Rational Polypharmacy in Pain Management

Charles Argoff, MD

Disclosures: Charles Argoff

- Financial Disclosure:
  - Consultant/Independent Contractor: Collegium; kaléo; Lilly; Novartis; Pfizer; Quest; Regeneron; Teva; US World Meds; Vertex
  - Grant/Research Support: Grüenthal; Vertex
  - Honoraria: Allergan; Amgen; AstraZeneca; BDSI; DSI; Novartis; Teva
  - Stock Shareholder: Depomed; Pfizer
  - Other/Royalty: Cambridge Press; Elsevier

- Drug/Product Off-Label Use Disclosure
  - Off-label use of a drug and/or product will be addressed in this presentation. This information will be verbally disclosed both at the beginning of the presentation and at the time of drug/product discussion.
Learning Objectives

- Define rational polypharmacy and when it is indicated for pain management
- List the array of medications and their MOAs that may be employed in polypharmacy
- Discuss the pharmacologic and clinical considerations of which the prescriber should be aware
- Explain painful conditions where polypharmacy might be considered

Real Patients to Consider in Our Discussion

- 60 year old male experiencing painful diabetic neuropathy and chronic LBP
- 50 year old female who experiences fibromyalgia and migraine
- 70 year old female who experiences osteoporosis, osteoarthritis, and postherpetic neuralgia
- 52 year old male who experiences post-laminectomy pain
- 28 year old female with chronic migraine
Selecting an Analgesic: Evidence and Guideline Limitations

- Paucity of trials on comparative effectiveness of different treatments
- Most treatment trials are of short duration with limited evidence for functional benefit
- Few trials evaluate strategies for choosing initial agent
- Various clinical practice guidelines may interpret evidence differently
- Clinical practice guidelines may not include latest evidence
  - Duloxetine for low back pain or osteoarthritis

What Is Polypharmacy?

- Defined as
  - Intentional use of 2 or more medications to treat 1 condition
    - Example: opioids + NSAIDs to treat low back pain, OR
  - Use of 2 or more medications by 1 patient to treat multiple conditions
    - Example: antihypertensives, antidepressants, NSAIDs, and statins, OR
  - Use of 2 or more agents of the same chemical class
- Polypharmacy should be minimized whenever possible; however, it may be warranted under certain circumstances
Rational Polypharmacy

- Rational polypharmacy
  - May help reduce chronic pain
  - Reduction of chronic pain can improve patient outcomes

Rational Polypharmacy (cont’d)

- Rational polypharmacy has become an acceptable component of chronic pain management
  - More therapeutic options are being made available
- Useful to target pain that has peripheral and central mechanisms
- Consider the following when selecting combined regimens:
  - Side effects (SEs)
  - Medication interactions
  - Ease of use
  - Costs
Why Is Rational Polypharmacy Used?

- Patients with pain
  - May experience only a partial response to monotherapy
  - Cannot tolerate adverse events at analgesic doses of monotherapy
  - May have positive synergistic effects with combined agents from different medication classes

Multidrug Therapy
Proposed Principles for Chronic Pain

- Purpose is to combine medications to achieve additive or synergistic analgesia
  - Potentially at lower doses (and fewer side effects) than those required with monotherapy
- Combine medications with differing mechanisms or sites of action, based on patient response, functional goals, clinical experience, and potential adverse interactions
- Consider interactions of newly added drug with current medications
- Select and use one drug at a time
- Start low, go slow for dosing and titration, particularly in older patients
- Ongoing reassessment is critical
  - Assess for clinically meaningful relief and document functional outcomes

The Chronic Pain PHARMACOLOGIC Armamentarium

- Nonopioids
  - Acetaminophen
  - NSAIDs
  - COX-2 inhibitors
  - Antidepressants
  - Anticonvulsants
  - Topical agents, other

