What a Pain!

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01/21/24

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Disclosure

- The speakers have no actual or potential conflicts of interest in relation to this presentation

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Pain Management and Stewardship Considerations

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Objectives

- Discuss the efficacy of pharmacologic and non-pharmacologic treatment options for acute and chronic pain
- Evaluate evidence-based recommendations for a patient specific approach to pain stewardship

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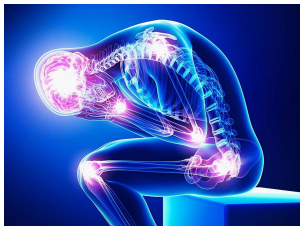
Pain Management

- The experience of pain has been recognized as a national public health problem with profound physical, emotional, and societal costs.
- ~50 million US adults experience chronic pain
  - 19.6 million of those adults experience high impact pain that interferes with daily life or work activities



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Approaches to Pain Management

- A multimodal approach to pain management consists of using treatments from multiple clinical disciplines incorporated into an overall treatment plan
- Multidisciplinary approaches address different aspects of chronic pain conditions, including biopsychosocial effects of the medical condition on the patient
- The efficacy of such a coordinated, integrated approach has been documented to reduce pain severity, improve Quality of Life (QoL), and increase overall function

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Types of Pain

Allodynia	**Pain due to a stimulus that does not normally provoke pain.**
Hyperalgesia	Increased pain from a stimulus that normally provokes pain.
Central sensitization	Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.
Nociceptive pain	Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system.
Nociplastic pain	Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.
Breakthrough Pain	Transient flare of moderate to severe pain occurring on a background of chronic pain

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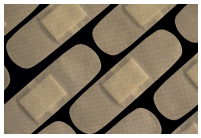
Acute Pain

- Acute pain is a universal human experience
- Acute pain is defined as a physiologic response to noxious stimuli that is sudden in onset and time limited
  - E.g., Burn or trauma or during perioperative period
- Acute pain flare can occur in chronic medical conditions
  - Arthritis
  - Neuropathies
  - Spinal conditions
  - Sickle cell
  - Migraine
  - Multiple sclerosis
  - Trigeminal pain or neuralgia



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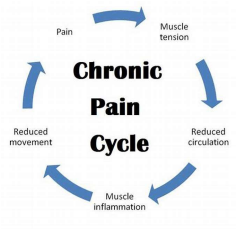
Chronic Pain

- Long standing pain, usually beyond 3 months, that persists beyond the usual recovery
- Often is found with chronic health conditions
- To appropriately manage chronic pain: the initial therapeutic strategy depends on an accurate evaluation on the cause and type of chronic pain



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Non-Pharmacological Treatments of Pain: Overview

Therapeutic exercise, massage therapy, cold/heat therapy

- Have shown to be efficacious in reducing pain.
- Heat wraps have been shown to be efficacious for the treatment of lower-back pain and can result in functional improvements

Bracing

- Sometimes been discouraged in pain management because of fears of deconditioning and muscle atrophy
- Evidence shows for at least a short period of time, nonrigid bracing may improve function and does not result in muscle dysfunction

Transcutaneous electric nerve stimulation (TENS)

- Has been applied to treat pain
- Considered a safe option for patients
- Studies demonstrating efficacy are lacking currently

Therapeutic ultrasound (TU)

- Thought to deliver heat to deep tissues for improved injury healing
- A 2001 review concluded that there was little evidence for pain treatment in a range of musculoskeletal conditions

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Common Categories of Pain Medications

- Acetaminophen
- Musculoskeletal agent
- Anticonvulsant
- NSAIDS
- Antidepressants
- Opioids
- Others

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Overview of Pain Mechanism of Action

Major analgesic target/activity	Drug/class
Binding site	
• Mu-opioid receptor	Opioids, tramadol
• Sodium ionic channel	Lidocaine, carbamazepine, lamotrigine
• Calcium ionic channel	Gabapentin, pregabalin
Neurotransmitter	
• Inhibition norepinephrine reuptake	Tricyclic and SNRI antidepressants
• Alpha$_2$-adrenoreceptor agonist	Tizanidine, clonidine
Enzyme inhibition	
• Cyclooxygenase types 1 ≥ 2	Non-selective NSAIDS
• Cyclooxygenase types 2 ≥ 1	Selective NSAIDs

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Acetaminophen

- **1st line for mild to moderate acute pain**
- Risk of acetaminophen include dose-dependent liver toxicity
  - Especially at high doses, with alcohol, or in liver disease
- Evidence for efficacy of Acetaminophen for chronic pain is limited
  - Well demonstrated efficacy in osteoarthritis
  - Not 1st line for chronic back pain
  - Chronic use may be associated with hepatotoxicity, chronic kidney disease, chronic daily headaches, peptic ulcer disease, and hypertension
- FDA recommended maximum dose is 4 grams per day
  - Due to liver toxicity concerns, manufacturers limit daily dose to 3 grams
  - 2-gram max for elderly patients or patients with established liver disease
- Mechanism is uncertain

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Nonsteroidal Anti-Inflammatory Drugs (NSAIDS): Overview

- More than 20 different NSAIDs are available for commercial purchase
  - Example include aspirin, ibuprofen, naproxen, ketorolac, meloxicam
- Used worldwide for pain, fever, and inflammation
- Primarily indicated for mild to moderate pain, particularly in patients with musculoskeletal pain
  - Often used for pain relief caused by inflammation such as bone fractures, arthritis, muscle pain, headache, pain caused by trauma (injury or surgery)
- NSAIDS are a relatively safe drug
  - Greater likelihood of adverse effects when NSAIDs are used in populations who are at increased risk for gastrointestinal, kidney, or cardiovascular adverse reactions

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NSAIDS: General Principles

- NSAIDs work through inhibition of Cyclooxygenase (COX) enzymes which are essential to the synthesis of prostaglandin
  - Prostaglandins have a local vasodilatory effect, which is key for their involvement in inflammatory effects, and inhibit aggregation
- Choosing between NSAIDs should be individualized for the patient's risk factors and comorbities
- There are two types of NSAIDS: **Cox-2 selective and non-selective**
  - Nonselective NSAIDs
    - Inhibit the activity of COX-1 and COX-2 enzymes
    - Associated with gastritis, gastric ulcers, and gastrointestinal (GI) bleeding.
    - e.g. aspirin, ibuprofen, naproxen, diclofenac
  - COX-2 selective inhibitors
    - Fewer GI adverse effects
    - e.g. celecoxib

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NSAIDS: Additional Considerations

- NSAIDS and Drug-Drug Interactions:
  - Methotrexate (MTX): can decrease renal clearance of MTX leading to potential toxic drug levels
  - Angiotensin-converting enzyme inhibitors (ACEi): can decrease the antihypertensive effect of ACEi medications, via blocking vasodilators and natriuretic prostaglandins, and can also worsen hyperkalemia
  - Glucocorticoids: significantly increases the risk of peptic ulcer disease
  - Anticoagulants: with non-selective NSAIDs can increase the risk of bleeding
- NSAIDs and Comorbidities:
  - Caution in patients with GI, CKD, and chronic liver disease
  - In patients with cardiovascular disease, use of NSAIDs may be restricted
- Wide variety of dosage forms
  - Topical, oral, intravenous, and intramuscular
- Patients who are treating their chronic pain with daily NSAIDs should receive annual:
  - complete blood count
  - blood urea nitrogen
  - creatinine
  - liver function test annually

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Musculoskeletal Agents: Overview

- Commonly used for pain treatment
  - Various pain conditions can be accompanied by painful muscles and muscle spasms
- Examples include baclofen, tizanidine, carisoprodol and cyclobenzaprine
- Medications categorized as muscle relaxants have a wide variety of pharmacological mechanisms, but none act directly on the muscle
  - Relief of spasms is affiliated with CNS effects, such as sedation, rather than providing an analgesic effect
- Muscle relaxants can cause CNS depression and have Anticholinergic properties
  - Caution when used in older patients (Beers Criteria) or when combining with other CNS depressant or antidepressant medications

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Musculoskeletal Agents: When to use

- Avoid use for chronic pain
- Primarily used in patients with acute lower back pain
- Anti-spasticity muscle relaxants: baclofen and tizanidine
- Carisoprodol is metabolized to meprobamate, which is both sedating and possibly addictive
  - Carisoprodol is not recommended, particularly because alternatives are available
- Cyclobenzaprine is often used in patients with mild to moderate symptoms of fibromyalgia
  - Mechanism resembles tricyclic antidepressants, specifically amitriptyline
  - FDA approved for short-term use only

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Antidepressants: Overview

- Both tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have analgesic properties
  - There is some evidence to support Selective serotonin reuptake inhibitors (SSRIs) can be effective for pain
  - No evidence it has effect on musculoskeletal pain
- Commonly used in various chronic pain conditions
  - Including, but not limited to, lower back pain, neuropathy, and fibromyalgia
- Used for the treatment of pain even in patient populations who are not clinically depressed nor have any mood disorders
- The analgesic effect of antidepressants usually occurs at lower doses than is needed to treat mood disorders
  - Can take several weeks to establish perceptible analgesic effect

Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. U.S. Department of Health and Human Services. Available at: https://www.hhs.gov/sites/default/files/pmtf-final-report-2019-03-21.pdf (August 4, 2022).

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Antidepressants: Class Comparison

Tricyclic Antidepressants (TCAs)

- Examples: desipramine, nortriptyline, amitriptyline
- 1st line for peripheral neuropathic pain

- Adverse effects:
  - Dry mouth, dizziness, sedation, memory impairment, orthostatic hypotension, urinary retention, and cardiac conduction abnormalities
- If pain management requires trials of multiple TCAs→ start low and titrate slow
- Some studies indicate that TCAs are as effective and have possible greater analgesic effect than SNRI

Serotonin-norepinephrine Reuptake inhibitors (SNRIs)

- Examples: duloxetine and venlafaxine
- 1st line for peripheral neuropathic pain

- Considerably fewer adverse effects than TCAs
- More effective than SSRI's for pain management
- Does not require starting at lowest possible dose and titrating slowly
  - Pain control may require increased norepinephrine reuptake- which occurs at higher doses

Remember: Both drug classes can cause withdrawal reactions when abruptly discontinued

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Anxiolytics: Overview

- Often prescribed to treat the anxiety that accompanies acute pain as well as anxiety resulting from fluctuations in chronic pain.
- May also be prescribed for co-morbid anxiety disorders
  - Generalized anxiety disorder
  - Panic disorder
  - Post-traumatic stress disorder (PTSD)
  - Agoraphobia
- Prevalence estimated in the range of 30% in patients with chronic pain
- Important to recognize and treat anxiety effectively because it can worsen the severity of pain as well as interfere with a patient's coping skills for managing pain

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Anxiolytics: Benzodiazepines

- Drugs that enhance or facilitate the action of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the CNS that suppresses the activity of nerves
  - In addition to anti-anxiety properties, benzodiazepines have sedative, hypnotic, anticonvulsant, and muscle relaxant effects.
  - Contraindicated in patients with myasthenia gravis, certain types of glaucoma, severe liver disease, pregnancy, patients with severe breathing problems
- Can be helpful in acute setting for patients with anxiety associated with pain
- Should be avoided in regular or long-term use
  - Increase risk of substance use disorder
  - Have cognitive effects which can prevent patients from using non-pharmacologic approaches to pain management
- **BLACK BOX WARNING**: Co-prescription of benzodiazepines and opioids are associated with enhanced risk of respiratory depression and death

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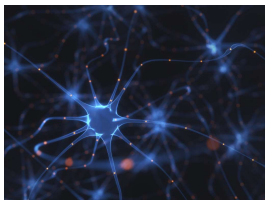
Anticonvulsants: Overview

- Anti-seizure medications (anticonvulsants) were originally designed to treat people with epilepsy
  - Nerve-calming qualities of some of these medications can also help quiet the burning, stabbing or shooting pain often caused by nerve damage
- Anti-seizure medications appear to interfere with the overactive transmission of pain signals sent from damaged nerves (neuropathy) or overly sensitized nerves, as in fibromyalgia
- Some anti-seizure drugs work particularly well for certain conditions
  - Carbamazepine is widely prescribed for trigeminal neuralgia, a condition that can cause searing facial pain that feels like an electric shock



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Anticonvulsants: Gabapentinoids

- Gabapentin and Pregabalin
  - Pregabalin is a Scheduled V Drug
- Medications originally developed to treat seizures
  - Also commonly used to treat different pain syndromes such as:
    - Postherpetic neuralgia
    - Peripheral neuropathy
    - Migraine
- They are often used as part of a multimodal approach to the treatment of perioperative pain
- May cause significant sedation and have recently been associated with a possible risk of misuse.
- These agents can effectively treat the neuropathic components of pain syndromes

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Anxiolytics and Anticonvulsants: When to use

- Several classes of medications can be used to treat anxiety
- Benzodiazepines do not have independent analgesic effects but may have indirect pain-relieving effects
- SSRIs and SNRIs are the medications most frequently used for the generalized anxiety that often accompanies chronic pain conditions
  - Gabapentinoids have shown to efficacious in treating anxiety in patients with pain
- For chronic anxiety disorders, usually a combination of medications indicated for that specific condition plus evidence-based psychotherapy, such as cognitive-behavioral therapy (CBT), works best

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Ketamine

- Ketamine is a schedule III N-methyl-D-aspartate (NMDA) antagonist that has medical uses as an anesthetic and pain killer
  - Associated with hallucinogenic and dissociative effects
  - Well tolerated hemodynamically and has little effect on respiratory drive
- Dosed at anesthetic doses or subanesthetic doses
  - Low doses provide analgesia and modulate central sensitization
- Acute pain
  - Often used for postoperative analgesia who undergo moderately to severely painful surgery
  - Used in severe nonsurgical pain
- Avoid ketamine in older adults
  - Consider a risk-benefit analysis

Orhurhu VJ, Roberts JS, Ly N, et al. Ketamine in Acute and Chronic Pain Management. [Updated 2023 Sep 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534824/

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Opioids: Overview

- Controlled substance group of analgesics that provide pain relief for a variety of conditions
- Opioids bind to opioid receptors in the brain, spinal cord, and other sites, activating analgesic and reward pathways
- Opioid medications vary in the ratio of their analgesic potency and their potential for respiratory depression, the major cause of opioid overdose death
- Opioid medications can be associated with significant side effects
  - Such as constipation, sedation, nausea, vomiting, irritability, pruritis, and respiratory depression

GENERIC	BRAND NAME
Hydrocodone	Vicodin, Lorcet, Lortab, Norco, Zohydro
Oxycodone	Percocet, OxyContin, Roxicodone, Percodan
Morphine	MSContin, Kadian, Embeda, Avinza
Codeine	Tylenol with Codeine, TyCo, Tylenol #3
Fentanyl	Duragesic
Hydromorphone	Dilaudid
Oxymorphone	Opana
Meperidine	Demerol
Methadone	Dolophine, Methadose
Buprenorphine	Suboxone, Subutex, Zubsolv, Bunavail, Butrans
Tramadol	Ultram

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep. 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1.

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Opioids: When to use

- Common prescription opioid medications can be considered for management of acute and chronic pain
  - Examples include hydromorphone, hydrocodone, codeine, oxycodone, methadone, and morphine
- Although effective for moderate to severe acute pain, the effectiveness of opioids beyond three months requires more evidence
  - Recommendation: Opioid treatment should be maintained for a period no longer than necessary for adequate pain control
- Accurate dose adjustment is critical because patients vary widely in the dose required for analgesic efficacy
- Wide variety of dosage forms!
  - Short acting vs Long acting
  - Oral, buccal, sublingual, spray, intravenous, intramuscular, intrathecal, suppository, transdermal patches, and lozenge

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Opioids: Pain Management

- Long term opioids should not be routinely used for chronic pain
  - Reserve for patients at a low risk for substance abuse, who have persistent pain despite ongoing multimodal non-drug treatments, trials of non-opioid pain medication, and benefit outweighs risk
- Initiation of opioid therapy, when the patient and the clinician deem the benefits to outweigh the risks
  - Start at a low dose and titrated upward to find the lowest dose required to optimally control the pain or improve function and QOL
- Assessing for tolerance and consideration of adjunctive therapies, opioid rotation, tapering, and discontinuation should be considered
- Start with Immediate release formulations at lowest effective dose
  - Reserve long-acting or extended-release formulations for patients who require continuously long-term opioid use

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Opioids: Clinical Considerations

- Safe opioid stewardship involves a proper history and examination, periodic reevaluation, and risk assessment, with a focus on measurable outcomes, including function and QOL
- Accurate dose adjustment is critical because patients vary widely in the dose required for analgesic efficacy
  - Risk of overdose increases with the dose
  - Therapeutic window varies
- The idea of a ceiling dose of opioids has been recommended, but establishing such a ceiling is difficult due to the tolerance effect of opioids and wide therapeutic window
  - CDC guidelines suggest a dose limit of 90 morphine milligram equivalents (MMEs) per day

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Opioids: Choosing Among The Class

- Patients who are opioid naïve and are unable to reach adequate pain control on non-opioid medication:
  - Can consider using opioid-nonopioid combinations
  - Can also consider using low dose pure mu-receptor agonist
    - e.g., morphine, oxycodone, hydromorphone

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Opioids: Choosing Among The Class

- Patients with kidney impairment:
  - Avoid meperidine since its metabolite accumulates in renal dysfunction which can lead to serious CNS toxicity
  - Avoid morphine and oxycodone as their metabolites are renally excreted
  - Select hydromorphone or an opioid that lacks active metabolites (e.g., fentanyl, buprenorphine, and methadone)
- Patients with chronic liver disease
  - Start a low initial starting dose as most opioids are at least partly metabolized by the liver
  - Avoid codeine and meperidine
    - Codeine is a prodrug which require CYP enzymes to metabolize
    - Meperidine half-life is prolonged, and clearance is reduced in these patients

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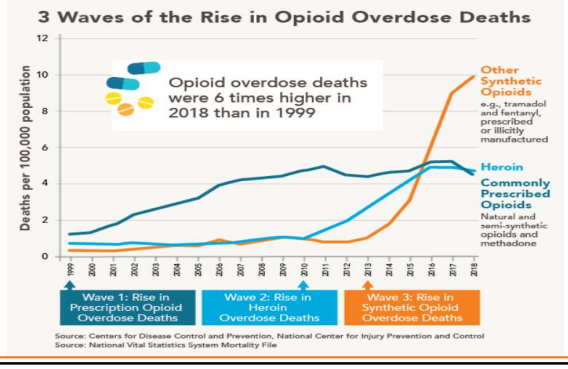

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Opioid Crisis: An Evolving Concern

- Synthetic opioids other than methadone (a category that includes prescribed and illicit fentanyl and fentanyl analogues) are now a leading cause of deaths from overdose in the United States
  - Greater risk of overdose when used in combination with alcohol or illicitly obtained heroin, cocaine, diverted prescription opioids, and other drugs such as benzodiazepines
- The source of illicit fentanyl and its analogues has been identified as international and rarely from diverted fentanyl pharmaceuticals in the United States
  - These sources currently come through the U.S. Postal Service, borders, and ports of entry

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Opioid Crisis: New Drugs, Old Problems

- Synthetic fentanyl and fentanyl analogues (e.g., carfentanil) are particularly potent for respiratory depression
  - Carfentanil is considered 100 times more potent than fentanyl
- The illicit fentanyl analogues used are not necessarily the same product that is legally prescribed
- A tranquilizer called **xylazine** is increasingly being found in the US illegal drug supply and linked to overdose deaths
- Xylazine can be life-threatening and is especially dangerous when combined with opioids like fentanyl
  - DEA has seized xylazine and fentanyl mixtures in 48 of 50 states, and the DEA laboratory system reported that approximately **23%** of fentanyl powder and **7%** of fentanyl pills seized by the DEA in 2022 contained xylazine

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Opioid Crisis: Xylazine Overview

- Xylazine (also called “tranq”) is a non-opioid sedative or tranquilizer
  - Not currently a controlled substance in the United States
  - Not FDA approved for use in humans
- Health risks of xylazine:
  - Sedation, difficulty breathing, hypotension, bradycardia, severe withdrawal symptoms, and death
- Xylazine and naloxone
  - Always give naloxone in response to any suspected drug overdose to reverse any possible opioid effects
  - Naloxone will not reverse any of the effects of xylazine

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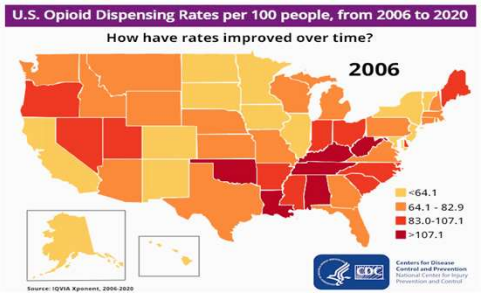
Opioid Crisis: Changes in Prescribing Practices



37

Opioid Crisis: Naloxone

- Naloxone is a medication designed to rapidly reverse opioid overdose
  - Should be prescribed alongside opioids
  - An opioid antagonist that binds to opioid receptors and can reverse and block the effects of other opioids
- Timely administered naloxone can reverse overdose from opioids whether the opioid is prescribed or illicitly obtained
  - This occurs through the quick restoration of normal respiration to a person whose breathing has slowed or stopped as a result of overdosing on an opioid
- The availability of naloxone as well as patient and family education about naloxone can mitigate the risks of fentanyl-related overdose
  - Currently pharmacists who maintain a current active license can dispense naloxone to emergency responders for administration

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1.

38

Opioids: Buprenorphine

- Partial agonist at the mu opioid receptor
  - Reduced potential for respiratory depression
  - Safer than full agonists such as morphine, hydrocodone, and oxycodone
  - As a partial opioid agonist it provides a "ceiling effect"
- Antagonist at the kappa receptor
  - Effect is to reduce anxiety, depression, and the unpleasantness of opioid withdrawal
- Adverse effects
  - Anticholinergic effects, hypotension, CNS depression, lower seizure threshold, and QT prolongation
- Buprenorphine is 1st line for treatment of OUD and is approved for the treatment of pain
  - **Detoxification without pharmacologic therapy is not recommended because of increased risks for resuming drug use, overdose, and overdose death**

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1.

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Opioids Crisis: Methadone

- Long-acting opioid agonist, binds to and occupies mu-opioid receptors, preventing withdrawal symptoms for 24 hours or longer
- May reduces craving for opioids
  - Reduces the euphoric effects of subsequent illicit opioid use by maintaining high levels of opioid tolerance
- Although individuals treated with methadone are physically dependent upon the medications
  - Do not typically have the pattern and severity of problematic behaviors associated with use and misuse of heroin or pharmaceutical opioids including fentanyl
  - Often able to return to a productive lifestyle
- Methadone has been associated with increased **QTc prolongation** and cardiac arrhythmias
- Full agonist so has a greater potential for lethal overdose compared with a partial mu-opioid agonist such as buprenorphine

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

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Opioids Crisis: Naltrexone

- Opioid antagonist
- Blocks the effects of opioids
  - Reinforces abstinence and decreases cravings
  - Preventing the user from experiencing any positive effects or physiologic dependence that leads to opioid dependence
- Should only be given after completion of medically supervised withdrawal from opioids and once the patient is no longer physically dependent
- Oral vs Long-acting injectable
  - Long-acting injectable is preferred over oral as established efficacy of oral naltrexone for sustained abstinence is limited

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

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Controlled Substances and Pain

- CI medications are those that are considered not to have medicinal value, including heroin, methamphetamine, and cannabis
- Opioids are mainly category CIII (relatively lower risk) or CII (higher risk)
  - CIII medications include acetaminophen with codeine and buprenorphine
  - CII medications include hydrocodone, oxycodone, morphine, fentanyl, and methadone
- CIV drugs are defined as drugs with a low potential for abuse and low risk of dependence, such as tramadol or benzodiazepines

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

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Other Pain Medications

Capsaicin

- An agonist of transient receptor potential vanilloid member 1 (TRPV1), a receptor prominent in small nerve fibers involved in pain
- Analgesia likely results from short-term desensitization and long term defunctionalization of nociceptor terminals with a dose-dependent impact
- Low concentrations are available over-the-counter

Topical Lidocaine

- Second-line therapy for some forms of neuropathic pain
  - Data suggests efficacy for postherpetic neuralgia and painful diabetic neuropathy
- Can be used in chronic pain
  - Usually in patch formulation
- A single 5% lidocaine patch contains 700mg lidocaine
  - Up to three patches in a single application for a 24 hour period
  - 12 on and 12 off- to allow for at least 12 hours of a lidocaine free period

Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. U.S. Department of Health and Human Services. Available at: https://www.hhs.gov/sites/default/files/pmtf-final-report-2019-05-23.pdf (August 4, 2022)

43

Other Pain Medications

Cannabis/Marijuana

- Remains a schedule 1 drug
- Lacking rigorous studies on the safety and efficacy of any specific cannabis product as treatment for pain
- Medical marijuana is available in Florida for patients with a doctor's recommendation
  - Pain is one of the major reasons patients seek a medical marijuana card with 42% of patients citing chronic pain

Botulinum Toxin

- Commonly called "Botox"
- Potent neurotoxin
- Limited literature
  - Suggests subcutaneous injection may reduce opioid requirement in patients with severe post herpetic neuralgia

Azcarate PM, Zhang AJ, Keyhani S, Steigerwald S, Ishida JH, Cohen BE. Medical Reasons for Marijuana Use, Forms of Use, and Patient Perception of Physician Attitudes Among the US Population. J Gen Intern Med. 2020;35(7):1979-1986. doi:10.1007/s11606-020-05800-7

44

Evidence Based Recommendations

Taken from CDC, HHS, and VA guidelines

45

Evidence-Based Recommendations:
Determining Whether to Initiate Opioids for Acute Pain

- Nonopioid therapies are at least as effective as opioids for many common types of acute pain
- Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient
- Before prescribing opioid therapy for acute pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

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Evidence-Based Recommendations:
Determining Whether to Initiate Opioids for Chronic Pain

- Nonopioid therapies are preferred for subacute and chronic pain
- Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient
  - Only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient
- Before starting opioid therapy for subacute or chronic pain, have a discussion with the patient
  - Topics should include:
    - Realistic benefits and known risks of opioid therapy
    - Treatment goals for pain and function that are realistic and achievable for the patient
    - Educate how opioid therapy will be discontinued if benefits do not outweigh risks

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

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Evidence-Based Recommendations:
Selecting Opioids and Determining Opioid Dosages

- When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids
- When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage
- Clinicians should not treat acute pain with ER/LA opioids or initiate opioid treatment for subacute or chronic pain with ER/LA opioids, and clinicians should not prescribe ER/LA opioids for intermittent or as-needed use

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

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Evidence-Based Recommendations:
Selecting Opioids and Determining Opioid Dosages

- ER/LA opioids should be reserved for severe, continuous pain
  - FDA has noted that some ER/LA opioids should be considered only for patients who have received certain dosages of opioids of immediate-release opioids daily for at least 1 week
- Clinicians should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or hepatic dysfunction
  - Decreased clearance of medications among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations
- Methadone should not be the first choice for an ER/LA opioid

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

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Evidence-Based Recommendations:
For Patients Already Receiving Opioid Therapy

- Carefully weigh benefits and risks and exercise care when changing opioid dosage
  - If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy
  - If benefits do not outweigh risks of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to lower dosages or, if warranted based on the individual circumstances of the patient, appropriately taper and discontinue opioids
- Unless there are indications of a life-threatening issue such as warning signs of impending overdose (e.g., confusion, sedation, or slurred speech), opioid therapy should not be discontinued abruptly, and clinicians should not rapidly reduce opioid dosages from higher dosages

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

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Evidence-Based Recommendations:
Additional Considerations When Considering Opioids

- Review of the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP)
  - Helpful to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose
  - Clinicians should use caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants
- Consider the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances
- Offer or arrange treatment with evidence-based medications to treat patients with opioid use disorder

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

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Special Considerations: Older Adults

- Chronic pain is one of the most common, costly, and incapacitating conditions in older adults
- Effective pain management for older adults requires an understanding of the special considerations associated with the physiology of aging, validated assessment tools, common pain presentations in the older adult population, and the use of evidence-informed CPGs for common conditions such as low-back pain
- Older patients may have increased risk of GI bleeding and renal damage from NSAIDs
- Managing pain in older adults can be complex because of:
  - Age-related physiologic changes
  - Associated medical and mental health comorbidities
  - Polypharmacy
  - Increases in pain thresholds
  - Decreases in pain tolerance
  - Alterations in pharmacokinetics and pharmacodynamics

Health Care Guideline: Pain: Assessment, Non-Opioid Treatment Approaches and Opioid Management Care for Adults. Institute for Clinical Systems Improvement. Available at: https://www.icsi.org/wp-content/uploads/2018/10/Pain-Interactive-7th-V2-64-X.7.pdf

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Special Considerations: Women

- Central to the unique issues women face in pain management are the differences between men and women with respect to pain sensitivity, response to pain medication, and predisposition to clinical pain conditions
  - Data and recent literature suggest that women experience more pain than men, have greater sensitivities to painful stimuli compared with men, and report experiencing more intense pain
- Women face unique pain management challenges in the pregnancy and postpartum periods
  - Pregnancy is not a reason to avoid treating acute pain
- In addition to the response and sources of pain, there exist sex differences in the patterns of nonmedical use and abuse of prescription opioids
  - Research has identified that women are more likely than men to misuse prescription opioids
  - From 1999 to 2010, the percentage increase in opioid-related overdose deaths was greater in women than in men

Health Care Guideline: Pain: Assessment, Non-Opioid Treatment Approaches and Opioid Management Care for Adults. Institute for Clinical Systems Improvement. Available at: https://www.icsi.org/wp-content/uploads/2018/10/Pain-Interactive-7th-V2-64-X.7.pdf

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Catering Pain Management To Disease States: Cancer

- Cancer pain affects millions of Americans
- As a result of advancement in cancer therapy, there are more than 14 million cancer survivors in the United States
  - An estimated 40% of cancer survivors continue to experience persistent pain due to treatments such as surgery, chemotherapy, and radiation therapy
- Persistent pain is also common and significant in patients with a limited prognosis, as often encountered in hospice and palliative care environments
  - Opioids are often prescribed in patients with cancer related pain

Health Care Guideline: Pain: Assessment, Non-Opioid Treatment Approaches and Opioid Management Care for Adults. Institute for Clinical Systems Improvement. Available at: https://www.icsi.org/wp-content/uploads/2018/10/Pain-Interactive-7th-V2-64-X.7.pdf

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Catering Pain Management To Disease States: Cancer

- Selecting an opioid:
  - For patients with cancer pain and opioid-naïve
    - Guidelines suggest a single-entity pure mu agonist orally at low dose; such as morphine, oxycodone, hydromorphone
      - Can consider transdermal fentanyl patch for patients with difficulty swallowing
  - For patients with cancer pain who are already on opioids
    - Consider long-acting formulations
    - Can utilize an "Opioid Rotation" Strategy
      - Pharmacologic and clinical observations suggest that a change in drug is likely to prove balance between pain relief and side effects
  - For management of breakthrough pain
    - "Rescue" dosing – short acting drug used on an as-needed basis

Reddy A, Yennurajalingam S, Pulivarthi K, et al. Frequency, outcome, and predictors of success within 6 weeks of an opioid rotation among outpatients with cancer receiving strong opioids. Oncologist. 2012;18(2):212-220. doi:10.1634/theoncologist.2012-0269

55

Catering Pain Management To Disease States: Sickle Cell

- Sickle cell disease is a group of inherited disorders characterized by complex acute and chronic symptoms, including pain
  - An estimated 90,000 people in the United States have SCD, which disproportionately affects minority populations, particularly African Americans
- Pain in SCD is unique in that it occurs throughout the patient's lifespan, from infancy to adulthood, and develops directly from the disease
  - The biology of SCD pain is complex and varied; it likely arises from multiple mechanisms depending on whether an individual is suffering from acute or chronic pain
  - Pulmonary, orthopedic, psychosocial, and other comorbidities of SCD can also give rise to painful complications in adults and children

Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1

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Catering Pain Management To Disease States: Sickle Cell

- Acute pain episodes, or "pain crises," associated with SCD are abrupt in onset and unpredictable
  - ~$2 billion per year in healthcare costs
  - Chronic, severe, daily pain occurs in approximately 30% to 40% of adolescents and adults with SCD
    - Daily pain can impair their functioning/QOL
    - Patient's pain often increases in incidence and severity with age
- Patients will be provided with medication on an as-needed basis for managing pain at home
  - Opioids are prescribed in this patient population
  - Short course of NSAIDs (five to seven days) can be utilized along side opioids
- If patients present to hospital/emergency department; they were not able to control pain on home oral opioids
  - Morphine is commonly used in hospital setting
  - 2020 American Society of Hematology guidelines suggest ketamine may be appropriate if pain is not responsive to opioids

Brandow AM. American society of hematology 2020 guidelines for sickle cell disease: Management of acute and chronic pain. *Blood advances*. 06;(2020;4(12):2656–2701. doi: 10.1182/bloodadvances.2020001851.

57

Question #1

True or False:

Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line treatment for most patients with acute mild to moderate pain

58

Question #1

True or False:

Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line treatment for most patients with acute mild to moderate pain

59

Question #2

True or False:

Non-selective cyclooxygenase (COX) NSAIDs are preferred over COX-2 selective NSAIDs for patients with a history of gastrointestinal bleeding

60

Question #2

True or **False**:

Non-selective cyclooxygenase (COX) NSAIDs are preferred over COX-2 selective NSAIDs for patients with a history of gastrointestinal bleeding

COX-2 selective NSAIDs are preferred for patients with a history of gastrointestinal bleeding

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Pharmacogenomic Considerations

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Objectives

- Describe the influence of pharmacogenomic variations that effect the use and dosing of select analgesics
- Evaluate dosing recommendations for analgesic use in patients with select genetic polymorphisms

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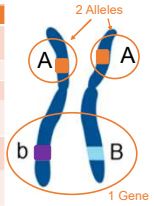
Pharmacogenomic Terminology

Term	Definition
Allele	One of 2 or more versions of a gene; an individual inherits 2 alleles for each gene, 1 from each parent
Gene	The basic physical unit of genetics
Genotype	Individual's collection of genes
Homozygous	Having inherited the same form (allele) of a particular gene from each parent
Heterozygous	Having inherited different forms (alleles) of a particular gene from each parent
Phenotype	Clinical presentation or observable characteristics that results from a genotype
Polymorphism	A variation in a gene, DNA sequence, or chromosome
Wild-type	Refers to the most common or "normal" form of an allele



Ann Pharmacother. 2021; 55(12): 1486 - 1501.

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Describing Genetic Variation

Various methods are used to describe genetic polymorphisms in clinical literature

- **Typical nomenclature**
  - Gene name, polymorphism location, wildtype allele, mutated allele
  - CYP2C19 c681G>A
- **Star allele method**
  - Gene name, star, number of the intended polymorphism
  - CYP2C19*2
- Reference single-nucleotide polymorphism number (rs#)
  - Assigned by the national center for biotechnology information
  - rs4244285

Kisor et al. Pharmacogenomics. 2e. 2022. *I Gammal et al.* Dipiro's Pharmacotherapy. 12e. 2023

65

Available Guidelines

- The **Clinical Pharmacogenetics Implementation Consortium (CPIC®)** and Food and Drug Administration (FDA) provide clinical recommendations for select analgesics
  - CPIC® is a group of international volunteers and staff
  - Developed to address barriers to clinical implementation of pharmacogenomic testing
  - **Create peer-reviewed, evidence-based guidelines**

"What is CPIC?" Clinical Pharmacogenetics Implementation Consortium (CPIC®). 2023. Web. Accessed. 12/2023.

66

Translating Pharmacogenomic Data into Clinical Recommendations

- Pain providers have noted that **response to medication (opioids) can vary widely**
  - Pharmacogenomics may explain part of this
  - Understanding the impact that pharmacogenomics has on pain and pain response remains limited
- Limitations in available data
  - **Most data are monogenic, overall effects are not**
  - Current data focused on pharmacokinetic changes and not clinical outcomes

J Pain Res. 2016; 9: 49-56. I *Pharmacogenomics.* 2021; 22(14): 927-937.

67

Impact on Pain Response

- Pain response is highly variable
- Many factors result in individual response
- Genetic factors may account for **24-60% of changes in pain response**
  - Lack of robust evidence to guide clinical use
  - Polymorphisms that could alter response do not always result in clinically significant changes

Drug Metab Pers Ther. 2016; 31 (3): 131-142. I *J Pain Res.* 2016; 9: 49-56. I *Pharmacogenomics Pers Med.* 2019; 12: 125-143. I *Supportive Care in Cancer.* 2022; 30: 10453-10459.

68

Impact on Pain Response

- Alterations of pain receptors determine how the body feels pain
- **Acute and chronic pain conditions are affected by these alterations**
  - Acute pain response is caused by the body's inflammatory process which causes temporary changes in pain receptor formation
  - Continued inflammation prompts permanent changes to pain receptors causing chronic pain

Drug Metab Pers Ther. 2016; 31 (3): 131-142. I *Pharmacogenomics Pers Med.* 2019; 12: 125-143..

