PainWeek

Rational Polypharmacy: An Update for Specific Conditions

Thomas B. Gregory, PharmD, BCPS, CPE, FASPE

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Disclosures

- Nothing to disclose

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Current pharmacy litigation related to pain management

- **Michigan pharmacist, pharmacy technician charged in $1.2M opioid scheme**

According to the indictment, Cosmos George, PharmD, a pharmacist working at Dearborn, Mich.-based Village Script East Pharmacy, conspired with Tarielle Dixon, a pharmacy technician working at Detroit-based Nottingham Pharmacy, to dispense prescription opioids for fictitious patients without a legitimate medical need for the drugs from September 2017 through June 2020.

Dr. George, 44 of Southfield, Mich., and Ms. Dixon, 33, of Detroit, primarily dispensed oxycodone and oxymorphone, two highly addictive opioids with high black market resale values, according to the indictment.

The indictment says the two pharmacies dispensed more than 41,995 dosage units of Schedule II opioid prescriptions from September 2017 to June 2020. It also says those substances had a conservative street value of $1.2 million.

https://www.beckershospitalreview.com/opioids/michigan-pharmacist-pharmacy-technician-charged-in-1-2m-opioid-scheme.html accessed 4.20.2021

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Current pharmacy litigation related to pain management, cont.

- **Federal Court Restrains Tampa Pharmacy and Two Individuals From Dispensing Opioids or Other Controlled Substances**

In a civil complaint unsealed in the Middle District of Florida, the United States alleges that WeCare Pharmacy, its pharmacist owner Qingping Zhang, and pharmacy technician Li Yang, and another related corporate entity, L&Y Holdings LLC, repeatedly dispensed opioids in violation of the Controlled Substances Act. The complaint alleges that over a period of several years, the defendants dispensed highly addictive and highly abused prescription opioids while ignoring "red flags" — that is, obvious indications of drug diversion and drug-seeking behavior. U.S. District Judge Mary Scriven granted the government's request for a temporary restraining order, which was filed along with the complaint.

"Pharmacists have an important role in ensuring that prescriptions for controlled substances are legitimate," said Acting Assistant Attorney General Brian Boynton of the Justice Department's Civil Division. "The Department of Justice will work with its partners to enforce the law where evidence shows pharmacists abdicated their responsibilities when dispensing these powerful drugs."

https://www.justice.gov/opa/pr/federal-court-restrains-tampa-pharmacy-and-two-individuals-dispensing-opioids-or-other accessed 4.20.2021

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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 painful conditions

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How Does Rational Polypharmacy Apply to My Practice?

- Synergistic combinations decreasing the amount of opioid needed for pain control
- Using non-opioids 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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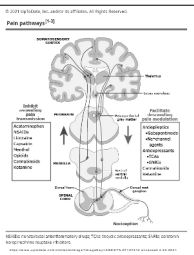
Hitting the Target, Shotgun or Sniper Approach?

- 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



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Medications in Pain Management for Specific Conditions

- Acetaminophen
- NSAIDs
- 5-$HT_{1\ B/D}$ agonists (Triptans)
- 5-HT_{1F} agonists (Ditans)
- Calcitonin gene-related peptide antagonists (Gepants)
- 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 = 3250 mg[1] daily
  - –Johnson and Johnson = 3000 mg[2] daily

1. http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm165107.htm accessed 4.20.2021
2. https://www.tylenol.com/safety-dosing/usage/dosage-for-adults accessed 4.20.2021

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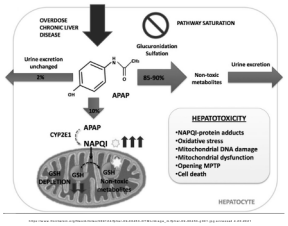
Acetaminophen (cont'd)

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



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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 co-morbidities limit the dosing on most NSAIDs
  - –Patients on anticoagulants
  - –Patients with renal dysfunction
  - –Pregnancy