- Opioids
  - Mu-opioid agonist
  - Partial agonists

Nonopioid Analgesics*

<table>
<thead>
<tr>
<th>Chemical Class/Examples</th>
<th>Class Examples</th>
<th>Brands/Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Para-aminophenols</td>
<td>Acetaminophen</td>
<td>Tylenol®</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Aspirin</td>
<td>Bayer®</td>
</tr>
<tr>
<td></td>
<td>Choline magnesium trisalicylate (CMT)</td>
<td>Bufferin®</td>
</tr>
<tr>
<td></td>
<td>Choline salicylate</td>
<td>Trilisate®</td>
</tr>
<tr>
<td></td>
<td>Magnesium salicylate</td>
<td>Arthoapan®</td>
</tr>
<tr>
<td></td>
<td>Diflunisal</td>
<td>Doan’s®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Argesic®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salgesic®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dolobid®</td>
</tr>
</tbody>
</table>

* Not an exhaustive list of class/examples.
Nonopioid Analgesics (cont’d)

<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>Class Examples</th>
<th>Brands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arylpropionic/propionic derivatives</td>
<td>Ibuprofen</td>
<td>Advil®</td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
<td>Motrin®</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen</td>
<td>Aleve®</td>
</tr>
<tr>
<td></td>
<td>Flurbiprofen</td>
<td>Anaprox®</td>
</tr>
<tr>
<td></td>
<td>Fenoprofen</td>
<td>Naprelan®</td>
</tr>
<tr>
<td></td>
<td>Oxaprozin</td>
<td>Naprosyn®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orudis®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oruvail®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ansaid®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nalfon®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daypro®</td>
</tr>
<tr>
<td>Indole and indene acetic acids</td>
<td>Indomethacin</td>
<td>Indocin®</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indocin® SR</td>
</tr>
</tbody>
</table>

Clinical Indications: Nonopioids

- Variety of acute and chronic pain types
  - Eg, trauma, post-op, cancer, arthritis
- Somatic pain
  - Muscle and joint pain, bone/dental pain, inflammatory pain, post-op pain
- APAP vs NSAIDs
  - Acetaminophen has analgesic, antipyretic effects
    - But lacks anti-inflammatory effect
  - NSAIDs have analgesic, anti-inflammatory, and antipyretic effects
    - But affect gastric mucosa, platelets
Clinical Indications: Opioids

- Moderate-severe pain unresponsive to nonopioids alone
  - Example: acute pain
    - Post-op, trauma
  - Breakthrough pain
  - Cancer pain
  - Chronic, noncancer pain

Mechanism of Action:
Opioids + NSAIDs
**Adjuvant Analgesics:**
**Tricyclic Antidepressants**

- **Examples**
  - TCAs include amitriptyline, desipramine, doxepin, imipramine, nortriptyline
- **MOA**
  - Inhibition of reuptake of norepinephrine and serotonin
  - Analgesia is independent of antidepressant function
- **Uses**
  - Chronic pain examples: migraine, other headaches, low back pain, cancer pain, fibromyalgia
  - Neuropathic pain examples: PDN, PHN, cancer-related pain
- **Common adverse events (AEs)**
  - Examples: sedation, orthostatic hypotension and anticholinergic effects (ie, dry mouth, blurred vision, constipation, urinary retention)

---

**Adjuvant Analgesics:**
**Selective Serotonin Reuptake Inhibitors**

- **Examples**
  - SSRIs include citalopram, paroxetine, fluoxetine, sertraline
- **MOA**
  - Selectively inhibit 5-HT reuptake without affecting norepinephrine
- **Uses**
  - Examples: neuropathic pain, diabetic neuropathy
- **Common AEs**
  - Examples: anxiety, insomnia, nausea, headache, drowsiness, sexual dysfunction, withdrawal symptoms upon abrupt cessation
Adjuvant Analgesics: Serotonin/Norepinephrine Reuptake Inhibitors

- **Examples**
  - SNRIs include duloxetine and venlafaxine
- **MOA**
  - Block reuptake of 5-HT and norepinephrine
- **Uses**
  - Example: diabetic peripheral neuropathy (DPN)
- **Common AEs**
  - Examples: nausea, somnolence, dizziness, constipation, dry mouth, hyperhidrosis, anorexia

