Rational Polypharmacy in Pain Management

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Disclosures: Charles Argoff

- Financial Disclosure:
  - Consultant: Teva, Daiichi Sakyo, Pfizer, Nektar, Purdue, Depomed, Arbor, Novartis, Quest, Gruenenthal, Braeburn, BDSI, Vertex
  - Speaker: Allergan, Depomed, Amgen, Teva, Daiichi Sakyo, Astra Zeneca, BDSI
  - Research Grant: Gruenenthal, Vertex
  - Stock Shareholder: Depomed, Pfizer
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  - 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.

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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

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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

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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

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Chappell AS, et al. *Pain*. 2009;146:253-260; Chappell AS, et al. *Pain Pract*. 2011;11:33-41; Kroenke K, et al. *Gen Hosp Psychiatry*. 2009;31:206-219; Skljarevski V, et al. *Pain Med*. 2010;11:648-657; Skljarevski V, et al. *J Pain*. 2010;11:1282-1290; Skljarevski V, et al. *Spine (Phila Pa 1976).* 2010;35:E578-585; Wallace M, et al. *Expert Rev Neurother*. 2011;11:15-27.

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

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Rational Polypharmacy

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

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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

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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

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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

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Backonja MM, et al. *Curr Pain Headache Rep*. 2006;10:34-38; Gilron I, et al. *Lancet*. 2009;374:1252-1261.

The Chronic Pain PHARMACOLOGIC Armamentarium

- Nonopioids
  - Acetaminophen
  - NSAIDs
  - COX-2 inhibitors
  - Antidepressants
  - Anticonvulsants
  - Topical agents, other
- Opioids
  - Mu-opioid agonist
  - Partial agonists

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Nonopioid Analgesics*

Chemical Class/Examples	Class Examples	Brands/Examples
Para-aminophenols	Acetaminophen	Tylenol®
Salicylates	Aspirin Choline magnesium trisalicylate (CMT) Choline salicylate Magnesium salicylate Diflunisal	Bayer® Bufferin® Trilisate® Arthropan® Doan's® Argesic® Salgesic® Dolobid®
* Not an exhaustive list of class/examples.		

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Nonopioid Analgesics (cont'd)

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

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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

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Clinical Indications: Opioids

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

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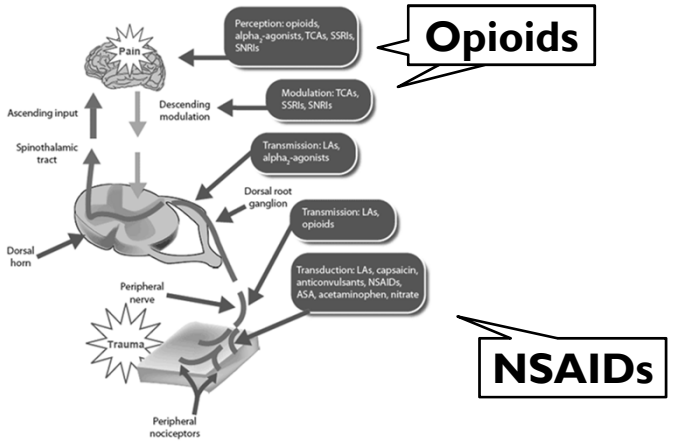
Mechanism of Action: Opioids + NSAIDs



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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)

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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

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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

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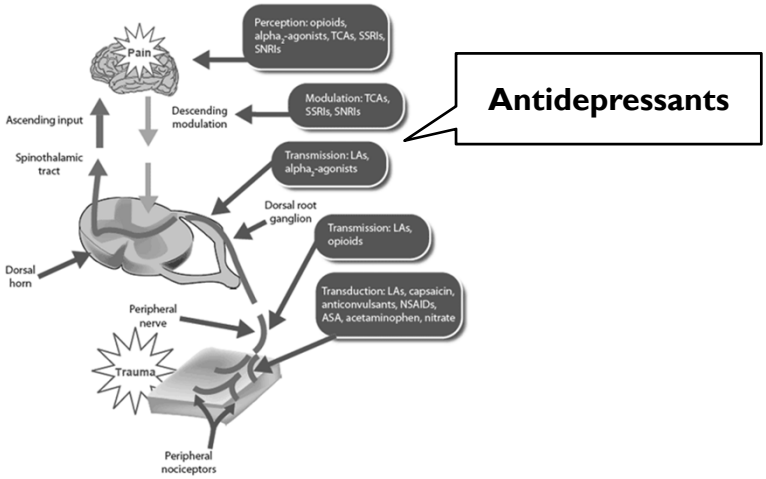
Mechanism of Action: Antidepressants



