PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

Adjuvant Analgesics

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Titles and Affiliations

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Disclosures

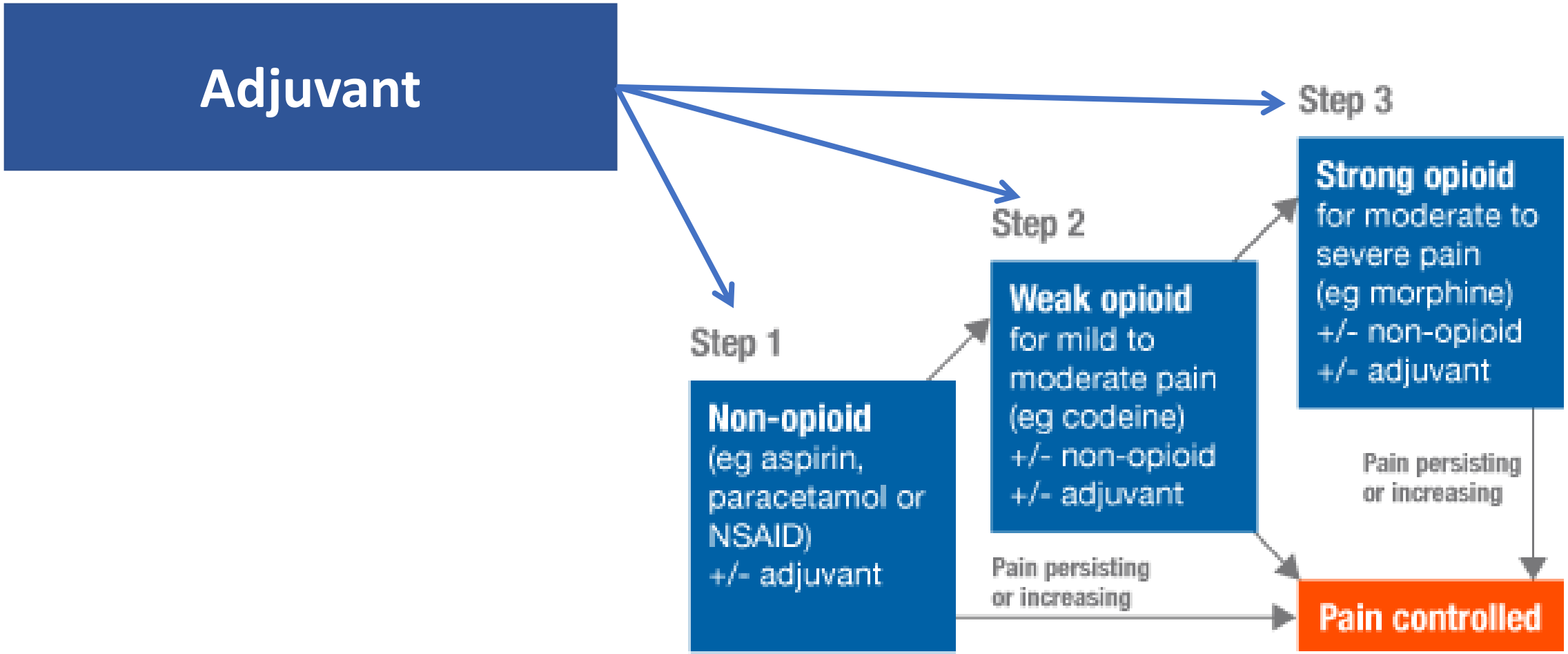
Learning Objectives

1. Describe where adjuvant analgesics act within the pain pathway.
2. List common adverse effects associated with adjuvant analgesics.
3. Given a patient case, select an appropriate adjuvant analgesic and recommended dosing.
4. Given a patient case, recommend appropriate monitoring parameters for both efficacy and toxicity.

Key Abbreviations

APAP	N-acetyl-para-aminophenol (acetaminophen)
BP	Blood pressure
CBC	Complete blood count
CNS	Central nervous system
CV	Cardiovascular
ECG	Electrocardiogram
GI	Gastrointestinal
LFTs	Liver function tests
NMDA	N-methyl-D-aspartate
NNT	Number needed to treat
NSAID	Nonsteroidal anti-inflammatory drug
SNRI	Serotonin norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

Who's Up for an Adjuvant Analgesic?



What is an adjuvant analgesic?

Drugs with a primary indication other than pain that have analgesic properties in some painful conditions.

Lussier, Huskey, Portenoy. Adjuvant analgesics in cancer pain management. *Oncologist*. 2004;9(5):571-591.

Common Indications for Adjuvant Analgesics

- Difficult to treat pain
- Pain that is unresponsive to opioids
- Neuropathic pain
- Bone pain

Medication Classes

- Corticosteroids
- Antidepressants
- Anticonvulsants
- Local anesthetics
- Skeletal muscle relaxants
- Capsaicin
- Cannabinoids
- Ketamine
- Bisphosphonates
- Miscellaneous agents

Where Do Adjuvants Work?

Peripheral Desensitization	Descending Modulator	Antinociceptive	Antihyperanalgesic
• Anticonvulsants • Local anesthetics • Capsaicin • Corticosteroids	• TCAs • SNRIs • Skeletal muscle relaxants	• Opioids • NSAIDS • APAP • Cannabinoids	• NMDA antagonists

Corticosteroids

- Several mechanisms of action
  - Prostaglandin inhibition, cell membrane stabilization, sodium channel blockade, inhibition of osteoclastic activity
- Multiple routes of administration
  - Topical
  - Oral
  - Parenteral
    - Intravenous
    - Intramuscular depot
    - Intra-articular

Corticosteroids

- Indications for use
  - Inflammatory neuropathic pain from peripheral nerve injuries; spinal cord compression
  - Bone pain
  - Pain from bowel obstruction, lymphedema
  - Pain from headache associated with increased intracranial pressure

Wide range of uses in advanced illness (beyond pain)!