Mechanism of Action: Antidepressants
Adjuvant Analgesics: Anticonvulsants

- **Examples**
  - AEDs include gabapentin, pregabalin, carbamazepine, phenytoin, divalproex sodium, clonazepam, levetiracetam, topiramate, lamotrigine
- **MOA:** exact mechanism of analgesic effect is unknown; it is thought they
  - Reduce membrane excitability
  - Suppress abnormal discharges in pathologically altered neurons
- **Uses**
  - Neuropathic pain (PDN, PHN, RSD, PSP, TN)
  - Cancer pain, HIV-related neuropathy, phantom limb pain
  - Migraine (prophylaxis), dysesthesia, deafferentation pain, thalamic pain
- **Common AEs**
  - Sedation, headache, dizziness, rash, vertigo, ataxia, nausea, diplopia

Adjuvant Analgesics: Topicals

- **Examples**
  - Lidocaine, Lidoderm, EMLA®, Capsaicin cream
- **MOA**
  - Lidocaine/prilocaine: block sodium channels and inhibit generation of abnormal impulses by damaged nerves
  - Capsaicin: depletion of substance P in sensory nerve endings
- **Uses**
  - Examples in acute and chronic pain
    - PHN, other neuropathic pain, mechanical allodynia
    - Pain associated with medical procedures: needle insertion, cannulation, epidural nerve blocks
- **Common AEs**
  - Examples: localized reaction including burning sensation
The Potential Benefits of Rational Polypharmacy

- Enhance current treatment
- Use a lower dose of a medication
- Target symptom clusters (e.g., pain and depression)
- Ease the treatment of a comorbid condition (e.g., control diabetes to reduce DPNP)
- Address different pain mechanisms (e.g., central and peripheral mechanisms)
- Treat AEs

Considerations for Rational Polypharmacy

- Know medication toxicities
- Avoid overlapping/additive toxicities
- Know medication MOAs
- Know medication PK/PD
  - Avoid drug-drug interactions
- Have convincing evidence that the combination is more effective vs monotherapy and should not pose significantly greater safety or tolerability risks
MOA Considerations for Polypharmacy

- When using multiple medications, consider carefully the MOA of each drug:
  - Each drug should have one MOA
  - Drugs should not have broad-acting MOA
  - Drugs should not have the same MOA
  - Drugs should not have opposing MOAs

Possible Drug-Drug Interactions

- Interaction of absorption: one drug may cause an increase/decrease in the absorption of the other in the GI system
- Interaction of protein binding
- Interaction of metabolism (eg, CYPs)
- Interaction of receptor binding
- Interaction of therapeutic action
Types of Drug-Drug Interactions

- Additive
- Synergistic
- Potentiation
- Antagonism
  - Functional/physiological
  - Chemical/inactivation
  - Dispositional
  - Receptor

P450 Enzymes

- Care should be taken when coadministering drugs whose metabolism might be inhibited by other drugs in order to prevent adverse drug reactions (ADRs)
  - For example, SSRIs inhibit the metabolism of drugs mediated by certain P450 enzymes
- > 30 human CYP isoenzymes have been identified
- ≥ 90% of drug oxidation can be attributed to 6 main P450 cytochromes:
  - 1A2
  - 2C9
  - 2C19
  - 2D6
  - 2E1
  - 3A4
Phases of Medication Metabolism

- Phase I: oxidation/reduction/hydrolysis
  - Oxidation to the parent compound or deletion of the alkyl group, reduction, and hydrolysis reactions
- Phase II: conjugation
  - Biotransformation links a parent medication molecule or product of Phase I metabolism with an endogenous substrate (e.g., glucuronic acid, sulfate, or glycine)

Induction and Inhibition

- Induction
  - Increase of enzyme metabolism by a medication
  - Increasing doses are needed to produce same effect, as the body metabolizes the drug more quickly
- Inhibition
  - Decreased enzyme activity due to direct interaction with a medication or chemical
  - Doses should be decreased due to a decrease in metabolism
When Is Polypharmacy Indicated in Pain Management?

