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Alternatives for Opioids in Pain Management; Created by Armen Fstkchian, PharmD student and Ben Chavez, PharmD

Non-opioid Analgesics	Role in Therapy	Dosing	Side Effects/Precautions	Comments
Acetaminophen (Tylenol) ***Available Dosage forms:*** Oral: ➢ Capsule (500mg) ➢ Tablets (325mg, 500mg, and 650mg) ➢ Suspension (160mg/5ml) ➢ Chewable tabs (80mg, 160mg) ➢ Disintegrating tabs (80mg, 160mg) Rectal: ➢ Suppository (120mg, 650mg)	➢ First-line monotherapy for mild to moderate pain ➢ Used in combination with opioids for moderate to severe pain	**Regular strength:** ➢ 650mg q4-6h prn ➢ MDD: 3,250mg ➢ MDD under medical supervision: ≤4,000mg **Extra Strength:** ➢ 1000mg q6h prn ➢ MDD: 3,000mg ➢ MDD under medical supervision: ≤4,000mg **Pediatric Dosing:** ➢ Infants and Children <60kg = 10-15 mg/kg/dose q4-6h ➢ MDD for infants: 75 mg/kg/day ➢ MDD for children <60kg: 1625 mg/day ➢ Children >60kg: Same adult dosing and adult MDD. **Hepatic Impairment:** ➢ MDD: 2,000mg **Renal Adjustment:** ➢ eGFR 10 to 50 ml/min: Administer every 6 hours ➢ eGFR <10 ml/min: Administer every 8 hours ➢ CRRT: Administer every 6 hours	**Boxed Warning:** Hepatotoxicity (may be fatal) ➢ Use with caution in patients with history of alcoholism ➢ Increased risk in patients with hypovolemia ➢ Increased risk in patients with chronic malnutrition Severe Skin Rash (rare) -Hypersensitivity Reactions (rare)	➢ Effective for noninflammatory pain and may be opioid-sparing ➢ Does not alter platelet function ➢ Interacts with warfarin (prolongs INR), isoniazid and CYP450-inducing drugs ➢ Advise patients about reading OTC preparation labels that may contain acetaminophen to avoid going over MDD.
Non-selective NSAIDs:	**Boxed Warning for ALL nonselective NSAIDs:** ➢ Increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. ➢ Increased risk of serious GI side effects including bleeding, ulceration, and perforation of the stomach and intestines, especially in elderly.	➢ Effective for treatment of acute pain and inflammatory conditions ➢ May decrease opioid requirements ➢ Use the lowest effective dose for the shortest duration that is consistent with treatment goals for the patient ➢ Short-to-moderate-acting NSAIDs (naproxen, ibuprofen) are preferred for most patients ➢ Reversibly inhibit platelet function and can alter cardioprotective effects of aspirin ➢ **If patient does not tolerate NSAIDs in one class (in yellow), can safely switch to another class.**		
Propionic acids:				
Ibuprofen (Advil, Motrin) ***Available Dosage forms:*** **Oral:** ➢ Capsule (200mg) ➢ Suspension (100mg/5ml) ➢ Tablet (200mg, 400mg, 600mg, 800mg) ➢ Chewable tabs (100mg)	➢ First-line therapy for mild to moderate pain	**Adults:** ➢ 200 to 400mg q4-6hrs prn ➢ MDD: 1,200mg **Pediatrics (**age 6 months to 12 years): ➢ 5 to 10 mg/kg q6-8hrs prn ➢ MDD = 4 doses/day **No dosage adjustments recommended in renal or hepatic impairment**	➢ Use with caution in patients with heart failure and in patients with stage 4 or 5 CKD	➢ Short duration of effect ➢ Doses >400 mg do not provide greater analgesic activity ➢ 200 to 400 mg dose has comparable analgesic effect with 650 mg acetaminophen ➢ If taking ASA for cardio-protection, take ibuprofen 1hr before or 8 hours after ASA.
Naproxen (Aleve, Naprosyn) ***Available Dosage forms:*** Naproxen sodium (Aleve) **Oral:** ➢ Tablet (220mg, 275mg, 550mg)	➢ First-line therapy for mild to moderate pain	**Adults:** ➢ Naproxen sodium: o OTC: 220mg-440mg q8-12hrs prn; MDD: 660 mg/day o Rx: 550mg q12hrs prn or 275mg q6-8hrs prn; MDD initial: 1,375mg; MDD for	➢ Use with caution in patients with heart failure and in patients with CKD	➢ May have less cardiovascular toxicity than comparable doses of other NSAIDs ➢ Naproxen sodium has more rapid absorption and onset of action than naproxen base.

