Pharmacological Management of Pain

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Objectives
• Review the types, pathogenesis & pathophysiology of pain
• Describe both the basic and clinical pharmacology of the most commonly used opioid analgesics.
• Compare and contrast the basic and clinical pharmacology of NSAIDS, COX-2 inhibitors and acetaminophen
• Discuss the pharmacological rationale and clinical utility of select antidepressants and antiepileptic medications in pain management
• Discuss the purported pharmacologic action(s) of medical cannabis and it's potential advantages/disadvantages in treating select pain conditions.

Two Types of Peripheral Pain Neurons
• A-delta fibers
  – Thick, myelinated, fast conducting
  – Carry information mainly from the nociceptive-mechanical or mechanothermal-specific nociceptors.
  – Mediate the feeling of initial fast, sharp, highly localized pain.
  – Receptive fields are small - provide precise localization of pain.

Pain Physiology

Two Types of Peripheral Pain Neurons
• C fibers
  – Thin, unmyelinated, slow-conducting
  – Receptive field is large - less precise for pain localization
  – Chemical (inflammation) or thermal stimuli
  – Multiple spinal synaptic connections
  – This type of pain is a more diffuse, slower to onset, and longer in duration
  – Mediate slow, dull, more diffuse, often burning pain
  – Motivational and emotional aspects of pain (interpretation)
Nociceptive pain
• Pain can be somatic or visceral in nature.
• Somatic pain tends to be well localized, constant pain described as sharp, aching, throbbing, or gnawing.
• Visceral pain tends to be vague in distribution, paroxysmal in nature and is usually described as deep, aching, squeezing and colicky in nature.
• Examples: post–operative pain, pain associated with trauma, chronic pain of arthritis.
• Usually responds to opioids and non–steroidal anti–inflammatories (NSAIDS).

Neuropathic pain
• Onset often delayed after injury or pain and sensory symptoms that persist beyond the normal healing period.
• Presents as continuous background pain, spontaneous pain or stimulus-evoked pain
• Chronic allodynia and hyperalgesia.
• Can be constant, intermittent, paroxysmal
• Pain described as: Electric shock, burning, icy cold, aching, tingling, needles and pins
• Pain tends to be only partially responsive to standard analgesics (NSAIDs, Opioids)

Acute pain
• Self–limiting
• Serves a protective biological function by acting as a warning of on–going tissue damage.
• A “symptom” of a disease process experienced in or around the injured or diseased tissue.
• Associated psychological symptoms are minimal and are usually limited to mild anxiety.
• Nociceptive in nature, and occurs secondary to chemical, mechanical and thermal stimulation of A–delta and C–polymodal pain receptors.

Chronic pain
• Serves no protective biological function
• Disease process instead of disease symptom
• Unrelenting and not self–limiting
  – Can persist for years - decades after initial injury
• Can be refractory to multiple treatment modalities.
• Inadequately treated - associated symptoms can include chronic anxiety, fear, depression, sleeplessness and impairment of social interaction.
• Chronic, non–malignant pain is predominately neuropathic in nature and involves damage either to the peripheral or central nervous systems.
Sites of action for Analgesics

Pain Medication Arsenal

Primary Analgesics
- Non-opioid
  - Acetaminophen, ASA, NSAIDs
- Opioid
  - PRN administration of IM/IV/oral short-acting
  - Regularly scheduled administration of long-acting agents
  - Topical / PCA

Adjuvant analgesics
- Antidepressants
- Anticonvulsants
- Local anesthetics
- Sympatholytics
- NMDA antagonists
- Topical products
- Muscle relaxants
- Benzodiazepines

Opioid Analgesics

“Drugs that can relieve pain without causing loss of consciousness”

The major class of analgesics used in the management of moderate to severe pain because of their effectiveness, ease of titration, and favorable risk-to-benefit ratio.

Opioid Actions

Do not alter the pain threshold of afferent nerve endings to noxious stimuli

Do not affect the conductance of impulses along peripheral nerves

Analgesia mediated through changes in the perception and descending modulation of pain at the spinal cord and in CNS

Opioid Mechanisms

Act only in CNS
- Inhibit pre and post synaptic fibers in doral horn of spinal cord
- Prevent ascending transmission of pain signal
- Turn on descending inhibitory systems
- Inhibit cells that release inflammatory mediators
- Alter perception of pain at higher cortical processes
**Opioid Mechanisms**

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**Opioid Targets**

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**Opioid Receptors**

- Mu receptors (mu-1 and mu-2)
  - Beta endorphins the natural agonist
  - Mu-1 receptors
    - supraspinal
    - responsible for central interpretation of pain
    - A number of subtypes exist (MOR, or MOP)
  - Mu-2
    - located throughout CNS
    - respiratory depression, spinal analgesia, euphoria, physical dependence, GI motility

- Kappa (κ₁, κ₂, κ₃)
  - Dynorphins natural agonist
  - Significant Spinal analgesia
  - Less respiratory depression / dependence
  - Miosis (pinpoint pupils), sedation, dysphoria, nausea
  - Activation may antagonize mu receptors
  - Basal ganglia, PAG, hypothalamus, cortex, spinal cord

- Delta (δ₁, δ₂)
  - Enkephalins natural agonist
  - Mostly spinal locations
  - Some analgesia (< mu-receptor)

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**Opioid Receptors and Effect**

- Response to an opioid depends on:
  - the receptor(s) to which it binds
  - its affinity for that receptor
  - if it’s an agonist, partial agonist of antagonist
- Each opioid is unique in its distinct binding affinity to the various classes of opioid receptors (e.g. the μ, κ, δ)
- Opioid receptors are activated at different magnitudes according to the specific receptor binding affinities of the opioid

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**Opioid Receptors and Effect**

- Subtle differences in receptors may be responsible for:
  - Inter-patient variability in analgesic responses, tolerability (side effects) and subjective experience
  - Incomplete cross-tolerance among mu opioids
  - Rationale for opioid rotation
### Opioid Receptors and Effect

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### Opioids

- Most effective for somatic or visceral pain
  - Post-op, cancer, deep pain
- Less effective for neurogenic/pathic pain
- Incident pain difficult to control
- Higher potency agents may be more effective
  - Greater mu affinity?
  - Multiple actions (ie, analgesic, anesthetic)
  - Greater fat solubility – CNS entry
- No predictable relationship between opioid serum levels and analgesic responses

### Opioid Agonists

<table>
<thead>
<tr>
<th><strong>Strong Agonists (C-II)</strong></th>
<th><strong>Weak or Partial Agonists</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Ceiling</strong></td>
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</tr>
<tr>
<td>Morphine</td>
<td>Codeine (C-III)</td>
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<tr>
<td>Hydromorphone</td>
<td>&lt; 90 mg/dose unit + APAP</td>
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<tr>
<td>Hydrocodone</td>
<td>Partial Agonists</td>
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<tr>
<td>Oxymorphone</td>
<td>Buprenorphine (C-III)</td>
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<tr>
<td>Oxycodone</td>
<td>Pentazocine (C-IV)</td>
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<tr>
<td>Fentanyl</td>
<td>Butorphanol (C-IV)</td>
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<tr>
<td>Methadone</td>
<td>Tramadol (C-IV)</td>
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<tr>
<td>Tapentadol</td>
<td></td>
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<tr>
<td>Codeine (&gt; 90 mg)</td>
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</tbody>
</table>

### Morphine

- Most commonly used opioid for moderate to severe pain
- Available in a wide variety of dosage forms
  - PO, SC, IM, Rectal, Epidural, Intrathecal
- Well-characterized pharmacokinetics and pharmacodynamics
- Relatively low cost

### Morphine Pharmacokinetics

- Poor oral bioavailability
- Significant 1st pass effect (non-CYP450)
  - Active metabolite M-6-G (~10%) estimated to be 2–5 times more analgesic than morphine
  - Inactive metabolite M-3-G (~50%) may cause allodynia, myoclonus, and seizures
  - All metabolites renally eliminated (caution in renal failure)
- Half life = 2.5 to 3 hrs (does not persist in body tissue)
- Duration of 10 mg dose is 3 to 5 hours
- SR and ER formulations (MS Contin, Avinza, Kadian)
  - Duration longer (8 – 24 hr)
  - Half-life remains the same as above

### Hydromorphone

- ~ 4x more potent than morphine (7.5 = 30)
- Primarily Mu receptor agonist (negligible Kappa, Delta)
  - Does not produce miosis (mostly mu receptor binding)
- Highly water-soluble - allows for very concentrated formulations
- Good choice when opioid dose (pill burden) an issue
  - opioid tolerant patients
  - trouble with swallowing multiple pills, etc
- More rapid onset and shorter half life
- Metabolite H-3-G (~40%) can lead to neutrotoxicity – caution in renal impairment.
- Tolerance and physical dependence is more intense than morphine because of its high potency
- Respiratory depression same as morphine
**Oxymorphone**
- Semi-synthetic - primarily mu receptor agonist
- 3x more potent than morphine
- Oral bioavailability ~ 10%  
  - Hepatic metabolism (non-P450)
- No active metabolites
- Less renal issues
- More lipid soluble than morphine  
  - IR – faster onset than morphine or oxycodone
- May be good for breakthrough pain
- Duration of action: IR 4–6 hours; ER 12 hours

**Fentanyl**
- Synthetic opioid  
  - Parenteral (IV, IM)  
  - Topical (patch, nasal spray)  
  - Transmucosal (lozenge, buccal film/tablet, sublingual)
- 80 to 100 times more potent than morphine
- Preferred to other opioids in anesthesia due to its ability to maintain cardiac stability
- Used for breakthrough pain ➔ chronic pain
- High potency can be an issue for naloxone reversal!!

**Oxycodone**
- Semi-synthetic  
- ~ 1.5x more potent than morphine (20 mg = 30 mg)
- Equally effective as morphine
- Available as immediate-release tablets, controlled-release tablets, or as oral solution
- No comparative trials showing that oxycodone is more effective than any other opioid
- May cause less sedation, pruritus, nausea than morphine
- Second most commonly abused prescription opioid (after hydrocodone)

**Hydrocodone (all IR & ER C-II)**
- Equianalgesic compared to Morphine  
  - 1 mg IV hydrocodone = 0.4 mg of IV morphine.
  - Due to morphine’s low oral bioavailability, a 1:1 relationship exists for PO hydrocodone and morphine
- 6x greater analgesia ~ 6X > codeine (PO)
- Hydrocodone (+ acetaminophen) most widely prescribed drug in US
- Also inactivated by CYP3A4

**CYP3A4 inhibitors**
- macrolides (not azith)  
-azole antifungals  
- protease inhibitors  
-verapamil, other CCBs  
grapefruit juice

**CYP3A4 inducers:**
- rifampin  
- phenytoin  
-carbamazepine  
-pioglitazone  
-St John’s wort

**Metabolized by CYP3A4 (major) and CYP2D6 (minor)**
- Inhibitors / genetics can increase toxicity
- Can accumulate in renal or hepatic impairment

**Onset of action**
- IV: Almost immediate
- IM: 7-8 minutes
- Transdermal (initial placement): 6 hours
- Transmucosal: 5-15 minutes
**Duration:**
- IV: 0.5-1 hour
- IM: 1-2 hours
- Transdermal (remove patch/no replacement): 12 hours
- Transmucosal: Related to blood levels / dose
- In all cases, respiratory depressant effect may last longer than analgesic effect
Methadone

Synthetic containing two isomers (d,l)
- One isomer = Mu receptor agonist
- One isomer = NMDA (glutamate receptor) antagonist
• Equianalgesic with morphine
  - not an easy conversion
  - non-linear relationship in opioid tolerant pts
• Tolerance and dependence develop more slowly than with morphine.
• Withdrawal signs and symptoms are milder but more prolonged.

