Brain or Pain:
Brain Alterations
in Chronic Pain Patients

Nancy Balch, PharmD, BCCCP
Emergency Medicine Pharmacist
nbalch@mgh.harvard.edu

Disclosure Statement

- I have no personal or financial conflicts of interest relating to this presentation

Objectives

- Develop treatment plans for chronic pain vs treatment plans for central pain secondary to chronic pain
- Differentiate between chronic pain with and without central pain
- Differentiate between opioid tolerance and/or increased pain vs new central pain secondary to chronic pain

Abbreviations

- **BMI: body mass index**
- **D/T: due to**
- **CC: chief complaint**
- **Etoh: alcohol**
- **Htn: hypertension**
- **HPI: history of present illness**
- **IR: immediate release**
- **L: left**
- **MVA: motor vehicle accident**
- **NKA: no known allergies**
- **NSAIDs: non steroidal anti-inflammatory drugs**
- **PMDP: prescription drug monitoring program (previously pmp)**
- **PMH: primary medical history**
- **R: right**
- **SNRI's: serotonin norepinephrine reuptake inhibitors**
- **S/P: status post**
- **TCA's: tricyclic antidepressants**

“As essential as the brain is to our existence, it's still as mysterious to us as a planet from a far-flung galaxy”

https://www.livescience.com/64345-amazing-brain-2018.html

Pain: a topic too large for one CE

- **Conferences just on pain**
- **Difficult to treat**
  - **Objective Pain**
    - **Open fracture**
  - **Subjective Pain**
    - **Difficult to treat patient with sprained ankle vs**
    - **Patient calmly asking if they can have more pain medications for their open fracture**

For this discussion

- **Chronic pain**
- **Acute on chronic pain**
- **Central pain**
- **Central pain secondary to chronic pain**

BASIC overview: Pain Medication Actions

Brain

opioids, alpha2 agonists = direct effect (oxycodone, morphine, tizanidine, clonidine, etc)

Spinal nerve

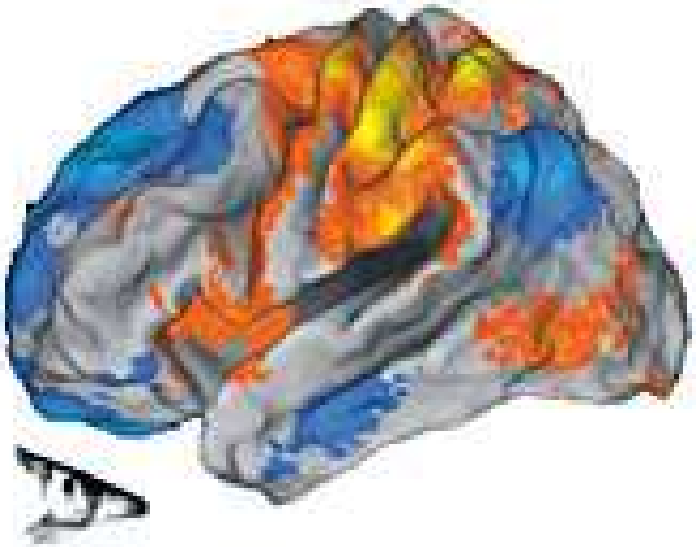
- as above and local anesthetics, skeletal muscle relaxants, anticonvulsants, TCA's, SNRI's = direct effect (as above + bupivacaine, baclofen, carbamazepine, amitriptyline, duloxetine, etc)

Peripheral nociceptor

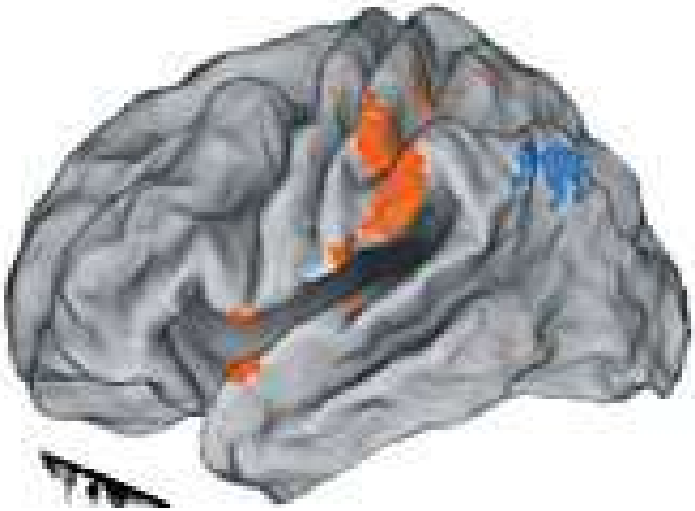
- local anesthetics, anti-inflammatory = direct effect (lidocaine, methyl salicylate, menthol, ibuprofen, nabumetone, naproxen, capsaicin, etc)

