PAINWEEK

Rational Polypharmacy:
An Update for Specific Conditions

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Disclosures

- Nothing to disclose

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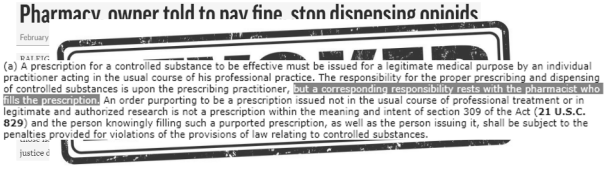
In the news now…



Pharmacy owner told to pay fine, stop dispensing opioids

February

(a) A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fill the prescription. An order purporting to be a prescription issued not in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of section 309 of the Act (**21 U.S.C. 829**) and the person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances.

justice.d

https://apnews.com/a3fe5bbb5ad71bc7e0c87 1b3b462df89 accessed 2.12.2020
https://www.deadiversion.usdoj.gov/21cfr/cfr/ 1306/1306_04.htm accessed 1.9.2020

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Learning Objectives

- Define rational polypharmacy as it pertains to the patient in pain
- Recognize the various pharmacological classes used in rational polypharmacy of migraine, neuropathic pain, and musculoskeletal pain conditions
- Distinguish between rational and irrational polypharmacy in managing pain

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How does rational polypharmacy apply to my practice?

- Synergistic combinations decreasing the amount of opioid needed for pain control
- Using nonopioids as first line therapy can minimize or even prevent the need for opioid medications on a chronic basis
- Shortages and regulatory constraints on the manufacture of opioids have lead to shortages and the inability of pharmacies to stock opioids and other medications used in pain management

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Definitions

- Polypharmacy:
  The use of two or more drugs together, usually to treat a single condition or disease
- Synergy:
  The cooperative action of two or more stimuli or drugs
- Rational:
  Proceeding or derived from reason or based in reason
- Irrational:
  Not endowed with the faculty of reason

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Goals of Rational Polypharmacy

- Minimize adverse effects
  - –Lower doses of individual medications
  - –Opioid sparing effects
- Increase adherence to the prescribed regimen
- Using synergistic combinations of medications to achieve improved outcomes compared to the individual medications
- Increase efficacy by utilizing long acting and short acting preparations

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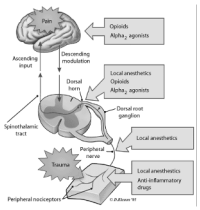
Hitting the Target(s)

- Stimulation of nociceptors causes signal transduction to the dorsal horn
  - –Transduction
- The spinothalamic tract transmits the signals to the brain where pain is first experienced
  - –Transmission and perception
- Descending pathways from the brain attempt to block the signal from the periphery
  - –Modulation



http://napaanesthesia.com/blog-pre-emptive-pain-management accessed 1.9.2020

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Medications Used in Pain Management

- Acetaminophen
- NSAIDs
- 5HT$_{3\text{-}1B/D}$ antagonists (Triptans)
- Calcitonin gene-related peptide antagonists
- Antidepressants
- Anticonvulsants
- Local anesthetics
- Skeletal muscle relaxants
- Opioids

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Acetaminophen

- Mechanism of action is still not entirely known
  - –Thought to be a partial COX inhibitor
- March 2014 FDA mandates all prescription drug combination products containing acetaminophen cap the dose at 325 mg
- Maximum daily dose limits vary based on comorbidities and who you ask
  - –FDA[1] vs Johnson and Johnson[2]

1. http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm165107.htm accessed 1.9.2020
2. https://www.tylenol.com/safety-dosing/usage/dosage-for-adults accessed 1.9.2020

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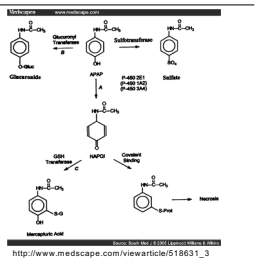
Acetaminophen (cont'd)

- Largest concern is unintentional overdoses
- Metabolism of acetaminophen by the liver is a saturable process
- Over the counter products and cumulative acetaminophen dosing



http://www.medscape.com/viewarticle/518631_3 accessed 1.9.2020

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Nonsteroidal Anti-Inflammatory Agents