Methadone Pharmacokinetics
- Rapid absorption and distribution
  - GI absorption nearly complete
  - onset of analgesia in 30-60 mins
- Slow elimination
  - $T1/2 = 15$-$40$ hours
  - $T1/2 = 22$ hours in chronic state
  - steady state in 4 - 5 days
  - accumulation likely – difficult to work with

Methadone Side Effects:
- Respiratory depression, QT prolongation, arrhythmia(s), bradycardia, cardiac arrest, constipation, diaphoresis

Interactions:
- CYP3A4 (inhibitors, inducers)
- Drugs prolonging QT interval
  - incl hypokalemia, hypomagnesemia, hypocalcemia
- Serotonin-enhancing drugs
- CNS depressants

Buprenorphine (C-III)
- Partial mu agonist <high affinity> / weak $\kappa$ antagonist
- Less reinforcing than a full agonist (milder)
  - Easier withdrawal (less dysphoria)
  - Safety – overdose ceiling effect
- Acute & Chronic moderate – severe pain
- Used in treating Opioid Dependence
- Strong safety profile
  - Little respiratory depression
  - Little overdose potential

Buprenorphine
- Poor oral absorption
  - IM, IV, sublingual, buccal
- 25 to 50 times more potent than morphine
- Maximal effects peak slower than morphine
- Analgesia lasts longer (6 hours)
- Cleared by CYP3A4
  - see oxycodone and methadone interactions

Codeine
- Pro-drug
  - Needs to be converted to morphine for analgesia
  - Approximately 8 – 10% of dose converted
- Used for mild to moderate pain
  - 60 mg = 1000 mg acetaminophen
  - > 200 mg only increases side effects
- Lower doses for diarrhea and cough suppression
- Less respiratory depression
- Less dependence liability
- Overdose can produce seizures
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Codeine

Inhibitors of CYP 2D6 may decrease analgesic benefit
- paroxetine
- fluoxetine
- ritonavir
- terbinafine
- amiodarone
- quinidine

Opioids and CYP 2D6 Polymorphism
- 2D6 substrates:
  - Codeine (prodrug), oxycodone, hydrocodone
- Poor Metabolizers -
  - 1:10 Caucasians, 1:30 African-Americans
  - Decreased “therapeutic” effects for codeine
  - Questionable regarding hydrocodone
- Ultraextensive Metabolizers ~ 7% Caucasians
  - Codeine: Complaints of “weird” codeine side effects (due to increased morphine formation)
  - Hydro / Oxycodone — may produce more hydromorphone / oxymorphone (more potent compounds)

Opioid Side Effects

Common
- Constipation
- Nausea & vomiting
- Sedation & mental clouding
- Pruritis / Flushing
- Respiratory depression — (subacute OD)

Less Common
- Hallucinations / Delirium
- Hypothermia
- Bradycardia/tachycardia
- Orthostatic hypotension
- Urinary retention
- Biliary spasm
- Opioid induced hyperalgesia
- Decrease testosterone levels (men)

Opioid Tolerance

- Involves glutaminergic neurons
  - NMDA receptors correlate with tolerance
  - Activation of NMDA receptors may upregulate mu receptors
- Rate of tolerance varies greatly
  - Intermittent use does not generally lead to tolerance
  - Repeated administration does
- Cross tolerance occurs — usually not complete
- Methadone less likely

Opioid Rotation

Change from an existing opioid regimen to another opioid w/ the goal of improving therapeutic outcomes or to avoid AEs attributed to the existing drug

Differences in pharmacologic or other effects make it likely that a switch will improve outcomes
- Effectiveness & AEs of different mu opioids vary among patients
- Patients show incomplete cross-tolerance to new opioid
  - Patient tolerant to first opioid can have improved analgesia from second opioid at a dose lower than calculated from an EDT
Other Reasons for Opioid Rotation

- Patient desire or need to try a new formulation
- Cost or insurance issues
- Adherence issues
- Change in clinical status requires an opioid with different pharmacokinetic profile (i.e., worsening renal or hepatic status)
- Problematic drug-drug interactions
- Opioid induced hyperalgesia

Guidelines for Opioid Rotation

- Start with equianalgesic table
- Calculate equianalgesic dose
- Reduce calculated dose by 25 – 50% based on clinical judgement
  - 50% when receiving a relatively high dose of current opioid regimen or elderly or medically frail
  - 25% low doses, otherwise healthy pt or changing route of administration
- Methadone (75-90% reduction)
- Fentanyl – use package insert recommendations
- Be prepared for breakthrough pain management

Physical Dependence:

The appearance of the abstinence syndrome defines physical dependence on opioids, which may occur after just 2 weeks of opioid therapy.

Physical dependence occurs with the development of tolerance.

Is not the same as addiction!

Physical Dependence

- Withdrawal
- A set of symptoms that occur due to specific physiological changes - rebound phenomena
  - Reduced release of dopamine in nucleus accumbens
  - Three-fold increase in norepinephrine release
- Abstinence vs Precipitated

Withdrawal - Abstinence

- Onset related to time-effect curve and 1/2 of narcotic.
  - 6-8hr => drug seeking behavior, restless, anxious.
  - 8-12hr => Pupils dilated, reactive to light; increased pulse rate, blood pressure, yawning; chills; rhinorrhea; lacrimation; gooseflesh; sweating; restless sleep.
  - 48-72 hrs (peak) => All of the above plus muscular weakness, aches (cramps) and twitches; nausea, vomiting and diarrhea; temperature and respiration rate elevated; heart rate and blood pressure elevated; dehydration.

Withdrawal - Abstinence

Can be life-threatening
Depends on degree of physical dependence and health status of patient
No seizures, no delirium, no disorientation

Treatment of withdrawal: symptoms => clonidine
Used to block autonomic symptoms of withdrawal

- tachycardia
- sweating
- hypertension
- cramping
- nausea
- vomiting
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Withdrawal - Precipitated

- Produced by administration of:
  - Opioid antagonists
    - naloxone, naltrexone, incl vivitrol
  - Mixed partial agonist / antagonists
    - Pentazocine, buprenorphine, butorphanol, nalbuphine
- Peaks sooner than abstinence withdrawal
- More severe - more difficult to reverse

Back to STEP 1 of the WHO Pain Ladder

Non-opioid analgesics, adjuvants

WHO Pain ladder

FDA Recommendations

- Patients should be offered evidence-based non-pharmacologic treatments:
  - Application of heat or cold, exercise, weight loss, or self-management programs
  - NSAID or non-NSAID topical treatments
  - NSAID regimens that minimize risk, using the lowest-risk agents at the lowest dose for short periods.

Inflammatory Pain

Mediators induce hyperalgesia and ectopic activity in both injured and adjacent uninjured primary afferent nociceptors at the lesion site

The Role of Prostaglandins in Inflammation and Pain

Prostaglandins
  Bradykinin

INFLAMMATION

Local Vasodilation
Hyperalgesia

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Inflammatory Pain

Quality
- Aching
- Throbbing
- Worse with movement

Clinical setting
- Postoperative
- Trauma
- Infection
- Arthritis

Physical findings
- Warm
- Red
- Swollen

Drug Management
NSAIDs
acetaminophen*
corticosteroids

* analgesic only

Prostaglandins in the CNS

Sites of action for Analgesics

For what conditions are NSAIDs recommended / used?
- RA
- OA
- Inflammatory arthritis, AS, psoriatic arthritis
- Acute gout
- Metastatic bone pain
- Dysmenohoea
- Headache, migrainw
- Postoperative pain
- Pyrexia (fever)
- Ileus
- Renal colic

Arachidonic Acid Cascade

Cyclooxygenase
- Prostaglandins
- Thromboxane
- vasodilation
- vasoconstriction
- hyperalgesia

Lipoxygenase
- Leukotrienes
- bronchoconstriction
- tissue edema
- mucus secretion
- chemotaxis

NSAIDs

Higher Centers
NSAIDs, opioid, acetaminophen

Spinal Cord
Opioids, NSAIDs

Somatic
NSAIDs
Common Pharmacological Effects
- Inhibit both COX1 & COX2
- Weak organic acids
- Highly protein bound (~ 96 – 99% to Albumen)
- Analgesic (CNS and peripheral effect)
- Antipyretic (CNS effect)
- Anti-inflammatory due mainly to PG inhibition
  - Low doses – central analgesia + antipyretic
  - High Doses – anti-inflammatory
- Same set of common side effects
- Differ only in potency, duration, selectivity for COX-1 or COX-2, cost

Efficacy of NSAIDs
- ~ 60% of patients will respond to any NSAID
- Those who do not respond to one may well respond to another.
- Pain relief starts from the first dose, with full analgesic effects obtained within a week.
- Anti-inflammatory effects may not be achieved for up to three weeks.

NSAID Side Effects
Common
- Gastrointestinal
- Cardiovascular
- Renal
Less Common
- Hepatic
- CNS
Low likelihood (in adults)
- Allergy / Bronchospasm (esp in asthma)
- Reye’s syndrome (ASA only)
- Rash

NSAIDs Contraindications
- Hypersensitivity to ASA or other NSAIDs
- Uncontrolled heart failure
- Active gastric/duodenal/peptic ulcer
- Cerebrovascular bleeding
- Severe hepatic impairment
- Severe renal impairment (CrCl <30 mL/minute)
  - deteriorating renal disease; known hyperkalemia;
- Breast-feeding; pregnancy (third trimester)
- Coronary artery bypass graft (CABG) surgery

Role of COX (1&2) and potential side effects due to inhibition

http://tmedweb.tulane.edu/pharmwiki/doku.php/nsaid_side_effects
### GI Risk

- Relative risk for a GI bleed or perforation increases about 4X in patients who use NSAIDs compared to those who don’t.
- Risk factors include:
  - Age over 65
  - History of GI bleed or ulcer
  - Concurrent use of drugs that increase the risk of GI adverse events
  - Heavy smoking or alcohol use
  - Prolonged NSAID use
  - Particular NSAID and high dose
  - Serious co-morbidity

### Cardiovascular Risk

- **Risks**
  - Hypertension, heart failure, MI, stroke, death (to varying degrees) even in healthy people.