69

Pharmacogenomic Effects on Pharmacotherapy

70

What is a CYP450 Enzyme?

- **Cytochrome P450 enzymes (CYPs) are responsible for 90% of drug metabolism**
  - Located in the liver, intestines, and kidneys
- A drug may be
  - Substrate (drug is metabolized by enzyme)
  - Inducer (drug increases enzyme activity)
  - Inhibitor (drug decreases enzyme activity)
- **Baseline enzyme activity level determined by genetics**

"Biochemistry, Cytochrome P450." *NCBI Stat Pearls*. 2023.

71

Pharmacogenomic Terminology

Term	Definition
Ultra-Rapid Metabolizer (UM)	Significantly increased metabolism
Rapid Metabolizer (RM)	Increased metabolism
Normal Metabolizer (NM)	Expected metabolism *may also be referred to as extensive metabolizer (EM)
Intermediate Metabolizer (IM)	Reduced metabolism
Poor Metabolizer (PM)	Significantly reduced metabolism
Activity Score	Numeric score that quantifies the metabolism level of a combination of alleles

Ann Pharmacother. 2021; 55(12): 1486 - 1501.

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Acetaminophen

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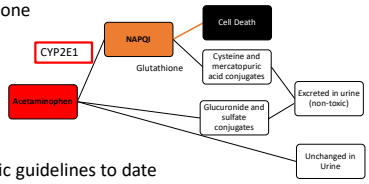
Acetaminophen

- Primarily metabolized by the liver
  - Hepatotoxicity is due to metabolism by CYP2E1
    - N-acetyl-p-benzoquinone imine (NAPQI)
    - Detoxified by glutathione



- No clinical pharmacogenomic guidelines to date

Pharmacogenetics and genomics. 2015; 25(8): 416-426. *I Exp Opin Drug Metab Tox.* 2023; 19(5):297-317.

74

Pharmacogenomics in Literature

Impact on Drug Exposure

- Cerezo-Arias *et al.* studied impact of UGT (metabolizing enzyme) polymorphisms on acetaminophen
- **UGT metabolizer status determined acetaminophen levels**
  - Specific polymorphisms (UGT1A6*2 or UGT1A6*4) significantly increased half-life and drug exposure

Impact on Hepatotoxicity

- Lee *et al.* showed that mice with CYP2E1 were more sensitive to acetaminophen-induced hepatotoxicity than mice without functioning CYP2E1
- **CYP2E1 metabolizer status may determine risk of acetaminophen-associated hepatotoxicity**

J Biol Chem. 1996; 271(20): 12036-7 *I J Pers Med.* 2022; 12(5): 720.

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NSAIDs

Non-steroidal anti-inflammatory drugs

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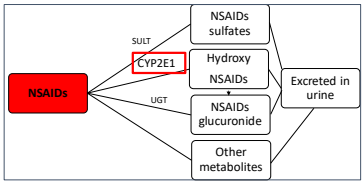
NSAIDs

- Mechanism of action is **inhibition of cyclooxygenases (COX)** which inhibits prostaglandin production
- **Hepatic metabolism primarily by CYP2C9**, followed by CYP1A2 and CYP3A4



Ann Pharmacother. 2021; 55(12): 1486-1501. I *Clin Pharmacol Ther.* 2020; 108(2): 191-200. I *Pharmacogenomics.* 2021; 22(14): 927-937. I *Pharmacogenomics Pers Med.* 2019; 12: 125-143. I *Sci Total Environ.* 2021; 791: 148251.

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Pharmacogenomic Considerations

- Polymorphisms in **COX enzymes may impact efficacy**
- Polymorphisms in the genes that code for COX enzymes (PTGS1 and PTGS2) predict NSAID response
  - Patients with additional copies of PTGS2 may respond better to COX-2 selective agents (e.g., celecoxib)
  - Patients with additional copies of PTGS1 may respond better to non-selective agents (e.g., ibuprofen)

Clin Biochem. 2014; 47 (13-14): 1169-1187. I *Pharmacogenomics Pers Med.* 2019; 12: 125-143.

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Pharmacogenomics in Literature

Impact Analgesic Response

- Lee *et al.* studied impact of PTGS1 and PTGS2 polymorphisms on NSAID response
- Patients with **increased PTGS2 expression had better pain control with rofecoxib (COX-2 selective)**
- Patients with **decreased PTGS2 expression had better pain control with ibuprofen (non-selective)**

Clin Pharmacol Ther. 2006; 79(5): 407-418.

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Pharmacogenomic Considerations

- Polymorphisms in **CYP enzymes are involved in safety**
  - Polymorphisms of **CYP2C9 are clinically significant**
    - CYP2C9 intermediate and poor metabolizers have reduced metabolism of NSAIDs causing higher risk of adverse effects
    - **Impact is drug specific**
- CPIC® provides clinical recommendations for select NSAIDs

Ann Pharmacother. 2021; 55(12): 1486-1501. I *Clin Pharmacol Ther.* 2020; 108(2): 191-200 I *Pharmacogenomics.* 2021; 22(14): 927-937. I *Pharmacogenomics Pers Med.* 2019; 12: 125-143.

80

Recommendations for Celecoxib, Flurbiprofen, and Ibuprofen Based on CYP2C9 Phenotype

Metabolism	Implication	Therapeutic recommendation	Other considerations
Normal	Normal metabolism	Initiate therapy with recommended starting dose	
Intermediate AS of 1.5	Mildly reduced metabolism		May have higher than normal risk of ADEs
Intermediate AS of 1	Moderately reduced metabolism	Initiate therapy with lowest recommended starting dose, titrate with caution, and monitor for ADEs	May have higher than normal risk of ADEs
Poor	Significantly reduced metabolism	Initiate therapy with 25-50% of lowest recommended starting dose; titrate to effect or 25-50% of maximum recommended dose	Consider alternative therapies not metabolized by CYP2C9

*AS = activity score, ADEs = adverse events

Clin Pharmacol Ther. 2020; 108(2): 191-200.

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Recommendations for Meloxicam Based on CYP2C9 Phenotype

Metabolism	Implication	Therapeutic recommendation	Other considerations
Normal	Normal metabolism	Initiate therapy with recommended starting dose	
Intermediate AS of 1.5	Mildly reduced metabolism		May have a higher than normal risk of ADEs
Intermediate AS of 1	Moderately reduced metabolism	Initiate therapy with 50% of lowest recommended starting dose; titrate up to clinical effect or 50% of maximum recommended dose	May have a higher than normal risk of ADEs
Poor	Significantly reduced metabolism	Choose alternative therapy not metabolized by CYP2C9	

*AS = activity score, ADEs = adverse events

Clin Pharmacol Ther. 2020; 108(2): 191-200.

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Recommendations for Piroxicam Based on CYP2C9 Phenotype

Metabolism	Implication	Therapeutic recommendation	Other considerations
Normal	Normal metabolism	Initiate therapy with recommended starting dose	
Intermediate AS of 1.5	Mildly reduced metabolism		May have a higher than normal risk of ADEs
Intermediate AS of 1	Moderately reduced metabolism	Choose alternative therapy not metabolized by CYP2C9	
Poor	Significantly reduced metabolism		

*AS = activity score, ADEs = adverse events

Clin Pharmacol Ther. 2020; 108(2): 191-200.

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Recommendations Based on CYP2C9 Phenotype

- Increased risk with
  - **Hepatic dysfunction or advanced age**
  - Patients co-prescribed **warfarin**
- Alternative NSAIDs that are **not primarily metabolized by CYP2C9**
  - Aspirin, ketorolac, and naproxen

Ann Pharmacother. 2021; 55(12): 1486-1501. | *Case Rep Med.* 2023; 6623269. | *Clin Pharmacol Ther.* 2020; 108(2): 191-200.

84

Opioids

85

Pharmacogenomic Considerations

- Mu, kappa, and delta opioid receptors
  - Analgesia, physical dependence, reward effects
- ***OPRM1* codes for mu-1 opioid receptor,** primary site of action for opioids
  - Over 100 polymorphisms
    - Decrease analgesic response and increase opioid requirements
    - Increase risk of opioid use disorder

Clin Pharmacol Ther. 2021; 110(4): 888-896. I *Drug Metab Pers Ther*. 2016; 31(3): 131-142. I *Pharmacogenomics*. 2021; 22(5): 275-290

86

Pharmacogenomic Considerations

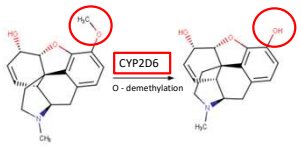
- **Catechol-O-methyltransferase (COMT)** responsible for conjugation of catecholamines, **key regulator of pain perception and opioid response**
  - Alteration in enzyme expression associated with changes in pain sensitivity
  - May alter opioid requirements

Clin Pharmacol Ther. 2021; 110(4): 888-896. I *Drug Metab Pers Ther*. 2016; 31(3):131-142. I *J Pain Res*. 2016; 9: 49-56. I *Pharmacogenomics*. 2021; 22(14): 927-937.

87

Pharmacogenomic Considerations

- **Hepatic metabolism primarily by CYP3A, CYP2B6, and CYP2D6**
- CYP2D6 involved in metabolism of tramadol, codeine, hydrocodone, oxycodone, and methadone



hydrocodone hydromorphone

Clin Pharmacol Ther. 2021; 110(4): 888-896. *J Pharmaco Exp Ther*. 2023; 387(2):150-169.

88

Recommendations for Codeine and Tramadol Based on CYP2D6 Phenotype

Metabolism	Implication	Therapeutic recommendation
Ultra-rapid AS > 2.25	Increased formation of active metabolite, higher risk of toxicity	Avoid codeine and tramadol opioids
Normal AS 1.25 ≤ x ≤ 2.25	Expected active metabolite formation	Initiate therapy with recommended starting dose
Intermediate AS 0 ≤ x ≤ 1.25	Reduced active metabolite formation	Initiate therapy with recommended starting dose, if no response consider non-tramadol/non-codeine opioid
Poor AS 0	Significantly reduced active metabolite, decreased pain control	Avoid codeine and tramadol use, if opioid use is warranted consider non-tramadol/non-codeine opioid

AS = Activity Score

Codeine active metabolite = morphine
Tramadol active metabolite = O-desmethyltramadol

Clin Pharmacol Ther. 2021; 110(4): 888-896.

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Recommendations for Codeine and Tramadol Based on CYP2D6 Phenotype

Metabolism	Implication	Therapeutic recommendation
Ultra-rapid AS > 2.25	Increased formation of active metabolite, higher risk of toxicity	Avoid codeine and tramadol opioids
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Poor AS 0	Significantly reduced active metabolite, decreased pain control	Avoid codeine and tramadol use, if opioid use is warranted consider non-tramadol/non-codeine opioid

AS = Activity Score

Codeine active metabolite = morphine
Tramadol active metabolite = O-desmethyltramadol

Clin Pharmacol Ther. 2021; 110(4): 888-896.

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Hydrocodone

- Primarily metabolized by **CYP2D6 to hydromorphone**
  - Active metabolite with greater affinity for mu opioid receptor
- CPIC® recommendation for hydrocodone
  - **Consider use of opioid not metabolized by CYP2D6 in intermediate and poor metabolizers with poor analgesic response to hydrocodone**

Clin Pharmacol Ther. 2021; 110(4): 888-896. I *Pharmacogenomics.* 2021; 22(14): 927-937. I *Pharmacogenomics Pers Med.* 2019; 12: 125-143.

91

Pharmacogenomics in Literature

Impact on Hydrocodone Response

- Monte *et al.* studied impact of CYP2D6 drug-drug interactions (DDI) on hydrocodone efficacy
- **DDIs that reduced CYP2D6 were 1/3 as likely to respond to hydrocodone**

Individualized Hydrocodone Dosing

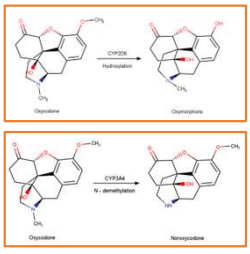
- Linares *et al.* studied CYP2D6 metabolism of hydrocodone
- CYP2D6 poor metabolizers had decreased hydromorphone formation compared with ultra-rapid and normal metabolizers
- **Developed patient specific dosing recommendations**

Acad Emerg Med. 2014; 21(8): 879-885. I *Clin J Pain.* 2015; 31(12): 1026-1035.

92

Oxycodone

- Metabolized by CYP2D6 to oxymorphone
  - Active metabolite with greater affinity for the mu opioid receptor
- Primarily inactived by CYP3A4 to noroxycodone
- CPIC® does not provide clinical recommendations
  - **Evidence for clinical effect of genetic polymorphisms is conflicting**



Ann Pharmcother. 2021; 55(12): 1486-1501. I *Clin Pharmacol Ther.* 2021; 110(4): 888-896. I *Pharmacogenomics.* 2021; 22(5): 275-290. I *Pharmacogenomics Pers Med.* 2019; 12: 125-143.

93

Impact of CYP2D6 Phenotype on Oxycodone

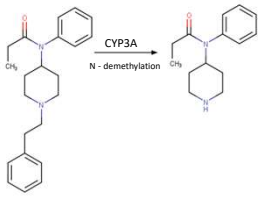
Zwisler *et al.* (2009)	i. Poor metabolizers had an increase in pain tolerance thresholds ii. Plasma oxymorphone/oxycodone ratio was lower in poor metabolizers compared to normal metabolizers
Samer *et al.* (2010)	i. Ultra-rapid metabolizers experienced increased pain tolerance thresholds ii. Inverse relation between activity and sedation
Andreassen *et al.* (2012)	i. Significant increase in serum concentrations of oxymorphone and noroxymorphone from poor metabolizers to normal metabolizers and from poor metabolizers to ultra-rapid metabolizers ii. No difference between the groups with regard to pain, tiredness and nausea
Naito *et al.* (2013)	Oxymorphone trough concentrations were higher in normal metabolizers than in intermediate metabolizers but did not affect dose escalation
Dagostino *et al.* (2018)	i. Poor and intermediate metabolizers were associated with therapeutic failure in chronic lower back pain compared ii. Ultra-rapid metabolizers had an increased risk of side effects

Pharmacogenomics. 2021; 22(5): 275-290.

94

Fentanyl

- Primarily metabolized by CYP3A4 and CYP3A5
- Clinical impact or differences in side effect of changes in plasma concentration have not been demonstrated
  - Most data involves postoperative populations



fentanyl norfentanyl

Pharmacogenetics Genom.2020; 30(1): 5-8. / *Pharmacogenomics Pers Med*. 2019; 12: 125-143.

95

Pharmacogenomics in Literature

Impact on Fentanyl Efficacy

- Zhang, Fan *et al.* assessed the impact of **COMT (transporter involved in pain response) polymorphisms**
  - Patients with ACCG polymorphisms required **significantly more fentanyl** post surgery
  - No difference was seen in rates of nausea, vomiting, or dizziness
- Zhang, Jingliang *et al.* assessed the impact of CYP3A4 and OPRM1 (opioid receptor) polymorphisms
  - Decreased CYP3A4 metabolism required **significantly less fentanyl** for pain control
  - OPRM1 with the A118G, GG polymorphism **required significantly more fentanyl**
  - No difference in adverse effects

Anesth Analg. 2015; 120(4): 933-940. / *Gene*. 2018. 661: 78-84.

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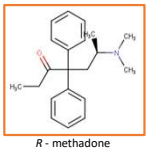
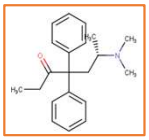
Methadone

- Agonist at mu, kappa, and delta opioid receptors; antagonist at NMDA receptor
  - R-enantiomer responsible for analgesia
  - S-enantiomer responsible for side-effects
- Primary metabolism for both isomers
  - 3A4/5
  - 2B6
  - 2C9/2C19
  - 2D6



R - methadone



S - methadone

Ann Pharmacother. 2021; 55(12): 1486-1501. | *Clin Pharmacol Ther.* 2021; 110(4): 888-896. | *Pharmacogenomics.* 2020; 21(12):871-887.

97

Methadone

- Evidence for impact of single gene-polymorphisms is weak
- OPRM1 polymorphisms, have been associated with opiate dose requirements and analgesic effect
  - Evidence for impact on methadone has been mixed

Basn J Basic Med Sci. 2021; 21(2):145-154. | *Pharmacogenomics.* 2020; 21(12):871-887.

98

Buprenorphine

- Synthetic opioid metabolized by CYP3A4
- **Available data primarily for use in opioid use disorder**
  - Patients with CYP3A4 normal or ultra-rapid metabolizers may require higher doses of buprenorphine to prevent withdrawal
    - Association between metabolizer status and success in opioid dependence treatment
  - Alterations in the OPRD1 (opioid receptor) have been associated with variable response to treatment

Ann Pharmacother. 2021; 55(12): 1486-1501. | *Pharmacogenomics J.* 2020; 21: 128-139. | *Pharmacogenomics Pers Med.* 2019; 12: 125-143.

99

Antidepressants

Selective-serotonin reuptake inhibitors (SSRIs)
Serotonin and norepinephrine reuptake inhibitors (SNRIs)
Tricyclic Antidepressants (TCAs)

100

Pharmacogenomic Considerations

- **SLC6A4** encodes for the serotonin transporter (5-HTT)
  - The polymorphism rs25531A>G results in greater serotonin reuptake
- **HTR2A** encodes for the pre-synaptic serotonin receptor (5-HT2A)
  - The rs6311A>G and rs6313C>T polymorphisms are associated with decreased HTR2A expression
  - Associated with severity of depression symptoms
- Data supporting these associations are currently mixed and insufficient to provide clinical recommendations

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Pharmacogenomic Considerations

- Patients may be predisposed to poor therapeutic outcomes due to polymorphisms in CYP2D6, CYP2C19, or CYP2B6
  - Fluvoxamine, **paroxetine**, **venlafaxine**, and vortioxetine are extensivity metabolized by **CYP2D6**
  - **Citalopram**, **escitalopram**, and **sertraline** are extensively metabolized by **CYP2C19**
    - **Sertraline** is also metabolized by **CYP2B6**
- Data support the use of CYP2D6 or CYP2C19 to guide the use and dosing of some antidepressants

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations

- Guideline recommendations for efficacy are based on trials of **antidepressant effect** and risk of adverse effects
  - Pharmacogenomic data do not address analgesic effect

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Paroxetine Based on CYP2D6 Phenotype

Metabolism	Implication	Therapeutic recommendation	Other considerations
Ultra-rapid	Increased metabolism	Select alternative drug not predominantly metabolized by CYP2D6	
Normal	Normal metabolism	Initiate therapy with recommended starting dose	
Intermediate	Reduced metabolism	Consider a lower starting dose and slower titrations schedule	Conversion to poor metabolizer status due to CYP2D6 autoinhibition
Poor	Significantly reduced metabolism	Consider a 50% reduction in recommended starting dose, slower titration schedule, and a 50% lower maintenance dose	Increased risk of side-effects

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Paroxetine Based on CYP2D6 Phenotype

Metabolism	Implication	Therapeutic recommendation	Other considerations
Ultra-rapid	Increased metabolism	Select alternative drug not predominantly metabolized by CYP2D6	
Normal	Normal metabolism	Initiate therapy with recommended starting dose	
Intermediate	Reduced metabolism	Consider a lower starting dose and slower titrations schedule	Conversion to poor metabolizers due to CYP2D6 autoinhibition may occur
Poor	Significantly reduced metabolism	Consider a 50% reduction in recommended starting dose, slower titration schedule, and a 50% lower maintenance dose	Increased risk of side-effects

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Fluvoxamine Based on CYP2D6 Phenotype

Metabolism	Implication	Therapeutic recommendation
Ultra-rapid	No data available	No recommendation due to lack of evidence
Normal	Normal metabolism	Initiate therapy with recommended starting dose
Intermediate	Reduced metabolism	
Poor	Significantly reduced metabolism	Consider a 25-50% lower starting dose and slower titration schedule or consider alternative therapy

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Venlafaxine Based on CYP2D6 Phenotype

Metabolism	Implication	Therapeutic recommendation	Other considerations
Ultra-rapid	Increased activation	No action recommended based on genotype due to minimal evidence regarding impact on efficacy and side effects	
Normal	Normal metabolism	Initiate therapy with recommended starting dose	
Intermediate	Decreased activation	No action recommended based on genotype due to minimal evidence regarding impact on efficacy and side effects	
Poor	Decreased activation	Consider a clinically appropriate alternative	Impact on efficacy is unclear but poor metabolizer status is associated with increased risk of side-effects

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Venlafaxine Based on CYP2D6 Phenotype

Metabolism	Implication	Therapeutic recommendation	Other considerations
Ultra-rapid	Increased activation	No action recommended based on genotype due to minimal evidence regarding impact on efficacy and side effects	
Normal	Normal metabolism	Initiate therapy with recommended starting dose	
Intermediate	Decreased activation	No action recommended based on genotype due to minimal evidence regarding impact on efficacy and side effects	
Poor	Decreased activation	Consider a clinically appropriate alternative	Impact on efficacy is unclear but poor metabolizer status is associated with increased risk of side-effects

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Venlafaxine Based on CYP2D6 Phenotype

Metabolism	Implication	Therapeutic recommendation	Other considerations
Ultra-rapid	Increased activation	No ac… minim… effect…	…to …d side
Normal	Normal metabolism	Initiat…	
Intermediate	Decreased activation	No ac… minim… effect…	…to …d side
Poor	Decreased activation	Consi…	Impact on efficacy is unclear but poor metabolizer status is associated with increased risk of side-effects

The Dutch Pharmacogenetics Working Group (DPWG) recommends avoiding venlafaxine in patients who are CYP2D6 poor or intermediate metabolizers

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Citalopram and Escitalopram Based on CYP2C19 Phenotype

Metabolism	Implication	Therapeutic recommendation	Other considerations
Ultra-rapid	Increased metabolism	Consider therapeutic alternative, may consider titrating to higher maintenance dose	
Rapid	Increased metabolism	Initiate at recommended starting dose, consider alternative therapy if patient does not have adequate response	
Normal	Normal metabolism	Initiate with recommended starting dose	
Intermediate	Reduced metabolism	Initiate with recommended starting dose, consider slower titration schedule and lower maintenance dose	
Likely Intermediate	Reduced metabolism		
Poor	Reduced metabolism	Consider therapeutic alternative, may consider a lower starting dose, slower titration, and a 50% reduction in maintenance dose	Due to risk of QTc prolongation: 20mg/day is the maximum FDA recommended dose in poor metabolizers

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Citalopram and Escitalopram Based on CYP2C19 Phenotype

Metabolism	Implication	Therapeutic recommendation	Other considerations
Ultra-rapid	Increased metabolism	Consider therapeutic alternative, may consider titrating to higher maintenance dose	
Rapid	Increased metabolism	Initiate at recommended starting dose, consider alternative therapy if patient does not have adequate response	
Normal	Normal metabolism	Initiate with recommended starting dose	
Intermediate	Reduced metabolism	Initiate with recommended starting dose, consider slower titration schedule and lower maintenance dose	
Likely Intermediate	Reduced metabolism		
Poor	Reduced metabolism	Consider therapeutic alternative, may consider a lower starting dose, slower titration, and a 50% reduction in maintenance dose	Due to risk of QTc prolongation: 20mg/day is the maximum FDA recommended dose in poor metabolizers

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Citalopram and Escitalopram Based on CYP2C19 Phenotype

Metabolism	Implication	Therapeutic recommendation	Other considerations
Ultra-rapid	Increased metabolism	Consider t… …YP2C19, may consi…	
Rapid	Increased metabolism	Initiate at … therapy if … …native	
Normal	Normal metabolism	Initiate wit…	
Intermediate	Reduced metabolism	Initiate wit… titration sc… …wer	
Likely Intermediate	Reduced metabolism		
Poor	Reduced metabolism	Consider t… …ower starting dose, slower titration, and a 50% reduction in maintenance dose	Due to risk of QTc prolongation: 20mg/day is the maximum FDA recommended dose in poor metabolizers

FDA product labeling also recommends a maximum dose of 20mg/day in patients taking a CYP2C19 inhibitor

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Sertraline Based on CYP2C19 Phenotype

Metabolism	Implication	Therapeutic recommendation
Ultra-rapid	Slightly increased metabolism	Initiate therapy with recommended starting dose
Rapid	Slightly increased metabolism	
Normal	Normal metabolism	
Intermediate	Reduced metabolism	Initiate therapy with recommended starting dose, consider slower titration and lower maintenance dose
Likely Intermediate	Reduced metabolism	
Likely Poor	Significantly reduced metabolism	Consider a lower starting dose, slower titration schedule, and a 50% reduction in standard maintenance dose or select a therapeutic alternative
Poor	Significantly reduced metabolism	

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Sertraline Based on CYP2B6 Phenotype

Metabolism	Implication	Therapeutic recommendation
Ultra-rapid	Increased metabolism	Initiate therapy with recommended starting dose
Rapid	Slightly increased metabolism	
Normal	Normal metabolism	
Intermediate	Reduced metabolism	Initiate therapy with recommended starting dose, consider slower titration and lower maintenance dose
Poor	Significantly reduced metabolism	Consider lower starting dose, slower titration, and 25% reduction of standard maintenance dose or select a therapeutic alternative

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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Recommendations for Sertraline Based on CYP2B6 and CYP2C19 Phenotype

METABOLISM	CYP2B6 Ultra-rapid or Rapid	CYP2B6 Normal	CYP2B6 Intermediate	CYP2B6 Poor
CYP2C19 Ultra-rapid or Rapid	Initiate at recommended starting dose			
CYP2C19 Normal	Initiate at recommended starting dose		Initiate at recommended starting dose, slower titration, and lower maintenance dose	Consider lower starting dose, slower titration, 25% of maintenance dose
CYP2C19 Intermediate or Likely Intermediate	Initiate at recommended starting dose	Initiate at recommended starting dose, slower titration, and lower maintenance dose	Consider lower starting dose, slower titration, and lower maintenance dose	Consider lower starting dose, slower titration, 25% of maintenance dose
CYP2C19 Poor or Likely Poor	Consider lower starting dose, slower titration, 50% of maintenance dose	Consider lower starting dose, slower titration, 50% of maintenance dose	Consider lower starting dose, slower titration, 50% of maintenance dose	Select an alternative antidepressant not metabolized by 2C19 and 2B6

Clin Pharmacol Ther. 2023; 114(1): 51-68.

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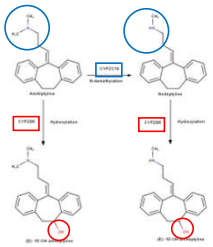
Tricyclic Antidepressants (TCAs)

- Mechanism of analgesia is mixed serotonin and norepinephrine reuptake inhibition
- Metabolism by CYP enzymes
  - **Tertiary amines are metabolized by CYP2C19 to secondary amines**
  - **Secondary amines are metabolized by CYP2D6** to less-active metabolites



Ann Pharmacother. 2021; 55(12): 1486-1501. I *Clin Trans Sci.* 2017; 10(2): 93-101. I *Pharmacogenomics.* 2021; 22(14): 927-937.

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Recommendations for TCAs

- CPIP® provides **recommendations for TCAs based on CYP2D6 and CYP2C19 phenotype**
- FDA labeling for amitriptyline, desipramine, imipramine, nortriptyline, and protriptyline warns that **CYP2D6 poor metabolizers** may have higher than expected plasma concentrations
  - May have increased risk of adverse effects
  - FDA labeling does not discuss CYP2C19

Ann Pharmacother. 2021; 55(12): 1486-1501. I *Clin Pharmacol Ther.* 2017; 102(1): 37-44. I *Pharmacogenomics.* 2021; 22(14): 927-937.

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Recommendations for TCAs

- Most data comes from studies of depression
- **Dosing for pain is frequently lower** than doses used for depression
  - As doses are lower the risk of adverse events is decreased
  - CPIC® **does not** recommend dose adjustments for CYP2C19 and CYP2D6 poor and intermediate metabolizers if using TCAs at a lower dose

Ann Pharmacother. 2021; 55(12): 1486-1501. I *Clin Pharmacol Ther.* 2017; 102(1): 37-44. I *Pharmacogenomics.* 2021; 22(14): 927-937.

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Pharmacogenomics in Literature

Impact of Dosing on Adverse Effects

- Halling *et al.* assessed impact of CYP2D6 polymorphisms on amitriptyline
  - 23 patients were given amitriptyline 5mg to 100mg per day
  - When using low doses (used for pain) poor metabolizers **were not at an increased risk of side-effects** compared to normal metabolizers

Brit J Clin Pharmco. 2007; 65(1): 134-138.

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Anticonvulsants

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Pharmacogenomic Considerations

- Recommendations for carbamazepine and oxcarbazepine
  - Risk of adverse effects, specifically Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are associated with the presence of HLA-B*15:02 and HLA-A*31:01
    - Human leukocyte antigens (HLAs)
- Guidelines
  - **FDA warning for use of carbamazepine in patients with HLA-B*15:02**
  - CPIC® provides recommendations for carbamazepine and oxcarbazepine

Ann Pharmacother. 2021; 55(12): 1486-1501. | *Clin Pharmacol Ther*. 2018; 103(4): 574-581.

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Recommendations for Carbamazepine Based on HLA-A and HLA-B Genotypes

Genotype	Implication	Therapeutic recommendation
HLA-B*15:02 negative and HLA-A*31:01 negative	Normal risk of ADEs	Use carbamazepine per standard dosing guidelines
HLA-B*15:02 negative and HLA-A*31:01 positive	Greater risk of ADEs	If patient is carbamazepine-naïve, do not use carbamazepine
HLA-B*15:02 positive and any HLA-A*31:01 genotype (or genotype unknown)	Greater risk of ADEs	If patient is carbamazepine-naïve, do not use carbamazepine

ADEs = adverse effects

Recommendations provide guidance to reduce the risk of carbamazepine-induced cutaneous reactions including
- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Maculopapular exanthema (MPE)

Clin Pharmacol Ther. 2018; 103(4): 574-581.

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Recommendations for Oxcarbazepine Based on HLA-B Genotype

Genotype	Implication	Therapeutic recommendation
HLA-B*15:02 negative	Normal risk of ADEs	Use oxcarbazepine per standard dosing guidelines
HLA-B*15:02 positive	Greater risk of ADEs	If patient is oxcarbazepine naïve and alternative agents are available, do not use oxcarbazepine

ADEs = adverse effects

Recommendations provide guidance to reduce the risk of carbamazepine-induced cutaneous reactions including
- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)

Clin Pharmacol Ther. 2018; 103(4): 574-581.

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Summary of Key Points

- Extensive evidence for impact of pharmacogenomics on pain and analgesic response exists
- The Clinical Pharmacogenetics Implementation Consortium (CPIC®) and Food and Drug Administration (FDA) provide clinical recommendations for select analgesics
- Further data and clinical trials emphasizing clinical outcomes are needed

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Self Assessment Question #2

True or False: A patient who is a CYP2D6 poor-metabolizer may experience toxicity from use of codeine

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Self Assessment Question #2

True or **False**: A patient who is a CYP2D6 poor-metabolizer may experience toxicity from use of codeine

Patients who are poor metabolizers should avoid codeine due to lack of efficacy due to reduced morphine formation

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Pain Stewardship

The Role of the Pharmacist

127

Learning Objectives

- Evaluate evidence-based recommendations for a patient-specific approach to pain stewardship
- Describe potential responsibilities and opportunities for pharmacist intervention in a comprehensive approach to pain stewardship

128

Need for Stewardship

- Chronic pain is one of the **most common reasons** for patients to seek medical attention
  - **1 in 3 Americans** experience chronic pain
    - Associated with mental health issues
    - Disproportionately impacts women, indigenous peoples, older adults, veterans, and people who abuse substances

Am J Health-Syst Pharm. 2019; 76(1): 17-25. I *Br J Clin Pharmacol.* 2021; 87: 3028-3042. I *Drug Metab Pers Ther.* 2016; 31(3): 131-142.

129

Need for Stewardship

- Healthcare Costs
- Lost Productivity
- Quality of Life
- Costs of Misuse
- Overdose and Mortality

Am J Health-Syst Pharm 2019; 76(1): 17-25. *J Pharmacogenomics Pers Med.* 2019; 12: 125-143.

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Role of the Pharmacist

- Pharmacists have up to **10 times the patient interaction** of other healthcare providers
- Pain management is multidisciplinary, **pharmacists can help bridge the gap between services**

Am J Health-Syst Pharm. 2013; 70: 2070-2075.

131

VA Stepped Care Model of Pain Care with Pain Management Clinical Pharmacist Practitioner Integration

Foundational: Patient/ Family/ Caregiver Learning and Self-Care

- **Nutrition/weight management**
- Exercise and stretching
- **Sufficient sleep**
- Mindfulness meditation/ relaxation techniques
- Engagement in meaningful activities; Family and social support
- Safe environment and surroundings

"To Clinical Pharmacist Practitioner (CPP) Role in Pain Management Fact Sheet." *Clinical Pharmacy Practice Office.* 2022.

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VA Stepped Care Model of Pain Care with Pain Management Clinical Pharmacist Practitioner Integration

Patient Aligned Care Team (PACT) in Primary Care

- Assessment and management of common pain conditions
- **Mental Health Integration includes brief CBT for pain**
- **Assessment and treatment of OUD**
- Physical therapy; Occupational therapy; Kinesiotherapy
- **Pharmacy pain care clinics**
- **Pain schools**
- **Integrative Health/CIH modalities including Battlefield Acupuncture**
- Whole health coaches
- Peers

"To Clinical Pharmacist Practitioner (CPP) Role in Pain Management Fact Sheet." *Clinical Pharmacy Practice Office*. 2022.

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VA Stepped Care Model of Pain Care with Pain Management Clinical Pharmacist Practitioner Integration

Secondary, Specialty Care

- **Interdisciplinary pain management clinics and teams**
- **Interdisciplinary pain rehabilitation program**
- **Functional restoration program**
- Behavioral Pain Management
- Rehabilitation Medicine
- **Mental Health/Substance Use Disorder Programs**

"To Clinical Pharmacist Practitioner (CPP) Role in Pain Management Fact Sheet." *Clinical Pharmacy Practice Office*. 2022.

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VA Stepped Care Model of Pain Care with Pain Management Clinical Pharmacist Practitioner Integration

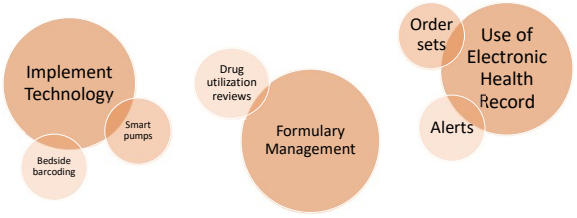
Tertiary, Interdisciplinary Pain Centers

- Advanced diagnostics and therapeutic interventions
- **Interdisciplinary pain centers**

"To Clinical Pharmacist Practitioner (CPP) Role in Pain Management Fact Sheet." *Clinical Pharmacy Practice Office*. 2022.

135

System-Wide Activities to Target Opioid Use



Am J Health-Syst Pharm. 2013; 70: 2070-2075. | *Am J Health-Syst Pharm.* 2019; 76(10): 17-25. | *Br J Clin Pharmacol.* 2021; 87: 3028-3042. | "To Clinical Pharmacist Practitioner (CPP) Role in Pain Management Fact Sheet." *Clinical Pharmacy Practice Office.* 2022.

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System-wide Activities to Target Opioid Use

- The **Comprehensive Addiction and Recovery Act (CARA)** of 2016 provides congressional requirements
  - Expanded VA Opioid Safety Initiative
  - VA pharmacists may **autonomously prescribe and monitor controlled substances for pain management** and in treatment of opioid use disorder
    - Data show pharmacists contribute to improved pain management **team efficiency, patient engagement, and patient satisfaction**

"To Clinical Pharmacist Practitioner (CPP) Role in Pain Management Fact Sheet." *Clinical Pharmacy Practice Office.* 2022.

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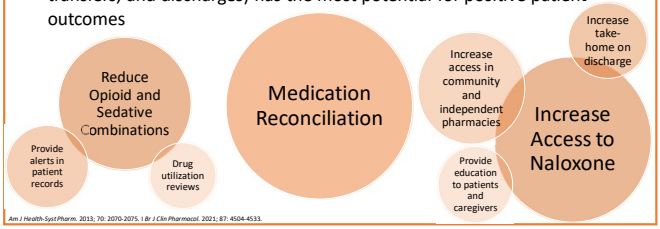
Involvement in Transitions of Care

- Pharmacist involvement during all transitions of care (admissions, transfers, and discharges) has the most potential for positive patient outcomes



Am J Health-Syst Pharm. 2013; 70: 2070-2075. | *Br J Clin Pharmacol.* 2021; 87: 4504-4533.