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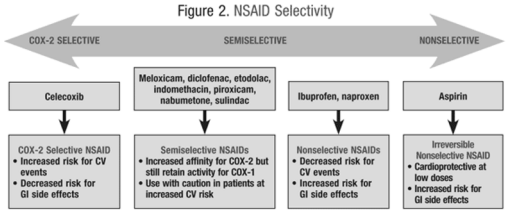
NSAIDs and COX Selectivity

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 4.21.2021

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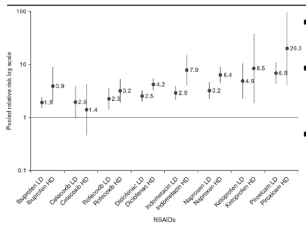
NSAIDs and GI Complications (GIC)



- 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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Use of NSAIDs and Fracture Healing

For decades, NSAIDs have been shunned by the orthopedic community due to weak data indicating NSAIDs impair fracture healing.

- –Concern related to NSAIDs reducing mechanical strength and increasing the risk of non-union
  - Decreased risk with the COX-2 specifics agents compared to non-COX specific NSAIDs
- Four studies have fueled this paradigm
- –Each had major flaws in study design
  - Three were retrospective in nature, did not account for confounders [smoking]
  - The prospective trial had a total of 13 patients, raising a concern for power

J Orthop Trauma 33; e158–e182: 2019

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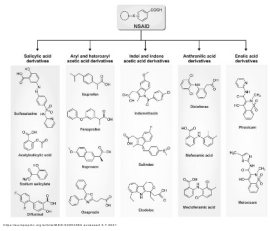
Use of NSAIDs and Fracture Healing, cont.

- Two meta-analyses concluded there are no high quality literature to support the thesis of NSAIDs leading to fracture non-union
- Opioids also impair immune function independently of NSAID use as well as other risks from the use of opioids
- NSAIDs should be considered for inflammatory pain conditions, even in those with fractures



J Orthop Trauma 33; e158–e182: 2019

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

- Serotonin receptor antagonists leading to
  - –Extra-cerebral vasoconstriction ($5\text{-}HT_{3\text{-}1B}$)
  - –Decreased inflammatory neuropeptide release ($5\text{-}HT_{3\text{-}1D}$)
- Indicated for acute migraine treatment
  - –Abortive therapy, not prophylactic
- Dosing involves administration of a repeat of the dose in one to two hours if the first dose was unsuccessful in aborting the migraine for specific agents
  - –Other agents are only indicated for use once in 24 hours

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Triptans (cont'd)

Longer time to onset and longer elimination

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

http://www.headache.mobi/uploads/1/1/7/5/11757140/triptans.pdf accessed 4.21.2021

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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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Newer Agents Available for Migraine

Calcitonin Gene-Related Peptide antagonists

- Monoclonal antibody agents
  - –Fremanezumab-vrfm (Ajovy®)
  - –Erenumab-aooe (Aimovig ®)
  - –Eptinezumab-jjmr (Vyepti®)
  - –Galcanezumab-gnlm (Emgality®)
- Gepant agents
  - –Ubrogepant (Ubrelvy®)
  - –Rimegepant (Nurtec®)

Serotonin1F receptor antagonist

- Ditan agents
  - –Lasmiditan (Reyvow®)

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Calcitonin Gene-Related Peptide (CGRP) Antagonists

Monoclonal antibodies that antagonize CGRP receptors
- –Preventing intracranial artery vasodilatation
- –Prevention of dural mast cell degranulation

- Monthly injections are indicated for the prevention of migraine
  - –Subcutaneous
    - •Erenumab-aooe
    - •Galcanezumab-gnlm
    - •Fremanezumab-vrfm (every one or three months)
  - – IV infusion
    - •Eptinezumab-jjmr (every one or three months)

Front Cell Neurosci.13.136 2019

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Calcitonin Gene-Related Peptide Antagonists, cont.