acetaminophen

CHRONIC PAIN



HEALTHY



MRI Images of pain

https://phys.org/news121498448.html

Chronic Pain

- **Generally pain lasting longer than 3 months**
- **Potentially unable able to be cured**
  - **Determine acceptable pain level vs**
  - **Determine functionality able to obtain**
  - **AND discussion on living with pain**
  - **Patient expectation**
- **Standing vs as needed treatments**
  - **Patient compliance**
  - **Correct treatment vs need for standing medication**

Chronic Pain Nonpharmacologic Therapy

- **Weight loss if adult with obesity**
  - **Decrease overall pain level**
  - **Potentially eliminate chronic pain**
  - **Potentially prevent central pain**
  - **Weight loss medications do not decrease pain**
  - **Weight loss may not remove all chronic pain**
  - **Weight loss may not decrease chronic pain, less common**

  - **BMI calculator:** https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm

Chronic Pain Nonpharmacologic Therapy

- **Therapy, even if tried in past**
  - **Physical therapy**
  - **Psychosocial therapy**
  - **Massage therapy**
  - **Heat vs cold**
  - **Transcutaneous Electrical Nerve Stimulation (TENS)**

Chronic Pain Med Therapy

Opioids

- **Rare patients will require life-long therapy**
  - **Primary chronic opioid use is cancer patients**
  - **If required: as needed**
  - **Monitor prescription fills, to ensure is not used standing**
- **Wean, to off, when data does not support**
- **Some patients may require very long wean**
- **Decreasing data for use**
- **Increased hyperalgesia risk**

Prescriptions (all columns are sortable)

Filled	ID	Written	Drug	QTY	Days
02/21/2018	1	02/21/2018	DEXTROAMP-AMPHETAMIN 20 MG TAB	60.0	30
01/20/2018	1	01/20/2018	DEXTROAMP-AMPHETAMIN 20 MG TAB	60.0	30
12/24/2017	2	12/20/2017	DEXTROAMP-AMPHETAMIN 20 MG TAB	60.0	30
11/08/2017	1	11/08/2017	DEXTROAMP-AMPHETAMIN 20 MG TAB	60.0	30
10/11/2017	2	10/11/2017	DEXTROAMP-AMPHETAMIN 20 MG TAB	60.0	30
09/08/2017	2	09/06/2017	DEXTROAMP-AMPHETAMIN 20 MG TAB	60.0	30
08/09/2017	2	08/09/2017	DEXTROAMP-AMPHETAMIN 20 MG TAB	60.0	30

Chronic Pain Pharmacologic Therapy

- **Non-opioid therapies**
  - **Acetaminophen: max of 4000 mg in 24 hours; decrease to max of 3000 mg in 24 hours in elderly + anyone chronically taking it. Max of 2000 mg per day in mild to moderate hepatic damage.**
  - **NSAIDs (oral and topical)**
  - **Lidocaine patches as needed**
  - **Inserted pumps (lidocaine, baclofen, etc)**
    - **Intrathecal**
    - **Subcutaneous**
  - **Temporary blocks**
  - **Topicals: methylsalicylate, menthol, capsaicin**

Chronic Pain

- **Increased pain**
  - **Progressing disease state**
    - **Alternate therapies**
    - **Increased dosing of current therapies**
  - **Acute on chronic pain**
    - **Separate injury, self-limiting**
  - **Opioid tolerance**
    - **Still a necessary therapy?**
    - **Increased dosing vs wean off**
  - **New central pain secondary to chronic pain**