- To reduce medication intolerance by using a second medication that allows a lower dose of the first
  - May increase treatment compliance
- To provide analgesic efficacy at certain times of the day by giving immediate-release with long-acting medications
  - Example: control breakthrough pain in a patient taking long-acting opioids

When Is Polypharmacy Indicated in Pain Management? (cont’d)

- To use a lower dose of a medication by using a second medication
  - Example: opioid-sparing
- To address partial or nonresponse to 1 medication by adding a second medication to increase efficacy
  - Example: using 2 different antidepressants with different MOAs
When Is Polypharmacy Indicated in Pain Management? (cont’d)

- To target different symptom clusters that are a product of the disease or of the comorbid disease
  - Example: pain with associated depression, which in turn is associated with suicidal ideation
- To treat the comorbid disease with ease by aggressively treating the index disease
  - Example: treat diabetes aggressively, thereby reducing the peripheral neuropathy severity

When Is Polypharmacy Indicated in Pain Management? (cont’d)

- To address different locations of the disease process
  - Example: pain with peripheral AND central mechanisms that require medications with peripheral and central activity
  - Example: topical lidocaine patch with antidepressant
- To treat an adverse event
Checklist for Controlling Pain in a Polypharmacy Environment

- Prescribers are charged with
  - Prudent attention to the patient's past medication history, including OTC preparations
  - Vigilant surveillance of systemic function
  - Pharmacologic alternatives when medications are inappropriate

5 Principles of Polypharmacy for Pain Associated Comorbidity

- Use medications for comorbid disease with proven analgesic efficacy
- First target symptoms should ALWAYS be pain
- Target all possible pain mechanisms (eg, peripheral and central) believed to be causing the pain
- Do not aim for absolute pain relief
  - Aim for tolerable pain levels that improve QoL or function
- Use medications to address more than 1 comorbidity
  - Example: sedating antidepressant for pain, sleep, and depression
Summary of Implementing Rational Polypharmacy in the Treatment of Pain

- Polypharmacy, the use of multiple medications in a patient, should be minimized whenever possible; however, it may be warranted under certain circumstances
- Rational polypharmacy may be employed when the benefits outweigh the risks

Summary of Implementing Rational Polypharmacy in the Treatment of Pain (cont’d)

- The benefits of rational polypharmacy include:
  - Enhancing current treatment
  - Using a lower dose of a medication
  - Targeting symptom clusters
  - Easing the treatment of a comorbid condition
  - Addressing different pain mechanisms
  - Treating AEs
Examples of “Rational” Polypharmacy in Specific Pain Conditions

- Neuropathic pain
- Fibromyalgia
- Chronic headache
- Low back pain

Nortriptyline and Gabapentin for Neuropathic Pain

- Significant improvements were also seen with combination therapy for pain interference with mood, sleep, and enjoyment of life.
- Combination therapy did not result in a markedly higher side effect burden.

Morphine, Gabapentin or their Combination for Neuropathic Pain

- Patients with postherpetic neuralgia or painful diabetic neuropathy
- Randomized, double-blind, active placebo-controlled, 4 period crossover trial
- Periods included active placebo (lorazepam), gabapentin, sustained release morphine, or a combination of both gabapentin and morphine each period 5 weeks
- Gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent

Postherpetic Neuralgia: 5% Lidocaine Medicated Plaster, Pregabalin, or a Combination of Both?

- Randomized, open label clinical effectiveness trial
- PHN patients with pain intensity score of greater than 4 were randomized to lidocaine plaster or pregabalin
- Patients experiencing pain intensity of 4 or less after 4 weeks remained on monotherapy
- Those who did not received both medications after 4 weeks
- Equal response between medications with monotherapy AND combining medications was well tolerated and improved response
Combination of Morphine with Nortriptyline for Neuropathic Pain

- Combination compared to monotherapy of each in patients with neuropathic pain (1:1:1)
- 3 6-week treatment periods
- Superior efficacy noted with morphine-nortriptyline combination over either monotherapy
- Constipation, dry mouth, and somnolence most frequent adverse effects

Pregabalin with Duloxetine for Fibromyalgia

- Randomized, double-blind 4 period crossover design
- 6 week periods
- Placebo, pregabalin, duloxetine, or combination
- Daily pain intensities improved most with combination
- Fibromyalgia Impact Questionnaire scores improved most with combination
- SF-36 scores improved most with combination
### MIGRAINE Preventive Medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>Divalproex*, Gabapentin, Topiramate*</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>TCAs, SSRIs, MAOIs, TCAs, SSRI, selective serotonin reuptake inhibitors, TCA, tricyclic antidepressant.</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Propranolol*, Timolol*</td>
</tr>
<tr>
<td>Ca channel blockers</td>
<td>Verapamil</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>5-HT antagonists, Methysergide*/methergine</td>
</tr>
<tr>
<td>Neurotoxins</td>
<td>Onabotulinum toxin A (Botox)*</td>
</tr>
<tr>
<td>Angiotensin system</td>
<td>ACE inhibitors, Antagonists</td>
</tr>
<tr>
<td>Acetylcholinesterase inhibitors?</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Riboflavin, coenzyme Q10, Feverfew, Petasites</td>
</tr>
</tbody>
</table>

FDA approved.

