbemazepine 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 #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 900-3600 mg/day(1), while pregabalin remains ≥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 #290
TRAMADOL IN PALLIATIVE CARE

Jennifer Pruskowski PharmD and Robert M Arnold MD

Background Tramadol is an important medication in palliative care. It is a Step II agent on the World Health Organization's (WHO) pain ladder (1) and has FDA approval for the treatment of moderate to severe pain in adults. This *Fast Fact* will review tramadol's pharmacology, its benefits, and limitations. Note that tramadol has similarities with tapentadol which is discussed in *Fast Fact* #228.

Pharmacology The analgesic effects of tramadol are likely due to mu-opioid agonist activity, and weak monoamine reuptake inhibition (specifically blocking norepinephrine and serotonin) in the CNS. Tramadol is a prodrug and must be metabolized via CYP2D6 to its pharmacologically active metabolite (O-desmethyl tramadol) (2). It is excreted 90% in the urine; therefore specific dosing adjustments are necessary in renal impairment (CrCl <30 mL/min). There are also dosing adjustments in the elderly and end-stage liver failure. Clinicians should be aware of tramadol's significant drug interactions with other CYP2D6 inhibitors (fluoxetine, paroxetine and amitriptyline) and CYP3A4 inhibitors (ketoconazole and erythromycin), which increase the risk of seizures and serotonin syndrome.

Dosing Tramadol is available as both generic and proprietary formulations: a 50 mg immediate-release (IR) tablet and 100 mg, 200 mg, and 300 mg extended-release (ER) tablet (Ultram ER®). Immediate-release tramadol also comes formulated with acetaminophen. Tramadol should be started at 25 mg/day in the morning and increased by 25-50 mg every 3 days. The maximum daily dose of tramadol is 400 mg/day (50-100mg every 4-6 hours). In patients with renal impairment (CrCl <30 mL/min), the dosing interval is 12 hours with a maximum daily dose of 200 mg/day. The maximal recommended dose for adult patients with cirrhosis is 50 mg every 12 hours. For elderly patients over 75 years old, the total daily should not exceed 300 mg/day. Approximately 120 mg of oral tramadol is equivalent to 30 mg of oral morphine (3). Oral morphine tablets are roughly half the cost of tramadol IR tablets, and one-sixth the price of tramadol ER tablets.

Adverse Drug Reactions Tramadol's adverse drug reaction profile is similar to other opioids, although it has a lower incidence of respiratory depression (4) and likely has a lower abuse potential. An early comparative study suggested that tramadol has less abuse potential than morphine (5) and more recent preclinical studies suggest that abuse-related behavioral effects of tramadol may be of lesser magnitude than other mu-opioid receptor agonists (6). However, there have been several reports of its abuse and misuse (7). Hence, in August of 2014 tramadol was made a Schedule IV controlled medication.

Cautions Tramadol carries four specific cautions:

1. Seizures have been reported with higher than recommended dosage and with concomitant use of SSRI/SNRIs, MAOIs, triptans, and other drugs that reduce the seizure threshold (8).
2. Serotonin-syndrome may occur only with the concomitant use of other serotonergic drugs and is characterized as a triad of clinical changes: cognitive (mental-status chances, agitation and hallucinations), neuromuscular (hyperreflexia, incoordination) and autonomic (tachycardia, labile blood pressure). Although the prevalence of serotonin-syndrome is unknown, the majority of cases present within 24 hours (and most within 6 hours), of a change in dose or initiation of a serotonergic medication (9).
3. A large population cohort study from the UK comparing tramadol with codeine found a significantly increased risk of hospitalization from hypoglycemia, especially in the first 30 days of initiation in non-diabetic patients (10).
4. Lastly in May of 2010, the FDA strengthened the warning for suicide risk for patients at high risk (defined as those who are addiction-prone, taking tranquilizers, or antidepressant drugs)(11).

Research Data Most of the literature examining tramadol's role in palliative care involves the management of cancer pain (12). In comparison studies, tramadol was favored over sublingual buprenorphine due to the lower prevalence of adverse drug reactions, but morphine was preferred in patients with more severe pain (13). It has been shown to be safe and effective following surgical procedures, for neuropathic pain (14), as well as a variety of other pain conditions.

Summary Tramadol has an important position as a Step II agent on the WHO pain ladder, where it is effective for a variety of syndromes in patients with mild to moderate pain intensity. Its recommended dosing adjustments, potential ceiling effect, cost, pertinent drug-interactions, and risk for significant adverse drug reactions may limit its chronic use in patients with significant pain.