Acute on chronic pain

- **Education**
  - **Less ability to tolerate acute pain**
  - **Treatment for acute only during acute phase**
- **Chronic pain treatments not yet used**
- **NOT central pain**
- **Opioids**
  - **Temporary therapy**
  - **Temporary increase in therapy**

Central Pain

- 1st noted in 1800's
- Different patients relate different symptoms
- Primary
  - Neurological disorders
  - Centralized location affected
- Secondary
  - Pain location changes
    - Chronic knee pain becomes more neuropathic, no change in knee imaging
    - Shoulder pain changes to spine pain, with no spinal or shoulder changes
  - Additional pain location
    - Primary dysmenorrhea pain with additional pain and no additional disease
  - Current treatments become less effective
    - Increased pain without increased disease state

Central Pain Secondary to Chronic Pain

- **Prevention?**
  - **Potential to remove chronic pain**
    - **Declined procedures**
    - **May not prevent central pain**
  - **Effective chronic pain treatment**
    - **Psychiatric and medication treatment**
    - **May not prevent central pain**
  - **Lacking solid data**
    - **Inability to prevent vs**
    - **Not yet known how to prevent**

Central Pain Secondary to Chronic Pain

- **Concurrent disease states**
  - **Musculoskeletal disease**
    - **Osteoarthritis**
    - **Rheumatoid arthritis**
  - **Nervous system disorders with widespread pain**
    - **Fibromyalgia**
    - **Irritable bowel syndrome (IBS)**
  - **Neuropathic diseases**
    - **Encephalomyelitis**
    - **Brain injuries**
  - **Spine disease**
    - **Sciatica**
    - **Radiculopathy**

Central Pain Secondary to Chronic Pain

- **Increased risks?**
  - **Psychiatric (depression, anxiety, emotional instability, etc)**
    - **Psychiatric disease increases risk of it OR**
    - **It increases risk of psychiatric diseases**
- **Personal traits**
  - **Genetics**
  - **Initial encounter to pain &/or chronic pain**
  - **Coping skills**
  - **Psychosocial**

BASIC overview: Pain Medication Actions

Brain

opioids, alpha2 agonists = direct effect (oxycodone, morphine, tizanidine, clonidine, etc)

Spinal nerve

- as above and local anesthetics, skeletal muscle relaxants, anticonvulsants, TCA's, SNRI's = direct effect (as above + bupivacaine, baclofen, carbamazepine, amitriptyline, duloxetine, etc)

Peripheral nociceptor

- local anesthetics, anti-inflammatory = direct effect (lidocaine, methyl salicylate, menthol, ibuprofen, nabumetone, etc)

acetaminophen

Central Pain Secondary to Chronic Pain

- **Treatment must be different than chronic pain**
  - **May be sole medication required for central pain**
  - **May still require other pain medications**

- **Data support addition for secondary central pain**

Central Pain Secondary to Chronic Pain

- **SNRI's (stronger data than SSRI's)**
  - **Duloxetine has the most data**
  - **Venlafaxine: may not see effect until titrate up to 150 mg per day dosing**
  - **Desvenlafaxine: may be as effective as venlafaxine, some data shows less effective**
  - **Milnacipran: most data is patients with fibromalgia**
  - **Levomilnacipran: should be as effective as milnacipran, but has less data**
- **TCA's (more side effects than SNRI's; SNRI's may have stronger, safer data)**
  - **Nortriptyline > amitriptyline: most data (amitriptyline becomes nortriptyline in body)**
  - **Imipramine, trimipramine,clomipramine**
  - **Doxepin: most anticholinergic side effects**
  - **Desipramine: may be least tolerated by patients**

Central Pain Secondary to Chronic Pain

- **Anticonvulsants**
  - **Lamotrigine**
    - **Some of the earliest data for treatment**
    - **Different studies = different dosing (low vs high), different patient populations**
  - **Gabapentin: absorption saturation, higher dose = less absorbed**
    - **Up to 300 mg per dose for best absorption**
    - **600 mg dose: 300 mg, then 300 mg in 1 hour**
    - **Caution with use: substance of abuse and has 'street value'**
  - **Pregabalin:**
    - **does not have absorption saturation**
    - **Caution with use: substance of abuse and has 'street value'**
  - **Carbamazepine, oxcarbazepine: less data than lamotrigine, conflicting data**
  - **Valproic acid, divalproex sodium: less data than other therapies**
  - **Topiramate: conflicting data, may be less effective than others**