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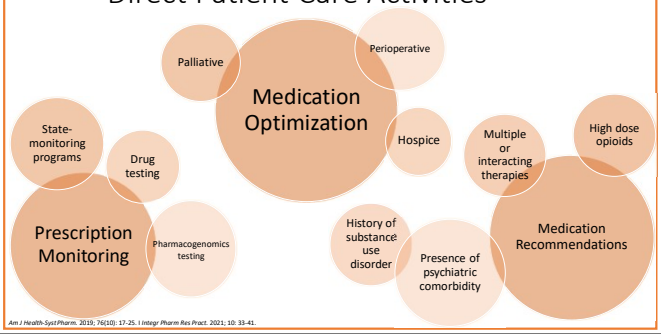
Direct Patient Care Activities



Am J Health-Syst Pharm. 2019; 76(10): 17-25. *J Integr Pharm Res Pract.* 2021; 10: 33-41.

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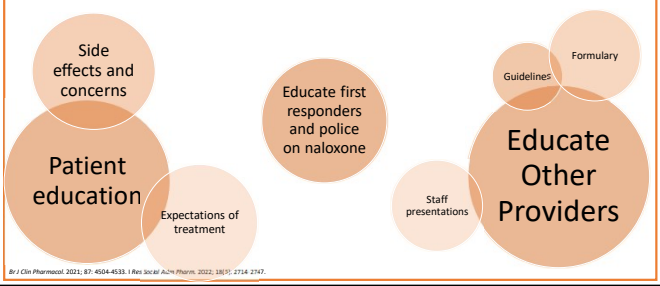
Education



Br J Clin Pharmacol. 2021; 87: 4504-4533. *J Res Social Adm Pharm.* 2022; 18(9): 2714-2747.

140

Pharmacogenomics in Literature

Evidence of Benefit

- Poirier *et al.* assessed impact of a 3-pharmacist pain-management team
  - Consult-based and stewardship functions
- **Improved patient satisfaction and indirect cost savings**
  - Decreased total institutional opioid use
  - Significantly decreased use of high-risk medications (e.g., parenteral hydromorphone, fentanyl, and transdermal fentanyl patches)
  - Increased use of non-opioid analgesics and adjunctive therapy
  - Decreased rapid response team and code blue events associated with opioid therapy

Am J Health Syst Pharm. 2019; 76(1): 17-25.

141

Future Directions

- Involvement of pharmacists in patient centered care
  - Address stigma and diversity
- Impact in areas with decreased access to care
  - Rural and inner-city areas

Integr Pharm Res Pract. 2021; 10: 33-41. ǀ *Res Social Adm Pharm.* 2022; 18(5): 2714-2747.

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Summary of Key Points

- Pharmacists can play an integral role in the management of opioids and other analgesics
- There are numerous ways pharmacists can contribute to pain stewardship
  - Including roles in direct-patient care, system management, and education

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Self Assessment Question #3

True or False: Chronic pain disproportionately impacts women, indigenous peoples, older adults, veterans, and people who abuse substance

144

Self Assessment Question #3

True or False: Chronic pain disproportionately impacts women, indigenous peoples, older adults, veterans, and people who abuse substances

145

Don't Think Too Hard

Managing Headaches and Migraines

Brittany Picardi, PharmD
Baptist Health - Boca Raton Regional Hospital
January 21, 2024

28 Years Featuring
South Florida Pharmacy Residents

1

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Disclosures

- The author of this presentation has nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interests in the subject matter of this presentation

2

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Abbreviations

- ACEi – Angiotensin-converting enzyme inhibitor
- ADR – Adverse drug reaction
- ARB – Angiotensin receptor blocker
- BCRP – Breast cancer resistance protein
- BP – Blood pressure
- CGRP – Calcitonin gene-related peptide
- CGRP(r)mAbs – Calcitonin gene-related peptide (receptor) monoclonal antibodies
- CNS – Central nervous system
- CrCl – Creatinine clearance
- DoD – Department of Defense
- ESRD – End stage renal disease
- GI – Gastrointestinal
- HR – Heart rate
- ICHD – International Classification of Headache Disorders
- IM – Intramuscular
- IV – Intravenous
- MAO-I – Monoamine oxidase inhibitor
- MOA – Mechanism of action
- NSAIDs – Nonsteroidal anti-inflammatory drugs
- NTCP – sodium taurocholate co-transporting polypeptide
- OATP – Organic-anion-transporting peptides
- ODT – Oral disintegrating tablet
- OTC – Over the counter
- P-gp – P-glycoprotein
- SubQ – Subcutaneous
- VA – Veterans Affairs

3

Generic – Brand Medication Names

- Almotriptan – Axert®
- Eletriptan – Replax®
- Frovatriptan – Frova®
- Naratriptan – Amerge®
- Rizatriptan – Maxalt®
- Zolmatriptan - Zomig®
- Sumatriptan – Imitrex®
- Lasmiditan – Reyvow®
- Atogepant – Qulipta®
- Rimegepant – Nurtec®
- Ubrogepant – Ubrelvy™
- Zavegepant – Zavzpret™
- Eptinezumab – Vyepti™
- Fremanezumab – Ajovy®
- Galcanezumab – Emgality®
- Erenumab – Aimovig®

4

4

Objectives

- Differentiate between the different types of headaches based on patient history and presenting signs and symptoms
- Identify non-pharmacologic and pharmacologic treatment strategies for the treatment and prevention of headache and migraine
- Discuss clinical pearls regarding pharmaceutical treatment options for headache and migraine

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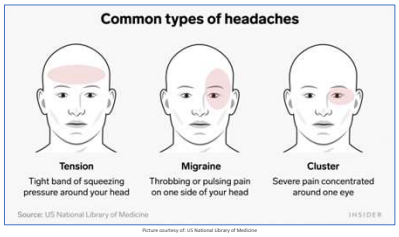
Background

6

6

Primary Headache

- No underlying cause
- Three common types
  - Tension-type
  - Migraine
  - Cluster
- Episodic headaches
  - < 15 days per month
- Chronic headaches
  - ≥ 15 days per month



Picture courtesy of: US National Library of Medicine

Am Fam Physician. 2021;104(3):316-320.

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Characteristics of Primary Headaches

Symptom	Migraine	Tension-Type	Cluster
Location	Unilateral	Typically bilateral	Always unilateral, begins around the temple or eye
Characteristics	Gradual onset, crescendo pattern, pulsating, aggravated by routine activity	Pressure or tightness, waxing and waning intensity	Pain begins quickly, reaching maximal intensity in minutes; deep, constant, excruciating, explosive
Duration	4 to 72 hours	30 minutes to 7 days	15 minutes to 3 hours
Associated symptoms	Nausea, vomiting, photophobia, phonophobia; may have aura	None	Lacrimation and redness to eye, nasal congestion or rhinorrhea, diaphoresis, restlessness

StatPearls. Acute Headache. Jan 2023.

8

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Secondary Headache

- Always have underlying cause that requires medical attention
- Utilize $SNOOP_{10}$ to identify features of secondary headache

Sign or Symptom	Related Secondary Headaches (most relevant ICHD-3b categories)
Systemic symptoms including fever	Headache attributed to infection or nonvascular intracranial disorders, carcinoid or pheochromocytoma
Neoplasm in history	Neoplasms of brain; metastasis
Neurologic deficit or dysfunction (including decreased consciousness)	Headaches attributed to vascular, nonvascular intracranial disorders; brain abscess and other infections
Onset of headache is sudden or abrupt (Thunderclap)	Subarachnoid hemorrhage and other headaches attributed to cranial or cervical vascular disorders
Older age (after 50 years)	Giant cell arteritis and other headache attributed to cranial or cervical vascular disorders; neoplasms and other nonvascular intracranial disorders
Pattern change or recent onset of headache	Neoplasms, headaches attributed to vascular, nonvascular intracranial disorders
Positional headache	Intracranial hypertension or hypotension
Precipitated by sneezing, coughing, or exercise	Posterior fossa malformations; Chiari malformation
Papilledema	Neoplasms and other nonvascular intracranial disorders; intracranial hypertension
Progressive headache and atypical presentations	Neoplasms and other nonvascular intracranial disorders
Pregnancy or puerperium	Headaches attributed to cranial or cervical vascular disorders; postdural puncture headache; hypertension-related disorders; cerebral sinus thrombosis; hypothyroidism; anemia; diabetes
Painful eye with autonomic features	Pathology in posterior fossa, pituitary region, or cavernous sinus; Tolosa-Hunt syndrome; ophthalmic causes
Posttraumatic onset of headache	Acute and chronic posttraumatic headache; subdural hematoma and other headache attributed to vascular disorder
Pathology of the immune system such as HIV	Opportunistic infections
Painkiller overuse or new drug at onset of headache	Medication overuse headache; drug incompatibility

Neurology. SNOOP10 list. 2019;92(3):134-144.

9

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Neurology. SNOOP10 Int. 2019;92(3):134-144.

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11

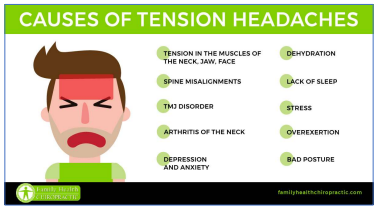
Pathophysiology

12

12

Pathophysiology of Tension-Type Headache

- Remains poorly understood
- May involve:
  - Increased sensitivity of central and peripheral pain receptors
  - Genetic and environmental factors
  - Muscle contractions in head and neck
- Triggered by stress, emotions, or busy days



Picture courtesy of: Family Health Chiropractic

Ann Indian Acad Neurol. 2012;15(Suppl 1):S83-S88.

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13

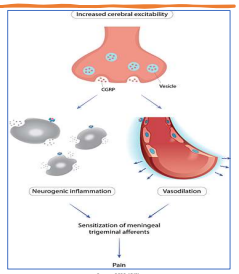
Pathophysiology of Migraine Headache

Neurogenic inflammation

- Release of substance P, CGRP, and neurokinin-A by trigeminal ganglion stimulation

Serotonin levels

- Deficiency in serotonin pain inhibition system, leading to activation of trigeminal system



Cureus. 2023 15(2):

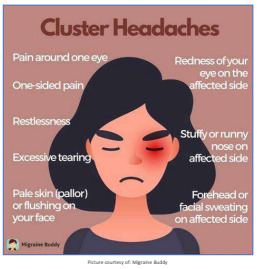
Cureus. 2023;15(2):e34553.

14

14

Pathophysiology of Cluster Headache

- No clear cause of cluster headaches
- Possible abnormalities of hypothalamus
  - Circadian periodicity present
- Activation of the trigeminal system
  - Increased concentrations of CGRP seen during attacks
- Activation of parasympathetic system
  - Vasodilation manifesting as lacrimation and rhinorrhea



Picture courtesy of: Migraine Buddy

Leone, M., May, A. (2020). Cluster Headache and other Trigeminal Autonomic Cephalgias.

15

15

Patient Case

MP is a 21-year-old male that presents to your clinic with complaints of a headache that started 6 hours ago. He states that he has been in bed all day due to the severe pulsating pain he feels on the right side of his head. He shares with you this is not the first time he has experienced this type of headache and when he has these episodes, he experiences severe nausea and sometimes vomiting. What kind of headache does MP present with based on his history and current symptoms?

A. Infrequent tension-type
B. Migraine headache
C. Cluster headache
D. Chronic tension-type

16

16

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Guideline Review

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Outpatient Primary Care Management of Headaches: Guidelines from the VA/DoD (2021)

	Non-pharmacologic:	Acute Relief:	Preventive:
Tension-Type Headache	Physical therapy, specifically manual therapy	Acetaminophen, ibuprofen	Amitriptyline
Migraine Headache	Avoid dietary triggers	NSAIDs, triptans	Some ACEi/ARB, CGRP inhibitors, magnesium, onabotulinmtoxinA, propranolol, topiramate
Cluster Headache	Noninvasive nerve stimulation	SubQ sumatriptan and oxygen	Galcanezumab

Am Fam Physician. 2021;104(3):316-326.

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Acute Migraine Headache Treatment Strategies: Guidelines from American Family Physician (2018)

Mild-moderate migraine

- Acetaminophen and NSAIDs preferred

Moderate-severe migraine

- Triptans preferred
- Second-line therapies
  - Intranasal dihydroergotamine
  - Antiemetics – chlorpromazine, droperidol, metoclopramide, and prochlorperazine
  - Ketorolac IM
  - Promethazine IM

Refractory migraine

- Parenteral dihydroergotamine (DHE 45), parenteral NSAIDS and/or antiemetics, IV magnesium sulfate for migraine with aura, parenteral corticosteroids

Am Fam Physician. 2018;97(4):249-251.

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Update on Integrating New Migraine Treatments into Clinical Practice: The American Headache Society Consensus Statement (2021)

Acute treatments with established efficacy

Migraine:
- Triptans
- Ergotamine derivatives
- Gepants (rimegepant and ubrogepant)
- Lasmiditan

Nonspecific:
- NSAIDs (including celecoxib oral solution)
- Combination analgesic with acetaminophen + aspirin + caffeine

Preventive treatments with established efficacy

Oral medications:
- Candesartan
- Divalproex sodium/valproate sodium
- Frovatriptan
- Metoprolol, propranolol, timolol
- Topiramate

Parenteral medication:
- Eptinezumab
- Erenumab
- Fremanezumab
- Galcanezumab
- OnabotulinumtoxinA

Headache. 2021;61(7):1021-1039.

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Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines (2016)

Acute Treatment
- Level A Recommendations:
  - Sumatriptan (SubQ), zolmitriptan (nasal spray), oxygen therapy
- Level B Recommendations:
  - Sumatriptan (nasal spray)
  - Zolmitriptan (oral)
  - Sphenopalatine ganglion stimulation

Preventive Therapy
- Level A Recommendations:
  - Suboccipital steroid injection
- Level B Recommendations:
  - Civamide (nasal spray)

Headache. 2016;56(7):1093-1106.

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Special Populations

Children and Adolescents

Commonly respond to nonprescription analgesics
- Acetaminophen, ibuprofen, naproxen

Triptans
- Almotriptan tablet
- Rizatriptan ODT
- Sumatriptan/naproxen combination tablet
- Zolmitriptan nasal spray

Pregnancy

Acetaminophen and metoclopramide

Triptans used in 2nd and 3rd trimesters associated with increased blood loss during labor and delivery

Lactation

Acetaminophen, ibuprofen, metoclopramide, droperidol, prochlorperazine, diphenhydramine, and sumatriptan are safe

Am Fam Physician. 2018;97(4):243-251.
Neurology. 2019;93(11):487-499.

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Treatment and Prevention of Headache Disorders

25

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Nonpharmacologic Interventions

- Avoiding triggers/stress
- Drinking adequate water
- Getting adequate sleep

- Riboflavin (vitamin B2)
- Coenzyme Q10 (CoQ10)
- Magnesium
- Butterbur root extract
- Feverfew

- Acupuncture
- Relaxation
- Thermal and electro-myographic biofeedback
- Cognitive behavioral therapy

- Neuro-modulation
- Spheno-palatine Ganglion Stimulation

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Pharmacological Treatment

Triptans ($5\text{-}HT_{1B \text{ and } 1D}$ receptor agonists)	• Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmatriptan
$5\text{-}HT_{1F}$ receptor agonist	• Lasmiditan
CGRP antagonists	• Rimegepant, ubrogepant, zavegepant
Ergot derivatives	• Ergotamine, dihydroergotamine
Combination regimens	• Acetaminophen-aspirin-caffeine, sumatriptan-naproxen, ergotamine-caffeine
OTC treatment options	• Acetaminophen, aspirin, diclofenac, ibuprofen, naproxen, celecoxib

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Pharmacological Prevention

Beta-blockers	• Metoprolol, propranolol, timolol, atenolol, nadolol
Anticonvulsants	• Valproic acid and derivatives, topiramate
Antidepressants	• Amitriptyline, venlafaxine
Triptans	• Naratriptan, zolmatriptan
CGRP antagonists	• Rimegepant, atogepant
CGRP(r)mAbs	• Eptinezumab, fremanezumab, galcanezumab, erenumab
ACEi/ARB	• Lisinopril, candesartan
Neuromuscular blocker agent	• OnabotulinumtoxinA

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Literature Review

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The comparative effectiveness of migraine preventive drugs: a systematic review and network meta-analysis (2023)

- 74 trials identified
- Total of 32,990 patients

Conclusion:

- CGRP(r)mAbs are most effective and tolerated, followed closely by gepants

Drug	50% reduction in monthly migraine days	Monthly migraine days	Adverse events leading to discontinuation
Baseline risk	275 per 1000	*NA*	*NA*
Results	*Risk difference in 1000 people (95% CI)*	*Difference in mean monthly migraine days (95% CI)*	*Risk difference in 1000 people (95% CI)*
fremanezumab	341,1 more (219 to 493,23)	2,22 fewer (-2,8 to -1.65)	3.9 more (-17,5 to 25,3)†
erenumab	206 more (122,7 to 306,74)	1,6 fewer (-2,05 to -1.6)	0.3 more (-19,2 to 19,8)
galcanezumab	223,9 more (132 to 336,7)	1,97 fewer (-2,48 to -1,47)	9.5 more (-11,5 to 30,4)†
eptinezumab	173 more (79,1 to 291,75)	1,85 fewer (-2,5 to -1,21)	9.4 more (-15,3 to 34,2)†
gepants	146-8 more (49,4 to 273,54)	1,12 fewer (-1,74 to -0,5)	2.6 more (-27,2 to 32,4)†
topiramate	123-5 more (49,6 to 214,16)	0,73 fewer (-1,16 to -0,3)	88.8 more (64,3 to 113,4) ‡
beta-blocker	136-6 more (43,2 to 257,47)*	0,69 fewer (-1,21 to -0,17)	23.9 more (-6,4 to 54,2)†
valproate	215 more (89,4 to 383,71)*	0,37 more (-0,44 to 1,19) *	87.1 more (27,2 to 157)
amitriptyline	143-6 (36,7 to 287,08)*	0,9 fewer (-1,91 to 0,1) *	84 more (24,1 to 163,9)
carisbamate	67-7 fewer (-159,7 to 97,61)†		2.6 more (-96,1 to 101,3)†
oxcarbazepine	41-3 more (-118,1 to 362.44)†	0.37 more (-1,06 to 1,8)	47,1 more (-54, to 149)†
gabapentin/pregabalin	80-2 more (-48,6 to 282,18)* †	0.03 more (-1,17 to 1,22)	50.4 more (-15,5 to 116,4)†
calcium channel blocker	101 more (-5,4 to 249,4)* † ‡	0.65 fewer (-1,29 to -0-,1) *	33.5 more (-5,7 to 72.7) * †
MCID/MID	*15%*	*-1 MMD*	*2%*

32

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Conclusion:

- CGRP(r)mAbs are most effective and tolerated, followed closely by gepants

Drug	50% reduction in monthly migraine days	Monthly migraine days	Adverse events leading to discontinuation
Baseline risk	275 per 1000	*NA*	*NA*
Results	*Risk difference in 1000 people (95% CI)*	*Difference in mean monthly migraine days (95% CI)*	*Risk difference in 1000 people (95% CI)*
fremanezumab	341,1 more (219 to 493,23)	2,22 fewer (-2,8 to -1,65)	3.9 more (-17,5 to 25,3)†
erenumab	206 more (122,7 to 306,74)	1,6 fewer (-2,05 to -1,6)	0.3 more (-19,2 to 19,8)
galcanezumab	223,9 more (132 to 336,7)	1,97 fewer (-2,48 to -1,47)	9.5 more (-11,5 to 30,4)†
eptinezumab	173 more (79,1 to 291,75)	1,85 fewer (-2,5 to -1,21)	9.4 more (-15,3 to 34,2)†
gepants	146-6 more (49,4 to 273,54)	1,12 fewer (-1,74 to -0,5)	2.6 more (-27,2 to 32,4)†
topiramate	123-5 more (49,6 to 214,16)	0,73 fewer (-1,16 to -0,3)	88.8 more (64,3 to 113.4) ‡
beta-blocker	136-6 more (43,2 to 257,47)*	0,89 fewer (-1,21 to -0,17)	23.9 more (-6,4 to 54,2)†
valproate	215 more (89,4 to 383,71)*	0,37 more (-0,44 to 1,19) *	67.1 more (27,2 to 107)
amitriptyline	143-6 (36,7 to 287,08)*	0,9 fewer (-1,91 to 0,1) *	84 more (26,1 to 163,9)
carisbamate	67-7 fewer (-159,7 to 97,61)†		2.6 more (-86,1 to 101,3)†
oxcarbazepine	41-3 more (-118,1 to 362.44)†	0.37 more (-1,06 to 1,8)	47.1 more (-54, to 149)†
gabapentin/pregabalin	80-2 more (-48,6 to 282,18)* †	0.03 more (-1,17 to 1,22)	50.4 more (-15,5 to 116,4)†
calcium channel blocker	101 more (-5,4 to 249,4)* † ‡	0.65 fewer (-1,29 to -0*,1) *	33.5 more (-5,7 to 72.7) * †
MCID/MID	*15%*	*≥ MMD*	*2%*

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Pharmacy Pearls

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Beta-Blockers

Indication
- Prevention of migraines

Contraindications
- Bronchial asthma (non-selective), sinus bradycardia, heart block greater than first degree, cardiogenic shock, uncompensated cardiac failure

ADRs
- Bradycardia, edema, hypotension, palpitations, dizziness

Monitoring
- ↓HR/BP, signs/symptoms of bronchospasm in patients with existing disease

Drug Name	Dosing
Propranolol	Initial: 40 to 80 mg in 1 to 4 divided doses Usual dose: 40 to 240 mg/day
Timolol	Initial: 5 mg once daily Usual dose: 10 to 30 mg/day in 2 divided doses
Metoprolol	Initial: 25 mg twice daily Usual dose: 200 mg/day in divided doses
Atenolol	Initial: 25 mg once daily Usual dose: 100 mg once daily
Nadolol	Initial: 20 mg once daily Usual dose: 240 mg daily

Propranolol. Timolol. Metoprolol. Atenolol. Nadolol. Lexi-Drugs.

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Anticonvulsants – Valproic acid and Derivatives

Indication
- Prevention of migraines

Contraindications
- Hepatic disease, pregnant women or women of childbearing potential who are not using effective contraception

ADRs
- Dizziness, drowsiness, coagulopathy, hepatotoxicity, hyperammonemia encephalopathy, pancreatitis, suicidal ideation/tendencies

Monitoring
- ↑liver enzymes, CBC with ↓platelets, ↑serum ammonia

Drug Name	Dosing
Valproic acid and derivatives	Initial: 500 mg in 1 or 2 divided doses Usual dose: 1 g/day in 1 to 2 divided doses

Valproic Acid and Derivatives. Lexi-Drugs. 37

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Anticonvulsants – Topiramate

Indication
- Prevention of migraines

Contraindications
- Recent alcohol use (ER formulation)

ADRs
- Dizziness/drowsiness, nephrolithiasis, suicidal ideation/tendencies, weight loss, can cause fetal harm, lower effectiveness of hormonal contraceptives

Monitoring
- Screen for history of eating disorders, seizures, hydration status

Drug Name	Dosing
Topiramate	Initial: 25 mg once daily Usual dose: Up to 200 mg daily CrCl < 70 mL/min: Reduce dose 50%

Topiramate. Lexi-Drugs. 38

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Antidepressants – Amitriptyline

Indication
- Prevention of migraine and chronic tension-type headaches

Contraindications
- Coadministration with or within 14 days of MAOIs

ADRs
- Anticholinergic effects, CNS depression, hyponatremia, serotonin syndrome, suicidal thinking, withdrawal syndrome

Monitoring
- ↓serum sodium, changes in behavior, ↑HR, ↓BP, serotonin syndrome

Drug Name	Dosing
Amitriptyline	Initial: 10 to 25 mg once daily at bedtime Usual dose: 10 to 150 mg once daily at bedtime

Amitriptyline. Lexi-Drugs. 39

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Patient Case

After many visits with your patient, it is determined they need prophylactic medication to prevent future migraines. GB is a 55-year-old female with past medical history of chronic obstructive pulmonary disease (COPD), hypertension, diabetes, and hyperlipidemia. She is prescribed propranolol 40 mg daily. Which of her comorbid conditions warrants a recommendation from the pharmacist for an alternative prophylactic therapy?

A. COPD
B. Hypertension
C. Diabetes
D. Hyperlipidemia

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Patient Case

After many visits with your patient, it is determined they need prophylactic medication to prevent future migraines. GB is a 55-year-old female with past medical history of chronic obstructive pulmonary disease (COPD), hypertension, diabetes, and hyperlipidemia. She is prescribed propranolol 40 mg daily. Which of her comorbid conditions warrants a recommendation from the pharmacist for an alternative prophylactic therapy?

A. COPD
B. Hypertension
C. Diabetes
D. Hyperlipidemia

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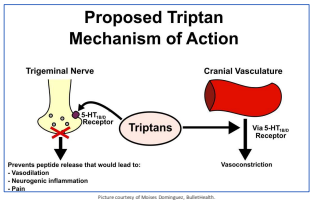
5-HT$_{1B \text{ and } 1D}$ Receptor Agonists

- Mechanism of action:
  - Selective agonist for serotonin receptors in cranial arteries causing vasoconstriction and reduced inflammation

Almotriptan | Eletriptan | Frovatriptan
Naratriptan | Rizatriptan | Sumatriptan
Zolmitriptan



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5-HT$_{1B \text{ and } 1D}$ Receptor Agonists Therapy

ADRs
- Cardiac arrhythmias, cardiac events, stroke
- CNS effects
- Ocular effects
- Serotonin syndrome
- Limit use < 10 days per month to avoid medication-overuse headache

Contra-indications
- Ischemic heart disease
- History cerebrovascular syndromes
- History of hemiplegic or basilar migraine
- Peripheral vascular disease
- Uncontrolled hypertension
- Severe hepatic impairment

Drug Interactions
- Avoid – ergot derivatives, MAO-I, duplicate triptan therapy
- Monitor therapy when using other drugs known to contribute to serotonin syndrome

Monitoring
- Headache severity
- Blood pressure/signs of CVD
- Signs/symptoms of serotonin syndrome
- Consider monitoring first dose with ECG in patients with multiple CV risk factors

Almotriptan. Eletriptan. Frovatriptan. Naratriptan. Rizatriptan. Zolmatriptan. Sumatriptan. Lexi-Drugs.

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5-HT$_{1B \text{ and } 1D}$ Receptor Agonists – Dosing Overview

Almotriptan
- Used in pediatric patients

Frovatriptan
- Used in menstrual associated migraine prevention

Naratriptan
- 2nd dose of rescue therapy can be administered ≥ 4 hours after the first
- Used in menstrual associated migraine prevention

Rizatriptan
- Used in pediatric patients

Zolmitriptan
- Used in menstrual associated migraine prevention
- Oral and intranasal formulations used for cluster headache treatment

Sumatriptan
- Intranasal solution & SubQ injections used for cluster headache treatment
- Intranasal solution, oral tablets, and SubQ injections used in pediatric patients

Almotriptan. Frovatriptan. Naratriptan. Rizatriptan. Zolmitriptan. Sumatriptan. Lexi-Drugs.

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5-HT$_{1B \text{ and } 1D}$ Receptor Agonists – Dosing

Drug Name	Dosing
Almotriptan	**Migraine, moderate to severe, acute treatment** **Oral:** 12.5 mg as a single dose; may repeat dose after ≥ 2 hours (MAX: 25 mg per 24 hours) **Migraine: Children ≥ 12 years and adolescents** **Oral:** 6.25 to 12.5 mg as a single dose, may repeat dose after ≥ 2 hours (MAX: 25 mg per 24 hours)
Eletriptan	**Migraine, moderate to severe, acute treatment** **Oral:** 20 to 40 mg as a single dose; may repeat dose after ≥ 2 hours (MAX: 80 mg per 24 hours)
Frovatriptan	**Migraine, moderate to severe, acute treatment** **Oral:** 2.5 mg as a single dose; may repeat dose after ≥ 2 hours (MAX: 5 mg per 24 hours) **Menstrual associated migraines prevention (off-label)** **Oral:** 2.5 mg daily or twice daily
Naratriptan	**Migraine, moderate to severe, acute treatment** **Oral:** 2.5 mg as a single dose; may repeat dose after ≥ 4 hours (MAX: 5 mg per 24 hours) **Menstrual associated migraines prevention (off-label)** **Oral:** 1 mg twice daily beginning 2-3 days prior to onset of symptoms, continue for 5-6 days total

Almotriptan. Eletriptan. Frovatriptan. Naratriptan. Lexi-Drugs.

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5-HT$_{1B \text{ and } 1D}$ Receptor Agonists – Dosing

Drug Name	Dosing
Rizatriptan	**Migraine, moderate to severe, acute treatment** **Oral:** 5 to 10 mg (ODT or tablet) or 10 mg (oral film) as a single dose; may repeat dose after ≥ 2 hours (MAX: 30 mg per 24 hours) **Migraine, acute treatment, children ≥ 6 years and adolescents** **< 40 kg:** 5 mg as a single dose **≥ 40 kg:** 10 mg as a single dose
Zolmatriptan	**Migraine, moderate to severe, acute treatment** **Oral:** 2.5 mg as a single dose; may repeat dose after ≥ 2 hours (MAX: 10 mg per 24 hours) **Intranasal:** 2.5 to 5 mg as a single dose; may repeat dose after ≥ 2 hours (MAX: 10 mg per 24 hours) **Menstrual migraine prevention (off-label)** **Oral:** 2.5 mg 2-3 times daily starting 2 days prior to expected onset of menses and continued through to 5 days after the onset of menses (7 days total) **Cluster headache, treatment (alternative agent) (off-label use)** **Oral:** 5 to 10 mg as a single dose at the onset of cluster headache (MAX: 10 mg per dose) **Intranasal:** 5 to 10 mg as a single dose at the onset of cluster headache; may repeat dose after ≥ 2 hours

Rizatriptan. Zolmatriptan. Lexi-Drugs. 46

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5-HT$_{1B \text{ and } 1D}$ Receptor Agonists - Dosing

Drug Name	Dosing
Sumatriptan	**Migraine, moderate to severe, acute treatment** **Oral:** 50 to 100 mg as a single dose; may repeat dose after ≥ 2 hours (MAX: 200 mg per 24 hours) **Intranasal:** Powder, breath-activated: 22 mg as a single dose; one 11 mg capsule in each nostril; may repeat dose after ≥ 2 hours (MAX: 44 mg per 24 hours) Spray: 10 mg as a single dose in 1 nostril; may repeat dose after ≥ 1 hour (MAX: 30 mg per 24 hours) **Migraine, moderate to severe, acute treatment & Cluster headache, acute** **Intranasal:** Solution: 20 mg as a single dose in 1 nostril; may repeat dose after ≥ 2 hours (MAX: 40 mg per 24 hours) **SubQ:** 6 mg once; may repeat dose after ≥ 1 hour (MAX: 12 mg per 24 hours) **Migraine, pediatrics** **Intranasal:** Children 5-12 years old: 5, 10, 20 mg in 1 nostril as a single dose Children ≥ 12 years old: 10 to 20 mg in 1 nostril as a single dose **Oral:** Children ≥ 10 years and adolescents: 25 to 50 mg as a single dose **SubQ:** Children ≥ 6 years and adolescents: 3 to 6 mg as a single dose

Sumatriptan. Lexi-Drugs. 47

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5-HT$_{1B \text{ and } 1D}$ Receptor Agonists Dose Adjustments

Drug Name	Renal Impairment	Hepatic Impairment
Almotriptan	CrCl ≤ 30 mL/min or any degree of hepatic impairment: 6.25 mg as a single dose; may repeat dose after ≥ 2 hours (MAX: 12.5 mg per 24 hours)	
Eletriptan	No adjustments necessary	Severe impairment: Use not recommended
Frovatriptan	No adjustments necessary	Severe impairment: Use with caution (has not been studied)
Naratriptan	Mild to moderate impairment: 1 mg (MAX: 2.5 mg per 24 hours) Severe (CrCl < 15 mL/min): Contraindicated	Mild to moderate impairment (Child-Pugh A/B): 1 mg (MAX: 2.5 mg per 24 hours) Severe (Child-Pugh C): Contraindicated
Rizatriptan	No adjustments necessary	No adjustments necessary
Zolmatriptan	No adjustments necessary	Moderate to severe impairment: Tablet - 1.25 mg (MAX: 5 mg per 24 hours) ODT/Nasal inhalation - Use is not recommended
Sumatriptan	No adjustments necessary	Moderate to severe impairment: Tablet - Do not exceed single doses of 50 mg Severe: Oral, intranasal, SubQ - Contraindicated

Almotriptan. Eletriptan. Frovatriptan. Naratriptan. Rizatriptan. Zolmatriptan. Sumatriptan. Lexi-Drugs. 48

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5-HT$_{1B \text{ and } 1D}$ Receptor Agonists – Available Formulations

Drug	Formulation	Strengths
Almotriptan	Oral tablet	6.25, 12.5 mg
Eletriptan	Oral tablet	20, 40 mg
Frovatriptan	Oral tablet	2.5 mg
Naratriptan	Oral tablet	1, 2.5 mg
Rizatriptan	ODT, Oral tablet	5, 10 mg
Sumatriptan	Nasal spray Nasal powder Oral tablet SubQ injection	5, 20 mg/act 11 mg/nosepiece 25, 50, 100 mg 3, 4, 6 mg/0.5 mL
Sumatriptan-naproxen	Oral tablet	10-60, 85-500 mg
Zolmitriptan	Nasal spray ODT, Oral tablet	2.5, 5 mg 2.5, 5 mg

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5-HT$_{1B \text{ and } 1D}$ Receptor Agonists – Available Formulations

Drug	Formulation	Strengths
Almotriptan	Oral tablet	6.25, 12.5 mg
Eletriptan	Oral tablet	20, 40 mg
Frovatriptan	Oral tablet	2.5 mg
Naratriptan	Oral tablet	1, 2.5 mg
Rizatriptan	ODT, Oral tablet	5, 10 mg
Sumatriptan	Nasal spray Nasal powder Oral tablet SubQ injection	5, 20 mg/act 11 mg/nosepiece 25, 50, 100 mg 3, 4, 6 mg/0.5 mL
Sumatriptan-naproxen	Oral tablet	10-60, 85-500 mg
Zolmitriptan	Nasal spray ODT, Oral tablet	2.5, 5 mg 2.5, 5 mg

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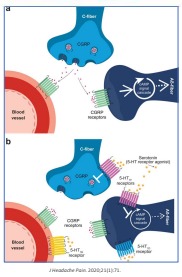
5-HT$_{1F}$ Receptor Agonist - Lasmiditan

- Mechanism of Action:
  - Selective agonism of receptor decreases stimulation of the trigeminal system and treats pain ***without vasoconstriction***
- Dosing:
  - **Migraine, moderate to severe, acute treatment (alternative agent)**
  - **Oral:** 50 to 100 mg as a single dose; repeat doses have not demonstrated efficacy
    - May increase to 100 or 200 mg as a single dose



J Headache Pain. 2020;21(1):71.

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5-HT_{1F} Receptor Agonist - Lasmiditan

Schedule	• C-V • Do not administer unless patient can wait at least 8 hours between dosing and operating heavy machinery/driving
Warnings	• CNS depression • Serotonin syndrome • Cardiovascular disease • Older adults
ADRs	• Dizziness, drowsiness • GI upset • Visual impairment
Onset of Action	• ~2 hours
Drug Interactions	• Avoid – concomitant use with other CNS depressants • Use not recommended in those with hepatic impairment (Child-Pugh class C)
Monitoring	• Hepatic function • Blood pressure • Heart rate

Lasmiditan. Lieu Drugs.

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Patient Case

BP is a 26-year-old female recently prescribed sumatriptan for her moderate acute migraines. She is curious to know what formulations of this medication are available for use. You tell the patient that sumatriptan is available as:

A. Oral tablets
B. Subcutaneous injections
C. Nasal spray
D. All of the above

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Patient Case

BP is a 26-year-old female recently prescribed sumatriptan for her moderate acute migraines. She is curious to know what formulations of this medication are available for use. You tell the patient that sumatriptan is available as:

A. Oral tablets
B. Subcutaneous injections
C. Nasal spray
D. All of the above

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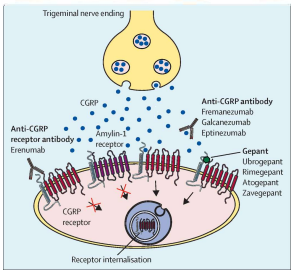
CGRP Antagonists & CGRP(r)mAbs

- Mechanism of Action:
  - Prevent CGRP from binding to its receptor

CGRP Antagonist	CGRP(r)mAbs
Ubrogepant	Fremanezumab
Rimegepant	Galcanezumab
Atogepant	Eptinezumab
Zavegepant	Erenumab



Lancet Neurol. 2022;21(3):284-294.

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CGRP Antagonist Therapy

Dosage Form	• Oral: atogepant, ubrogepant • ODT: rimegepant • Nasal spray: zavegepant
Warnings	• Avoid use or dose adjust in patients with severe hepatic/renal dysfunction
ADRs	• GI upset, dizziness • Zavegepant: taste disorder, nasal discomfort
Onset of Action	• Atogepant, ubrogepant: 1-2 hours • Rimegepant: <2 hours for treatment, <4 weeks for prevention • Zavegepant: ~15 minutes post administration
Drug Interactions	• Atogepant, ubrogepant, rimegepant: avoid use with strong CYP3A4 inducers/inhibitors • Zavegepant: avoid use with OATP1B1/1B3 inducers/inhibitors
Monitoring	• Assessment of monthly migraine days when used for prevention • Assessment of response to pain at 2 hours post-administration

Atogepant. Rimegepant. Ubrogepant. Zavegepant. Lexi-Drugs.