➢ Extended Release (375mg, 500mg) ➢ Liquid gel caps (220mg) Naproxen base (Naprosyn) **Oral** ➢ Tablet (250mg, 375mg, 500mg) ➢ Enteric Coated (375mg, 500mg) ➢ Suspension (125mg/5ml)		maintenance: 1100 mg/day ➢ Naproxen base: o 500mg initially, followed by 250mg q6-8hrs prn; MDD: 1250mg/day **Renal adjustment:** ➢ CrCl <30 ml/min = Use not recommended **Hepatic adjustment:** ➢ Use lowest effective dose and when high doses are necessary, a dosage adjustment may be necessary **Geriatric:** ➢ Consider 50% reduction in initial dose for elderly patients		➢ Naproxen base and naproxen sodium are not interchangeable ➢ Can be used in pediatric patient >12 years old
Acetic Acids:				
Diclofenac (Voltaren) *Available Dosage forms:* **Oral:** ➢ EC Tablet (25mg, 50mg, 75mg) ➢ ER Tab (100mg) ➢ Liquid Cap (25mg) ➢ Powder for Solution (50mg) **Topical:** ➢ Patch ER 1.3% ➢ Gel 1%	➢ For mild to moderate acute pain (only IV) ➢ For moderate to severe acute pain with or without opioids (only IV) ➢ For acute pain due to minor strains, sprains, and contusions (patch)	**Adults:** ➢ Oral: o EC tabs: 50mg BID-TID; MDD: 150mg/day o ER tab: 100mg once daily; may titrate to BID; MDD: 200mg/day ➢ Topical: o Apply 4g to lower extremities/ 2g to upper extremities QID; MDD: 32g/day to lower extremities, 16g/day to upper extremities o Apply one patch (180mg) to most painful site BID **Renal adjustment:** ➢ Oral: o Mild to moderate impairment: no adjustment necessary o Severe impairment or ESRD: use not recommended **Hepatic adjustment:** ➢ Oral: No manufacturer's specific dosage adjustments provided but may require adjustment due to extensive hepatic metabolism o Mild impairment: No adjustment o Moderate to severe impairment: Dose reduction maybe necessary	➢ Interacts with drugs that are strong inhibitors or inducers of CYP2C9	➢ Only patch and IV formulations are approved for acute pain ➢ Topical formulations can be used in combination with oral NSAIDs for further pain relief
Etodolac (Lodine) *Available Dosage forms:* **Oral** ➢ Capsule (200mg, 300mg) ➢ IR tab (400mg, 500mg) ➢ ER tab (400mg, 500mg, 600mg)	➢ For the treatment of mild to moderate acute pain	**Adults:** ➢ Oral: o 200 to 400mg q6-8hrs prn; MDD: 1,000mg/day o Patients <60kg MDD: 20mg/kg/day **Renal adjustment:** ➢ Use with caution in patients with pre-existing mild-to-moderate renal failure as medication may cause cumulative effects on renal function **Hepatic adjustment:** ➢ May need to decrease dose in patients with severe hepatic failure	➢ Use with caution in patients with heart failure and/or CKD	➢ No dose adjustment needed for elderly patients, mild to moderate renal failure, or compensated hepatic cirrhosis ➢ Relatively COX-2 selective at lower daily doses of 600 to 800mg, thus less GI side effects ➢ 200mg dose has comparable analgesic effect with 400mg ibuprofen

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Indomethacin (Tivorbex, Indocin) *Available Dosage forms:* **Oral:** ➢ IR Capsule (25mg, 50mg) ➢ ER Caps (75mg) ➢ Suspension (25mg/5ml) **Rectal:** ➢ Suppository (50mg)	➢ For the treatment of mild to moderate acute pain ➢ For the treatment of acute shoulder pain	**Adults:** **Mild to Moderate Pain:** ➢ IR caps: 20mg TID or 40mg BID-TID; MDD: 150mg/day **Shoulder Pain:** ➢ IR caps or Suppository: 75 to 150mg in 3 to 4 divided doses for 7 to 14 days ➢ ER caps: 75mg once or twice daily for 7 to 14 days **Renal adjustment:** ➢ Not recommended in advanced renal disease **Hepatic adjustment:** ➢ No dosage adjustment provided in manufacturer's labeling; use with caution in hepatic impairment **Geriatric adjustment:** ➢ Initiate at lower end of dosage range	➢ Use with caution in patients with psychiatric conditions ➢ Potent inhibitory effects on renal prostaglandins ➢ Contraindicated in patients with history of proctitis or recent rectal bleeding	➢ More likely to cause CNS side effects than other NSAIDs ➢ 100% oral bioavailability
Ketorolac (Toradol) *Available dosage forms:* ➢ IV (15mg/mL, 30mg/mL) ➢ IM (30mg/mL) ➢ Oral tablet (10mg) ➢ Ophthalmic Solution (0.4%, 0.5%) ➢ Intranasal (15.75mg/1 actuation)	➢ For the treatment of moderate to severe short-term pain and headache	**Adults: MAX duration of treatment = 5 days for all routes of administration** **Short-term Pain:** ➢ IV o 17 to 65 y.o.: 30 mg IV as single dose or 30mg IV q6h prn; MDD: 120mg/day o >65 y.o. OR <50kg: 15mg IV single dose or 15mg IV q6h prn; MDD: 60mg/day ➢ IM o 17 to 65 y.o.: 60mg single dose OR 30mg q6h prn; MDD: 120mg/day o >65 y.o. OR <50kg: 30mg single dose or 15mg q6h; MDD: 60mg/day ➢ Intranasal o 17 to 65 y.o.: 1 spray (15.75mg) in each nostril q6-8hrs; MDD: 126mg/day (4 doses) o >65 y.o. OR <50kg: 1 spray (15.75mg) in 1 nostril q6-8h; MDD: 63mg/day (4 doses) ➢ Oral tablet: o 17 to 65 y.o.: 20mg once followed by 10mg q4-6hrs prn; MDD: 40mg/day o >65 y.o. OR <50kg: 10mg once followed by 10mg q4-6hrs prn; MDD: 40mg/day **Renal adjustment:** ➢ Mild to moderate impairment: Follow dosing for patients >65 y.o. OR <50kg as seen above. ➢ Avoid use in advanced renal disease **Hepatic adjustment:** ➢ More information is needed	➢ Use longer than 5 days increases risk for serious or fatal adverse events (use along or combined with other forms of ketorolac) ➢ Dose adjust in patients <50kg	➢ Provides analgesia comparable to morphine, meperidine and other narcotic agents. ➢ Can help reduce opioid requirements ➢ Does not produce respiratory depress or cause drug dependence ➢ Not indicated for use in chronic pain patients