- **Proposed Mechanisms**
  - **NSAID-associated HF** - due to increased peripheral vascular resistance and reduced renal perfusion caused by PG inhibition.
  - **MI / Stroke** – imbalance between platelet thromboxane A$_2$ (vasoconstriction produced by COX-1) and vascular endothelium produced PGI$_2$ (prostacyclin produced by COX-2)
  - NSAIDs that are the safest from a CV standpoint tend to have higher GI toxicity and vice versa.

### Increased Risk of MI/Stroke

**The important balance between TxA$_2$ and PGI$_2$**

- Low dose ASA vs COX-2 inhibition


### Nephrotoxicity

- **Risk factors for acute kidney injury include:**
  - Older age, diabetes, renal insufficiency, HF
  - NSAIDs can increase blood pressure, cause fluid retention, and worsen renal function in above
  - Patients with HTN, NSAID use > 3 months (~ 30%) more likely to develop CKD vs nonusers
  - In high-risk patient (including those taking an ACEI, ARB, or diuretic), consider checking serum creatinine and potassium weekly for several weeks
  - Monitor renal function
  - Avoid NSAIDs with t½ > 12 hours (ie., oxaprozin (Daypro), ketorolac, nabumetone, naproxen, meloxicam, or piroxicam)

### Balancing the Risk of all NSAIDs

NSAID medication selection should consider both the individual patient’s GI and CV risk profile.
Reducing GI Risk

- Lowest dose that provides benefit
- Shortest amount of time
- Use of gastroprotective drugs:
  - PPIs, Misoprostol
  - H2 Blockers (high dose)
- Long term PPI use risky in elders
- Remember to DC PPIs

Do NSAIDs increase cardiovascular risk in those with and without a history of known cardiovascular disease

- Both selective & nonselective NSAID use associated with increased risk of CV events such as ischemic CV disease and heart failure.
- This effect for all NSAIDs appears to be both dose and time dependent.
- Low dose NSAIDs:
  - Ibuprofen < 1200mg daily
  - Diclofenac < 100mg daily
  - Naproxen < 500 mg daily
  - Celecoxib < 200 mg daily

Reducing Cardiovascular Risk

- For patients with CV disease or risk factors for ischemic heart disease
  - Consider acetaminophen, aspirin or other salicylates, tramadol, IR opioids (short-term) before moving to an NSAID
  - Consider adding aspirin 81 mg and a proton pump inhibitor in patients with increased CV risk
  - Monitor renal function and blood pressure. Watch for edema and GI toxicity
  - After a myocardial infarction, there does not seem to be a safe time frame for using an NSAID

Summary – ACC, AHA, and ACR

- Discourage use of all NSAIDs in patients with chronic heart failure
- Recommend against use of NSAIDs, particularly COX-2 inhibitors, in patients with established CV disease
- Recommend NSAIDs be avoided in patients taking aspirin for cardioprotective benefit
  - If treatment becomes necessary in ASA patient, ibuprofen should be avoided (insufficient data to assess other NSAIDs)
- If the patient is at moderate to high risk of a potential cardiovascular event and treatment becomes necessary then initial management should be attempted initially with acetaminophen then naproxen

NSAID/Aspirin Interaction

- Competition between some NSAIDs and ASA for binding to COX-1 in platelet
- Recommended:
  - Take immediate release aspirin 1-2 hrs before ibuprofen / naproxen
  - Avoid enteric-coated ASA if using NSAIDs
  - Also use IR NSAIDs
- Little is known about other NSAIDs and ASA platelet interactions

Safety Comparison of NSAIDs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>COX-2 Selectivity</th>
<th>GI RISK</th>
<th>CV RISK</th>
</tr>
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<tbody>
<tr>
<td>Aspirin</td>
<td>Low</td>
<td>Moderate</td>
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<tr>
<td>Celecoxib</td>
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<td>Diclofenac</td>
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Summary Recommendations

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<th>Low GI risk</th>
<th>Moderate GI risk</th>
<th>High GI risk</th>
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<tr>
<td>Low CV risk</td>
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<tr>
<td>Celecoxib or other NSAID</td>
<td>1. Celecoxib alone</td>
<td>1. Avoid NSAIDs if possible</td>
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<tr>
<td></td>
<td>2. NSAID plus PPI, misoprostol, or double-dose H2-blocker (second line)</td>
<td>2. Celecoxib plus PPI or misoprostol</td>
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<tr>
<td>High CV risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen* or low-dose celecoxib (if on aspirin, naproxen plus gastroprotection)</td>
<td>1. Naproxen* PPI, misoprostol, or double-dose H2-blocker (second line)</td>
<td>Avoid NSAIDs</td>
</tr>
</tbody>
</table>

* Limit to 500 mg BID


Topical analgesics in osteoarthritis (OA) guidelines

American Association of Orthopaedic Surgeons (2013)
- Knee OA: Strongly recommend oral or topical NSAIDs or tramadol for the pharmacologic management of patients with symptomatic OA of the knee
- Hand OA: Initial management of hand OA should include one or more of the following: topical capsaicin, topical NSAIDs, oral NSAIDs, tramadol

American College of Rheumatology (ACR) 2012
- Knee OA: Initial management of knee OA should include one of the following: acetaminophen, oral NSAIDs, topical NSAIDs, tramadol, intra-articular corticosteroid injections. Topical rather than oral NSAIDs should be used in patients with hand or knee OA aged ≥75 years

- Good levels of pain relief in acute conditions such as sprains, strains and overuse injuries, probably similar to that provided by oral NSAIDs.
- Gel formulations of diclofenac, ibuprofen, and ketoprofen, and some diclofenac patches, provided the best effects. (NNT < 4)
- Topical diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin demonstrated significantly higher rates of clinical success (≥ 50% pain relief) v. topical placebo (moderate or high quality data)
- Local skin reactions are most common - generally mild and transient

Topical NSAIDs
- Peak plasma concentration 0.2 – 8% of concentrations observed with appropriate oral dosing
- Tissue concentrations (ie., meniscus, tendon sheath) from 4 -100 times greater than that observed from oral dosing
- Tmax about 10 times longer than oral with Cmax ranging from 2.2 – 23 hrs.

Another thing to consider:
- CYP2C9 responsible for metabolism of many NSAIDs
  - celecoxib, ibuprofen, naproxen
  - diclofenac, meloxicam, piroxicam
- Inhibitors of CYP2C9 may increase risk of NSAID SEs.
  - Fluconazole, voriconazole, metronidazole, amiodarone, cotrimoxazole
- Genetically poor metabolizers- 3 – 16% caucasian

Should Topical NSAIDs Have Strict Heart Risk Warnings? Jeffrey Fudin. Pharmacy Ties. 2015

Alan P. Agins, Ph.D. 2017
CYP2C9 variants as a risk modifier of NSAID-related gastrointestinal bleeding: a case-control study
Pharmacogenetics and Genomics 26:66–73 2016
Conclusion
• The presence of the CYP2C9*3 variant increases the risk for UGIB associated with NSAID for DDDs* greater than 0.5. The presence of the CYP2C9*2 allele shows no such effect.

* Exposure defined as the mean number of defined daily doses (DDDs) of NSAIDs metabolized by CYP2C9 in the week preceding the index date

2015 Statement from the US Food and Drug Administration (FDA):
• Poor Metabolizers of CYP2C9 Substrates:
  – Patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution.
  – Consider starting treatment at half the lowest recommended dose in poor metabolizers (i.e., CYP2C9*3/*3).
  – Consider using alternative management in junior rheumatoid arthritis (JRA) patients who are poor metabolizers.

Acetaminophen

• Mechanism of Action:
  – Not fully understood
  – Inhibits COX-3?
  – Inhibits COX-2
  – Local antioxidant may reduce prostaglandin synthesis
  – Effects on TRPV-1 in brain (antipyretic)

Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials BMJ 2015;350:h1225
• High quality evidence that “Tylenol” ineffective in treating low back pain or disability.
• Found evidence that acetaminophen quadruples risk of having abnormal LFT
  – but clinical significance of that finding unclear
• Studies of pain from knee and hip arthritis found small but clinically insignificant short-term pain-relief effect for acetaminophen compared with a placebo.

Why is FDA limiting the maximum strength of acetaminophen in oral prescription products?
• By limiting the maximum amount of acetaminophen in oral prescription products to 325 mg per tablet, capsule, or other dosage unit, patients will be less likely to overdose on acetaminophen if they mistakenly take too many doses of acetaminophen-containing products.
• Under new dosage limit, HCPs can direct patients to take 1 or 2 tablets (etc) of a prescription product containing 325 mg of acetaminophen up to 6 times a day (12 dosage units) and still not exceed the maximum daily dose of acetaminophen (4000 mg)
Pharmacological Management of Pain

Acetaminophen Toxicity
- Alcohol induces CYP2E1
- Glutathione, Glucuronide, Sulfate

Adjuvant agents

Drug Targets
- **Ascending**
  - Na channel
    - Peripheral
    - Central
  - Ca channel
    - Central
  - Glutamate receptor
  - SNS tone
  - Inflammatory mediators

- **Descending**
  - Noradrenergic enhancement
  - Serotonergic enhancement
  - Opioid agonists
  - GABA enhancement

Adjuvant Agents
- Defined as drugs with other indications that may be analgesic in specific circumstances
- Not classified as "analgesic"
- Many used in "neuropathic pain" conditions
  - however - all chronic pain has an element of neuropathy

Adjuvant Meds - alone or in combinations with other analgesics
- Multi-purpose analgesics???
  - Neuropathic pain
  - Musculoskeletal pain
  - Cancer pain
  - Headache
- Typically not effective for acute pain
- Lower doses may be effective compared to their primary indications
Adjuvant Medication Classes

- Antiepileptics
- Antidepressants
  - TCA, SSRIs, SNRIs
- Local anesthetics
- Topicals
  - Muscle relaxants
  - Corticosteroids

Modulation – Descending Pathways

Antidepressants

In general, antidepressants seem to be most effective on continuous burning pain
C-fiber mediated
  - multiple interneuron connections
  - more "synaptic" sites
  - synapses in lamina (I, II and V)
  - Pain reduction independent of antidepressant effect

Antidepressants

- Analgesic effect of antidepressant has been classically attributed primarily to inhibition of reuptake of NE rather than 5HT
- Involvement of 5HT varies with the type of pain
- Serotonin elevation appears to be the primary mechanism of the acute analgesic effects of antidepressants
- Norepinephrine elevation plays more critical role in chronic pain states

Tricyclic Antidepressants

Multiple Mechanisms:
- Block reuptake of NE and 5HT
- Neuromodulatory effect on opioid systems
- NMDA receptor antagonism
- Blockade of voltage gated Na⁺ channels
- alpha-adrenergic blockade
Antidepressants

