Duloxetine: You’re Working on My Last Nerve (but in a good way)
Palliative Care ECHO
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No Conflicts of Interest

Objectives

- Describe known mechanisms of action of duloxetine
- Explain the FDA approved and off-label uses of duloxetine in various clinical situations
- Describe interplay of palliative care and hospitalist services, and provide tips for each from either perspective

Case Summary

- 50yo F with past hx of breast cancer s/p chemo and bilateral mastectomies
- March started to have pruritic rash on her hands that progressed to chest/ face and facial/angioedema
- Developed ear and axillary ulcerations and proximal muscle weakness
- She was started on steroids and antihistamines but no improvement
- Admitted at our hospital from 4/25-5/10

Case Summary

- ANA high titer; positive Anti-TIF 1gamma Ab
- CT Abdomen showed large pelvic mass
- Biopsy: High grade serous ovarian cancer, Stage IIIc
- Thigh MRI showed myofascitis
- Muscle biopsy: myopathic changes and myofiber atrophy

Case Summary

- Dermatomyositis incidence is rare 0.5-0.89/100k; female to male predominance 2:1[1]
- 5-7 fold increase in malignancy with 13-26% being ovarian[1]

1. UptoDate; Field C, Goff B. Dermatomyositis-key to diagnosing ovarian cancer, monitoring treatment and detecting recurrent disease: Case report. Gynecol Oncol Rep 2018

Case Summary

- IVIG, high dose steroids
- ECOG 3
- Treating cancer treats autoimmune disease
- Carboplatin/paclitaxel x2 cycles
- Now more functional, DM symptoms all but resolved
- 3rd round of chemo then to undergo TAH, BSO and debulking surgery with more chemo after

Case Summary

- She had neuropathic pain complaints
- Was using 10-20mg oxycodone and IV hydromorphone 0.8-1mg daily
- Started on duloxetine 30mg daily inpatient
- Improvement in pain with reduction in PRNs down to 5-10mg oxycodone only
- Followed up in clinic: only on duloxetine now

Duloxetine MOA

Serotonin-Norepinephrine Reuptake Inhibitor

- Increased NE→directly inhibits neuropathic pain through alpha-2 adrenergic receptors in dorsal horn and is more effective in neuropathic pain as it alters the plasticity of alpha-2 adrenergic receptors

- Increased NE on the locus ceruleus (in the Pons)→ improves function of the descending NE inhibitory system (major pain pathway in CNS)

- Serotonin and dopamine may reinforce NE effect to inhibit neuropathic pain

- Pain modulation quicker than antidepressive effects (days-weeks vs weeks-months)

- Concept of “Total Pain”

Obata H. Analgesic Mechanisms of Antidepressants for Neuropathic Pain. Int J Mol Sci 2017

Duloxetine

FDA approved for:

- Unipolar MDD, GAD
- Fibromyalgia
- Chronic MSK pain (low back and OA)
- Diabetic Peripheral Neuropathy

Off label use:

- CIPN
- Stress urinary incontinence

Duloxetine

Contraindications:

- Avoid with MAOis due to risk of serotonin syndrome
- Uncontrolled narrow-angle glaucoma (b/c of pupil dilation)

Risks/Side effects:

- Most common: nausea, somnolence, constipation, dry mouth, decreased appetite
- Be careful in pts with seizure history
- May uncover mania in patient’s with undiagnosed bipolar disorder

Duloxetine

Risks/Side effects:

- Black Box warning: may increase risk of SI in young/peds patients
- Monitor for hepatotoxicity
- Avoid in patient with liver dysfunction or ESRD
- Orthostatic hypotension-risk of falls
- Hyponatremia
- Bleeding risk
- Cannot crush delayed release capsule; comes in Drizalma Sprinkle capsule which can be opened

Questions to the Audience

- What’s the dose that you prescribe to patients?
- What’s the time frame you notice patients’ symptoms improve and/or
- What’s the timecourse you counsel patients to expect improvement?
- Have you ever used any other SNRIs for neuropathic pain?

Duloxetine in CIPN

- ASCO guidelines 2020: moderate recommendation for pt with cancer experiencing painful CIPN[1]

Data limited on efficacy or only moderate benefit:

- Study in JAMA 2013 showed 60mg dose decreased pain scores by 1.06 vs placebo[2]
- Most patients had GI or breast cancers and patient's treated with oxalaplatin had better response than paclitaxel

1. Lavoie Smith, et al. Effect of Duloxetine on Pain, Function and QOL Among Patients with CIPN-A randomized Clinical Trial. JAMA 2013

2. Loprinzi, et al. Prevention and Management of CIPN in Survivors of Adult Cancers: ASCO Guideline Update. J Clin Oncol 2020

Efficacy of Duloxetine on electrodiagnostic findings of Paclitaxel-induced peripheral neuropathy, does it have a prophylactic effect? A randomized clinical trial