For subcutaneous formulations, patient or caregiver instructions should be provided for proper use
- Erenumab-aooe
  - –70 mg monthly, may increase to 140 mg monthly
- Galcanezumab-gnlm
  - –Migraine: 240 mg at the beginning of therapy then 120 mg monthly thereafter
  - –Episodic cluster headache: 300 mg at the onset of the cluster period then monthly until the end of the cluster period
- Fremanezumab-vrfm
  - –225 mg monthly or 675 mg every three months
- Eptinezumab-jjmr
  - –100 mg infused over 30 minutes monthly or 300 mg infused over 30 minutes every three months

https://fco.factsandcomparisons.com/fco/action/home accessed 4.22.2021

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Calcitonin Gene-Related Peptide Antagonists, cont.

Gepants have been in development for more than 15 years
- –Currently approved agents are second generation agents

- Small molecules which block CGRP receptors
  - –Ubrogepant
    - •Oral tablet
    - •50 mg to 100 mg at onset of migraine and may take a second dose two hours after the initial dose
      - –Maximum of 200 mg in 24 hours
  - –Rimegepant
    - •Orally disintegrating tablet
    - •75 mg at onset of migraine
      - –Maximum of 75 mg in 24 hours

https://fco.factsandcomparisons.com/fco/action/home accessed 4.22.2021

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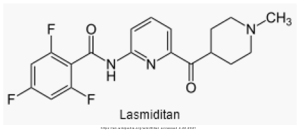
Serotonin$_{1F}$ Receptor Antagonist

Ditan agents selectively block the serotonin 1F subtype receptor

- Triptans block serotonin subtypes 1B and 1D
- Do NOT have the same concerns for vasoconstriction [serotonin subtype 1B] compared to the triptan agents

▪ Lasmiditan

- 50 mg to 200 mg at the onset of migraine
- Only one dose to be administered in 24 hours, regardless of dose strength



Lasmiditan

Journal of headache and pain 20; 37 2019

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Drug Interactions and Side Effects of CGRP Antagonists

- Drug interactions
  - None reported with the monoclonal antibody CGRP antagonist agents
  - Gepants and concurrent administration with strong CYP 3A4/5 inhibitors
  - Ditans and potential for serotonin syndrome
- Renal dose adjustment
  - Only for the Ditan agent with severe renal impairment
- Side effects
  - Injection site reactions for the monoclonal antibody agents
  - Sedation and low heart rate (Lasmiditan) with Ditans
- Pregnancy and lactation safety data in humans are not available

https://fco.factsandcomparisons.com/fco/action/home accessed 4.26.2021

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Summary for Newer Migraine Agents

- Patient directed prophylactic migraine management for injection
  - Fremanezumab
  - Erenumab
  - Galcanezumab
- Acute migraine management
  - Ubrogepant
  - Rimegepant
  - Lasmiditan
- Available for every one or three month prophylactic administration
  - Eptinezumab
  - Fremanezumab
- Episodic cluster headache
  - Galcanezumab

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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
  - –Duloxetine 60 mg BID versus duloxetine 60 mg daily
- 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

Topiramate	**Valproic acid**
Lamotrigine	**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
  - –CDC issued guidance advising against misapplication of the guidelines in 2019

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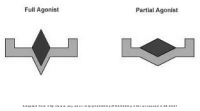
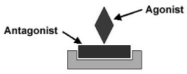
Opioids (cont'd)

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





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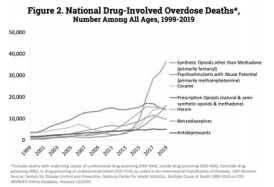
Opioid Statistics

- Medication overdose deaths in 2019: 70,630
  - –Synthetic opioids [primarily fentanyl] accounted for over 50% of the overdose deaths
  - –Prescription opioid involvement with overdose deaths have decreased since 2017, still accounted for 20%
  - –Notable increase in methamphetamine and cocaine involvement with overdose deaths



https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates accessed 4.28.2021

