



Case Conference: Adjuvant Analgesics in Pain Management

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Case Conference: Adjuvant Analgesics in Pain Management

- A 76-year-old woman requests an early appointment because of "severe burning pain in the chest"
- A quick review of her chart prior to the visit reveals that she has been a patient of the clinic since 2000
 - She was seen annually for years
 - Visits then became more frequent 5 years ago, after a diagnosis of chronic myeloid leukemia
 - This is one of several visits during the past few months, which have been necessitated by a new diagnosis of herpes zoster infection



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- The patient's diagnoses include:
 - Acute zoster
 - Chronic myeloid leukemia
 - Hyperuricemia
 - Hyperlipidemia
 - GERD
 - Eczema

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- Medications include:
 - Imatinib 400 mg daily
 - Allopurinol 100 mg daily
 - Famotidine 20 mg daily
 - Simvastatin 20 mg daily
 - ASA 81 mg daily
 - Hydrocodone 5 mg/acetaminophen 325 mg twice daily PRN
 - Ibuprofen 400 mg four time daily PRN

Background to the Case

- The patient was seen about 4 months ago for a chief complaint of burning pain in the left breast
- The PCP noted several vesicles in the area of pain, and suspected acute herpes zoster
 - The diagnosis was confirmed by Tzanck smear
- The patient received valacyclovir 1000 mg three times daily for 7 days and she was able to manage the pain with cold compresses and ibuprofen

Background to the Case

- The patient was again seen by the PCP two weeks after the eruption of the zoster
 - The rash had resolved
 - Burning pain was constant but usually mild and ibuprofen taken PRN twice daily was sufficient to control more severe periods of pain
 - The patient was reassured that the condition had been effectively managed; she was told to return for follow-up in 4-6 weeks

Background to the Case

- When seen about 1 month ago, the patient reported continued burning discomfort extending from the left scapula around her chest and into the left breast
 - Overall, the pain was less than weeks earlier
 - Pain was usually mild, but periods of more intense pain had been occurring 2-3 times per day
 - Occasionally, the patient experienced uncomfortable itch in the same area as the pain

Background to the Case

- The PCP's note from 1 month ago documented slow resolution of acute herpes zoster, but the patient was nonetheless treated for continuing pain with:
 - Lidocaine 5% patch
 - Ibuprofen 400 mg up to four times daily PRN
 - Hydrocodone 5 mg/acetaminophen 325 mg 1-2 tablets up to twice daily PRN

Background to the Case

- Medical history:
 - CML was diagnosed about 5 years ago after leukocytosis was found on a routine CBC
 - She underwent induction chemotherapy with daunorubicin and cytarabine and subsequently received daily imatinib therapy
 - She has been stable, with mildly pancytopenic counts, for the past 4 years

Background to the Case

- Medical history:
 - The patient had been generally healthy until the diagnosis of CML was made
 - The hyperuricemia and GERD followed treatment of the CML
 - Both conditions are controlled with the current medications

Background to the Case

- Social history:
 - Retired clerk, living on Social Security and a small pension
 - Divorced many years ago
 - Lives in one-bedroom apartment in a NORC
 - Two daughters live in the area and are very involved and caring
 - Minimal involvement in Christian faith community
 - No substance use issues: no tobacco, occasional glass of wine

Background to the Case

- Family history:
 - Mother died from breast cancer at 82 years
 - Father died from MI at 60 years
 - Two sisters, both alive and well
 - Daughters ages 55 and 50, both healthy
 - Four adult grandchildren

Background to the Case

- Advance care planning:
 - In the chart is a legally executed health care proxy designating her two sisters as agents
 - The proxy does not include any instructional directives

Back to the Visit

- The patient starts the current visit by stating that she needed to be seen for an early appointment because the burning pain had worsened
 - The pain began to increase several weeks ago and it has steadily worsened
 - The location of the pain has not changed but there has been some 'spreading' so that the lateral chest is more involved than before
 - The pain is still mild during part of the day but it now increases frequently—about 6-8 times per day—and each 'flare' lasts longer than before, sometimes an hour
 - The pain increases with movement and stress, and decreases when she lies on the right side

