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Back Talk: The Medicine Cabinet

Dane L. Shiltz
Butler University, dshiltz@butler.edu

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The Medicine Cabinet

Dane Shiltz, PharmD, BCPS
Inpatient Family Medicine
Methodist Hospital

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Disclosure

- None

Objectives

- Differentiate between traditional therapies for back pain of nociceptive origin
- Discuss the debate regarding long-term opioid use & its impact on psychosocial functioning
- Differentiate between neuropathic back pain agents

General Back Pain Details

- Lifetime incidence ~50-80%
- Peak onset ages 30-40
- Direct US medical costs $12.2-90.6 BILLION/yr
- Lost productivity & disability compensation
- Frequently associated with depression or anxiety

Duffy. Prim Care Clin Office Pract. 2010;37:729-741.
Chou. Drugs. 2010;70:387-402.
Schnitzer, et al. J Pain Symptom Manage. 2004;28:72-95.

Definition & Classification

- Low back pain (LBP): pain localized to lumbar area between inferior ribcage & waistline
  - May include sciatica, with pain radiating down to posterior-lateral thigh distal to the knee

Classification	Duration
Acute	**<6 weeks**
Subacute	**6-12 weeks**
Chronic	**>12 weeks**

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Chou. Drugs. 2010;70:387-402.
Schnitzer, et al. J Pain Symptom Manage. 2004;28:72-95.

4 Main Classes of Low Back Pain

	Non-specific	Mechanical	Visceral / referred	Non-mechanical
Prevalence	70%	27%	2%	1%
Attributed Conditions	• Lumbar sprain • Lumbar strain • **No identifiable origin**	• Degenerative disc disease • Herniated disc • Osteoporotic compression fracture* • Spinal stenosis	• Aortic aneurysm • Pelvic organ disease • GI disease • Renal disease*	• Cancer • Infection* •Inflammatory arthritis • Paget disease of bone

Chronic LBP: A Mixed Pain Syndrome

- Nociceptive pain component (nonspecific pain)
  - Inflammatory response from tissue injury
  - Dull, aching, or throbbing pain
  - Usually adaptive & temporary once injury heals
- Neuropathic pain component (mechanical pain)
  - Lesion or disease affecting somatosensory system
  - Originates from lumbar spine and/or nerve roots
  - Paroxysmal, dysaesthetic and/or thermal

Acute nociceptive pain → Chronic nociceptive & neuropathic pain

LBP Treatment Goals

- Effectively reduce, if not resolve, pain
  - Fewest interventions (meds) necessary
  - Shortest duration at lowest dose
  - Most cost-effective
- Prevent and/or minimize treatment-related side effects
  - Avoid drug-drug & drug-disease interactions
- Restore physical functioning
- Decrease disease burden on patient & society

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Schnitzer, et al. J Pain Symptom Manage. 2004;28:72-95.

Factors Influencing Nonspecific LBP Pharmacologic Treatment Choice

- Symptom duration – acute vs. chronic
- Symptom intensity & quality
- Evidence
- Prior response to medications
- Adverse effect profile
- Drug-drug & drug-disease interactions
- Cost
- Convenience - # doses/day

Chou. Drugs. 2010;70:387-402.

Methodological Limitations

Most studies of only moderate quality

- Limited description of randomization & blinding
- Few active comparisons; most placebo only
- Small sample size
- Safety reporting limited & vague
- Short study duration & insufficient follow-up period
- Variation in pain assessment & efficacy criteria
- Multiple pain assessment scales used

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Chou. Drugs. 2010;70:387-402.
Schnitzer, et al. J Pain Symptom Manage. 2004;28:72-95.

Treatment Pearls

- 2/3 cases resolve within 6 weeks of onset
- LBP >12 weeks = ↓ likelihood for improvement
- Medication does not alter natural course
  - Meds target symptoms & functional status
- Best evidence for acute, short-term use
- Use shortest duration necessary, stop when no longer pain relief
- Chronic LBP does not mandate long-acting meds

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Schnitzer, et al. J Pain Symptom Manage. 2004;28:72-95.

