Evidence for the Use of Chronic Opioid Therapy for Chronic Pain

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Disclosures

- Receive consulting fees from Pfizer, Nektar, Depomed, Salix, Daiichi Sankyo, Grunenthal, and Quest.
- Receive honoraria from Allergan, Depomed, AstraZeneca, Daiichi Sankyo, BDSI, Collegium, and Avanir.
- Stockholder of Pfizer and Depomed.
- Receives royalties from Elsevier.

Key Facts (Let’s be real please)

- Chronic pain affects a large number of Americans – more than 100 million as per IOM and other sources. Were you aware of this fact?
- Most health care providers currently treat patients who as a part and in the course of their various medical disorders experience severe chronic pain. These facts CANNOT be ignored.
Evidence-based Argument

Question
Evidence
Conclusion
Recommendation

Randomized Masked Trial
Anecdote (Case Report)

Strong
Weak

Class I  Class II  Class III  Class IV

Establishing realistic treatment outcome expectations for ALL analgesic therapies (OR DO WE SELECTIVELY CALL OUT OPIOID THERAPIES?)

- Non-opioid analgesics
- Invasive pain management
- Opioid analgesics
Non-Opiate Pharmacotherapy

- NSAIDs/Cox-2
- Acetaminophen
- Antidepressants
- Anticonvulsants
- Oral local anesthetics
- Alpha adrenergic agents
- Neuroleptics
- NMDA receptor antagonists
- Muscle relaxants
- Topical analgesics
- Emerging Agents

Anticonvulsants

- Carbamazepine*
- Divalproex sodium*
- Gabapentin*
- Pregabalin*
- Clonazepam
- Phenytoin
- Lamotrigine
- Topiramate*
- Zonisamide
- Oxcarbazepine
- Levatriacetam
- Lacosamide

*New indication for pain/headache

Clinical Syndromes and Anticonvulsant Use

- Postherpetic neuralgia
  - gabapentin
  - pregabalin
- Diabetic neuropathy
  - carbamazepine
  - phenytoin
  - gabapentin
  - Lamotrigine
  - pregabalin
- HIV-associated neuropathy
  - lamotrigine
- Trigeminal neuralgia
  - carbamazepine
  - lamotrigine
  - oxcarbazepine
- Fibromyalgia
  - pregabalin
- Central poststroke pain
  - lamotrigine
### Gabapentin in the treatment of painful diabetic neuropathy*

![Graph showing mean pain score over weeks with Gabapentin and Placebo groups.](image)

- *Not approved by FDA for this use
- †P<0.01; ‡P<0.05

### Currently Available Alpha-Adrenergic Agonists

- **Clonidine**
- **Tizanidine**

### Possible Effective Uses of Tizanidine

- Trigeminal neuralgia (Fromm 1993)
- Chronic low back pain (Berry 1988)
- Cluster headache (D’alessandro 1996)
- Chronic tension-type headache (Nakashima 1994)
- Spasmodic torticollis (Houten 1984)
- Neuropathic pain
- Chronic headache (2002)
### Muscle Relaxants
- Cyclobenzaprine (Flexeril®)
- Carisoprodol (Soma®)
- Methocarbamol (Robaxin®)
- Metaxalone (Skelaxin®)
- Orphenadrine citrate (Norflex®)

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### Non-Opiate Pharmacotherapy
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### Emerging Analgesics
- Botulinum Toxin (Type A, Type B)
- New intraspinal agents
- New topical agents
- Cannabinoids
- Bisphosphonates
Challenges in applying high levels of evidence to surgical or minimally invasive procedures

- Ethical limitations of blinded surgical techniques
- Placebo use that prolong suffering and yet expose to surgical risk
- Cost prohibition
- Difficulties in blinding sham procedures
- Ability to recruit adequate numbers

Interventional Therapies to be Reviewed

- Trigger point injections/Botulinum toxin
- Epidural Steroid Injection
- Sacroiliac Joint Injection and RFA
- Facet Joint Injection and RFA
- Discography
- IDET, Nucleoplasty, Disc RFA
- Spinal Cord Stimulation
- Spinal Drug Delivery