- Meta-analysis of several studies
  - TCAs (NNT* = 2-3)
  - SNRI (NNT = 4-5)
  - SSRIs (NNT = 7)
- On balance, NA mechanisms are deemed more important than 5-HT mechanisms in the analgesic actions of antidepressants
- to obtain one patient with 50% pain relief

Future Neurology. 2007;2(6):661-671
MEDSCAPE 2012

SNRIs

- Duloxetine (neuropathy, musculoskeletal pain)
- Milnacipran (fibromyalgia)
- Levomilnacipran (not labelled for pain)
- Venlafaxine (not labelled for pain)
  - Block reuptake of both NE and 5HT
  - Better tolerated / safer than TCAs
  - May not be as effective as TCAs
- Remember – all antidepressants regardless of use have warning regarding increased risk of suicidal ideation

Antiepileptic Drugs

Sodium-Channel Modulators

- Peripheral nerve injury → abnormal accumulation of Na+ channels within nociceptors & dorsal root ganglia
- Na+ channel blocking actions:
  - Carbamazepine
  - Phenytoin
  - Valproate
  - Topiramate
  - Also blocks glutamate receptors
  - Lamotrigine
  - Also inhibits release of glutamate

Antiepileptic Drugs

Calcium Channel Effects

- Gabapentin
  Also have (+) action on GABA activity
- Pregabalin
  Also have (+) action on GABA activity

Interactions

CYP1A2 Inhibitors
- Quinolone antibiotics

CYP1A2 Inducers:
- Cigarette smoke
- Omeprazole
- Broccoli / cauliflower

Increase risk of adverse effects from duloxetine

Increased clearance

duloxetine (Cymbalta)

Antiepileptic Drugs

Sodium-Channel Modulators

• Side effects / Interactions
  - Phenytoin and carbamazepine
  - Cytochrome P450 inducers
  - Rash
  - Blood dyscrasias
  - Valproate – high protein binding, ammonia
  - Lamotrigine – rash / aseptic menengitis
  - Topiramate – cognitive/memory issues

Antiepileptic Drugs

Calcium Channel Effects

- Gabapentin
  Also have (+) action on GABA activity
- Pregabaline
Gabapentin
- May also help with anxiety / sleep
- Renal excretion, caution renal impairment
- Side effects: somnolence, peripheral edema, weight gain, cognitive effects

Pregabalin
- Better & predictable absorption
- Stronger binding affinity to target, increased potency, and a steeper dose-response curve that does not plateau over recommended dosing levels.
- May be better tolerated

Topicals - Capsaicin
- OTC topical creams and ointments commonly used for treating arthritis and other painful conditions contain low concentrations (typically .025 to .075%)
- Needs to be applied 4-5 times a day for several weeks
- Compliance may be a problem
- Side effects
  - pain at the site of application
    - due to chemical itself
    - due to allodynia to touch

Topicals - Lidocaine Patch
- 5% lidocaine in a non-woven polyester patch
- Approved for postherpetic neuralgia
- Binds more readily to sodium channels in an activated state, thus onset of neuronal blockade is faster in neurons that are rapidly firing.
- Small myelinated axons (e.g. those carrying nociceptive impulses) and non-myelinated axons > large myelinated axons (pain > other sensations)

List of meds that have been compounded for topical use for pain
- Amitriptyline
- Baclofen
- Bupivacaine
- Capsaicin
- Carbamazepine
- Clonidine
- Cyclohexaprin
- Diclofenac
- Diphenhydramine
- Gabapentin
- Guaifenesin
- Ibuprofen
- Indomethacin
- Ketamine
- Ketoprofen
- Lidocaine
- Lipoic Acid
- Loperamide
- Naproxen
- Nifedipine
- Phenytoin

Cannabinoids
- Plant
  - Leaves, flowers, stems, seeds collected from Cannabis sativa plant (aka phytocannabinoids)
- Purified
  - Purified from plant sources: Cannabidiol (CBD), ∆9 tetrahydrocannabinol (THC), and Sativex (mixture of THC and CBD)
- Synthetic
  - Synthesized in laboratory: Nabilone, Dronabinol, others in development as potential cannabinoid agonists and antagonists for therapeutic use
- Endogenous (2-AG, AEA)
Pharmacological Management of Pain

Cannabinoids

- Endogenous - Endocannabinoids
- Discovered in 1992
  - Anandamide (AEA)
  - 2-arachidonoylglycerol (2-AG)
  - Activity is limited by metabolism or reuptake

Cannabis

- Complex alkaloid mixture of more than 400 compounds derived from the cannabis sativa plant
- 60 different compounds described with activity on the cannabinergic system
  - ∆9-tetrahydrocannabinol - THC
  - Tetrahydrocannabinolic acid (THCA)
  - Cannabidiol - CBD
  - Cannabinol - CBN
  - Cannabigerol
  - Cannabichromene
  - Cannabicyclol
  - Cannabiolsin
  - Cannabitol
  - ∆8-tetrahydrocannabinol
  - Miscellaneous

Cannabinoid Receptors

CB1 (metabotropic – G-protein coupled)
- Highest on GABA neurons in forebrain
- Highest on Glutamate releasing neurons in hippocampas and cerebellum
- Highly expressed in axon terminals within medullary nuclei which control emesis (ie., postrema)
- Relatively low levels within medullary respiratory control centers
- High in Periaqueductal Grey area
- Differences in distribution within CNS structures allows for specialized control

Endocannabinoids

- Released from depolarized postsynaptic neurons in a calcium-dependent manner
- Act on presynaptic cannabinoid receptors (retrograde) to suppress neurotransmitter release.
- Activation of the CB1 causes suppression of synaptic transmission in various regions of the CNS.
- Can affect both excitatory (Glutamate) and inhibitory (GABA) pathways involved in neuroplasticity.

Endocannabinoids

Example: Spinal cord
Descending NA input (antinociceptive) from the brainstem usually under inhibitory control by GABA.
Cannabinoids modulate activity by reducing GABA release freeing NA neurons to more freely release NE in Dorsal horn and ganglia – net result – attenuation of incoming pain signals
Acetaminophen – Possible Mechanism

**Cannabinoid Receptors**

**CB₁ in the Periphery**
- Found in majority (89%) of DRG sensory neurons - similar degree of localization in nociceptor & non-nociceptor
  - excitatory (glutamatergic) terminals of Aδ- and C-fiber primary afferents in the spinal cord

**CB₂**
- Located peripherally, with high density on immune-modulating cells, including monocytes, macrophages, B and T-cells
  - highest expression on B-lymphocytes, NK cells, brain microglial cells and astrocytes
- Modulates cytokine release and immune response
- May have a protective effect on autoimmunity and inflammation

**But – flooding the brain with exogenous CB1 agonists/partial agonists**

None selective stimulation of CB receptors in all regions – affecting memory, emotion, cognition, appetite, decision-making, movement, etc

**Pharmacodynamics of various cannabinoids**

- **Anandamide**
  - Acts as indirect antagonist of THC
  - Powerfully opposes the action of THC at the CB1 receptor, muting psychoactive effects of THC
  - Mechanism unknown – possibly effects other neurotransmitters (ie., adenosine, serotonin)
- **Cannabidiol (CBD)**
  - Very low affinity for CB₁ and CB₂ receptors
  - Acts as indirect antagonist of THC
  - Powerfully opposes the action of THC at the CB1 receptor, muting psychoactive effects of THC
  - Mechanism unknown – possibly effects other neurotransmitters (ie., adenosine, serotonin)
  - Stimulates release of endogenous 2-AG that activates both CB1 and CB2 receptors
  - Suppresses the enzyme fatty acid amide hydroxylase ("FAAH") – the enzyme that breaks down anandamide.
Cannabidiol (CBD)

Additionally, CBD . . .
- Stimulates TRPV-1 receptor, which is known to mediate pain perception, inflammation and body temperature (useful for Neuropathic pain).
- May exert an anti-anxiety effect by activating adenosine receptors / also neuroprotection.
- At high concentrations, directly activates 5-HT1A serotonin receptor (possible antidepressant effect).

CBD
- Tolerability
  - Chronic high doses of up to 1500 mg per day are well tolerated and produce no noticeable physiological effects.
- Optimal dosage levels of CBD are uncertain due to a lack of human studies.
  - Evidence suggests medical benefits of CBD disappear when dosages become excessive.
  - Bell shape dose-response.
- Fewer than 5% of recent cannabis samples tested show appreciable amounts of CBD.

Differing Actions of THC and CBD

The THC – CBD paradox
- THC is not necessarily the most relevant cannabinoid with medical applications.
- Research indicates that CBD mitigates euphoria associated with THC - resulting in efforts to remove CBD from marijuana (genetically manipulate).
- Composition of marijuana has changed significantly over past two decades – due to hybridization.
- Some strains may have 30% THC w very low CBD.
- Others have higher CBD concentrations (since it was found to be a potential money-maker).

Why do people use medical marijuana

<table>
<thead>
<tr>
<th>REASON FOR USE</th>
<th>% REPORTING REASON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Relief</td>
<td>82.6%</td>
</tr>
<tr>
<td>To Sleep</td>
<td>70.6%</td>
</tr>
<tr>
<td>To Relax</td>
<td>55.6%</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>41.3%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>38.1%</td>
</tr>
<tr>
<td>To Stimulate Appetite</td>
<td>38.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>27.7%</td>
</tr>
<tr>
<td>Depression</td>
<td>26.1%</td>
</tr>
</tbody>
</table>

Pain and Cannabinoids

CB1 stimulation
- Decrease peripheral & spinal transmission of ascending pain signals (antinociceptive).
- Activate descending inhibitory pathways from PAG area.
- Alter perception of pain?
  - May have most robust effects on neuropathic pain – remember, there’s an element of neuropathy in all forms of chronic pain.

CB2 stimulation
- Decrease peripheral and/or central inflammatory pain (hyperalgesic) signalling.
Pain

- 2015 – study found 80% of MM users reported substituting cannabis for prescribed medications, particularly among patients with pain-related conditions.
- Literature review of 38 studies evaluating medical marijuana’s efficacy for treating pain found 71% concluded cannabinoids had empirically demonstrable and statistically significant pain relieving effects.
- 2015 meta-analysis of 79 studies found a 30 percent or greater reduction of pain with the use of cannabinoids compared to placebos.

Pain

- Cannabis use associated with a 64% lower opioid use in patients with chronic pain (Michigan Survey).
- 2014 JAMA - States with M.M. laws are associated with a significant reduction in mortality from opioid abuse; these states saw a 25 percent reduction in opioid overdose deaths, compared to states without such laws, resulting in 1,700 fewer deaths in 2010 alone.
- Used in combination with opioid analgesics, cannabis may lower opioid dose requirements, side effects, cravings and withdrawal severity.