Fenamates:				
Meclofenamate (Meclomen) *Available dosage forms:* **Oral:**	➢ For the treatment of mild to moderate pain ➢ Treatment of acute	**Adults:** **Mild to Moderate Pain/Acute Shoulder Pain:** ➢ 50mg to 100mg orally q4-6hrs; MDD = 400mg/day **Primary Dysmenorrhea:**	➢ Concomitant use with ASA not recommended ➢ Can cause severe hepatic reactions (i.e. fatal	➢ Associated with higher incidence of GI side effects including diarrhea ➢ Alternate NSAID for acute or chronic pain, inflammation and

➢ Capsules (50mg, 100mg)	shoulder joint pain ➢ Treatment of primary dysmenorrhea	➢ 100mg orally TID up to 6 days **Renal adjustment:** ➢ Avoid in advance renal disease **Hepatic adjustment:** ➢ No recommendation found	fulminant hepatitis <1%) ➢ Avoid in advanced renal disease	dysmenorrhea
Mefenamic Acid (Ponstel) *Available dosage forms:* Oral: ➢ Capsule (250mg)	➢ For treatment of acute mild to moderate pain ➢ Treatment of dysmenorrhea	**Adults and children >14 years old:** **Mild to Moderate Acute Pain:** ➢ Initial 500mg orally, followed by 250mg q6h prn; treat no longer than a week **Dysmenorrhea:** ➢ Initial 500mg orally, followed by 250mg q6h beginning at onset of bleeding and symptoms and continued for 2 to 3 days **Renal adjustment:** ➢ Avoid in patients with preexisting renal disease or significant renal impairment **Hepatic adjustment:** ➢ No dosage adjustments are provided by the manufacturer but adjustment may be needed in impairment due to extensive hepatic metabolism	➢ Hyperkalemia has occurred in patient with or without renal impairment ➢ May elevate ALT or AST >3 or more the ULN ➢ Severe or fatal hepatic injury ➢ May exacerbate asthma	➢ Alternate NSAID choice for treatment of acute pain and dysmenorrhea. ➢ Duration of use not to exceed seven days (acute pain) or three days (dysmenorrhea). ➢ Anti-inflammatory efficacy is comparatively low. ➢ Not indicated for treatment of chronic pain or inflammation. ➢ Extensive CYP2C9 metabolism ➢ Rapid Absorption
Oxicams				
Meloxicam (Mobic) *Available dosage forms:* Oral: ➢ Tablet (7.5mg, 15mg) ➢ ODT (7.5mg, 15mg) ➢ Capsule (5mg, 10mg) ➢ Suspension (7.5mg/5ml)	➢ For the treatment of osteoarthritis and pain associated with rheumatoid arthritis	**Adults:** **Osteoarthritis:** ➢ Suspension/Tabs/ODT: 7.5mg once daily; MDD: 15mg ➢ Capsule: 5mg once daily; MDD: 10mg **Rheumatoid Arthritis:** ➢ Suspension/Tabs/ODT: 7.5mg once daily; MDD: 15mg **Renal Adjustment:** ➢ CrCl >15ml/min: No adjustment necessary ➢ CrCl <15 ml/min: Use not recommended **Hepatic adjustment:** ➢ Mild to moderate impairment: No adjustment necessary ➢ Severe impairment: Use with caution	➢ Caution in cardiovascular and kidney disease	➢ Long duration of action; slow onset (5 days to reach steady state) ➢ Not good for acute pain ➢ More COX-2 selective (less GI side effects) ➢ Minimal effect on platelet function at lower dose of 7.5mg ➢ CYP2C9 subtrate
Selective COX-2 Inhibitors				
Celecoxib (Celebrex) *Available dosage forms:* Oral: ➢ Capsule (50mg, 100mg, 200mg, 400mg)	➢ For the treatment of acute pain including postoperative pain ➢ Treatment of primary dysmenorrhea	**Adults:** **Acute pain:** ➢ Initial 400mg once, plus one additional 200mg dose if needed on 1st day ➢ Maintenance 200mg BID prn **Acute Postoperative Pain:** ➢ 400mg once post-procedure **Primary dysmenorrhea:** ➢ 400mg initial, plus one additional 200mg dose if needed day 1 ➢ Maintenance 200mg BID prn **Renal adjustment:** ➢ Mild to moderate impairment: No adjustment	➢ May exacerbate asthma ➢ Risk for MI increased within first week of treatment ➢ Contraindicated in patient with known hypersensitivity to sulfonamides	➢ Less GI toxicity relative to nonselective NSAIDs ➢ No effect on platelet function ➢ CV and renal risks are dose-related and similar to those of nonselective NSAIDs ➢ Peak plasma levels delayed with high fat meals ➢ Extensive CYP2C9 metabolism ➢ Inhibitor of CYP2D6

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		necessary ➢ Severe impairment: Use not recommended **Hepatic impairment:** ➢ Mild impairment (Child-Pugh A): No adjustment necessary ➢ Moderate impairment (Child-Pugh B): Reduce dose by 50% ➢ Severe impairment (Child-Pugh C): Use not recommended		
Anticonvulsants	➢ The following anticonvulsants have been FDA approved for the treatment of neuropathic pain ➢ These medications require adequate trials of treatment before considering failure of treatment ➢ Other anticonvulsant medications outside of this list have been utilized anecdotally and in randomized trials for various pain conditions however, the evidence for their effectiveness is not as robust as the listed agents ➢ Consider these agents when patient has other co-morbid conditions that these may also treat			
