Thoughts on Treating Chronic Non-Cancer Pain: Non-Opiate Medication

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Thoughts to Consider

- Pain is the most common reason cited for a provider visit
- Competing agendas of TJC & DEA
- Deaths from ODs due to prescribed opiates now exceeds deaths from cocaine and heroin ODs combined
- The incidence of alcoholism and addiction in the general population is 5%-10%
- Pain ≠ Percocet

Thoughts to Consider

- Nothing gets better w/o diet & exercise
- Healing begins w/ a good nights sleep
- Nothing responds to medications alone
- Rarely does anything respond to only one medication; polypharmacy may be a good thing

Thoughts to Consider

- In patients w/ chronic pain also need to consider:
  - Depression
  - TSH level
  - Low testosterone
  - Low Vit D
  - Obesity
  - Sleep apnea
  - PMH of PTSD; PMH of sexual or physical abuse
  - PMH of substance abuse/addition

Types of Pain

- Nociceptive
- Neuropathic

Low Back Pain Practice Guidelines

- Focused history to subclassify low back pain
  - Nonspecific low back pain
  - Back pain assoc. w/ radiculopathy or spinal stenosis
  - Back pain assoc. with other spinal cause
- Imaging
  - None – nonspecific low back pain (strong rec)
  - MRI – progressive neurologic deficits (strong rec)
  - CT – candidate for surgery or epidural steroid injection (strong rec)
- Education
  - Expected course, advise to remain active, self-care options
- Treatment
  - 1st line APAP or NSAIDs + self care options (strong rec)
  - Spinal manipulation, intensive interdisciplinary rehab, exercise, yoga, CBT, progressive relaxation (weak rec)

Chou R, et al. Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med 2007;147:478-491.

Osteoarthritis Practice Guidelines

- Oral
  Acetaminophen
  COX-2-specific inhibitor
  Nonselective NSAID plus misoprostol or a proton pump inhibitor**
  Nonacetylated salicylate Other pure analgesics Tramadol

- Opioids Intraarticular
  Glucocorticoids
  Hyaluronan
- Topical
  Capsaicin
  Methylsalicylate
  - http://www.rheumatology.org/practice/clinical/guidelines/oa-mgmt.asp. Accessed 3.31.13

Fibromyalgia recommendations

- Address and treat sleep hygiene
- Pharmacotherapy
  - TCAs
  - Pregabalin, Duloxetine, Milnacipran
  - Cardiovascular exercise
- Cognitive behavioral therapy
- Intense patient education
  - Goldenberg DL, et al. Management of fibromyalgia syndrome. JAMA 2004;292:2388-95

Summary of recommendations

- **Recommended drug and dose**
- **Level A**
  - Pregabalin, 300–600 mg/d
- **Level B**
  - Gabapentin, 900–3,600 mg/d
  - Sodium valproate, 500–1,200 mg/d
  - Venlafaxine, 75–225 mg/d
  - Duloxetine, 60–120 mg/d
  - Amitriptyline, 25–100 mg/d
  - Dextromethorphan, 400 mg/d
  - Morphine sulphate, titrated to 120 mg/d
  - Tramadol, 210 mg/d
  - Oxycodone, mean 37 mg/d, max 120 mg/d
  - Capsaicin, 0.075% QID
  - Isosorbide dinitrate spray
  - Electrical stimulation, percutaneous nerve stimulation 3–4 weeks

- **Not recommended**
  - Lamotrigine
  - Lacosamide
  - Clonidine
  - Pentoxifylline
  - Mexiletine
  - Magnetic field treatment
  - Low-intensity laser therapy
  - Reiki therapy

WHO Ladder

- Step 1: NSAIDs; APAP
- Step 2: opiate mixture
- Step 3: opiates alone

NSAIDs

- MOA
  - inhibition of prostaglandin synthesis and inflammation
- ADRs
  - GI
  - renal toxicity w/prolonged use
  - hepatic toxicity w/prolonged use.
- Caution
  - +PMH of UGIB
  - decreased renal function
  - uncontrolled HTN
  - uncontrolled bronhcospasm disease

Tricyclic Antidepressants (TCAs)

- imipramine (Tofranil®), nortriptyline (Pamelor®), & amitriptyline (Elavil®).
- MOA:
  - Antagonist of 5-HT_2 receptors inhibiting the reuptake of serotonin and causing an increased concentration of serotonin in the synaptic cleft.
- ADRs
  - Sedation
  - constipation
  - blurred vision
  - HPOTN
- Contraindications:
  - Glaucoma
  - pregnancy
- Drug Interactions:
  - MAOIs

So which antidepressant?

- TCAs (NE > 5HT)
  - amitriptyline
  - imipramine
  - desipramine
  - nortriptyline
- SSRIs (5HT > NE)
  - paroxetine
  - fluoxetine
  - sertraline
- SNRIs (? NE = 5HT)
  - bupropion
    - dopaminergic
  - venlafaxine
    - dopaminergic
  - mirtazapine
    - Alpha-adrenergic
  - fluvoxamine
  - Duloxetine, Milnacipran

Anticonvulsants.

- Valproic Acid (Depakene®) and divalproex sodium (Depakote®), Topiramate (Topamax®), Lamotrigine (Lamictal®); gabapentin (Neurontin®); pregabalin (Lyrica®)
- MOA:
  - Increased availability of GABA-inhibitory transmitter
  - membrane stabilization.
- Contraindications:
  - liver disease--monitor-liver enzymes
- ADRs:
  - tremor
  - weight gain,
  - Nausea
  - hair loss
- Drug interactions
  - other anticonvulsants
  - CNS depressants.