Pain

“Many pain clinicians and researchers agree that cannabinoids are clinically promising chemical compounds, and there is a critical need for robust research on herbal cannabis to identify targets for medical development”

American Pain Society June 23, 2016

Summary
Cardiovascular Pharmacology (Review and Update)

Alan P. Agins, Ph.D.
President, PRN Associates
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Objectives
- Discuss recent guidelines and clinical studies related to the pharmacological management of hypertension
- Review the basic pharmacology of the statins and the most recent guidelines regarding their use in the clinical management of dyslipidemia and CV risk
- Compare and contrast the basic pharmacology and clinical utility of the new oral anticoagulants
- Describe the basic and clinical pharmacology of select medications that have been recently approved for heart failure.

Hypertension

HTN Statistics
- About 75 million American adults (32%) have HTN
- About 1 in 3 adults has prehypertension
- Only about half (54%) of people with high blood pressure have their condition under control.
- High blood pressure costs the nation $48.6 billion each year. This total includes the cost of health care services, medications to treat high blood pressure, and missed days of work.

But - HTN not controlled in 46%

Why?
- Lack of treatment initiation
- Lack of or poor medication adherence
- Lack of prescription coverage
- Lack of adequate titration
- Difficulty sustaining lifestyle changes
- Confusion about which guidelines should be followed

HTN Statistics
- High blood pressure was a primary or contributing cause of death for more than 410,000 Americans in 2014—that's more than 1,100 deaths each day.
- First heart attack: About 7 of every 10 people having their first heart attack have high blood pressure.
- First stroke: About 8 of every 10 people having their first stroke have high blood pressure.
- Chronic heart failure: About 7 of every 10 people with chronic heart failure have high blood pressure.
- HTN is a major risk factor for kidney disease.
Hypertension Guidelines around the world

- JNC- 8 (JAMA, 2014)
- American Diabetes Association (ADA) (2014)
- Hypertension Canada (2015)
- European Society of Hypertension (ESH) (2013)
- American Society of Hypertension (ASH) & The International Society of Hypertension (ISH) (2013)
- International Society on Hypertension in Blacks (2013)
- Journal of Clinical Hypertension (JCH)
- National Institute for Health and Clinical Excellence (NICE) (2011)

JNC-8 Recommendations for Management of Hypertension

<table>
<thead>
<tr>
<th>Blood Pressure Goals</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elder Population</td>
<td>Diastolic BP (general population)</td>
</tr>
<tr>
<td></td>
<td>Systolic BP (general population)</td>
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<tr>
<td></td>
<td>Systolic BP - CKD</td>
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<tr>
<td></td>
<td>Systolic BP - Diabetes</td>
</tr>
<tr>
<td>General population</td>
<td>Black Patients</td>
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<tr>
<td></td>
<td>CKD Patients</td>
</tr>
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<td>Treatment with multiple drugs</td>
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What is the goal blood pressure?

**JNC-8**

- Patients > 60 years of age: <150/90 mmHg
- Patients <60 years of age: <140/90 mmHg
- Patients with diabetes: <140/90 mmHg
- Patients with CKD: <140/90 mmHg

**ASH:**

- Patients younger than 80 years of age: <140/90 mmHg
- Patients ≥ 80: systolic of up to 150 mmHg is acceptable
  - Goal of <140/90 can be considered for diabetes or CKD.
  - Patients 18 to 55 years of age: lower target (e.g., <130/80 mmHg) can be considered, per prescriber discretion, if treatment is tolerated.
  - However, evidence of additional benefit vs goal of <140/90 mmHg is lacking.
  - CKD with albuminuria: some experts recommend <130/80 mmHg.

Who should be treated with pharmacotherapy?

**JNC-8**

- Patients ≥ 60 years of age: start meds at ≥ 150/90
- Patients < 60: start meds at ≥ 140/90
- Diabetics: Start meds at ≥ 140/90
- CKD patients: start meds at ≥ 140/90 mmHg

**ASH:**

- Patients < 80 years of age: start pharmacotherapy at 140/90
  - Patients ≥ 80: start pharmacotherapy at 150/90 - with diabetes or CKD - Consider starting at 140/90
  - Patients with uncomplicated stage 1 HTN: (140 -159 / 90-99 without CV abnormalities or risk factors):
    - consider six to 12 months of lifestyle changes (e.g., weight loss, sodium restriction, exercise, smoking cessation) alone before pharmacotherapy
Drug Recommendation – JNC-8

- In non-black population + diabetes, initial treatment should include
- Each of the 4 drug classes show comparable benefits on overall mortality and CV cerebrovascular and kidney outcomes
- One exception: heart failure

Drug Recommendations – JNC-8

Nonblack, including those with diabetes: thiazide, CCB, ACEI, or ARB
- African American, including those with diabetes: thiazide or CCB
- CKD: regimen should include an ACEI or ARB (including African Americans)
- Can initiate with two agents, especially if systolic >20 mmHg above goal or diastolic >10 mmHg above goal.

Drug Recommendations - ASH

Nonblack <60 years of age:
- First-line: ACEI or ARB
- Second-line (add-on): CCB or thiazide
- Third-line: CCB plus ACEI or ARB plus thiazide

Nonblack 60 years of age and older:
- First-line: CCB or thiazide preferred, ACEI, or ARB
- Second-line (add-on): CCB, thiazide, ACEI, or ARB
- Third-line: CCB plus ACEI or ARB plus thiazide

African American:
- First-line: CCB or thiazide
- Second-line (add-on): ACEI or ARB
- Third-line: CCB plus ACEI or ARB plus thiazide

Drug Recommendations with comorbidities (ASH):

Diabetes
- First-line: ACEI or ARB (can start with CCB or thiazide in African Americans)
- Second-line: add CCB or thiazide (can add ACEI or ARB in African Americans)
- Third-line: CCB plus ACEI or ARB plus thiazide

CKD
- First-line: ARB or ACEI (ACEI for African Americans)
- Second-line (add-on): CCB or thiazide
- Third-line: CCB plus ACEI or ARB plus thiazide

Drug Recommendations with comorbidities (ASH):

Stroke history
- First-line: ACEI or ARB
- Second-line: add CCB or thiazide
- Third-line: CCB plus ACEI or ARB plus thiazide

CAD
- First-line: BB plus ARB or ACEI
- Second-line (add-on): CCB or thiazide
- Third-line: BB plus ARB or ACEI plus CCB plus thiazide

Drug Recommendations with comorbidities (ASH):

Heart failure
ACEI or ARB plus BB plus diuretic plus aldosterone antagonist. Amlodipine can be added for additional BP control.
(Start with ACEI, BB, diuretic. Can add BB even before ACEI optimized. Use diuretic to manage fluid.)
And then came the Sprint Trial results

- SPRINT focused on an especially high-risk population of adults with hypertension who were aged 50 years or older and had an average Framingham risk score of 20%.
- Patients with diabetes or a history of a stroke were not included.
- Study of 9361 participants who were randomized to either a lower, more intensive goal of less than 120 mm Hg systolic blood pressure (SBP) compared with a goal of less than 140 mm Hg systolic.

Who were the SPRINT patients

- Inclusion criteria:
  - Patients > age 50 with high blood pressure
  - Increased CV risk: (At least one of the following)
    - actual blood vessel disease, chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] 20 to <60), Framingham risk greater than 15%, or age >75.
- Exclusion criteria:
  - Patients with diabetes (majority), but not all
  - Patients with diabetes and prior stroke
  - Patients with 1-minute standing BP less than 110

SPRINT Trial results

- **Rapid and sustained difference in SBP achieved between the two treatment arms**

  ![Graph showing SBP difference between treatment arms](image)

- **Primary end point:**
  - Over the 3.2 years of the trial, intense BP control prevented 76 events; the difference was 1.62% overall.
  - The number needed to treat (NNT) was 61. The percent same result was 98.4%.
  - Other benefits: intensive treatment group had lower rates of:
    - heart failure (38% lower RR)
    - death from CV causes (43% lower RR)
    - death from any cause (27% lower RR)

SPRINT (Adverse Effects)

- Adverse events overall: There were 1793 (38%) serious adverse events in the intensive group and 1736 (37.1%) in the standard group.
- So, no difference overall.
- Adverse-events specifics:
  - Investigators reported more hypotension, syncope, electrolyte abnormalities, and acute kidney injury in the intensive group.
  - Falls with injury were not increased, and orthostatic hypotension was less frequent in the intensive arm.

SPRINT - Summary and Conclusions

- Trial stopped early, due to benefit, after median follow-up of 3.26 years
- Incidence of primary outcome (composite of CVD events) 25% lower in Intensive compared to Standard Group and all-cause mortality reduced by 27%.
- Treatment effect similar in all six pre-specified groups of interest.
- The “number needed to treat” to prevent primary outcome event or death: 61 and 90, respectively
Clinical Implications

- Role of patient selection:
  - Although there are millions of people with high blood pressure, the SPRINT trial had specific entry and exclusion criteria.
  - Use caution extrapolating SPRINT results to all patients
  - SPRINT-trial benefits apply to SPRINT-like patients.
  - Given that SPRINT included patients 50 years of age and older, the 2013 JNC 8 decision to relax blood-pressure goals in those 60 years and older to less than 150 mm Hg appears to be wrong!

Considerations common to all Guidelines

- Choose once-daily or combination products to simplify the regimen - increase adherence
- Most meds work fairly quickly - usually 1 - 2 week - however in general, wait two to three weeks before up titrating dose or adding new drug
- Thiazides and CCBs reduce systolic BP < diastolic BP.
- Consider chlorthalidone or indapamide over HCTZ due to better evidence of benefit
- ACEIs and ARBs should be considered as 1st line in diabetes due to secondary renal and CV benefits benefits
- Discourage long-term and/or high dose NSAID use esp with ACEIs and ARBs

Considerations common to all Guidelines

- African Americans have high stroke risk. CCBs and thiazides provide better stroke prevention and blood pressure reduction in African Americans vs ACEIs.
- African Americans tend to be “salt-sensitive.” This may explain their relatively poor response to ACEIs. Encourage sodium restriction.
- Most African Americans will need at least two antihypertensives to control blood pressure.
- African Americans and nonblacks have similar responses to combination therapy (i.e., thiazide plus ACEI; CCB plus ACEI).