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CGRP Antagonists - Dosing

Drug Name	Dosing
Atogepant	**Migraine, chronic, prevention (alternative agent)** **Oral:** 60 mg once daily **Migraine, episodic, prevention (alternative agent)** **Oral:** 10 mg, 30 mg, or 60 mg once daily
Rimegepant	**Migraine, moderate to severe, acute treatment (alternative agent)** **Oral:** 75 mg as a single dose (MAX: 75 mg in 24 hours) **Migraine, prevention (alternative agent)** **Oral:** 75 mg every other day
Ubrogepant	**Migraine, moderate to severe, acute treatment (alternative agent)** **Oral:** 50-100 mg as a single dose; if symptoms persist, may repeat dose after ≥ 2 hours (MAX: 200 mg in 24 hours)
Zavegepant	**Migraine, moderate to severe, acute treatment (alternative agent)** **Intranasal:** One spray (10 mg/spray) in 1 nostril as a single dose (MAX: one spray per 24 hours)

Atogepant. Rimegepant. Ubrogepant. Zavegepant. Lexi-Drugs.

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CGRP Antagonist Dose Modifications

- Atogepant

Dosage Modifications	Recommended Once Daily Dosage for Episodic Migraine	Usage and Recommended Once Daily Dosage for Chronic Migraine
Concomitant Drugs		
Strong CYP3A4 Inhibitors	10 mg	Avoid use
Strong, Moderate, or Weak CYP3A4 Inducers	30 or 60 mg	Avoid use
OATP Inhibitors	10 or 30 mg	30 mg
Renal Impairment		
CrCl < 30 mL/min	10 mg	Avoid use

Atogepant (package insert). Revised 2023.

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CGRP Antagonist Dose Modifications

- Ubrogepant

Dosage Modifications	Initial Dose	Second Dose (if needed)
Concomitant Drug		
Strong CYP3A4 Inhibitors	Avoid use	
Moderate CYP3A4 Inhibitors	50 mg	Avoid within 24 hours
Weak CYP3A4 Inhibitors	50 mg	50 mg
Strong CYP3A4 Inducers	Avoid use	
Weak & Moderate CYP3A4 Inducers	100 mg	100 mg
BCRP and/or P-gp Inhibitors	50 mg	50 mg
Specific Populations		
Severe Hepatic Impairment (Child-Pugh Class C)	50 mg	50 mg
Severe Renal Impairment (CrCl 15-29 mL/min)	50 mg	50 mg
ESRD (CrCl < 15 mL/min)	Avoid use	

Ubrogepant (package insert). Revised 2023.

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CGRP Antagonist Dose Modifications

- Rimegepant

Dosage Modifications	Recommendation
Concomitant Drugs	
Strong CYP3A4 Inhibitors	Avoid use
Moderate CYP3A4 Inhibitors	Avoid a 2nd dose within 48 hours
Strong or Moderate CYP3A4 Inducers	Avoid use
P-gp Inhibitors	Avoid a 2nd dose within 48 hours
Special Populations	
Severe Hepatic Impairment (Child-Pugh C)	Avoid use
ESRD (CrCl < 15 mL/min)	Avoid use

Rimegepant (package insert). Revised 2023.

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CGRP Antagonist Dose Modifications

- Zavegepant

Dosage Modifications	Recommendation
Concomitant Drugs	
OATP1B3 or NTCP Inhibitors	Avoid use
OATP1B3 or NTCP Inducers	Avoid use
Intranasal Decongestants	Intranasal decongestants should be administered at least 1 hour after zavegepant administration
Special Populations	
Severe Hepatic Impairment (Child-Pugh C)	Avoid use
Renal Impairment (CrCl < 30 mL/min)	Avoid use

Zavegepant (package insert). Revised 2023. 61

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CGRP(r)mAbs Therapy

Dosage Form
- IV: eptinezumab
- SubQ: fremanezumab, galcanezumab, erenumab

Warnings
- Eptinezumab: polysorbate 80
- Fremanezumab and galcanezumab: cardiovascular disease, polysorbate 80
- Erenumab: constipation, hypertension

ADRs
- Hypersensitivity/injection site reactions
- Antibody development

Onset of Action
- Eptinezumab – immediate relief
- Fremanezumab – 5-7 days
- Galcanezumab – 5 days
- Erenumab – 6 days

Drug Interactions
- Efgartigimoid alfa
- Rozanolixizumab

Monitoring
- Blood pressure
- Have patient keep a diary of their migraine days per month

Eptinezumab. Fremanezumab. Galcanezumab-Erenumab. Lead-Drugs. 62

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CGRP(r)mAbs - Dosing

Drug Name	Dosing
Eptinezumab	**Migraine, prevention (alternative agent)** **IV:** 100 mg every 3 months; some patients may benefit from 300 mg every 3 months
Fremanezumab	**Migraine, prevention (alternative agent)** **SubQ:** 225 mg monthly OR 675 mg every 3 months
Galcanezumab	**Cluster headache, prevention** **SubQ:** 300 mg at the onset of the cluster period and then once monthly until the end of the cluster period **Migraine, prevention (alternative agent)** **SubQ:** 240 mg as a single loading dose, followed by 120 mg once monthly
Erenumab	**Migraine, prevention (alternative agent)** **SubQ:** 70 to 140 mg once monthly

Eptinezumab. Fremanezumab. Galcanezumab-Erenumab. Lead-Drugs. 63

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Patient Case

ML is 30-year-old male who was diagnosed with cluster headaches a few months ago. He has been using oral abortive therapy with no relief. He asks you if there are any injectable treatments for cluster headache. Which CGRP monoclonal antibody has an approval for use in the treatment of cluster headaches?

A. Eptinezumab
B. Fremanezumab
C. Galcanezumab
D. Erenumab

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Patient Case

ML is 30-year-old male who was diagnosed with cluster headaches a few months ago. He has been using oral abortive therapy with no relief. He asks you if there are any injectable treatments for cluster headache. Which CGRP monoclonal antibody has an approval for use in the treatment of cluster headaches?

A. Eptinezumab
B. Fremanezumab
C. Galcanezumab
D. Erenumab

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Summary

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Summary

- To guide appropriate treatment, a diagnosis of the presenting headache must be made using clinical signs and symptoms in addition to patient history
- There are many nonpharmacologic and pharmacologic treatment options for patients presenting with tension-type, migraine, and cluster headaches
- To determine which acute treatment and preventive treatment options are best for patients, their complete health history must be assessed
- Newer headache and migraine medications provide options to patients who have exhausted or were unable to use standard therapies

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Thank You!

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- Ubrelvy (ubrogepant) [package insert]. North Chicago, IL 60064: AbbVie Inc; June 2023.
- Nurtec ODT (rimegepant) [package insert]. New York, NY 10001: Pfizer Labs; June 2023.
- Zavzpret (zavegepant) [package insert]. New York, NY 10001: Pfizer Labs; June 2023.
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Don’t Think Too Hard

Managing Headaches and Migraines

Brittany Picardi, PharmD
Baptist Health - Boca Raton Regional Hospital
January 21, 2024

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Acute Ischemic Stroke Management

Eilin Ramos, Pharm.D., BCPS
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Baptist Hospital of Miami
January 21st, 2024

28 Years Featuring
South Florida Pharmacy Residents

1

Disclosure

- The authors of this presentation have nothing to disclose concerning possible financial or personal relationships with the commercial entities that may have a direct or indirect interest in the subject matter of this presentation
- This presentation will discuss the off-label use of medications

2

Objectives

1. Recognize the pathophysiology of acute ischemic stroke
2. Discuss the management ischemic stroke and complications of treatment
3. Describe the role of pharmacists in fulfilling stroke core measures

3

Abbreviations

- **AF:** atrial fibrillation
- **AIS:** acute ischemic stroke
- **DAPT:** dual antiplatelet therapy
- **DTN:** door-to-needle time
- **DM:** diabetes mellitus
- **EVT:** endovascular therapy
- **ICH:** intracranial hemorrhage
- **LAA:** left atrial appendage
- **LVO:** large vessel occlusion
- **MCA:** middle cerebral artery
- **mRS:** modified Rankin scale
- **NIHSS:** national institutes of health stroke scale
- **NINDS:** national institute of neurological disorders and stroke
- **TIA:** transient ischemic attack

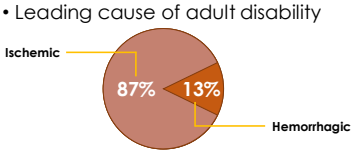
4

Background

5

Stroke Background

- **~800,000** individuals experience a stroke
  - ~600,000 of these are new strokes
- **$56.5 billion** in healthcare costs
- Leading cause of adult disability

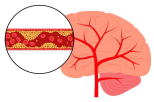


EVERY **40** SECONDS
Someone in the US has a stroke

Tsao CW, et al. Stroke Statistics 2023;147:e93–e621
National Center for Chronic Disease Prevention and Health Promotion, Division for Heart Disease and Stroke Prevention

6

Pathophysiologic Processes of Stroke

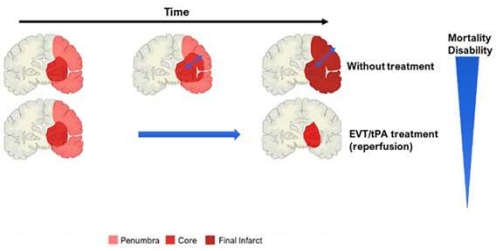


Ischemic Stroke
- Intrinsic vessel abnormality
- Embolism
- Inadequate blood flow

Hemorrhagic Stroke
- Vessel rupture

7

Ischemic Penumbra



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TOAST Classifications

Classification	Incidence	Definition	Support for Diagnosis	2-Year Survival	2-Year Recurrence
Cardioembolic	29%	Arterial embolism of cardiac origin	High-risk cardiac sources (AF, mechanical valve, LAA thrombus, etc.)	55%	22%
Small-artery "lacunar"	21%	No recognizable lesion on CT or MRI or subcortical or brain stem lesion <1.5 cm	Lacunar syndrome History of DM and/or hypertension	85%	11%
Large-artery atherosclerosis	15%	>50% stenosis of a large artery with >1.5 cm lesion, no cardioembolic source	History of intermittent claudication, carotid bruit, TIAs, or diminished pulses	58%	10%
Stroke of other cause	5%	Identified source of stroke different from earlier classifications	Hypercoagulable states Vasculopathies Hematologic disorders	Variable	Variable
Undetermined causes	31%	a. ≥2 causes identified b. Negative evaluation OR c. Incomplete evaluation	Diagnosis of exclusion	61%	14%

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Acute Ischemic Stroke: Risk Factors

MODIFIABLE
- Hypertension
- Hyperlipidemia
- Tobacco smoking
- Diabetes mellitus
- Coronary artery disease
- Obesity

NON-MODIFIABLE
- Older age (>55 years old)
- Race & ethnicity
- Female gender
- Family history
- History of prior stroke

National Center for Chronic Disease Prevention and Health Promotion, Division for Heart Disease and Stroke Prevention

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Early Recognition & Diagnosis

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Clinical Presentation

B **BALANCE** difficulties

E **EYES** changes

F **FACE** droop

A **ARM** weakness

S **SPEECH** difficulties

T **TIME** Call 911

BE-FAST (Balance, Eyes, Face, Arm, Speech, Time): Sushanth Aroor

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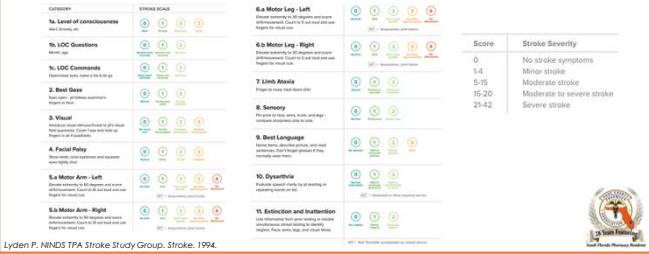
Slide 10

MA0 it says "The older you are, the more likely you are to have a stroke. The chance of having a stroke about doubles every 10 years after age 55. Although stroke is common among older adults, many people younger than 65 years also have strokes" on cdc website
Manar H. Alkahby, 2023-12-29T22:59:18.101

MA1 website says female more likely
Manar H. Alkahby, 2023-12-29T22:59:55.118

Acute Ischemic Stroke Assessments

National Institutes of Health Stroke Scale (NIHSS)



Score	Stroke Severity
0	No stroke symptoms
1-4	Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
21-42	Severe stroke

Lyden P. NINDS TPA Stroke Study Group. Stroke. 1994.

13

Acute Ischemic Stroke Assessments

Modified Rankin Scale (mRS)

Saver, J. Standardized Nomenclature for Modified Rankin Scale Global Disability Outcomes. Stroke. 2021.

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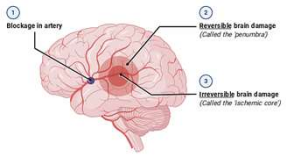
Management of Ischemic Stroke

15

Therapeutic Goals

- **ACUTE**
  - Restore blood flow
  - Preserve the penumbra
  - Limit volume of ischemic core
- **CHRONIC**
  - 2° prevention of ischemic events



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Early Management

- Airway, breathing, and circulation
- Establish time of stroke onset
- STAT Imaging: CT/MRI
- NIHSS Score
- IV thrombolytic/mechanical thrombectomy eligibility

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Door to Needle (DTN) Goals

PHASE III
TARGET: STROKE℠
SUGGESTED TIME INTERVAL GOALS

American Heart Association. Target: Stroke

Arrival	15 minutes: stroke team activation	25 minutes: door to CT	45 minutes: door to CT interpretation	60 minutes: door to needle time

heart.org/targetstroke

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Comparison of AHA/ASA Guidelines

	2013 Guideline	2019 Guideline
DTN time for thrombolysis	Goal <60 min	• Establish internal goals • Thrombolysis & thrombectomy performed as fast as possible
Tenecteplase over Alteplase	Unknown usefulness	• Reasonable to consider in candidates for thrombectomy with LVO • May consider in minor neurological impairment without LVO
Alteplase eligibility	Listed as inclusion, exclusion & relative exclusion criteria	Listed as indications, contraindications & additional recommendation (significantly more inclusive)
Alteplase extended window (3 – 4.5 hr)	Contraindicated in: warfarin (regardless of INR), age >80, history of both stroke & DM, NIHSS >25	• Beneficial in warfarin use with INR<1.7, age >80, history of both stroke & DM • Uncertain benefit in NIHSS >25
DAPT	No recommendation	21 days of aspirin and clopidogrel started within the first 24 hrs is effective in reducing the risk of recurrent ischemic stroke
Thrombectomy	No recommendation	Extended time window to 24 hrs if meeting eligibility criteria

Powers et al. AHA/ASA Stroke 2019;50(12):e344-e418

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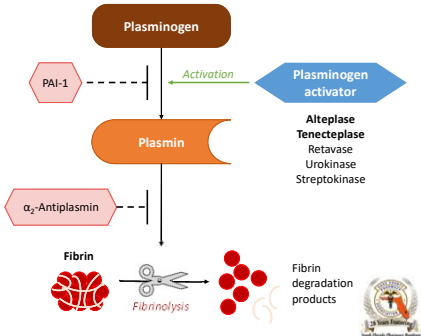
Intravenous Fibrinolytics

Alteplase
Tenecteplase
Retavase
Urokinase
Streptokinase



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Eligibility Criteria for IV Alteplase Administration in AIS

Treatment Timing	Inclusion Criteria	Absolute Exclusion Criteria	Relative Exclusion Criteria
Within **3 hours** of symptom onset or patient last known well or at baseline state	• Ischemic stroke diagnosis • Measurable neurologic deficit • ≥ 18 years of age	• Significant head trauma or stroke within last 3 months • Symptoms suggestive of SAH • Arterial puncture at noncompressible site within last 7 days • History of ICH, intracranial tumor, AVM or aneurysm • Recent intracranial or intraspinal surgery • Hypertension (SBP > 185 mmHg or DBP > 110 mmHg) • Active internal bleeding • Risk factors for acute bleeding, including but not limited to: - Low PLT count (< 100,000/mm³) - Heparin within the last 48 hrs and an aPTT > ULN - On anticoagulation and an INR >1.7, PT >15 sec, or elevated results on other sensitive laboratory tests (e.g., aPTT, INR, PLT count or ECT; TT or appropriate factor Xa activity assays) - DOAC within last 48 hrs (assuming normal renal function) - Blood glucose <50 mg/dL or 2.7 mmol/L • Multilobar infarction on CT	• Minor or rapidly improving stroke symptoms (clearing spontaneously) • Pregnancy • Seizure at onset • Major surgery or serious trauma within past 14 days • Gastrointestinal malignancy or recent gastrointestinal or urinary tract hemorrhage within past 21 days • Recent acute MI within past 3 months
Within **3 - 4.5 hrs** of symptom onset or patient last known well or at baseline state	• Ischemic stroke diagnosis • Measurable neurologic deficit	In addition to the exclusion criteria for treatment within 3 hours of symptom onset: • Current anticoagulant therapy (INR > 1.7) • History of ischemic stroke within previous 3 months	• ≥ 80 years of age with history of both DM and prior stroke

Powers et al. AHA/ASA Stroke 2019;50(12):e344-e418

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Alteplase vs Tenecteplase

	Alteplase	Tenecteplase
FDA-Approved Indication	Acute ischemic stroke Acute MI Massive pulmonary embolism	Acute MI
Dosing for AIS	0.9 mg/kg IV (max 90 mg) 10% as a bolus, remainder over 1 hr	0.25 mg/kg IV (max 25 mg) Single IV bolus
Binding Affinity	Fibrin + PAI ++	Fibrin +++ PAI +
Initial/Circulating t ½ Terminal t ½	5 minutes 1 hour	2-24 minutes 2 hours
Metabolism	Hepatic	Hepatic
Average Wholesale Price	$10,560.43 (100 mg vial)	$8,854 (50 mg vial)

Nelson A et al. Am J Emerg Med. 2019; 37:344-348

22

Tenecteplase vs Alteplase

Trial	N	Population	Time	Intervention	Result
ATTEST (2015)	104	NIHSS 11-12	≤ 4.5 hrs	• Tenecteplase 0.25 mg/kg • Alteplase 0.9 mg/kg	**Percent of salvaged penumbra at 24-48 hrs: 68% vs 68% (p=0.81)** sICH: 15% v 27% (p0.51
NORTEST (2017)	1100	NIHSS 4	≤ 4.5 hrs	• Tenecteplase 0.4 mg/kg • Alteplase 0.9 mg/kg	**mRS 0-1 at 90 days: 64% vs 63% (p=0.52)** Major clinical improvement: 42% vs 39% (p=0.97)
EXTEND-IA TNK (2018)	202	NIHSS 17	≤ 4.5 hrs	• Tenecteplase 0.25 mg/kg + thrombectomy • Alteplase 0.9 mg/kg + thrombectomy	**Substantial reperfusion: 22% vs 10% (p=0.002)** Early neurological improvement: 71% vs 68% (p=0.70)
AcT (2022)	1577	NIHSS 17	≤ 8 hrs	• MT + alteplase • Alteplase alone	**mRS 0-1 at 90-120 days: 36.9% vs 34.8%** sICH at 24 hrs: 3.4% vs 3.2%

Huang X, et al. Lancet Neurol. 2015 Apr;14(4):368-76
Logallo N, et al. Lancet Neurol. 2017 Oct;16(10):781-788.
Campbell BC, et. al. N Engl J Med 2018; 378:1573-1582.
Menon B, et al. AcT. Lancet. 2022;400(10347):161-169

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Tenecteplase Practical Implications

- Faster reconstitution and administration
- Lower average wholesale price compared to alteplase
- No replacement/reimbursement from the manufacturer due to non-FDA approved indication
- Formulary decision – hospital to carry both alteplase and Tenecteplase

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Knowledge Check

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Knowledge Check #1:

- A patient comes in with symptoms consistent with AIS. The neurology team decides to pursue thrombolysis with tenecteplase. What is the appropriate dose for administration? The patient weights 110 kg.
  - A. Tenecteplase 50 mg IV push over 5 seconds
  - B. Tenecteplase 44 mg IV push over 5 seconds
  - C. Tenecteplase 27.5 mg IV push over 5 seconds
  - D. Tenecteplase 25 mg IV push over 5 seconds

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Acute Blood Pressure Management

- ~**70%** of patients present with BP ≥170/110 mmHg
- Hypertension on admission may increase the risk of death and long-term dependence by 1.5-5 times

BP Targets: IV Thrombolytics	BP Targets: Mechanical Thrombectomy	BP Targets: Medical Management Only
• <185/110 mmHg to initiate alteplase • ≤180/105 mmHg while infusing and for the following 24 hours	• ≤185/110 mmHg	• If BP ≥220/120 mmHg may lower BP by 15% in the first 24 hours • Treatment to maintain BP <220/120 mmHg is **not** effective to prevent death or dependency

Bath PM et al. Stroke. 2022;53:1074-1084.
Wilmot M et al. Hypertension. 2004;43:18-24

27

Evidence for BP Targets

- **ENCHANTED** trial

Study Design	International, partial-factorial, open-label, blinded-endpoint trial
Population	2227 AIS patients eligible for thrombolysis
Intervention	• Intensive SBP control (130 – 140 mmHg) • Guideline SBP control (<180 mmHg)
1° Outcome	Functional status at 90 days (mRS)
Safety Outcome	Any intracranial hemorrhage (ICH)
Results	• Primary outcome did not differ between groups (OR 1.01, 95% CI 0.87-1.17, p=0.8702) • Decreased risk of ICH in intensive group (OR 0.75, 95% CI 0.6-0.94, p=0.0137)

Anderson CS et al. Lancet. 2019;393:877-888.

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Antihypertensive Agents

Medication	Dose	Onset	Duration
Labetalol	10–20 mg IVP q5min, doubling dose until effect May follow with 2 mg/min IV (max 8 mg/min)	<5 min	16-18 hr (dose-dependent)
Nicardipine	5 mg/hr IV, titrate by 2.5 mg/hr q5–15min (max 15 mg/hr)	<5 min	50% decrease in effect 30 min after discontinuation
Clevidipine	1–2 mg/hr IV, titrate by doubling dose q2–5min (max 21 mg/hr)	2–4 min	5–15 min
Hydralazine	10–20 mg IV push q4–6hr (max single dose 40 mg)	10–80 min	Up to 12 hr
Enalaprilat	1.25 mg slow IV push over 5 min q6hr	<15 min, peak effect 1–4 hr	6 hr

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Continuous vs Intermittent

	Kamp et al.	Poyant et al.
Study Design	Multicenter, retrospective, observational cohort study	Single-center, retrospective chart review
Population	179 AIS patients	272 ICH patients
Intervention	• Intermittent agents (INT, n=122) • Continuous infusion (CI, n=57)	• INT IV antihypertensive bolus (n=164) • IV nicardipine (NIC, n=108)
1° Outcome	Door to needle (DTN) time	Blood pressure variation (BPV)
Results	• DTN time: INT 53 min vs. CI 57 min (p=0.17) • Similar rates of achieving BP goal within 15 min (83.7% vs. 77.4%) • No difference in adverse events	• NIC group had significantly less BPV (p=0.04) • Patients with SBP goal <140 mmHg were more likely to achieve goal with NIC (13.5% vs 37%, p<0.01)

Kamp A et al. Am J Emerg Med. 2022;52:220-224.
Poyant JO et al. Neurocrit Care. 2019;30:118-125

30

Knowledge Check

?

31

Knowledge Check #2:

- What is the appropriate SBP goal for a patient eligible for thrombolysis?
  - A. >185 mmHg
  - B. <160 mmHg
  - C. <185 mmHg
  - D. <200 mmHg

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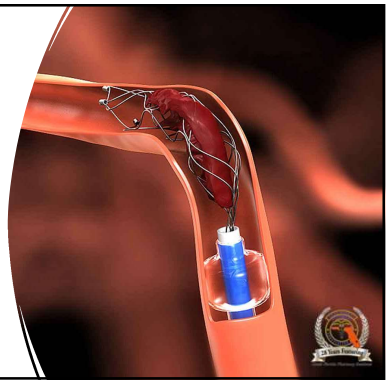
Thrombectomy

- Medical procedure used to treat ischemic stroke
- Involves removal of a blood clot that is blocking cerebral blood flow



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Criteria for Thrombectomy

- **Guideline-based criteria within 6 hrs of stroke onset:**
  - Age ≥ 18 yr
  - ASPECTS of ≥ 6
  - LVO demonstrated on CTA or MRA
  - NIHSS score ≥ 6
- **DAWN Criteria within 6 to 24 hrs of stroke onset:**
  - Anticipated life expectancy of at least 6 months
  - LVO in ICA or MCA
  - One of the following:
    - Age ≥ 80 and NIHSS ≥ 10 and core infarct < 21 mL
    - Age < 80 and NIHSS ≥ 10 and core infarct < 31 mL
    - Age < 80 and NIHSS ≥ 20 and core infarct 31–51 mL
  - Prestroke mRS score of 0 to 1

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Thrombectomy Trials

Trial	N	Population	Time	Intervention	Result
MR CLEAN (2015)	500	NIHSS 17-18	≤ 6 hrs	• MT + alteplase • Alteplase/urokinase alone	**mRS ≤ 2: 32.6% vs 19.1%** sICH: 7.7 v 6.4% 30-day mortality: 18.9% vs 18.4%
EXTEND-IA (2015)	70	NIHSS 12-17	≤ 6 hrs	• MT + alteplase • Alteplase alone	**mRS ≤ 2: 71% vs 40%, p=0.01** sICH: 0 vs 6%, p=0.49 90-day mortality: 9% vs 20%, p=0.18
ESCAPE (2015)	316	NIHSS 16-17	≤ 12 hrs	• MT + alteplase • Alteplase alone	**mRS ≤ 2: 53.0%, vs 29.3%, p<0.001** sICH: 3.6% vs 2.7%, p=0.75 90-day mortality: 10.4%, vs 19.0%, p=0.04
REVASCAT (2015)	206	NIHSS 17	≤ 8 hrs	• MT + alteplase • Alteplase alone	**mRS ≤ 2: 43.7% vs 28.2%** sICH: 1.9% in both 90-day mortality: 18.4% vs 15.5%, p=0.60
SWIFT PRIME (2015)	196	NIHSS 17	≤ 6 hrs	• MT + alteplase • Alteplase alone	**mRS ≤ 2: 60% vs 35%, p<0.001** sICH: 0% vs 3%, p=0.12 90-day mortality: 9% vs 12%, p=0.50

Fransen PS et al. Trials. 2014;15:343.
Campbell BC et al. N Engl J Med. 2015;372(11):1009-1018
Binaray C et al. JAMA. 2005;294(13):1625-1633
Molina CA et al. Int J Stroke. 2015;10(4):619-626.
Saver JL et al. N Engl J Med. 2015;372(24):2285-2295

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Knowledge Check

36

Knowledge Check #3:

- A patient who presents with AIS can receive both IV thrombolytic (such as alteplase) and undergo mechanical thrombectomy
  - True
  - False

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Management of Adverse Events

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Hemorrhagic Conversion

- Devastating complication of fibrinolytic administration
  - Rates of hematoma expansion up to 40%
  - 3-month mortality up to 60%
- Incidence depends on several factors:
  - Age
  - Weight
  - Current antiplatelet therapy
  - Baseline NIHSS
  - SBP
  - Time from symptom onset

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Management of Symptomatic ICH within 24 hrs of Thrombolytics

AHA/ASA 2019	NCS 2016
Discontinue alteplase	Discontinue thrombolytic infusion when ICH is present or suspected
Obtain CBC, PT (INR), PTT, fibrinogen concentration, type, and cross-match	No recommendation made for pretreatment laboratory tests
Cryoprecipitate 10 units over 10–30 min Additional dose if fibrinogen < 200 mg/dL	Cryoprecipitate 10 units initially Additional dose if fibrinogen < 150 mg/dL
Tranexamic acid 1 g IV over 10 min OR Aminocaproic acid 4–5 g IV over 1 hr, followed by 1 g/hr IV until bleeding controlled	If cryoprecipitate contraindicated or unavailable: Tranexamic acid 10–15 mg/kg IV over 20 min OR Aminocaproic acid 4–5 g IV
No recommendation for platelet transfusion	Unclear whether platelet transfusion is useful; therefore, no recommendation offered

Powers et al. AHA/ASA Stroke. 2019;50(12):e344-e418.
Frontera et al. Neurocrit Care. 2016;24(1):6-46

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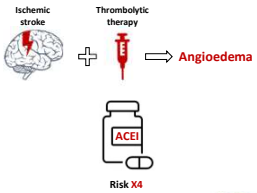
Angioedema

- Up to 8% of patients treated with alteplase or tenecteplase for AIS
  - Typically mild and transient
  - Severe orolingual angioedema is rare but may cause partial airway obstruction
- **Increased risk if:**
  - Use of angiotensin converting enzyme inhibitors
  - CT evidence of ischemia in the frontal and insular cortex



Mysliwiec V et al. Stroke. 2016;47(7):1825-1830

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Management of Severe Angioedema

- Maintain airway
- Discontinue alteplase infusion and hold angiotensin converting enzyme inhibitor
- **Give the following in rapid sequence:**
  - Methylprednisolone 125 mg IV
  - Diphenhydramine 50 mg IV
  - Famotidine 20 mg IV
- **If angioedema doesn't resolve, may consider:**
  - Epinephrine (0.1%) 0.3 mL SC or 0.5 mL by nebulizer
  - Note: epinephrine has a risk of causing BP elevation and hemorrhage
- **Alternative Therapies:**
  - Icatibant 30 mg SC once (selective bradykinin B2 receptor antagonist)

Qi X et al. Medicine (Baltimore). 2022;101(52):e32474

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Post-Thrombectomy Complications

- Might be as high as 30%
  - Symptomatic ICH is the most severe
  - Also includes:
    - Access site infection and damage
    - Reperfusion injury after recanalization
    - Infarction, edema, or hemorrhagic transformation

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Post-Stroke Management & Secondary Stroke Prevention

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First 24 Hours

- BP checks, neurologic exam, and angioedema screening
  - Every 15 min for the first 2 hrs
  - Every 30 min for the next 6 hrs
  - Every 1 hr until 24 hrs after thrombolytic administration
- CT scan or MRI imaging ~24 hrs after alteplase, prior to initiating anticoagulant or antiplatelet agents

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Secondary Prophylaxis

- DAPT/Anticoagulation
- Antihypertensive Agents
- High-intensity statins
- Diabetes management
- Smoking cessation
- Lifestyle modifications

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Dual Antiplatelet Therapy (DAPT)

- Up to 80% of recurrent strokes occur within the first 14 days of the ischemic stroke or TIA
- Administration of aspirin is recommended within 24 to 48 hours of an AIS
- Early stroke prevention: treatment with aspirin and clopidogrel initiated within 24 hours for 21 to 90 days, followed by long-term monotherapy with aspirin

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DAPT in Transient Ischemic Attach (TIA)

- Temporary blockage of blood flow to the brain
- The clot usually dissolves on its own or gets dislodged and symptoms resolve with 24 hours
- The clinical symptoms are reversible, not the cerebral injury
- **21 days** of DAPT recommended for high-risk TIA
  - ABCD score >3

ABCD[2] scoring for transient ischemic attack[4]

	Risk factor	Category	Score
A	Age of patient	≥60 years	1
		<60 years	0
B	Blood pressure	≥140/90 mm Hg	1
		<140/90 mm Hg	0
C	Clinical features	Unilateral weakness	2
		Speech disturbance (no weakness)	1
		Other	1
D	Duration of TIA	Symptoms ≥60 minutes	2
		Symptoms 10-59 minutes	1
		Symptoms <10 minutes	0
D	Diabetes	Yes	1
		No	0

ABCD[2] score key

ABCD[2] score	2-day stroke risk	7-day stroke risk	90-day stroke risk
0-3 (low risk)	1%	1.2%	3.1%
4-5 (moderate risk)	4.1%	5.9%	9.8%
6-7 (high risk)	8.1%	12%	18%

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DAPT Trials

	CHANCE (2013)	POINT (2018)
Design	Randomized, double-blind, placebo controlled; thrombolysis excluded	
N	5170	4881
Stroke vs. TIA	TIA: 28%; Minor stroke: 72%	TIA: 43%; Minor stroke: 57%
Intervention	Clopidogrel: 300 mg x1 then 75 mg daily Aspirin: 75–300 mg x1 then 75 mg daily	Clopidogrel: 600 mg x1 then 75 mg daily Aspirin 50–325 mg daily
Control	Aspirin: 75-300 mg x1 then 75 mg daily	Aspirin LD: None; MD: 50–325 mg daily
Onset to randomization	≤ 24 hrs	≤ 12 hrs
DAPT duration	21 days	90 days
Efficacy (DAPT vs Monotherapy)	Stroke: 8.2% vs 11.7% (HR 0.68; 95% CI, 0.57–0.81; p<0.001)	Major ischemic events: 5.0% vs 6.5% (HR 0.75; 95% CI, 0.59–0.95; p=0.02)
Safety (DAPT vs Monotherapy)	Moderate or severe hemorrhage: 0.3% vs 0.3% (p=0.73) Hemorrhagic stroke was 0.3% in each group	Major hemorrhage: 0.9% vs 0.4% (HR 2.32; 95% CI, 1.10–4.87; p=0.02)

Wang Y et al. N Engl J Med. 2013;369(1):11-19.
Venturelli PM et al. Curr Neurol Neurosci Rep. 2018;18(11):77

49

Anticoagulation

- For cardioembolic strokes, commonly seen in AF
- Most patients with AF should receive long-term anticoagulation to decrease their risk of stroke & other embolic events
- **2023 AHA/ACC/HRS Guidelines recommend anticoagulation if the CHA_2DS_2-VASc:**
  - ≥ 2 points for male
  - ≥ 3 points for female

CHA_2DS_2-VASc		
C	Congestive HF	1
H	HTN	1
A	Age ≥ 75 y	2
D	Diabetes Mellitus	1
S	Stroke/TIA/TE	2
V	Vascular Disease	1
A	Age 65-74 y	1
Sc	Sex Category (F)	1

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Anticoagulation Agents

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran	Warfarin
Class	**Factor Xa Inhibitor**	**Factor Xa Inhibitor**	**Factor Xa Inhibitor**	**Direct Thrombin Inhibitor**	**Vitamin K Antagonist**
Dose	5 mg BID	20 mg daily with food	60 mg daily (only if CrCl ≤95)	150 mg BID	5 mg daily Adjust to INR 2-3
Reduced Dose	2.5 mg BID	15 mg daily with food	30 mg daily	75 mg BID	≤2.5 mg daily
Indication for Reduction	If 2 of 3 present: • Age ≥80 years • SCr ≥1.5 mg/dL • Weight ≤60 kg	CrCl 15 to ≤50 mL/min	CrCl 15 to ≤50 mL/min	CrCl 15 to ≤30 mL/min	• Age ≥65 years • Weight ≤70 kg • Known warfarin sensitivity
Half-life (hr)	12	7-11	10-14	8-15	~40
Reversal	Andexxa® PCC	Andexxa® PCC	PCC	Praxbind®	Vitamin K PCC

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Antihypertensive Agents

First-Line Agents	Second-Line Agents
• Angiotensin converting enzyme inhibitors (ACE-I) • Angiotensin receptor blockers (ARBs) • Thiazide diuretics • Calcium Channel Blockers	• Beta Blockers • Loop Diuretics • Potassium Sparing Diuretics • Alpha-1 Blockers • Aldosterone Antagonists • Centrally acting alpha-2 agonists • Direct acting vasodilators • Direct renin inhibitors

- **Additional considerations**:
  - **African Americans**: Thiazides, CCB
  - **CKD:** ACE-I or ARB
  - **Diabetes + Albuminuria:** ACE-I or ARB

BP goal < 130/80 mmHg

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High-Intensity Statins

- High-intensity statins are recommended regardless of baseline LDL-C
  - Atorvastatin 80 mg daily
  - Rosuvastatin 40 mg daily
- If unable to tolerate high-intensity statins, the **maximum tolerated dose** can be used
- If LDL-C level remains > 70 mg/dL, the addition of ezetimibe or a PCSK9 inhibitor should be considered
  - Evolocumab 140 mg SubQ every 2 weeks or 420 mg once monthly
  - Alirocumab 75 mg SubQ every 2 weeks or 300 mg once monthly
- Monitor LDL-C levels starting **4 to 12 weeks** after starting therapy

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Lifestyle Modifications

- Weight loss: Maintain a BMI of 18.5-24.9
- Smoking cessation
- Sodium restriction to < 2.4 grams a day or < 1.5 grams for BP reduction
- Moderate-vigorous intensity exercise (30-40 minutes most days of the week)
- Alcohol intake: limit to < 2 drinks a day for males and < 1 drink a day for females

