

Evidence-Based Review of Opioids for Chronic Low Back Pain

Pete Vonderau, MD
Physical Medicine and Rehabilitation
The Rehab Doctors

Objectives

- Review the efficacy of Opioids for CLBP (CNCP)
- Review the safety of chronic opioid treatment
- Review physiologic response to chronic opioid use

First: What is a Physiatrist?

- ◆ A physician trained in Physical Medicine and Rehabilitation
 - ◆ 4 year residency
 - ◆ Training in neurology, non-operative orthopedics, rheumatology
- ◆ Field of medicine involving improving the functional ability and quality of life of people with congenital or acquired disabilities
- ◆ There are several subspecialties within this field
 - ◆ Stroke Rehabilitation
 - ◆ Spinal Cord Injury Rehabilitation
 - ◆ Brain Injury Rehabilitation
 - ◆ Amputee Rehabilitation
 - ◆ Work injuries
 - ◆ Sports Medicine
 - ◆ Spine Care/Interventional Procedures
 - ◆ Pain Medicine

My Expertise

- ◆ Non-operative Spine care
 - ◆ Arthritis, Radiculopathies, Herniated discs, Spinal Stenosis
 - ◆ Fluoroscopically-guided spine injections
- ◆ Musculoskeletal injuries/Sports medicine/Work-related
 - ◆ Shoulders, hips, knees, ankles
- ◆ Peripheral nerve injuries
 - ◆ Electrodiagnostic testing (EMGs)
 - ◆ Carpal Tunnel Syndrome, Ulnar neuropathy, Peripheral neuropathy, etc...

Opioids: General Information

- Opium is a powder derived from seedpod of the *Papaver somniferum* poppy
- Has been used for pain for thousands of years
- Pharmacologic production began in 1806 after the morphine alkaloid was identified
 - Used to cure colic, diarrhea, boredom, "travails"
- Legal controls began in the late 1800s due to prevalent street use, with the most strict controls in the 1940s

Opioids: General Information

- Due to advocacy for pain control over the last 30 years, opioids have become a mainstay of treatment for acute pain and pain due to terminal cancer
- Advocacy groups have pushed for use of opioids for chronic, non-malignant pain
- General consensus has been that opioids can provide satisfactory analgesia with minimal risk of addiction
- Porter (NEJM, 1980)
 - Survey of 11,882 patients receiving opioids, only 4 cases of addiction

Questions arising out of my practice

- Why do patients continue to report severe pain (8-10/10) despite opioid therapy, yet endorse that it helps?
- Why is there a seemingly inevitable demand for increased doses with time?
- Why does the small percentage of opioid-treated patients account for 95% of my headaches
- Why are narcotics magnetically drawn to drains?

Ballantyne (Clin J Pain, 2008)

- Review of the efficacy of opioid treatment for chronic pain (not a meta-analysis)
- Conclusions
 - RCTs show strong evidence that opioids provide INITIAL relief for chronic pain conditions, with much less clarity about long-term effectiveness
 - Open-label follow-up studies show that up to 56% of patients abandon opioid treatment due to lack of analgesic efficacy or side effects

Kalso (Pain, 2004)

- Review of literature regarding effectiveness and safety of WHO step 3 opioids for chronic non-cancer pain
 - RCTs and Open-Label studies were included
- 80% of patients experienced adverse reactions
- Only 44% continued treatment beyond 7 months
- Mean pain relief 30% (without placebo comparison)
- Conclusion: Only a minority of patients benefit from long-term treatment with opioids

Noble (J Pain Symp Mngmt, 2008)

- Meta-analysis of efficacy of opioids for CNCP
 - Evaluated studies of patients on opioids for >6 months
 - Of 115 studies, 17 met criteria
 - Pain refractory to tx for 3 months
 - Pts failed pharmacotherapy prior to opioids
 - Subjects on opioid tx followed for at least 6 months
 - Prospective studies only
 - Note: No placebo-controlled, long-term, RCTs exist addressing the efficacy and safety of opioids for CNCP

Noble (J Pain Symp Man, 2008)

- Results
 - 44% of subjects did not complete their study
 - 32% intolerable adverse effects, 12% lack of efficacy
- Conclusions
 - Many patients were so dissatisfied with the adverse events or insufficient pain relief that they withdrew from studies
 - Among those continuing treatment, there is only weak evidence that their pain scores were lower than before they started and that the relief can be maintained long term
 - All available studies were of low quality

Martell (Annals of Int Med, 2007)