Considerations common to all Guidelines

- NEVER use an ACEI plus an ARB; no added benefit, more side effects (e.g., hyperkalemia).
- Use of ACEI or ARB will commonly increase serum creatinine and may produce hyperkalemia, particularly in patients with decreased kidney function.
- In CKD population requires close monitoring of electrolyte and serum creatinine levels
- For HTN, alpha and beta-blockers have been shown to have worse CV outcome data than the recommended agents. Use only if recommended agents are not tolerated or do not work

The “New” Combo Antihypertensives

- Dietary salt restriction
  - Reducing average population sodium intake from 3,300 mg to 2,300 mg per day may reduce cases of high blood pressure by 11 million and save 18 billion health care dollars annually
- Weight loss
- DASH diet
- Exercise
- Limited alcohol intake
- Vitamin D
- Patient education
Adoption of lifestyle changes (EHS/ESC)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Surrogate markers</th>
<th>Cost effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt restriction to 5–6 g per day is recommended.</td>
<td>I</td>
<td>A B</td>
<td></td>
</tr>
<tr>
<td>Moderation of alcohol consumption to no more than 20–30 g</td>
<td>I</td>
<td>A B</td>
<td></td>
</tr>
<tr>
<td>of ethanol per day in men and to no more than 10–20 g of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethanol per day in women is recommended.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased consumption of vegetables, fruits, and low-fat dairy products is recommended.</td>
<td>I</td>
<td>A B</td>
<td></td>
</tr>
<tr>
<td>Reduction of weight to BMI of 25 kg/m² and of waist circumference to &lt;102 cm in men and &lt;88 cm in women is recommended, unless contraindicated.</td>
<td>I</td>
<td>A B</td>
<td></td>
</tr>
<tr>
<td>Regular exercise, i.e. at least 30 min of moderate dynamic exercise on 5 to 7 days per week is recommended.</td>
<td>I</td>
<td>A B</td>
<td></td>
</tr>
<tr>
<td>It is recommended to give all smokers advice to quit smoking and to offer assistance.</td>
<td>I</td>
<td>A B</td>
<td></td>
</tr>
</tbody>
</table>

Causes for Inadequate Response to Drug Therapy

- Nonadherence to therapy / lifestyle
- Alcohol use
- Volume overload
- Failure to switch drugs after no response
- Failure to combine drugs where indicted
- Non-steroidal anti-inflammatories
- Identifiable causes of hypertension
- Clinical inertia !!!!!

ACC/AHA Cholesterol Guideline 2013

- Summary:
  - New CV risk calculator
  - Percent reduction in LDL cholesterol (ie. 20 – 50%) instead of titration to specific LDL goal (ie., < 100 mg/dL)
  - LDL cholesterol is main target for therapy
  - Other targets are secondary (HDL, TGs, etc)
  - Non-statin drugs not considered 1st choice for most patients

Who should be assessed for cardiovascular risk, and how?

Patients without atherosclerotic cardiovascular disease:

- Assess traditional risk factors
  - Lipids, BP, diabetes q4-6 years in pts 20-79 years of age
- Pts 40 -75 yrs with LDL 70 to 189 mg/dL & not receiving cholesterol-lowering therapy
- Estimate 10-year risk using the Pooled Cohort Equations Cardiovascular Risk Calculator
- http://my.americanheart.org/cvriskcalculator
- Apps available for IOS and Android

New CV Risk Calculator (.xls)

Included

- Sex
- Age*
- Race (White or AA)
- Total Cholesterol
- HDL Cholesterol
- Systolic BP
- Treatment for HTN
- Diabetes
- Smoker

Missing

- Family History of premature CVD
- Triglycerides
- Waist circumference
- BMI
- Lifestyle habits
- Smoking history

41% of men and 27% of women ages 60 to 69 years without a history of CVD will be found to have a 10% or greater risk
Who should be treated with a statin?

Four major statin benefit groups:

- Patients with clinical atherosclerotic CVD
- Patients with LDL > 190 mg/dL
- Patients 40 to 75 yrs with diabetes (but without clinical atherosclerotic CVD) and LDL 70 to 189 mg/dL
- Patients without clinical atherosclerotic CVD or diabetes with LDL 70 to 189 mg/dL - with estimated 10-year risk of atherosclerotic CVD > 7.5%

Who should be treated with a statin?

- Pts who don’t fit into a “statin benefit group”
  - e.g LDL 70 -189 mg/dL with 10-year risk 5% - 7.5% with clinical suspicion that they may benefit from statin
- Additional factors can be taken into consideration:
  - LDL > 160 mg/dL
  - Evidence of genetic hyperlipidemia
  - CVD onset in a 1º male relative < 55 yrs, or in a 1º female relative < 65 yrs
  - Elevated lifetime risk of atherosclerotic CVD

Who should be treated with a statin?

Pharmacologic Treatment Options

High-dose Statin
- Average LDL reduction ~ 50% (or higher)
  - Atorvastatin 80 mg / 40 mg (if 80 not tolerated
  - Rosuvastatin 20 - 40 mg
- 2º prevention in adults < 75 years of age
- 1º prevention in adults with LDL > 190 mg/dL
- 1º prevention in adults 40 - 75 yrs with LDL 70 to 189 mg/dL and est 10-year risk of CVD > 7.5%

Pharmacologic Treatment Options

Moderate-dose Statin
- average LDL reduction ~30 to 49%
  - Atorvastatin 10 to 20 mg
  - Rosuvastatin 5 to 10 mg
  - Lovastatin 40 mg
  - Pitavastatin 2 to 4 mg
  - Pravastatin 40 to 80 mg
  - Simvastatin 20 to 40 mg
  - Fluvastatin 80 mg (XL) or 40 mg bid

Pharmacologic Treatment Options

Low-dose Statin
- average LDL reduction < 30%
  - Fluvastatin 20 to 40 mg
  - Lovastatin 20 mg
  - Pitavastatin 1 mg
  - Pravastatin 10 to 20 mg
  - Simvastatin 10 mg
- For patients who cannot tolerate a high or moderate-dose statin.

2016 USPSTF recommendation endorses statins for people ages 40 to 75 with at least a > 10% risk of a heart attack or stroke over the next decade and at least one cardiovascular risk factor like diabetes or high blood pressure.
### Lowering Total-C, LDL-C & TGs

<table>
<thead>
<tr>
<th>TLCs - Diet and Exercise</th>
<th>Pharmacologic Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>For pts who cannot tolerate recommended statin dose or do not achieve the expected statin response and are high-risk</td>
</tr>
<tr>
<td>Bile Acid Resins</td>
<td>• Nonstatin alone</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>• Bile acid sequestrant, ezetimibe, niacin, fibrate, omega-3 fatty acids</td>
</tr>
<tr>
<td>Niacin</td>
<td>• Triglycerides &gt; 500 mg/dL</td>
</tr>
<tr>
<td>Fibrates</td>
<td>• use omega-3s, niacin, or fenofibrate</td>
</tr>
<tr>
<td>Omega-3 FAs</td>
<td>• No proof adding a nonstatin to a statin further reduces cardiovascular risk</td>
</tr>
</tbody>
</table>

- **Statins**: Reduce total & LDL-C. Modest or no effect on TGs.
- **Bile Acid Resins**: Lower TGs.
- **Ezetimibe**: Lower TGs. Moderate effect on LDL-C. May alter LDL size.

### HMG COA Reductase Inhibitors

**The “Statins”**
- lovastatin, fluvastatin, pravastatin, simvastatin
- atorvastatin, rosuvastatin, pitavastatin

- Most effective for ↓ LDL 28 – 55%
- Will ↑ HDL (3 – 9%) and ↓ TG (5 – 30%)
- Fewest adverse effects & tolerated best

**Mechanism**
- Inhibits hepatic HMG CoA reductase
- Inhibition of cholesterol synthesis causes upregulation of LDL receptors

### Cholesterol Biosynthesis

**A “12-Step” Program**

- Acetate → HMG-CoA → mevalonic acid → Cholesterol

### Which Statin Is the Best Choice for Which Patient?

**Natural Statins** - Lovastatin, Simvastatin, Pravastatin
**Synthetic Statins** - Fluvastatin, Atorvastatin, Rosuvastatin, Pitavastatin

- The synthetic and natural statins have essentially equivalent efficacy at improving the lipid profile.
- The statins do have different:
  - abilities to lower low-density lipoprotein (LDL) cholesterol levels
  - pharmacokinetics
  - interactions with drugs and foods
  - costs
Statins and CV Outcomes
Cholesterol-lowering vs Pleiotropic effects

- In addition to lowering cholesterol, Statins:
  - Improve endothelial function
  - Inhibit platelet aggregation
  - Decrease LDL oxidation
  - Reduce vascular inflammation
  - Stabilize atherosclerotic plaques

Statins Side Effects
- Generally occur in <10% of patients
  - Majority of SEs are mild - do not require DC
  - GI = diarrhea, constipation, dyspepsia, flatus, nausea
  - Headache, rash, blurred vision, sleep disturbances
  - Myopathy
  - Generalized fatigue
  - Cognitive impairment ??
  - Increased risk for developing Type 2 diabetes
  - Some statin side effects may be agent specific, not always class specific

Statins: Myopathy & Vitamin D
- Low serum vitamin D can cause myalgia, myositis, myopathy, and myonecrosis.
- Low serum vitamin D and statins, additively or synergistically, cause myalgia, myositis, myopathy, and/or myonecrosis.
- Statin-induced myalgia in vitamin D deficient patients can often be resolved by vitamin D supplementation, normalizing serum vitamin D levels.

Statins – Link to diabetes?
- JUPITER - 1st placebo-controlled clinical trial to formally document increased risk of diabetes in statin patients
  - Statistically significant 27% relative increase in risk in pts treated with rosuvastatin Sub-group analysis - 48% increased risk of diabetes among women
  - Analysis of PROVE-IT, A to Z, TNT, IDEAL, and SEARCH showed that high-dose statin therapy increased the risk of diabetes by 12%
  - Statin treatment increased the risk of type 2 diabetes by 46%, attributable to decreases in insulin sensitivity and insulin secretion

Statin Interactions
Pharmacokinetic
- CYP 3A4
  - Atorvastatin, lovastatin, simvastatin
  - Inhibitors: Macrolides, antifungals, PIs, etc) increase risk of statin toxicity
  - Inducers: (Tegretol, Rifampin) decrease efficacy
- CYP 2C9
  - Fluvastatin:
  - Inhibitors: Diffucan, Flagyl, Prilosec
Pharmacodynamic
- Additive effect on myotoxicity when used in combo with others - Fibrates or Niacin
- Possible additive effects on liver toxicity when used in combo with SR - Niacin?

Coenzyme Q10
- Uniquinone / Ubiquinol
  - Located in the inner membrane system of the mitochondria, other membranes, and in plasma lipoproteins (LDLs). Lipid Soluble!
  - Cellular Energetics
    - Essential part of the electron transport chain leading to production of ATP
  - Antioxidant - scavenger of free radicals (ROS)
    - Especially well suited in an environment with significant redox potential as it is well located in the membranes in close proximity to the unsaturated lipid chains (prevents lipid peroxidation, protects mitochondrial DNA).
    - Also regenerates other antioxidants (ie., vitamin E)
CoEnzyme Q10
- Deficiency may result from:
  - Genetic or acquired defect in synthesis or utilization
  - Increased tissue needs resulting from illness
  - CoQ10 levels decline with advancing age
  - Impaired synthesis due to nutritional deficiencies or pathway inhibitors (i.e., statins)
- Up to 40% reduction in levels

Where does CoQ10 come from?
- Endogenous Synthesis
- Diet
  - Richest sources
    - Heart
    - Liver
    - Muscle meat
    - Herring, sardines, mackerel
  - Soybean
  - Broccoli
  - legumes

Statins and Coenzyme Q10
- Cholesterol
  - Acetate
  - HMG-CoA
  - mevalonic acid
  - HMG-CoA reductase
  - CoEnzyme Q10

PCSK9 Inhibitors and Cholesterol
- Who may need PCSK9 Inhibitors?
  - Statin intolerant
  - Genetic disorder (FH)
  - Uncontrolled on statin

Life cycle of LDL receptors

Effects of PCSK9 inhibitor (mAb) on LDL Receptor Expression
PCSK9 Inhibitors

**“Pros”**
- Greater reduction in LDL
- Additive with Statins
- Useful in FH
- Well tolerated

**“Cons”**
- Bi-weekly or monthly injections
- COST: $14,000+/year

PCSK9 inhibitor (monoclonal antibody)
- Repatha (evolocumab)
- Praluent (alirocumab)

Indications – as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH)
- Parenteral only
- Side Effects
  - Nasopharyngitis, URIs, influenza
  - Back pain
  - Injection site reactions

FOURIER Trial
Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk

**Purpose:**
The primary hypothesis is that additional LDL-C lowering with Evolocumab when used in addition to other treatment for dyslipidemia is well tolerated and decreases the risk of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization in subjects with clinically evident cardiovascular disease.