Traditional Back Pain Options

- Acetaminophen (APAP)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Corticosteroids
- Muscle relaxants
- Tramadol
- Opioids

- Indications
- Efficacy
- Place in therapy
- Side effects, contraindications
- Monitoring

Acetaminophen (APAP)

- 1st line agent for acute & chronic LBP

- May be equivalent NSAIDs for acute back pain
  - Possibly inferior for **chronic** back pain
  - Ineffective for neuropathic pain
- Max 4 grams in 24 hours
  - 1000mg 4x/day, up to 28 days studied
  - Educate patients on APAP-containing meds!
- Caution use in alcohol users

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Schnitzer, et al. J Pain Symptom Manage. 2004;28:72-95.
Davies, et al. Eur Spine J. 2008;17:1423-1430.
Chou, et al. Ann Intern Med. 2007;147:505-514.

NSAIDs

- 1st line agent for acute & chronic LBP
- Superior vs. placebo
  - Strongest evidence for acute pain
  - Better data for chronic pain vs. APAP
  - Ineffective for neuropathic pain
- No agent superior NSAIDs ≈ celecoxib
- Toxicities limit more prevalent use
  - Studies not designed to assess GI & CV outcomes
  - Avoid in age >75, GI/CV disease history

Duffy. Prim Care Clin Office Pract. 2010;37:729-741.
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Chou, et al. Ann Intern Med. 2007;147:505-514.

NSAID & Dose	Duration (days)	LBP Type
Ibuprofen 400mg TID	2, 7	Acute
Ibuprofen 600mg TID	10	Acute
Ibuprofen 800mg TID	7	Acute
Naproxen 250mg TID	42	Acute
Naproxen 250mg 3-4x/day	15	Acute
Naproxen 250mg 4x/day	14	Acute
Naproxen 550mg BID	14	Chronic
Diflunisal 500mg BID	7-15	Acute
Diflunisal 500mg BID	14, 28	Chronic

NSAID Toxicities

- Gastrointestinal
  - Dyspepsia (~30-40%)
  - Gastroduodenal ulceration 1-2 cases/1,000 patients/year
- Cardiovascular
  - Concurrent aspirin
  - ASA doses <150mg/day