Gabapentin (Neurontin, Gralise, Neuraptine, FusePaq) *Available Dosage forms:* Oral: ➢ Capsule (100mg, 300mg, 400mg) ➢ Tablets (600mg, 800mg) ➢ ER Tabs (300mg, 600mg) ➢ Suspension (25mg/mL) ➢ Solution (250mg/mL) **Topical:** ➢ Cream (10%)	➢ For the treatment of diabetic peripheral neuropathy, fibromyalgia, and postherpetic neuralgia ➢ For the preemptive treatment of acute postoperative pain	**Adults:** **Peripheral neuropathy:** ➢ 1200 to 3600 mg/day in 3 divided doses **Fibromyalgia:** ➢ Initial 300mg daily QHS; titrate over 6-weeks to MAX 2400 mg/day, given as 600mg BID and 1200mg QHS **Postherpetic neuralgia:** ➢ *IR caps and tabs*: o 300mg on Day 1: 300mg once o Day 2: 300mg BID o Day 3 300mg TID o MDD: 1800mg/day divided in to 3 doses ➢ *ER Tabs*: o Day 1: 300mg qdaily o Day 2: 600mg once daily o Days 3 to 6: 900mg once daily o Days 7 to 10: 1200mg once daily o Days 11 to 14: 1500mg once daily o Days 15 and on: 1800mg once daily ➢ Renal adjustment: o CrCl >60 ml/min: No adjustment o CrCl 30 to 59 ml/min: ▪ IR: 400 to 1400 mg/day in 2 divided doses ▪ ER: 600 to 1800 mg once daily o CrCl 15 to 29 ml/min: ▪ IR: 200 to 700 mg/day once daily ▪ ER: Do not administer in CrCl <30 ml/min	➢ Avoid concomitant use with other sedating agents as this may increase risk of falls ➢ Can cause respiratory depression ➢ Known to cause peripheral edema	➢ Do not abruptly discontinue, taper over a minimum of 1 week ➢ In pregnancy, fetal risk cannot be ruled out, however, major congenital malformation was reported in 1.7% of infants. ➢ Found in breast milk but in low amounts (1.3% to 3.8% of mother's dose) ➢ Can be used as adjunct to acetaminophen or NSAIDs for chronic pain ➢ Adequate trial is 2 months or more
Pregabalin (Lyrica) *Available dosage forms:* Oral: ➢ IR Capsule (25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg)	➢ For the treatment of diabetic peripheral neuropathy, fibromyalgia, and postherpetic neuralgia	**Adults:** **Peripheral Neuropathy:** ➢ IR caps: Initial, 50mg TID; may increase to MDD: 100mg TID w/in 1 week based on efficacy and tolerability ➢ ER tabs: Initial, 165mg once daily after evening meal,	➢ Increased risk of peripheral edema in HF patients ➢ May cause weight gain especially if given concomitantly with TZDs	➢ Can also be used for general anxiety disorder and restless legs syndrome ➢ If discontinuing, taper over 1 week ➢ Do not split, crush, or chew ER tabs ➢ Take ER formulation with food ➢ May provide analgesia quicker than

➢ ER Tab (82.5mg, 165mg, 330mg) ➢ Solution (20mg/mL)	➢ For the preemptive treatment of acute post-operative pain (off-label)	may increase to MDD: 330mg daily within 1 week ➢ IR to ER conversion: take IR morning dose, then begin ER dose after evening meal on same day o 75mg/day = 82.5mg o 150mg/day = 165mg o 225mg/day = 247.5mg (82.5mg tab X 3) o 300mg/day = 330mg **Fibromyalgia:** ➢ IR caps: Initial, 75mg BID, may increase to 150 BID within 1 week; MDD: 225mg BID ➢ No evidence of additional benefit with doses >450mg/day **Postherpetic neuralgia:** ➢ IR caps: o Initial 75mg BID or 50mg TID, may increase to 300mg/day within 1 week; Maintenance: 75mg to 150mg BID or 50mg to 100mg TID o Insufficient pain relief after 2-4 weeks with 300mg/day, may increase to 300mg BID or 200mg TID ➢ ER tabs: Similar dosing and conversion as neuropathy treatment; MDD: 660mg/day (330mg tab X 2) **Postoperative pain:** ➢ No optimal dosage established ➢ 150mg to 600mg per day used in trials ➢ 150mg to 300mg 2hrs prior to surgery **Renal Adjustment:** ➢ CrCL >60 ml/min: No adjustment ➢ CrCl 30-60 ml/min: o ER tabs: Reduce usual dosage by 50% o IR caps: 75 to 300mg/day BID or TID ➢ CrCl 15-30 ml/min: o ER tabs: Use not recommended, switch to IR o IR caps: 25 to 150mg/day once daily or BID ➢ CrCl <15 ml/min: o IR caps: 25 to 75mg once daily	➢ Can cause respiratory depression if given concomitantly with other analgesics and sedatives	Gabapentin
Carbamazepine *Available dosage forms:* Oral: ➢ ER capsule (100mg, 200mg, 300mg) ➢ Suspension (100mg/5mL) ➢ Tablet (200mg) ➢ Chew Tab (100mg) ➢ ER Tab (100mg, 200mg, 400mg)	➢ For the treatment of trigeminal neuralgia	**Adults:** **Trigeminal neuralgia:** ➢ ER cap: o Initial, 200mg once daily on day 1, may increase by 200mg/day q12 as needed for efficacy and tolerability, then dosed once daily o Most patients find relief between 400mg to 800mg per day; MDD: 1200 mg ➢ IR/chew tab/ER tab: o Initial, 100mg BID on day 1, may increase by 100mg q12 as needed for efficacy and tolerability	➢ Use with caution in elderly as SIADH or hyponatremia may occur or be exacerbated ➢ Risk of hypersensitivity including SJS, especially in patients with HLA-A*1502 allele ➢ Can cause hypotension ➢ Most common side effects are GI related (29% incidence of Nausea) ➢ High incidence of	➢ Studies show it is moderately effective for treatment of trigeminal neuralgia ➢ Consider alternative if patient has tried and failed other therapies ➢ Need baseline CBC, LFTs, urinalysis, BUN, and eye exam prior to initiation ➢ CYP3A4 substrate ➢ Inducer of CYP3A4 and CYP1A2 ➢ Avoid rapid withdrawal

		○ Most patients find pain relief 400mg to 800 mg/day; MDD: 1200mg/day ➢ Suspension: ○ Initial, 50mg 4 times daily on day 1, may increase by 200mg/day (50mg 4 times daily) as needed for efficacy and tolerability. ○ Most find pain relief between 400mg to 800mg/day ○ Oral suspension has higher peak levels than tablets thus must initiate at lower dose and increase slowly **Renal adjustment:** ➢ Mild renal impairment: No adjustment needed ➢ Moderate to Severe renal impairment: Use not recommended ➢ Per Lexicomp (recommendation use by clinicians): GFR <10 ml/min: Administer 75% of dose **Hepatic adjustment:** ➢ No manufacturer recommendations available ➢ Use with caution and consider dose reduction as it is primarily metabolized in the liver.	phonophobia (21.28%)	