Epidural Steroid Injection Techniques

Interlaminar (1), Transforaminal (2), Caudal (3)
**Antidepressants**

*Headache Studies*

- Most drugs not rigorously evaluated
- Amitriptyline — limited evidence
  - As effective as propranolol and superior to placebo
  - Benefit independent of depression
  - Other TCAs: insufficient evidence
- SSRIs
  - Some evidence for fluoxetine
- Others: MAOIs, etc
  - Little scientific evidence


**Migraine Prevention**

*AEDs*

- Placebo-controlled, double-blind trials established efficacy

1. Carbamazepine: fair
2. Divalproex: good
3. Gabapentin: fair
4. Topiramate: good
5. Levetiracetam: no
6. Oxcarbamazepine: no
7. Phenytoin: ?
8. Pregabalin: ?
9. Zonisamide: fair
10. Lacosamide: ?


**Divalproex Sodium**

- Comments
  - Effective in 5 double-blind, placebo-controlled migraine trials; used in cluster headache and CDH
  - Check LFTs before and as needed during therapy

LFT, liver function test.
Responder Rates for Divalproate

Topiramate Responder Rate

Headache Conclusions
- Acute Treatment
  - Stratify care
  - Monitor effectiveness
  - Consider preventative treatment as needed
  - Avoid analgesic overuse
- Preventative treatment
  - Be realistic with expectations
  - Consider co-morbidities when choosing medication
  - Acute treatment may still be needed

PBO, placebo; TPM, topiramate.
Shoud Healthcare providers Prescribe Opioids for Chronic Pain? Key Considerations

- Adequate Training
- Methods to do so safely in their Practice
- Respecting the evidence as well as its limitations for the use of opioid analgesics for chronic pain

Opioids on the NNT map of pharmacotherapy of neuropathic pain

![Diagram showing NNT values for various treatments]

CBZ, carbamazepine; LTG, lamotrigine; NNT, number needed to treat; PHT, phenytoin
SSRI, selective serotonin reuptake inhibitor

There is abundant evidence for use of opioid analgesics for chronic pain

AND THERE ARE SERIOUS RISKS: Opioid Analgesic Overdoses = Public Health Epidemic

- Opioid analgesics are among the most commonly misused or abused pharmaceuticals
- Overdose deaths from prescription painkillers have increased
  - 16,651 in 2010; >4x # in 1999

Improper use of any opioid can result in serious side effects, including overdose and death


Improper use of any opioid can result in serious side effects, including overdose and death.

Opioid therapy: benefits and risks

BEFORE starting a trial of opioid therapy, benefits/risks, alternatives to opioid therapy, and patient concerns should be discussed.

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
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<tbody>
<tr>
<td>Reduction in pain</td>
<td>Sedation/confusion</td>
</tr>
<tr>
<td>Reduction in pain-related impairment</td>
<td>Nausea/dizziness</td>
</tr>
<tr>
<td>Improved function and quality of life</td>
<td>Constipation</td>
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<td></td>
<td>Gonadal suppression</td>
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<tr>
<td></td>
<td>Respiratory depression</td>
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<td></td>
<td>Sleep apnea</td>
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<tr>
<td></td>
<td>Fracture</td>
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<tr>
<td></td>
<td>Physical dependence</td>
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<tr>
<td></td>
<td>Pruritus</td>
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<tr>
<td></td>
<td>Addiction</td>
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<td></td>
<td>Withdrawing</td>
</tr>
<tr>
<td></td>
<td>Increased pain</td>
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<tr>
<td></td>
<td>Death</td>
</tr>
</tbody>
</table>

NEVER HCP” routinely prescribe treatments that have serious risks associated with their use.

Neuropathic pain recommendations of various societies

<table>
<thead>
<tr>
<th>EFNS, Europe Neurology</th>
<th>Canadian Pain Society</th>
<th>IASP NeuPSIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>TCA (Gabapentin/Lamotrigine/Capsaicin)</td>
<td>TCA (Gabapentin)</td>
</tr>
<tr>
<td></td>
<td>Lidocaine 5% patch</td>
<td></td>
</tr>
<tr>
<td>Second line</td>
<td>SNRI (Pregabalin)</td>
<td>SNRI</td>
</tr>
<tr>
<td>Third line</td>
<td>Opioid (except methadone)</td>
<td></td>
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<tr>
<td>Fourth line</td>
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</tr>
</tbody>
</table>

EFNS, European Federation of Neurological Societies; IASP, International Association for the Study of Pain; NeuPSIG, Neuropathic Pain Special Interest Group.