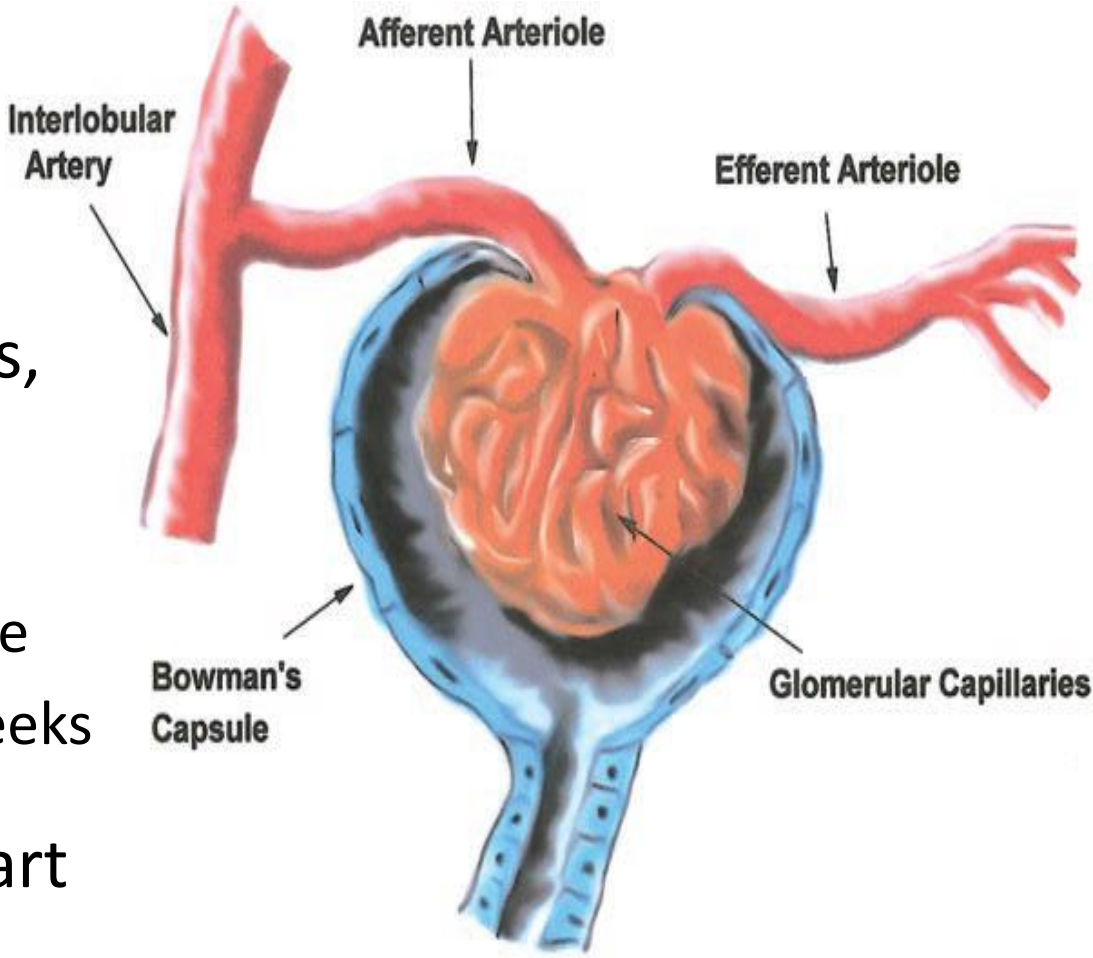
Risk for ulcer on NSAIDs

- Age >60
- H/o peptic ulcer disease
- Multiple NSAIDs
- High-dose NSAIDs
- Long-term use
- Concurrent corticosteroids

Lichtenstein DR.. Arthritis Rheum. 1995;38:5-18.
Henry D, et al. Gastroenterology. 1993;105:1078-1088.
Ruoff G. Am J Med. 1998;105:53S-60S.

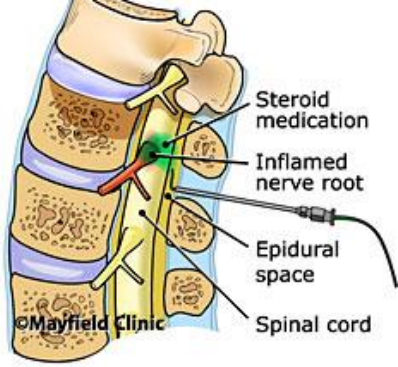
NSAIDs & Nephrotoxicity

- ↓ Renal blood flow
- ↑ Na^+, H_20 retention
- Caution use with ARB's, ACE inhibitors, and/or diuretics!
  - Elderly, CKD susceptible
  - Monitor Cr, K in 1-2 weeks
- Caution CKD, HTN, heart failure, cirrhosis



Ruoff G. Am J Med. 1998;105:53S-60S.

Corticosteroids



- Epidural injections for radiculopathy (sciatica)
  - Benefit minimal, variable & only short-term
  - IM, IV methylprednisolone 160mg, 500mg x 1
- No benefit for any corticosteroid vs. placebo via any route for acute or chronic LBP
- Adverse events poorly described
  - Rare injection site infection risk
- Not recommended for acute or chronic LBP

Johnson M, et al. J Fam Pract. 2011;60:297-298
Staal JB, et al. Spine. 2008;34:49-59.
Deyo RA, et al. J Am Board Fam Med. 2009;22:62-68.

Duffy. Prim Care Clin Office Pract. 2010;37:729-741.
Chou, et al. Ann Intern Med. 2007;147:505-514.
Staal JB. Cochrane Database of Systemic Reviews. 2008.

