The Aftermath of the Decade of Pain:
Alternatives to Opioids in Chronic Pain Management

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Disclosures

- No relevant financial disclosures
- I will discuss off-label uses of antiepileptics, antidepressants, NSAIDs, acetaminophen, and topical products for the management of chronic pain

Objectives

- Review adjuvant medications used in chronic pain
- Describe relevant pharmacokinetic information, concurrent medications and disease states that impact the tapering of opioids

2000-2010

- Congress designated as the Decade of Pain
- Opioid prescriptions increased from 76 million in 1991 to 219 million in 2011
- Increase in opioid prescriptions has been in parallel to opioid overdose and prescription pain medication addiction treatment increases

Reuben DB et al. Ann Int Med 2015;162:295-300

Recommendations for opioid use in Chronic pain

Previous statements

- "Healthcare professionals (HCPs) who prescribe opioids for the treatment of pain should use clear and reasonable medical judgment to establish that a pain state exists and to determine whether opioids are an indicated component of treatment. "-APS 2004 Public Policy Statement on the Rights and Responsibilities of Healthcare Professionals in the Use of Opioids for the Treatment of Pain
- "there is consensus among pain specialists that opioid therapy is appropriate for selected patients with CNCP and can provide sustained benefit to such patients." –ANN; Pain 1986;25:171–186.

Recent Statements

- "Although evidence is limited, an expert panel convened by APS and AAPM concludes that COT can be an effective therapy for **carefully** selected and monitored patients with CNCP. However, opioids are also associated with potentially serious harms…." –Chou et al. J Pain. 2009; 10: 113-130
- "the risk of death, overdose, addiction or serious side effects with prescription opioids outweigh the benefits in chronic, non-cancer conditions such as headache, fibromyalgia and chronic low back pain." –AAN; Neurology 2014;83:1277-1284

Adjuvant medications

Alternatives to opioids

Type of pain should influence management

- Nociceptive (tissue damage or inflammation)
  - Pain: Acute, Arthritis, Back pain, Cancer
  - Pharmacological treatment options: NSAIDS, Acetaminophen, muscle relaxants, Opioids
- Peripheral neuropathic (damage or dysfunction of peripheral nerves)
  - Pain: DPN, PHN
  - Pharmacological treatment options: antidepressants, anticonvulsants, topical anesthetics
- Centralized (dysfunction in processing pain)
  - Pain: Fibromyalgia, Migraines, CRPS
  - Pharmacological treatment options: antidepressants, anticonvulsants, others

NOCICEPTIVE PAIN

SPINE Volume 33, Number 2, pp 199–204
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Early Opioid Prescription and Subsequent Disability Among Workers With Back Injuries

The Disability Risk Identification Study Cohort

Gary M. Franklin, MD, MPH,*† Bert D. Stover, PhD,* Judith A. Turner, PhD,‡§
Deborah Fulton-Kehoe, MPH, PhD,* and Thomas M. Wickizer, PhD¶

- Prospective study with work related back injuries 9n=1843)
- One third received opioid prescription within 6 weeks
- At 1 year 14% of sample on diasability
- Early prescription for opioid in acute occupational low back injury associated with increased risk or work disability at 1 year
- odds ratio 2.2; 95% confidence interval, 1.5–3.1
  - Adjustment for pain severity, function and initial injury severity

Analgesics – NSAIDS, Acetaminophen

FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes

- NSAIDs including Coxibs
  - Meta-analsyis of coxibs, diclofenac, naproxen, and ibuprofen.
    - Increased vascular events (not naproxen, ibuprofen increased major coronary events but not vascular), increased vascular deaths (not naproxen, increased non-significantly by ibuprofen)
    - Hospitalization risk due to heart failure risk ~doubled for all agents
    - Gastrointestinal complications increased significantly by all, greatest effect with ibuprofen and naproxen
  - Long-term administration; benefits must be weighed with risks
- Acetaminophen
  - Majority of guidelines recommend acetaminophen as first line treatment in low back pain
  - Meta-analysis of RCTs with acetaminophen to no treatment, placebo or another treatment for the treatment of low back pain
    - Only 7 eligible trials, 1 chronic pain of 4 week duration
    - No trial reported stat sign difference in favor of acetaminophen