- COX 1 more specific to the GI tract and renal homeostasis
- COX 2 more specific to inflammation and platelet aggregation
- Certain comorbidities limit the dosing on most NSAIDs
  - –Patients on anticoagulants
  - –Patients with renal dysfunction
  - –Pregnancy

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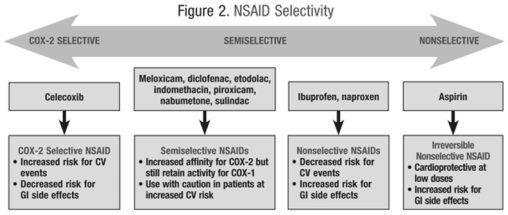
NSAIDs and COX Selectivity

Figure 2. NSAID Selectivity



COX: cyclooxygenase; CV: cardiovascular; GI: gastrointestinal; NSAID: nonsteroidal anti-inflammatory drug. Source: References 3, 17.

https://www.uspharmacist.com/article/cardiovascular-risk-associated-with-nsaids-and-cox2-inhibitors accessed 1.9.2020

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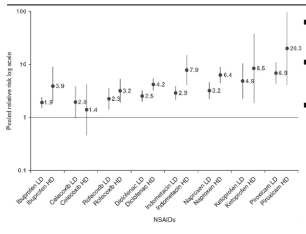
NSAIDs and GI Complications (GIC)



- Meta-analysis of GIC from individual NSAIDs
- GIC included ulceration, perforation, obstruction, and bleeding
- All COX nonspecific NSAIDs increase in risk of GIC when taken on a daily basis

Individual NSAIDs and Upper Gastrointestinal Complications. Drug Safety 2012; 35(12): 1127-1146

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Nonsteroidal Anti-Inflammatory Drugs

- Topical vs systemic NSAIDs
  - –Patch, cream, lotion, etc
    - Range in application frequency from twice to four times daily
  - –Topical can provide NSAID relief at the site of inflammation without the systemic side effects
  - –Cost can be a limiting factor
  - –Still carry a black box warning on the labeling for cardiovascular complications

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$5HT_{3-1B/D}$ Antagonists (Triptans)

- Serotonin receptor antagonists leading to
  - –Extra-cerebral vasoconstriction ($5\text{-}HT_{1B}$)
  - –Decreased inflammatory neuropeptide release ($5\text{-}HT_{1D}$)
- Indicated for migraine treatment
  - –Abortive therapy, not prophylactic
- Dosing in general involves administration of a second dose in 1 to 2 hours if the first dose was unsuccessful in aborting the migraine

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Triptans (cont'd)

Drug	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan[1]	Zolmitriptan
Brand Name (Manufacturer)	Axert (Janssen)	Relpax (Pfizer)	Frova (Endo)	Amerge (GSK)	Maxalt, Maxalt-MLT (Merck)	Imitrex (GSK) Onzetra Xsail (Avanir) Sumavel DosePro (Endo) Zembrace SymTouch (Promius)	Zomig, Zomig ZMT (Impax)
Generic Available	Yes	No	Yes	Yes	Yes	Yes – for Imitrex products only	Yes – for oral tabs and ODTs only
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral; Nasal; SC	Oral; Nasal
Formulations	6.25, 12.5 mg tabs	20, 40 mg tabs	2.5 mg tabs	1, 2.5 mg tabs	5, 10 mg tabs and 5, 10 mg ODTs	Imitrex and generics – Oral: 25, 50, 100 mg tabs SC: 4, 6 mg/0.5 mL auto-injector pen and refill cartridge, vials[2] Nasal: 5, 20 mg/0.1 mL nasal spray Onzetra Xsail: 11 mg nasal powder caps Sumavel DosePro: 6 mg/0.5 mL SC needle-free delivery system Zembrace SymTouch: 3 mg/0.5 mL SC auto-injector	Oral: 2.5, 5 mg tabs and 2.5, 5 mg ODTs Nasal: 2.5, 5 mg/0.1 mL nasal spray
Onset of Action	30-60 min	30-60 min	~ 2 hrs	1-3 hrs	30-60 min	Tabs: 30-60 min SC: ~10 min Nasal: 10-15 min	Tabs: 30-60 min Nasal: 10-15 min
Elimination Half-life	3-4 hrs	~4 hrs	~25 hrs	~6 hrs	2-3 hrs	~2 hrs	2-3 hrs

