Pharmacological and Nonpharmacological Approaches

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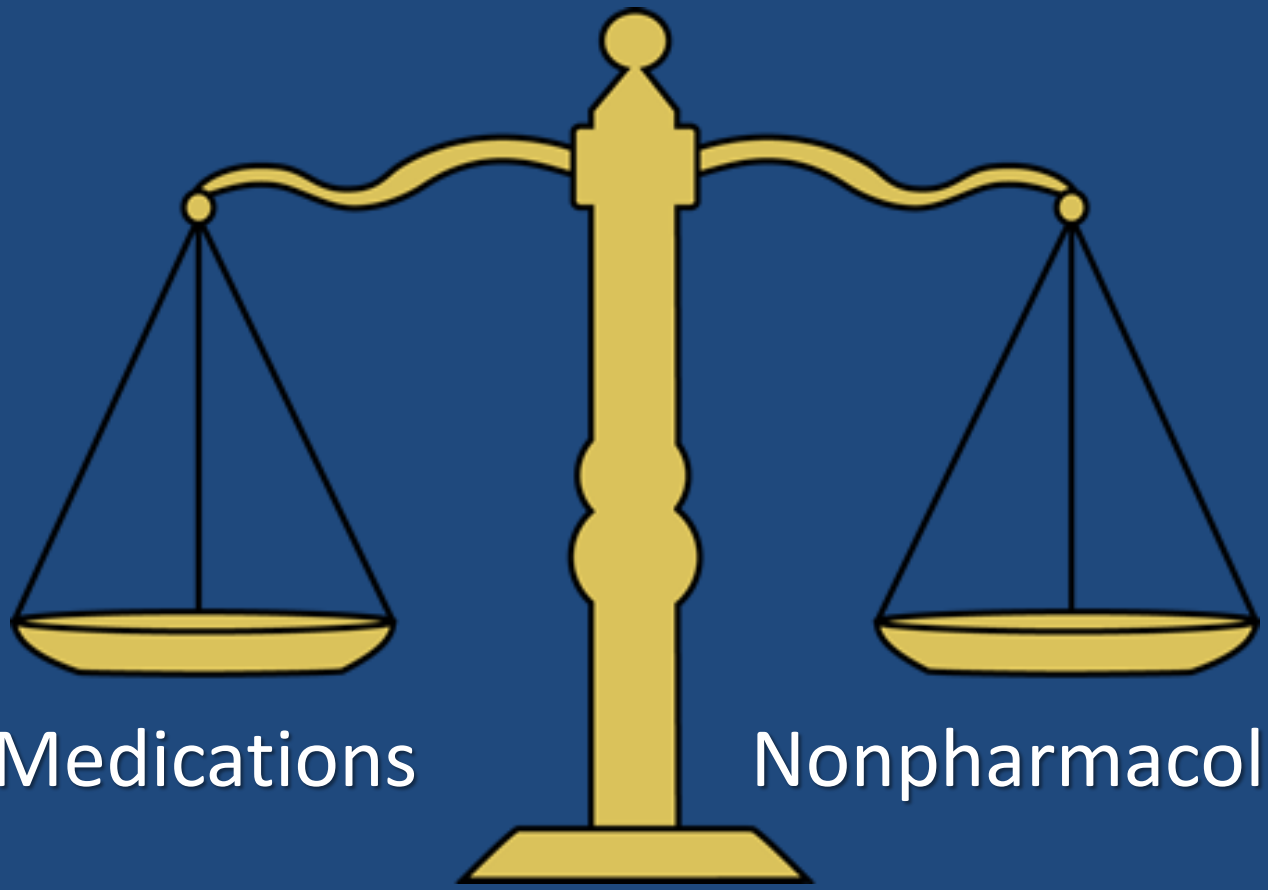
Balanced Treatment Options



Medications

Nonpharmacological

Scope of Presentation

- Chronic (not acute) pain
- Musculoskeletal pain (> 75% of all chronic pain)
- Empiric data (not mechanisms)
- Pharmacological focus is greater because
  - Rest of workshop is on nonpharmacological
  - Historically, a predominant modality
  - Limited evidence for combined modalities

Searching Literature

- Using variety of broad terms did not yield relevant studies → e.g., *nonpharmacological, behavioral, pharmacological, medication, drug, combined, combination, …*
- The few articles or reviews found combined 2 nonpharmacological or 2 pharmacological modalities (rather than pharm + nonpharm)
- More effective search would need to list every medication and nonpharmalogical therapy by specific name (but still would have to determine which were combination trials)

Years Lived with Disability

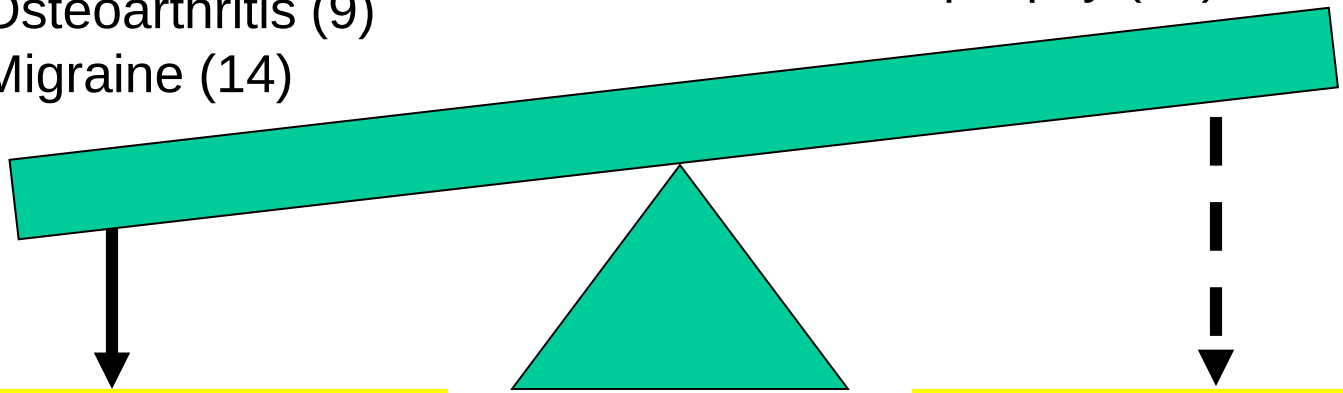
(JAMA 2013;310:591-608)

Depression/Anxiety
6 million YLDs

PAIN

- Low back pain (1)
- Neck pain (4)
- Other musculoskeletal (5)
- Osteoarthritis (9)
- Migraine (14)

- COPD (6)
- Diabetes (8)
- Asthma (10)
- Alcoholism (12)
- Dementia (13)
- Ischemic heart disease (16)
- Stroke (17)
- Hearing loss (19)
- Chronic kidney disease (22)
- Vision loss (26)
- Road injury (27)
- Epilepsy (30)



9.7 million YLDs

8.8 million YLDs

Chronic Pain is Seldom a Single Site

# Pain Sites	2 Pain Trials (n=544)
1	5.9%
2	11.8%
3	18.4%
4	16.4%
5-6	22.0%
≥ 7	20.6%

Kroenke et al, Contemp Clin Trials 2013 and 2018

Analgesic Ladder in 5 Trials

1a	Acetaminophen
1b	Nonsteroidal anti-inflammatory drug (NSAID)
2a	Tricyclic
2b	Muscle relaxant
3a	Gabapentinoids *(gabapentin, pregabalin)*
3b	SNRIs *(duloxetine, milnacipran)*
4a	Tramadol
4b	Opioid
--	Topical *(nsaids, capsaicin, lidocaine)*

Kroenke, JAMA 2009; Kroenke, JAMA 2010; Bair, JAMA Int Med 2015; Krebs, JAMA 2018; Kroenke, J Gen Intern Med 2019

Analgesic Ladder in 5 Trials

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CAMMPS Trial Modifications

Drugs for LBP (Chou, Ann Intern Med 2017)

Medication	# Trials	Effect
NSAIDs	70	Small
Opioids	38	Small
Muscle relaxants	25	Small (acute LBP)
Duloxetine	3	Small
Antidep (TCA, SSRI)	13	No effect
Pregab/gabapent/other	12	No effect
Acetaminophen	10	No effect
Systemic corticosteroids	10	No effect
Benzodiazepines	9	No effect

NSAIDs

Osteoarthritis → a benefit vs. risk balancing act

- Slightly better analgesia than acetaminophen
- One type of NSAID not superior to another
- Cautious use in those with known CV disease or > 2 CV risks; or GI or renal disease

LBP → probably only small effect

- 13 trials, with 6 (n=1354) placebo-controlled
- Small benefit (3.3 points) on 0-100 scale
- All trials were short-term (< 12 weeks)
- NSAID adverse events not greater than placebo

Chou AHRQ 2006 ; Enthoven, Cochrane Review 2016

Opioids for Chronic Low Back Pain

- 13 RCTs (n=3419 participants) studied short-term effects (up to 3 months)
  - Small significant effect (10 points on 0-100 scale)
- 6 RCTs (n = 2605 participants) studied intermediate effects (3-12 months)
  - Small significant effect (8 points on 0-100 scale)
- No RCTs examined long-term (> 12 mo) effects
- No RCTs examined acute LBP
- Half of the trials had > 50% drop-out due to adverse events or lack of efficacy

Shaheed, JAMA Intern Med 2016

Acetaminophen for OA or LBP

- Meta-analysis of 13 trials (5366 patients) in OA of knee/hip (n=10) or LBP (n=3)
- Standardized outcomes to 0-100 scale where 10 points is considered clinically important.
- LBP = no significant effect (similar to placebo)
- OA = only small effect (< 4 points) vs. placebo

Gabapentinoids for Chronic LBP

- Gabapentin: 3 negative placebo-controlled trials
- Pregabalin: 5 negative trials vs. active comparator (n = 2) or as adjunct (n = 3)

Machado, BMJ 2015; Roberts, Ann Rheum Dis 2015; Shanthanna, PLOS Med 2017

Cannabis for Chronic Pain

- 27 chronic pain trials → low strength evidence that cannabis alleviates neuropathic pain, but insufficient evidence for other types of pain.[1]
- Harms (from 11 reviews in population studies) → motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment.
- Most trials were short duration (2-15 weeks) and used synthetic FDA-approved cannabinoids rather than more complex marijuana products
- Results similar in another systematic review.[2]

1) Nugent, Ann Intern Med 2017; 2) Hill, JAMA 2015

Placebo Effects

- Pain responses to placebo range from 30-50%.
- Placebo responses have a biological underpinning: effective placebo manipulations trigger the release of endogenous opioid peptides that act on the same receptors as synthetic opioid drugs such as morphine
- Analgesic responses induced by placebo and by opioid medications are mediated by largely overlapping pain-modulating circuits in the brain
- Since current practice does not condone administration of placebos, taking advantage of both the specific and nonspecific effects of evidence-based treatments doubles the benefit of either effect alone

Kroenke and Cheville, JAMA 2017

Seven Caveats of Nonpharmacological Treatments for Chronic Pain

1. Evidence standards: not as strict as FDA
2. Imperfect placebo: active vs. control cannot be as completely matched (masked) as drug trials
3. Usually requires multiple sessions and, more importantly, patient motivation and "work"
4. Superiority to analgesics is not established
5. Long-term (> 12 mo.) benefits not well-established (as is true of drugs and other pain treatments)
6. Shortage of trained & interested providers
7. Variable reimbursement

Kroenke & Cheville, JAMA 2017

Pharmacological & Nonpharmacological in 4 Trials

Trial	N	SYMP TOMS	TELE-CARE	INTERVENTION	COMPARATOR
SCAMP SUPERIOR	250	Pain Dep	+	Antidepressants + Self-Management	Usual Care
ESCAPE SUPERIOR	240	Pain	+	Optimized Analgesics + CBT	Usual Care
CAMEO EQUIVALENT	260	Pain	+	Optimized Opioids	CBT
CAMMPS SUPERIOR	294	Pain Dep Anx	++	Optimized Analgesics + Mood Treatment + Self-Management	Self-Management

Kroenke, JAMA 2009; Bair, JAMA Int Med 2015;
Bair, in preparation; Kroenke, J Gen Intern Med 2019

Example "Antique" Combination Trials

- Chronic tension headache (n = 203) → Nortriptyline + Stress Management marginally more effective than either as monotherapy (and all were more effective than placebo).
- Fibromyalgia (n = 55) → Guided imagery was effective, and amitriptyline (AMT) → no added benefits. However better placebo control for AMT
- Fibromyaliga (n = 45) → Fitness training + AMT marginally more effective than either alone. However, no placebo/control group.

Holroyd, JAMA 2002, Fors, J Psych Res 2002, Isomeri, J Musculoskel Pain 1993

Challenges with Combined Modality Trials

- Most/all pain treatments have only modest (not strong) efficacy – no "dominant" therapy
- There are numerous medication & nonpharmacological options. Even if one limits possibilities to only 6 drug classes and 6 nonpharm. modalities → 36 trials *(next slide)*
- If study 4 common pain conditions: ≥ 120 trials
- If add devices as modality, even more trials

36 theoretical drug-nonpharm. trials

NONPHARMACOLOGICAL

DRUG

	A	B	C	D	E	F
1	A1	B1	C1	D1	E1	F1
2	A2	B2	C2	D2	E2	F2
3	A3	B3	C3	D3	E3	F3
4	A4	B4	C4	D4	E4	F4
5	A5	B5	C5	D5	E5	F5
6	A6	B6	C6	D6	E6	F6

Future Research on Combined Modalities

- Systematic review of combined modality trials
- Patient preferences regarding pain modalities
- Optimal sequencing of modalities
- Which treatments are generically effective for chronic pain vs. site or mechanism-specific?
- What defines “long-term” effectiveness (is it 12 months or some other duration)?
- Alternative trial designs (SMART, pragmatic, preference-based, propensity-adjusted observational, adaptive, …)

Imperfect treatments do not justify therapeutic nihilism.

A broad menu of partially effective treatment options maximizes the chances of achieving at least partial amelioration of chronic pain.

Kroenke and Cheville
JAMA 2017

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