Lancet 2013; 382:769-79
Davies RA et al. Eur Spine J. 2008;17:1423-1430

Muscle relaxants

- Most of studies are short duration (2-8 weeks) with the focus of acute pain
- FDA approvals for spasticity (baclofen, tizanidine, dantrolene) or musculoskeletal conditions
- Insufficient evidence to evaluate safety or efficacy between agents for musculoskeletal
- Greatest head to head trials is for cyclobenzaprine vs diazepam and results are inconclusive
  - Carisoprodol is metabolized to meprobamate and is most associated with abuse and addiction
  - Cyclobenzaprine is structurally similar to TCAs; studies to support 5 mg= 10 mg with fewer ADRs
  - Tizanidine is a centrally acting alpha 2 receptor agnonist

Chou R, Peterson K. Drug Class Review on Skeletal Muscle Relaxants. Final Report. Portland (OR): Oregon Health and Science University; 2005.

Antidepressants?

- Duloxetine FDA approved for musculoskeletal chronic pain, generally Low back pain (LBP) and osteoarthritis(OA)
  - Mechanism unknown – CNS pain mechanisms such as loss of descending analgesic activity, central sensitization may play a role
  - 3 -12 week RCT in chronic LBP
    - 60 mg and 120 mg studied, only 60 mg showed statistically significant benefits for decreased pain and QOL measures, 120 mg associated with greater discontinued due to ADRs
  - 2-13 weeks studies of OA of knee
    - 60-120 mg studied, both doses showed statistically significant benefits for decreased pain and QOL measures

Smith HS et al. Therap Clin Risk Manag. 2012:8 267-277.

Herbal/ supplements

- Chronic pain is the leading reason for complimentary medicine use
- Frequently used for chronic pain indication: CoQ 10, Vitamin D, Fish Oil, Glucosamine, Alpha Lipoic Acid, Bromelain, acetyl L-carnitine, others
- Tumeric and curcumin
  - Major ingredient in curry powder
  - Osteoarthritis – evidence of improved pain and functionality with reduced use of NSAIDS; compared to ibuprofen 400 mg bid and found to be comparable
  - Mechanism: Curcumin seems to have anti-inflammatory activity, possibly by inhibiting cyclooxygenase-2 (COX-2), prostaglandins, leukotrienes, and other cytokines involved in pro-inflammatory signaling pathways

Austin JA. JAMA. 1998.279:1548-53
Kuptniratsaikul V et al. J Altern Complement Med 2009;14:891-7
Belcaro G et al. Al Med Rev 2010:15:337-14

PERIPHERAL NEUROPATHIC PAIN (NP)

Stepwise Pharmacological Management for NP

Step 1: establish diagnosis; treat cause of NP; identify relevant comorbidities
Step 2: initiate symptom treatment with one or more of the following:
-secondary-amine TCA or an SNRI
-Calcium channel α2-δ ligand
-for localized NP, topical lidocaine used alone or in combination with one of the other 1st line agents
-for acute NP, opioid in addition to 1st line agents during dose titration
Step 3: reassess pain and QOL measures
-if substantial pain relief and tolerable ADRs continue treatment
-if partial pain relief, add one of the other 1st line agents
-if no or inadequate pain relief at target dose, switch to alternative 1st line agent
Step 4: if trials of 1st line agents alone or in combo fail, consider 2nd or 3rd line agents

Modified from Dworkin RH et al. Mayo Clin Proc 2010 Mar;85(3 suppl) S3-14..

Antidepressants

- TCAs (Typically studied doses of 25-100 mg amitriptyline equivalent)
  - Most commonly studied amitriptyline, nortriptyline, desipramine
  - Most trials smaller samples and several decades old
- SNRIs
  - Duloxetine, venlafaxine, milnacipran
- SSRIs
  - Multiple studies demonstrating weak analgesic effect, questionable clinical relevance

Anticonvulsants

- 1st line: Calcium channel α2-δ ligand agents
  - Gabapentin
  - Pregabalin – trials exclude patients who fail gabapentin
- 2nd/3rd line:
  - Lamotrigine, + trial central post-stroke, DPN, - trials for mixed neuropathic, MS
  - Topiramate, 3 – trials for DPN
  - Lacosamide, oxcarbazepine (conflicting results in DPN trials)