Oxcarbazepine *Available dosage forms:* Oral: ➢ IR Tablet (150mg, 300mg, 600mg) ➢ ER Tablet (150mg, 300mg, 600mg) ➢ Suspension (300mg/5mL)	➢ For the treatment of neuropathic pain including trigeminal neuralgia (off-label)	**Adults:** **Neuropathic pain:** ➢ Initial, 300mg/day (150mg BID); increase dose after 3 days to 300mg BID, then adjust dose based off of efficacy and tolerability in increments of 300mg every 5 days; MDD: 1800mg (900mg BID) ➢ Mean maintenance dose during trials: 1,445mg/day **Renal adjustment:** ➢ CrCl <30 ml/min: Initiate at 50% of usual dose and increase slowly to achieve desired response (300mg-450mg daily at weekly intervals) **Hepatic adjustment (no manufacturer recommendations):** ➢ IR: use with caution in severe impairment (Child-Pugh C—not studied) ➢ ER: Use not recommended (not studied)	➢ Risk of SJS, especially in patients with HLA-B*1502 allele ➢ Can cause clinically significant hyponatremia and SIADH, especially during first 3 months of therapy	➢ Equally as effective as carbamazepine for trigeminal neuralgia ➢ Avoid rapid withdrawal ➢ CYP3A4/5 inducer ➢ CYP2C19 inhibitor ➢ CYP3A4 substrate
Antidepressants	➢ Both TCA's and SNRIs possess analgesic qualities, specifically for neuropathic pain ➢ Evidence for SSRIs for their effectiveness for the management of pain remains weak ➢ TCA's used for pain relief are usually used at lower doses compared with doses used to treat depression, thus mitigating some of the side effects ➢ Ensure patient does not have history of mania or hypomania as an antidepressant may exacerbate this condition ➢ Failure with one antidepressant is not a class effect, can switch to another drug for therapeutic effect ➢ If decision is made to discontinue any of these medications, a gradual taper is recommended to avoid withdrawal symptoms ➢ **Black Box warning** for all antidepressants: May increase risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 y.o.). There is a reduction in this risk in patients aged 65 and older.			
Duloxetine (Cymbalta) *Available dosage forms:* Oral ➢ Delayed-Release Capsule (20mg, 30mg, 40mg, 60mg)	➢ For the treatment of peripheral neuropathy, fibromyalgia, and chronic	**Adults:** **Peripheral neuropathy:** ➢ 60mg once daily; can consider lower starting dose; MDD: 60mg **Fibromyalgia and Chronic Musculoskeletal Pain:**	➢ Most common side effects include nausea, headache, dizziness, insomnia, constipation, and decrease appetite	➢ Can be used as an alternative for lower back pain and osteoarthritis of the knee if patients do not tolerate NSAIDs or acetaminophen or are found to be ineffective

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	musculoskeletal pain (FDA-approved for these indications)	➢ Initial, 30mg once daily for 1 week, increase to usual dosage of 60mg once daily based on tolerability; MDD: 60mg **Renal adjustments:** ➢ Avoid use if GFR <30 ml/min **Hepatic adjustment:** ➢ Avoid use in any level of hepatic impairment, chronic liver disease, or cirrhosis	➢ Syncope is more common with concomitant antihypertensives or potent CYP1A2 inhibitors ➢ Use with caution in patients with CV disease as duloxetine may increase BP ➢ Use with caution in patients with history of seizures	➢ Can be used as an adjunct to NSAIDs for further pain control ➢ Capsule can be opened and sprinkled on food (i.e. apple sauce) if swallowing is an issue ➢ Avoid use with potent CYP1A2 inhibitors such as cimetidine and ciprofloxacin. ➢ Start at 30mg for 1 week before starting 60mg dose to improve tolerability ➢ Patients may need at least 4 weeks of treatment to see effects
Venlafaxine (Effexor) *Available dosage forms:* Oral: ➢ ER Capsule (37.5mg, 75mg, 150mg) ➢ ER Tablet (37.5mg, 75mg, 150mg, 225mg) ➢ IR Tablet (25mg, 37.5mg, 50mg, 75mg, 100mg)	➢ For the treatment of peripheral neuropathy (Off-label)	**Adults:** **Peripheral neuropathy:** ➢ ER tab/capsule: Initial, 37.5mg or 75mg once daily, increase by 75mg each week to max dose of 225mg once daily based on tolerance and effect. **Renal adjustment:** ➢ CrCl 30 to 89 ml/min: Reduce total daily dose by 25% to 50% ➢ CrCl <30 ml/min: Reduce total daily dose by 50% or more **Hepatic adjustment:** ➢ Mild to moderate impairment (Child-Pugh A or B): Reduce total daily dose by 50% ➢ Severe impairment (Child-Pugh C): No adjustments provided by manufacturer but a reduction in total daily dose of at least 50% or more is advised.	➢ Use with caution in patients with CVD as this medication can increase BP and HR ➢ May increase anxiety, nervousness, and insomnia	➢ Some studies show patient's experienced pain relief by week 2 of treatment ➢ Adequate duration to determine effect and accomplish titration is 4-6 weeks ➢ Studies showed most reduction in pain occurred at dosed between 150mg to 225mg. ➢ May reduce weight ➢ Metabolized via CYP2D6