Muscle Relaxants (MRs)

- Superior to placebo for acute LBP
- 2nd line or adjunct option due to side effects
  - Short courses (2-7, max 14 days) recommended
  - Tizanidine + APAP/NSAID = better pain relief
- No single MR superior or best tolerated
- Not recommended for chronic LBP
  - Limited evidence, sedation, dizziness, dependence
  - No benefit for neuropathic pain (sciatica)

See S, et al. Am Fam Physician. 2008;78:365-370.
Chou R. Drugs. 2010;70:387-402.
Duffy RL. Prim Care Clin Office Pract. 2010;37:729-741.
Chou, et al. Ann Intern Med. 2007;147:505-514.
van Tulder MW, et al. Cochrane Database Syst Rev. 2008:CD004254.

Variation in Selecting a MR

- Tizanidine (Zanaflex®) 2-4mg q6-8h
  - Dose-dependent hypotension, dry mouth, sedation
  - Monitor LFTs at baseline, 1 month, 3 months
- Cyclobenzaprine (Flexeril®) 5-10mg TID
  - Anticholinergic
  - 5mg=10mg, but less sedation
- Carisoprodol (Soma®) – avoid use!
  - Physical or psychological dependence possible

See S, et al. Am Fam Physician. 2008;78:365-370.
Chou R. Drugs. 2010;70:387-402.

Tramadol (± APAP)

- Combination with APAP provides synergy
  - Lower doses, longer duration, better pain relief
- Caution SSRI, SNRI drugs
- No evidence in acute LBP
- 2nd line agent for moderate-severe chronic LBP
  - Benefits similar to NSAIDs, weak opioids
  - Abuse & withdrawal potential
  - Potential benefit in nociceptive & neuropathic LBP

Ruoff GE. Clin Ther. 2003;25:1123-1141.
Chou R. Drugs. 2010;70:387-402.
Barkin RL. Am J Ther. 2001;8:433-442.
Duffy RL. Prim Care Clin Office Pract. 2010;37:729-741.

Tramadol + APAP Literature

- Tramadol 37.5mg TID – 75mg 4x/day + APAP x 12 weeks vs. placebo in moderate chronic LBP
  - Moderate improvement in chronic LBP
  - Minimal improvement in functional status
- Side effects: nausea (~13%), sedation (~12%), constipation (~11%) generally less vs. opioids
- Promising results, yet little data >12 weeks

Peloso PM, et al. J Rheumatol. 2004;31:2454-63.
Ruoff GE, et al. Clin Ther. 2003;23:1123-1141.
Schnitzer TJ, et al. J Rheumatol. 2000;27:772-778.

Opioids for Acute LBP

- Potent, short-term pain relief vs. placebo
- May be no better vs. NSAIDs or SMRs
- No specific opioid superior
- Effective for nociceptive & neuropathic pain
- 2nd or 3rd line for severe, disabling acute pain not controlled/not likely to respond to APAP/NSAIDs
  - Alternative for high risk of NSAID-induced toxicity
  - Screen for substance abuse prior to initiation
  - Time-limited course (1 month) to determine response

Schnitzer, et al. J Pain Symptom Manage. 2004;28:72-95.
Palangio, et al. Clin Ther. 2002;24:87-98.
Chou R. Ann Intern Med. 2007;147:478-491.
Duffy RL. Prim Care Clin Office Pract. 2010;37:729-741.
Kuijpers T, et al. Eur Spine J. 2011;20:40-50.
Chou, et al. Ann Intern Med. 2007;147:505-514.

Dose-Dependent Side Effects

Complaint	Incidence	Comments
Constipation**	20-40%	Prophylactic bowel regimen
N/V	30%	Resolves days-weeks
Sedation	30%	Usually decreases with time
Dry mouth	25%	Caution dental carries
Dizziness	14%	Risk for falls, caution elderly
Pruritis	13%	Antihistamines?
Hypogonadism	??	Monitor fatigue, libido

Barkin RL. Am J Ther. 2001;8:433-442.
Kalso E, et al. Pain. 2004;112:372-380.
Colameco S, et al. J Am Osteopath Assoc. 2009;109:20-25.
Morlion B. Curr Med Res Opin. 2011;27:11-33.
Chou R, et al. J Pain. 2009;10:113-130.
Jamison RN. Spine. 1998;23:2591-2600.