- Nausea/Vomiting
- Fatigue
- Appetite stimulation

Corticosteroids

Corticosteroid Conversion Chart				
Glucocorticoid	Approximate Equivalent Dose (mg)	Relative Anti-Inflammatory (Glucocorticoid) Potency	Relative Mineralocorticoid (Salt Retaining) Potency	Biological Half-Life (Hours)
Short-Acting				
Cortisone	25	0.8	0.8	8 - 12
Hydrocortisone	20	1.0	1.0	8 - 12
Intermediate-Acting				
Methylprednisolone	4	5	0.5	18 - 36
Prednisolone	5	4	0.8	18 - 36
Prednisone	5	4	0.8	18 - 36
Long-Acting				
Dexamethasone	0.75	25	0.0	36 - 54

Meikle AW et al. Potency and Duration of Action of Glucocorticoids. AM J of Med. 1977. 63 (2);200 - 207. PMID: 888843

Corticosteroids

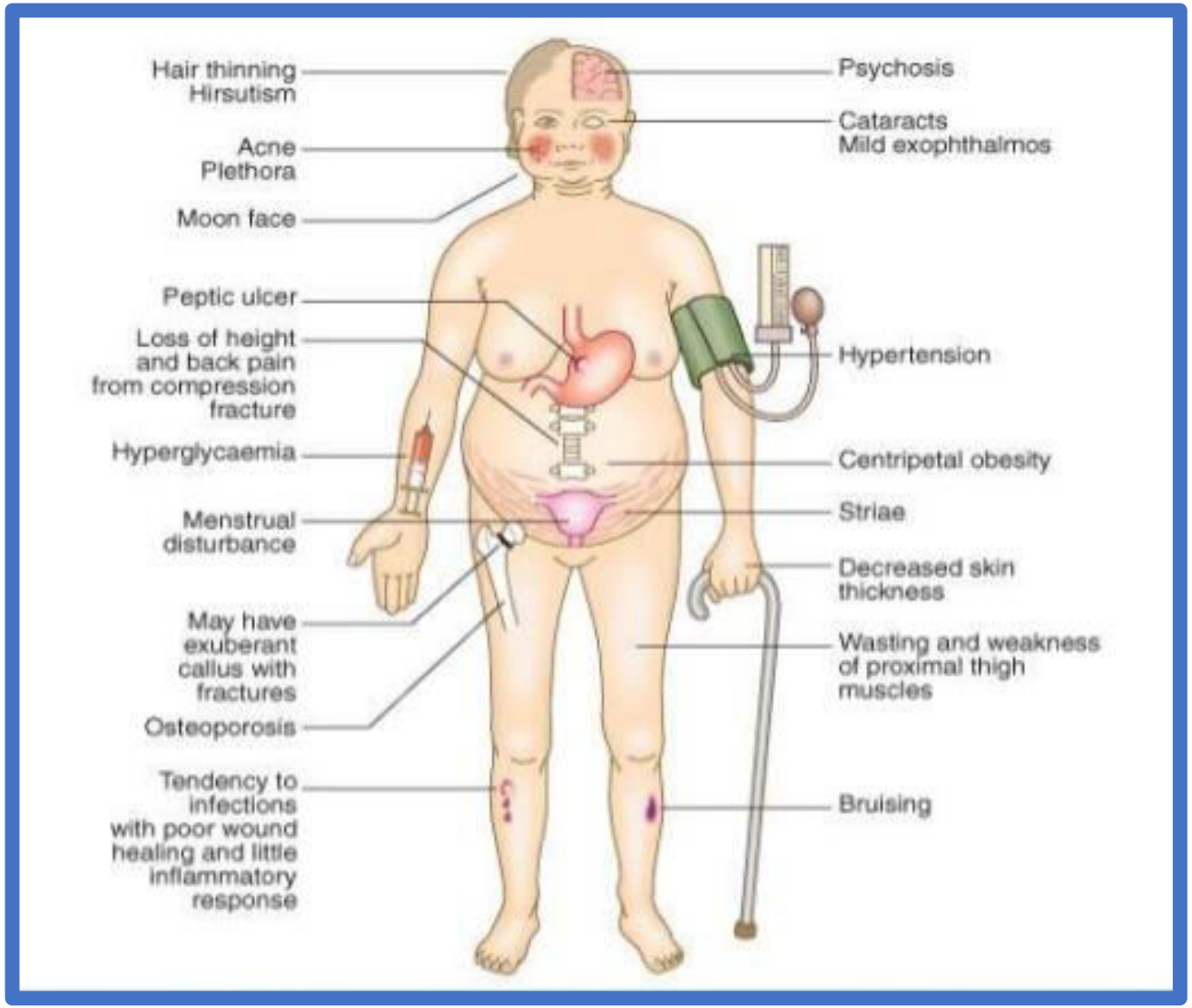
Dexamethasone

Indication	Dose
Anorexia and cachexia	2-4 mg/day
Cancer-related fatigue	2-4 mg/day
Nausea and vomiting	4-8 mg/day
Pain	8 mg/day
Malignant bowel obstruction	8 mg/day
Metastatic extradural spinal cord compression	10 mg IV x1; then 16 mg/day

Mori, Ramos. Fast Facts and Concepts #395. Corticosteroids for Common Palliative Care Symptoms. April 2020. www.mypcnow.org.

Corticosteroids

Adverse effects associated with steroid use



Canadian Family Phy. 2010;56:1295-1297.