Patient Interactions

- **“That never works” or “That’s not strong enough”**
  - **Explain multi-modal pain relief**
  - **Multiple medications should be used together, for overall pain relief**
  - **Acetaminophen, nsaids, etc, are not just for mild pain**
- **“I’ll try that if you prescribe ---”**
  - **Never bargain with patients for treatments**
- **“None of you care about my pain”**
  - **It’s because we care about you that we want to make your pain plan better**
  - **Using the most current data will help us take care of your pain better**
- **“I’ve been on oxycodone/etc for years, it works, why stop” or “Why can’t we just increase my dose?”**
  - **We didn’t know about opioid-induced hyperalgesia then**
  - **Unfortunately, having you take it for chronic pain makes your pain worse**

“Clinicians also loathe chronic pain, perhaps the symptom that brings more patients into our practices than any other but also the symptom most likely to make us feel helpless as healers.”

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4530716/

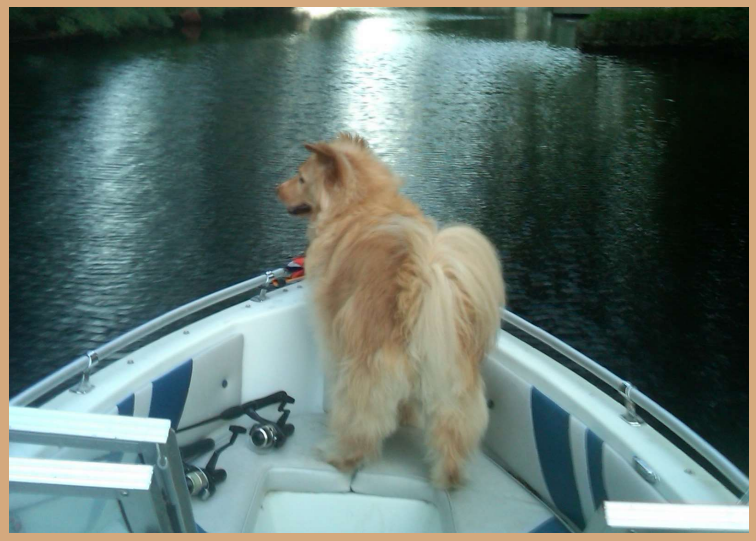
Questions?

Please feel free to email me with any questions

Nancy Balch, PharmD, BCCCP

nbalch@mgh.harvard.edu

The End



-- CC: DL presents stating increased pain requesting higher dose of oxycodone
-- HPI: DL is a 45 yo male with chronic R shoulder osteoarthritis s/p 2 surgical repairs (2008, 2012). Acetaminophen daily dose decreased to 3000 mg due to chronic use (15 years). Labs normal at annual physical 7 days ago.
-- NKA
-- Pmh: htn, chronic osteoarthritis (no nerve damage)
-- Social history: quit smoking 2015, social etoh on weekends, medical marijuana license. Works assisting with tax preparations.
-- Meds: nabumetone 500 mg every 12 hrs, acetaminophen 500 mg every 4 hrs prn pain, oxycodone 2.5 mg every 6 hrs prn severe pain, lisinopril 10 mg daily. Does use oral medical marijuana at night, to decrease pain for sleep

What is your treatment recommendation?

A. Increase acetaminophen to 4000 mg daily, with increased liver function testing; DL has chronic pain but is only at 3000 mg in 24 hr acetaminophen dosing.

B. Urine test for oxycodone, PDMP review, and if no red flags, increase oxycodone to 5 mg every 6 hours standing, as DL has chronic pain and has been on a low dose of oxycodone; his pain has most likely increased and no nerve damage has ever been identified.

C. Increase medical marijuana, to use throughout the day as it treats all pain effectively and is legal where he lives.

D. Add duloxetine 30 mg once daily for his chronic osteoarthritis pain which most likely now has additional central pain.