Milnacipran (Savella) *Available dosage forms:* Oral: ➢ Tablet (12.5mg, 25mg, 50mg, 100mg)	➢ For the treatment of fibromyalgia ➢ For the treatment of depression (off-label)	**Adults:** **Fibromyalgia:** ➢ Initial, 12.5mg once daily on day 1, then 12.5mg BID on days 2 and 3, then 25mg BID on days 4-7, and lastly, 50mg BID thereafter; MDD: 100mg BID (200mg/day) **Renal adjustment:** ➢ CrCl ≤29 ml/min: Reduce maintenance dose to 25mg BID; MDD: 50mg BID **Hepatic adjustment:** ➢ No adjustment necessary	➢ Use with caution in CVD because drug is known to increase BP and HR and may cause palpitations ➢ Common side effects include constipation, nausea, headache, dizziness, and insomnia. ➢ Can also cause diaphoresis and hot sweats; caution in post-menopausal women experiencing hot flashes	➢ No significant drug-drug interactions due to lack of CYP metabolism ➢ Although no FDA indication for depression, several studies has shown milnacipran to be efficacious for treatment
Amitriptyline (Elavil) *Available dosage forms:* Oral: ➢ Tablet (10mg, 25mg, 50mg, 75mg, 100mg, 150mg)	➢ For the treatment of fibromyalgia, postherpetic neuralgia, peripheral neuropathy, and chronic non-malignant pain. (All	**Adults:** **Fibromyalgia:** ➢ Initial 10mg once daily, 1-3hrs before bedtime, gradually increase dosage based on response and tolerability in 5-10mg increments at ≥2-week intervals up to 75mg/day; maintenance dose between 25mg to 50mg is often adequate.	➢ Use with caution in elderly due to high anticholinergic activity ➢ Use with caution in patients with CVD, including arrhythmias, as this medication is	➢ May reduce opioid-use and other forms of analgesia ➢ Start at lower dose in geriatric population ➢ Has the highest level of anticholinergic activity amongst TCAs ➢ Analgesia may occur in days but may

	off-label indications)	**Chronic neuropathic pain/Postherpetic neuralgia:** ➢ Initial 10 to 25mg once daily at bedtime, may gradually increase based on response and tolerability in 10 to 25mg increments at intervals ≥ 1 week up to 150mg/day once at bedtime or in 2 divided doses **Renal/Hepatic adjustment:** ➢ No adjustments necessary	associated with QT prolongation and sudden cardiac death ➢ Pretreatment ECG is recommended prior to use ➢ Common side effects include constipation, blurred vision, drowsiness, and dry mouth ➢ Avoid use or reduce dose in poor CYP2D6 and poor CYP2C19 metabolizers	take weeks to see an effect ➢ Amitriptyline is the most widely studied and used TCA for pain management
Nortriptyline *Available dosage forms:* Oral: ➢ Capsule (10mg, 25mg, 50mg, 75mg) ➢ Solution (10mg/5mL)	➢ For the treatment of postherpetic neuralgia and peripheral neuropathy ➢ For the treatment of chronic non-malignant pain including orofacial and myofascial pain (off-label)	**Adults:** (All daily doses can be given in divided doses as well) **Neuropathy:** ➢ Initial, 10 to 25mg once daily qhs, may gradually increase based on response and tolerability to target dose of 25 to 100mg/day **Postherpetic neuralgia:** ➢ Initial, 10 to 20mg once daily qhs; may increase every 3 to 5 days in 10mg increments up to 160mg/day **Chronic Pain:** ➢ Initial, 10 to 25mg once daily qhs, may increase every 3 days up to 150mg/day. **Myofascial pain:** ➢ Initial, 12.5mg once daily qhs, may increase to 35mg/day. If no change in pain intensity after 4 weeks at 25 to 35mg/day, consider alternative **Orofacial pain:** ➢ Initial, 10 to 30mg once daily qhs, titrate up to 100mg/day if needed **No adjustments for renal or hepatic impairment (use with caution)**	➢ Avoid use or reduce dose in poor CYP2D6 metabolizers ➢ Consider alternative in ultra CYP2D6 metabolizers ➢ Episodes of hypo- and hyperglycemia have been reports ➢ Caution in elderly and those with history of CVD ➢ Most common side effect is constipation	➢ Improved efficacy in neuropathic pain in combination with gabapentin ➢ Less anticholinergic AEs relative to amitriptyline. ➢ Less incidence of weight gain, drowsiness, and orthostatic hypotension compared with amitriptyline ➢ Evidence for use is less robust compared with amitriptyline
Desipramine *Available dosage forms:* Oral: ➢ Tablet (10mg, 25mg, 50mg, 75mg, 100mg, 150mg)	➢ For the treatment of peripheral neuropathy and postherpetic neuralgia (off-label)	**Adults:** **Peripheral neuropathy:** ➢ Initial, 10mg once daily qhs, then increased based on response and tolerability in 10 to 25mg increments every 2 to 3 days; MDD: 250mg/day ➢ Can divide dose into twice daily dosing for tolerability **Postherpetic neuralgia:** ➢ Initial, 10mg to 25mg once or twice daily in divided doses, increase dose every 2 to 7 days based on response up to 150mg/day **No adjustments for renal or hepatic impairment (use with**	➢ Use with caution in CVD ➢ Expect anticholinergic side effects ➢ May cause fluctuations in blood sugars	➢ No CYP interaction ➢ Better tolerated than amitriptyline as it is a less potent anticholinergic ➢ Less incidence of weight gain, orthostatic hypotension, and drowsiness than amitriptyline but more incidence of insomnia/agitation ➢ Evidence for use not as robust compared with amitriptyline

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		caution)		