Corticosteroids

Cataracts

Ulcers

Skin: striae, thinning, bruising

Hypertension/hirsutism/hyperglycemia

Infections

Necrosis, avascular necrosis of the femoral head

Glycosuria

Osteoporosis, obesity

Immunosuppression

Diabetes

Corticosteroids

- Caution should be exercised in patients with the following conditions:
  - Diabetes
  - Psychiatric history
  - Heart failure
  - Adrenal suppression
    - Taper needed when therapy exceeds 10-14 days
  - Immunocompromised

Tricyclic Antidepressants (TCAs)

- Mechanism of action
  - Inhibition of norepinephrine and serotonin reuptake
  - Inhibition of sodium channel action potentials
- Indications for use
  - Neuropathic pain
  - Depression
  - Insomnia [off-label]
- The antidepressant effects and the neuropathic pain analgesia are independent
  - Higher dosing and longer treatment time needed for antidepressant effects

Brunton, Hilal-Dandan, Knollmann. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 13th ed. McGraw-Hill Education; 2018. Chap 15, Drug Therapy of Depression and Anxiety Disorders.

TCAs – Dosing

- Amitriptyline, nortriptyline, desipramine
  - Starting dose: 10-25 mg po qhs
  - Usual effective dose: 50-150 mg po qhs
- Nortriptyline available as oral solution (10 mg/5 ml)
  - Can consider for patients with difficulty swallowing

Arbuck. The use of antidepressants in multimodal pain management. *Pract Pain Manag*. 2019.

TCAs – Anticholinergic Properties

- Secondary amines
  - Nortriptyline (Pamelor®), desipramine (Norpramin®)
- Tertiary amines
  - Amitriptyline (Elavil®), imipramine (Tofranil®)
  - Doxepin (Sinequan®), clomipramine (Anafranil®)
- Tertiary amines are associated with more anticholinergic side effects compared to secondary amines

- Anticholinergic side effects include:
  - Blurred vision
  - Urinary retention
  - Dry mouth
  - Constipation
  - Sedation
  - Delirium

Arbuck. The use of antidepressants in multimodal pain management. *Pract Pain Manag*. 2019.

TCAs – Cardiovascular Risk

- Orthostatic hypotension
  - Alpha adrenergic blockade (even at low doses)
- Slowed cardiac conduction, tachycardia, ventricular fibrillation, heart block, and premature ventricular complexes
- Sudden cardiac death
  (unclear association with QTc prolongation)
- Screen for known heart disease, syncope, palpitations, dyspnea, or chest pain
- Consider obtaining baseline ECG

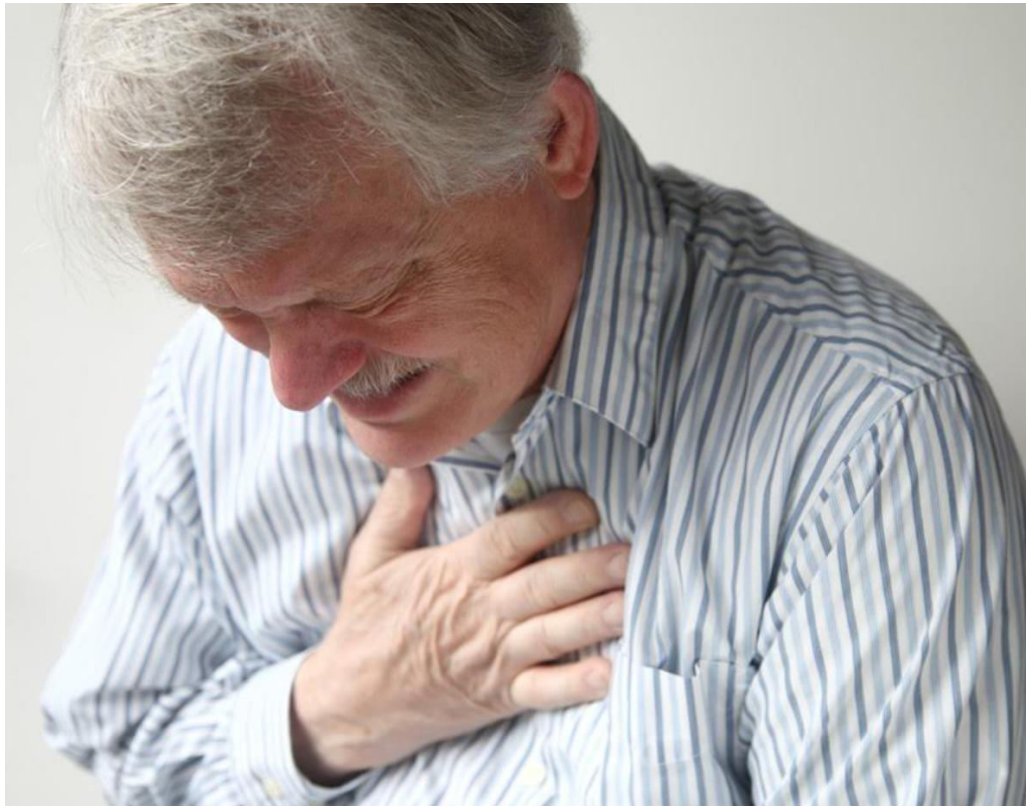
Avoid use in patients with cardiovascular disease or established conduction abnormalities

TCAs – Drug Interactions

Medication or Class	Effect
SSRIs	Increased plasma levels of TCAs, increased risk of serotonin syndrome
Anticholinergic agents	Increased anticholinergic side effects (blurred vision, constipation, confusion, etc)
Antiarrhythmics	Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
Carbamazepine	Decreased plasma levels of TCAs
Clonidine	Decreased antihypertensive effectiveness of clonidine
Lithium	Increased risk of serotonin syndrome
Tramadol	Increased risk of seizure, serotonin syndrome, and paralytic ileus
QTc-prolonging medications	Increased risk of QT prolongation

TCAs – Patient-Specific Factors

- Caution should be exercised in patients
  - > 65 years old
  - Cardiovascular disorders
    - Conduction disorders
    - Arrhythmias
    - Heart failure
  - Autonomic neuropathy
  - Medically ill
  - Seizure history
  - Glaucoma
  - Orthostasis



Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

- Mechanism of action
  - Inhibition of norepinephrine and serotonin reuptake
- Medications include:
  - Duloxetine
  - Venlafaxine
  - Milnacipran
- Dosing is generally higher for treating neuropathic pain compared to treating depression
- Withdrawal syndromes can occur if SNRI therapy is discontinued abruptly
  - Anxiety, irritability, headache, paresthesia, nervousness

SNRIs – Duloxetine

Indications for use

- Painful diabetes neuropathy
- Major depressive disorder
- Generalized anxiety disorder
- Fibromyalgia
- Chronic musculoskeletal pain

Dosing

- Initial dose: 20 or 30 mg po daily
- Increase to 60 mg po daily
- No advantage seen with 60 mg po BID
- Discontinuing therapy should be done over 2-4 weeks

SNRIs – Duloxetine

Adverse effects

- Nausea (dose related, start dose low and titrate)
- Dry mouth, somnolence, fatigue, bleeding events
- Constipation, decreased appetite, hyperhidrosis

Precautions

- Hepatotoxicity, serotonin syndrome, neuroleptic malignant syndrome
- Activation of mania/hypomania, suicidality
- Seizures, effect on BP, narrow angle glaucoma
- Contraindicated with CLcr < 30 ml/min

Drug Interactions

- Avoid potent 1A2 inhibitors, use caution with 2D6 inhibitors
- Duloxetine moderately inhibits 2D6

SNRIs – Venlafaxine

Indications for use

- Major depressive disorder
- Generalized anxiety disorder
- Social anxiety disorder
- Panic disorder

Dosing

- Initial dose: 37.5 or 75 mg ER po daily
- Increase dose by 37.5 – 75 mg ER po daily every week
- Maximum dose 225 mg ER po daily
- Discontinuing therapy should be done over 2-4 weeks
- Dose adjust in renal and hepatic dysfunction

SNRIs – Milnacipran

Indications for use

- Fibromyalgia

Dosing

- **Day 1**: 12.5 mg po daily
- **Days 2-3**: 12.5 mg po BID
- **Days 4-7**: 25 mg po BID
- 50 mg po BID thereafter (target dose); maximum dose 100 mg po BID
- Reduce dose in severe renal impairment

Milnacipran. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated March 25, 2021.

Summary of Adverse Effects – TCAs and SNRIs

Drug	Agitation	Seizure	Sedation	Hypo-tension	Anti-Ach	GI	Weight Gain	Sexual	Cardiac
Amitriptyline	0	++	+++	+++	+++	0/+	++	++	+++
Desipramine	+	+	0/+	+	+	0/+	+	++	++
Nortriptyline	0	+	+	+	+	0/+	+	++	++
Duloxetine	+	0	0/+	0/+	0	0/+	0/+	0/+	0/+
Venlafaxine	0/+	0	0	0	0	+++	0	+++	0/+

Brunton, Hilal-Dandan, Knollmann. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 13th ed. McGraw-Hill Education; 2018. Chap 15, Drug Therapy of Depression and Anxiety Disorders.

Anticonvulsants

- The primary anticonvulsants used in pain management are gabapentin and pregabalin
  - Other anticonvulsants have had mixed results regarding neuropathic pain (valproic acid, phenytoin)
  - Carbamazepine is used for trigeminal neuralgia
- Mechanism of action
  - Modulates the α_2-δ protein subunit of the voltage-gated Ca^{2+} channel
  - Binding of gabapentin/pregabalin to this protein inhibits Ca^{2+} influx into the neuron and thereby diminishes the neuronal hyperactivity that has been associated with neuropathic pain states

Anticonvulsants – Indications for Use

- **Gabapentin**
  - Adjunct for treatment of partial seizures with and without secondary generalized seizures
  - Adjunct for treatment of partial seizures in pediatric patients 3-12 years of age
  - Management of postherpetic neuralgia in adults
  - Restless legs syndrome (gabapentin enacarbil)
- **Pregabalin**
  - Management of pain associated with diabetic neuropathy, management of postherpetic neuralgia, fibromyalgia, neuropathic pain associated with spinal cord injury
  - Adjunctive therapy for partial-onset seizures disorder in adults

Anticonvulsants

- Few drug interactions
  - May potentiate opioids, alcohol, benzodiazepines
- Adverse effects
  - Dose-dependent dizziness, ataxia, sedation, diplopia
  - Nausea, dyspepsia, weight gain, peripheral edema
  - Neurocognitive effects
    - Decreased psychomotor reaction time
    - Issues with learning, memory, and executive function
    - Considerable variance based on age, multiple anticonvulsants, serum drug concentrations
- Precautions
  - Lower doses in elderly and renal insufficiency
  - Caution in pregnancy

Calcium Channel α2-Δ Ligands

- Gabapentin dosing
  - Immediate-release
    - Day 1: 300 mg; Day 2: 300 mg BID; Day 3: 300 mg TID. Titrate further as needed for pain relief
  - Extended-release
    - Day 1: 300 mg once daily; Day 2: 600 mg once daily; Day 3: 900 mg once daily; Days 7-10: 1,200 mg once daily; Days 11-14: 1500 mg once daily; Days ≥ 15: 1,800 mg once daily
  - Slower titration in elderly, medically fragile, renal insufficiency
- Usual effective dose
  - Routine 900-3600 mg daily in 2-3 divided doses
  - Elderly, medically frail, renal insufficiency 300-1800 mg daily
  - Renal failure 100-300 mg qhs

Renal dose adjustment required

Gabapentin. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated July 20, 2021.

Calcium Channel α2-Δ Ligands

- Gabapentin enacarbil dosing
  - Postherpetic neuralgia
    - Initial: 600 mg once daily in the morning for 3 days, then increase to 600 mg BID
    - Increasing to > 1200 mg daily provided no additional benefit and increased side effects
  - Restless legs syndrome
    - 600 mg once daily (at 5 pm)
    - Increasing to 1200 mg daily provided no additional benefit and increased side effects

Gabapentin. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated July 20, 2021.