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Role of the Pharmacist

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Role of the Pharmacist

- Immediate Intervention & Emergency Response
- Medication Expertise
- Patient Education & Adherence
- Collaboration with other Healthcare Providers
- Secondary Prevention Strategies
- Medication Safety & Monitoring

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Pharmacists' Impact

- Reduce DTN when directly involved in acute stroke teams
- **Substantially affect several aspects of AIS management**
  - Proficient reconstitution of thrombolytics
  - Knowledge of appropriate dosing
  - Ability to quickly screen for contraindications
  - Provide recommendations for, and access to, acute BP-lowering agents
  - Optimize protocols and order sets for AIS treatment
  - Education to stroke team
  - Performance review & performance improvement initiatives

Jacoby JS et al. Neurohospitalist. 2018;8(2):60-65

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Key Takeaways

- Data are mostly non-inferior regarding Tenecteplase vs alteplase for AIS
- Tenecteplase offers practical administration advantages
- Variability in blood pressure is likely the key factor to success

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Acute Ischemic Stroke Management

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January 21st, 2024

DADE COUNTY PHARMACY ASSOCIATION
28 Years Featuring
South Florida Pharmacy Residents

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Unraveling the Mind's Maze

Luke Manda, PharmD, PGY1 Resident
Abraham Felix, PharmD, PGY1 Resident
Baptist Health
January 21st, 2024

28 Years Featuring
South Florida Pharmacy Residents

1

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No one in control of the content of this activity has a relevant financial relationship (RFR) with an ineligible company

As defined by the Standards of Integrity and Independence in Accredited Continuing Education definition of an ineligible company. All relevant financial relationships have been mitigated prior to the CPE activity

2

Objectives

- Review the definition, incidence, and pathophysiology of delirium in the intensive care unit (ICU)
- Evaluate the different screening tools and prediction models
- Discuss potential complications and outcomes of ICU delirium
- Determine strategies to minimize delirium through non-pharmacological and supportive treatment
- Analyze appropriate pharmaceutical treatment in patients with ICU delirium
- Discuss the future of ICU delirium treatment

3

Abbreviations

- ICU: Intensive care unit
- DSM-5: Diagnostic and Statistical Manual of Mental Disorders
- RAS: Reticular Activating System
- SSRIs: Selective Serotonin Reuptake Inhibitors
- TCAs: Tricyclic Antidepressants
- PRE-DELIRIC: Prediction of Delirium in ICU Patients
- E-PRE-DELIRIC: Early Prediction of Delirium in ICU Patients
- AUROC: Area Under the Receiver Operating Characteristic Curve
- CAM-ICU: Confusion Assessment Method for the ICU
- RASS: Richmond Agitation Sedation Scale
- ICDSC: Intensive Care Delirium Screening Checklist

4

Delirium: DSM-5 Definition

Acute Confusional State

Attention	Cognition	Onset
• Reduced ability to direct, focus, sustain, and shift attention	• Disturbance in memory, orientation, speech difficulty, perception	• Onset is acute (hours to days) and symptoms are variable throughout the day

Note:
- Diagnosis of exclusion
- Medication induced in ≈30% of cases

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders

5

Additional Features of Delirium

Hypoactive State
- Lethargy
- Psychomotor Retardation

Hyperactive State
- Anxiety, fear
- Euphoria, mania
- Hallucinations, delusions

Variable Emotional Disturbance

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders

6

Distribution of Delirium Types in the ICU

Hypoactive State
43.5%

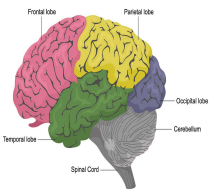
Hyperactive State
1.6%

Mixed Delirium
54.9%

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders

7

Pathophysiology: Cerebral Cortex



Frontal Lobe: Personality, decision-making, movement, speech

Parietal Lobe: Pain, physical stimuli, spatial awareness, language recognition

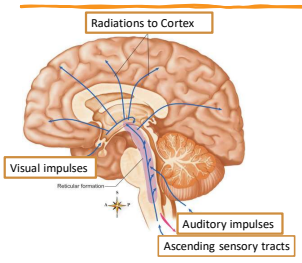
Occipital Lobe: Vision

Temporal Lobe: Short term memory, speech

John Hopkins Medicine. (2023). Brain Anatomy and How the Brain Works

8

Pathophysiology: Reticular Formation



Reticular Activating System (RAS)

Promotes arousal and consciousness

Continuously transmits impulses from sensory tracts to the cerebral cortex

Filters 99% of sensory inputs

Inhibited by the hypothalamus during sleep

Moini, J., et al. (2023). Foundations of the Mind, Brain, and Behavioral Relationships

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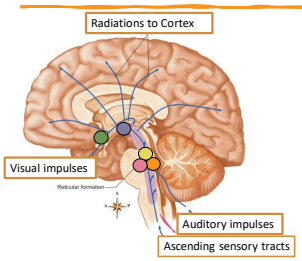
Pathophysiology: Reticular Formation



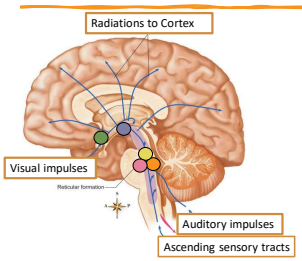
Structures involved in RAS

- **Hypothalamus**: releases orexin in response to visual stimuli
- **Locus Coeruleus**: releases norepinephrine in response to orexin to stimulate wakefulness
- **Raphe Nuclei**: release serotonin to regulate circadian rhythms
- **Tuberomammillary Nucleus**: releases histamine to stimulate wakefulness and cognition
- **Pedunculopontine Tegmentum**: releases acetylcholine to transition from sleep rhythms to wake rhythms

Moini, J., et al. (2023). Foundations of the Mind, Brain, and Behavioral Relationships

10

Pathophysiology: Reticular Formation



Neurotransmitters involved in sleep-wake cycles

- Orexin
- Norepinephrine
- Serotonin
- Histamine
- Acetylcholine

Moini, J., et al. (2023). Foundations of the Mind, Brain, and Behavioral Relationships

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Etiology of Delirium in the ICU

Neurotransmitter Imbalance

- Disruption of normal sleep-wake cycles due to the ICU setting
- Medication overdose, withdrawal, or side effect
- Metabolic disorders: hypercalcemia, uremia, hepatic encephalopathy, hypoglycemia

Cortical or Subcortical Brain Injury

- Trauma
- Malignancy
- Fluid/electrolyte disturbance
- Infections
- Shock, decreased perfusion

Stollings, J. L., et al. (2021). Delirium in critical illness: clinical manifestations, outcomes, and management

12

2018 PADIS Guidelines: Risk Factors for ICU Delirium

Modifiable Risk Factors

- Strong evidence: benzodiazepines, blood transfusions
- Moderate evidence: history of hypertension, antipsychotics, anticonvulsants
- Opioid use and mechanical ventilation do **not** increase the risk of delirium

Nonmodifiable Risk Factors

- Older age
- Dementia
- Prior coma
- Pre-ICU emergency surgery or trauma
- Higher APACHE scores

Devlin, J. W., et al. (2018). Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

13

Medications that Effect RAS Neurotransmitters

1. Anticholinergics	2. Antihistamines	3. Anti-Epileptics	4. Antidepressants	5. Antihypertensive Agents
• Atropine • Benztropine • Scopolamine • Dicyclomine • Oxybutynin • Baclofen • Cyclobenzaprine	• Diphenhydramine • Meclizine • Famotidine	• Benzodiazepines • Levetiracetam • Phenobarbital • Valproic acid	• SSRIs • TCAs • Mirtazapine	• Propranolol • Metoprolol • Carvedilol

Clegg, A., & Young, J. B. (2010). Which medications to avoid in people at risk of delirium

14

Prediction Models

PRE-DELIRIC Model: Prediction of Delirium

- Based on patient characteristics in the **24 hours after ICU admission**
- Ten predictive variables
  - Age
  - Admission category
  - Urgent admission
  - Blood urea nitrogen
  - Infection
  - Coma
  - Sedation
  - Morphine use
  - Metabolic acidosis
  - APACHE-II score

E-PRE-DELIRIC Model: Early Prediction of Delirium

- Based on patient characteristics available **upon ICU admission**
- Nine predictive variables
  - Age
  - Admission category
  - Urgent admission
  - Blood urea nitrogen
  - History of cognitive impairment
  - History of alcohol abuse
  - Mean arterial pressure
  - Use of corticosteroids
  - Respiratory failure

Wassenaar, A., et al. (2015). Multinational development and validation of an early prediction model for delirium in ICU patients
Boogaard, M. v. d., et al. (2012). Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients

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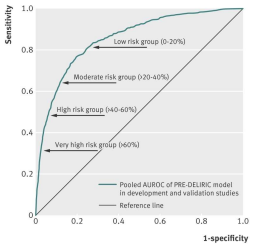
PRE-DELIRIC Prediction Model

Prediction of Delirium in ICU Patients

- Based on patient characteristics in the 24 hours after ICU admission
- Validation conducted for over 3,000 ICU patients
- Risk categorization by Pre-DELIRIC score
  - 0-20%: Low risk
  - 20-40%: Moderate risk
  - 40-60%: High risk
  - >60%: Very high risk
- Area under the receiver operating characteristic curve (AUROC)= 0.84-0.85
  - Indictive of high predictive capability



Boogaard, M. v. d., et al. (2012). Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients

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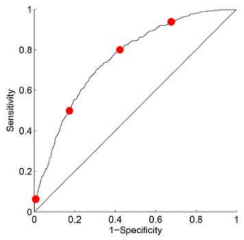
E-PRE-DELIRIC Prediction Model

Early Prediction of Delirium in ICU Patients

- Based on patient characteristics available upon ICU admission
- Validated: assessed in over 2,900 patients
- Risk Categorization by E-PRE-DELIRIC Score
  - 0-10%: Very low risk
  - 10-20%: Low risk
  - 20-35%: Moderate risk
  - >35%: High risk
- AUROC 0.75-0.76
- Predictive value improved significantly over time



Wassenaar, A., et al. (2015). Multinational development and validation of an early prediction model for delirium in ICU patients

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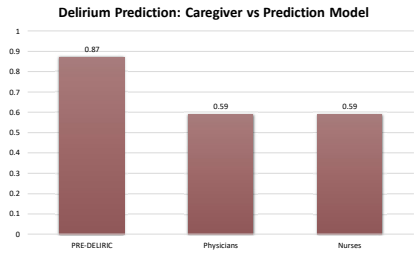
Delirium Prediction By Caregiver



Boogaard, M. v. d., et al. (2012). Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients

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Limitations of Prediction Models

PRE-DELIRIC Model:

- Risk of delirium = 1/(1+exp−(−6.31 +
  - 0.04 × age
  - 0.06 × APACHE-II score
  - 0 for non-coma, 0.55 for drug induced coma, 2.70 for miscellaneous coma, 2.84 for combination coma
  - 0 for surgical patients, 0.31 for medical patients, 1.13 for trauma patients, 1.38 for neurosurgical patients
  - 1.05 for infection
  - 0.29 for metabolic acidosis
  - 0 for no morphine use, 0.41 for 0.01-7.1 mg/24 h morphine use, 0.13 for 7.2-18.6 mg/24 h morphine use, 0.51 for >18.6 mg/24 h morphine use
  - 1.39 for use of sedatives
  - 0.03 × urea concentration (mmol/L)
  - 0.40 for urgent admission

E-PRE-DELIRIC Model:

- Risk of delirium = 1/[1+exp−(−3.907 +
  - 0.025 × age
  - 0.878 for history of cognitive impairment
  - 0.505 for history of alcohol abuse
  - 0 for surgery, 0.370 for medical, 1.219 for trauma, 0.504 for neurology/neurosurgery
  - 0.612 for urgent admission
  - − 0.006 × MAP at the time of ICU admission
  - 0.283 for use of corticosteroids
  - 0.982 for respiratory failure
  - 0.018 x BUN in mmol/l at time of ICU admission

Wassenaar, A., et al. (2015). Multinational development and validation of an early prediction model for delirium in ICU patients
Boogaard, M. v. d., et al. (2012). Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients

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Screening for Delirium

- Without practical prediction models, nurses and physicians may fail to recognize delirium
- Screening tools are necessary for the early recognition of delirium and prompt response from the treatment team to initiate treatment and correct underlying causes

Devlin, J. W., et al. (2007). Use of a validated delirium assessment tool improves the ability of physicians to identify delirium in medical intensive care unit patients

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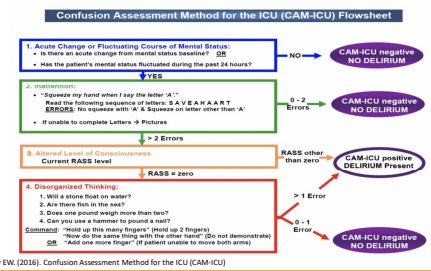
Assessment of Delirium: CAM-ICU



Developed and validated for identification of delirium in the ICU, but can also be used across multiple clinical settings such as long-term care and emergency departments

- **Sensitivity**: 94-100%
- **Specificity**: 90-95%

Ely EW. (2016). Confusion Assessment Method for the ICU (CAM-ICU)

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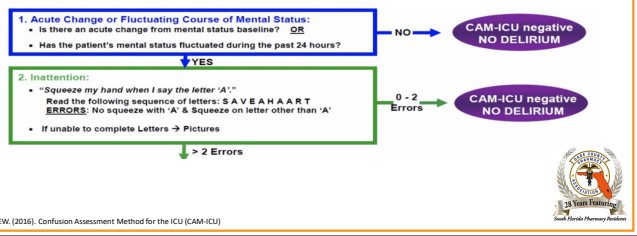
Assessment of Delirium: CAM-ICU



Ely EW. (2016). Confusion Assessment Method for the ICU (CAM-ICU)

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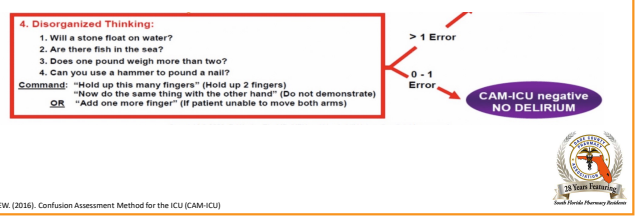
Assessment of Delirium: CAM-ICU

Richmond Agitation-Sedation Scale	
+4	Combative
+3	Very Agitated
+2	Agitated
+1	Restless
0	Alert and Calm
-1	Drowsy
-2	Light Sedation
-3	Moderate Sedation
-4	Deep Sedation
-5	Unarousable

Ely EW. (2016). Confusion Assessment Method for the ICU (CAM-ICU)

23

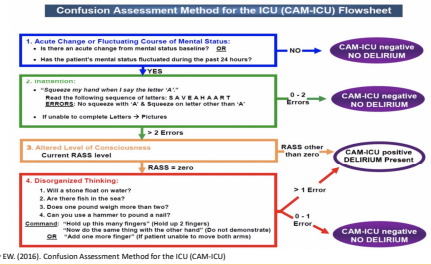
Assessment of Delirium: CAM-ICU



Ely EW. (2016). Confusion Assessment Method for the ICU (CAM-ICU)

24

Assessment of Delirium: CAM-ICU



Developed and validated for identification of delirium in the ICU, but can also be used across multiple clinical settings such as long-term care and emergency departments

- **Sensitivity**: 94-100%
- **Specificity**: 90-95%

Ely EW. (2016). Confusion Assessment Method for the ICU (CAM-ICU)

25

Assessment of Delirium: ICDSC

High agreement rates with the CAM-ICU screening tool

Checklist of eight items based on DSM criteria and features of delirium to identify a score from 0-8

- Agitation/sedation (RASS or SAS score)
- Inattention
- Disorientation
- Hallucination, delusion, psychosis
- Hyperactive or hypoactive state
- Inappropriate speech or mood
- Sleep-wake cycle disturbance over the past 24 hours
- Symptom fluctuation over the past 24 hours

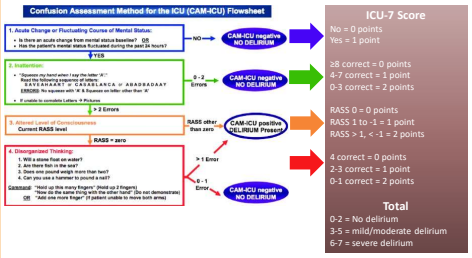
Score of ≥ 4 = delirium

Score of 1-3 = subsyndromal delirium

Plaschke, K., et al. (2007). Comparison of the confusion assessment method for the intensive care unit (CAM-ICU) with the Intensive Care Delirium Screening Checklist (ICDSC) for delirium in critical care patients gives high agreement rate(s)

26

Assessment of Delirium: ICU-7



- Evaluates severity of delirium
- Patients with severe delirium had significantly higher odds of death (OR 2.92; 95% CI = 1.17-7.26; p=0.02) compared to those with mild/moderate delirium
- Not currently recommended by the 2018 PADIS guidelines

Khan, B. A., et al. (2017). The Confusion Assessment Method for the ICU-7 Delirium Severity Scale.

27

Limitations of Screening for Delirium

- False-positive screenings may result in unnecessary pharmacologic or nonpharmacologic treatment
  - ICU antipsychotic use is associated with continued administration after ICU and hospital discharge
- Current screening tools may be influenced by subjectivity
- Screening may be burdensome for nursing staff
- PADIS 2018 Guidelines Statement: "Benefits of widespread delirium assessment with CAM-ICU or ICDSC far outweigh any potential disadvantages"

Devlin, J. W., et al. (2018). Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU.

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Complications of Delirium

Strong Evidence	• Cognitive impairment at 3 and 12 months after ICU discharge • Longer Hospital stay
Weak Evidence	• ICU Length of Stay • Depression • Reduced functionality/dependence • Mortality
No Association	• Post-traumatic stress disorder (PTSD) • Post-ICU distress

Devlin, J. W., et al. (2018). Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU.

29

Assessment Question

- Benzodiazepine and opioid use are the only modifiable risk factors with strong evidence for an association with delirium.
  - True
  - False

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Assessment Question

- Benzodiazepine and opioid use are the only modifiable risk factors with strong evidence for an association with delirium.
  - True
  - False

FALSE

Benzodiazepines and blood transfusions are the only two modifiable factors with strong evidence for an association with delirium. Opioid use has strong evidence against risk for delirium occurrence.

31

Assessment Question

- Delirium can be predicted in ICU patients using either the PRE-DELIRIC or E-PRE-DELIRIC predictive models based on availability of predictors.
  - True
  - False

32

Assessment Question

- Delirium can be predicted in ICU patients using either the PRE-DELIRIC or E-PRE-DELIRIC predictive models based on availability of predictors.
  - True
  - False

TRUE

The PRE-DELIRIC model can be used for patients admitted to the ICU for at least 24 hours while the E-PRE-DELIRIC model is used upon ICU admission

33

Assessment Question

Which outcomes have strong evidence to support an association with delirium in critically ill adults?

A: Prolonged cognitive impairment 12 months after ICU discharge
B: Post-traumatic stress disorder
C: Increased ICU length of stay
D: Increased hospital length of stay

34

Assessment Question

Which outcomes have strong evidence to support an association with delirium in critically ill adults?

A: Prolonged cognitive impairment 12 months after ICU discharge
B: Post-traumatic stress disorder
C: Increased ICU length of stay
D: Increased hospital length of stay

35

Objectives

- Review the definition, incidence, and pathophysiology of delirium in the intensive care unit (ICU)
- Evaluate the different screening tools and prediction models
- Discuss potential complications and outcomes of ICU delirium
- Determine strategies to minimize delirium through non-pharmacological and supportive treatment
- Analyze appropriate pharmaceutical treatment in patients with ICU delirium
- Discuss the future of ICU delirium treatment

36

Objectives

- Review the definition, incidence, and pathophysiology of delirium in the intensive care unit (ICU)
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- Analyze appropriate pharmaceutical treatment in patients with ICU delirium
- Discuss the future of ICU delirium treatment

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2018 PADIS Guidelines

- The 2018 **P**ain, **A**gitation/Sedation, **D**elirium, **I**mmobility, and **S**leep (PADIS) guidelines have a total of 37 recommendations that address these different domains
- Most of these recommendations, except for two, are conditionally appropriate in most, but not all, critically ill patients
- Conditional recommendations were based on evidence that was low quality, conflicting, ungeneralizable, and/or when the benefit-to-risk ratio was almost equal

Devlin JW, Skrobik Y, Gélinas C, et al. Executive Summary: Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med*. 2018;46(9):1532-1548. doi:10.1097/CCM.0000000000003259

38

2021 KSCCM Guidelines

- The Korean Society of Critical Care Medicine (KSCCM) reviewed and updated the 2010 Guideline for the Use of Sedatives and Analgesics in the Adult Intensive Care Unit (ICU) based on the 2018 PADIS Guidelines.
- Total of 42 recommendations were issued for the management of PADIS
- Quality of evidence for their recommendations were categorized as:
  - High = Level A
  - Moderate = Level B
  - Low and very low = Level C

Seok Y, Lee HJ, Ha EJ, Ha TS. 2021 KSCCM clinical practice guidelines for pain, agitation, delirium, immobility, and sleep disturbance in the intensive care unit. Acute Crit Care. 2022;37(1):1-25. doi:10.4266/acc.2022.00094

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Addressing Delirium

Step 1: Prevention
- Screen upon admission to identify high risk patients and progression
- Implement ABCDEF bundle to optimize care

Step 2: Screening
- Complete diagnostic questionnaire

Step 3: Intervention and Treatment
- Identify possible triggers
- Standardize intervention
- Select optimal treatment

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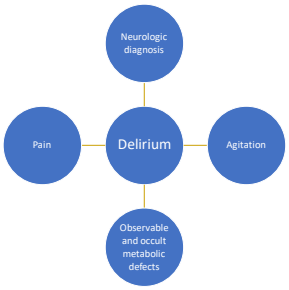
Contributing Factors for ICU Delirium



Neurologic diagnosis	○ Preexisting mental impairment ○ Medical comorbidity ○ Severe illness ○ Advanced age
Observable and occult metabolic abnormalities	○ Sedatives ○ Substance abuse/withdrawal (e.g., benzodiazepines, opioids, alcohol) ○ Sleep deprivation ○ Noise

Sedation and delirium in the intensive care unit | NEJM. Sedation and Delirium in the Intensive Care Unit. (2014, January 30).

41

Non-Pharmacologic Interventions

42

Nonpharmacological Interventions

- Treat modifiable contributor of delirium (e.g., infections, pain)
- Maintain comfort and minimize stringent environmental factors
- Invite family members to help their care plan
- Hospital Elder Life Program (H.E.L.P.)
- Avoid using restraints
- Restore patient normal functions

Diagnostic and statistical manual of mental disorders, 4th ed. text rev.: DSM-IV-TR. Arlington, VA: American Psychiatric Association, 2011.

43

2018 PADIS Guideline Recommendations

Recommendation	Strength of Recommendation	Quality of Evidence
Bright light therapy alone should not be used to prevent ICU delirium	Conditional	Moderate
Nonpharmacologic interventions should be used for prevention of ICU delirium and may include strategies to reduce modifiable ICU delirium risk factors and improve cognition, sleep, mobility, hearing, and vision	Conditional	Low

Strategies to reduce modifiable risk factors for ICU delirium	Reorientation and regular reminders
	Cognitive stimulation
	Use of clocks
	Minimizing light and noise to improve sleep
	Early rehabilitation and mobilization
	Reduce sedation to improve wakefulness
	Promote use of hearing aids and/or glasses

PADIS – Pain, Agitation/Sedation, Delirium, Immobility, and Sleep

Devlin JW, Skrobik Y, Gélinas C, et al. Executive Summary: Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med*. 2018;46(9):1532-1548. doi:10.1097/CCM.0000000000003259

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2021 KSCCM Guidelines

Recommendation	Quality of Evidence
The recommended nonpharmacologic strategy for prevention of ICU delirium is the ABCDEF bundle	Level B
Pharmacological interventions are not recommended for the prevention of ICU delirium	Level B
The routine use of haloperidol, atypical antipsychotics, statins, or dexmedetomidine is not recommended for prevention of ICU delirium	Level B

So Y, Lee HJ, Ha EJ, Ha TS. 2021 KSCCM clinical practice guidelines for pain, agitation, delirium, immobility, and sleep disturbance in the intensive care unit. Acute Crit Care. 2022;37(1):1-25. doi:10.4266/acc.2022.00094

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ABCDEF Bundle

- A • Assess/Manage Pain
- B • Both Spontaneous Awakening Trails (SATs) and Spontaneous Breathing Trials (SBTs)
- C • Choice of Analgesia and Sedatives
- D • Delirium Monitoring and Management
- E • Early Mobility and Exercise
- F • Family Engagement and Exposure

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Sleep Fragmentation and Deprivation

Symptoms	• Excessive daytime sleepiness & fatigue • Headaches • Dizziness	• Slowed speech during interactions • Short sleep duration • Frequent errors
Causes of sleep fragmentation	Medical conditions Medications Lifestyle factors Environmental factors Stress Aging	
Strategies for addressing sleep fragmentation	Develop a regular sleep schedule Create a sleep-conducive environment Avoid caffeine and alcohol Practice relaxation techniques Exercise regularly Limit screen time before bed Consider cognitive behavioral therapy for insomnia (CBT-I)	

Sleep fragmentation: Mastering the art of perfect sleep. Empower Sleep: Sleep Fragmentation: Mastering: Perfect Sleep. (2023, April 20)

47

Pharmacologic Treatment

48

Pharmacologic Causes of Delirium

- Analgesics
- Antibiotics
- Anticholinergics
- Antiepileptics
- Antidepressants
- Antihypertensives
- Corticosteroids
- Dopamine agonists
- Gastrointestinal agents
- Herbal preparations
- Hypoglycemic agents
- Muscle relaxants
- Sedative hypnotics
- Polypharmacy

Francis J. Drug-induced delirium: Diagnosis and treatment. CNS Drugs 1996;5:103.

49

Mitigation Strategies for ICU Delirium

Drug	Substitutes or Alternatives Strategies	Comments
Benzodiazepines/Alcohol	Nonpharmacological sleep protocol	Associated with delirium in hospitalized patients. Do not discontinue abruptly
Nonbenzodiazepine (e.g., zolpidem)		
Opioid analgesics	Non-psychoactive pain medications; reserve opioids for breakthrough/severe pain	Consider risk vs benefit. Patients with renal dysfunction are at an elevated risk
Anticholinergics	Lower dose or use behavioral approaches for urinary incontinence	Delirium may continue despite therapeutic drug concentrations
Antipsychotics	Discontinue entirely or use low doses if necessary	Consider risk vs benefit
Histamine H_2 – receptor antagonists	Lower doses or substitute with proton pump inhibitors	Anticholinergic toxic effects occur primarily with high doses of intravenous infusion
Antiparkinsonian agents (e.g., levodopa)	Lower dose or adjust dosing schedule	Dopaminergic toxicity occurs primarily in advanced disease or at high doses

Delirium in hospitalized older adults | Nejm. Delirium in Hospitalized Older Adults. (n.d.). (2017, October 12)

50

50

Assessment Question

DF is a 58-year-old Hispanic male who arrives to the ICU with syncope from a myocardial infarction while teaching after-school football. He is alert with fits of agitation. His pain score is 0 and he is positive for delirium by CAM-ICU. His medications include lisinopril 40 mg daily, ibuprofen 600 mg every 6 hours as needed, rosuvastatin 10 mg daily, famotidine 20 mg twice daily, alprazolam 1 mg daily, and diphenhydramine 25 mg daily for sleep.

What are the best recommendations for managing his complaints of difficulty sleeping?

a. Initiate zolpidem 10 mg daily
b. Discontinue diphenhydramine and initiate nonpharmacologic strategies to promote sleep
c. Add doxylamine to patient's current sleep regimen
d. Make no adjustments to the patient's current regimen

*CAM-ICU → Confusion Assessment Method – Intensive Care Unit

51

51

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d. Make no adjustments to the patient's current regimen

Initiating a nonpharmacologic sleep protocol with low noise, a back rub, warm drink, minimized awakenings, a dark room, and relaxation tapes are recommended for patients having difficulty sleeping. Use of this sleep protocol can decrease the use sedative hypnotics. If the patient continues to have difficulty after 1 hour, the nurse may administer a low dose sedative hypnotic

*CAM-ICU → Confusion Assessment Method – Intensive Care Unit

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Pharmacologic Treatment Options

Typical Antipsychotic (Off-label)	Atypical Antipsychotics (Off-label)	Benzodiazepine (Off-label)
• Haloperidol	• Ziprasidone • Risperidone • Olanzapine • Quetiapine	• Lorazepam

Because benzodiazepines are also an independent risk factor for ICU delirium, they play a limited role in treatment

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Typical Antipsychotic

Agent	Dosing	Route	EPS Risk	Clinical Pearls
Haloperidol	Initial: 0.25- 0.5 mg Elderly Max.: 3 mg/day Daily Max: 5 mg/day	Oral, IM, IV	High	Longest use for delirium; more evidence on use

IM: Intramuscular
IV: Intravenous
EPS: Extrapyramidal symptoms

Delirium in hospitalized older adults | Nejm. Delirium in Hospitalized Older Adults. (2017, October 12)

54

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Atypical Antipsychotic

Agent	Dosing	Route	EPS Risk	Clinical Pearls
Risperidone	Initial: 0.25- 0.5 mg Maximum: 3 mg	Oral or IM	High	Similar to haloperidol in use
Ziprasidone	Initial: 5-10 mg Elderly Max: 40 mg Maximum: 80 mg	Oral or IM	Moderate	Risk of cardiac arrythmia , heart failure, agranulocytosis, and close monitoring needed
Olanzapine	Initial: 2.5- 5 mg Oral Maximum: 20 mg IM Maximum: 30 mg	Oral, IM, or SL	Moderate	Oral route is not recommended to be used for acute treatment
Quetiapine	Initial: 12.5 - 25 mg Maximum: 50 mg	Oral	Low	Most sedating antipsychotic; risk of hypotension present

IM: Intramuscular
SL: Sublingual
EPS: Extrapyramidal symptoms

Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. Cochrane Database Syst Rev (2007)
Delirium in hospitalized older adults | Nejm. Delirium in Hospitalized Older Adults. (2017, October 12)

55

Benzodiazepine

Agent	Dosing	Route	Degree of Sedation	Clinical Pearls
Lorazepam	Initial: 0.25- 0.5 mg Maximum: 2 mg	Oral, IM, IV	Very High	Second-line agent of use; may use in patients with history of alcohol withdrawal or benzodiazepine withdrawal

IM: Intramuscular
IV: Intravenous

Delirium in hospitalized older adults | Nejm. Delirium in Hospitalized Older Adults. (2017, October 12)

56

2018 PADIS Guidelines

Recommendation	Strength of Recommendation	Quality of Evidence
Pharmacological interventions, such as haloperidol, atypical antipsychotics, dexmedetomidine, or ketamine, are not recommended for the prevention of ICU delirium	Conditional	Very low to low
It is not recommended to initiate pharmacologic interventions in patients with subsyndromal delirium	Conditional	Very low to low
The routine use of haloperidol, atypical antipsychotics, or statins is not recommended for treatment of ICU delirium	Conditional	Low
Dexmedetomidine is recommended in patients who are mechanically ventilated and become agitated prior to weaning/extubation	Conditional	Low

Devlin JW, Skrobik Y, Gélinas C, et al. Executive Summary: Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med.* 2018;46(9):1532-1548. doi:10.1097/CCM.0000000000003259
Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018;46(9):e825-e873.doi:10.1097/CCM.0000000000003299

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2018 PADIS Guidelines

Patients with significant distress caused by ICU delirium (e.g., anxiety, fearfulness, hallucinations, or delusions, or who are agitated and may be physically harmful to themselves or others	Short term use of haloperidol or atypical antipsychotics
Mechanically ventilated patients who become agitated prior to weaning and extubation	Dexmedetomidine

Devlin JW, Skrobik Y, Gélinas C, et al. Executive Summary: Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med*. 2018;46(9):1532-1548. doi:10.1097/CCM.0000000000003259
Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018;46(9):e825-e873.doi:10.1097/CCM.0000000000003299

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2021 KSCCM Guidelines

Patients with significant distress caused by ICU delirium	Short term use of haloperidol or atypical antipsychotics
Mechanically ventilated patients who become agitated prior to weaning and extubation	Dexmedetomidine
Patients with delirium due to alcohol or benzodiazepine withdrawal	Benzodiazepines

Sea Y, Lee HJ, Ha EJ, Ha TS. 2021 KSCCM clinical practice guidelines for pain, agitation, delirium, immobility, and sleep disturbance in the intensive care unit. Acute Crit Care. 2022;37(1):1-25. doi:10.4266/acc.2022.00094

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Lorazepam vs Dexmedetomidine

Study Objective:

Compares the sedative effects of lorazepam and dexmedetomidine in medical and surgical adult ICU patients

Primary Outcome:

Number of days alive without delirium or coma

Study	Design	Patient population	Intervention	Results
MENDS Pratik P. Pandharipande, MD, MSClsco; et al. JAMA, 2007	Randomized, double-blind, intention-to-treat, multi-centered	- Adult medical and surgical ICU - Required mechanical ventilation for longer than 24 hours	N = 100 - Dexmedetomidine max of 1.5 µg/kg/hr - Lorazepam 1 mg/hr	Primary Outcome Sedation with dexmedetomidine resulted in more days alive without delirium or coma (median days, 7.0 vs 3.0; P = .01) and a lower prevalence of coma (63% vs 92%; P < .001) than sedation with lorazepam

Conclusion:

This trial supports effective use of dexmedetomidine greater than that of lorazepam

LOS: Length of Stay

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Propofol vs Dexmedetomidine

Study Objective:
Compare propofol and dexmedetomidine, for delirium reduction, survival, and long-term brain function

Primary Outcome:
Number of days alive without delirium or coma within 14 days

Study	Design	Patient population	Intervention	Results
MENDS 2 Christopher G. Hughes, M.D., M.S.C.R., et. al. NEJM, 2021	Randomized, double-blind, intention-to-treat multi-centered	- Admitted to a medical or surgical ICU - Had suspected or known infection - Treated with continuous sedation for invasive mechanical ventilation	N = 438 Dexmedetomidine 0.15 to 1.5 µg/kg/hr Propofol 5 to 50 µg/kg/min	Primary Outcome Number of days alive without delirium or coma over the 14-day intervention period was not significantly different. Dexmedetomidine group (Median 10.7 days; 95% confidence interval [CI], 8.5 to 12.5) Propofol group (Median, 10.8 days; 95% CI, 8.7 to 12.6)

Conclusion:
This trial supports effective place in therapy with propofol as it is non-inferior with dexmedetomidine

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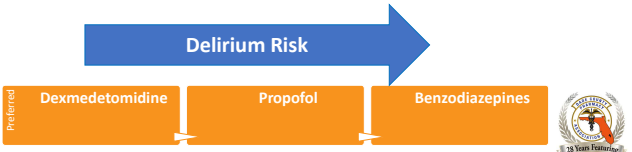
MENDS: Sedation Optimization

- Sedation is not first-line for sleep; Sedation ≠ Sleep
- Monitor patient for sleep fragmentation and deprivation as it may lead to clinical manifestation
- Decrease risk of sleep fluctuations



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Assessment Question

RC is an 82-year-old male who has a past medical history of hypertension, CKD, alcoholism, diabetes mellitus, anxiety, dyslipidemia, and bipolar disorder. RC has been restless while on fentanyl in the ICU for the past 3 days due to pneumonia that has led to septic shock. Patient has been placed on medical ventilation for the past 32 hours.

Physician suspects the patient is developing ICU delirium and wants to limit the risk of delirium. What would you recommend?
a. Midazolam
b. Zolpidem
c. Haloperidol
d. Dexmedetomidine

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Assessment Question

RC is an 82-year-old male who has a past medical history of hypertension, CKD, alcoholism, diabetes mellitus, anxiety, dyslipidemia, and bipolar disorder. RC has been restless while on fentanyl in the ICU for the past 3 days due to pneumonia that has led to septic shock. Patient has been placed on medical ventilation for the past 32 hours.

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a. Midazolam
b. Zolpidem
c. Haloperidol
d. Dexmedetomidine

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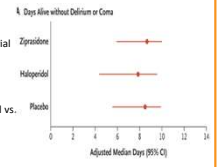
DJO

MIND-USA

- Purpose
  - To clarify any conflicting data on the effects of antipsychotic medications on delirium in patients in the intensive care unit
- Methods
  - Multicenter (16 hospitals in the US), double-blind, randomized, placebo-controlled trial
  - 14-day intervention period with 90 days of follow-up
  - N = 566
- Primary outcome
  - Median days alive without delirium or coma when comparing placebo vs. haloperidol vs. ziprasidone
- Results
  - Haloperidol: 7.9 days without delirium (95% CI, 4.4 - 9.6)
  - Ziprasidone: 8.7 days without delirium (95% CI, 5.9 to 10.0)
  - The use of haloperidol or ziprasidone, as compared with placebo, had no significant effect on the primary end point (odds ratios, 0.88 [95% CI, 0.64 to 1.21]
- Conclusion
  - There was no significant difference in the duration of delirium.