Antispasmodics/ Muscle Relaxants	➢ Use with caution in elderly as this population may be more sensitive to the CNS effects of these medications and start at lower initial doses ➢ Concomitant use with other CNS depressants (e.g. benzodiazepines) may increase possibility of harm ➢ Comprehensive reviews concluded that there is insufficient evidence to suggest that any other skeletal muscle relaxant is more effective than others in patients with musculoskeletal conditions ➢ This class is often used in conjunction with other forms of analgesia if muscle spasms are present in addition to pain			
Baclofen *Available dosage forms:* Oral: ➢ Tablet (5mg, 10mg, 20mg) ➢ Solution (5mg/5mL) ➢	➢ For the treatment of spasticity and concomitant pain associated with multiple sclerosis or spinal cord lesions ➢ For the treatment of trigeminal neuralgia (off-label)	**Adults:** **Spasticity:** ➢ Initial, 5mg TID, may increase after 3 days based on response to 10mg TID, and can keep increasing in increments of 5mg TID every 3 days to MDD of 80mg/day (20mg four times daily) ➢ Usual maintenance dose is 40 to 80mg/day **Trigeminal Neuralgia:** ➢ Initial, 5 to 10mg TID, may increase dose by 10mg every other day over 1 to 2 weeks. ➢ Dose may be as low as 10mg daily ➢ Dosage range studied: 30 to 80mg/day in 3 to 4 divided doses **Renal Adjustments:** ➢ CrCl >80 ml/min: No adjustment ➢ CrCl 50 to 80 ml/min: Initial, 5mg q12h or reduce dose by one-third ➢ CrCl 30 to 50 ml/min: Initial, 2.5mg q8h or reduce dose by one-half ➢ CrCl <30 ml/min: Initial, 2.5mg q12h or reduce dose by two-thirds **Hepatic adjustments:** ➢ No adjustment necessary	➢ Start at lower initial doses in elderly population ➢ Use with caution with concomitant sedatives ➢ Use with caution in patients with respiratory disease, seizure disorders, and psychiatric disorders ➢ Withdrawal symptoms have occurred in neonates whose mothers were treated throughout pregnancy—gradually reduce dose and discontinue prior to delivery if therapy continued in pregnancy ➢ Common side effects include drowsiness, hypotonia, dizziness, somnolence, and dyspepsia	➢ Poorly tolerated in patients that have had a stroke ➢ Effective at reducing number of trigeminal neuralgic attacks in patients resistant to carbamazepine ➢ Can be combined with carbamazepine as adjunct treatment for trigeminal neuralgia ➢ Slow titration will reduce incidence of side effects ➢ Onset of action is 3 to 4 days with peak response at 5 to 10 days ➢ Slowly taper when drug is discontinued to avoid adverse reactions
Cyclobenzaprine *Available dosage forms:* Oral: ➢ ER capsule (15mg, 30mg) ➢ Tablet (5mg, 7.5mg, 10mg) ➢ Suspension (1mg/mL)	➢ For the treatment of skeletal muscle spasms associated with acute, painful musculoskeletal conditions as adjunct to rest and physical therapy ➢ For the treatment of fibromyalgia (off-label)	**Adults:** **Skeletal muscle spasm:** ➢ IR tabs: 5mg TID, may increase to 10mg TID based on response ➢ ER caps: 15mg once daily, may increase to 30mg once daily **Fibromyalgia:** ➢ IR tabs: 10 to 30mg qhs **Renal adjustment:** ➢ No adjustments provided in manufacturer labeling **Hepatic adjustment:** ➢ IR tabs: o Mild impairment: Initial 5mg and titrate slowly, consider less frequent dosing o Moderate to severe impairment: Use not recommended ➢ ER caps:	➢ Common side effects include dry mouth, dizziness, somnolence, and fatigue ➢ Use with caution in patients with CVD, can cause QT prolongation ➢ Use with caution in patients with history of urinary retention ➢ Avoid use in combination with anticholinergic medications	➢ Food increases bioavailability of ER capsule, thus monitor for increased effects ➢ Extensive CYP3A4, 1A2, and 2D6 metabolism, check for drug-drug interactions prior to use ➢ Limit therapy to 2-3 weeks; efficacy not established for longer periods of use ➢ Onset of action is within 1 hour and lasts 12 to 24hrs for IR tabs ➢ Can be used as monotherapy or adjunct (to NSAIDS or acetaminophen) therapy for acute and subacute lower back pain ➢ For treatment of fibromyalgia, cyclobenzaprine was comparable to

		○ Mild to Severe impairment: Use not recommended		amitriptyline but less tolerated
Tizanidine (Zanaflex) *Available dosage forms:* Oral: ➢ Capsule (2mg, 4mg, 6mg) ➢ Tablet (2mg, 4mg)	➢ For the treatment of muscle spasticity associated with multiple sclerosis and spinal cord injury ➢ For the treatment of drug withdrawal/rebound headaches, chronic daily headaches, and acute pain in combination with NSAID	**Adults:** **Muscle spasticity:** ➢ Initial, 2mg q6-8h prn, may increase in 2mg to 4mg increments per dose based on response and tolerability with a minimum of 1 to 4 days between dose increases ➢ MDD: 36mg/day; Single Doses >16mg have not been studied **Acute Pain (dosing based on clinical trial):** ➢ 4mg TID in combination with ibuprofen 400mg TID **Chronic Headache disorder prophylaxis (dosing based on clinical trial):** ➢ Initial, 2mg qhs, then titrated to max 24mg/day or maximum tolerated dose in three divided doses over 4 weeks; mean dose = 18mg/day ➢ In conjunction to patient concurrent preventative therapy with simple analgesics and "migraine-specific" abortive agents	➢ Most common side effects include dry mouth, fatigue, and loss of strength and energy ➢ Also known to cause hypotension ➢ Avoid concomitant use of other CYP1A2 inhibitors (e.g. cimetidine, amiodarone, ciprofloxacin) ➢ Do not abruptly stop treatment, especially in patients treated with concomitant narcotics or doses 20 to 28mg/day for 9 weeks or more, do to risk for rebound hypertension, tachycardia, and hypertonia.	➢ Capsule and tablet are not interchangeable ➢ Once a regimen is established, do not alter it ➢ Patient must take consistently with or without food ➢ Capsule can be opened and sprinkled on food, but this will lead to alteration in absorption and clinical effect ➢ There is evidence that tizanidine may have gastroprotective properties when given in combination with NSAIDs ➢ If discontinued, taper by slowly decreasing dose by 2mg to 4mg per day to minimize side effects