Calcium Channel α2-Δ Ligands

- Pregabalin dosing
  - Linear pharmacokinetics, dosing more straightforward
  - Starting dose 150 mg/day in 2-3 divided doses
  - Increase to 300 mg/day after 3-7 days, then by 150 mg/day every 3-7 days as tolerated
  - Reduce dosage in renal impairment
  - Provides analgesia more quickly than gabapentin because the initial dose has been shown to be efficacious, and the time to titrate to a full dosage is less

6:1 conversion ratio from gabapentin to pregabalin

Gabapentin. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated July 20, 2021.
Ifuku, Iseki, Hidaka, et al. Replacement of gabapentin with pregabalin in postherpetic neuralgia therapy. *Pain Med*. 2011;12(7):1112-1116.

FDA In Brief: FDA requires new warnings for gabapentinoids about risk of respiratory depression

Share | Tweet | Linkedin | Email | Print

December 19, 2019

Media Inquiries

Nathan Arnold
301-796-6248

The following quote is attributed to Douglas Throckmorton, M.D., deputy director for Regulatory Programs in the FDA's Center for Drug Evaluation and Research:

> **"With the evolution of the opioid crisis, getting ahead of new concerns or addressing those that are already evident requires examining signs of misuse and abuse as soon as any signal emerges.**

Image retrieved from: www.fda.gov/news-events/fda-brief/fda-brief-fda-requires-new-warnings-gabapentinoids-about-risk-respiratory-depression.

Anticonvulsants – Alternative Options

- **Carbamazepine**
  - Drug of choice for trigeminal neuralgia
  - Starting dose 100 mg po BID; may require titration of dose to maximum of 1200 mg/day
  - Consider obtaining baseline CBC and LFTs
    - Consider periodic monitoring of CBC and LFTs thereafter
- **Oxcarbazepine**
  - Better tolerability compared to carbamazepine
  - Titration begins at 150 mg twice daily to a maximum dose of 1800 mg/day
  - Patients allergic to carbamazepine should also avoid oxcarbazepine, 25% allergic cross-reactivity

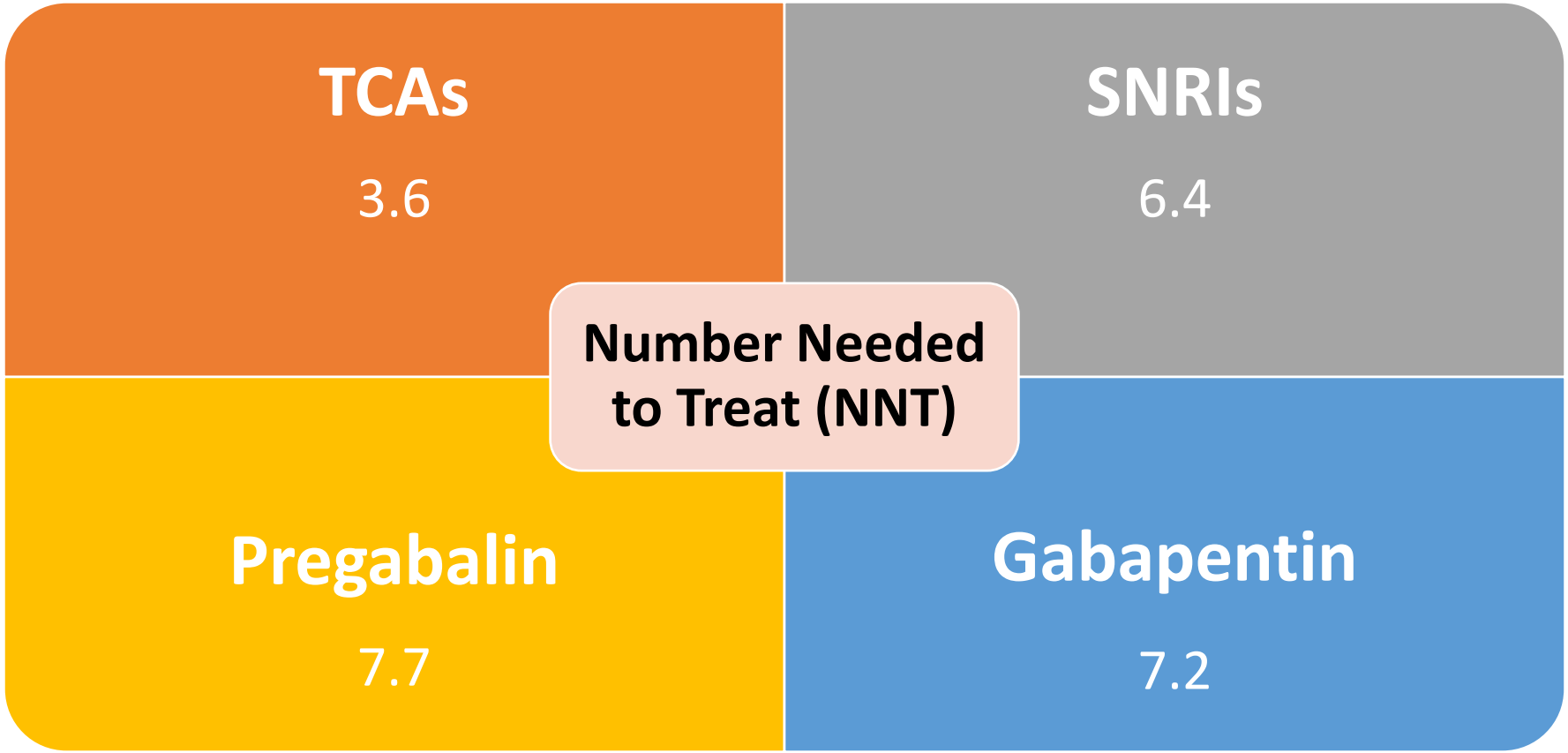
Carbamazepine. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated July 23, 2021.
Oxcarbazepine. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated July 9, 2021.