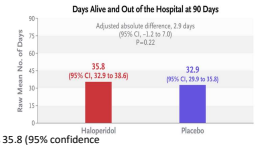
Haloperidol and ziprasidone for treatment of delirium in critical ... Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness. (2018, December 27)

65

AID-ICU

- Purpose
  - To provide evidence on the use of haloperidol in patients experiencing delirium in the ICU
- Methods
  - Multicenter, double-blind, randomized, placebo-controlled trial
  - N=1000
- Primary outcome
  - Duration of days alive and out of hospital at 90 days

  Composite Outcome: Death and length of hospital stay at 90 days
- Results
  - At 90 days, the mean number of days alive and out of the hospital was 35.8 (95% confidence interval [CI], 32.9 to 38.6)
- Conclusion
  - Treatment with haloperidol show significantly greater number of days alive and out of the hospital at 90 days than placebo but did show lower all-cause mortality and length of hospital stay was higher in the haloperidol group than in the placebo group



Haloperidol for the treatment of delirium in ICU patients | Njeim. Haloperidol for the Treatment of Delirium in ICU Patients. (2022, December 29)

66

Slide 65

DJ0 There should be some transition to introduce what the study is addressing because coming straight from the guideline, if it is only mentioned verbally, looking at the slides alone may lose the translation

Daniel Julien, 2024-01-04T04:17:02.125

Assessment Question

True or False? Haloperidol is the preferred agent for the treatment of ICU delirium as it has been shown to decrease length of stay in the hospital.

T: True

F: False

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Assessment Question

True or False? Haloperidol is the preferred agent for the treatment of ICU delirium as it has been shown to decrease length of stay in the hospital.

T: True

F: False

Haloperidol is used off-label for the treatment of ICU delirium in the United States. Length of hospital stay was higher in the haloperidol group than in the placebo group

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Ongoing Studies

- Limiting sedation therapy
  - Limiting sedation and postoperative delirium risk in older patients
- Combining therapy
  - Effect of intravenous acetaminophen combined with propofol or dexmedetomidine on postoperative delirium among older patients in medical and surgical ICU
- Implementing non-pharmacological options
  - Decreasing Delirium Through Music in Critically Ill Older Adults (DDM)

Study	Design	Patient population	Intervention	Results
Decreasing Delirium Through Music: A Randomized Pilot Trial Babar Khan, MD, MS, et. al. Indiana University, 2024	Randomized, paralleled, triple-masking, multi-centered	- Age 50 years or older - English speaking - Admitted to the intensive care unit (medical or surgical) - Expected mechanical ventilator support for ≥48 hours - Consent able through a legally authorized representative - Have access to a telephone	Slow tempo music 60-80 beats per minute relaxing music vs Attention Control One-hour sessions of a silence track twice daily through noise-cancelling headphones for up to 7 days.	Results will be released in 2024 Song Ex: 1. Celine Dion – All by myself 2. Earth Wind & Fire - Spirit 3. Harry Styles - Signs of the times

Subramaniam B et. al. The DEXACET Randomized Clinical Trial. JAMA. 2024 Feb 19
Sieber FE et al. Effect of depth of sedation in older patients undergoing hip fracture repair on postoperative delirium: The STRIDE randomized clinical trial. JAMA Surgery. Aug. 08. 2018

69

Implementation of an Interdisciplinary Effort

- Pharmacists
- Psychiatrists
- Nurses
- Physical therapists
- Physicians
- Respiratory therapists

	Task	Discipline
A	Access, manage, and treat pain	RN, MD, PharmD
B	Breathe when awakened	RN, RT, ER, PharmD
C	Choice of sedation	RN, RT, MD, PharmD
D	Delirium assessment, prevention	RN, PT, PharmD, MD
E	Early mobility and exercise	RN, PT, RT
F	Family engagement	ALL

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Pharmacist Role In Addressing Delirium

- Avoid unnecessary use of pharmacologic interventions through the optimization of a patient's environment, sleep patterns, and mobility.
- Collaborate with nursing staff and provide guidance on Nurses Improving Care for Health System Elders – NICHE
- Identify and resolve the underlying cause: (MIND SPACES)
  - **M**edications
  - **I**nfections
  - **N**umber of co-occurring conditions/comorbidities
  - **D**rug or alcohol use disorder (including withdrawal)
  - **S**urgery
  - **P**ain
  - **A**ge
  - **C**ognitive
  - **E**motional
  - **S**leep disturbances, altered patterns, and sensory deprivation

Pharmacists play a crucial role in ensuring that the antipsychotic is discontinued before hospital discharge

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Key Takeaways

- There are several strategies to mitigate ICU delirium, including mitigating environmental factors, proper screening, and optimizing medication therapy
- Benzodiazepines remains controversial due to its increased risk of delirium
- The 2018 PADIS and 2021 KSCCM guidelines provide several recommendations for the prevention and treatment of ICU delirium, such as recommending supportive care as first line
- The US Food and Drug Administration (FDA) has not approved any medications for delirium
  - Drugs like dexmedetomidine, haloperidol, melatonin, and risperidone have been used in the management of ICU delirium

72

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Unraveling the Mind's Maze

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Baptist Health

January 21st, 2024

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Venous Thromboembolism Management in Special Populations

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January 21st, 2024

28 Years Featuring
South Florida Pharmacy Residents

1

Disclosure

All authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation

2

2

Objectives

- Describe the epidemiology and pathophysiology of deep vein thrombosis and pulmonary embolism
- Review risk factors, diagnosis, and clinical presentation of venous thromboembolism
- Describe guideline-directed medical therapy for prophylaxis and treatment of deep vein thrombosis and pulmonary embolism in obesity and renal impairment
- Discuss diagnosis and pharmacological treatment of heparin induced thrombocytopenia

3

3

Background

4

Definitions

Venous Thromboembolism

Deep Vein Thrombosis:
Blood clot that forms within the deep veins of the legs, arms, mesenteric, or cerebral veins

Pulmonary Embolism:
Deep venous thrombi that has detached and embolized to the pulmonary circulation

5 *Int J Crit Illn Inj Sci.* 2013;3(1):69-72.

5

Epidemiology

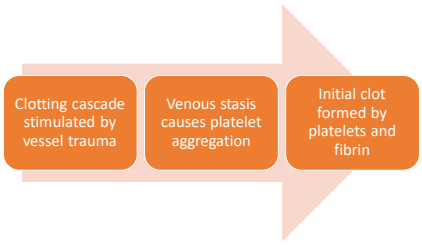
- Definite number of people affected by VTE is unknown, although as many as 900,000 people could be affected each year in the United States
- About one-quarter of patients who have a PE experience sudden death as the first symptom
- Estimates suggest that 60,000-100,000 Americans die of DVT/PE yearly
- Among people who have had a DVT, one third to one half will have long-term complications

6 CDC. Venous Thromboembolism. 2023.

DVT: deep vein thrombosis
PE: pulmonary embolism

6

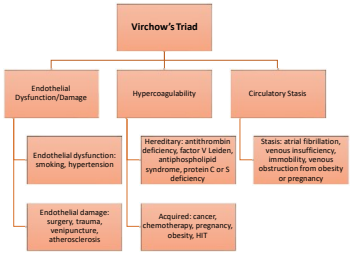
Pathophysiology



7 *Cardiovasc Diagn Ther.* 2017;7(Suppl 3):S276-S284.

7

Risk Factors



8 *Clin Med Res.* 2010;8(3-4):168-172.

HIT: heparin induced thrombocytopenia

8

Clinical Presentation

Deep Vein Thrombosis

- Lower extremity
  - Unilateral calf or thigh pain, described as cramping or pulling discomfort
  - Swelling or localized redness in leg
- Upper extremity
  - Shoulder or neck discomfort
  - Paresthesia of the affected arm
  - Hand or arm swelling

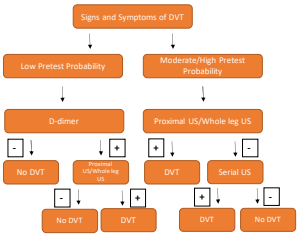
Pulmonary Embolism

- Chest pain
- Cough
- Dyspnea
- Hypoxemia
- Shock
- Tachycardia
- May be asymptomatic or present with sudden death

9 *Best Pract Res Clin Haematol.* 2012;25(3):243-251.

9

Diagnosis: Deep Vein Thrombosis



 Blood Adv. 2020;4(19):4693-4738. US: Ultrasound

10

Diagnosis: Deep Vein Thrombosis

Wells Prediction Rule for DVT

Variable	Points
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for >3 days or major surgery within 12 weeks	1
Localized tenderness along distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by >3 cm compared with asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Past history of DVT	1
Alternative diagnosis as likely or greater that of DVT	-2

Low risk: ≤0 points
Intermediate risk: 1-2 points
High risk: ≥3 points

 Am Fam Physician. 2012;86(10):913-919.

11

Diagnosis: Deep Vein Thrombosis

Constans Clinical Decision Score for Upper Extremity DVT

Patient Characteristics	Points
Venous material present (Central venous catheter or pacemaker thread)	1
Localized pain	1
Unilateral edema	1
Other diagnosis at least as plausible	1

Low risk: ≤0 points
Intermediate risk: 1 point
High risk: 2-3 points

 Am Fam Physician. 2012;86(10):913-919.

12

Diagnosis: Deep Vein Thrombosis

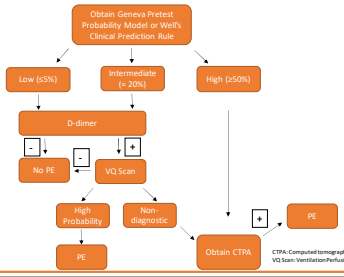
D-Dimer Assay

- D-dimer is the degradation product of a cross-linked fibrin blood clot and is usually elevated in patients with acute venous thromboembolism
- Sensitivity and specificity vary based on the type of assay ordered
  - D-dimers have a high sensitivity but low specificity for detecting pulmonary embolism or deep vein thrombosis in low-risk populations
- Test interpretation
  - Positive D-dimer ≥0.50 mcg/mL FEU

13 *Am Fam Physician.* 2012;86(10):913-919. FEU: fibrinogen equivalent units

13

Diagnosis: Pulmonary Embolism



14 *Blood Adv.* 2020;4(19):4693-4738. CTPA: Computed tomography pulmonary angiography VQ Scan: Ventilation Perfusion Scan

14

Diagnosis: Pulmonary Embolism

Well's Clinical Prediction Rule for PE

Variable	Points
Cancer	1
Hemoptysis	1
Previous PE or DVT	1.5
Heart rate >100 beats/minute	1.5
Recent surgery or immobilization	1.5
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3

Probability of PE:
- Low probability: 0-1 points
- Moderate probability: 2-6 points
- High probability: ≥7 points

Geneva Pretest Probability Model

Variable	Points
Age ≥65 years	1
Previous DVT or PE	3
Surgery or fracture within one month	2
Active malignant condition	2
Unilateral limb pain	3
Hemoptysis	2
Heart rate 75 to 94 beats per minute	3
Heart rate ≥95 beats per minute	5
Pain on deep palpation	4

Probability of PE:
- Low probability: 0-3 points
- Intermediate probability: 4-10 points
- High probability: 11 points

15 *Blood Adv.* 2020;4(19):4693-4738.

15

Diagnosis: Pulmonary Embolism

Pulmonary Embolism Rule-out Criteria

Variable	No	Yes
Is the patient older than 49 years of age?	0	+1
Is the pulse oximetry <95% while on room air?	0	+1
Is the heart rate above 99 beats per minute?	0	+1
Does the patient have a prior history of venous thromboembolism?	0	+1
Has the patient had recent surgery or trauma or hospitalization in the last 4 weeks?	0	+1
Is there a history of hemoptysis?	0	+1
Is the patient taking estrogen?	0	+1
Does the patient have unilateral leg swelling?	0	+1

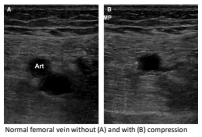
16 *Blood Adv.* 2020;4(19):4693-4738.

16

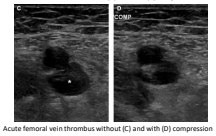
Diagnosis: Deep Vein Thrombosis

Imaging

- Venous compression ultrasonography
  - Gold standard
  - Use limited in clinical practice
  - Test interpretation
    - Lack of compressibility is the most sensitive and specific criterion for diagnosis
- Duplex ultrasonography
  - Typically used in clinical practice
  - Diagnostic method include both visual and sound technology



Normal femoral vein without (A) and with (B) compression



Acute femoral vein thrombus without (C) and with (D) compression

17 *Am Fam Physician.* 2012;86(10):913-919.

17

Classification of Pulmonary Embolism

PE

Acute: sudden obstruction of the pulmonary arteries by an embolism

Chronic: persistent pulmonary hypertension for at least 6 months following acute PE

18 *Med Clin North Am.* 2019;103(3):549-564.

18

Classification of Pulmonary Embolism

Acute PE		
Low Risk PE	**Sub-massive PE**	**Massive PE**
• Absence of hypotension, shock, right ventricular dysfunction, and myocardial necrosis	• Right ventricular dysfunction OR • Myocardial necrosis AND • Absence of systemic hypotension (SBP >90 mm Hg)	• Sustained hypotension (SBP <90 mm Hg) not due to arrhythmia, hypovolemia, sepsis, or left ventricular dysfunction, and either lasting for at least 15 minutes or necessitating the administration of inotropes OR • Pulselessness OR • Persistent profound bradycardia (heart rate <40 bpm) plus findings of shock

19 *Med Clin North Am.* 2019;103(1):549-564.

SBP: systolic blood pressure
bpm: beats per minute

19

Assessment Question

True or False: Endothelial injury, stasis, and hypercoagulability are 3 factors that contribute to development of venous thrombosis and are often referred to as Virchow's triad.

a. True ✓
b. False

20

20

Anticoagulation Therapy

21

Pharmacological Therapy

Medication	Mechanism of Action	Important Points
Unfractionated Heparin (UFH)	Binds to antithrombin and prevents the conversion of fibrinogen to fibrin	• Side effects: bleeding, HIT, hyperkalemia • Monitoring: CBC, PTT or anti-Xa levels
Enoxaparin (Lovenox®)	Potentiates antithrombin to inactivate Factor Xa and Factor IIa	• BBW: Epidural/spinal hematomas in those receiving neuraxial anesthesia or undergoing spinal puncture • Side effects: bleeding, thrombocytopenia, hyperkalemia • Monitoring: CBC, SCr

CBC: complete blood count
PTT: partial thromboplastin time
BBW: black box warning
SCr: serum creatinine

22 US Food and Drug Administration. Heparin. Package insert. Fresenius Kabi. 2017
US Food and Drug Administration. Enoxaparin. Package insert. Sanofi-Aventis. 2009.

22

Pharmacological Therapy

Direct Factor Xa Inhibitors	
Medication	**Important Points**
Apixaban (Eliquis®)	• BBW: Spinal/epidural hematomas, premature discontinuation increases the risk of thrombotic complications • Side effects: bleeding • Monitoring: CBC, SCr • Important points: o Not recommended with prosthetic heart valves or antiphospholipid syndrome o Fondaparinux contraindicated if CrCl <30 mL/min when used for active treatment of VTE
Rivaroxaban (Xarelto®)	
Edoxaban (Savaysa®)	
Fondaparinux (Arixtra®)	

US Food and Drug Administration. Apixaban. Package insert. Bristol-Myers Squibb. 2012.
US Food and Drug Administration. Rivaroxaban. Package insert. Janssen Pharmaceuticals. 2016.
US Food and Drug Administration. Edoxaban. Package insert. Daiichi Sankyo. 2015.
23 US Food and Drug Administration. Fondaparinux. Package insert. Daiichi Sankyo. 2009.

CrCl: creatinine clearance

23

Pharmacological Therapy

Direct Thrombin Inhibitors	
Medication	**Important Points**
Dabigatran (Pradaxa®)	• BBW: Spinal/epidural hematomas, premature discontinuation increases the risk of thrombotic complications • Side effects: Dyspepsia, gastritis symptoms, bleeding • Monitoring: CBC, SCr • Important points: o Not recommended for mechanical prosthetic heart valves o Avoid use if CrCl ≤ 30 mL/min
Argatroban	• Side effects: bleeding • Monitoring: CBC, PTT • Important points: o Indicated for HIT and in patients undergoing PCI who are at risk for HIT o Use with caution in patients with hepatic impairment

24 US Food and Drug Administration. Edoxaban. Package insert. Boehringer Ingelheim Pharmaceuticals. 2011.
US Food and Drug Administration. Argatroban. Package insert. Sandoz. 2011.

ACS: acute coronary syndrome
PCI: percutaneous coronary intervention

24

Pharmacological Therapy

Direct Thrombin Inhibitors	
Medication	**Important Points**
Bivalirudin (Angiomax®)	• Side effects: bleeding, acute stent thrombosis • Monitoring: CBC, PTT • Important points: ○ Indicated for patients with ACS undergoing PCI, including those with HIT

25 US Food and Drug Administration. Bivalirudin. Package insert. The Medicines Company. 2016.

ACS: acute coronary syndrome

25

Pharmacological Therapy

Medication	Mechanism of Action	Important Points

Warfarin (Coumadin®)	Blocks Vitamin K epoxidase reductase and inhibits coagulation factors 2,7,9,10 and protein C&S of the intrinsic and extrinsic pathway	• BBW: teratogenic and bleeding risk
		• Side effects: bleeding, purple toe syndrome, skin necrosis
		• Monitoring: CBC, PT/INR
		  ○ Goal INR 2-3 for most indications
		  ○ Goal INR 2.5-3.5 for mechanical mitral heart valve or 2 mechanical heart valves
		• Important points:
		  ○ Warnings: tissue necrosis, gangrene, HIT, presence of CYP2C9*2 or *3 alleles and/or polymorphism of VKORC1 gene

26 US Food and Drug Administration. Warfarin. Package insert. Bristol-Myers Squibb. 2011.

PT: prothrombin time
INR: international normalized ratio

26

Treatment of Pulmonary Embolism

Low Risk PE	Sub-massive PE	Massive PE

• Anticoagulation: Direct oral anticoagulants are preferred
• Candidates for early discharge
	• Anticoagulation: Consider unfractionated heparin over others if any of the therapies below are possible
	  ○ Systemic thrombolytic
	  ○ High risk of bleeding: Half-dose thrombolytic
	  ○ Catheter-directed therapy
	  ○ Surgical embolectomy
	  ○ High-risk PE and cardiogenic shock: Mechanical support to allow stability for thrombolysis, catheter-directed therapy, or surgical embolectomy	

27 *Blood Adv.* 2020;4(19):4693-4738.

27

Prophylaxis and Treatment of DVT and PE in Obesity

28

Association Between Obesity and Venous Thromboembolism

Obesity and First Occurrence of VTE

- Case-control study
- N=732 patients
- Obesity was associated with a 6.2-fold increased risk for VTE
- Risk of VTE associated with obesity was highest in patients aged >50 years and in cases included in classes II (BMI ≥35 and <40) and III (BMI ≥40) of obesity

29 *Med Pharm Rep.* 2020;93(2):162-168.

29

DOACs Use in Obese Patients with DVT

- Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis (ISTH)
  - 2016 Guidance: Suggested against using DOACs in patients >120 kg or BMI >40 kg/m^2
  - 2021 Guidance: Suggested that it is okay to use apixaban and rivaroxaban in obese and severely obese patients
- 2023 Expert Consensus Panel
  - Multidisciplinary panel reviewed guidelines and evidence through 2022
  - Survey results
    - DOACs should be considered in all obese patients but data is limited in patients with BMI >50 kg/m^2
    - Peak and trough levels should not influence management decisions
    - Data about efficacy of dose reduction for extended VTE prophylaxis in obese patients is limited

30 *Am J Med.* 2023;136(6):523-533.

DOACs: direct oral anticoagulants
BMI: body mass index

30

DOACs and the Risk of Adverse Clinical Outcomes Among Patients with Different Body Weight Categories: a Large Hospital-Based Study

- Retrospective, hospital-based cohort study sampled adult patients receiving DOACs
- N=97,413
- Outcomes: All-cause mortality, clinically relevant non-major bleeding events, ischemic stroke, and any thromboembolic events
- Results:
  - All-cause mortality: Normal weight (74%), obese (63%), and morbidly obese BMI classes (57%)
  - Clinically relevant non-major bleeding events: 246 events (30.3%) in overweight, 38 events (4.7%) in obese patients, and 527 events (65.0%) in normal-weight patients
  - Ischemic stroke: Lower in morbidly obese patients compared to normal body weight patients (OR 0.42, 95% CI: 0.36–0.88, p=0.001)
  - Thromboembolic events: Higher in morbidly obese patients than in normal-weight patients (OR 3.63, 95% CI: 2.82–4.68, p=0.001)

31 *Eur J Clin Pharmacol*. 2023;6(8):e2328033

OR: odds ratio
CI: confidence interval

31

Comparing DOACs and Vitamin K Antagonist Use in Morbidly Obese Patients with VTE

- Retrospective single-center cohort study
- Included patients with a BMI of at least 40 kg/m^2 with acute VTE and initiated on a DOAC or warfarin
- N=2,175
- Outcomes: Recurrent VTE confirmed by ultrasound for DVT or CTA for PE and determined through individual review of clinical medical records
- Results:
  - 247 (11.8%) morbidly obese (≥40 kg/m^2) patients
  - Thirty percent of the study population had a BMI >50 kg/m^2
  - Hazard of experiencing a recurrent thrombosis was not statistically significantly different among morbidly obese patients treated with a DOAC compared with VKA (HR 0.28, CI 0.07-1.11, p=0.07)

32 *EJHaem*. 2022;3(2):457-462.

VKA: vitamin K antagonist

32

Direct Oral Anticoagulants

Apixaban	Rivaroxaban	Edoxaban	Dabigatran
• VTE Prophylaxis ○ 2.5 mg oral twice daily for 12 days after knee or 35 days after hip replacement surgery • VTE/PE Treatment ○ 10 mg oral twice daily for 7 days, then 5 mg oral twice daily	• VTE Prophylaxis ○ 10 mg oral once daily for 31-39 days after knee/hip replacement surgery (avoid if CrCl <30 mL/min) • VTE/PE Treatment ○ 15 mg oral twice daily for 21 days, then 20 mg oral once daily with food (avoid if CrCl <30 mL/min)	• VTE/PE Treatment ○ 60 mg oral once daily ○ 30 mg oral once daily if CrCl 15-50 mL/min, <60 kg ○ Not recommended if CrCl <15 mL/min ○ Requires bridging with parenteral therapy • **Not recommended if BMI ≥40 kg/m^2 or weight >120 kg**	• VTE Prophylaxis after knee/hip surgery ○ 110 mg on day 1, then 220 mg daily • DVT/PE Treatment ○ 150 mg oral twice daily • Avoid if CrCl <30 mL/min) • **Not recommended if BMI ≥40 kg/m^2 or weight >120 kg**

US Food and Drug Administration. Eliquis®. Package insert. Bristol-Myers Squibb. 2012.
US Food and Drug Administration. Xarelto®. Package insert. Janssen Pharmaceuticals. 2016.
US Food and Drug Administration. Savaysa®. Package insert. Daiichi Sankyo. 2019.
33 US Food and Drug Administration. Pradaxa®. Package insert. Boehringer Ingelheim Pharmaceuticals. 2011.

33

Parenteral Anticoagulation Therapy

Enoxaparin

- VTE Prophylaxis
  - 40 mg subcutaneously daily or 30 mg subcutaneously every 12 hours
  - 30 mg subcutaneously daily if CrCl <30 mL/min
  - **BMI ≥40 kg/m²:**
    - **40 mg subcutaneously every 12 hours**
    - **40 mg subcutaneously every 24 hours if CrCl <30 mL/min**
- VTE Treatment and ACS
  - 1 mg/kg subcutaneously every 12 hours or 1.5 mg/kg subcutaneously every 24 hours
  - 1 mg subcutaneously every 24 hours if CrCl <30 mL/min

Heparin

- VTE prophylaxis:
  - **BMI ≥30 kg/m²: 5,000 to 7,500 units subcutaneously every 8 hours**
  - **BMI >50 kg/m²: Consider 7,500 units subcutaneously every 8 hours**
- VTE treatment:
  - 80 units/kg bolus followed by 18 units/kg/hr IV

34 US Food and Drug Administration. Enoxaparin. Package insert. Sanofi-Aventis. 2009.
US Food and Drug Administration. Heparin. Package insert. Fresenius Kabi. 2017

IV: Intravenous
ACS: Acute Coronary Syndrome

34

Strategies Involving LMWH for the Treatment and Prevention of VTE in Patients with Obesity: A Systematic Review and Meta-Analysis

- Included 11 studies (a total of 6266 patients) in the prevention group, and 6 studies (a total of 3225 patients) in the treatment group
- Primary outcomes: Occurrence or recurrence of PE or DVT, and the incidence of major and minor bleeding events during hospitalization or follow-up
- Secondary outcomes: Incidence of supratherapeutic and subtherapeutic anti-Xa levels
- Results:
  - VTE prophylaxis: The high-dosage group* had a lower incidence of VTE (OR: 0.47, 95% CI: 0.27-0.82, P=0.007) and a similar incidence of bleeding events (OR: 0.86, 95% CI: 0.69-1.08, P=0.020)
  - VTE therapy: The reduced-dosage group† had a similar incidence of VTE recurrence (OR: 0.86, 95% CI: 0.11-6.84, P=0.89) but a lower incidence of bleeding events (OR: 0.30, 95% CI: 0.10-0.89, P=0.03)

*Scholten 2002 (enoxaparin 40 mg/12h), Miranda 2017 (enoxaparin 60 mg/day), Hamad 2005 (enoxaparin 60 mg/12 h)
†Thompson-Moore 2015 (enoxaparin 0.83 mg/kg/ 12 h), Curry 2018 (enoxaparin 0.8 mg/kg/12 h), Van Oosterom 2019 (enoxaparin <0.85 mg/kg/12 h)

35 *Front Endocrinol (Lausanne). 2023;14:1084511.*

35

Assessment Question

Standard dosing of direct oral anticoagulants should still be considered for venous thromboembolism prevention and treatment for patients with a body mass index less than or equal to:

a) 28 kg per m^2
b) 30 kg per m^2
c) 35 kg per m^2
d) 40 kg per m^2 ✓

36

36

Prophylaxis and Treatment of DVT in Renal Impairment

37

Renal Impairment

- Patients with chronic kidney disease are at an increased risk for both VTE and bleeding
- The relative risk of VTE increases with decreasing renal function, from 1.28 for those with an estimated glomerular filtration rate (eGFR) of 60-89 mL/min to 2.09 for those with an eGFR between 15-59 mL/min
- Patients with end-stage renal disease (ESRD) receiving hemodialysis have a 2.3- to >13-fold increased risk of VTE
- Patients with chronic kidney disease also have an increased risk of bleeding

38 *Clin Cardiol.* 2019;42(8):774-782.

38

Guideline-Directed Therapy in Renal Impairment

39

Oral Anticoagulants

- Warfarin has been traditionally used in the treatment of VTE therapy after initial acute treatment with intravenous heparin or subcutaneous LMWH
- Warfarin has many limitations, including:
  - Narrow therapeutic window
  - Frequent international normalized ratio (INR) monitoring
  - Food-drug and drug-drug interactions
  - Dosing
- In recent years, the direct oral anticoagulants (DOACs) have slowly replaced warfarin in the management of VTE prophylaxis/ treatment
- Randomized clinical trials in patients with VTE have shown that DOACs, such as rivaroxaban and apixaban, provide similar efficacy as warfarin, with a lower risk of major bleeding

40 *Clin Cardiol*. 2019;42(8):774-782.

40

Direct Oral Anticoagulants

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Onset of Action	2-3 hr	2-4 hr	1-2 hr	1.5 hr
Renal Clearance	27%	36%	50%	80%
Removed by Dialysis	No	No	No	Yes
Clinical Trials*	ARISTOTLE/ AMPLIFY	ROCKET- AF	ENGAGE-AF TIMI	RE-LY

*Patients with CrCl <30 mL/min (<25 mL/min for apixaban) were excluded from these trials

41 *Clin Cardiol*. 2019;42(8):774-782.

41

Apixaban

- Excreted in both feces and urine as metabolites
  - 27% of total clearance
- Usual dose:
  - 10 mg orally twice daily for 7 days, followed by 5 mg twice a day
- Dose Adjustments in renal impairment:
  - CrCl <25 mL/min: Use with caution as these patients were not included in clinical trials
  - Recent, retrospective studies suggest similar efficacy of apixaban to warfarin, with limited bleeding risk in patients with advanced renal impairment and dialysis patients
- Monitor:
  - Hemoglobin (Hgb), hematocrit (Hct), serum creatinine, signs of bleeding

42 Eliquis (apixaban) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; April 2021.

42

Standard versus Reduced Dose Apixaban

- Warfarin and apixaban are the only oral anticoagulants approved by the US Food and Drug Administration (FDA) for use in patients with ESRD on hemodialysis (HD) for the treatment of acute VTE
- The optimal apixaban dosing strategy with respect to safety and efficacy for the treatment of VTE in severe or end-stage renal disease remains unknown
- A recent retrospective cohort study was conducted at four large academic medical centers within the United States between January 1st, 2013 and August 31st, 2021
- The study compared the clinically relevant bleeding rate between standard (5 mg twice daily) and reduced dose (2.5 mg twice daily) apixaban for the treatment of VTE in patients with severe or ESRD

43 *Thromb Res.* 2022;220(2022):91-96.

43

Standard versus Reduced Dose Apixaban

Primary outcome: the rate of clinically relevant bleeding during anticoagulation with apixaban, including all major and clinically relevant non-major bleeds

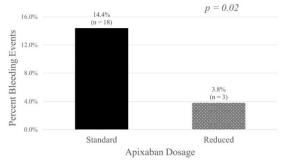


Fig. 2. Percent bleeding events by apixaban dosage.

Secondary outcomes: were rate of VTE recurrence during anticoagulation with apixaban, time to clinically relevant bleed, and time to VTE recurrence

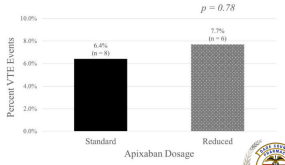


Fig. 3. Percent VTE events by dose.

44 *Thromb Res.* 2022;220(2022):91-96.

44

Standard versus Reduced Dose Apixaban

Conclusion:

- The results suggested that standard dose apixaban may result in a significantly higher rate of clinically relevant bleeding compared to reduced dose apixaban, with similar rate of recurrent VTE, in patients with severe or end-stage renal disease requiring VTE treatment
- More studies are needed to confirm these findings
- In patients with severe or end-stage renal disease a reduced dose of apixaban may be considered, especially in the setting of additional risk factors for bleeding

45 *Thromb Res.* 2022;220(2022):91-96.

45

Rivaroxaban

- Approximately one-third of the dose of rivaroxaban administered is excreted in the urine as unchanged drug
  - Active renal secretion accounts for 30% and glomerular filtration accounts for 6%
- Usual dose:
  - VTE treatment: 15 mg twice daily for 21 days followed by 20 mg once daily
  - VTE prevention: 10 mg once daily
- Dose Adjustments in renal impairment:
  - CrCl <15 mL/min: Use should be avoided due to limited data
  - Hemodialysis/peritoneal dialysis: Use should be avoided
- Monitor:
  - Hgb, Hct, serum creatinine, signs of bleeding

46 Xarelto (rivaroxaban) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals Inc; January 2022.

46

Edoxaban

- Renal excretion is approximately 50%
- Usual dose for DVT treatment:
  - Patient weight >60 kg: 60 mg once daily, after at least 5 days of initial treatment with a parenteral anticoagulant
  - Patient weight ≤60 kg: 30 mg once daily, after at least 5 days of initial treatment with a parenteral anticoagulant
- Dose Adjustments in renal impairment:
  - CrCl 15 to 50 mL/min: 30 mg once daily
  - CrCl <15 mL/min: Use is not recommended
  - Hemodialysis/peritoneal dialysis: Use should be avoided
- Monitor:
  - Hgb, Hct, serum creatinine, signs of bleeding

47 Savaysa (edoxaban) [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo Inc; September 2023.

47

Dabigatran

- Renal elimination of dabigatran is approximately 80%, and thus dabigatran should be avoided in patients with severe renal impairment
- Usual for DVT treatment:
  - 150 mg twice daily, after at least 5 days of initial therapy with a parenteral anticoagulant
- Dose adjustments in renal impairment:
  - CrCl of 30–50 mL/min: 75 mg twice daily
  - CrCl ≤30 mL/min: Use should be avoided
  - Hemodialysis/peritoneal dialysis: Use should be avoided
- Monitor:
  - Hgb, Hct, serum creatinine, signs of bleeding

48 Pradaxa (dabigatran) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; July 2020.

48

Assessment Question

Which direct oral anticoagulant has the highest proportion of drug that is cleared renally?

a) Dabigatran ✓
b) Apixaban
c) Rivaroxaban
d) Edoxaban

49

49

DOACs versus Warfarin/LMWH

- Direct Oral Anticoagulant Use in Chronic Kidney Disease and Dialysis Patients With Venous Thromboembolism: A Systematic Review of Thrombosis and Bleeding Outcomes
  - Evaluated how treatment with DOACs affected VTE and bleeding outcomes compared with warfarin in patients with chronic kidney disease (CKD) and/or on dialysis
  - Included randomized control studies (RCT), observation studies, and case series which enrolled patients > 18 years of age, who were on one of the DOACs for the treatment of VTE (PE and/or DVT), and had concomitant CKD, with eGFR < 60 mL/min/1.73 m^2 or on dialysis
  - Total of 9 articles were included
    - 2 were RCT and 7 were prospective or retrospective cohort studies
  - Outcomes:
    - All studies reported recurrent VTE as primary outcomes, except for 2 studies that reported only bleeding outcome
    - All studies compared bleeding outcomes between the DOAC group and the warfarin group

50 *Ann Pharmacother.* 2021;55(6):711-722.

50

DOACs versus Warfarin/LMWH

Thrombosis Outcomes		
Apixaban	**Rivaroxaban**	**Dabigatran**

• Four studies compared apixaban with warfarin for recurrent VTE as a primary outcome
  ○ Three studies had patients with CKD stage 4/5 and end-stage kidney disease (ESRD)
  ○ One study only included patients on dialysis
• In these studies, there was no significant difference in incidence of recurrent VTE reported between apixaban and warfarin
	• Two studies compared incidence of recurrent VTE between rivaroxaban and warfarin
	• Both studies included patients with various stages of kidney function
	• One study reported that rivaroxaban was noninferior to enoxaparin/VKA for the prevention of recurrent VTE across various renal function
	• The other study reported that the incidence rates of recurrent VTE were significantly lower in the rivaroxaban group compared with the warfarin group
		• One study was included and was a pooled analysis of RE-COVER and RE-COVER II
		• Compared the incidence of recurrent VTE between dabigatran and warfarin in CKD subgroups
		• Concluded there was no apparent difference between the dabigatran and warfarin patients

51 *Ann Pharmacother.* 2021;55(6):711-722.

51

DOACs versus Warfarin/LMWH

Bleeding Outcomes		
Apixaban	**Rivaroxaban**	**Dabigatran**
• One study of ESRD patients found that the apixaban group experienced fewer major bleeding events than the warfarin group • One study of ESRD patients on HD, found there were 7 major bleeding events in the warfarin group compared with zero in the apixaban group, although not statistically significant • One study of patients with CKD stage 4/5, there was no difference in bleeding rates with apixaban or warfarin regardless of CKD stage, but apixaban was less associated with bleeding than warfarin at 6 to 12 months	• One study found that in patients receiving rivaroxaban, major bleeding occurred in: ○ 1.4% in rivaroxaban group vs 3.0% in warfarin group of patients with mild kidney impairment ○ 0.9% in rivaroxaban group vs 3.9% in warfarin group of those with moderate kidney impairment ○ 0% in rivaroxaban group vs 9.1% in warfarin group of those with severe kidney impairment	• One RCT compared major bleeding rates between dabigatran and warfarin • There was no apparent difference between the dabigatran (5.7%) and warfarin (4.4%) patients

52 *Ann Pharmacother.* 2021;55(6):711-722.

52

DOACs versus Warfarin/LMWH

- Conclusion:
  - With the exception of 1 study where dabigatran showed better efficacy than warfarin in elderly patients with moderate kidney impairment, there was no significant difference between DOACs and warfarin for reducing recurrent VTE events
  - There was no significant difference between DOACs and warfarin in overall bleeding risk
  - Except with apixaban use, the risk of overall major bleeding from DOACs increased as the degree of kidney impairment increased
  - Apixaban had less overall bleeding when compared with warfarin in patients on hemodialysis

53 *Ann Pharmacother.* 2021;55(6):711-722.