Methocarbamol (Robaxin) *Available dosage forms:* Oral: ➢ Tablet (500mg, 750mg) Injection: ➢ Solution (100mg/mL)	➢ Used as an adjunct treatment of muscle spasms associated with acute painful musculoskeletal conditions	**Adults:** **Musculoskeletal pain, Adjunct:** ➢ Tablets: ○ Initial, 1500mg po 4 times a day for 48-72hrs; 8g/day may be given for severe conditions ○ Maintenance, 750mg po q4h, 1500mg TID, or 1000mg 4 times a day; usual dosage = 4g/day ➢ IM injection: ○ For moderate symptoms: 1g IM a single dose, transition to oral tablets ○ For severe symptoms: 1g IM q8h; MAX 3g/day for no more than 3 consecutive days; need drug-free interval of 48hrs prior to repeating course **Renal adjustment:** ➢ No dosage adjustment provided in manufacturer's labeling **Hepatic adjustment:** ➢ No dosage adjustment provided in manufacturer's labeling. Elimination may be reduced in patients with cirrhosis.	➢ Most common side effects include nausea, vomiting, fatigue, headache, flushing, insomnia, metallic taste, and rhinitis ➢ Use with caution in patients with history of seizure disorder ➢ Use with caution in elderly as half-life is prolonged in this population ➢ Avoid use during pregnancy especially early pregnancy unless benefit outweighs the risk of adverse effects on fetal development	➢ Oral formulation not as effective for muscle spasticity compared to parenteral formulation ➢ Drug is efficacious within first 48hrs but did not maintain a significant advantage over placebo for the remaining 5 to 7 days in a randomized study. ➢ Can be used in pediatric patients >16 y.o. ➢ Tablets can be crushed and mixed with food or liquid if needed

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Topical Agents				
	➢ These agents can help reduce use of systemic analgesia and help mitigate any medication-related side effects ➢ Majority of these preparations are available over the counter and may not be covered by insurance ➢ Topical NSAID (diclofenac) is discussed in the NSAID section			
Capsaicin *Available dosage forms:* Topical: ➢ Patch (0.025%,0.03%, 0.0375%, 0.05%, 8%) o Only 8% requires RX o Most patches also contain Menthol ➢ Cream (0.025%, 0.033%, 0.035%, 0.075%, 0.1%) ➢ Lotion (0.025%) ➢ Gel (0.025%) ➢ Liquid (0.15%)	➢ For the treatment of arthritic pain, musculoskeletal pain, and neuropathic pain associated with postherpetic neuralgia ➢ For treatment of diabetic neuropathy (off-label)	**Adults:** **Muscle/joint pain:** ➢ **Topical cream/gel/liquid/lotion;** o Apply thin film to affected areas 3 to 4 times daily ➢ **Patch (0.025%, 0.03%, 0.0375%, 0.05%):** o Apply 1 patch to affected area for up to 8 hours; MDD: 4 patches/day; do not use for >5 consecutive day (product specific) **Postherpetic neuralgia:** ➢ **Patch 8%: Has to be applied in providers office** o Apply patch to most painful area for 60 minutes. Up to 4 patches may be applied in single application. Treatment may be repeated every ≥3 months as needed. Pre-treat area with topical anesthetic prior to patch application and clean treatment area after removal of patch with provided Cleansing Gel for 1 min o Must use nitrile gloves when handling; Latex gloves do not provide adequate protection **Diabetic neuropathy:** ➢ **Topical cream (0.075%, 0.1%)**: o Apply to affected area 4 times daily	➢ Most common side effects include application site irritation and local pain ➢ May cause a transient increase in blood pressure	➢ If local discomfort from therapy is intolerable, patients can pre-treat area with topical lidocaine ➢ Patch maybe more practical due to less frequent application ➢ Need at least 4 weeks of consistent application to see effect ➢ Remind patients to wash hands immediately after use and to only apply to intact, non-irritated skin.
Lidocaine (Lidoderm, Xylocaine) ***Available dosage forms:*** **Topical: Any strength ≥5% needs RX** ➢ **Cream (3%, 4%, 5%)** ➢ **Ointment (5%)** ➢ **ER Patch (5%)**	➢ For the treatment of postherpetic neuralgia ➢ For the treatment of diabetic neuropathy (off-label)	**Adults:** **Post-herpetic neuralgia:** ➢ **Topical Patch (5%)** o Apply 1 to 3 patches for 12 hours within a 24-hour period (12hrs on and 12hrs off); Patches may be cut into smaller sizes **Topical local anesthetic:** ➢ **Cream/Ointment** o Apply to affected area no more often than 3 to 4 times daily ➢ **Patch (4%)** o Apply 1 patch to affected area for up to 12 hours; limit use to 1 week; MAX: 1 patch on body at a time	➢ Very well tolerated	➢ Avoid applying heat to area where patch is applied ➢ Apply only to intact, non-irritated skin ➢ Can be used in combination with other forms of analgesia for further pain relief