Anticonvulsants – Alternative Options

- **Lamotrigine** (off-label indication)
  - Data supports use in refractory trigeminal neuralgia, central poststroke pain, SCI pain with incomplete cord lesion and brush-induced allodynia, HIV-associated neuropathy in patients on ART, and diabetic neuropathy
  - Most effective at doses between 200-400 mg/day
  - Note: follow strict titration schedule to reduce the risk of serious skin reactions
- **Topiramate** (off-label indication)
  - Data supports use in diabetic neuropathy, refractory trigeminal neuralgia, and for migraine prophylaxis
  - Dosing generally ranges from 50-100 mg/day
  - Dosing over 200 mg is generally limited by side effects

Lamotrigine. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated July 14, 2021.
Oxcarbazepine. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated July 15, 2021.

Neuropathic Agents – Efficacy



Finnerup et al. *Lancet Neurol*. 2015;14:162-173.

Self-Assessment!

MJ is a 67-year-old female with a past medical history of hypertension (well controlled on medication) and metastatic lung cancer. She presents with severe hip and back pain, which have been attributed to metastatic disease. Which of the following options would likely be most effective in managing her bone pain?

A. Acetaminophen
B. Cyclobenzaprine
C. Dexamethasone
D. Ketamine

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Local Anesthetics

- Mechanism of action
  - Membrane stabilization of sodium channels preventing depolarization and signal transduction
- Indications for use
  - Acute uses for local anesthesia (procedures, etc)
  - Refractory pain
  - Lidocaine patches are indicated for the management of post herpetic neuralgia
- Multiple formulations available
  - Topical application
    - Lidocaine patch available in 0.5% to 5% concentrations
  - Intradermal injection
  - Intravenous

Lidocaine. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated July 14, 2021.
Lidocaine Hydrochloride. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated July 15, 2021.

Local Anesthetics – Adverse Effects

- Ester and amide sub families of local anesthetics
  - Esters include chloroprocaine and procaine
  - Amides include bupivacaine, lidocaine and others
- Allergies are possible to the ester types secondary to the metabolic by-product para-amino-benzoic acid (PABA)
  - Amide type local anesthetics do not metabolize to a PABA moiety
- Adverse events can affect CNS, CV and hematologic systems
  - Local anesthetics can be proarrhythmogenic, especially bupivacaine, if given parenterally

www.ncbi.nlm.nih.gov/pubmed/8826570.

Topical Lidocaine (LIDODERM®)

- 5% lidocaine patch is approved for the treatment of post-herpetic neuralgia (applied to intact skin)
- Efficacy demonstrated in other disease states with peripheral neuropathy
- Lidocaine is an amide-type local anesthetic agent thought to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses
- Penetration of lidocaine into intact skin after application of LIDODERM® is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block

Topical Lidocaine (LIDODERM®)

- Useful for well-localized pain
- FDA approved dosage schedule is 12 hours on, 12 hours off
- Up to 3 patches are approved for simultaneous use
- Patches may be cut and shaped for application to affected areas
- Do not apply to burned, broken or inflamed skin; may result in increased absorption and possible toxicity
- Lidocaine does not accumulate with normal hepatic function
- Caution with severe hepatic disease

Topical Lidocaine (LIDODERM®)

- Generally well tolerated
  - Adverse effects include mild skin reactions such as erythema or ash
  - Concurrent use of a class I antiarrhythmic agent (eg, mexiletine) may increase the risk for toxicity
- 5% lidocaine gel is less expensive than topical lidocaine patch, but has also been shown to be effective in treating post-herpetic neuralgia with allodynia

Skeletal Muscle Relaxants

- Multiple medications are included in this general taxonomy
  - Certain agents approved for muscle spasticity
    - Baclofen through activity on GABA
    - Tizanidine through activity on alpha-2
- Others stand out for reasons other than their indication
  - Cyclobenzaprine and orphenadrine regarding their anti-cholinergic effects
  - Chlorzoxazone and potential for hepatotoxicity
  - Carisoprodol and meprobamate and potential for abuse

Skeletal Muscle Relaxants

- Antispasticity agents
  - **Spasticity:** upper motor neuron disorder characterized by muscle hypertonicity and involuntary jerks (multiple sclerosis, cerebral palsy, stroke, spinal cord injury)
  - Includes:
    - Tizanidine
    - Baclofen
    - Diazepam
    - Dantrolene

Chou et al. *J Pain Symptom Manage*. 2004;28:140-175; Van Tulder et al. *Cochrane Database Syst Rev*. 2003;(2):CD004252; *Pharmacotherapy*. 2008;28(2):207-213; *Ann Intern Med*. 2007 Oct 2;147(7):478-491; Skeletal Muscle Relaxants Quick Reference. Compiled by Nolan, Fudin; Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc,; Hudson, OH.

Skeletal Muscle Relaxants

Baclofen

- GABA analogue
- Selective GABA-B receptor agonist
  (↑ K^+ conductance, ↓ Ca^{2+} conductance)
- Muscle relaxant and analgesic
- Dose: 5 mg po TID, may titrate q3 days to effect
- Max dose: 80 mg/day
- Side effects:
  somnolence, increased seizure activity

Tizanidine

- Agonist of α_2 receptors (presynaptic)
- Reduces adrenergic input to alpha motor neurons
- No effect on spinal cord reflex
- Less antihypertensive effect than clonidine
- Dose: 2 to 8 mg po TID
- Max dose: 36 mg/day
- Side effects: hypotension, asthenia, elevated LFTs, hepatotoxicity

Baclofen. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated July 22, 2021.
Tizanidine. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated June 22, 2021..
Pharmacotherapy. 2008;28(2):207–213; Skeletal Muscle Relaxants Quick Reference. Compiled by Nolan, Fudin.