ACE, angiotensin converting enzyme; MAOIs, Monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant.


### Migraine Comorbid Conditions

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Mood disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Heart attack/angina</td>
<td>– Depression</td>
</tr>
<tr>
<td>– Mitral valve prolapse</td>
<td>– Mania</td>
</tr>
<tr>
<td>– Hypertension or hypotension</td>
<td>– Anxiety</td>
</tr>
<tr>
<td>– Stroke</td>
<td>– Panic</td>
</tr>
<tr>
<td>– Raynaud’s syndrome</td>
<td></td>
</tr>
</tbody>
</table>

Migraine Comorbid Conditions (cont’d)

- CNS
  - Epilepsy
  - Essential tremor
  - Fibromyalgia

- GI disorders
  - Ulcer disease
  - Colitis
  - Irritable bowel syndrome

• Allergy/Asthma


Drug Treatment

- Assess coexisting conditions
- Do not treat migraine with drug contraindicated for other condition
- Do not use drug for other condition that exacerbates migraine
- Beware of drug interactions
- Pay attention to women of childbearing potential
- Select 1 drug to treat both disorders?

Comorbid and Coexisting Disorders
Monotherapy?

- Preferred, but may be exception rather than rule
  - May not be best choice for either disorder
    • β-blocker not first choice for hypertension
  - Dose for one may not be adequate for second
    • TCA migraine dose too low for depression

Comorbid and Coexisting Disorders
Monotherapy? (cont’d)

- Therapeutic opportunities
  - Angina: β-blocker
  - Epilepsy: divalproex or topiramate

- Therapeutic limitations
  - Depression or asthma: avoid β-blockers
  - Epilepsy: caution with TCAs or neuroleptics

Comorbid and Coexisting Disease
Therapeutic Independence

- Treat each disorder with best drug
  - Benefits: use first-line drug for each disorder at correct dose
    - Less adverse effects?
  - Concerns
    - Drug interactions or more adverse effects
    - Contraindicated for one of the disorders


Comorbid and Coexisting Disease
Therapeutic Independence (cont’d)

- Examples
  - Depression: SSRI or SNRI plus AED (divalproex or topiramate)
  - Hypertension: ACE inhibitor or antagonists plus AED or TCA

AED, antiepileptic drug; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
Comorbid and Coexisting Disease Depression

- Migraine and depression comorbid
- TCAs often recommended for migraine
  - However, appropriate dose for depression often higher
    - More adverse effects


Comorbid and Coexisting Disease Depression (cont’d)

- Better approach
  - Treat depression with SSRI or SNRI and
  - Treat migraine with AED (divalproex or topiramate), β-blocker, Ca channel blocker, or even low-dose TCA

Tizanidine and ibuprofen in acute low back pain

- Patients with acute low back pain randomized to receive either tizanidine 4 mg po 3 times daily with ibuprofen 400 mg 3 times daily or placebo plus ibuprofen 3 times daily
- Earlier improvement occurred in combination group, significantly better than ibuprofen alone by day 3
- More GI side effects noted with ibuprofen alone group supporting animal data that tizanidine can reduce GI side effects from NSAIDs

Conclusions

- Rational use of polypharmacy is indicated for pain management especially in specific painful conditions
- The prescriber should survey the array of medications and their MOAs that may be employed in polypharmacy
- Available studies suggest that rational approaches to polypharmacy in pain management can lead to improved analgesia and greater treatment tolerability
References


References (cont’d)

- Silberstein SD et al. Neurology 2012; 78(17):1337-1345
- Gilron I et al. Pain 2016;157(7):1532-1540