3-4 hour half life

25 hour half life

http://www.headache.mobi/uploads/1/1/7/5/11757140/triptans.pdf accessed 1.9.2020

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Triptans (cont'd)

- Patients that are NOT candidates for triptan agents
  - –Ischemic heart disease
  - –Uncontrolled hypertension
  - –Peripheral vascular disease
  - –History of cerebrovascular syndromes (stroke or transient ischemic attack)
- Multiple formulations exist for
  - –Sumatriptan (nasal, SQ, oral)
  - –Zolmatriptan (nasal and oral)

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Calcitonin Gene-Related Peptide (CGRP) Antagonists

- Monoclonal antibodies that bind to CGRP
  - Preventing intracranial artery vasodilatation
  - Prevention of dural mast cell degranulation
- Monthly injections are only indicated for the prevention of migraine
  - Not indicated for the management of acute migraine symptoms
- Orally administered agent is indicated for the acute management of migraine

AnnRevPharmacolTox.55.533-52 2015

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CGRP Antagonists Currently Available

- Erenumab-aooe [Aimovig®]
  - Subcutaneous injection 70 mg once monthly
- Fremanezumab-vfrm [Ajovy®]
  - Subcutaneous injection 225 mg once monthly or 675 mg every three months
- Galcanezumab-gnlm [Emgality®]
  - Subcutaneous injection 240 mg once then 120 mg monthly
- Ubrogepant [Ubrelvy®]
  - Orally 50 mg to 100 mg once at onset of migraine, may repeat dose in 2 hours

Lexicomp accessed 1.9.2020

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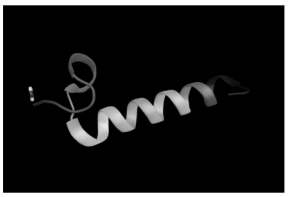
CGRP Antagonists (cont'd)

- Questions that remain unanswered regarding their long term safety include
  - Hypertension
  - Nitric oxide synthase
  - Platelet aggregation
  - Negative impact on microvasculature
    - Heart failure
    - Diabetes



https://www.practicalpainmanagement.com/pain/headache/stake-possible-long-term-side-effects-cgrp-antagonists accessed 1.13.2020

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Tricyclic Antidepressants (TCA)

- Mechanism of action is through inhibition of norepinephrine and serotonin reuptake and inhibition of sodium channel action potentials
- The antidepressant effects and the neuropathic pain analgesia are independent
  - –Higher dosing and longer treatment time needed for antidepressant effects
- Caution should be exercised in patients
  - –With cardiac arrhythmias
  - –Over the age of 65

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Serotonin Norepinephrine Reuptake Inhibitors (SNRI)

- Mechanism of action is through inhibition of norepinephrine and serotonin reuptake
- Dosing is generally higher for treating neuropathic pain compared to treating depression
- Withdrawal syndromes can occur if patients are taken off SNRI therapy abruptly
  - –Anxiety, irritability, headache, paresthesia, nervousness
- Caution should be exercised in patients with liver dysfunction, uncontrolled hypertension, or moderate cardiovascular disease

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Antiepileptics

- The primary antiepileptics used in pain management work on calcium channels
  - –Gabapentin
  - –Pregabalin
- Other antiepileptics have had mixed results regarding neuropathic pain
  - –Valproic acid
  - –Phenytoin
- Carbamazepine for trigeminal neuralgia

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Local Anesthetics

- Mechanism of action is through membrane stabilization of sodium channels preventing depolarization and signal transduction
- Acute uses for local anesthesia (procedures, etc)
  - –Topical application
    - •Cream, ointment, patch, etc
  - –Intradermal injections
  - –Nerve blocks
- Patches are indicated for the management of postherpetic neuralgia

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Skeletal Muscle Relaxants

- Multiple medications are included in this general taxonomy
  - –Certain agents approved for spasticity
    - •Baclofen and tizanidine
- Others stand out for reasons other than their indication
  - –Cyclobenzaprine and orphenadrine regarding their anticholinergic effects
  - –Chlorzoxazone and potential for hepatotoxicity
  - –Carisopradol and meprobamate and potential for abuse

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Opioids

- Opioids work on multiple receptors within the CNS
  - –Analgesia and adverse effects are derived from mostly mu receptors
- There is no ceiling dose for analgesia; however, as doses increase the incidence of adverse effects increases
- CDC (2016) and VA/DoD (2017) guidelines outlining the use of opioids in chronic pain have been published