Skeletal Muscle Relaxants

- Antispasmodic agents
  - Primarily used for treatment of musculoskeletal conditions, such as back pain, sciatica, herniated discs, spinal stenosis, myofascial pain
  - Includes:
    - Carisoprodol
    - Cyclobenzaprine
    - Metaxalone
    - Methocarbamol
    - Orphenadrine citrate

Indicated for **acute** use in low back pain!

- Less than 4 weeks use to treat an episode
- May be effective for an acute-on-chronic pain episode

Skeletal Muscle Relaxants

- **Mechanism of action**
  - Carisoprodol – Not fully understood, CNS depressant
  - Cyclobenzaprine – Not fully understood, CNS depressant; similar to TCAs
  - Dantrolene – Inhibits Ca release from sarcoplasmic reticulum; only direct acting agent
  - Metaxalone – Not fully understood, CNS depressant
  - Methocarbamol – Not fully understood, CNS depressant; derivative of guaifenesin

Fudin et al. *PPM*. 16(5); Deer et al. *Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Behavioral Approaches: The American Academy of Pain Medicine Textbook on Patient Management*. Chapter 7- Role of Muscle Relaxants in the Treatment of Pain. P69-77.

Self-Assessment!

JH is a 62-year-old male who was diagnosed with herpes zoster 3 weeks ago along the T-6 dermatome. The lesions have dried and healed, but he has significant post-herpetic neuralgia pain. He would like to have pain relief but does NOT want to be sedated. Which of the following would be the best choice at this time?

A. Amitriptyline (Elavil®)
B. Duloxetine (Cymbalta®)
C. Gabapentin (Neurontin®)
D. Topical 5% Lidocaine (LIDODERM®)

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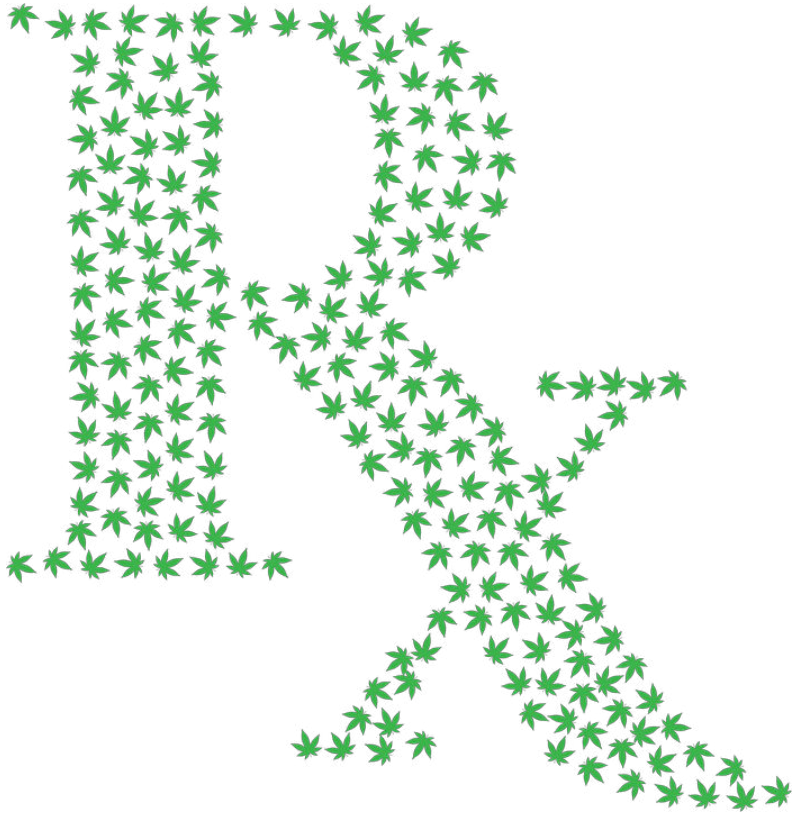
Capsaicin

- Mechanism of action is though stimulation of the TRPV1 receptor in order to deplete substance P release from the periphery
- Indications include:
  - Neuropathic pain associated with post-herpetic neuralgia
  - Arthritis and musculoskeletal pain
- Topical formulations and an 8% Rx patch are available
  - The patch requires significant resources as it is applied in-office every 3 months
- Localized irritation is the most common side effect
- Pain relief is usually noted within 14 days but can take up to 6 weeks
- Adherence is important!

Goncalves, Rebelo, Barbosa, Gomes. *Pain Physician*. 2020;23(5):E541-E548.
Capsaicin. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated June 12, 2021.

Cannabinoids

- Indications
  - Anorexia and cachexia
  - Nausea/vomiting
  - Neuropathic pain
  - Treatment-resistant epilepsy
- Numerous available routes of administration
- Legality is largely state-dependent



Cannabinoids – Adverse Effects

- Nausea
- Fatigue/weakness
- Dry mouth
- Cough
- Dizziness or vasovagal symptoms
- Tachycardia
- Feelings of intoxication, disorientation, confusion
- Hallucinations, behavioral or mood changes
- Psychosis, euphoria/dysphoria, anxiety

Koppel et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the AAN. *Neurology* 2014;82(17):1556-1563.