53

Vitamin K Antagonist

- There are currently no dosage adjustments recommended for patients with renal impairment
- The narrow therapeutic window and high variability of warfarin in different individuals often lead to supratherapeutic INR in renal impairment
- To prevent the risk of hemorrhage, an average reduction of warfarin doses is usually considered:
  - Reduce by 10% in patients with eGFR between 30-59 mL/min/1.73m^2
  - Reduce by 19-20% in patients with eGFR < 30 mL/min/1.73m^2
  - Unlikely to be dialyzed (highly protein bound)
- Monitor:
  - INR, Hgb, Hct, signs of bleeding

54 Jantoven (warfarin) [prescribing information]. Maple Grove, MN: Upsher-Smith Laboratories Inc; 2013.

54

Unfractionated Heparin

- Unfractionated heparin (UFH) is a preferred agent in renal impairment because it has a short half-life that allows for the anticoagulant effect to wear off within 1 to 4 hours
- VTE prophylaxis dosing:
  - 5000 units subcutaneous every 8 hours
- VTE treatment dosing:
  - 80 units/kg bolus followed by a continuous infusion of 18 units/kg/hour or 5,000 units bolus followed by 1,333 units/hour
- No renal adjustment is recommended
- Monitor:
  - Activated partial thromboplastin time (aPTT) or anti-factor Xa, Hgb, Hct, platelets, signs of bleeding

55 Heparin sodium in 0.9% sodium chloride [prescribing information]. New York, NY: Pfizer Labs; September 2019.

55

Enoxaparin

- Low-molecular-weight heparins (LMWHs) are preferred agents due to their pharmacokinetic predictability, and ease of administration without the need for monitoring
- Renal clearance is indirectly proportional to molecular weight and requires dose adjustments in CKD stages 4 and 5
- Usual dosing:
  - VTE prophylaxis dosing: 40 mg subcutaneous once daily
  - VTE treatment: 1 mg/kg subcutaneous every 12 hours (preferred) or 1.5 mg/kg once every 24 hours
- Dose adjustments in renal impairment:
  - CrCl <30 mL/min:
    - VTE prophylaxis dosing: 30 mg subcutaneous once daily
    - VTE treatment: 1 mg/kg subcutaneous once daily
  - Hemodialysis/peritoneal dialysis: Use should be avoided
- Monitor: anti-factor Xa monitoring is not recommended, but should monitor for signs of bleeding

56 Lovenox [enoxaparin] [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US LLC; April 2022.

56

LMWH versus Unfractionated Heparin

- Safety and Efficacy of Enoxaparin Compared With Unfractionated Heparin for Venous Thromboembolism Prophylaxis in Hemodialysis Patients
  - The purpose of the study was to compare the safety and efficacy of enoxaparin with unfractionated heparin for VTE prophylaxis in HD patients
  - Single-center, retrospective, cohort study
  - Included:
    - Any patient who received HD with at least 2 consecutive days of concomitant VTE prophylaxis with enoxaparin 30 mg daily or UFH 5000 units every 8 hours was screened for enrollment
  - Outcomes:
    - The primary outcome was a composite of bleeding events attributed to enoxaparin or UFH during the hospitalization
    - Secondary outcomes evaluated the occurrence of confirmed DVT or PE during the hospital admission assessed

57 *Hosp Pharm*. 2017;52(9):623-627.

57

LMWH versus Unfractionated Heparin

Outcome, n (%)	UFH (n = 150)	Enoxaparin (n = 75)	*P* value
Leg Doppler ultrasounds confirming VTE	0 (0)	0 (0)	NA
Chest CT confirming VTE	0 (0)	0 (0)	NA
VQ scan confirming VTE	0 (0)	0 (0)	NA
Elevated D-dimer	0 (0)	0 (0)	NA
Documented bleed	1 (0.7)	1 (1.3)	1
Documented bleed related to prophylaxis	0 (0)	0 (0)	NA
Major bleed	0 (0)	0 (0)	NA
CRNM	0 (0)	0 (0)	NA
Minor bleed	0 (0)	0 (0)	NA

Note. CRNM = clinically relevant non-major; CT = computed tomography; NA = not applicable; UFH = unfractionated heparin; VTE = venous thromboembolism.

58 *Hosp Pharm.* 2017;52(9):623-627.

58

LMWH versus Unfractionated Heparin

- Conclusion:
  - Enoxaparin 30 mg daily may be as safe and effective as UFH 5,000 units every 8 hours for VTE prophylaxis in medically ill patients receiving HD
  - 1 patient in each cohort had a bleeding event, yet no patients in either cohort experienced a bleeding event directly attributed to the prophylactic regimen administered during their hospitalization
  - This was a single-center study and more data is needed to conclude findings may be applicable to the general population

59 *Hosp Pharm.* 2017;52(9):623-627.

59

Prophylaxis and Treatment of DVT in Renal Impairment

- Patients with chronic kidney disease and those with ESRD receiving hemodialysis have an increased risk of VTE and an increased risk of bleeding, making their management complex
- Warfarin as been increasingly been replaced with DOACs given their ease of use and safety profile
- Apixaban is a commonly used DOAC in patients with renal impairment given findings from literature and its limited renal clearance, but more studies are needed to conclude the optimal dosing in patients with renal impairment
- Unfractionated heparin and LMWH are also safe alternatives for prophylaxis and treatment of DVT in patients with renal impairment, although dosing adjustments may be necessary in the case of LMWH

60

60

Heparin-Induced Thrombocytopenia

61

Heparin-Induced Thrombocytopenia (HIT)

HIT Type I

- Non- immune mediated
- Develops 2-4 days after initiation
- Platelets rarely <100,000/µL
- Spontaneous recovery

HIT Type II

- Immune mediated
- Develops 5-14 days after initiation
- Platelets <150,000/µL or ≥50% decrease from baseline
- No spontaneous recovery

62 *J Am Coll Cardiol*. 1998;31(7):1449-1459.

62

HIT Type II

- An immune-mediated IgG drug reaction
- A hypercoagulable state that if left untreated can lead to many complications, including amputation and death
- Higher frequency in patients receiving unfractionated heparin (UFH) than in those receiving low-molecular weight heparin (LMWH)
- Around 12 million patients in the U.S. receive heparin each year and up to 1% develop HIT

63 *Blood Adv*. 2018; 2(22):3360–3392.
Chest. 2012; 141(2 suppl):e495S–e530S.

63

When to Suspect HIT

- Platelet count <150,000/µL or a decrease in platelet count by ≥50% from baseline
- Venous or arterial thrombosis
- Necrotic skin lesions at heparin injection sites
- Acute systemic reactions occurring after intravenous heparin administration

64 *Blood Adv.* 2018; 2(22):3360–3392.

64

4Ts Clinical Probability Scoring System

4 Ts	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall >50% **and** platelet nadir ≥20 x 10^9/L	Platelet count fall 30-50% **or** platelet nadir 10-19 x 10^9/L	Platelet count fall <30% **or** platelet nadir <10 x 10^9/L
Timing of platelet count fall	Clear onset between days 5-14 **or** platelet fall ≤1 day (prior heparin exposure within 30 days)	Consistent with days 5-14 fall, but not clear (e.g., missing platelet counts) **or** onset after day 14 **or** fall ≤1 day (prior heparin exposure 30-100 days ago)	Platelet count fall ≤ 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus; adrenal hemorrhage	Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not confirmed)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

65 *Blood Adv.* 2018; 2(22):3360–3392.

65

Probability of HIT Based on 4T's Score

Probability of HIT	Points
High	6-8
Intermediate	4-5
Low	≤ 3

66 *Blood Adv.* 2018; 2(22):3360–3392.

66

Diagnosis & Initial Treatment

Obtain 4T Score
- Score ≤3: HIT unlikely
- Score ≥4: Stop all forms of heparin and begin non-heparin anticoagulation; stop warfarin and administer Vitamin K if applicable

Obtain immunoassay (anti-PF4 ELISA)
- Negative: HIT unlikely
- Positive: Continue treatment and obtain functional assay

Obtain Functional Assay (SRA)
- Negative: HIT unlikely
- Positive: HIT likely

67 *Blood Adv.* 2018; 2(22):3360–3392.

67

Management of HIT

- All forms of heparin must be discontinued
- A non-heparin anticoagulant must be initiated at therapeutic intensity
- Patients taking warfarin at the onset of HIT should have the warfarin discontinued and vitamin K should be administered concomitant with initiation of a non-heparin anticoagulant
- Treatment should not be delayed while awaiting laboratory testing
- Anticoagulation with a non-heparin anticoagulant should be administered for ≥ four weeks in patients with HIT and for ≥ three months if a thrombotic event occurred

68 *Blood Adv.* 2018; 2(22):3360–3392.
Chest. 2012; 141(2 e):495S–530S.

68

Non-Heparin Anticoagulants

Parenteral Direct Thrombin Inhibitors	Parenteral Indirect Factor Xa Inhibitor	DOAC
• Argatroban • Bivalirudin	• Fondaparinux	• Apixaban • Dabigatran • Rivaroxaban

69 *Blood Adv.* 2018; 2(22):3360–3392.

69

Assessment Question

True or False: Anticoagulation with a non-heparin anticoagulant should be administered for at least four weeks in patients with heparin induced thrombocytopenia and for at least three months if a thrombotic event has occurred

a) True ✓
b) False

70

70

Parenteral Direct Thrombin Inhibitors

- Argatroban or bivalirudin are recommended in patients with:
  - Critical illness
  - Increased bleeding risk
  - Increased potential need for urgent procedures
- The ASH guidelines suggest treatment with bivalirudin in patients requiring percutaneous cardiovascular intervention (PCI)
- In patients with moderate or severe hepatic dysfunction (Child-Pugh class B and C), it is advisable to avoid argatroban or use a reduced dose
- The effect of argatroban and bivalirudin must be monitored and adjusted by activated partial thromboplastin time (aPTT)
- There are no antidotes available for either agent

71 *Blood Adv.* 2018; 2(22):3360–3392.

71

Parenteral Direct Thrombin Inhibitors

	Argatroban	Bivalirudin
Dosing	• Patients without hepatic impairment: 1-2 mcg/kg/min IV infusion • Patients with heart failure, severe anasarca, post-cardiac surgery, and hepatic impairment: 0.5–1.2 mcg/kg/min IV infusion	• Normal organ function: 0.15 mg/kg/hour IV infusion • Renal impairment: -CrCl 30-60 mL/min: 0.08-0.12 mg/kg/hour -CrCl <30 mL/min: 0.04-0.07 mg/kg/hour
Half-life	• 40-50 minutes • 180 min in hepatic impairment	• 25 minutes • 3.5 hours in end-stage kidney disease
Monitoring	• Adjust aPTT 1.5-3.0 times baseline • Platelets • Hgb • Hct	• Adjust aPTT 1.5- 2.5 times baseline • Platelets • Hgb • Hct • Renal function

Blood Adv. 2018; 2(22):3360–3392.
Argatroban injection 125 mg per 125 mL dextrose [prescribing information]. Princeton, NJ: Sandoz Inc; April 2019.
J Thromb Thrombolysis. 2012;33(3):287-295.
72 Angiomax (bivalirudin) [prescribing information]. Princeton, NJ: Sandoz Inc; June 2019.

72

Parenteral Indirect Factor Xa Inhibitor

- Fondaparinux is used off-label for the treatment of HIT
- The ASH guidelines suggest the use of fondaparinux for suspected or confirmed HIT in patients that are clinically stable and with average risk of bleeding
- Patients being treated with fondaparinux for prolonged periods should have periodic monitoring of renal function
- No antidote available

	Fondaparinux
Dosing	• <50 kg: 5 mg subcutaneously once daily • 50–100 kg: 7.5 mg subcutaneously once daily • >100 kg: 10 mg subcutaneously once daily • Contraindicated in CrCl < 30 mL/min
Half-Life	17-24 hours
Monitoring	• Anti- Xa levels 3 hours post dose (if needed) • Platelets • Hgb/Hct • Renal function

73 *Blood Adv.* 2018; 2(22):3360–3392.
Arixtra (fondaparinux) [prescribing information]. Morgantown, WV: Mylan Institutional LLC; August 2020.

73

DOACs

- Dosing of DOACs in HIT has not been well-established based on clinical trials
- DOACs are not preferred in patients complicated by life- or limb-threatening thromboembolism due to limited clinical data
- The dosing recommended for patients with acute VTE is usually used, and that dosing would be continued for a minimum of the standard VTE treatment period or until the platelet count is normal, whichever is longer
- Most of the published experience in HIT is with rivaroxaban

74 *Blood Adv.* 2018; 2(22):3360–3392.

74

DOACs

- Dosing (Off- label):
  - Apixaban
    - Heparin-induced thrombocytopenia with thrombosis (HITT): 10 mg by mouth (PO) twice daily x 1 week, then 5 mg PO twice daily
    - HIT: 5 mg PO twice daily until platelet count recovery
  - Dabigatran
    - HITT: 150 mg PO twice daily after ≥5 days of treatment with a parenteral non-heparin anticoagulant
    - HIT: 150 mg PO twice daily until platelet count recovery
  - Rivaroxaban
    - HITT: 15 mg PO twice daily x 3 weeks, then 20 mg once daily
    - HIT: 15 mg PO twice daily until platelet count recovery
- Monitor:
  - No monitor of efficacy required
  - Platelets
  - Hgb
  - Hct
  - Renal function

75 *Blood Adv.* 2018; 2(22):3360–3392.

75

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Venous Thromboembolism Management in Special Populations

Carina Diaz, Pharm.D.
Lesly Rapado, Pharm.D.
PGY-1 Pharmacy Residents
South Miami Hospital

January 21st, 2024

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Pharmacological Management of Weight Loss in Adults

Cristina M. Sprouse, Pharm.D.
PGY-2 Health System Pharmacy Administration and Leadership
Miami VA Healthcare System
01/20/2024-01/21/2024

28 Years Featuring
South Florida Pharmacy Residents

1

Acknowledgements & Disclosures

- The presenter has no financial disclosures or conflict of interest to disclose relative to the content in this presentation.

2

Objectives

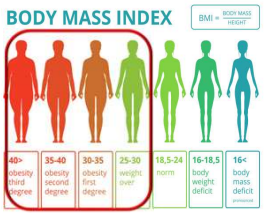
By the end of the presentation, the learner should be able to

- Discuss the pharmacological management of weight loss in adults
- Recognize adverse drug reactions, contraindications for use, and safety concerns for these medications
- Identify the role of how non-pharmacological and surgical interventions assist in weight loss management
- Evaluate patients for achieving weight loss goals upon medication monitoring and follow-up

3

Body Mass Index (BMI) [1-2]

BMI = kg/m^2



- BMI appears to be strongly correlated with various adverse health outcomes
- **Overweight:** BMI 25 to 29.9
- **Obese:** BMI ≥ 30
  - Class 1: BMI 30 to 34.9
  - Class 2: BMI of 35 to 39.9
  - Class 3: BMI of ≥ 40
- Additional measures of body fat include skinfold thickness, bioelectrical impedance, and underwater weighing

4

Patient Case

- A 46-year-old Hispanic woman presents to the clinic for a weight management consultation with the pharmacist
- Medical history: obesity, type 2 diabetes, hypertension
- Weight = 220 pounds, Height = 5 feet 4 inches, BP = 144/86 mm Hg
- The internet is currently down and we can't use a BMI calculator online

- What is her calculated BMI? Where does she fall on the BMI scale?

5

Patient Case

- Weight = 220 pounds, Height = 5 feet 4 inches (64 inches)

- What is her calculated BMI?
  - 1 kilogram = 2.2 pounds
  - 1 inch= 2.54 centimeters
  - 1 centimeter = 0.01 meters

$$220\ lbs\ x\ \frac{1kg}{2.2lbs} = \square$$

$$64\ inches\ x\ \frac{2.54cm}{1in}\ x\ \frac{0.01m}{1cm} = \square$$

6

Patient Case

- Weight = 220 pounds, Height = 5 feet 4 inches (64 inches)

$$220\ lbs\ x\ \frac{1kg}{2.2lbs} =$$

$$64\ inches\ x\ \frac{2.54cm}{1in}\ x\ \frac{0.01m}{1cm} =$$

BMI = kg/m^2

=

7

Patient Case

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- Medical history: obesity, type 2 diabetes, hypertension
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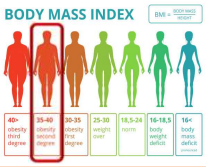
  BMI =
- Where does she fall on the BMI scale?
  -



8

Other Obesity Measures[1]

	Waist Circumference	Body fat
Men	>40 in	>30%
Women	>35 in	>35%

9

BMI Trends for U.S. Adults[2]

- The prevalence of adult BMI greater than or equal to 30 kg/m2 has greatly increased since the 1970s
- Over recent years, this has begun to stabilize except it has continued to increase in women 60 years of age and older
- All states and territories had an obesity prevalence higher than 20% (more than 1 in 5 adults)

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, 2022

10

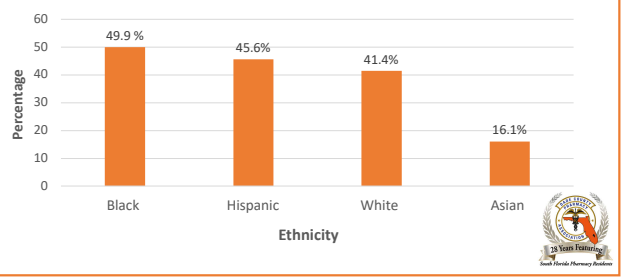
BMI Trends for U.S. Adults[2]

Obesity prevalence decreases by level of education. Without a high school degree or equivalent had the highest self-reported obesity (37.6%), followed by adults with some college (35.9%) or high school graduates (35.7%), and then by college graduates (27.2%)

Young adults were half as likely to have obesity as middle-aged adults. Adults aged 18–24 years had the lowest self-reported obesity (20.5%) compared to adults aged 45–54 years who had the highest prevalence (39.9%)

11

Obesity Prevalence Based on Ethnicity[2]



12

Projected Obesity Prevalence in Adults[3]

High-risk populations

- Women > 60 years of age
- Non-Hispanic black adults
- Low-income adults

By the year 2030 it is expected that:

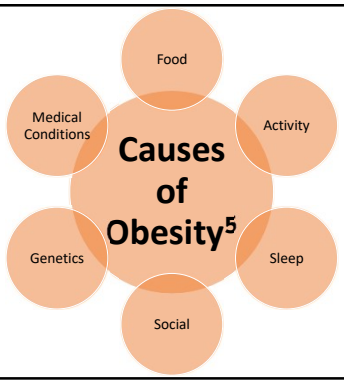
- 1 in 2 adults will have obesity
- 1 in 4 adults will have severe obesity

13

Consequences of Obesity[4]

- Health Conditions
  - High blood pressure and cholesterol
    - Risk factors for heart disease
  - Type 2 Diabetes
  - Asthma and sleep apnea
  - Osteoarthritis and musculoskeletal discomfort
  - Gallstones and gallbladder disease
- U.S. Annual Economic Impact
  - Obesity-related medical care costs in 2019 ~ $173 billion
  - Productivity costs due to obesity-related absenteeism
    - ~$3.38 billion – $6.38 billion

14



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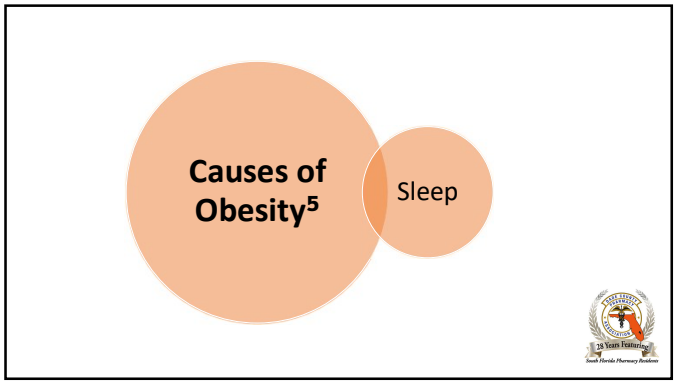

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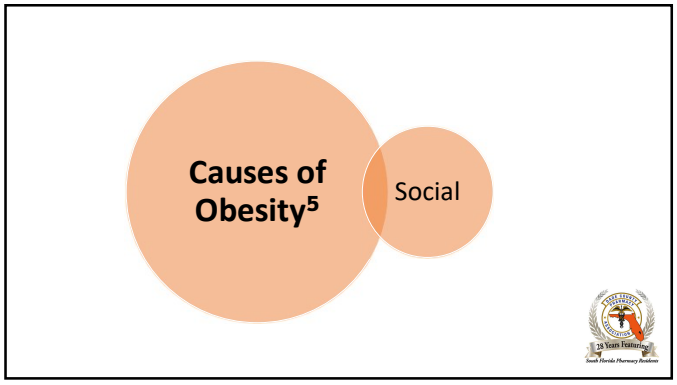
Causes of Obesity- Sleep

- Sleeping patterns (insufficient sleep)
  - Shorter sleep durations can results in metabolic changes that may be linked to obesity
  - Epidemiologic studies show an association between short sleep duration and excess body weight
    - More of a factor in children- insufficient sleep may adversely affect the function of the hypothalamus, which regulates appetite and the expenditure of energy
  - Newborns need 14 to 17 hours of sleep per day
  - Teenagers need 8 to 10 hours of sleep per day
  - Adults need 7 or more hours of sleep per day

17

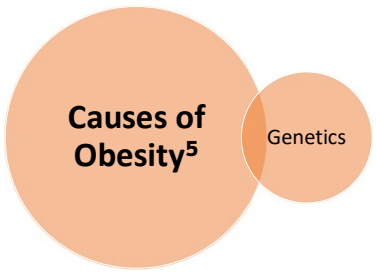


18

Causes of Obesity- Social

- Social Determinants of Health (SDOH)
  - The conditions in which we live, learn, work, and play
    - It can be difficult to make healthy food choices and get enough physical activity if these conditions do not support health
    - Differences in SDOH affect chronic disease outcomes
  - Tools to help remove barriers to health
    - Federal plan- approach to strengthen vital conditions for improving individual and community resilience and well being
    - State toolkit- create systems and environmental changes that will reduce obesity disparities and achieve health equity
    - Community efforts- maximize the effects of policy, systems, and environmental improvement strategies to reduce health disparities and advance health equity

19

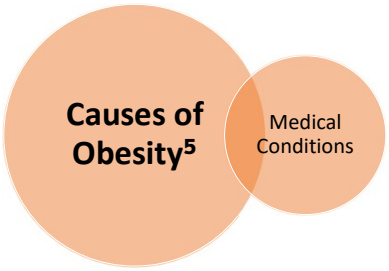


20

Causes of Obesity- Genetics

Genetic Changes Occur Slowly	Variants Impact Hunger & Thirst
Not Just A Single Gene	Family History & Prevention

21



22

Causes of Obesity- Medical Conditions

Medical conditions that can cause weight gain include but are not limited to the following

- Hypothyroidism
- Cushing's Syndrome
- Menopause
- Polycystic Ovary Syndrome
- Depression
- Narcolepsy

23

Medications That Cause Weight Gain[6]

Medications that can cause weight gain include but are not limited to the following

- Antipsychotics and other mood stabilizers
- Certain diabetic agents
- Steroids
- Gabapentin and pregabalin

24

Medications That Cause Weight Loss[6]

- Medications that can cause weight loss include but are not limited to
  - Amphetamine and methylphenidate containing agents
  - GLP-1 agonists
  - SGLT2 inhibitors
  - Orlistat
    - Xenical®
    - Alli®
  - Phentermine/topiramate
  - Naltrexone/bupropion
  - Roflumilast

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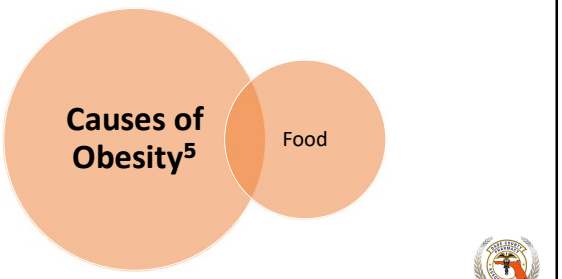

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Causes of Obesity- Eating Patterns

- Healthy eating as recommended by the CDC follows the 2020-2025 Dietary Guidelines for Americans[7]
  - Vegetables and fruits
  - Whole grains
  - Lean protein foods
  - Low-fat and fat-free dairy products
  - Limits foods and beverages with added sugars, solid fats, or sodium

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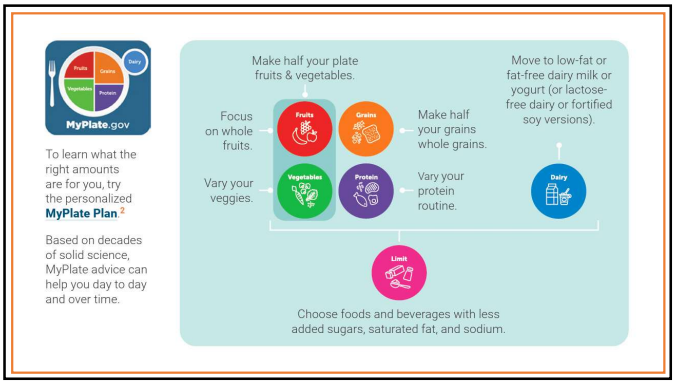
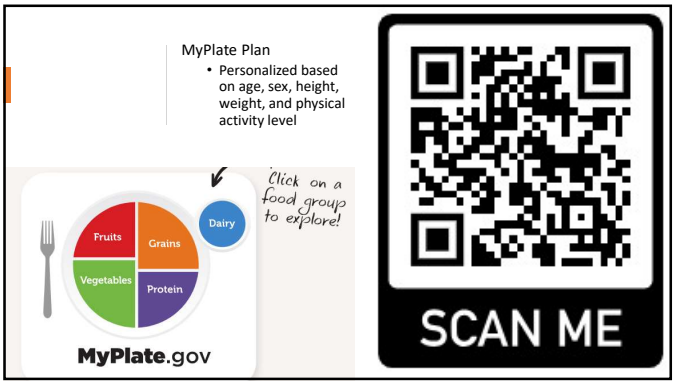

MyPlate.gov
To learn what the right amounts are for you, try the personalized MyPlate Plan.[2]
Based on decades of solid science, MyPlate advice can help you day to day and over time.
Make half your plate fruits & vegetables.
Focus on whole fruits.
Vary your veggies.
Make half your grains whole grains.
Vary your protein routine.
Move to low-fat or fat-free dairy milk or yogurt (or lactose-free dairy or fortified soy versions).
Fruits
Grains
Vegetables
Protein
Dairy
Limit
Choose foods and beverages with less added sugars, saturated fat, and sodium.

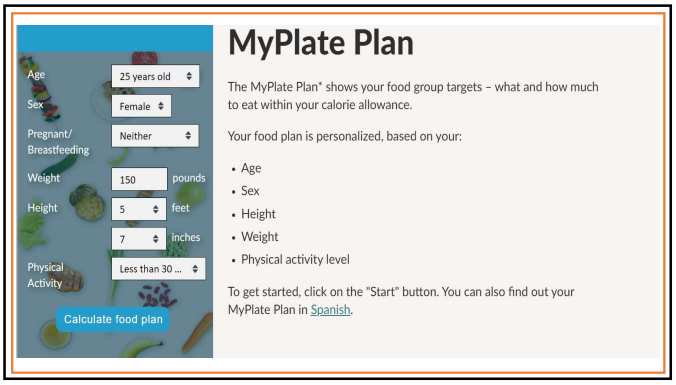
28


MyPlate Plan
• Personalized based on age, sex, height, weight, and physical activity level
Click on a food group to explore!
Fruits
Grains
Vegetables
Protein
Dairy
MyPlate.gov
SCAN ME

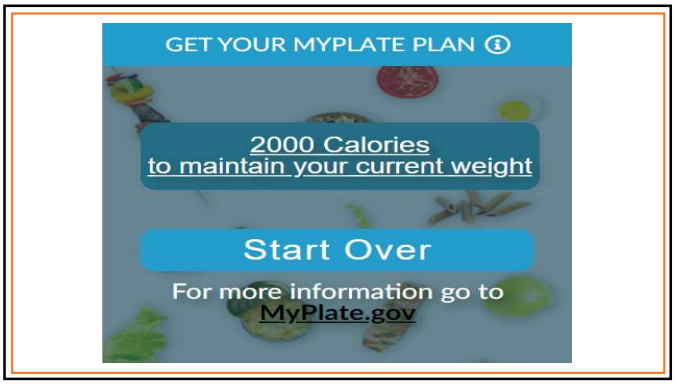
29


Get Your MyPlate Plan
Start
MyPlate Plan
The MyPlate Plan* shows your food group targets – what and how much to eat within your calorie allowance.
Your food plan is personalized, based on your:
• Age
• Sex
• Height
• Weight
• Physical activity level
To get started, click on the "Start" button. You can also find out your MyPlate Plan in Spanish.

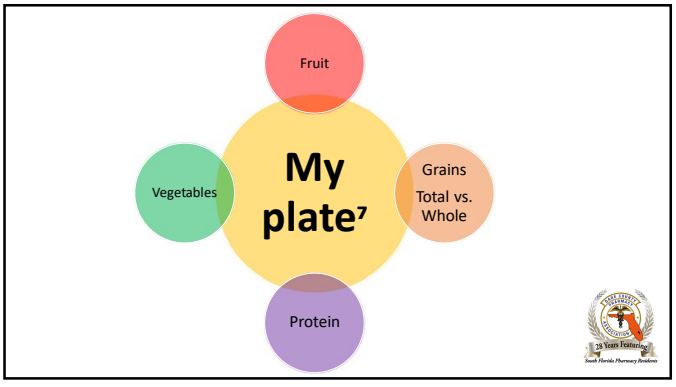
30


MyPlate Plan
Age
25 years old
Sex
Female
Pregnant/ Breastfeeding
Neither
Weight
150
pounds
Height
5
feet
7
inches
Physical Activity
Less than 30 ...
Calculate food plan
The MyPlate Plan* shows your food group targets – what and how much to eat within your calorie allowance.
Your food plan is personalized, based on your:
• Age
• Sex
• Height
• Weight
• Physical activity level
To get started, click on the "Start" button. You can also find out your MyPlate Plan in Spanish.

31


GET YOUR MYPLATE PLAN
2000 Calories
to maintain your current weight
Start Over
For more information go to
MyPlate.gov

32


Fruit
Vegetables
My plate7
Grains
Total vs. Whole
Protein

33

What Counts as a Cup of Vegetables?[7]

The following examples count as 1 cup from the Vegetables Group:

1 cup of raw or cooked vegetables or vegetable juice
2 cups of raw leafy salad greens

Women	19-30 yrs	2½ to 3 cups
	31-59 yrs	2 to 3 cups
	60+ yrs	2 to 3 cups
Men	19-30 yrs	3 to 4 cups
	31-59 yrs	3 to 4 cups
	60+ yrs	2½ to 3½ cups

34

What Counts as a Cup of Fruit?[7]

In general, the following counts as 1 cup from the Fruit Group:

1 cup of fruit
½ cup of dried fruit
1 cup of 100% fruit juice

Women	19-30 yrs	1½ to 2 cups
	31-59 yrs	1½ to 2 cups
	60+ yrs	1½ to 2 cups
Men	19-30 yrs	2 to 2½ cups
	31-59 yrs	2 to 2½ cups
	60+ yrs	2 cups

35

What counts as an ounce-equivalent (oz-equiv) of grains?[7]

The following are some grain food portions that are equal to one ounce:

1 slice of bread
1 cup of ready-to-eat cereal
½ cup of cooked rice, cooked pasta, or cooked cereal

		Total Grains in ounce-equivalents	Whole Grains in ounce-equivalents
Women	19-30 yrs	6 to 8 oz-equiv	3 to 4 oz-equiv
	31-59 yrs	5 to 7 oz-equiv	3 to 3½ oz-equiv
	60+ yrs	5 to 7 oz-equiv	3 to 3½ oz-equiv
Men	19-30 yrs	8 to 10 oz-equiv	4 to 5 oz-equiv
	31-59 yrs	7 to 10 oz-equiv	3½ to 5 oz-equiv
	60+ yrs	6 to 9 oz-equiv	3 to 4½ oz-equiv

36

What counts as an ounce-equivalent in the Protein Foods Group?[7]

The following examples count as 1 ounce-equivalent from the Protein Foods Group:

1 ounce of meat, poultry or fish
¼ cup cooked beans
1 egg
1 tablespoon of peanut butter
½ ounce of nuts or seeds
¼ cup (about 2 ounces) of tofu

Women	19-30 yrs 31-59 yrs 60+ yrs	5 to 6½ oz-equiv 5 to 6 oz-equiv 5 to 6 oz-equiv
Men	19-30 yrs 31-59 yrs 60+ yrs	6½ to 7 oz-equiv 6 to 7 oz-equiv 5½ to 6½ oz-equiv

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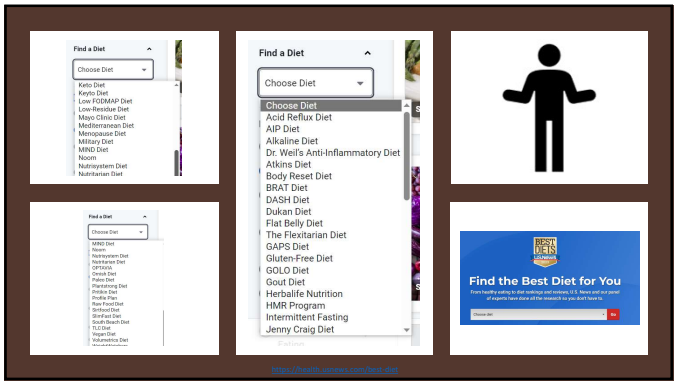
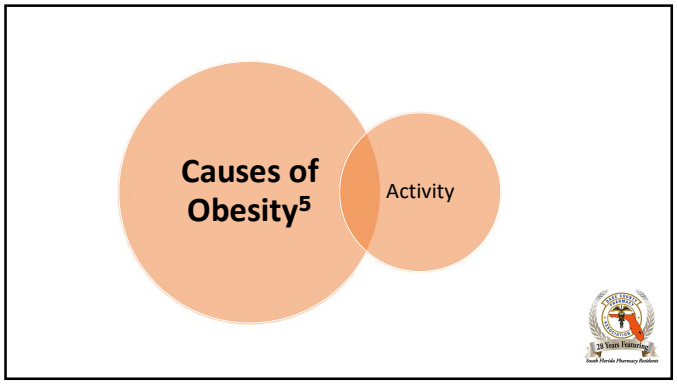


38

Heart Healthy Diets[8]

- Dietary Guidelines for Americans emphasize the following heart-healthy dietary patterns that are associated with lower CVD risk
  - Dietary Approaches to Stop Hypertension (DASH)
    - Emphasizes fruits, vegetables, whole grains, lean protein and low-fat dairy
    - Limits foods with added sugar and high in saturated fat
    - Max sodium at 2,300 milligrams daily, stricter goal of 1,500 milligrams
  - Mediterranean
    - Wide range of foods
    - Eat fruits, vegetables, whole grains, beans, nuts, legumes, olive oil, herbs and spices daily
    - Eat seafood and fish at least twice a week
    - Poultry, eggs, cheese and yogurt in moderation
    - Red meat and sweets are best reserved as occasional treats
    - The occasional glass of red wine is acceptable

39



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Causes of Obesity- Activity

- The Physical Activity Guidelines for Americans
  - Children aged 3 through 5 years should be physically active throughout the day
  - Children aged 6 – 17 years need at least 60 minutes of moderate to vigorous physical activity every day
  - Adults need 150 minutes of moderate intensity physical activity a week
- Communities can create or modify environments to make it easier for people to walk or bike to everyday destinations

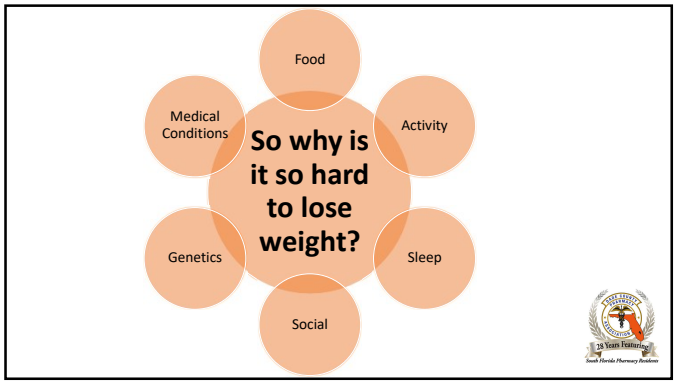
41

Caloric (kcal) Deficits- Diet & Exercise

~1 lb = 3500 kcal

- Calorie deficit of 500 – 750 kcal/day (~3500 kcal/week)
- Very low-calorie diet < 800 kcal/day

42



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So why is it so hard to lose weight?[9]

- *Why it is so hard to lose weight? An exploration of patients' and dietitians' perspectives by means of thematic analysis*
- Authors: M. Poraj-Weder, G. Wąsowicz, and A. Pasternak
- Goal: understand the importance of motivation in ensuring the success of the dietary change process
- Introduction
  - There are limited tools like the addition of medications or dieticians that result in a lasting change in eating habits and the maintenance of the desired weight
  - Most obesity interventions are only effective as long as the patient remains in treatment
  - Helping patients shift their locus of motivation from weight loss alone to intrinsically meaningful areas requires an understanding of their needs

44

Regulatory style	Generic definition	Themes and sub-themes Contextual definitions of six regulatory styles
Amotivation	Associated with a sense of incompetence, confusion, and lack of control over the given situation.	**Themes:** Powerlessness, reluctance, lack of responsibility for dietary change effects, hopelessness regarding success ("I'll be fat anyway" rhetoric) **Contextual definition:** Associated with resistance to change, aversion to take the effort required to change one's diet (and subject oneself to the required restrictions), belief that one lacks the resources needed to bring about the change, and the lack of conviction that the effort will be successful.
External regulation	Involves activities undertaken under external pressure to obtain a reward or avoid negative consequences.	**Themes:** Perceiving healthful eating as unpleasant, restrictive, imposed, and temporary ("being on a diet" rhetoric). Frequent deviations from dieting and irrational fillers. Entitlement mentality regarding their dietitian (transferring responsibility for effects onto dietitian)
Introjected regulation	Involves activities performed under external pressure, to reduce anxiety/guilt or to enhance self-esteem.	**Contextual definition:** Strongly goal-oriented (with the goal being narrowly defined in terms of the loss of a certain number of kilograms), lacks consistency because the principles of healthful eating have not been internalized and are perceived as external and imposed.
Identified regulation	Associated with more autonomic behaviors and internal locus of control.	**Themes:** Perceiving healthy eating as a set of tasks to achieve desired results. Continuous need to be in treatment. Strong focus on effects **Contextual definition:** Associated with partial internalization of the principles of healthful eating and recognition of the values governing behavior as „one's own". Activities are still motivated extrinsically. The goal is to obtain certain benefits (e.g. slim figure).
Integrated regulation	Associated with behaviors that are a natural consequence of one's identity and values system, but are still subservient to an external goal.	**Themes:** Healthful eating as a way of life **Contextual definition:** Akin to intrinsic regulation and similar in character to identification. The difference lies in the degree to which the principles of healthful eating have been internalized.
Intrinsic regulation	Its essence is the ability to derive satisfaction from the very fact of engaging in it.	**Themes:** Healthful eating as a source of joy and satisfaction **Contextual definition:** Associated with full internalization of the principles of healthful eating. Not observed in the present study.