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Opioids (cont'd)

- Agonists vs partial agonists vs antagonists
  - –Morphine, fentanyl, methadone, etc
  - –Buprenorphine, nalbuphine, butorphanol
  - –Naloxone and naltrexone
- Awareness of other nonpain combination products
  - –Naltrexone-bupropion for weight loss

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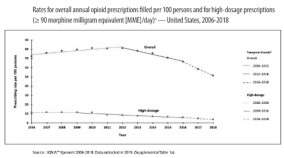
Opioid Statistics

- Medication overdose deaths in 2017: 70,237
  - –Opioids (illicit and prescription) were involved in 67.8% of those fatalities
- Patients on > 90 morphine milligram equivalents have decreased from 11.5 to 3.9 per 100 patients in the US



https://www.cdc.gov/drugoverdose/pdf/pubs/2019-cdc-drug-surveillance-report.pdf accessed 1.13.2020

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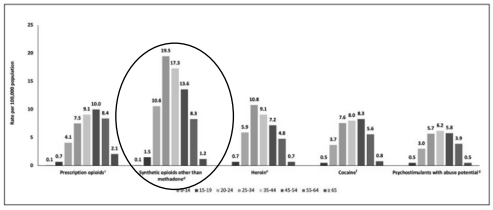
Opioid Statistics (cont'd)



Source: National Vital Statistics System, Mortality File, CDC WONDER.

https://www.cdc.gov/drugoverdose/pdf/pubs/2019-cdc-drug-surveillance-report.pdf accessed 1.13.2020

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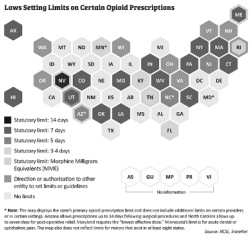
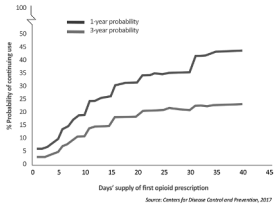
Opioid Statistics (cont'd)





http://www.ncsl.org/research/health/prescribing-policies-states-confront-opioid-overdose-epidemic.aspx accessed 3.6.2019

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Patients at Risk for Opioid Adverse Events

- Patients with sleep apnea and sleep disordered breathing
- Pregnancy
- Hepatic or renal dysfunction
- Age greater than 65
- Mental health or substance use disorders
- Nonfatal overdose history

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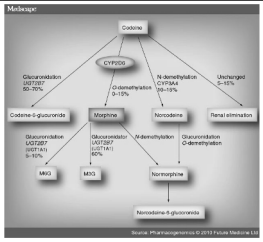
Opioid Metabolism



- Metabolic pathways can become saturated leading to metabolism by other pathways
  - –Codeine
  - –Oxycodone
    - •2D6 → noroxycodone
    - •3A → oxymorphone

http://www.medscape.com/viewarticle/723131_2 accessed 1.13.2020

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Immediate Release (IR) vs Extended Release (ER)

- Initial therapy should include the use of IR formulations
- ER preparations are appropriate for patients
  1. That routinely use the IR preparation with relief of pain
  2. That are not experiencing adverse effects that decrease quality of life
  3. That are on stable doses of IR preparations and have been for an appropriate time frame
- IR and ER preparation use should be re-evaluated for safety and efficacy periodically or per state guideline

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Nonrational Polypharmacy

- Utilizing two medications in the same family for the same condition
  - –Ibuprofen and naproxen
  - –Morphine immediate release and oxycodone immediate release
- Adding a medication that may be contraindicated based on the patients other comorbidities
  - –Methadone use in a patient with a history of QTc prolongation
  - –Tramadol or use in a patient with underlying seizure history

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Rationalizing Migraine Pain Management

- Use of abortive medications at the beginning of a migraine
  - –NSAIDs, triptans
  - –Opioids and dopamine antagonists (severe)
- Use of prophylactic therapy once patients meet criteria
  - –More than two migraines per month
  - –Migraine lasts for more then 24 hours
  - –Use of abortive therapy more than twice per week

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Rationalizing Migraine PROPHYLACTIC Management

First line	High efficacy	Beta blockers Tricyclic antidepressants Divalproex Topiramate
	Low efficacy	Verapamil
Second line	High efficacy	Methysergide Flunarizine MAOIs CGRP inhibitors Botulinum toxin
	Unproven efficacy	Cyproheptadine Gabapentin

