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Palliative Care Pharmacy
PHAST PHACT

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TODAY'S QUESTION:

Ouch That Hurts! Medications That Cause Pain
Group #1: Boney Pain

Palliative Care Pharmacy Team:

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: pruskowskija@upmc.edu

Background:
Bone pain in patients with cancer is commonly caused by cancer cells that have spread to the bones. However, there are a group of medications that weaken the bone matrix, therefore potentially causing bone pain.

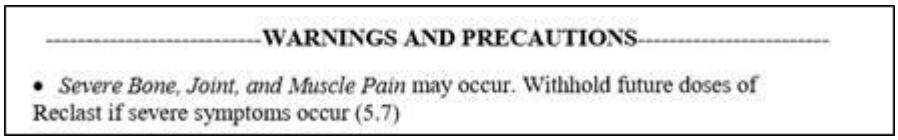
Importance:
Palliative care providers often treat patients with bone pain, therefore it is important to recognize which medications can cause this. In some cases, it may be more appropriate to discontinue the offending agent(s) before considering additional medications to treat.

The Literature:
There are four main classes of medications that can cause bone pain.

1. *Granulocyte colony stimulating factors (GCSFs): filgrastim and pegfilgrastim:*
   - Ann Pharmacother. 2017 Sep;51(9):797-803.
     Pegfilgrastim-Induced Bone Pain: A Review on Incidence, Risk Factors, and Evidence-Based Management.
     - Objective: To review the incidence, risk factors, and management of pegfilgrastim-induced bone pain (PIBP).
     - Methods: PubMed was searched from 1980 to March 31, 2017, using the terms pegfilgrastim and bone pain.
     - Results: A total of 3 randomized, prospective studies and 2 retrospective studies evaluated pharmacological management of PIBP. Naproxen compared with placebo demonstrated a reduction in the degree, incidence, and duration of bone pain secondary to pegfilgrastim. Loratadine was not effective in reducing the incidence of bone pain prophylactically, but a retrospective study evaluating dual antihistamine blockade with loratadine and famotidine demonstrated a decreased incidence in bone pain when administered before pegfilgrastim.
     - Conclusion: "Naproxen is effective at managing PIBP. Although commonly used, antihistamines have a paucity of data supporting their use. Dose

reductions of pegfilgrastim and opioids may also be potential management options; however, data supporting these treatment modalities are scarce."

2. *Bisphosphonates and RANKL antibodies (ex: denosumab) (yes, I know this sounds weird):*
   - According to the zoledronic acid package insert:



----------WARNINGS AND PRECAUTIONS----------

• *Severe Bone, Joint, and Muscle Pain* may occur. Withhold future doses of Reclast if severe symptoms occur (5.7)

     - "In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been infrequently reported in patients taking bisphosphonates. The time to onset of symptoms varied from one day to several months after starting the drug. Consider withholding future treatment if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate"

   - Clin Cases Miner Bone Metab. 2015 Jan-Apr; 12(1): 69–74.
     Severe polyarthritis secondary to zolendronic acid: a case report and literature review.
     - Discussion: "Adverse musculoskeletal reactions following treatment with oral bisphosphonates have been reported, including both acute and delayed onset of painful joints, synovitis and development of arthritis in structurally normal joints. These reactions have typically been self-limiting, not requiring hospitalisation or aggressive medical intervention. Musculoskeletal side effects following intravenous zolendronic acid, have also been reported, including the onset of new arthritis, painful joints and flare of existing osteoarthritis"

3. *The following oncologic agents: bortezomib (Velcade®), brentuximab (Adcetris®), cabozantinib (Cabometyx®), daratumumab (Darzalex®), decitabine (Dacogen®), erlotinib (Tarceva®), interferon alfa-2a, lenalidomide (Revlimid®), nilotinib (Tasigna®), panitumumab (Vectibix®), pomalidomide (Pomalyst®), rituximab (Rituximab®), trastuzumab (Herceptin®), and vinblastine (Velban®) and vincristine (Oncovin®):*
   - Acta Oncol. 1991;30(6):707-11.
     Muscle cramps associated with vincristine therapy.
     - Case report

4. *Hormone altering agents: bicalutamide, fulvestrant, goserelin, letrozole, leuprolide, megestrol, and tamoxifen:*
   - Breast Cancer Res. 2011; 13(2): 205.
     Aromatase inhibitor-associated bone and musculoskeletal effects: new evidence defining etiology and strategies for management
     - Narrative review
     - Discussion: "Musculoskeletal symptoms have arisen as important adverse effects of aromatase inhibitors (AIs). In the major phase III clinical trials that

compared AI to tamoxifen, the reported incidence of musculoskeletal symptoms ranged from 5 to 36%. However, case series have reported an even higher incidence of emergence of new or worsening joint symptoms in up to 61% of AI-treated women. By contrast, tamoxifen has not been associated with increased joint symptoms. While AI-induced arthralgias were reported as mild to moderate in severity and did not result in significant discontinuation of medication in the large trials, in more recent analyses, severe AI-induced arthralgias resulted in therapy interruption in up to 20% of patients. Therefore, AI-associated arthralgia may account for reduced medication compliance, leading to decreased efficacy and an increase in recurrence rates. Despite the frequent reporting of AI-induced arthralgias, the etiology of this adverse effect remains unknown."

So… What does this all mean Jenn?

- Be on the lookout for these medications when you have someone complaining of bone pain!

Geriatric Considerations:

- It appears these medications can cause bone pain in older and younger patients alike

Stay tuned for future PCP Phast Phact on bone pain!

CLINICAL PEARL:
There are four main classes of medications that can cause bone pain: GCSFs (ex: filgrastim), bisphosphonates, some oncological agents, and hormone altering agents.