Cannabinoids – Adverse Effects

- Cannabinoid hyperemesis syndrome
  - Characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and the learned behavior of hot bathing
  - Typically seen in young adults with a long history of cannabis use
  - 3 phases
    - *Pre-emetic or prodromal*
      - Can last for months or years
      - Patients develop early morning nausea, a fear of vomiting, and abdominal discomfort
    - *Hyperemetic*
      - Paroxysms of intense and persistent nausea and vomiting
      - Patients take numerous hot showers throughout the day to alleviate symptoms (learned behavior); rapidly becomes a compulsive behavior
    - *Recovery*
      - Can last for days, weeks, or months
      - Relative wellness and normal eating patterns
      - Weight is regained and bathing returns to regular frequency

Galli, Sawaya, Friedenberg. *Curr Drug Abuse Rev*. 2011;4(4):241-249.

Cannabinoids – Adverse Effects

- Cannabinoid hyperemesis syndrome
  - Management
    - Supportive care with IV hydration
    - Dopamine antagonists (haloperidol)
    - Topical capsaicin cream
    - Benzodiazepines
    - Cessation of cannabinoids

Sorenson, DeSanto, Borgelt, et al. *J Med Toxicol*. 2017;13(1):71-87.
Richards, Gordon, Danielson, Moulin. *Pharmacotherapy*. 2017:37(6):725-734.
McConachie, Caputo, Wilhelm, Kale-Pradhan. *Ann Pharmacother*. 2019;53(11):1145-1152.

Cannabinoids – Patient-Specific Factors

- Use caution in the following patient populations:
  - Cannabis allergy
  - Bipolar disorder
  - Patients suffering from or at risk of developing schizophrenia
  - Substance abuse (past or current)
  - Pregnant and/or breastfeeding women
  - Coronary heart disease

Smith. Medical cannabis: basic science & clinical applications: what clinicians need to know and why. Beverly Farms, MA: OEM Press, 2016.
Bultman, Kingsley. Medical Cannabis Primer for Healthcare Professionals. Minnesota Medical Solutions, 2014.

Ketamine

- Mechanism of action
  - NMDA receptor antagonist
  - Weak mu opioid receptor agonist (potentiates effect of opioids)
  - Potentiates the effects of GABA
- Consider ketamine for:
  - Escalating pain, hyperalgesia, allodynia, intolerable side effects to opioids, opioid nonresponsiveness, depression, PTSD
- Multiple available routes of administration
  - IV, IM, SQ, PO, rectal, intranasal, topical, etc

Ketamine Dosing

- IV bolus: 0.1-0.3 mg/kg, slow IV push over 1 min
- IV infusion: 0.1 mg/kg/hr titrated up to max 1 mg/kg/hr
- SC/IM: 0.1-0.3 mg/kg
- Nasal: 0.3-1 mg/kg (50 mg in most adults). Administer ½ the dose to each nostril via nasal atomizer
- Oral: starting dose 5-10 mg TID

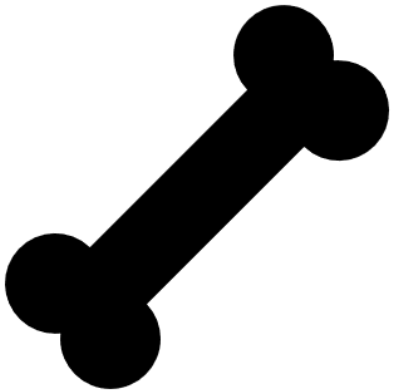
Schwenk et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med.* 2018;43(5):456-465.

Ketamine – Adverse Effects

- Adverse effects
  - Confusion, hallucination, delirium, hypertension, tachycardia, myoclonus, increased secretions
- Side effect management
  - Patient education, dose reduction, slow titration of infusion, low dose benzodiazepines or haloperidol

Bisphosphonates

- Mechanism of action
  - Inhibition of osteoclast bone resorption and overall decrease in osteoclast activity
- More effective for prevention than for treatment
- Dosing
  - Zoledronic acid – 4 mg IV over 15 minutes q3-4 weeks
  - Pamidronate – 90 mg IV over 2 hours q3-4 weeks
  - Require renal dose adjustment; contraindicated in renal failure
- Adverse effects
  - Injection site reactions
  - Flu-like symptoms
  - Osteonecrosis of jaw



Zoledronic acid. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated August 12, 2020.
Pamidronate. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated December 28, 2020.

Miscellaneous Agents

- **Ziconotide**
  - Mechanism of action
    - Potent and selective blockade of presynaptic neuronal N-type calcium channels in the spinal cord
  - Administered intrathecally
- **Onabotulinum toxin-A (Botox®)**
  - Mechanism of action
    - Blocks neuromuscular transmission by binding and entering sites of nerve terminals on sympathetic or motor neurons and inhibiting acetylcholine release
  - FDA-approved for chronic migraine, upper limb spasticity, and cervical dystonia
  - Other potential uses include other types of spasticity, myofascial pain, pelvic muscle pain, osteoarthritis, neuropathic pain, and maxillofacial pain

Ziconotide. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated July 15, 2020.
OnabotulinumtoxinA. Micromedex Solutions. Greenwood Village, CO: Truven Health Analytics. micromedex.com/. Updated May 3, 2021.

Principles of Adjuvant Analgesic Use

- Complete a comprehensive pain assessment
  - Determine relationship to underlying disease
  - Consider comorbidities (depression, insomnia, etc)
- Select adjuvant analgesic based on knowledge of pharmacology, available evidence base, drug-drug interactions, and potential adverse effects
- Initiate treatment with low doses and titrate gradually according to analgesic response and adverse effects
- Avoid initiating several adjuvant analgesics concurrently

Additional Resources

- Portenoy RK. A practical approach to using adjuvant analgesics in older adults. *JAGS*. 2020;68:691-698.
- van den Beuken-van Everdingen M, de Graeff A, Jongen J, et al. Pharmacological treatment of pain in cancer patients: The role of adjuvant analgesics, a systematic review. *Pain Pract*. 2017;17(3):409-419.
- Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162-173.
- Fornasari D. Pharmacotherapy for neuropathic pain: A review. *Pain Ther*. 2017;6(Suppl 1):25-33.

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Adjuvant Analgesics

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