So which anticonvulsant?

- Non-obese, co-morbid anxiety
  - gabapentin
  - pregabalin
- Obese, or co-morbid seizure disorder
  - zonisamide
  - topiramate
- Co-morbid bipolar disorder or seizure disorder
  - oxcarbazepine
  - lamotrigine(?)
  - carbamazepine

Centrally Acting Skeletal Muscle Relaxants

- These agents are used to afford a degree of relief from muscle spasms & hyper-reflexia resulting from conditions such as inflammation, anxiety, stress & other neurologic d/o.

Skeletal Muscle Relaxants

- Centrally Acting
  - Goal: To produce decreased muscle tone and involuntary movement w/out loss of voluntary motor fxn or consciousness.
  - Work either:
    - Directly—on the contractile mechanism of the skeletal musculature
    - Or on transmission in spinal cord motor reflex pathways, primarily to elicit varying degrees of skeletal muscle relaxation.

Which Muscle Relaxant?

- Cyclobenzaprine
- Baclofen
- Tizanidine
- Carisoprodol (NOT A GOOD CHOICE)
- Diazepam
- Metaxalone
- Dantrolene
- Methocarbamol
- ~ botulinum toxin

Topical

- Local Anesthetic
  - Lidocaine
    - ointment
    - patch
- NSAID
  - Diclofenac
    - ointment
    - patch
- Compound
  - NSAID, local anesthetic, clonidine, gabapentin, ketamine, muscle relaxant

Topical

- Capsacin (Qutenza™)
- MOA
  - activates TRPV1 ligand-gated cation channels on nociceptive nerve fibers; capsaicin exposure results in subsequent desensitization of the sensory axons and inhibition of pain transmission initiation
  - capsaicin induces release of substance P; capsaicin depletes the neuron of substance P and prevents reaccumulation
- Dose
  - OTC: TID-QID
  - Rx: Apply patch to most painful area for 60 minutes; max 4 patchs; may repeated ≥3 months as needed for return of pain ; no < 3 months; pre-treat w/ local anesthetic cream
- ADR
  - erythema
  - pain
- Caution
  - Avoid contact w/ eyes & sensitive areas

Novel agent

- Tramadol
- MOA
  - weak opioid agonist
  - weak SSRI reuptake inhibitor
- ADR:
  - CNS effects
  - GI effects
- Drug Interactions:
  - MAOIs, TCA, SSRI, SNRI may increase seizure risk
  - CYP2D6 inhibitors may increase tramadol effects

Novel Agents

- Tapentadol (Nucynta®)
- MOA
  - binds to mu-opioid receptors
  - inhibits norepinephrine re-uptake
- ADR
  - most common adverse events are nausea, dizziness, vomiting, somnolence and headache
- Caution: weaker mu binding than traditional opiates, need to wean or risk withdrawal. Theoretically, increased activation with some antidepressants

Novel Agents

- Vitamin D
- Sx of Vit D def: deep bone pain muscular discomfort, weakness
- 40%-60% of pts w/ FMS may have Vit D def
- Dose: 800units- 2000units/day; 400 units probably to low

Novel Agents

- Clonidine
- MOA
  - Central alpha 2 agonist
  - blocking the action of norepinephrine on a receptors that can become active in neuropathic pain
  - synergistic antinociceptive effect with opioids
- Dose
  - 0.1 mg hs to max 2.4mg/day
- ADR
  - hypotension
  - dry mouth
  - urinary retention & constipation
  - sedation

Novel Agents

- Ketamine
- MOA
  - Anesthetic
  - NMDA receptor antagonist
  - “re-sets” opiate receptors
- ADR
  - disassociation
  - anxiety & also alter cognition, affect, perception and judgment
  - alivation
  - increase cardiac output
- Caution
  - cardiac
  - CNS

Novel Agents

- Ketamine
- Dose
  - 5 consecutive weekdays, Monday through Friday, on two consecutive weeks
  - **Treatment Phase**
  - Day One: 50 mg over 4 hours
  - Day Two: 75 mg over 4 hours
  - Day Three: 100 mg over 4 hours
  - Day Four through Day Five 150 mg over 4 hours
  - A set of 4 booster infusions follow our 10 Day Ketamine Protocol as follows:
  - 2 weeks after end of treatment phase
  - 1 month after end of treatment phase
  - 2 months after end of treatment phase
  - 3 months after end of treatment phase

Novel Agents

- Low dose naltrexone
- MOA
  - inhibit microglial activity
  - may increase concentration of glial endorphins
  - may increase concentration of glial endorphin receptors
- Dose
  - 4.5 mg 1-2 hours before bed
  - compounded
- ADR
  - Insomnia
  - Vivid dreams
- Caution
  - Must be off all opiates

Closing Thoughts

- Treating chronic non-malignant pain is complex and utilizes all the principles of treating any other chronic condition
- As w/ other chronic condition, it is never just medication utilized and rarely us just one medication effective
- As w/ other chronic conditions the same principles of monitoring and adjusting therapy apply
- Always be aware of the impact of complicating issues of behavioral health, lack of sleep, culture, language, etc
- Always keep an open mind, but keep your eyes open and believe the data