MAOIs = monoamine oxidase inhibitors

Comorbid Condition	Medication
Hypertension	Beta blockers
Angina	Beta blockers
Stress	Beta blockers
Depression	Tricyclic antidepressants, SSRIs
Overweight	Topiramate, protriptyline
Underweight	Tricyclic antidepressants (nortriptyline, protriptyline)
Epilepsy	Valproic acid, topiramate
Mania	Valproic acid

SSRIs = selective serotonin reuptake inhibitors

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https://emedicine.medscape.com/article/1142556-treatment accessed 1.13.2020

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Rationalizing Neuropathic Pain

- Scheduled use of tricyclic or SNRI antidepressants at appropriate doses
  - –Caution regarding the use of anticholinergic tricyclic agents
- Use of antiepileptics at appropriate doses
  - –Opioids may be used in combination with the use of an antiepileptic
  - –Topical local anesthetics such as patches and creams with the above

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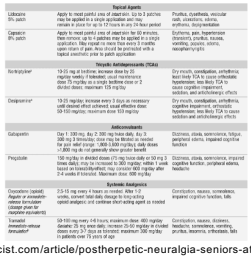
Rationalizing Neuropathic Pain (cont'd)

- NSAIDs and acetaminophen are unlikely to alleviate neuropathic pain
- Anticonvulsants, local anesthetics, and tricyclic antidepressants are mainstays in neuropathic pain management
- Opioids may have a place but not first or second line
- Muscle relaxants are controversial in terms of efficacy



Topical Agents		
Lidocaine 5% patch	Apply to most painful area of discomfort. Up to 3 patches may be applied in a single application and may remain in place for up to 12 hours in any 24 hour period	Pruritus, dysesthesia, erythema, vascular rash, ulcerations, edema
Capsaicin 8% patch	Apply to most painful area of discomfort for 60 minutes, then remove; up to 4 patches may be applied in a single application. May repeat no more than every 3 months. Pretreatment pain with oral analgesics and cooling with a topical anesthetic prior to patch application	Erythema, pain, hypertension characterized by pruritus, nausea, vomiting, papules, edema, neuropharyngitis
Tricyclic Antidepressants (TCAs)		
Nortriptyline*	10-25 mg at bedtime; increase dose by 25 mg/day every 1-2 weeks as tolerated to maximum dose 75 mg/day as a single bedtime dose or 2 divided doses; maximum 125 mg/day	Dry mouth, constipation, orthostatic hypotension, sedation, tachycardia, hypertension; less likely TCA to cause cognitive impairment, sedation, and anticholinergic effects
Desipramine*	10-25 mg/day; increase every 3 days as necessary until desired effect achieved; usual effective dose 50-150 mg/day; maximum dose 300 mg/day	Dry mouth, constipation, orthostatic hypotension, tachycardia, hypertension; less likely TCA to cause sedation and anticholinergic effects
Anticonvulsants		
Gabapentin	Day 1: 300 mg; day 2: 300 mg 2 times/day; day 3: 300 mg 3 times/day; dose may be titrated as needed for pain relief (range: 1,800-3,600 mg/day); daily doses >1,800 mg do not generally show greater benefit	Dizziness, ataxia, somnolence, fatigue, peripheral edema, impaired cognitive function
Pregabalin	150 mg/day in divided doses (75 mg twice daily or 50 mg 3 times daily); may be increased to 300 mg/day within 1 week, based on tolerability/effect; may consider 600 mg/day after 2-4 weeks if tolerated. Maximum dose: 600 mg/day	Dizziness, ataxia, somnolence, impaired cognitive function, peripheral edema, headache
Systemic Analgesics		
Oxycodone (opioid) *Regular or immediate-release formulation (cluster given for morphine equivalents)*	2.5-5 mg every 4 hours as needed. After 1-2 weeks, convert total daily dosage to long-acting opioid analgesic and continue short-acting agent as needed	Constipation, nausea, somnolence, impaired cognitive function, falls
Tramadol *Immediate-release formulation*	50-100 mg every 4-6 hours; maximum dose: 400 mg/day. Geriatric: 25 mg once daily; increase 25-50 mg/day in divided doses every 3 days to desired effect; maximum: 300 mg/day in patients over 75 years of age	Constipation, nausea, dizziness, headache, somnolence, vomiting, pruritus, insomnia, orthostasis, falls

https://www.uspharmacist.com/article/postherpetic-neuralgia-seniors-at-risk accessed 1.13.2020