Finnerup NB et al. Pain. 2010; 150:573-581

Antidepressant vs anticonvulsant comparator trials

- Six comparator trials with TCAs and gabapentin or pregabalin for NP
  - No differences
  - Equal number of patients had a 50% or moderate pain relief (49% TCA vs. 43% G/P)
  - No difference in patients withdrawn due to ADRs (14.3% TCA vs. 10.5% G/P)

Finnerup NB et al. Pain. 2010; 150:573-581

- Combination approach in DPN
- Response to 8 weeks at either 60 mg/day of duloxetine or 300 mg/day of pregabalin then randomized to combo of two drugs compared to either 600 mg of pregabalin or 120 mg duloxetine per day
  - Combo not significantly superior but considered to be effective, safe, well tolerated
  - Limitation of short duration = 8 weeks

Topical agents

- 1st line option: Lidocaine patches – approved for PHN but often used as a supplement for osteoarthritis or low back pain
  - 3 published + trials PHN
  - 2 – trials for peripheral nerve injruy
  - Most appropriate for well-localized NP
  - $$
- New compounded topical formulas (multi-ingredients)
  - Often not covered by insurance and costly
  - Lack of RCTs

Branvold A and Carvalho M. J Gen Practice. 2014;2:2-6.

CENTRALIZED PAIN

FDA approved Fibromyalgia Medications: A comparison

Hauser W et al. *J of Pain;* 2010; 6.

- Current evidence based, placebo-controlled randomized trials:
  - Duloxetine – 4 trials, 12-28 week (20 mg - 120 mg)
  - Milnacipran – 3 trials, 12-27 weeks (25-200 mg)
  - Pregabalin – 4 trials, 8-14 weeks (150-600 mg)

FDA approved Fibromyalgia Medications: A comparison

Hauser W et al. *J of Pain;* 2010; 6.

- Comparison of efficacy:
- Duloxetine:
  - Effects were small, statistically significant improvement:
    - Pain benefit (NNT = 7.2)
    - Sleep disturbances
    - Depressed mood
    - Health-related quality of life
  - Not significant differences for improvement:
    - Fatigue

FDA approved Fibromyalgia Medications: A comparison

Hauser W et al. *J of Pain;* 2010; 6.

- Comparison of efficacy:
- Milnacipran:
  - Effects were small, statistically significant improvement:
    - Pain benefit (NNT = 19)
    - Fatigue
    - Depressed mood
    - Health-related quality of life
  - Not significant differences for improvement:
    - Sleep disturbance

FDA approved Fibromyalgia Medications: A comparison

Hauser W et al. *J of Pain;* 2010; 6.

- Comparison of efficacy:
- Pregabalin:
  - Effects were small, statistically significant improvement:
    - Pain benefit (NNT = 8.6)
    - Sleep disturbances
    - Health-related quality of life
    - Fatigue (very small effect)
  - Not significant differences for improvement:
    - Depressed mood

Opioid Discontinuation: It's an art, not a s

SYMPOSIUM ON PAIN MEDICINE

MAYO CLINIC

Tapering Long-term Opioid Therapy in Chronic Noncancer Pain: Evidence and Recommendations for Everyday Practice

Chantal Berna, MD, PhD; Ronald J. Kulich, PhD; and James P. Rathmell, MD

= ~~Lack of solid evidence for tapering~~

= ~~Taper speed advise:~~

- ~~25% reduction of previous daily dose to prevent acute withdrawal~~
- ~~Fast or ultrafast taper can be considered when inpatient taper is needed~~
- ~~First reduce to smallest available dose unit and then increase time between doses~~
- ~~Author center experience: decrease by 10% every 5-7days until 30% of original dose is reached, followed by weekly 10% reductions~~

Berna C et al. Mayo Clin Proc. 2015;90:828-842

Opioid Detoxification Regimens:

- US Veterans Affairs Administration (USVA); 2010
  - Slow: Reduce 20-50% per week of original dose
  - Rapid:
    - Methadone:
    - – Decrease dose by 20-50% per day until you reach 30 mg/day,
    - – Then decrease by 5 mg/day every 3-5 days to 10 mg/day,
    - – Then decrease by 2.5 mg/day every 3-5 days.