-- CC: IH presents requesting relief from R shoulder pain, difficult to use arm due to pain; played golf Saturday and Sunday.
-- HPI: IH, a 42 yo female, takes ibuprofen 200 mg every 8 hours as needed. States pain previously controlled with ibuprofen (occasional pain d/t injured R shoulder playing amateur lacrosse), pain has increased with increased activity.
-- Pmh: L shoulder pain
-- Allergies: seasonal allergies to pollen
-- Social history: Runs 1 to 2 miles each day. (-) etoh, smoking, illicits
-- Meds: ibuprofen 200 mg every 8 hrs as needed, multivitamin every morning

What is your treatment recommendation?

A. Add acetaminophen 1000 mg every 4 hours standing until pain resolves.

B. Add Duloxetine 30 mg once daily.

C. Add acetaminophen 650 mg every 6 hours, increase ibuprofen to 600 mg every 8 hours and add lidocaine patch. Decrease back to previous regimen once acute pain resolved.

D. Add oxycodone 5 mg every 6 hours as needed for pain not relieved by ibuprofen.

-- CC: BP presents stating you are his last chance at pain relief. He states: “everyone treats me like a drug addict because my pain is not controlled. I just want it a little better so I can work more.”
-- HPI: BP, a 62 yo male, required jaws of life, 30 years ago, to be extricated from mva, a drunk driver hit his vehicle head on. Both legs were crushed and required 12 surgeries to complete reconstruction.
-- Pmh: Bilateral leg pain
-- Allergies: Ibuprofen: hives
-- Social history: Assists his brother, who has his own plumbing and heating company, when pain permits (-) etoh, illicits. Occasional cigar in evening. Snorted heroin, to assist with pain relief, until started working with his brother, in sustained remission x 20 years.
-- Meds: oxycodone ir 15 mg every 4 hours prn mod pain, fentanyl patch 25 mcg/hr q72 hrs, acetaminophen 325 mg every 8 hours.
-- What is your treatment recommendation?

A. Add Lidocaine patches to bilat legs daily prn, increase acetaminophen to 1000 mg every 4 hrs.

B. Wean oxycodone and fentanyl patch to off, titrate gabapentin to 800 mg mg every 6 hours, once at 800 mg dose, use 800 mg tablets.

C. Slowly decrease oxycodone and fentanyl patch dosing (to off, if able), increase acetaminophen to 650 mg every 8 hrs, add lidocaine patches to bilateral legs prn, add duloxetine 30 mg daily.

D. Increase oxycodone, then the fentanyl patch if pain is still severe, while increasing acetaminophen to 1000 mg every 6 hours.

References

- Crawley, B.K., Malkmus, S. Fitzsimmonds, B.L., Hua, X.-Y., Yaksh, T.L. (2007, January). Acetaminophen Prevents Hyperalgesia in Central Pain Cascade. doi:10.1016/j.neulet.2008.06.062
- Reg Anesth Pain Med 2014;39: 13–17
- https://pubmed.ncbi.nlm.nih.gov/24042347/
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3412202/pdf/CDTH-6-296.pdf
- https://pubmed.ncbi.nlm.nih.gov/24310048/
- https://www.tandfonline.com/doi/pdf/10.1185/03007995.2014.925439
- http://dx.doi.org/10.1097/j.pain.0000000000001183
- https://pubmed.ncbi.nlm.nih.gov/30461429/
- https://www.physio-pedia.com/Chronic_Pain_and_the_Brain
- https://phys.org/news121498448.html
- https://doi.org/10.1016/j.phrs.2018.06.030
- https://www.practicalpainmanagement.com/pain/neuropathic/new-insights-understanding-chronic-central-pain
- https://www.tannlegetidende.no/i/2016/1/d2e1410

References

- https://www.medicaldaily.com/chronic-pain-immune-system-371332
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6650904/
- https://nccih.nih.gov/sites/nccam.nih.gov/files/NBMBPT_transcript6.pdf
- https://www.thepainproject.com/exactly-how-chronic-pain-affects-the-brain/
- https://www.painresearchforum.org/news/85296-how-changes-cortex-give-rise-chronic-pain
- https://www.ncbi.nlm.nih.gov/books/NBK553027/
- https://paininjuryrelief.com/chronic-pain-brain/
- https://augustapaincenter.com/mind-not-body-psychological-effects-chronic-pain/
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4530716/