APS/AAPM Clinical Guidelines For The Use Of Chronic Opioid Therapy In Chronic Noncancer Pain (2009)

- Patient selection and risk stratification
- Informed consent and opioid management plans
- Initiation and titration of COT
- Methadone
- Monitoring
- High-risk patients
- Dose escalations, high-dose opioid therapy, opioid rotation, indications for discontinuations of therapy


APS, American Pain Society; AAPM, American Academy Of Pain Medicine; COT, chronic opioid therapy

APS/AAPM Clinical Guidelines For The Use Of Chronic Opioid Therapy In Chronic Noncancer Pain (2009)

- Opioid-related adverse effects
- Use of psychotherapeutic cointerventions
- Driving and work safety
- Identifying a medical home and when to obtain consultation
- Breakthrough pain
- Opioids in pregnancy
- Opioid policies


APS, American Pain Society; AAPM, American Academy Of Pain Medicine

CDC Guidelines -1

- Determining when to initiate or continue opioids for chronic pain outside end-of-life care
- Selection of opioid therapy, non-pharmacologic therapy, non-opioid pharmacologic therapy
- Establishment of treatment goals
- Discussion of risks and benefits of therapy with patients

http://www.cdc.gov/drugoverdose/prescribing/guideline.html - accessed 11/1/15
**CDC Guidelines-2**

- Opioid selection, dosage, duration, follow-up, and discontinuation
- Selection of extended-release and long-acting opioids
- Dosage considerations
- Duration of treatment for acute pain and chronic opioid use
- Considerations for follow-up and discontinuation of opioid therapy


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**CDC Guidelines-3**

- Assessing risk and addressing harms of opioid use
- Evaluation of risk factors for opioid-related harms and integration into the management plan
- Review of prescription drug monitoring program data
- Use of urine drug testing
- Considerations for concurrent use of opioids and benzodiazepines
- Arrangement of treatment for opioid use disorder


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**All Prescribers Play an Active Role in Reducing the Risks Associated With Opioids**

- When opioids are being considered as part of a chronic pain treatment plan:
  - Establish diagnosis
  - Perform a history and physical
  - Order and evaluate the results of relevant diagnostic tests
  - Review current and past treatments
  - Complete an appropriate risk assessment PRIOR to prescribing
  - Monitor the patient regularly on an ongoing basis
  - Prescribe opioids as part of a multimodal treatment regimen

Should Healthcare Providers Prescribe Opioids for Chronic Pain
OR is Their Evidence for such use?

- The question “should” (or should not) a healthcare provider prescribe opioids is a false dichotomy/question! The only question is not should but how well are we prepared to prescribe opioids for the best benefits to our patients with minimal risks.
- Healthcare providers through their training and experience as well as their oath to relieve suffering must be able to:
  - Learn how to select patients for opioid therapy, when indicated
  - Manage patients on opioid therapy as safely and effectively as possible

Need to balance access to pain medications with abuse prevention

- Increased rate of misuse, abuse, and diversion
- Reduced access to opioids for legitimate pain problems


Proposed critical thinking model for chronic opioid therapy

Patient selection
- Initial patient assessment
  - Comprehensive pain management plan
    - Trial of opioid therapy
      - Patient reassessment
        - Continue opioid therapy
        - Implement exit strategy
  - Alternatives to opioid therapy
**Urine Drug Testing (UDT)**

- Two methods of testing typically used:
  - Immunoassay (screening test)
    - Lab based or conducted at point of care
    - Tests only for drug classes; cannot pinpoint specific opioids
    - Less sensitive to semi-synthetic and synthetic opioids; negative response does not exclude use of these agents
  - Gas Chromatography-Mass Spectrometry (GC-MS; confirmation test)
    - Lab based, using either GC-MS or another form of liquid chromatography and MS
    - Used to supplement immunoassay test; GC-MS can identify drugs that immunoassay may miss