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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

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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

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The Potential Benefits of Rational Polypharmacy

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

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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

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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

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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

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Types of Drug-Drug Interactions

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

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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

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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 (eg, glucuronic acid, sulfate, or glycine)

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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

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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

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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

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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

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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

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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

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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

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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

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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

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Examples of ”Rational” Polypharmacy in Specific Pain Conditions

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

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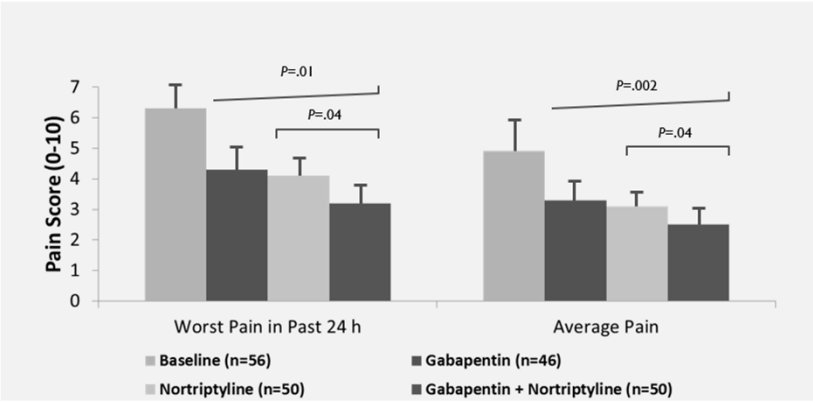
Nortriptyline and Gabapentin for Neuropathic Pain



- 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

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Gilron I, et al. *Lancet*. 2009;374:1252-1261.

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

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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

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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

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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

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MIGRAINE Preventive Medications

- Anticonvulsants
  - Divalproex*
  - Gabapentin
  - Topiramate*
- Antidepressants
  - TCAs, SSRIs, MAOIs
- β-Blockers
  - Propranolol*/Timolol*
- Ca channel blockers
  - Verapamil
- NSAIDs
- 5-HT antagonists
  - Methysergide*/methergine
- Neurotoxins
  - Onabotulinum toxin A (Botox)*
- Angiotensin system
  - ACE inhibitors
  - Antagonists
- Acetylcholinesterase inhibitors?
- Other
  - Riboflavin, coenzyme Q10, Feverfew, Petasites

FDA approved.
ACE, angiotensin converting enzyme; MAOIs, Monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant.
Modi S, et al. *Am Fam Physician.* 2006;731:72-78; Nicolodi M, et al. *Headache.* 2002;42:596-602; Silberstein SD, et al. *Cephalalgia.* 2002;22:491-512.

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Migraine Comorbid Conditions

- Cardiovascular
  - Heart attack/angina
  - Mitral valve prolapse
  - Hypertension or hypotension
  - Stroke
  - Raynaud's syndrome
- Mood disorders
  - Depression
  - Mania
  - Anxiety
  - Panic

Silberstein SD, et al. *Cephalalgia*. 2002;22:491-512

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Silberstein SD, et al. *Cephalalgia*. 2002;22:491-512.

Migraine Comorbid Conditions (cont'd)

- CNS
  - Epilepsy
  - Essential tremo
  - Fibromyalgia
- GI disorders
  - Ulcer disease
  - Colitis
  - Irritable bowel syndrome

• Allergy/Asthma

CNS, central nervous system; GI, gastrointestinal. Silberstein SD, et al. *Cephalalgia*. 2002;22:491-512.

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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?

Silberstein SD, et al. *Headache.* 2007;47:585-599.

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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

Silberstein SD, et al. *Headache.* 2007;4740:585-599.

Silberstein SD, et al. *Headache.* 2007;4740:585-599.

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

Silberstein SD, et al. *Headache.* 2007;4Silberstein SD, et al. *Headache.* 2007;4740:585-599. 740:585-599.

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

Silberstein SD, et al. *Headache.* 2007;4740:585-599.

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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.
Silberstein SD, et al. *Headache.* 2007;4740:585-599.

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Comorbid and Coexisting Disease Depression

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

Silberstein SD, et al. *Headache.* 2007;4740:585-599.

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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

Silberstein SD, et al. *Headache.* 2007;47:585-599.

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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

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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

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References

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