- Rigorous meta-analysis of efficacy and safety of opioids for chronic low back pain
- Criteria: adults, non-obstetric, no pre-existing opioid dependence, focus on CLBP (>3 mo pain)
- Assessed quality of studies using standardized methods to select those of "excellent" quality
- Of 2378 studies, 38 met criteria

Martell: Efficacy of Opioids

- Subset: Studies comparing opioids with non-opioids or placebo
 - 2 studies met criteria (Jamison, Hale)
 - The pooled statistical analysis of active treatment vs placebo/NSAID showed no significant reduction in pain
 - Meta-analysis conclusion
 - Opioids have limited efficacy in treating chronic LBP

Martell: Substance Abuse

- Five studies of adequate quality were assessed
- Prevalence of SA among opioid users: 5-24%
- Lifetime prevalence was reported to be as high as 54% in one study

Martell: Conclusions

- Opioids may only be efficacious for short-term treatment of low back pain
- Up to 25% of patients are exhibiting aberrant medication-taking behaviors

Hale (Journal of Pain, 2005)

- ◆ Multicenter, randomized, double-blind study assessing analgesic efficacy and safety of oxymorphone compared to oxycodone CR and placebo
- ◆ Subjects were opioid-experienced patients with chronic moderate to severe LBP (DDD, HNP, Spondylosis, Stenosis)

Hale: Methods

- ◆ 330 Patients entered 14 day titration period
 - ◆ Received either OxyContin or Opana BID (blinded) to establish stable dose requiring minimal or no rescue meds
 - ◆ Baseline characteristics were similar between groups
- ◆ Then entered 18 day treatment phase
 - ◆ Either continued same BID opioid tx or switched to BID placebo (1/3 Opana, 1/3 OxyContin, 1/3 placebo)
 - ◆ Dose did not change
 - ◆ Subjects who could not tolerate the meds or needed more than 2 rescue meds (MS 15mg) per day were excluded

Hale: Outcomes

- Outcome measure
 - Change in VAS Score (100) from baseline (end of titration: all subjects on opioids) to end of treatment period
 - Other variables assessed
 - Categorical pain intensity, pain relief, Brief Pain Inventory
 - They calculated 198 subjects needed to detect 15pt VAS change to reach 90% power

Hale: Results

- 329 were enrolled in titration phase subjects received at least one dose of the medication
 - 95 (29%) subjects dropped out during titration phase
 - Adverse events, lack of efficacy, non-compliant, other
- 235 patients entered the treatment phase
 - 96 (29%) subjects withdrew (same reasons)
- 139 completed the study (42%)
- 213 included in intent to treat population
 - 35% not included in intent to treat
- Average doses: 155mg OxyContin, 80mg Opana

Hale: Results

- Mean difference in pain between placebo and opioid
 - Opana -18.2/100
 - OxyContin -18.5/100
- Average Pain Score in last 24 hours of study
 - Opana 5.1/10
 - OxyContin 5.4/10
 - Placebo: 6.2/10
- Current Pain level at end of study
 - Opana 58/100
 - OxyContin 59/100
 - Placebo 64/100

Hale: Conclusions

- “Treatment with oxymorphone provided superior analgesic efficacy relative to placebo as determined by change in baseline intensity”
 - ** Note: Martell’s analysis showed no statistically significant pain relief with the opioids compared to placebo in this study

Hale: Comments

- Is a 15/100 pts clinically significant?
- This is not a CHRONIC narcotic trial (<5 weeks), so expect relief to decrease with time due to tolerance
- Rescue meds (MS) allowed
- 58% dropped out in all
 - 1/3 dropped out during titration (when ALL rec’d opioids)
 - Most dropouts NOT included in intent to treat analysis
- We’d expect NSAIDS, tramadol, adjuvants to be better than placebo
- Sponsored by Endo Pharmaceuticals

Jamison (Spine, 1998)

- Randomized, non-blinded, comparison of NSAID with 2 opioid regimens
- Criteria
 - CLBP > 6 mo
 - Average Pain >40/100
 - Non-obstetric, no h/o substance abuse, no cancer or acute pain issues
 - Subjects discouraged from other tx during study (PT, etc)
- Demographics
 - 36 subjects (average age 46)
 - Dx included failed back, radiculopathy, myofascial, DDD
 - Average pain duration 79 months
 - Average pain intensity 68/100