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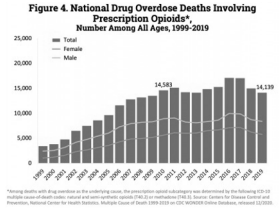
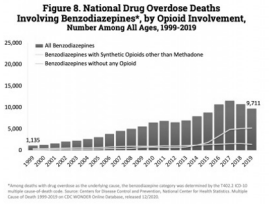
Opioid Statistics (cont'd)





https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates accessed 4.28.2021

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Opioid Statistics (cont'd)

Figure 6. National Drug Overdose Deaths Involving Psychostimulants with Abuse Potential (Primarily Methamphetamine)[a], by Opioid Involvement Number Among All Ages, 1999-2019

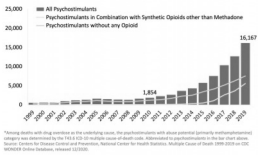
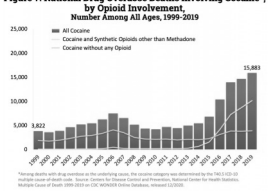


Figure 7. National Drug Overdose Deaths Involving Cocaine[a], by Opioid Involvement, Number Among All Ages, 1999-2019



https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates accessed 4.28.2021

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Patients at Risk for Opioid Adverse Events

- Sleep apnea or sleep disordered breathing
- Pregnancy
- Hepatic or renal dysfunction
- Age greater than 64
- Mental health conditions
- Substance use disorder
- Nonfatal overdose history

- Offer naloxone to patients when any of the above risk factors are present

https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm accessed 4.28.2021

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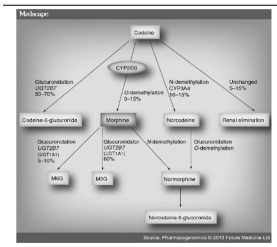
Opioid Metabolism



- 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 4.28.2021

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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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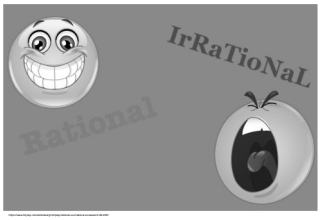
Which Appears to Be More Effective?



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Irrational Polypharmacy Practices

- Utilizing two medications in the same pharmacologic family and formulation for the same condition
  - –Ibuprofen and naproxen
  - –Methocarbamol and carisoprodol
  - –Hydrocodone-acetaminophen 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 meperidine use in a patient with underlying seizure history
  - –Long term use of anti-spasmodic agents past the acute injury

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Rationalizing Migraine Pain Management

- Use of preventative therapy once patients meet any of the following criteria
  - –Attacks significantly impact daily routine despite acute treatment
  - –At least four migraine days per month
  - –Overuse of acute treatments or contraindications to acute treatment
    - Ten or more days per month using ergo derivatives, triptans, opioids or combination analgesics
    - Fifteen days per month using non-opioid analgesics
  - –Adverse events to acute treatments
  - –Patient preference
- Monoclonal antibody CGRP therapy IF non-CGRP antagonist prevention strategies are not tolerated/ appropriate

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Headache 59;1:1-18 2019

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Rationalizing Migraine Pain Management, cont.

Table 7.—Assessment of Acute Treatments for Migraine[18]

Established efficacy[†]	Probably effective
Triptans	Ergotamine and other forms of DHE
Ergotamine derivatives	NSAIDs: ketoprofen, IV and IM ketorolac, flurbiprofen
NSAIDs: aspirin, diclofenac, ibuprofen, naproxen	IV magnesium[†]
Opioids[‡]	Isomethepiene-containing compounds
Combination medications	Combinations: codeine/acetaminophen, tramadol/acetaminophen[†]
	Antiemetics: prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide

DHE, dihydroergotamine; IV, intravenous; IM, intramuscular; NSAID, nonsteroidal antiinflammatory drug.
[†]Consider single-pulse transcranial magnetic stimulation, noninvasive vagus nerve stimulation, or electrical trigeminal nerve stimulation in patients who prefer nondrug treatments or in whom drug treatment is ineffective, intolerable, or contraindicated.
[‡]In migraine with aura.
[§]Use is not recommended.