FOURIER: Outcome Measures

**Primary**
- Time to CV death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization whichever occurs first.

**Secondary**
- Time to CV death, MI, or stroke, whichever occurs first
- Time to cardiovascular death
- Time to death by any cause
- Time to first myocardial infarction
- Time to first stroke
- Time to first coronary revascularization
- Time to cardiovascular death or first hospitalization for worsening heart failure, whichever occurs first
- Time to ischemic fatal or non-fatal stroke or TIA, whichever occurs first

https://clinicaltrials.gov/ct2/show/NCT01764633

FOURIER: Design

>27,500 patients with clinically evident CVD (prior MI, stroke or PAD)
Age 40 to 85 years, 21 other high-risk features

https://clinicaltrials.gov/ct2/show/NCT01764633
Summary

- Evolocumab significantly reduces risk of hard major adverse cardiovascular events by 20%
- Risks of heart attack, stroke and coronary revascularization were nominally reduced by 27 percent, 21 percent and 22 percent, respectively
- The risk reduction at 2 years translated to a number needed to treat (NNT) of 74 to prevent a CV death, MI, or stroke.
- At 3 years, the NNT was about 50

The New Oral Anticoagulants: NOACs

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Prototype</th>
<th>Action</th>
<th>Clinical Use</th>
<th>1930s</th>
<th>1950s</th>
<th>1980s</th>
<th>1990s</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant</td>
<td>Heparin</td>
<td>Inactivation of clotting Factors</td>
<td>Prevent venous Thrombosis</td>
<td>Parenteral Narrow TI</td>
<td>Unpredictable Req Monitoring HIT</td>
<td>Bleeding risk Antidote (protamine)</td>
<td>Warfarin</td>
<td>Parenteral Narrow TI</td>
</tr>
<tr>
<td>Oral</td>
<td>Warfarin</td>
<td>synthesis of clotting factors</td>
<td>Prevent venous Thrombosis</td>
<td>Parenteral</td>
<td>Unpredictable Req Monitoring HIT</td>
<td>Diet Interactions Lifestyle interactions Bleeding risk Antidote (Vit K)</td>
<td>Warfarin</td>
<td>Parenteral Narrow TI</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Aspirin</td>
<td>Platelet aggregation</td>
<td>Prevent arterial Thrombosis</td>
<td>Parenteral</td>
<td>Unpredictable Req Monitoring HIT</td>
<td>Diet Interactions Lifestyle interactions Bleeding risk Antidote (Vit K)</td>
<td>Warfarin</td>
<td>Parenteral Narrow TI</td>
</tr>
</tbody>
</table>

The ‘Ideal’ Anticoagulant

- Oral, preferably once daily
- Rapid onset and offset
- Predictable PK and PD
- Good tolerability
- Low propensity for food and drug interactions
- Fixed doses (one size fits all)
- Wide therapeutic window
- Easy to use with no need for monitoring
- Quick, effective and safe antidote

The Newer Oral Anticoagulants

- Direct Thrombin Inhibitors:
  - Dabigatran
- Factor Xa inhibitors:
  - Rivaroxaban
  - Apixaban
  - Edoxaban

Do they meet the IDEAL criteria?
Atrial Fibrillation and the need for effective anticoagulation

- Estimated 2.3 – 2.7 million Americans suffer from non-valvular atrial fibrillation.
  - Projected to increase to 6 – 12 million by 2050
- Median age for patients with atrial fibrillation is 66.8 years for men and 74.6 years for women.
- Stroke & heart failure are two most common complications.
- In addition to the five times greater risk of stroke compared with people without the condition, strokes for those affected are twice as likely to be fatal or seriously disabling.

dabigatran (Pradaxa)

- Oral Direct Thrombin Inhibitor
- Reversible
- Prodrug, converted to dabigatran
  - Binds clot-bound and free thrombin with high affinity and specificity
- Twice daily dosing
- More predictable pharmacology than warfarin
- No requirement for monitoring

dabigatran – PK considerations

Absorption
  - Requires acidic pH for optimal absorption
  - Capsules contain a tartaric acid core
  - Possible explanation for dyspepsia and GI bleeding

Half-life:
- 12–17 hours = BID dosing
- 14-17 hours (Elderly)
- 15 – 18 hours (Mild-to-moderate renal impairment)
- ≥28 hours (Severe renal impairment)

Hepatic impairment
  - No dosage adjustment required

Renal impairment
  - CrCl cut point and dosing adjustments vary by indication

dabigatran - Drug Interactions

- No cytochrome P450 issues
- Substrate for P-glycoprotein efflux transporter
  - P-gp inducers or inhibitors may alter dabigatran bioavailability
    - Inducers: rifampin
    - Inhibitors: quinidine, ketoconazole, verapamil, amiodarone, clarithromycin
- PPIs may decrease bioavailability
Is dabigatran
The ‘Ideal’ Anticoagulant

- Oral (although b.i.d)
- Rapid onset and offset
- Predictable PK and PD
- Easy to use with no need for monitoring
- Low propensity for drug (food, lifestyle) interactions
- Fixed doses (one size fits all)
- Good tolerability ??? GI issues
- Effective & safe antidote Yes? (but short t½ and dialyzable)

- Renal status for dosing is critical
- Increased risk of MIs (appears to be DTI class effect)
- Contraindicated in Pts w Mechanical Prosthetic Valves

Direct Factor Xa inhibitors

- First oral direct factor Xa inhibitor
- Intrinsic pathway
- Extrinsic pathway
- Factor Xa

rivaroxaban

Currently indicated for

- Prevention of stroke & systemic embolism in pts with nonvalvular atrial fibrillation
  - Non-inferior to warfarin
  - Major & non-major bleeding = warfarin
  - Intracranial hemorrhage < warfarin
  - Fatal bleeding < warfarin
- DVT prophylaxis after knee or hip surgery
  - Reduced composite of symptomatic VTE and all-cause mortality compared to enoxaparin
  - Major bleeding events = LMWH

rivaroxaban

- Deep vein thrombosis / pulmonary embolism
  - Acute, systematic, proximal DVT w/o pulm embolism (PE)
  - Daily b.i.d. similar efficacy & safety to standard therapy
- Acute symptomatic PE with or without DVT:
  - Non-inferiority to LMWH/VKA for efficacy
  - Similar findings for principal safety outcome
  - Superiority for reducing major bleeding
- Reduction in the risk (secondary prevention) of recurrent DVT/PE after an initial 6 months of treatment:
  - EINSTEIN-Extension Study was 6 to 12 months in addition to the initial treatment duration of 6 to 12 months

COMPASS
Cardiovascular Outcomes for People using Anticoagulation Strategies

- Purpose: To evaluate whether treatment with rivaroxaban and ASA or rivaroxaban alone is better than ASA alone in prevention of major cardiac events in patients with CAD or PAD
- Trial participants
  - >20,000 patients ≥18 years with documented atherosclerosis related to CAD or PAD plus one of the following inclusion criteria:
    - age ≥65 years
    - age <65 years plus documented atherosclerosis in at least two vascular beds or at least 2 additional risk factors
- Treatment groups
  - rivaroxaban 2.5 mg bid + aspirin 100 mg/day
  - rivaroxaban 5 mg bid daily without aspirin
  - aspirin 100 mg/day without rivaroxaban
- Endpoints
  - Primary efficacy endpoint: composite of CV death, myocardial infarction and stroke
  - Primary safety endpoint: major bleeding
  - Secondary outcome measures: composite of myocardial infarction, stroke, cardiovascular death, venous thromboembolism and cardiovascular hospitalization, all-cause mortality
COMPASS
Cardiovascular Outcomes for People using Anticoagulation Strategies

- Trial recently halted more than a year ahead of its planned March 2018 completion because the primary end point of MI, stroke, or cardiovascular death reached its prespecified criteria for superiority.
- Companies have not yet disclosed which rivaroxaban-containing regimen was superior for the primary end point.

rivaroxaban - PK Considerations

- Absorption: Rapid and complete
- Half-life: Terminal: 5-9 hours; Elderly: 11-13 hours
- Hepatic Impairment
  - Metabolized (30%) via hepatic via CYP3A4/5*
  - Moderate-to-severe hepatic impairment and patients with any hepatic disease associated with coagulopathy: Avoid use
- Renal Impairment
  - Cl\(_{\text{cr}}\) >50 mL/minute: No dosage adjustment necessary
  - Cl\(_{\text{cr}}\) 15-50 mL/minute: 15 mg qdaily with evening meal
  - Cl\(_{\text{cr}}\) <15 mL/minute: Avoid use.
  - Variations to above based on specific indication

Drug interactions - rivaroxaban

- CYP3A4 substrate
  - Inhibitors: Increase risk of bleeds
    - Erycin, clarithromycin, azole antifungals, verapamil, amiodarone, protease inhibitors, grapefruit juice
  - Inducers: Decrease efficacy (↑ clot risk)
    - Rifampin, phenytoin, carbamazepine, pioglitazone, St John’s wort

Is rivaroxaban
The ‘Ideal’ Anticoagulant

- Oral, preferably once daily YES
- Rapid onset and offset
- Predictable PK and PD
- Good tolerability
- Fixed doses (one size fits all)
- Easy to use with no need for monitoring

Low propensity for drug (etc) interactions (CYP3A4)
Renal impairment dose adjustments
Effective & safe antidote (short 1/2 potential benefit)

apixaban
Currently indicated for
Prevention of stroke or systemic embolism in patients with atrial fibrillation
- Apixaban superior to warfarin in preventing stroke or systemic embolism
- Associated with less bleeding than warfarin
- Associated with lower all cause mortality vs warfarin

DVT & PE
- Postoperative thromboprophylaxis (orthopedic surgery)
- Treatment and prevention of DVT and PE
- *reduction in the risk of recurrence*: 2.5 mg twice daily after at least 6 months of treatment for DVT

Drug interactions - apixaban

- CYP3A4 substrate
  - Inhibitors: Increase risk of bleeds
    - Erycin, clarithromycin, azole antifungals, verapamil, amiodarone, protease inhibitors, grapefruit juice
  - Inducers: Decrease efficacy (↑ clot risk)
    - Rifampin, phenytoin, carbamazepine, pioglitazone, St John’s wort
Is apixaban
The ‘Ideal’ Anticoagulant

- Oral (although b.i.d)
- Rapid onset and offset
- Predictable PK and PD
- Good tolerability
- Fixed doses (one size fits all)
- Easy to use with no need for monitoring

Low propensity for drug (etc) interactions (CYP3A4)
Wide therapeutic window
Effective & safe antidote (short t½ potential benefit)

Edoxaban (Savaysa)

Clinical Trials

- Atrial Fib
  - Higher dose (60 mg)* similar to warfarin (non-inferior) for the reduction in the risk of stroke with significantly less major bleeding compared to warfarin.
- DVT / PE
  - 3.2 percent of participants had a symptomatic recurrent VTE compared to 3.5 percent of those taking warfarin.