Back to the Visit

- There were new pains:
 - An intense brief stabbing in the lateral breast occurs unpredictably, sometimes once or twice daily and sometimes every hour
 - Itching has worsened and is usually over the scapula; it feels like severe eczema but there is never a skin lesion
 - There is moderate sensitivity of the skin in the entire area affected by the pain; clothing is uncomfortable

Back to the Visit

- The patient describes adverse consequences of the pain:
 - Sleep is interrupted and she has daytime fatigue
 - Mood is very poor
 - Appetite is poor and she is trying to use supplements to keep her weight up
 - She can still take care of her apartment and can go shopping for food, but is otherwise staying in and has not been interested in social activities

Back to the Visit

- The PCP asked additional questions to clarify the severity of the mood disorder
 - The patient denied feeling hopeless but indicated that she was frightened about the diagnosis (“Why is the pain getting worse?”)
 - She was not anhedonic, stating that when the pain was mild she still enjoyed being with family
 - She said that she knows that she can “bounce back” if the pain can be lessened

Back to the Visit

- The patient had tried the lidocaine patch when it was first given and it helped slightly with pain and itch
 - She then stopped it and recently tried it again, but this time there was no benefit
 - Ibuprofen 400 mg is being taken four or five times daily, but the patient is uncertain that it is having an effect
 - The hydrocodone 5 mg/acetaminophen 325 mg tablet transiently reduces the pain and she has been taking 1-2 tablets twice per day

Back to the Visit

- A focused examination reveals the following:
 - The patient appears uncomfortable and is sitting forward in her chair to avoid contact with her back
 - Skin in the affected region is normal in appearance except for a few small areas of postherpetic scarring
 - There is allodynia (pain with light touch) in the area of the pain, most severe over the left scapula but extending anteriorly in a T4-T6 dermatomal distribution
 - Limb strength, gait, coordination, and deep tendon reflexes are all normal
 - Examination of the heart, lungs and abdomen is normal

Back to the Visit



- Summary:
 - The patient is a 76-year-old woman with chronic myeloid leukemia and a history of worsening neuropathic pain following acute herpes zoster
 - At four months after the onset of zoster, the diagnosis is now postherpetic neuralgia
 - The initial decline in pain followed by an increase is unexplained but consistent with this diagnosis
 - No further work-up is indicated because the history and examination does not suggest that there has been an intercurrent event or disorder that could explain the course of the pain
 - The deterioration in mood and function is a consequence of the pain, not an intercurrent major depression

Back to the Visit



- Summary:
 - The PCP informs the patient that the symptoms are all consistent with PHN
 - The plan of care will continue to focus on pharmacotherapy
 - The PCP makes a note that other pain management strategies may be needed soon

Symptomatic Treatment of Pain: Modalities



Pharmacotherapy:

- Non-opioids
- Opioids
- “Adjuvant” analgesics

Psychological:

- Psycho-educational
- CBT
- Others

Interventional:

- Injection therapy
- Neural blockade
- Implant therapies

Rehabilitative therapies:

- Physical/Occupational therapy
- Modalities/orthotics

Integrative therapies:

- Acupuncture
- Chiropractic
- Music therapy
- Others

Neuromodulation:

- TENS and transcranial
- Invasive types

Lifestyle changes:

- Weight loss

Management of Chronic Pain: Pharmacotherapy



- There is broad agreement that:
 - Non-opioid analgesics are first-line for mild to moderate chronic pain of any type and should be considered coanalgesics during opioid therapy
 - Opioid analgesics are first-line for moderate or severe chronic pain due to an active, serious, or life-threatening illness, particularly when the disease is advanced
 - Long-term opioid therapy is not first-line in other types of chronic pain
 - Adjuvant analgesics should be considered for all patients with chronic pain, either as primary agents or as co-analgesics during opioid therapy

Back to the Visit

- The patient has a hematological malignancy but it is controlled and stable
 - The PCP decides that the current opioid can be continued as a PRN drug; continuous opioid therapy for long-term management will not be considered at this point
 - Numerous studies have confirmed the efficacy of opioid therapy for neuropathic pain

Gimbel JS et al: *Neurology*. 2003;60:927-934; Watson CP, Babul N: *Neurology*. 1998;50:1837-1841; Morley JS et al: *Palliat Med*. 2003;7:576-587; Raja SN et al: *Neurology*. 2002;59:1015-1021; Rowbotham MC, et al: *NEJM*. 2003;348:1223-1232; Gilron I, et al: *NEJM*. 2005;352:1324-1334

Back to the Visit

- Although it is generally believed that NSAIDs are inefficacious for neuropathic pain, anecdotal observations and limited data suggest that some patients benefit
- The PCP decides to recommend continued ibuprofen therapy based on the patient's report of pain relief

Widerstrom-Noga and Turk, *Spinal Cord*. 2003;41:600. Cohen et al, *Arch Intern Med*. 1987;147:1442

Back to the Visit

- The PCP decides to implement a trial of an adjuvant analgesic and plan for sequential trials if needed
- Adjuvant analgesics are:
 - Drugs with primary clinical uses other than pain, which may be analgesic in specific circumstances
 - Categories:
 - Multipurpose analgesics
 - Drugs used for neuropathic pain
 - Drugs used for bone pain
 - Drugs used for pain due to bowel obstruction

Multipurpose Adjuvant Analgesics

- Classes:
 - Corticosteroids
 - Antidepressants
 - Alpha-2 adrenergic agonists
 - Cannabinoids
 - Botulinum toxin type A
 - Topical therapy: Lidocaine, capsaicin, and others

Corticosteroids

- Based on clinical experience, used as an analgesic for varied types of chronic cancer-related pain:
 - Bone pain
 - Peripheral neuropathic pain
 - Pain due to bowel obstruction
 - Pain due to expansion of organ capsules
 - Pain related to lymphedema
 - Headache
 - Other conditions
- Risk profile only supports long-term use in an advanced cancer and severe inflammatory diseases

Leppert W, Buss T, Curr Pain Headache Rep 2012;16:307

Analgesic Antidepressants

- Based on safety and likelihood of efficacy, best choices would be a **SNRI** or a **2° amine tricyclic drug**
 - Most evidence supports **duloxetine**
 - Also consider
 - The 2° amine tricyclic drugs **desipramine** or **nortriptyline**
 - Other SNRIs
- Other antidepressants rarely used

Beal BR, Wallace MS. Med Clin NA 2016;100:65-79

α -2 Adrenergic Agonists

- Clonidine, tizanidine, and dexmedetomidine are multipurpose analgesics based on RCT data in varied acute and chronic pain syndromes
- In RCT, intrathecal clonidine worked for cancer-related neuropathic pain
- Tizanidine usually better tolerated than clonidine
- Consider early use of tizanidine for painful muscle spasm

Giovannini MP, et al, Med Res Rev 29:339, 2009

Cannabinoids

- Strong preclinical support for analgesic efficacy of both CB1 and CB2 agonists
- Positive RCTs of THC in central pain, nabilone in fibromyalgia, and nabiximols in central pain and in cancer pain
- Medical cannabis can be recommended for chronic pain or neuropathy
 - Overall, results support designation as a multipurpose analgesic, but more data is needed

Finnerup NB, et al, Lancet Neurol 2015;14:162-173 Svendsen et al, BMJ, 329:253, 2004; Skrabek et al, J Pain 9:164, 2008; Berman et al, Pain, 112:299-306, 2004; Portenoy RK et al, J Pain 13:438, 2012

Topical Adjuvant Analgesics

- Level of evidence varies, but there are data from RCTs supporting benefit in neuropathic pain, joint pain, and wound pain:
 - Lidocaine 5% patch and creams
 - NSAIDs, e.g., ASA and diclofenac
 - Low concentration (0.025% or 0.075%) capsaicin
 - Amitriptyline
 - Amitriptyline plus ketamine
 - Clonidine
 - Menthol
 - Opioids

Topical Adjuvant Analgesics

- Capsaicin 8%:
 - Approved in the US for postherpetic neuralgia
 - Apply for 60 min
 - When efficacious, benefit can persist for months
 - 1 year of safety day with repeated use

Simpson DM, et al. JPSM 2010;39:1053-64.
Webster LR, et al. J Pain. 2010;11:972-82

Adjuvant Analgesics for Neuropathic Pain

- First-line:
 - Antidepressants and gabapentinoids
 - Corticosteroids in advanced cancer
 - Topical agents
- Other multipurpose drugs:
 - Botulinum toxin
 - Alpha-2 adrenergic agonists
 - Cannabinoids
- Others

Gabapentinoids

- Mechanism primarily related to modulation of calcium channels, not GABA
- Many RCTs demonstrate that patients may respond to gabapentin, to pregabalin, to both, or to neither
- Pregabalin has more stable PK than gabapentin, with easier titration and faster onset of effect

Moore RA et al Cochrane Database Syst Rev 2014;Apr 27: CD007938

Gabapentinoids

- Gabapentin:
 - Starting dose 100 - 300 mg qd
 - Usual effective dose 600 – 1800 mg BID
- Pregabalin:
 - Starting dose 25 - 75 mg qd
 - Usual effective dose 150 – 300 mg BID

Non-gabapentinoid Anticonvulsants

- Other anticonvulsants are occasionally tried for neuropathic pain, though evidence of efficacy is limited
 - Older anticonvulsants have some evidence:
 - Carbamazepine (trigeminal neuralgia)
 - Divalproex sodium (migraine)
 - Phenytoin
 - Very limited evidence of analgesic efficacy:
 - Oxcarbazepine
 - Lacosamide

Moulin D et al. Pain Res Manag 2014;19:328-335; Wiffen P, et al. Cochrane Database Syst Rev., 2005;20:CD001133; Wiffen P, et al. Cochrane Database Syst Rev. 2014 Apr 10;(4):CD005451

Non-gabapentinoid Anticonvulsants

- Some newer anticonvulsants have minimal to no evidence of analgesic efficacy:
 - Clonazepam
 - Levetiracetam
 - Topiramate
 - Zonisamide
 - Tiagabine
 - Lamotrigine

Moulin D et al. Pain Res Manag 2014;19:328-335; Wiffen P, et al. Cochrane Database Syst Rev., 2005;20:CD001133; Wiffen P, et al. Cochrane Database Syst Rev. 2014 Apr 10;(4):CD005451

Other Drugs Considered for Neuropathic Pain

- Sodium channel blockers, e.g., IV lidocaine and oral mexiletine
- NMDA receptor antagonists, e.g., ketamine
- GABA B agonist, e.g., baclofen

Back to the Visit



- The PCP started gabapentin 300 mg at night and advised the patient to try topical low-concentration capsaicin 0.075%
- After the dose of the gabapentin was doubled 5 days later, the patient called the clinic to report that she could not tolerate it due to somnolence
- She also reported that the capsaicin “burned her skin” and was stopped
- Duloxetine 20 mg/day was ordered along with a lidocaine 5% cream
- She continued the ibuprofen and took the opioid 3-4 times daily

Back to the Visit



- The patient’s pain declined and her mood and sleep improved
- At a 4 week follow-up visit, she reported that her functioning was much better
- The patient declined an increase in the dose of the duloxetine or a trial of another medication at this time

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- Summary of treatment strategy for neuropathic pain:
 - First-line is an opioid if serious medical illness; otherwise, consider for PRN use and as second-line
 - First-line adjuvant analgesic is antidepressant if comorbid depression present, otherwise a gabapentinoid
 - If initial therapy has benefit, but more is needed, consider adding a second drug
 - If initial therapy has no benefit, rapidly taper and try a second drug
 - If an antidepressant was used first, start a gabapentinoid; if a gabapentinoid was used first, start an antidepressant
 - Always consider a coadministered topical drug

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- Summary of treatment strategy for neuropathic pain:
 - Consider further sequential trials if needed
 - Systemic:
 - Alpha-2 adrenergic agonists
 - Other anticonvulsants
 - Cannabinoids or medical cannabis
 - Others
 - Local:
 - Botulinum toxin injection
 - Topical:
 - High concentration capsaicin 8%
 - Others



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Q&A