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Headache 59;1:1-18 2019

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Rationalizing Migraine Pain Management, cont.

Table 4.—Treatments With Evidence of Efficacy in Migraine Prevention (Adapted from Silberstein et al[19])

Established efficacy[†]	Probably effective[‡]	Possibly effective[§]
Antiepileptic drugs:	Antidepressants	ACE inhibitors: Lisinopril
Divalproex sodium[#]	Amitriptyline	Alpha-agonists
Valproate sodium[#]	Venlafaxine	Clonidine
Topiramate[‖]	Beta-blockers	Guanfacine
Beta-blockers	Atenolol	Antiepileptic drugs: Carbamazepine
Metoprolol	Nadolol	Beta-blockers
Propranolol		Nebivolol
Timolol		Pindolol
Triptans: Frovatriptan[¶]		Antihistamines: Cyproheptadine
OnabotulinumtoxinA[#]		Angiotensin receptor blockers: Candesartan

ACE, angiotensin-converting enzyme.
[†]More than 2 Class I trials based on AAN Scheme for Classification of Evidence.[33]
[‡]One Class I or 2 Class II studies based on AAN Scheme for Classification of Evidence.[33]
[§]One Class II study based on AAN Scheme for Classification of Evidence.[33]
[‖]Not for use in women of childbearing potential who are not using an appropriate method of birth control.[34,35]
[¶]Short-term prevention of menstrual migraine.
[#]For prevention of chronic migraine.

PainWeek

Headache 59;1:1-18 2019

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Rationalizing Neuropathic Pain

- Amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)
  - Carbamazepine as initial treatment for trigeminal neuralgia
- Tramadol only if acute rescue therapy is needed
- Capsaicin cream for people with localized neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments

https://www.nice.org.uk/guidance/cg173/resources/neuropathic-pain-in-adults-pharmacological-management-in-nonspecialist-settings-pdf-35109750554053 accessed 4.29.2021

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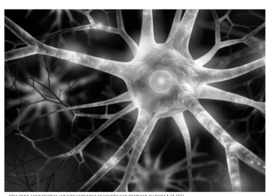
Irrational Neuropathic Pain Management

Do not start the following to treat neuropathic pain without consulting a specialist

- Cannabis sativa extract
- Capsaicin patch
- Lacosamide
- Lamotrigine
- Levetiracetam
- Morphine
- Oxcarbazepine
- Topiramate
- Tramadol (short-course therapy only)
- Venlafaxine
- Sodium valproate



https://www.nice.org.uk/guidance/cg173/resources/neuropathic-pain-in-adults-pharmacological-management-in-nonspecialist-settings-pdf-35109750554053 accessed 4.29.2021

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Rationalizing Post Herpetic Neuralgia