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So why is it so hard to lose weight?[9]

- Methods & Procedure
  - The first group consisted of individuals who were dieting to lose weight at the time of the study (N = 6)
  - All of them worked with health care professionals for a minimum of 3 months, three at the time of the study, and three before the study began
  - The second group were health care professionals (N = 7)
  - Each participant in this group had nutrition counseling in the private practice setting
  - Semi-structured, open-ended, in-depth interviews (IDIs) were conducted in both groups

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So why is it so hard to lose weight?[9]

Results

- Amotivation
  - None of the participants- All participants in the study wanted to change their eating habits
- Extrinsic motivation/regulation
  - All participants from both groups exhibited a range of the following regulations
    - External regulation
    - Introjected regulation
    - Identified regulation
    - Integrated regulation
- Intrinsic motivation/regulation
  - None of the participants- All patients in the study exhibited extrinsic motivation, which was associated with result-oriented activity

47

So why is it so hard to lose weight?[9]

- Discussion
  - The results of this study show that when autonomous motivation is greater, the chance of success also increases
  - The more external the patients' motivations are to change their eating habits, the less interest they will have to achieve the goal
  - The more autonomy patients have in the change process, the greater the chances that their planned activities will be effective
- Limitations
  - Small sample size in the country of Poland
  - The second group of participants included health professionals including 4 dieticians

48

So why is it so hard to lose weight?[9]

- Conclusions
  - The introduction to motivation is a key discussion point for helping patients manage weight loss from diet and exercise
  - The more external the patients' motivations are to change their eating habits, the less interest they will have to achieve the goal and the more internal motivations will increase the chances they will achieve their goal
  - More studies with increased sample sizes and including a wider variety of patients from different backgrounds are needed for additional conclusions

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Discussing Obesity

- Motivational Interviewing
  - Remember the "5As" for smoking cessation?
    - Ask
      - Permission
    - Assess
      - Causes
    - Advise
      - Risks
    - Agree
      - Treatment & Goals
    - Assist
      - Resources

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Discussing Obesity

- Motivational Interviewing
  - Expressing empathy
    - Make patients feel heard and understood
  - Supporting self-efficacy
    - Help patients believe they can change
  - Roll with resistance
    - Facilitate patients to define their issues & solutions to reduce resistance
  - Develop discrepancy
    - Help patients to see the difference of where they are now and where they want to be

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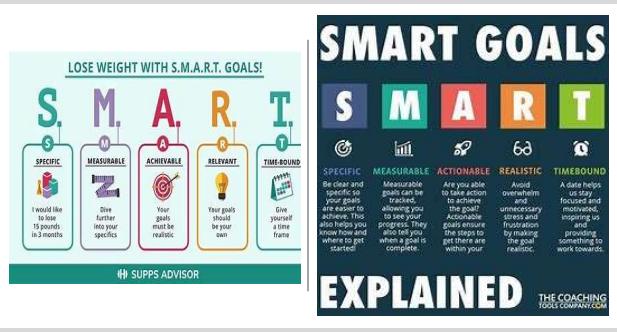

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Knowledge Check

1. True or False: Pharmacologic management of weight loss is the sole recommended treatment for adults struggling with overweight and obesity

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Knowledge Check

1. True or False: Pharmacologic management of weight loss is the sole recommended treatment for adults struggling with overweight and obesity
   - Lifestyle modifications, pharmacologic and non-pharmacologic treatments, and surgical interventions all have been shown to improve weight loss outcomes in these patients

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Pharmacologic Management Key Points[10]

- Many weight loss medications work by increasing satiety or decreasing appetite
- Weight loss medications should only be used in addition to lifestyle measures ONCE lifestyle measures alone have failed
- In patients with weight-related complications (HTN, diabetes, dyslipidemia, sleep apnea), weight loss medications may be started at the same time as lifestyle measures
- OTC supplements are generally ineffective and not recommended due to risk of harm, especially in patients with cardiovascular disease
- In general, prescription medications are not appropriate in patients with small amounts of weight to lose
- Weight loss medications should be discontinued if they do not produce at least 5% weight loss at 12 weeks

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OTC Supplements

- Stimulants & Caffeine
  - Bitter orange
  - Guarana
  - Green tea powder
- OTC supplements are generally ineffective and not recommended due to risk of harm, especially in patients with cardiovascular disease

56

Pharmacological Agents Summary[10]

- Older stimulant agents are used short-term only and used to "jump start" a diet
  - Phentermine
  - Diethylpropion
- Newer agents can be continued long-term for weight maintenance
  - Phentermine/topiramate (Qsymia®)
  - Naltrexone/bupropion (Contrave®)
  - Liraglutide, semaglutide, tirzepatide (Saxenda®, Wegovy®, Zepbound®)
- Removed from the market
  - Lorcaserin (Belviq®, Belviq XR®)- due to increased risk of cancer

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Pharmacological Agents Summary Avoid or Use Caution[10]

- Pregnancy- avoid all weight loss medications
- Hypertension
  - Avoid: Naltrexone/bupropion (Contrave®)- contraindicated with uncontrolled BP (bupropion)
  - Caution: Phentermine/topiramate (Qsymia®)- caution with HR (phentermine)
- Depression
  - Caution: Naltrexone/bupropion (Contrave®)- suicide risk in young adults and adolescents (bupropion)
- Seizures
  - Avoid: Naltrexone/bupropion (Contrave®)- lowers seizure threshold (bupropion)
  - Caution: Phentermine/topiramate (Qsymia®)- must taper off slowly (topiramate)

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Phentermine (Adipex-P®, Lomaira®)[11]

- Mechanism of action: increases norepinephrine to decrease food seeking behavior by lowering hunger (appetite suppressant)
- Dosing
  - Adipex-P®: 15-37.5 mg PO QAM before breakfast or 1-2 hours after
  - Lomaira®: 8 mg PO TID before meals
- Projected average weight loss: 5-7.9 lbs in 12 weeks
- Controlled substance: C-IV
- Contraindications: MAOi within past 14 days, CVD, glaucoma, hyperthyroidism, history of drug abuse
- Adverse effects: tachycardia, HTN, agitation, tremor, dizziness, constipation, dry mouth, headache, insomnia (take QAM)

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Phentermine/Topiramate (Qsymia®)[12]

- Mechanism of action: increase GABA/block glutamate, inhibit carbonic anhydrase, and work on hypothalamus to increase satiety and decrease appetite
- Dosing: 3.75/23 mg PO QAM x 14 days, then titrated to 7.5/46 mg PO QAM x 12 weeks, 11.25/69 mg PO QAM x 14 days and then to a max of 15/92 mg PO QAM
  - CrCl less than 50 mL/min: max dose 7.5/46 mg per day
- Projected average weight loss: 19-20 lbs in 52 weeks
- Controlled substance: C-IV
- Contraindications: REMS medication (teratogenic), drug interactions (MAOi), comorbidities (hyperthyroidism, glaucoma)
- Adverse effects: tachycardia, insomnia, HTN, serum bicarbonate, potassium, glucose, mood/behavior changes, constipation, increased SCr, kidney stones, headache, dizziness, vision changes

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Orlistat (Alli®, Xenical®)[13]

- Mechanism of action: decrease absorption of dietary fats by ~30% and must be used with a low-fat diet plan
- Dosing:
  - Alli® (OTC)→ 60 mg PO TID with meals
  - Xenical®→ 120 mg PO TID with meals
- Projected average weight loss: 7-7.6 lbs in 52 weeks
- Contraindications: chronic malabsorption syndrome, cholestasis, severe renal impairment, taking with cyclosporine
- Adverse effects: vitamin deficiency, headache, influenza or URTI, GI distress, back pain, hepatotoxicity, kidney stones

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Naltrexone/Bupropion (Contrave®)[14]

- Mechanism of action: opioid antagonist (lower reward behavior of seeking food) and antidepressant (reduce appetite and food cravings)
- Dosing: 90/8 mg PO QAM x 7 days, then titrate weekly then 90/8 mg PO BID x 7 days, then 180/16 mg PO QAM and 90/8 mg PO QPM x 7 days and the maintenance dose of 180/16 mg PO BID
  - Do not cut, chew or crush & do not take with a high-fat meal
- Projected average weight loss: 9 lbs in 52 weeks
- Contraindications: MAOi, chronic opioid use, HTN uncontrolled, seizure disorder, chronic opioid use, anorexia or bulimia
- Adverse effects: headache, tachycardia, hepatotoxicity, GI upset, dizziness
- Black Box Warning: not approved for major depressive disorder can increase the risk of suicidal ideation in adolescents and children

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Liraglutide (Saxenda®)[15]

- Victoza® is for the management of diabetes
- Mechanism of action: GLP-1RA→ It signals the pancreas to release insulin, delays gastric emptying and signals the brain that the body is not hungry
- Dosing: 0.6 mg SC daily x 1 week, and titrate weekly by 0.6 mg→ 0.6, 1.2, 1.8, 2.4, then to max 3 mg daily
- Projected average weight loss: 11-12 lbs in 52 weeks
- Contraindications: medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2
- Adverse effects: injection reactions, pancreatitis, URTI, tachycardia, GI upset, hypoglycemia

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Semaglutide (Wegovy®)[16]

- Ozempic® is for the management of diabetes
- Mechanism of action: GLP-1RA→ It signals the pancreas to release insulin, delays gastric emptying and signals the brain that the body is not hungry
- Dosing: 0.25 mg SC weekly x 4 weeks, 0.5 mg SC weekly x 4 weeks, 1 mg SC weekly x 4 weeks, 1.7 mg SC weekly x 4 weeks then 2.4 mg SC weekly thereafter as tolerable
- Projected average weight loss: 33 lbs in 52 weeks
- Contraindications: medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2
- Adverse effects: injection reactions, pancreatitis, URTI, tachycardia, GI upset, hypoglycemia

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Tirzepatide (Zepbound®)[17]

- Mounjaro® is for the management of diabetes
- Mechanism of action: GLP-1RA→ It signals the pancreas to release insulin, delays gastric emptying and signals the brain that the body is not hungry
- Dosing: 2.5 mg SC weekly, increasing by 2.5-mg increments after at least 4 weeks on the current dose. The maximum dose is 15 mg.
- Projected average weight loss: 33 lbs in 52 weeks
- Contraindications: medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2
- Adverse effects: injection reactions, pancreatitis, URTI, tachycardia, GI upset, hypoglycemia

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Key Counseling Points

- In general, weight loss can improve diabetes and hypertension→ monitor these conditions closely and make dose adjustments as needed to prevent hypotension or hypoglycemia
- Phentermine/topiramate (Qsymia®)→ can cause insomnia (recommend to take in the morning), monitor HR (can cause tachycardia)
- Naltrexone/bupropion (Contrave®)→ do not take with opioids and avoid in patients with history of seizures, monitor BP (can cause HTN)
  - Naltrexone blocks opioids and buprenorphine, which blocks analgesia and can induce withdrawal; discontinue opioids or buprenorphine 7-14 days prior to use

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Key Counseling Points

- Liraglutide, semaglutide, tirzepatide (Saxenda®, Wegovy®, Zepbound®)→ subcutaneous injection that can cause hypoglycemia, pancreatitis, and nausea
- Orlistat (Xenical® and Alli®)→ increased risk of GI side effects
- Patients should be followed at least monthly during dose escalation and then at least every 3 months when on a stable dose for continued weight loss or maintenance of weight

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Knowledge Check

2. True or False: Medications that can be used for the management of weight loss in adults include but are not limited to semaglutide, combination phentermine-extended release topiramate, combination extended-release bupropion-naltrexone, and orlistat.

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Knowledge Check

2. True or False: Medications that can be used for the management of weight loss in adults include but are not limited to semaglutide, combination phentermine-extended release topiramate, combination extended-release bupropion-naltrexone, and orlistat.

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Shortages[18]

- Novo Nordisk manufactures semaglutide (Wegovy®) and liraglutide (Saxenda®) as of December 2023:
  - "Novo Nordisk is experiencing a short-term stock-out of the Wegovy® 1.7 mg dose strength in the U.S. through December. **This is due to demand continuing to be greater than our ability to supply**".
  - "We expect to resume shipments of the Wegovy® 1.7 mg dose strength into the U.S. market in early January 2024. "
  - "At this time, we do not recommend switching to Saxenda® (liraglutide) injection 3 mg as a viable alternate treatment, as we cannot guarantee supply to match the continuous rising demand for weight management medications".
  - "We currently have sufficient supply to meet the needs of U.S. patients currently taking or ready to dose escalate to the Wegovy® 2.4 mg dose strength. **However, a significant influx of additional patients could result in supply constraints for this dose strength in the U.S.** We will continue to monitor the situation and share updates as needed".
  - "**Importantly, given the high continued interest in Wegovy®, we anticipate ongoing supply disruptions in the U.S., resulting in some patients having difficulty filling their Wegovy® prescriptions**."

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When do we consider surgery?[19]

WEIGHT LOSS SURGERY PROCEDURE OPTIONS: OVERVIEW

Upper GI Surgery

Procedure	Description	BMI	Est. Loss	Advantages	Disadvantages
	Laparoscopic Gastric Band	35 or 30+ comorbidities	15%-20%	Low complication rate, reversible	Challenging for patient to adapt to.
	Laparoscopic Sleeve Gastrectomy	40 or 35+ comorbidities	25%-35%	Easiest procedure to adapt to	Irreversible. Vitamin requirement for life. Reflux risk.
	Laparoscopic Gastric Bypass	40 or 35+ comorbidities	30%-50%	Powerful operation	Moderately challenging adaptation for patient vitamin requirement for life, nutritional risks.
	Laparoscopic Omega Loop Bypass	40 or 35+ comorbidities	30%-50%	Lower risk of bowel twists cf bypass, also simpler operation cf bypass.	Larger risk of reflux and ulcers than Gastric Bypass.
	Lap. Single Anastomosis Duodenal Switch (SADI)	40 or 35+ comorbidities	30%-50%	Powerful operation	Largest nutritional risks

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Common Nutrition Deficiencies following Bariatric Surgeries

- Calcium- commonly absorbed in the duodenum which may be bypassed, calcium citrate is preferred
- Anemia- vitamin B12 and iron deficiency may require supplementation
- Fat soluble Vitamins- A, D, E, K supplementation may be needed due to fat malabsorption

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Medication Concerns Following Bariatric Surgeries

- Medications may require dose reduction
- Consideration for agents that can be safely crushed and put in liquid for up to two months after surgery
- Rapid weight loss can cause gallstones
  - Ursodiol
  - Gallbladder removal

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Knowledge Check

3. True or False: If patients do not lose 4 to 5 percent of body weight after 12 weeks of therapy (at the maximum tolerated dose), the medication should be tapered and discontinued.

74

Knowledge Check

3. True or False: If patients do not lose 4 to 5 percent of body weight after 12 weeks of therapy (at the maximum tolerated dose), the medication should be tapered and discontinued.

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Pharmacological Management of Weight Loss in Adults

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Pharmacologic Management of Weight Loss in Pediatrics

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January 21, 2024

Disclosures

I have no relevant financial or nonfinancial relationships to disclose.

Learning Objectives

- **Review**: Published guidelines and current literature in the treatment of obesity in children and adolescents
- **Discuss**: Pharmacologic options available for the treatment of obesity
- **Apply**: Guidelines and pharmacotherapy options to a pediatric patient case

Incidence of Childhood Obesity

Around 14.4 million children and adolescents are affected by obesity, one of the most common pediatric chronic diseases

The cause of obesity is multifactorial with genetic, physiologic, socioeconomic, and environmental components

As our pediatric population's environment has become increasingly obesogenic, the increasing need for evidence-based treatment is critical

Hampl SE, et al. *Pediatrics*. 2023

Impact of Childhood Obesity

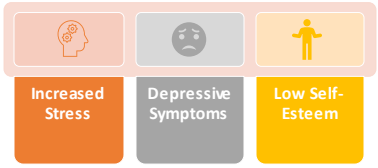
At risk for serious short- and long-term adverse health outcomes later in life including:

- Cardiovascular diseases
- Dyslipidemia
- Insulin resistance
- Type-2 diabetes mellitus

Vajravelu ME, et al. *Life (Basel)*. 2023

Impact of Childhood Obesity

- In addition to the physical and metabolic implications, obesity during childhood and adolescence is associated with poor psychological and emotional health including:



Vajravelu ME, et al. *Life (Basel)*. 2023

Screening and Diagnosis

- Dual-energy x-ray absorptiometry
  - The gold standard for the measurement of body composition
  - Identifies, locates, and quantifies body fat
  - Often expensive and unrealistic to implement in clinical practice
- Body Mass Index (BMI)
  - Most commonly used as both a screening and diagnostic tool in clinical practice
  - Validated proxy measure of excess body fat
  - Easy to use, inexpensive, replicable, and can track weight status and trajectory in children and adolescents over time
  - Clinicians are able to use BMI to assess the success of interventions implemented to improve the weight status

Vajravelu ME, et al. *Life (Basel)*. 2023

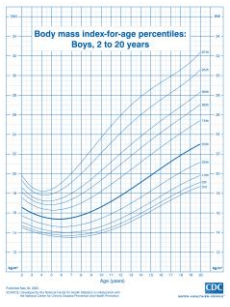
Body Mass Index (BMI)

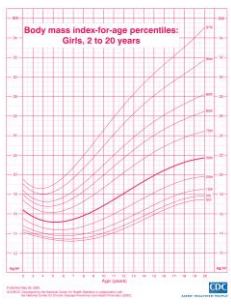
$$\text{BMI} = \frac{weight\ (in\ kg)}{height\ (in\ m^2)}$$

- Pediatric weight classifications are based on the percentile range the BMI falls within

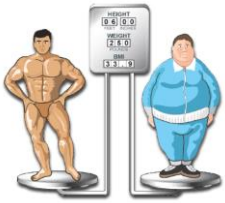
Classification	Percentile Range of BMI
Severe Obesity	approximately the 99th percentile (≥ 120% above the 95th percentile)
Obese	95th percentile
Overweight	85th to < 95th percentile
"Normal" Weight	5th to < 85th percentile
Underweight	< 5th percentile

Vajravelu ME, et al. *Life (Basel)*. 2023





Limitations to BMI



- High specificity and low sensitivity for detecting excess body fat
- Does not directly measure body composition and fat content, thus may under- or over-estimate excess body fat, especially in certain racial and ethnic groups
- Children and adolescents who have high fat-free mass may have a high BMI and subsequently be inaccurately dassified as overweight or having obesity

Vajravelu ME, et al. *Life (Basel)*. 2023

Risk Factors for Childhood Obesity

- Public Health Factors
- Family/Home Factors
- Community Factors
- Individual Factors

Hampl SE, et al. *Pediatrics*. 2023

Risk Factors for Childhood Obesity

Public Health Factors	Family/Home Factors	Community Factors
• Marketing of unhealthy foods • Under-resourced communities • Food insecurity	• Parental feeding style • Portion sizes • Snacking behavior • Dining out and family meals • Screen time and/or sedentary behavior • Sleep duration • Psychosocial stress	• School environment • Lack of fresh food access • Fast food proximity • Access to safe physical activity • Environmental health

Hampl SE, et al. *Pediatrics*. 2023

Individual Risk Factors

Genetic Factors	Prenatal Risk	Postnatal Risk	Childhood Risk
• Monogenetic syndromes and polygenetic effects • Epigenetic Effects	• Parental obesity • Maternal weight gain • Gestational diabetes • Maternal smoking	• Birth weight • Early breastfeeding cessation and formula feeding • Rapid weight gain during infancy and early childhood • Early use of antibiotics	• Endocrine disorders • Children and youth with special health care needs • Attention-deficit/hyperactivity disorder • Medication use • Depression

Hampl SE, et al. *Pediatrics*. 2023

Commonly Prescribed Medications and Weight Gain in Pediatric Patients

Asthma Management	• Antihistamines • Steroids (systemic)
Antidepressant	• Amitriptyline • Nortiptyline • Paroxetine • Sertraline
Antipsychotic/ Antimania	• Aripiprazole • Clozapine • Haloperidol • Lithium • Mirtazapine • Olanzapine • Perphenazine • Quetiapine • Risperidone • Ziprasidone
Antiepileptic	• Divalproex sodium • Carbamazepine • Gabapentin • Pregabalin • Valproate • Vigabatrin

Hampl SE, et al. *Pediatrics*. 2023

Assessment Question 1

In children and adolescents, a BMI of ___ is classified as overweight.

a) ≥ 75th percentile to < 90th percentile
b) ≥ 85th percentile to < 95th percentile
c) ≥ 90th percentile to < 99th percentile
d) ≥ 80th percentile to < 90th percentile

Assessment Question 1

In children and adolescents, a BMI of ___ is classified as overweight.

a) ≥ 75th percentile to < 90th percentile
b) ≥ 85th percentile to < 95th percentile
c) ≥ 90th percentile to < 99th percentile
d) ≥ 80th percentile to < 90th percentile

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"Normal" Weight	5th to < 85th percentile
Underweight	< 5th percentile

Vajravelu ME, et al. *Life (Basel)*. 2023

Guidelines

- Journal of Clinical Endocrinology and Metabolism (JCEM) – "Pediatric Obesity – Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline"
  - Last Updated: January 2017
  - Addresses prevention of obesity and lifestyle interventions for the treatment of obesity
  - Does not cover pharmacologic therapy
- American Academy of Pediatrics (AAP) – "Clinical Practice Guidelines for the Evaluation and Treatment of Children and Adolescents With Obesity"
  - Last Updated: January 2023
  - Does not cover the prevention of obesity
  - Does not include guidance for overweight and obesity evaluation and treatment of children younger than 2 years of age

Hampl SE, et al. *Pediatrics*. 2023

American Academy of Pediatrics (AAP)

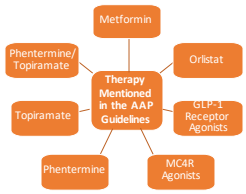
- Pharmacologic Therapy Guideline Recommendations
  - The use of pharmacotherapy in patients ≥ 12 years of age who require additional treatment options to manage their obesity
    - More immediate/life-threatening comorbidities, older, and higher severity of obesity
  - May offer children ages 8 through 11 years of age with obesity weight loss pharmacotherapy according to medication indications, risks, and benefits as an adjunct to health behavior and lifestyle treatment
  - No current evidence supports the use of pharmacotherapy alone for weight loss; for children who are prescribed weight loss medication intensive behavioral interventions should also be provided

Hampl SE, et al. *Pediatrics*. 2023

Patient Case

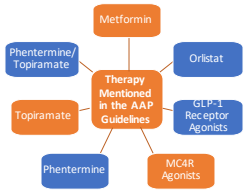
DH, is a 14-year-old male, identified by his primary care provider to have a BMI in the 98th percentile. Previous attempts at lifestyle modifications for weight management has failed and he is now looking for pharmacologic therapy options.

Pharmacologic Therapy



Hampl SE, et al. *Pediatrics*. 2023

Pharmacologic Therapy



Hampl SE, et al. *Pediatrics*. 2023

Metformin

- Biguanide Antidiabetic Agent
  - Reduces blood glucose levels by decreasing blood glucose production in the liver, decreasing intestinal absorption, and increasing insulin sensitivity
- FDA Approval
  - Children 10 years of age and older with T2DM
- BMI Reduction
  - Effectiveness is inconsistent across different populations and the evidence for effectiveness of metformin for weight loss in pediatrics is conflicting
- Associated Adverse Events
  - Bloating, nausea, flatulence, and diarrhea
    - Dose-dependent
  - Lactic acidosis is a rare but serious complication in pediatric populations

Hampl SE, et al. *Pediatrics*. 2023

Orlistat (Xenical®/Alli®)

- Intestinal Lipase Inhibitor
  - Blocks fat absorption through inhibition of pancreatic and gastric lipase, these inactivated enzymes are then unable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids
- FDA Approval
  - Long-term treatment of obesity in children 12 years of age and older
- Associated Adverse Events
  - Steatorrhea, fecal urgency, and flatulence
  - Limits tolerability and is uncommonly used in pediatric obesity treatment due to these adverse events

Chanoine JP, et al. *JAMA* 2005

Orlistat (Xenical®/Alli®)

Orlistat (Xenical®)

Chanoine JP, et al; *JAMA*. 2005	
Objective	Determine the efficacy and safety of orlistat in weight management of adolescents
Methods	Multicenter, 54-week, randomized, double-blind study
Population	539 obese adolescents, aged 12 to 16 years, with a body mass index ≥2 units above the 95th percentile
Results	• BMI decreased by 0.55 with orlistat, compared to 0.31 increase with placebo (p=0.001) • 26.5% of orlistat group had 5% or higher decrease in BMI, compared to 15.7% of placebo group (p=0.005) • 13.3% of orlistat group had 10% or higher decrease in BMI, compared to 4.5% of placebo group (p=0.002)
Conclusion	In combination with diet, exercise, and behavioral modifications, orlistat statistically significantly improved weight management in obese adolescents compared with placebo

Glucagon-like Peptide-1 Receptor Agonist

- GLP-1 Receptor Agonists
  - Decrease hunger by delaying gastric emptying and acting on targets in the central nervous system
  - Liraglutide, exenatide, dulaglutide, and semaglutide
- FDA Approval
  - Liraglutide (Saxenda®): long-term treatment of obesity (with or without T2DM) in children 12 years and older
  - Semaglutide (Wegovy®): long-term treatment of obesity (with or without T2DM) in children 12 years and older
- Associated Adverse Events
  - Nausea and vomiting, slightly increased risk of medullary thyroid cancer in patients with a family history of multiple endocrine neoplasia

Glucagon-like Peptide-1 Receptor Agonist

Liraglutide

Kelly AS, et al; *N Engl J Med.* 2020	
Objective	Evaluate the efficacy and safety of subcutaneous liraglutide (3.0 mg) as an adjunct to lifestyle therapy for weight management in adolescents with obesity
Methods	Phase III, randomized, double-blind, placebo-controlled trial
Population	Adolescents, 12 to < 18 years of age, with obesity and poor response to lifestyle therapy alone
Results	Liraglutide was superior to placebo with regard to change from baseline in the BMI standard-deviation score at week 56 (estimated difference, -0.22; 95% CI, -0.37 to −0.08; p=0.002)
Conclusion	In adolescents with obesity, the use of liraglutide (3.0 mg) plus lifestyle therapy led to significantly greater reduction in the BMI standard-deviation score than placebo plus lifestyle therapy.

Semaglutide

Weghuber D, et al; *N Engl J Med.* 2022	
Objective	Assessed the efficacy and safety of once-weekly subcutaneous semaglutide plus lifestyle intervention among adolescents with obesity
Methods	Multinational, double-blind, parallel-group, randomized, placebo-controlled phase 3a clinical trial
Population	Adolescents, 12 to < 18 years of age, with obesity (BMI in the 95th percentile or higher) or with overweight (BMI in the 85th percentile or higher) and at least one weight-related coexisting condition
Results	At week 68, estimated mean percentage BMI change from baseline: • -16.1% with semaglutide and 0.6% with placebo • (estimated difference, -16.7 percentage points; 95% CI, -20.3 to -13.2; p<0.001)
Conclusion	Among adolescents with obesity, once-weekly treatment with a 2.4 mg dose of semaglutide plus lifestyle intervention resulted in a greater reduction in BMI than lifestyle intervention alone.

Setmelanotide (Imcivree®)

- Melanocortin 4 Receptor (MC4R) Agonist
  - MC4 receptors in the brain are involved in the regulation of hunger, satiety, and energy expenditure
  - Acts on the MC4R pathway to restore normal function for appetite regulation that has been disrupted due to genetic deficits upstream of the receptor
- FDA Approval
  - Patients 6 years of age and older with:
    - Proopiomelanocortin (POMC) deficiency, proprotein subtilisin or kexin type-1 deficiency, and/or leptin receptor deficiency confirmed by genetic testing
- BMI/Weight Reduction
  - Found to result in a weight loss of 12% to 25% over one year, in a small uncontrolled study of patients with these rare deficits
- Associated Adverse Events
  - Injection site reaction and nausea

Setmelanotide (Imcivree®)

Phentermine (Adipex®)

- Sympathomimetic Amine
  - Exact mechanism unknown, however thought to be mediated by release of catecholamines in the hypothalamus, resulting in reduced appetite and decreased food consumption
- FDA Approval
  - Short-course therapy (3 months) for adolescents 16 years of age and older
- Associated Adverse Events
  - Elevated blood pressure, irritability, insomnia, mood alterations, dizziness, headache, tremor, dry mouth, and abdominal pain
- Contraindications
  - History of past or uncontrolled cardiovascular disease, hyperthyroidism, glaucoma, and/or current use of monoamine oxidase inhibitors

Phentermine

Ryder JR, et al; *Int J Obes (Lond)*. 2016	
Objective	Examine the weight loss effectiveness of phentermine added to standard of care (SOC) lifestyle modifications versus SOC alone
Methods	Retrospective chart review, with patients receiving phentermine plus SOC matched with a comparison group of SOC alone
Population	Adolescents with obesity treated at the University of Minnesota Masonic Children's Hospital Pediatric Weight Management Clinic • 25 patients (mean age 16.1±1.3 years; mean BMI 41.2±6.9 kg/m²)
Results	Phentermine use was associate with a greater percent change in BMI at: • 1 month (−1.6% [95% CI (−2.6%, −0.6%); p=0.001), • 3 months (−2.9% [95% CI (−4.5%, −1.4%); p<0.001]) • 6 months (−4.1% [95% CI (−7.1%, −1.0%); p=0.009])
Conclusion	Compared to SOC alone, phentermine added to SOC resulted in statistically significant weight loss at 1-mont, 3-months, and 6-months among adolescents with obesity.

Topiramate

- Carbonic Anhydrase Inhibitor
  - Suppresses appetite centrally through largely unknown mechanisms
- FDA Approval
  - Children 2 years of age and older with epilepsy
  - Prevention of headaches in children 12 years of age and older
  - Binge eating disorder in patients 18 years of age and older
- Associated Adverse Events
  - Suicidal behavior and ideation, mood and sleep disorders, and cognitive impairment which may interfere with concentration in academics or other activities of daily life

Phentermine and topiramate (Qsymia®)

- Combination product of a Sympathomimetic Amine (phentermine) and Carbonic Anhydrase Inhibitor (topiramate)
- FDA Approval
  - Chronic weight management in pediatric patients 12 years of age and older
- Associated Adverse Events
  - Increase heart rate, suicidal behavior and ideation, mood and sleep disorders, cognitive impairment, slowing of linear growth, metabolic acidosis, decrease in renal function, acute myopia, secondary angle closure glaucoma, and visual problems
  - Can cause fetal harm if taken while pregnant
    - Only available through the Qsymia Risk Evaluation and Mitigation Strategy (REMS)

Phentermine and topiramate (Qsymia®)

Phentermine and topiramate (Qsymia®)

VIVUS LLC; *Clinical Trial: NCT03922945*, 2022	
Objective	Assess weight loss efficacy, as determinedby changes in BMI , and safety of Qsymia or placebo, takenfor 56 weeks accompanied by a lifestyle modification program
Population	Obese adolescents ages 12-16years
Methods	Phase IV, multi-center, randomized, double-blind, placebo-controlled, parallel-design study
Results	Participant's BMI changes, on average, wereas follows: Qsymia 7.5mg/46mg: 4.8% decrease Qsymia 15mg/92mg: 7.1% decrease Placebo: 3.3% increase

Assessment Question 2

True or False?

Orlistat is FDA approved for long-term treatment of obesity in children 12-years and older.

Assessment Question 2

True or False?

Orlistat is FDA approved for long-term treatment of obesity in children 12-years and older.

a) True

Summary of FDA Approved Pharmacologic Therapies

Medication	Dosage Form	FDA Approved Ages	Indication	Other Clinical Pearls
Orlistat (Xenical®/Alli®) lower dosage (Alli, 60mg available OTC	PO, capsule	≥ 12 years of age	Long-term weight management	Can interfere with absorption of fat-soluble vitamins, all patients should take daily supplementation
Liraglutide (Saxenda®)	SQ, injection	≥ 12 years of age	Long-term weight management	Once weekly injection
Semaglutide (Wegovy®)	SQ, injection	≥ 12 years of age	Long-term weight management	Once weekly injection
Phentermine (Adipex®)	PO, capsule and tablet	≥ 16 years of age	Short-term (3 months) weight management	Controlled substance
Phentermine + topiramate (Qsymia®)	PO, extended-release capsule	≥ 12 years of age	Long-term weight management	Controlled substance, requires REMS

Assessment Question 3

Current evidence supports using which of the following weight loss medications as monotherapy in pediatric patients?

a) Antidiabetic agent, metformin
b) Melanocortin 4 receptor (MC4R) agonist, such as setmelanotide
c) Glucagon-like peptide-1 receptor agonists, such as liraglutide or semaglutide
d) None of the above

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d) None of the above

"No current evidence supports the use of pharmacotherapy alone for weight loss; for children who are prescribed weight loss medication intensive behavioral interventions should also be provided."

Patient Case

DH, is a 14-year-old male, identified by his primary care provider to have a BMI in the 98th percentile. Previous attempts at lifestyle modifications for weight management has failed and he is now looking for pharmacologic therapy options.

Which of the following pharmacologic therapies is **not** FDA approved for use for DH's weight management?

a) Orlistat
b) Liraglutide
c) Phentermine + topiramate
d) Phentermine
e) All of the above therapies are FDA approved options

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DH, is a 14-year-old male, identified by his primary care provider to have a BMI in the 98th percentile. Previous attempts at lifestyle modifications for weight management has failed and he is now looking for pharmacologic therapy options.

Which of the following pharmacologic therapies is **not** FDA approved for use for DH's weight management?

a) Orlistat
b) Liraglutide
c) Phentermine + topiramate
d) Phentermine
e) All of the above therapies are FDA approved options

Phentermine is FDA approved for short-term weight management in patients ≥ 16 years of age

Patient Case

DH, is a 14-year-old male, identified by his primary care provider to have a BMI in the 98th percentile. Previous attempts at lifestyle modifications for weight management has failed and he is now looking for pharmacologic therapy options.

In discussion with DH's mother it is identified he has high anxiety associated with injections. Which of the following is the best initial pharmacologic option for DH?

a) Orlistat
b) Liraglutide
c) Semaglutide
d) Phentermine + topiramate

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Summary

- Childhood obesity is a chronic disease with negative short and long-term implications on, not only physical and metabolic, but also psychosocial and emotional health
- Currently there are five pharmacological therapies with FDA approved indications for weight-management in pediatric patients
- As our pediatric population's environment has become increasingly obesogenic the need for evidence-based treatment is crucial

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Pharmacologic Management of Weight Loss in Pediatrics

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