Chronic Opioid Debate in LBP

- Limited quality data for long-term effectiveness
  - Reduce pain VAS score ~30% vs. placebo
  - Opioid naïve & experienced with moderate-severe pain
- Initially improve pain, but long-term pain relief unproven combined with known side effects
  - Mood improvement ≠ pain improvement
- Do not improve activity or facilitate return to work!
- Generally not appropriate for chronic LBP
  - Requires monitoring of benefit, side effects & misuse

Grady D, et al. Arch Intern Med. 2011;E1-E2.
Kalso E, et al. Pain. 2004;112:372-380.
Deshpande A, et al. Cochrane Database Syst Rev. 2007;18:CD004959.
Duffy RL. Prim Care Clin Office Pract. 2010;37:729-741.
Kuijpers T, et al. Eur Spine J. 2011;20:40-50.
Chou, et al. Ann Intern Med. 2007;147:505-514.

Long-Term Use: What Formulation?

- Chronic LBP ≠ continuous 24/7, unrelenting pain
- More consistent opioid exposure may reduce euphoric effects & reduce abuse potential
- No evidence long-acting formulations are more effective vs. short-acting or PRN doses
  - Continuous exposure may facilitate tolerance
  - Tolerance → dose escalations → endocrine problems
- No reason to switch to long-acting opioids if doing well on a short-acting, PRN regimen

Chou R. Drugs. 2010;70:387-402.

Serious Concerns for Opioids

- Analgesic tolerance
  - increasing doses to attain same pain relief
  - vs. disease progression vs. addiction vs. diversion
- Abuse, misuse, addiction, diversion - INSPECT
  - major depression, psychiatric conditions: more likely to initiate, abuse & not respond to opioids
- Physical dependence
- Overdose – incidence on the rise
  - dose-related, formulation-dependent
  - depression, substance abuse, benzodiazepines

Deyo RA, et al. J Am Board Fam Med. 2009;22:62-68.

Grady D, et al. Arch Intern Med. 2011;E1-E2.

Opioids & Psychosocial Functioning

- Opioids do not improve functional status or facilitate return to work
- Duration >7 days, ↑ dose, >1 prescription within 6 weeks of acute back injury associated with notable increase in work disability at 1 year
- Opioids may:
  - impair cognition
  - contribute to poor treatment outcomes
  - foster reliance on the healthcare system

Jamison RN. Spine. 1998;23:2591-2600.
Franklin GM. Spine. 2008;33:199-204.
Moore JE. Phys Med Rehabil Clin N Am. 2010;21:801-815.

Opioids & Addiction in Chronic LBP

- Most trials not designed to assess
- Few use a validated detection tool
- Poor quality trials used to define prevalence
- Current prevalence estimate of aberrant opioid-related behavior in chronic back pain: 5-24%
- Possible predictors for addiction
  - Additional comorbidities -- Younger age
  - Other substance abuse disorders -- Female

Martell BA. Ann Intern Med. 2007;146:116-127.

Methadone

- Less potential for abuse
- Long, variable half-life 15-60 hours
  - Not used for PRN or breakthrough pain
- No active metabolites
- Variable pharmacokinetics & pharmacodynamics
- High risk for side effects – start low, go slow!
- QTc interval prolongation & arrhythmias
  - Dose-related, concomitant drugs, drug interactions

Chou R, et al . J Pain. 2009;10:113-130.
Grady D, et al. Arch Intern Med. 2011;E1-E2.

My Patient is on Chronic Opioids….