- 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 *intact* skin. 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, dysethesia, vesicular rash, ulcerations, edema, erythema, depigmentation
Capsaicin 8% patch	Apply to most painful area of *intact* skin for 60 minutes, then remove; up to 4 patches may be applied in a single application. May repeat no more than every 3 months upon return of pain. Area should be pretreated with a topical anesthetic prior to patch application	Erythema, pain, hypertension (transient), pruritus, nausea, vomiting, papules, edema, nasopharyngitis
Tricyclic Antidepressants (TCAs)		
Nortriptyline[a]	10-25 mg at bedtime; increase dose by 25 mg/day weekly if tolerated; usual maintenance dose 75 mg/day as a single bedtime dose or 2 divided doses; maximum 125 mg/day	Dry mouth, constipation, arrhythmia; least likely TCA to cause orthostatic hypotension; less likely TCA to cause cognitive impairment, sedation, and anticholinergic effects
Desipramine[a]	10-25 mg/day; increase every 3 days as necessary until desired effect achieved; usual effective dose: 50-150 mg/day; maximum dose 150 mg/day	Dry mouth, constipation, arrhythmia, cognitive impairment, orthostatic hypotension; less likely TCA to cause sedation and anticholinergic effects
Anticonvulsants		
Gabapentin	Day 1: 300 mg, day 2: 300 mg twice daily, 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 (dosage given for morphine equivalents)*	2.5-15 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*[b]	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 3-7 days as tolerated; maximum 300 mg/day in patients over 75 years of age	Constipation, nausea, dizziness, headache, somnolence, vomiting, pruritus, insomnia, orthostasis, falls

* Not FDA approved for this indication
https://www.uspharmacist.com/article/postherpetic-neuralgia-seniors-at-risk accessed 4.29.2021

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Rationalizing Musculoskeletal Pain Management

- Acute pain from non–low back, musculoskeletal injuries with topical nonsteroidal anti-inflammatory drugs (NSAIDs) with or without menthol gel as first-line therapy Strong recommendation
- Acute pain from non–low back, musculoskeletal injuries with oral NSAIDs
- Acute pain from non–low back, musculoskeletal injuries with specific acupressure, with transcutaneous electrical nerve stimulation, or oral acetaminophen to reduce pain
- Acute pain from non–low back, musculoskeletal injuries with opioids, including tramadol

Annals of Internal Medicine 173; 9: 739-48 2020

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Rationalizing Musculoskeletal Pain Management, cont.

- Use multi-modal analgesia including NSAIDs, acetaminophen, gabapentin and immediate release opioids
  - –Lowest effective dose of opioids for the shortest course possible
  - –Do NOT use extended release opioids
- Discuss cognitive strategies with the patient preoperatively (if operative candidate)

J Orthop Trauma 33; e158–e182: 2019

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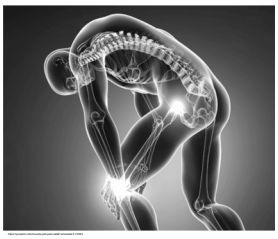
Rationalizing Musculoskeletal Pain Management, cont.

- Immobilize the injury, use cold therapy and elevate as appropriate
  - –Consider TENS or cryotherapy
- For patients on opioids at baseline, use a balance of physical cognitive and pharmacologic strategies to alleviate pain
- Ensure only one prescriber coordinates patient care with other prescribers (addiction medicine, psychiatry, etc.) when in the inpatient or outpatient setting



J Orthop Trauma 33; e158–e182: 2019

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Rationalizing Musculoskeletal Pain Management, cont.

TABLE 4. Pain Medication Recommended Taper* Following a Nonoperative Musculoskeletal Injury (eg, Closed Management of Injury, Laceration Repair, etc.)

Injury Category	Opioid	Nonopioid
Minor injury (eg, small bone fracture, sprain, laceration, etc.)	Tramadol 50 mg (only if necessary—2 Rx Max) 1 tab po q 6 h PRN Dispense #20, then #10	NSAIDs PRN as directed Scheduled acetaminophen 1000 mg po q8 hours, then PRN as directed
Major injury (eg, large bone fracture, rupture, etc.)	Hydrocodone/acetaminophen 5 mg/325 mg or tramadol 50 mg (only if necessary—2 Rx Max) 1 tab po q 6 h PRN Dispense #20, then #10	NSAIDs PRN as directed Scheduled acetaminophen 1000 mg po q12 h, then PRN as directed

Dosage and duration can be less if tolerated.
*In conjunction with other best practice recommendations and individualized per treating physician discretion according to patient characteristics, local practice preferences, and state law.

J Orthop Trauma 33; e158–e182: 2019

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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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