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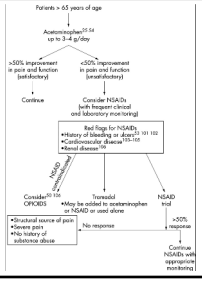
Rationalizing Musculoskeletal Pain Management

- Bone pain
- Muscle pain
- Tendon and ligament pain
- Fibromyalgia
- Joint pain
- Nerve compression syndromes

- More than 150 diagnoses all of which affect the locomotor system



https://pmj.bmj.com/content/79/937/627 accessed 1.13.2020

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Rationalizing Musculoskeletal Pain Management (cont'd)

Table 1. ACR Recommendations: Initial Medications

Hip OA	
Strongly Recommend	None
Conditionally Recommend	• Acetaminophen • Oral NSAID • Tramadol • Intra-articular corticosteroid injections
Conditionally Not Recommend	• Chondroitin sulfate • Glucosamine
No Recommendation	• Topical NSAID • Intra-articular hyaluronic acid injections • Duloxetine • Opioid analgesics
Knee OA	
Strongly Recommend	None
Conditionally Recommend	• Acetaminophen • Oral NSAID • Topical NSAID • Tramadol • Intra-articular corticosteroids
Conditionally Not Recommend	• Chondroitin sulfate • Glucosamine • Topical capsaicin
No Recommendation	• Intra-articular hyaluronic acid injections • Duloxetine • Opioid analgesics

ACR, American College of Rheumatology; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis

https://www.practicalpainmanagement.com/treatment-osteoarthritis accessed 1.13.2020

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Rationalizing Musculoskeletal Pain Management (cont'd)

Table 1. Drugs Used to Treat Fibromyalgia

Drug (Brand)	Class	Status	Dosing
Amitriptyline (Elavil)	TCA	Off-label	Initiate at 10 mg po qhs; may titrate up to 50 mg, if needed
Duloxetine (Cymbalta)	SNRI	FDA-approved	Initiate at 30 mg po qd for 1 wk, then increase to 60 mg qd
Cyclobenzaprine (Flexeril)	Skeletal muscle relaxant	Off-label	Initiate at 10 mg po qhs, then slowly titrate to 10 mg po qua and 20 mg po qhs
Milnacipran (Savella)	SNRI	Off-label	Initiate at 25 mg po qd and gradually titrate up to response; max 80 mg in 1 day
Pregabalin (Lyrica)	GABA agonist	FDA-approved	Initiate at 75 mg po bid, may increase to 150 mg bid based on tolerability and response; max 225 mg bid
Gabapentin (Neurontin)	GABA agonist	Off-label	Initiate at 300 mg hs over 1 wk. After 1 wk, gradually increase to target dosage (2,400 mg/day) according to the following schedule: 300 mg bid for 1 wk, 300 mg tid with 600 mg hs for 2 wk, 600 mg tid for 2 wk, and 600 mg bid with 1,200 mg hs
Milnacipran (Savella)	SNRI	FDA-approved	Initiate at 12.5 mg po once on day 1; then 12.5 mg po bid on days 2–3, 25 mg po bid on days 4–7, and 50 mg po bid thereafter
Venlafaxine (Effexor)	SNRI	Off-label	Initiate at 37.5 mg or 75 mg po qd. The 37.5-mg dosage may be useful for newer patients while adjusting to the medication prior to higher titration
Tramadol (Ultram, and others)	Analgesic	Off-label	Initiate at 25 mg po qd, then titrate in 25-mg increments on separate doses every 3 days to reach 100 mg/day po in divided doses (25 mg po qhs, qid). After titration, 50–100 mg po q4–6h prn, not to exceed 400 mg/day po

GABA, gamma-aminobutyric acid; max, maximum; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. Source: References 1, 6, 7.

https://www.uspharmacist.com/article/treatment-of-fibromyalgia-pain accessed 1.13.2020

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Conclusion

- Pain management typically involves more than one modality in order to manage
- Safety must take into consideration patient specific factors that will change over time
- Certain combinations can put patients at risk for adverse effects but having a complete picture of a patients medications can help prevent this

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