- Evaluate pain, functional status & side effects regularly
- No max dose, but total doses >200mg/day morphine equivalent should permit evaluation of effectiveness
  - Switch to another opioid at reduced dose
  - Taper & discontinue opioid therapy altogether
  - Consider pain specialist referral
- Reemphasize opioid use as a therapeutic trial run
- Lack of alternatives not reason to continue unproven & unsafe chronic opioids when no clear end point exists

Chou R, et al . J Pain. 2009;10:113-130.
Grady D, et al. Arch Intern Med. 2011;E1-E2.

Neuropathic Back Pain Options

- Tricyclic antidepressants (TCAs)
- Duloxetine (Cymbalta®)
- Gabapentin (Neurontin®)
- Pregabalin (Lyrica®)
- Opioids

TCAs – Nortriptyline, Desipramine

- Target neuropathic component of LBP
- Analgesia independent of antidepressant actions
- TCAs might be more effective vs. placebo for chronic pain; no data in acute LBP
  - Mild reduction in pain
  - No benefit on functional impairment, ADL
- Side effects: S.L.U.D.G.E. , sedation, weight gain
- 2nd/3rd line agent for chronic LBP after insufficient relief to other agents

Chou, et al. Ann Intern Med. 2007;147:505-514.
Kuijpers T, et al. Eur Spine J. 2011;20:40-50.
Duffy. Prim Care Clin Office Pract. 2010;37:729-741.
Morlion B. Curr Med Res Opin. 2011;27:11-33.

TCA Prescribing Considerations

- Undiagnosed depression
- Body mass
- Social drug use history & abuse potential
- Baseline cardiac arrhythmias
- Seizure history
- Elderly comorbidities
  - BPH, diabetes, constipation, dementia
  - Beer's Criteria
- Existing medications – tramadol, opioids

Duloxetine

- Quality & overall favorable data for reducing chronic LBP vs. placebo
- Maintained benefit up to 41 weeks duration
- Duloxetine 60mg daily
  - Usually start at 30mg, then increase after 1 week
  - Fewer side effects (nausea, dry mouth) vs. 120mg
- Reliable option for chronic LBP
  - Also useful if underlying depression

Morlion B. Curr Med Res Opin. 2011;27:11-33.
Skljarevski V. Eur J Neurol. 2009;16:1041-1048.
Skljarevski V. J Pain. 2010;11:1282-1290.
Skljarevski V. Pain Med. 2010;11:648-657.

Gabapentin

- Limited data specifically in chronic back pain
- Reduced pain, increased walking distance in lumbar spinal stenosis, lumbar disc hernia vs. placebo
- TID dosing titrated to target 2400mg/day
- Well tolerated
  - Mild, transient sedation, dizziness
- Well-tolerated option with possible benefit in neuropathic chronic back pain

Duffy RL. Prim Care Clin Office Pract. 2010;37:729-741.
Yaksi A. Spine. 2007;32:939-942.
Kasimcan O. Neurol Med Chir (Tokyo). 2010;50:1070-1073.