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FAST FACTS AND CONCEPTS #302
ORAL VS INTRAVENOUS ACETAMINOPHEN

Jahnavi Gollamudi MD, Sean Marks, MD

Background Acetaminophen (Tylenol) is one of the most commonly prescribed analgesics. Until recently, only oral and rectal formulations were available in the US. In 2010, the FDA approved intravenous (IV) acetaminophen (Ofirmev) for treatment of mild to moderate pain, fever, and as an opioid adjunct for moderate to severe pain. This *Fast Fact* will examine the clinical role of IV acetaminophen and compare its efficacy with oral acetaminophen.

Mechanism of Action Though the exact mechanism of action is unknown, acetaminophen's analgesic effects are thought to occur via inhibition of prostaglandin synthesis in the CNS and blockage of peripheral pain receptors (1).

Pharmacokinetics There are several potential pharmacokinetic benefits of IV acetaminophen. The time to peak analgesic effect of IV acetaminophen is within 10 minutes after its administration compared with 1 hour for oral acetaminophen. It is also associated with significantly higher mean cerebrospinal fluid concentrations than oral or rectal formulations (2). This makes it well suited for settings where quick analgesia is required, such as the perioperative period, especially since the duration of action appears to be the same between both formulations (4 to 6 hours). IV acetaminophen has better bioavailability when gastric function is compromised (i.e. post-operative ileus) (3). Finally, due to differences in first pass metabolism, IV acetaminophen may expose the liver to 50% less initial acetaminophen (4).

Efficacy in Perioperative Pain Management IV acetaminophen has been well studied in perioperative settings. Despite the theoretical pharmacokinetic benefits of IV acetaminophen, research has shown that the number need to treat (NNT) for a 50% reduction in post-operative pain is 5.3 for IV acetaminophen compared with 3.8 for oral when both are dosed at 1000 mg every 6 hours (5,6). In a direct comparison trial, no significant differences in intraoperative or post-operative pain measures were identified between 1000 mg of oral versus IV acetaminophen (7). A separate head-to-head trial demonstrated a significant opioid sparing effect with IV acetaminophen compared with oral; however, the reduction in opioid dosing did not correlate with a decrease in nausea and vomiting and its comparative effects on delirium, inpatient length of stay, and constipation were not evaluated (8). Hence the clinical significance is still in question. When 1000 mg of IV acetaminophen was compared with 30 mg of IV ketorolac (a reasonable therapeutic alternative to IV acetaminophen) there was no significant difference in pain relief (9).

Potential Uses of IV Acetaminophen IV acetaminophen has not been well studied in patients with terminal illnesses. Empirically some experts hope that it may have an unique clinical role for fever and pain management in imminently dying patients who cannot swallow, especially in situations when rectal acetaminophen is not preferred or possible (e.g. neutropenic or post-colectomy patients) (10).

Safety IV acetaminophen can be safely administered at doses of 1000 mg in patients who weigh over 50 kg, with a maximum daily limit of 4000 mg. For patients and children over 2 years, who weigh less than 50 kg, the dose is weight based at 15 mg/kg. Given its favorable first pass effects, the theoretical risk of hepatotoxicity with IV acetaminophen is believed to be low. A review of the literature suggests that when hepatotoxicity occurs, it is mostly due to dosing errors and can be potentiated by malnutrition (11). Of note, IV acetaminophen overdose has no validated nomogram for treatment decision-making. The most common side effects are similar to oral acetaminophen and include nausea, vomiting, and insomnia (12).

Cost IV acetaminophen costs more than 20 times the equivalent dose of oral acetaminophen. Therefore, there is controversy whether IV acetaminophen is a cost-effective analgesic.

Summary IV acetaminophen has only been evaluated in a perioperative setting, which limits its extrapolation to other clinical settings. Even in the post-operative period, IV acetaminophen has not shown clinical superiority; hence, the increased cost of IV acetaminophen may outweigh any benefit it offers. Until further investigation shows otherwise, IV acetaminophen may be best reserved for clinical

settings where GI absorption is compromised or the use or the use of reasonable therapeutic alternatives such as NSAIDS and opioids may be undesirable.

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FAST FACTS AND CONCEPTS #340
SKELETAL MUSCLE RELAXANTS

Brittany Hardek, PharmD; Jennifer Pruskowski, PharmD

Background Skeletal muscle relaxants (SMRs) are a heterogeneous class of medications used for the management of spasticity or muscle spasms. This *Fast Fact* reviews their role in palliative care.

Pharmacology SMRs are known CNS depressants. Dizziness, drowsiness, confusion, and an increased risk of injury are consistently reported adverse effects, especially in ages ≥ 65 (1-3). Most SMRs are predominantly metabolized by the liver, except for baclofen (only 15% hepatic metabolism). Therefore, SMRs require extra caution and dose reduction in patients with cirrhosis (4).