Jamison: Methods

- Pre-Treatment Washout (4 wks) - No opioids
- Experimental Phase (16 wks)
 - Randomized into one of 3 treatment regimens
 - Naproxen 250mg QID
 - Oxycodone 5mg QID
 - Titrated oxycodone and Morphine SR (Oramorph)
- Titration Phase (12 wks)
 - All pts then offered titrated opioids
- Taper Phase (12 wks)
 - All tapered off opioids over 12 weeks

Jamison: Results

■ Differences During the Experimental Phase

	NSAID	Oxycodone	Oxycodone and MS
■ Average Pain	65	59	55
■ Highest Pain	78	75	71
■ Activity Level	51	49	49
■ Hours of Sleep	6.1	5.9	5.9

Jamison: Results

■ % Adverse Reactions During Experimental Phase

	NSAID	Oxycodone	Oxycodone and MS
■ Dry Mouth	19	26	34
■ Drowsiness	14	22	36
■ Headache	15	20	31
■ Constipation	10	17	30
■ Nausea	4	13	31

Jamison: Conclusions

- Both opioid groups were found to have “significantly less pain” than naproxen-only group
- Chronic opioid therapy seems to benefit some patients
- Opioids relieve pain but do not affect activity level
- A trial of opioids does not necessarily contribute to long term benefit

Jamison: Comments

- Not blinded
- Small sample size (36)
- Use of opioid rescue meds during controlled trial
- No mention of specific outcome measure
 - How much pain relief is considered a success?
- No comparison to other adjuvant pain meds
- Not a long-term study

Why not provide opioids to everyone who is in pain?

Eriksen (Pain, 2006)

- Cross-sectional study of 1906 Danish patients to determine effect of opioids on chronic non-cancer pain
- 3% of the Danish population uses opioids on a regular basis
 - They consume more opiates per patient than any other country
- Assessed the outcomes of chronic pain pts receiving opioids compared matched cohorts not receiving opioids

Eriksen: Results

- Opioid users:
 - More moderate to severe pain
 - Poorer self-rated health
 - Lower QOL scores
 - Less physically active
 - Fewer employed
- Among chronic pain patients, 51% report pain as moderate, severe, or very severe
 - 90% of opioid users rate pain as moderate to very severe
 - 46% of Non-opioid users rate pain as moderate-very severe

Eriksen: Conclusions

- Obviously opioids did not reduce this group's pain sufficiently to achieve a functional status equal to the non-opioid users
- If opioids provided adequate pain relief, a greater percentage should be in the no pain or mild pain group
- An explanation may be that opioids are not very helpful, or even deleterious, in the long run
- Opioid treatment of long-term non-cancer pain does not seem to fulfill any of the key outcome opioid tx goals, including pain relief, QOL, and improved function.
- Causation cannot be ascertained by this cross-sectional study, but the findings do suggest not all patients benefit from opioids
- Liberalization of opioids does not appear to demonstrate benefit

Opioid Analgesic Failure: Possible Explanations

- Ballantyne (NEJM, 2003)
 - Analgesic Tolerance
 - Phenomenon of reduced analgesic efficacy with time
 - Tolerance to the euphoria has been recognized for many yrs (need increased doses to achieve intoxication)
 - May be due to cell receptor desensitization or down-regulation
 - Endogenous peptides may oppose the analgesic effect

Analgesic Failure: Possible Explanations

- Opioid-induced hyperalgesia (OIH)
 - First observed in methadone pts
 - Pts undergoing high dose opioid infusions develop hyperalgesia and allodynia that resolves when the tx is weaned
 - Possibly due to changes at NMDA receptors in dorsal horn of spinal cord
 - Repeated administration of opioids leads to a pro-nociceptive (sensitization) process
 - This can contribute to perceived decrease in analgesic efficacy

Ballantyne (NEJM, 2003)

- Evidence now suggests that prolonged, high-dose opioid therapy may be neither safe nor effective
- It is therefore important that physicians make every effort to control indiscriminate prescribing, even when under pressure by patients to increase the dose of opioids

Nüesch (Cochrane Library, 2009)

- Meta-analysis of efficacy and safety of oral and transdermal opioids for moderate to severe OA of hips and knees
- ACR guidelines (2000) suggested opioids may be used as a last resort for severe OA pain
- Randomized or Quasi-randomized controlled trials were included (3541 initial references)
- 10 studies were selected with a total of 2268 subjects
 - Opioids studied included: morphine, naltrexone/oxycodone combination, codeine/paracetamol, transdermal fentanyl, codeine, oxymorphone ER, oxycodone CR

Nüesch

- Results
 - Pain reduction
 - Opioids 27/100
 - Placebo 18/100
 - Difference in pain reduction = 9/100 (15%)
 - Adverse Reactions
 - 23% of opioid group, 15% of placebo group
- Conclusions
 - Small to moderate beneficial effects of opioids are outweighed by the large risk of adverse events
 - Non-tramadol opioids should not be routinely used, even if osteoarthritic pain is severe

Markenson (Clin J Pain, 2005)

- Double-blind, randomized, placebo-controlled study evaluating the efficacy and safety of oxycodone CR for moderate to severe pain due to OA
- 109 subjects
- Continued use of NSAID/APAP was permitted
- Randomized to titrated OxyContin Q12 or placebo
 - Max dose of OC = 120mg/day
- Subjects were followed for up to 90 days

Markenson

- ITT inclusion (107/109)
 - All subjects receiving at least one dose of medication
- Outcome Measure
 - Change in pain of 1.25/10
- Results
 - 36 completed the study (58.9% dropout in OC group)
 - Difference in average pain intensity between OC and Placebo ranged from 9/100 to 13/100
 - Adverse events: 55% Placebo, 93% OC
- Conclusion
 - Oxycodone CR is superior to placebo

Kivitz (Clin Ther, 2006)

- 2 week, multi-center, randomized, double-blind, placebo-controlled trial comparing Opana ER (3 dosing regimens) to placebo for moderate to severe OA of knee or hip
- 2-7 day analgesic washout
- Outcome Measure: Reduction in pain of 15/100
- Criteria:
 - On suboptimal tx with NSAIDs, APAP, or opioids for at least 90 days
 - Pain >4/10
- Patients requiring arthroplasty were excluded
- No rescue meds

Kivitz

- Randomized to:
 - Opana ER: Wk1 10mg BID, Wk2 10mg BID
 - Opana ER: Wk1 20mg BID, Wk2 40mg BID
 - Opana ER: Wk1 20mg BID, Wk2 50mg BID
 - Placebo for 2 weeks
- Endpoint
 - Mean change in pain intensity from baseline to final visit
- ITT Inclusion
 - All patients who took medication at least once
- 370 were Randomized, 198 completed study (53%)

Kivitz: Results

- | Group | Δ Intensity |
|-----------------|-------------|
| Opana ER 10/10: | -21/100 |
| Opana ER 20/40: | -28/100 |
| Opana ER 20/50: | -29/100 |
| Placebo: | -17/100 |
- Adverse Events
 - Opana ER: Nausea (39%), Vomiting (23%), Dizziness (22%), Constipation (22%), Somnolence (17%), HA (14%)
 - 63% of the Opana 40mg Group withdrew from study

Kivitz

- Conclusions
 - Opana ER 40mg and 50mg provided significantly more pain relief than placebo
 - Opana ER 10mg did NOT provide significantly greater pain relief than placebo
- Comments
 - This is NOT a long-term study
 - High dose had some minimal benefit, but very few were able to complete the study
 - Supported by Endo Pharmaceuticals

Matsumoto (Pain Med, 2005)

- Multicenter, Double-blind, Placebo-controlled 4 week study comparing Opana ER and OxyContin for moderate to severe pain due to OA
- Methods: Nearly identical to Kivitz Study
- Dose titrated from 50% over first two weeks to full dose (listed below) for last two weeks
- Randomization
 - Oxymorphone ER 20mg BID
 - Oxymorphone ER 40mg BID
 - Oxycodone CR 20mg BID
 - Placebo
- Endpoint: Change in VAS (baseline to week 3)
- ITT: All patients receiving at least one dose of medication

Matsumoto

- 489 received at least one dose of medication
- 269 completed the study
- Results (change in baseline compared to placebo)

■ Oxymorphone ER 20mg BID	-9/100
■ Oxymorphone ER 40mg BID	-7/100
■ Oxycodone CR 20mg BID	-5/100 (Not Sig)

Matsumoto

- Conclusions
 - This study failed to show that OC is effective for controlling moderate to severe pain due to OA
 - Oxymorphone provided superior pain relief compared to placebo
- Comments
 - Not a long term study
 - OC dose equivalency was lower than OM dose
 - Supported by Endo Pharmaceuticals

Manchikanti (Pain Phys, 2006)

- Review based upon his testimony before Congress on the prescription drug abuse epidemic
- Statistics based on the 2004 National Survey of Drug Use and Health and CASA (Center on Addiction and Substance Abuse) Report of 2004
 - Prescription drug abuse is the second most prevalent category of drug abuse (marijuana)
 - 19% of kids aged 12-17 have abused Rx drugs
 - Lifetime non-medical use of Rx drugs: 20% of population

Manchikanti (Pain Phys 2006)

- From 1992 to 2004
 - US population increased by 12%
 - Abuse of prescription opioids by teens increased 542%
- Oxycodone sales increased >550% from 1997 to 2004
- 10% of 12th graders abuse Vicodin, 5.5% abuse OC
- 3.2 million people were using OC for non-medical purposes in 2004 (US population 306 million)
- Opioids account for more OD deaths than cocaine or heroin
- Street value of 100 OxyContin 80mg = \$7000-8000!!

Manchikanti (Pain Phys 2006)

- Reasons for exponential increase in opioid Rx
 - Pharmaceutical company marketing
 - Numerous organizations providing guidelines unsupported by EBM
 - Patient advocacy groups demanding opioids for benign pain
 - Enactment of the Patient's Bill of Rights in many states
 - Perceived patient's right to pain relief
 - Availability of Internet prescriptions
 - Unscrupulous pill mills
 - High street value of prescription pain medications
 - Perceived legitimacy of prescription pain medications
 - Perceived safety of prescription medications

CASA Report

- Indicated that the majority of physicians:
 - Are not aware that the long-term efficacy and safety of opioids for CNCP has not been substantiated
 - Are not aware that patients seeking relief of CNCP often have underlying psycho-social issues and would benefit more from psychological intervention
 - Have not pursued a thorough diagnostic workup to substantiate the presenting complaints and therefore treatment is based upon hearsay rather than sound objective information
 - Relied on false marketing provided by Perdue about OxyContin without full disclosure of the risks of the medication

<http://forum.opiophile.org>

Opiophile: Hydrocodone

- Q: "After cold water extracting a bunch of vicodens to get rid of the apap, would you get more of a potent high using a p-450 inhibitor such as tagament or grapefruit juice and drinking the liquid, or squirting it up your rectum which has a larger mucus membrane area to absorb more faster (I heard 10% more)? Weird question I know, but any response would be appreciated because i just got 200 liver killing vicodins and want to know the best way to take them. Thanks guys."

Opiophile: Oxycodone

- What is the street price for roxy 15s?
 - RESPONSE: "It all depends on your area man. Around where I'm at they'd probably be \$10-15. I don't see many of those around though I'm just guessing basing on the prices of 30s. A 30 goes for \$25-30, 40s are \$30-35, and 80s are \$60-70."

Opiophile: Opana (Oxymorphone)

- Opana IR
 - "Usually rectal absorption is best, after injecting obviously"
 - "There is an awesome guide on here for IV'ing Opana IR. They say its the most insane rush."

Opiophile: Opana ER

- “I have no prob removing the coating, just suck on it for a couple seconds, then hit it wit a wash cloth. When it comes to the ER I like snorting. They are the bomb.”
- “It sounds to me like the drug company f___ up when they designed that ER pill to be "abuse proof". Whenever snorting any powder, there is lost product eventually running down and being swallowed. This gel might just be the perfect thing for keeping all the powder up your nose where you want it for proper absorption.”

Opiophile: Doctor Shopping

- “I’ve been trying to think of good ways to locate a croaker or quack-type doctor, the kind where you can get what you want.”
- RESPONSE: “The key to everything is to have as much info as possible walking into the appointment. Don't waste the Dr.'s time, he's a busy guy. Be prepared the first few times to agree to ANYTHING he prescribes. Even if it's not what you want. You have to build a relationship with these people. Take whatever they give you, wait a few days, make an appointment a few days later and tell them it's not working. Repeat until you get what you want. It does help if you pick a few non narcotic solutions as well. Even though he never takes it, my friend ALWAYS asks for 800mg Motrin tabs every time he goes in. Don't be obvious about wanting strictly narcs.”

Parting Thoughts

- Opiates may be appropriate for some patients
- Opioids have shown a minimal reduction in pain over short periods of time for some patients
- There are NO high quality studies assessing the long term benefit of opioids
- Opioids ARE abused recreationally
- The potential for abuse is high according to some studies
- The street value is an undeniable reason for secondary gain
- Are you prescribing opioid medications for chronic pain based upon clinical evidence, or patient demands and expectations?
 - Get help from a physiatrist to do a thorough workup

Parting Thoughts

- Are we doing patients a disservice if we do not inform them that they can expect, on average, a 15% improvement in pain with “pain killers”?
 - Are we contributing to the problem by not reducing their expectations so that they do not chase 100% relief?

Thank You

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