- Chain of possession of urine sample
  - Must be reliable, consistent, free from risk of tampering by person providing sample, efficient, personnel transporting sample, and lab personnel

Consult with lab regarding:
- Routine procedures and what drugs are screened for routinely
- Assay limitations
- Drug(s) that you want to screen for
- Confirmation of reporting unexpected results
- Confirmation of checking for adulterated urine (specific gravity, creatinine)

*Oxycodone, oxymorphone, buprenorphine, fentanyl, methadone

**Opioid metabolism and drug-drug interactions**

- Many opioids* react with cytochrome P450 (CYP 450) isoenzymes, primarily CYP 2D6 and CYP 3A4
  - Many nonopioid medications metabolized by same CYP 450 enzyme may alter plasma levels of opioids
- Result: increase or decrease opioid effectiveness
- Many drugs also have other pharmacologic and pharmacodynamic interactions with opioids
  - Pharmacokinetics = what the body does to the drug (absorption, distribution, metabolism, excretion)
  - Pharmacodynamics = what the drug does to the body (the effects)

*Including codeine, hydrocodone, oxycodone, tramadol, and others

**When to consider an opioid exit strategy**

- No convincing benefit from opioid therapy despite
  - Dose adjustment
  - Side-effect management
  - Opioid rotation
- Poor tolerance at analgesic dose
- Persistent compliance problems despite
  - Treatment agreement
  - Limits
- Presence of a comorbid condition that makes opioid therapy more likely to harm than help

Opioid exit strategy: possible paths

- Patient's behavior consistent with drug addiction
  - Refer for addiction management or consultation
- Patient unable or unwilling to cooperate with outpatient taper
  - Provide sufficient opioid for 1-month taper or maintain until admission
  - Refer to inpatient or outpatient program or similar service as available
- No apparent addiction problem
  - Patient able to cooperate with office-based taper
  - Taper gradually over 1 month
  - Implement nonopioid pain management (psychosocial support, CBT, PT, nonopioid analgesics)

CBT, cognitive behavioral therapy; PT, physical therapy

Opioid therapy: New and emerging treatments

- Abuse-resistant
  - Physical barriers
    - If barriers defeated, drug becomes available
- Abuse-deterrent
  - Pharmacologic barriers
    - If altered, antagonist or irritant released

Pragmatics before prescribing

- Assess patient suitability
- Local arrangements for secure prescribing
  - Contract (tripartite; bipartite)
  - Involve only 1 pharmacy
  - PCP role vs Pain Specialist
  - System in place to tackle complications, noncompliance, withdrawal
- Other reasonable treatment options have been considered

PCP, primary care physician
Key principles for successful opioid prescription—summary

- Diagnosis
- Natural history of disease (likely progression or not)
- Drug interactions
- Opioid hyperalgesia - ?
- Management of adverse effects
- Opioid rotation
- Awareness and action regarding co-morbidities including addiction, diversion, aberrant drug related behaviors

How good is the Evidence?

Evidence Based Medicine

- Evidence-based medicine (EBM) has been defined as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.” — Sackett, D. Evidence-Based Medicine —
- Evidence-based medicine: The judicious use of the best current available scientific research in making decisions about the care of patients. Evidence-based medicine (EBM) is intended to integrate clinical expertise with the research evidence and patient value

An estimated 5-8 million people in the US use opioids for long-term pain management.

The CDC guideline DOES point out that chronic opioid therapy is a Viable option for certain people.

Placebo controlled trials DO show modest pain reduction with COT AND in general, there is a paucity of long term evidence for ANY analgesic therapy, or NON-pharmacologic therapy.

Avoid the use of the term “opioid epidemic”

Imperfect treatments do not justify therapeutic nihilism.

JAMA. Published online May 11, 2017. doi:10.1001/jama.2017.4884

Conclusions

- Appropriate pain prescribing is an urgent need
- Multimodal therapies for addressing pain are available – opioid sparing approaches are preferred
- Accurate assessment is important for diagnosis and risk stratification
- Resources are available to assist clinicians in prescribing opioid therapy when deemed appropriate for people experiencing chronic pain
- Yes- there is evidence for the use of chronic opioid therapy for chronic pain