* Patients receive 30 mg once daily if they meet one or more of the following criteria: CrCl 30 to 50 mL/min, body weight ≤ 60 kg, or concomitant use of specific P-gp inhibitors (verapamil and quinidine or the short-term concomitant administration of azithromycin, clarithromycin, erythromycin, oral itraconazole or oral ketoconazole).

Summary of Clinical Trial Results (vs warfarin) in AF Stroke Prevention

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Dabigatran (BEET)</th>
<th>Rivaroxaban (ROCKET-AF)</th>
<th>Apixaban (ARISTOTLE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic Stroke</td>
<td>74% reduction</td>
<td>40% reduction</td>
<td>50% reduction</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Similar to warfarin</td>
<td>Similar to Warfarin</td>
<td>30% reduction</td>
</tr>
<tr>
<td>Ischemic Strokes</td>
<td>Reduction</td>
<td>Similar to warfarin</td>
<td>Similar to warfarin</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>No difference</td>
<td>No difference</td>
<td>11% Reduction</td>
</tr>
</tbody>
</table>

Comparing them all

Edoxaban (Savaysa)

- 3rd Oral Factor Xa inhibitor (4th NOAC)
- Once-daily dosing
- Approved to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Also to treat DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant.
Apples-to-Oranges Problems with comparing new drugs

- Differences between the trial designs
  - RE-LY open label / ROCKET & ARISTOTLE blinded
- Patient Populations
  - Dabigatran: Mean age 82, mean CHADS₂ score 2.1
    - (31% having a score of 0 or 1)
  - Rivaroxaban: Mean age 73, mean CHADS₂ score 3.5
  - Apixaban: Median age 70, mean CHADS₂ score 2.1
- Warfarin comparators – Time in therapeutic range (INR)
  - RE-LY (dabigatran) 64%, ROCKET (rivaroxaban) 57.8%, ARISTOTLE (apixaban) 62%

Oranges-to-Tangerine Comparing Clinical Trial to Real World

**Efficacy (Clinical trial data)**

- Does it work under ideal circumstances?
- Controlled clinical trial environment
- Geared to get FDA approval
- Fixed regimen with highly motivated patients
- Compliance usually high
- External validity - low to medium

**Effectiveness (Real-world data)**

- Does it work under usual circumstances?
- Real world clinical practice
- Drug performance in the real world
- Flexible regimen with your regular day to day clinic patient
- Low to high compliance
- External Validity - Medium to high
Real-world analyses show similar or better effectiveness and safety of NOACs compared to warfarin

Conclusion

- In these real-world effectiveness and safety analyses, apixaban was associated with better effectiveness and safety, dabigatran was associated with similar effectiveness but better safety, whereas rivaroxaban was associated with similar outcomes for both effectiveness and safety, when compared to warfarin.

Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation (Real World)

<table>
<thead>
<tr>
<th></th>
<th>Risk of stroke vs warfarin</th>
<th>Risk of major bleeding vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Similar</td>
<td>Lower</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Lower</td>
<td>Lower</td>
</tr>
</tbody>
</table>

http://jaha.ahajournals.org/content/5/6/e003725

Indirect comparison of BID vs QD with the CEs and results from respective NOACs.

Converting to a NOAC from Warfain

- **Dabigatran**
  - Discontinue warfarin and initiate dabigatran when INR < 2.0

- **Rivaroxaban**
  - Discontinue warfarin and initiate rivaroxaban as soon as INR falls to < 3.0

- **Apixaban**
  - Discontinue warfarin and initiate apixaban when INR is < 2.0

What about surgery?

Risk of bleeding weighed against urgency of procedure

- **Dabigatran**
  - Discontinue 24 – 48 hours (Clcr ≥ 50 mL/minute) or 3-5 days (Clcr < 50 mL/minute) before invasive or surgical procedures

- **Rivaroxaban**
  - Discontinue at least 24 hours prior to procedure

- **Apixaban**
  - Discontinue at least 24 hrs prior to procedures with low risk of bleeding: At least 48 hours moderate-to-high risk

- **Edoxaban**
  - Discontinue edoxaban at least 24 hours prior to elective surgery or invasive procedures

Monitoring

- **Not routine / not for dosage adjustment**

- **Dabigatran**
  - Bleeding risk can be assessed by ecarin clotting time (ECT)

- **Rivaroxaban and Apixaban**
  - Prothrombin time (PT), INR, and aPTT may be used to detect presence of Factor Xa inhibitors (qualitative only)

- **Anti-FXa assay** may be helpful in guiding clinical decisions
  - Plasma concentrations exhibit linear relationship with anti-FXa activity
The Issue of Antidotes

- **Prothrombin complex concentrate (PCC) (theoretical)**
  - Usefulness in clinical settings not yet established
- **Fresh frozen plasma**
  - Short-term reversal, short half-life of 3-5 hours
- **Dabigatran**
  - Maintain adequate diuresis (60% dialyzable 2 – 3 hrs
  - Praxbind® (idarucizumab) approved 10/2015
- **Factor Xa inhibitors**
  - Andexanet alfa (Phase 3)
  - Decoy protein (looks like Xa – but not functional)

Idarucizumab (Praxbind)

**Pharmacology**
- Humanized monoclonal antibody fragment that binds to dabigatran and its metabolites
  - Neutralizes anticoagulant effect
  - Binds to dabigatran with higher affinity than dabigatran binds to thrombin
  - Does NOT reverse Factor Xa inhibitors
- **Indication**
  - For urgent reversal of the anticoagulant effect of dabigatran
  - Given intravenously
  - Half-life ~ 10.3 hours
  - Cost: $3500 per 5 gm dose

Summary: Benefits of New Agents

- All new agents associated with lower rates of intracranial hemorrhage (ICH) vs warfarin
- Predictable PD/PK
- No monitoring necessary
- No diet / lifestyle interactions
- No genetic polymorphism
- Apixaban and Rivaroxaban require no “bridging” with parenteral anticoagulants with DVT Dx

Summary: Limitations of New Agents

- **No monitoring**
  - Unable to titrate dose
  - Treatment failure vs. poor compliance (no INR)
- **Short t\(_1/2\)**
  - Poor compliance may affect efficacy more than vitamin K antagonists (eg., warfarin)
- **Renal / hepatic dose adjustments likely required**
  - Elderly
  - Renal disease / Hepatic disease
  - Use with CYP3A inhibitors / Pgp inhibitors
- **High Cost**

Heart Failure

Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF
Stepwise treatment of patients with symptomatic (NYHA II–IV) heart failure with reduced ejection fraction.

- Combination of Neprilysin inhibitor (blocks breakdown of BNP) and valsartan (ARB)
- Indicated to reduce the risk of cardiovascular death and hospitalization for heart failure (HF) in patients with chronic heart failure (CHF) (NYHA class II-IV) and reduced ejection fraction
- Although BNP levels typically rise with increasing severity of HF, much of the measured BNP is ineffective biologically

**Entresto – sacubitril / valsartan**

- Neprilysin inhibition potentiates actions of endogenous vasoactive peptides that counter maladaptive mechanisms in heart failure

**Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure**

- **Endogenous vasoactive peptides**
  - natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide
- **Neprilysin**
- **Neprilysin inhibition**
- **Inactive metabolites**

**Mechanisms of Progression in Heart Failure**

- Myocardial or vascular stress or injury
- Increased activity or response to maladaptive mechanisms
- Decreased activity or response to adaptive mechanisms

**Evolution and progression of heart failure**

**PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)**

- **Enalapril**
  - (n=4212)
  - HR = 0.80 (0.73-0.87)
  - P = 0.000002
  - Number needed to treat = 21

- **Valsartan/sacubitril**
  - (n=4187)
  - HR = 0.80 (0.71-0.89)
  - P = 0.00004
  - Number needed to treat = 32

**PARADIGM-HF: Cardiovascular Death**

- **Enalapril**
  - (n=4212)
  - HR = 0.80 (0.71-0.89)
  - P = 0.00004
  - Number needed to treat = 32

- **Valsartan/sacubitril**
  - (n=4187)
  - HR = 0.80 (0.71-0.89)
  - P = 0.00004
  - Number needed to treat = 32
PARADIGM-HF: Summary of Findings

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

Valsartan/sacubitril better tolerated than enalapril . . .

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

* Risk of angioedema ~ 1:200 with valsartan/sacubitril ~ 1:300 with ACEI

PARADIGM-HF: All-Cause Mortality

Enalapril (n=4212)
835
HR = 0.84 (0.76-0.93) P<0.0001

Valsartan/sacubitril (n=4187)
711

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

0 180 360 540 720 900 1080 1260
0 8 16 24 32

PARADIGM-HF: Summary of Findings

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

Valsartan/sacubitril more effective than enalapril in . . .

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by incremental 20%
- Reducing the risk of HF hospitalization by incremental 21%
- Reducing all-cause mortality by incremental 16%
- Incrementally improving symptoms and physical limitations

Sacubitril/Valsartan (Entresto®)

Safety

- BLACK BOX WARNING
  - Fetal toxicity – discontinue as soon as pregnancy detected
  - Symptomatic hypotension – 14%
  - Elevated serum creatinine – 3.3%
  - Cough – 11.3%
  - Angioedema – 0.5%
  - Drug interactions
    - Do not combine with an ACE inhibitor (angioedema)
    - K-sparing diuretics/potassium supplements (hyperkalemia)
    - NSAIDS (worsening of renal function possible)

Take home

- Still not first line - continue to use standard regimen of an ACEI or ARB, beta-blocker, and an aldosterone antagonist in most patients.
- If no benefit in patients titrated to target doses of above, consider swapping out ACEI or ARB for valsartan/sacubitril
- especially after a recent heart failure hospitalization
- But only in pts with systolic BP is > 100 mmHg
- High cost - approx $375/month.

Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF