

Optimizing Analgesic Management

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Outline

1. Urgency of analgesia
2. Non-opioid analgesics
3. Opioids – resetting the pendulum
4. Monitoring pain and its siblings
5. More than analgesics

Annual Clinic Visits in USA for Pain

Back pain	19.8 million
Knee or hip pain	12.6 million
Leg or foot pain	12.3 million
Abdominal pain	12.3 million
Headache	9.6 million
Hand/wrist pain	7.9 million
Chest pain	8.4 million
Neck pain	8.1 million
Shoulder pain	5.5 million

Schappert, National Ambulatory Medical Care Survey (1989)

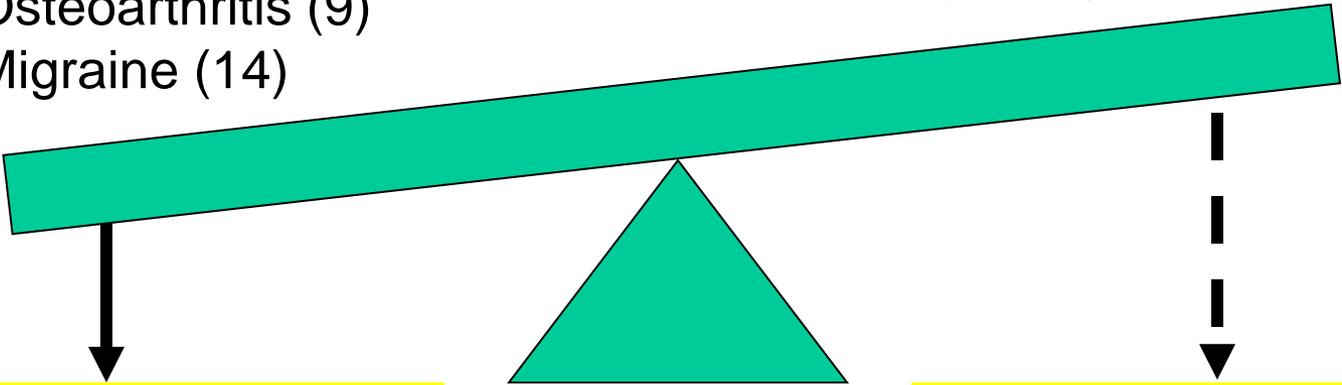
Years Lived with Disability

(JAMA 2013;310:591-608)

Depression/Anxiety
6 million YLDs

- P** • Low back pain (1)
A • Neck pain (4)
I • Other musculoskeletal (5)
N • 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



Pain cannot recollect
When it began – or if
there were
A time when it was
not –
It has no future – but
itself ...

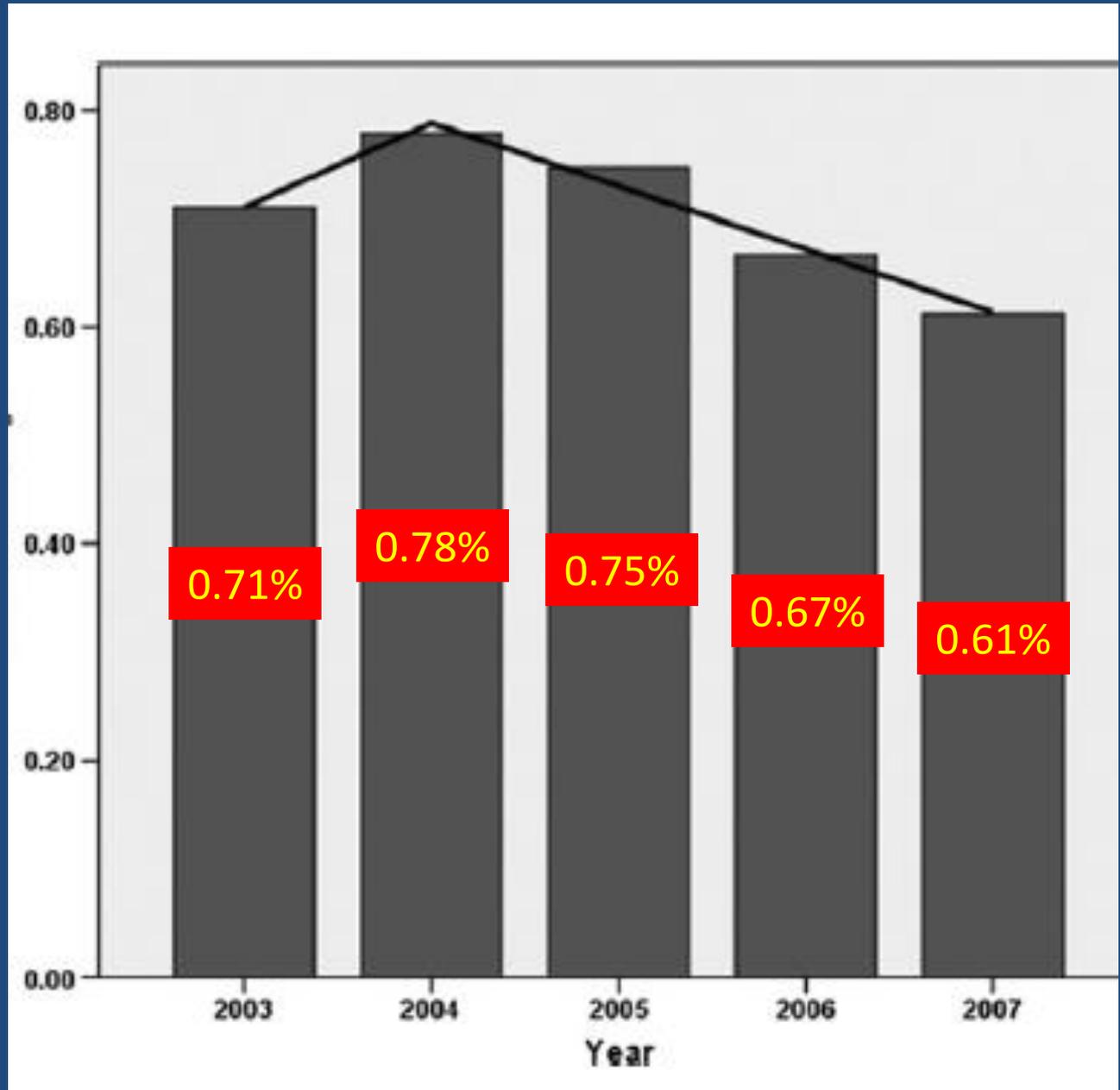
Emily Dickinson, Poem 650

Pain by the Numbers

- 30% of U.S. adults (116 million) have **chronic pain**
- 20% of all **outpatient visits** and 10% of all **drug sales**
- 80% of patients undergoing **surgery** have post-operative pain; < 50% report adequate pain relief.
- 60% of those visiting **emergency department** with acute pain receive analgesics (median = 1½ hr.); 74% are discharged in moderate to severe pain.
- 62% of U.S. **nursing home** residents report pain
- 60% of women report severe pain with first **child birth**
- 1 trillion dollars annual **costs** to developed countries

Institute of Medicine, 2011; Max, National Rev Drug Discov 2008

**Pain
Research
Funding as
% of NIH
Total Budget
(2003-2007)**



Bradshaw
J Pain 2008

Pain is not ...

- Fatal
- Visible
- Reimburseable
- Excisable
- Eradicable

nor efficient or rewarding to treat

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Current Status of Pain Treatments



Analgesic Ladder: Fragile Rungs

1	Acetaminophen/NSAID
2a	Tricyclic
2b	Muscle relaxant
3a	Gabapentinoids (<i>gabapentin, pregabalin</i>)
3b	SNRIs (<i>duloxetine, milnacipran</i>)
4	Tramadol
5	Opioid
--	Topical (<i>nsaids, capsaicin, lidocaine</i>)

Six Classes in 4 Common Conditions

#	Drug	LBP	OA	FM	Neuro
1	Acetaminophen/NSAIDs	+	+	+	+
2a	Tricyclics			+	+
2b	Muscle relaxants	+		+	
3a	Gabapentinoids			+	+
3b	SNRIs			+	+
4	Tramadol	+	+	+	+
5	Opioids	+	+		+
--	Topical analgesics	+	+		+

3 Classes for 2 Conditions

#	Drug	Fibro- myalgia	Neuro- pathic
2a	Amitriptyline	+	+
	Nortriptyline	+	+
3a	Gabapentin	±	++
	Pregabalin	++	++
3b	Duloxetine	++	++
	Milnacipran	++	
	Venlafaxine	±	±

Acetaminophen

- Meta-analysis of 13 trials (5366 patients) in OA of knee/hip (n=10) or LBP (n=3)
- High doses: 4000 mg (n=10) or 3000 mg (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
- Risk ratio for 1.5 ↑ transaminases = 3.8 (however, not clear if clinically important).
- Pooling of 8 cohort studies → 28% ↑ mortality, and 2x ↑ risk of CV events, GI bleeds, renal ↓

Machado, BMJ 2015; Roberts, Ann Rheum Dis 2016

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
- Naprosyn may have slightly less CV risk

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

Headache (Tension vs. Migraine)

- Up to one-third of population have tension headache, and 10% report migraine.
- Classic migraine (only 20% of migraine) has aura, most a visual prodrome, such as blind spots (scotomas), zigzag patterns (fortification spectra), or flashing lights (scintilla).
- Migraine without aura includes at least 2 of:
 - a) nausea; b) light sensitivity; c) interference with activities with some of attacks
- Tension HA includes at least 2 of:
 - a) bilateral HA; b) nonpulsating; c) not interfering with activities; d) only mild to moderate in intensity

Headache Pharmacotherapy

	Migraine	Tension
Abortive <ul style="list-style-type: none">• Step 1• Step 2• Step 3	NSAID Triptan [Opioid]	Acetamin./NSAID
Preventive <ul style="list-style-type: none">• Step 1• Step 2• Step 3	Beta-blocker Topiramate Divalproex	Acetamin./NSAID

Chronic Daily Headache

- Headache > 2 weeks/month for > 3 months
- Often headache upon awakening that responds only transiently to analgesic, leading to vicious cycle of increasing analgesic use
- Common reversible cause is medication overuse headache (MOH)
- MOH risk ↑ if analgesics taken > 2-3 times/wk
- MOH greatest with opioids or combination meds with butalbital or caffeine; intermediate with triptans; and lowest with NSAIDs.

3 CAM Medications

	Hyaluronic Acid	Glucosamine and/or Chondroitin
Route	Intra-articular	Oral
Evidence	> 50 trials	> 20 trials
Beneficial?	YES	NO

Bannuru, Osteoarthritis Cartilage 2011; Miller & Block 2013;
Wandel, BMJ 2010; Wu, Int J Clin Practice 2013

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Opioid “Storm”



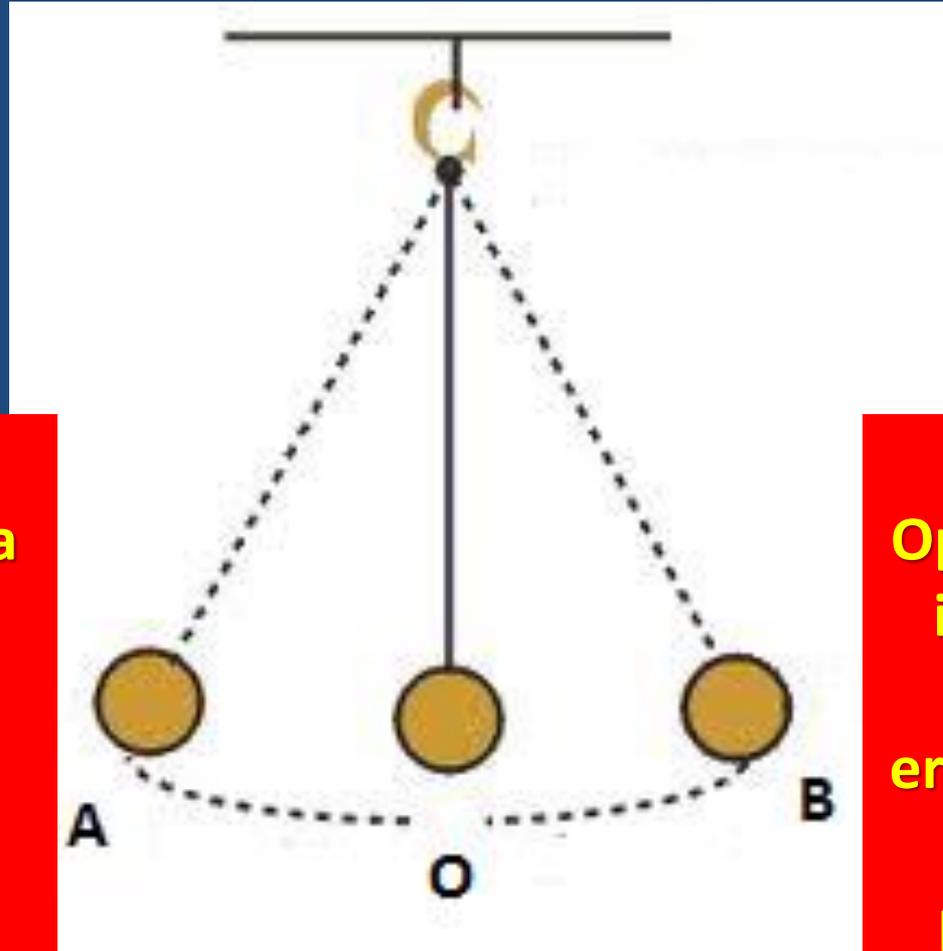
Opioid “dark side”

- Addiction
- Diversion
- Adverse effects
- Overdose deaths

On the other hand

- Non-opioid analgesics often fail
- Many patients do not abuse opioids
- Opioids help some

Opioid Pendulum



1990's
Chronic pain is a disease that warrants aggressive and humane treatment

2016
Opioid "epidemic" is a plague that must be eradicated even at the cost of persistent pain

Opioid Use Problems

Opioid Use Disorder (OUD)

- Inability to reduce or control use resulting in social problems
- Failure to fulfill roles obligations at work, school, or home

Physical Dependence

- Withdrawal symptoms if opioid is discontinued

Tolerance

- Diminished analgesic effects requiring \uparrow dose

Misuse/Aberrant Behavior

- Using additional opioids than those prescribed
- Failed urine drug screen
- Diverting/selling opioids
- Lost/stolen prescriptions
- Opioids from ≥ 1 provider

Is opioid epidemic an exaggeration?

- 143 million enrollees in Market Scan U.S. pharmacy database (2003-2013)
- 27.9 million (20%) received a 1st opioid prescription at age 14 or older
- 10.3 million had 12 months continuous enrollment before script and no cancer diagnosis
- Percent going to long-term opioid use by 3 yrs.
 - 2.1% by liberal definition (90 day supply in 6 mo)
 - 1.0% by stricter definition (183 day supply in 6 mo)

Fatal Opioid Overdose Risk

compared to 1 to < 20 mg morphine per day

Daily Dose & Risk	Morphine	Hydrocodone	Oxycodone
Medium dose (mg)	≥ 50	≥ 50	≥ 35
NNH (ARI)	667 (0.15% ARI)		
Higher dose (mg)	≥ 100	≥ 100	≥ 70
NNH (ARI)	400 (0.25% ARI)		
Safer ceiling dose of usual formulations	30 mg BID	10 mg QID	10 mg TID

NNH = number needed to harm. ARI = absolute risk increase

Dowell, CDC Opioid Guidelines, JAMA 2016

Opioid Risk Mitigation Strategies

1. Aim for lower dose use (< 50-100 MMED/day)
2. Opioid agreement/contract (at initiation)
3. Opioid risk screening tool (at initiation)
4. Urine drug screen (periodic)
5. Prescription drug monitoring program [PDMP] data review (periodic)
6. Naloxone co-prescription (in high-risk patients)
7. Treat OUD with buprenorphine or methadone
8. Treat comorbid psychiatric conditions

Opioid Use Allowed in CDC Guidelines

- **Palliative** & end-of-life care (cancer, other)
- Chronic pain that has failed non-pharmacologic and non-opioid analgesic therapy (“**last resort**”)
 - Therapeutic trial → stop if pain/function not improved
 - Keep MME to ≤ 50 mg/day (ideally) and rarely ≥ 90
 - Try to avoid methadone and fentanyl
- Cautious, short-term use in **acute pain** (injuries, postoperative, dental pain, etc.)
 - Limit duration to $< 3-7$ days

Other Opioid Issues

- Conditions where chronic opioid use should generally be avoided: **headache & fibromyalgia**.
- Fatal overdose risk is greater with **methadone** and co-administration of **benzodiazepines**
- Do not start with long-acting opioids.
- **Switching opioids** → use 30-50% lower MME dose to start due to pharmacokinetic variability
- When **tapering**, ↓ dose by 10% q 1-4 weeks.

Management of Chronic Pain in the Aftermath of the Opioid Backlash

Kroenke K, Cheville AC.
JAMA 2017 (May 11)

1. 5 to 8 million people in US use long-term opioids
2. Advocacy for liberal opioid use began in 1990's
3. Consensus guidelines in the past 5 years still included opioids as a later step in the analgesic ladder.
4. NIH and CDC guidelines recognize opioids as a viable "last resort" option in selected patients.
5. Clinical trials show modest analgesic effect of opioids
6. Long-term efficacy not shown for most pain treatments
7. Given small analgesic effect of most pain treatments, the few classes of analgesic options, and the frequent need for combination therapy, eliminating any class of analgesics from the current menu is undesirable.

Opioids Out, Cannabis In

Negotiating the Unknowns in Patient Care
for Chronic Pain

Choo, Feldstein, Lovejoy
JAMA 2016;136:1763-64.

From Kroenke & Chevillie, JAMA 2017

1. Emerging advocacy movement for greater use of marijuana for chronic pain parallels changing statutes regarding medical use and also legalization.
2. However, small number of trials evaluating marijuana for chronic pain have
 - a. Typically used synthetic cannabinoids rather than more complex marijuana products
 - b. Shown modest benefits
 - c. Had limited follow-up of 2-15 weeks
 - d. Included neuropathic more often than musculoskeletal pain
3. Thus, clinicians must be careful of replacing the opioid epidemic with a marijuana epidemic

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PEG Pain Scale (3-item BPI)

1. What number best describes your pain on average in the past week:

0 1 2 3 4 5 6 7 8 9 10

No pain

Pain as bad as
you can imagine

2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0 1 2 3 4 5 6 7 8 9 10

Does not
interfere

Completely
interferes

3. What number best describes how, during the past week, pain has interfered with your general activity?

0 1 2 3 4 5 6 7 8 9 10

Does not
interfere

Completely
interferes

Surgeon General's Mailing to 2.3 million prescribers

TURN
THE
TIDE



PRESCRIBING OPIOIDS FOR CHRONIC PAIN

ADAPTED FROM CDC GUIDELINE

Opioids can provide short-term benefits for moderate to severe pain. Scientific evidence is lacking for the benefits to treat chronic pain.

IN GENERAL, DO NOT PRESCRIBE OPIOIDS AS THE FIRST-LINE TREATMENT FOR CHRONIC PAIN (for adults 18+ with chronic pain > 3 months excluding active cancer, palliative, or end-of-life care).

BEFORE PRESCRIBING

1

ASSESS PAIN & FUNCTION

Use a validated pain scale. Example: PEG scale where the score = average 3 individual question scores (30% improvement from baseline is clinically meaningful).

Q1: What number from 0 – 10 best describes your PAIN in the past week?
(0 = "no pain", 10 = "worst you can imagine")

Q2: What number from 0 – 10 describes how, during the past week, pain has interfered with your ENJOYMENT OF LIFE? (0 = "not at all", 10 = "complete interference")

Q3: What number from 0 – 10 describes how, during the past week, pain has interfered with your GENERAL ACTIVITY? (0 = "not at all", 10 = "complete interference")

SOAAP Screener

Score ≥ 4 = 67% PPV of Aberrant Opioid Behavior at 6 mo.

How often ...	NEVER	SELDOM	SOMETIMES	OFTEN	VERY OFTEN
Do you have mood swings?	0	1	2	3	4
Do you smoke a cigarette within an hour after you wake up?					
Have you taken a medication other than the way it was prescribed?					
Have you used illegal drugs (for example, marijuana, cocaine, etc.) in the past 5 years?					
Have you had legal problems or been arrested in your lifetime?					

PHQ-4

Over the <u>last 2 weeks</u> , how often have you been bothered by the following problems?	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
Feeling nervous, anxious, or on edge				
Not being able to stop or control worrying				
Little interest or pleasure in doing things				
Feeling down, depressed, or hopeless				

GAD-2

PHQ-2

Score ≥ 3 on subscale suggests possible anxiety (GAD-2) or depression (PHQ-2)

AUDIT (Alcohol Screener)

	0	1	2	3	4
How often do you have a drink containing alcohol	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
How many standard drinks containing alcohol do you have on a typical day	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
How often do you have 6 or more drinks on one occasion	Never	Less than monthly	Monthly	Weekly	Daily or almost daily

Score ≥ 4 in men (≥ 3 in women) = heavy/hazardous use

3 Criteria for Changing Treatment

1. Pain score → **Not improving***
2. Global → **Unchanged or Worse**
3. Treatment change desired? → **Yes**

* Improved = 30% decrease in pain score or 1-2 point change on a 0-10 point scale (NRS, PEG, BPI)

Chronic Pain is Seldom a Single Site

# Pain Sites	% Patients
1	7.6%
2	12.4%
3	19.2%
4	18.0%
5-6	16.8%
7-10	15.2%
≥ 11	10.8%

SCOPE Trial (n = 250), Kroenke, JAMA 2014

SPADE Symptom Cluster

- **S**leep
- **P**ain
- **A**nxiety
- **D**epression
- **E**nergy

SPADE Prevalence in Primary Care

PROMIS 4-item symptom scale T-score ≥ 55

SPADE Symptoms	Chronic Pain (n=250)	SPADE screen + (n=300)
0	9.6 %	5.3 %
1	20.0 %	11.0 %
2	15.6 %	13.0 %
3	22.8 %	18.0 %
4	11.6 %	21.3 %
5	20.4 %	31.3 %

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Nonpharmacological Treatments

Strongest Evidence

- Cognitive-behavioral therapy (CBT)
- Exercise
- Pain self-management

Moderate Evidence

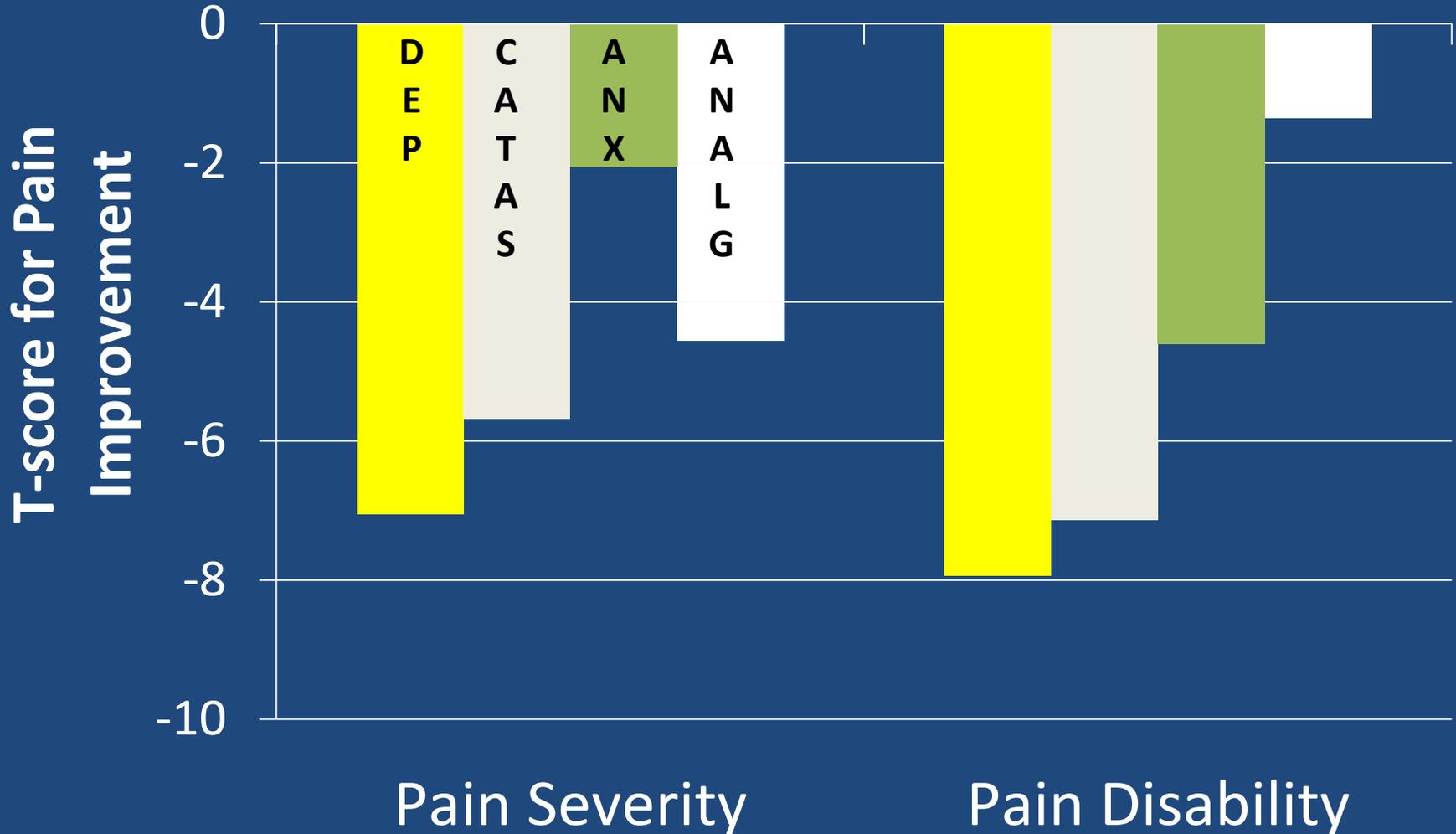
- Acupuncture
- Chiropractic
- Massage
- Mindfulness/Meditation/Acceptance
- Yoga and Tai Chi

Six 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. Shortage of trained & interested providers
6. Variable reimbursement

Predictors of Pain Improvement

■ ↓ Depression ■ ↓ Catastrophizing ■ ↓ Anxiety ■ Analgesics



Scott, Kroenke, et al, J Pain 2016

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, JAMA 2017

Editorial on Positive Trial on MBSR and CBT for Chronic Low Back Pain

Although some of the effects of each behavioral intervention may derive from nonspecific factors such as therapist attention, for patients it really may not matter if the intervention helps their condition...

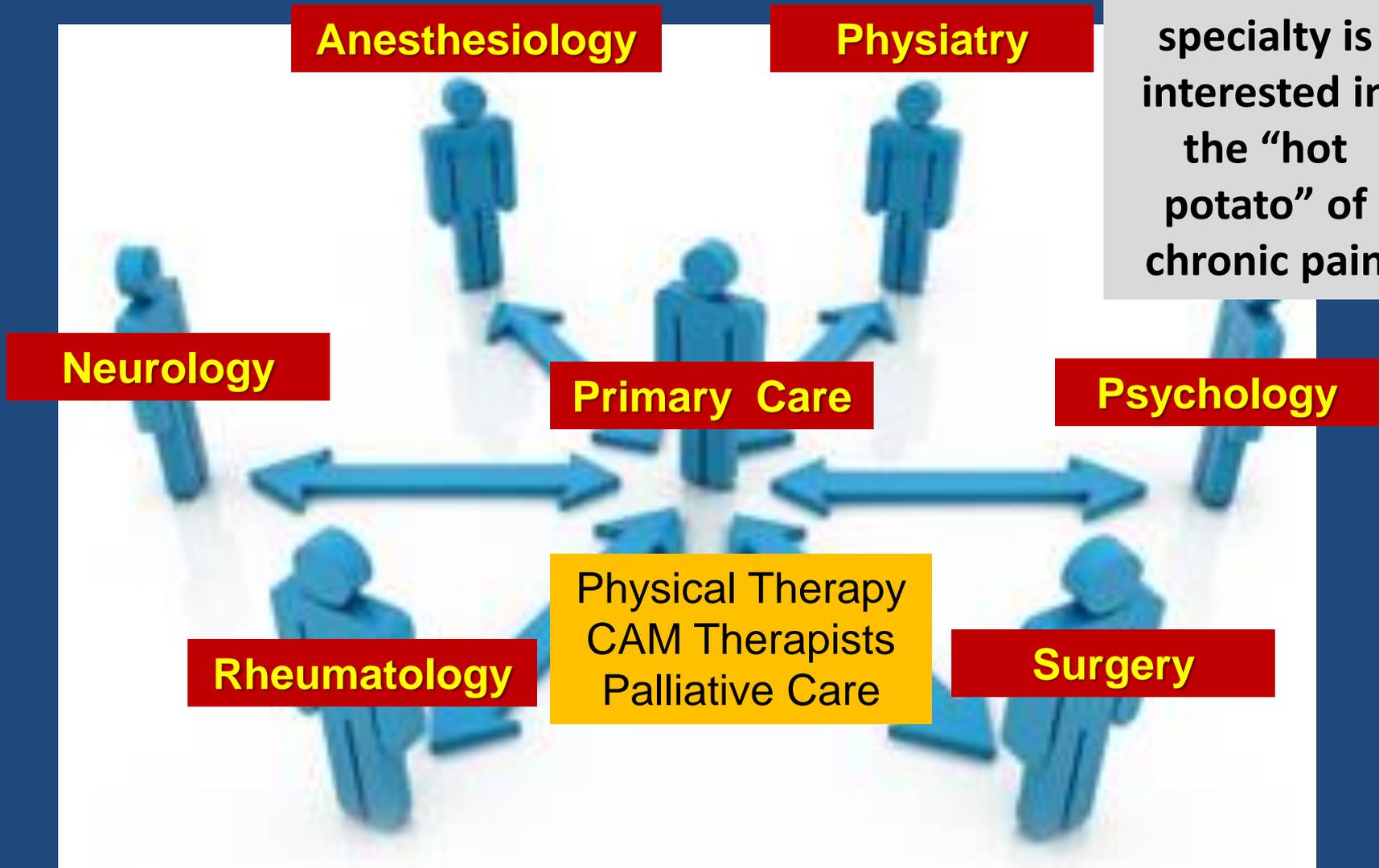
Although understanding the specificity of treatment effects, mechanisms of action, and role of mediators are important issues for researchers, they are merely academic for many clinicians and their patients.

For patients with chronic painful conditions, options are needed to help them live with less pain and disability now.

Goya, JAMA 2016

Perplexity of Pain Referrals

Only a minority of those in each specialty is interested in the “hot potato” of chronic pain



10 Pain Effectiveness Trials by our VA Group

Trial	PI	N	Fund-ing	MEDS	BE-HAV	TELE-CARE	KEY TREATMENTS
SCAMP	KK	250	NIH	✓	✓	+	Antidep + Self-Mgt
INCPAD	KK	405	NIH	✓		++	Analgesics
SCOPE	KK	250	VA	✓		++	Analgesics
ESCAPE	MB	240	VA	✓	✓	+	Analgesics + CBT
CAMEO	MB	260	VA	✓	✓	+	Opioids vs. CBT
SPACE	EK	240	VA	✓		+	Opioids vs Analges
CAMMPS	KK	294	VA	✓	✓	++	Analges +Mood Rx
POYSE	MB	300	VA		✓		Exercise vs. Yoga
ECLIPSE	MM	215	VA		✓	+	Peers with Pain
TOMCATT	MB	460	VA		✓		Massage

SCOPE Trial Design

Musculoskeletal Pain in Primary Care

stratified randomization

Opioid use (yes or no)

(n = 124)

(n = 126)

**Analgesic
Optimization**

**Usual
Care**

Outcome Assessment at 1, 3, 6, and 12 months

Key Findings in SCOPE Trial

- Strong intervention effect on pain
 - Twice as many in intervention group were a pain responder (52% vs. 27%) at 12 months
 - Number needed to treat = 4
 - 1-point difference on BPI. Effect size = 0.53
 - One-third in usual care worsened over 12 months
- Very few patients (< 4%) started on opioids (one-third who were on opioids at baseline stayed on stable dose)
- Good adherence and satisfaction with automated and nurse components of intervention

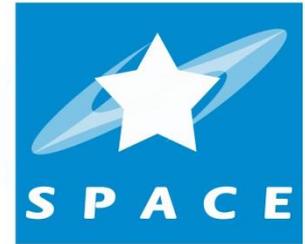
Kroenke et al, JAMA 2014

Effectiveness of opioid therapy vs. non-opioid medication therapy for chronic back & osteoarthritis pain over 12 months

A pragmatic randomized trial

Erin Krebs, Siamak Noorbaloochi, Matthew Bair, Beth DeRonne, Amy Gravely, Agnes Jensen, Kurt Kroenke

Interventions



- All medications in both arms on VA formulary
- Each arm included 3 medication steps

Table: Example medications within arms

	Opioid arm	Non-opioid arm
Step 1	Morphine IR* Hydrocodone/APAP	Acetaminophen* Naproxen
Step 2	Morphine SR Oxycodone SA	Nortriptyline Capsaicin topical Gabapentin
Step 3	Fentanyl transdermal	Tramadol

* Preferred initial medication selection

Stepped Care

Use lowest rung that works



- Specialty physician
- Primary care physician
- Non-MD health care professional (nurse, pharmacist, psychologist, physical therapist, CAM provider,)
- Peers with symptom (individual or group)
- Self-management

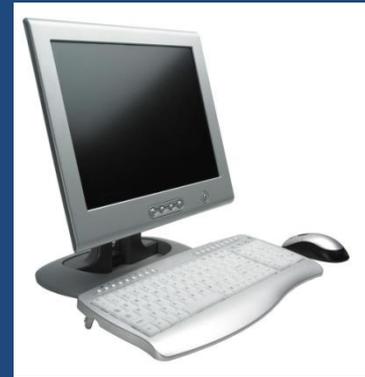
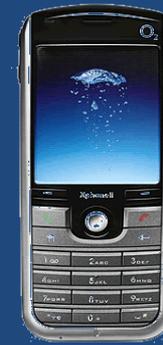
Site of Care

stay at home as much as possible

1. Automated

a) Internet/web-based

b) Interactive voice-
recorded (IVR) calls



2. Telecare

3. Office visits to health care



Value Added by Automation

- Asynchronous data gathering (convenient to patient's schedule)
- Simple data can be gathered that does not require human interview
- Reduces unnecessary phone calls
- Patients like the extra attention
- Simple treatments can be added (education, self-management, ...)

Going to Scale

- Increasing patient participation in & access to evidence-based nonpharmacological therapies
- Team-based/care management/telecare approach to chronic pain. Options include

PACT Team	Pain specialist(s)
Telehealth nurse	TIDES for pain

- Stepped care analgesic strategy, including a decision – is there *any* role for opioid use?



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.

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**I'm very brave
generally
Only to-day I
happen to have a
headache.**

Lewis Carroll

*Through the
Looking Glass*