- 40 patients with breast cancer receiving Paclitaxel: 20 intervention and 20 placebo
- Dosage was 30mg first week then 60mg BID for 8weeks
- Patient neurotoxicity questionnaire: 50% placebo patients had neurotoxicity vs 10% in duloxetine group
- Nerve conduction results also had significant differences
- Limitations small study: systematic reviews have not shown difference
- ASCO guidelines counsel against using as ppx

Aghabozorgi R, Hesam, M, Zahed G, Babaee M, Hashemi M, Rayegani SM. Anticancer Drugs 2023

Comparative Study of Effects of Venlafaxine and Duloxetine on CIPN

- Double blinded clinical trial: 52 patients in each group
- Dosages: 37.5mg daily Venlafaxine and 30mg daily Duloxetine
- Statistically significant decrease in neuropathic pain grade after 2-4weeks in both groups but significantly more in Duloxetine group

Farshchian N, Alavi A, Heydarheydari S, Moradian N. Cancer Chemother Pharmacol 2018

Combination Therapy with Methadone and Duloxetine for Cancer-related pain

- Retrospective study on University Clinic pts from 2012-2019
- Pts had mixed nociceptive and neuropathic pain
- 131 patients on combination therapy, 43 met study criteria
- Median dosage was 40-60mg duloxetine
- ESAS total, emotional symptom and pain scores had statistically significant decrease after combination therapy
- 28% reported >= 2 point reduction in pain scores; 1/3 had at least 1 point reduction in pain scores

Curry ZA, Dang MC, Sima AP, Abdulaziz S, Del Fabbro EG. Ann Palliat Med 2021

Efficacy of Duloxetine in Patients with Central Post-stroke Pain: A Randomized, Double-Blind Placebo Controlled Trial

- Pain manifested where stroke lesions are
- 4 week trial, 41 patients in each group; 30-60mg
- Response to treatment defined as >= 2pts reduction in pain
- Reduction by ~3pts on pain scale

Mahesh B, et al. Pain Med 2023

Efficacy and Safety of Different Antidepressants and Anticonvulsants in Central Poststroke Pain: A network meta-analysis and systematic review

- Total of 13 RCTs, 1040 patients and 9 different medications included
- Duloxetine was less effective than gabapentin, pregabalin, and SSRI interestingly Fluoxetine

Chen KY, Li RY. PLoS One 2022

Any evidence of decreased pain soon after taking dose?

Preoperative Duloxetine to improve acute pain and quality of recovery in patients undergoing modified radical mastectomy: A dose-ranging randomized controlled trial

- 81 patients; ~20 per group
- Duloxetine 0, D30mg, D60mg, D90mg
- Post-op analgesia with scheduled IV Tylenol 1g q8hr + morphine PCA 2mg PRN w/ q5min lockout
- Significant difference at 24hrs D60/90 patients used 0 morphine 24hrs post-op compared to 10 and 9mg with the 0 and 30mg duloxetine doses however D90 had more side effects

  Concluded pre-op dose of 60mg was safe and effective

Hetta DF, Elgalaly NA, Hetta HF, Mohammad MAF. J Clin Anesth 2020

Perioperative Duloxetine to Improve Postoperative Recovery After Abdominal Hysterectomy

- Prospective, Randomized, double-blinded placebo-controlled study
- Surgery done for non-malignancy related reasons; 63patients
- Excluded those on chronic opioids or antidepressants
- 60mg, 2hrs pre-op and again 24hrs post-op
- Used regional block during surgery and then NSAIDs as part of multi-modal pain regimen
- Found with duloxetine, morphine usage was only 1mg IV vs 5.5mg IV for placebo
- Improved physical comfort, emotional and pain components in quality of recovery score (QOR-40)

Castro-Alves L, et al. Anesth Analg 2016

Duloxetine for the Treatment of Acute Postoperative Pain in Adult Patients: A systematic review and meta-analysis

- 13 studies included: post-hysterectomy and mastectomy; post-lumbar disk herniation; hip and knee surgery
- Duloxetine decreased pain scores after 48hrs
- Decreased morphine dosage by 8.21mg at 24hrs and 7.71mg at 48hrs
- No effect of duloxetine in sub group that used PCA post-op
- No effect in prevalence of post-op n/v, headache or dizziness
- Concluded that there was statistically significant effects of duloxetine on post-op pain and opioid consumption during first 48hrs, but “high risk-of-bias and inter-study heterogeneity caused very-low quality of evidence”

Rodrigues de Oliveira Filho G, Kammer RS, Dos Santos H. J Clin Anesth 2020

60mg Duloxetine seems to be safe and effective dose that could work within minimum 24hrs to 7days

Intersection of Palliative Care and Hospital medicine

- Family meetings

-manager gathering the specialists which is kind of like palliativists

- HELP
- Communication
- Continuity

Intersection of Palliative Care and Hospital medicine

- Symptom management
- Teaching of residents (and your fellow attendings) outside of rotating with us on palliative consult service

Thank you!

Questions?