Mechanism of Action Though their mechanism of action is largely unknown, many experts believe it largely stems from their sedative effects. There are two general types of muscle relaxants:

- Antispasticity agents: these aim to reduce muscle hypertonicity and involuntary jerks associated with neurological disorders like multiple sclerosis (MS) or cerebral palsy (CP). Baclofen is the most commonly prescribed agent in this class (4).
- Antispasmodic agents: these aim to treat striated muscle spasms from peripheral musculoskeletal conditions like low back pain (4). Cyclobenzaprine and methocarbamol are examples (4). Most experts recommend limiting their use to 2-4 weeks because of the associated CNS risks.

Clinical Evidence The most compelling evidence for muscle relaxants is for MS (5). Placebo-controlled trials have shown a similar reduction in daily muscle spasms and clonus in MS patients receiving baclofen or tizanidine (6-8). To date, no head to head trials have adequately compared their effectiveness in controlling MS-related muscle spasms with botulinum injections. For other conditions:

- There is no published evidence firmly establishing the efficacy or safety of SMRs compared with opioids, acetaminophen, or NSAIDs. It is also unknown if SMRs have an opioid-sparing effect.
- For acute back pain, carisoprodol, cyclobenzaprine, and tizanidine have been shown to be moderately effective for short term relief (2 weeks) compared with placebo (1,5).
- For musculoskeletal back pain lasting > 2 weeks, a 2003 systematic review of placebo controlled trials found insufficient evidence to support skeletal muscle relaxants as effective agents (6).
- There is no compelling evidence that one skeletal muscle relaxant is more effective than another.
- For cancer patients, use of baclofen and diazepam has been described as adjuvants for cancer-related spasticity or muscle spasms, although controlled evidence supporting such use is lacking (9).

Patient Selection When assessing patients, first determine whether you are treating spasticity or peripheral muscle spasm. Spasticity is a state of increased muscular tone with exaggeration of tendon reflexes most commonly associated with conditions like MS, traumatic brain injury, and CP (2,4). In contrast, muscle spasm is a sudden involuntary contraction of one or more muscle groups and is typically associated with a muscle strain, fibromyalgia, or mechanical low back pain (2,4). Avoid muscle relaxants in elderly patients or patients with preexisting cognitive impairment who may be at high risk for delirium. For patients <65 with insomnia related to muscle spasms, cyclobenzaprine, tizanidine, and diazepam are the most sedating SMRs while methocarbamol and metaxalone are least sedating.

Pediatric Use: Although mostly off-label, SMRs are commonly prescribed as anti-spasticity agents for children with hypertonicity from conditions such as CP. Baclofen has the most established pediatric dosing: start 5 mg BID or TID; max daily dose is 40 mg in ages 2-7 and 60 mg for ages 8-17. Caution in children with seizure disorders as baclofen can lower the seizure threshold.

Cost As a class, skeletal muscle relaxants are fairly affordable. Diazepam is the least expensive with a usual cost of $0.22/tablet; tizanidine is the most expensive at about $1.22/tablet. For comparison, immediate release morphine sulfate is usually about $0.43/tablet.

Summary Outside their role as anti-spasticity agents, the risks of adverse effects from SMRs is high and may outweigh benefits. When prescribed as anti-spasmodic agents for common conditions such as low back pain or fibromyalgia, SMRs should be limited to short term use (e.g. 2-4 weeks), with a prescription only being renewed after an in-person reassessment. The choice of a SMR should be based on its adverse-effect profile and tolerability (2). See the table below (4).

Medication	**T 1/2 Hours**	**Starting Dose**	**Special Considerations**
Anti-spasticity Agents			
Baclofen	5	5 mg TID	Lowers seizure threshold. Can increase Alk Phos and AST. Available intrathecally. Adult max dose 80 mg/day. Reduce dose when CrCl <80 mL/min. Also prescribed for alcohol use disorder and hiccoughs (10). FDA approved ages ≥ 12.
Anti-spasmodic Agents			
Cyclo-benzaprine	18	5 mg TID	Structurally akin to tricyclic antidepressants; caution when cardiac issues present as patients are at risk for anticholineric effects like orthostasis, and QTc prolongation. Adult max daily dose 30 mg. FDA approved ages 15 and above.
Carisoprodol	8	250 mg QID	Metabolized to meprobamate which has significant abuse potential. Max adult daily dose 1400 mg.
Metaxalone	9	800 mg TID	Caution in liver failure. Max daily adult dose 2400 mg.
Metho-carbamol	1-2	750 mg QID	May cause brownish/green urine discoloration. Consider 1500 mg QID as a loading dose for 2-3 days. FDA approved ages 16 and above.
Combination Agents			
Diazepam	48	2-10 mg TID	Significant abuse potential.
Tizanidine	20-40	4 mg TID	Hypotension, asthenia, dry-mouth may result. Contra-indicated with ciprofloxaxin and other CYP A12 inhibitors. Dose reduce when CrCl <25 mL/min. Max daily dose 36 mg.

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