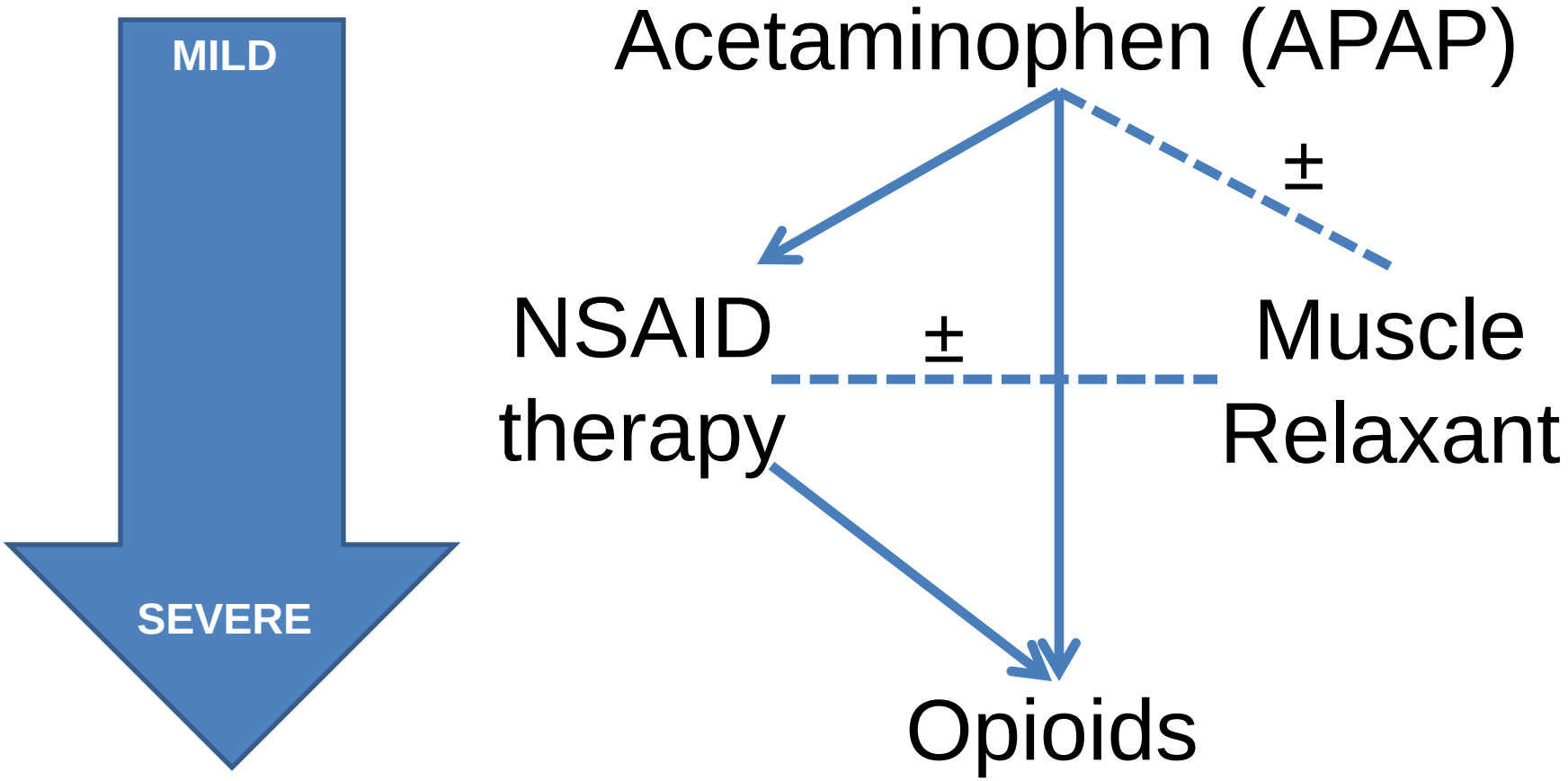
Pregabalin

- No more effective as monotherapy vs. placebo for chronic LBP
- No benefit for refractory neuropathic chronic back pain due to spinal stenosis or radiculopathy

- Not proven useful as monotherapy for chronic LBP

Romano CL. J Orthopaed Traumatol. 2009;10:185-191.
Morlion B. Curr Med Res Opin. 2011;27:11-33.

Acute LBP Treatment Algorithm



Chronic LBP Treatment Algorithm

Acetaminophen (APAP)

NSAID

Tramadol

Opioids

Evaluate use for duloxetine, gabapentin, or TCAs at any severity

Take Home Points

- Screen for depression
- Determine potential for neuropathic pain involvement
  - Assess not only pain intensity, but also pain quality
- Individualize treatment decisions
  - Caution polypharmacy in the elderly
- Meds may reduce pain; little effect on functional status
- Opioids – clear evidence for harm; ?? long-term benefit
- False perceptions & expectations about opioid use drive patient requests for chronic opioids when risk > benefit
- Never overlook non-pharmacologic approaches
- Active comparator, combination therapy , topical & long-term quality safety/efficacy studies desperately needed

Questions

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