2010 VA/DoD Clinical Practice Guideline
Management of Opioid Therapy for Chronic Pain

Opioid Detoxification Regimens:

- US Veterans Affairs Administration (USVA); 2010
  - Rapid:
    - Morphine SR/CR:
    - – Decrease dose by 20-50%per day until you reach 45 mg/day,
    - – Then decrease by 15 mg/day every 2-5 days.
    - Oxycodone CR: (IR use similar schedule)
    - – Decrease dose by 20-50% per day until you reach 30 mg/day,
    - – Then decrease by 10 mg/day every 2-5 days.

2010 VA/DoD Clinical Practice Guideline
Management of Opioid Therapy for Chronic Pain

Additional Opioid Taper recommendations:

American Pain Society/American Academy of Pain Medicine (2009)- Chou et al. Ann Int Med 2015;162:276-286

- Slow: 10% reduction weekly
- Rapid: 25-50% reduction every few days

Outpatient regimens:- Kral LA et al. MHC 2015; 5(3):102-8.

- Last stage of tapering most difficult
- May need to slow upon reaching 30-45% of original dose

Opioid Withdrawal Adjuvant Therapy:

- Alpha 2 adrenergic agonists (clonidine, tizanidine):
  - Autonomic symptoms (HTN, nausea, cramps, diaphoresis, tachycardia)
  - Various protocols have used oral or transdermal patches
- Antihistamines/Trazodone
  - Insomnia
- NSAIDs
  - Muscle aches
- Loperamide
  - Diarrhea

Berna C et al. Mayo Clin Proc. 2015;90:828-842

Mayo Clinic Pain Rehabilitation Center (PRC) opioid taper guidelines

- Taper completed with existing opioid
  - Dose reductions based on current formulation and dose options
  - Opioid may be switched to an immediate release product for smaller strengths as dose decreases
- Daily dosage reductions are made during program days (M-F)
- For larger initial opioid doses, reductions may be larger, until ~50-80% of original daily dose is decreased, then smaller
  - 10-20% daily reductions for the first 1/2 to 2/3 of taper, then 2.5-10% during final taper perioid
- Patient factors effecting speed of taper: Long duration of opioid use (>2 years), coexisting psychiatric morbidities, gastric complaints of chronic diarrhea or high output conditions, use of daily steroids with adrenal suppression

Cunningham et al. Pain Med. 2015 In press

Withdrawal symptoms based on drug

- Opioids = short half-lives (3-8 hours)
  - Exceptions
    - Fentanyl patch – 17 hours or more are required for a 50% decrease in serum levels (Duragesic® PI)
    - Methadone – 8-59 hours dependent on patient and duration of administration
- When to expect withdrawal symptoms?
  - Generally 24-48 hours for most opioids
  - Methadone 3-5 days see peak effect
- Prolonged withdrawal effect?

Opioid taper case example – low dose (40 mg Morphine equivalent)

- LB is a 46 year old female with fibromyalgia. She has been on hydrocodone/acetaminophen 10/325 mg tablets, 1 tablet by mouth four times daily for 2 years. Opioid tapering plan is to decrease hydrocodone by 5 mg each day, holding the dose stable on weekends (Friday, Saturday, and Sunday) when patient is not in pain rehabilitation program. Continue to administer the medication in divided doses.

Taper example

Day	Total daily dose hydrocodone (mg)
1	40
2	35
3	30
4	25
5,6,7	20
8	15
9	10
10	5
11	completed

Opioid taper case example – high dose (150 mg Morphine equivalent)

- AC is a 58 year old female with fibromyalgia who has been on oxycodone extended release (ER) 40 mg twice daily and oxycodone immediate release (IR) 5 mg four times daily for the past 5 years. Opioid tapering plan is to decrease oxycodone ER by 10 mg each day, holding the dose stable on weekends (Friday, Saturday, and Sunday) when patient is not in pain rehabilitation program and continue oxycodone IR until the ER formulation is completed. Then taper oxycodone IR by 5 mg each day. Continue to administer in divided doses similar to patient home regimen.

Taper Example

Day	Total daily dose oxycodone ER (mg)	Total daily dose oxycodone IR (mg)
1	80	20
2	70	20
3	60	20
4	50	20
5,6,7	40	20
8	30	20
9	20	20
10	10	20
11	completed	20
12,13,14		15
15		10
16		5
		completed

Questions?