Non-Opioid Pharmacologic Management of Chronic Pain: A Primer

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Disclosures

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Dr. Severino will disclose off-label uses of medications in today's presentation

Outline

- **Types of Pain and Diagnosis**
- **Why Non-opioids?**
- **Non-opioid analgesics, antidepressants, anticonvulsants, antispasmodics and topicals**
- **Wrap Up**

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Types of Pain
&
Accurate Diagnosis

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Chronic Non-Cancer Pain

CNCP is defined by the American Society of the Interventional Pain Physicians as: 1) Pain that persists beyond the usual course of an acute disease or a reasonable time for any injury to heal that is associated with chronic pathologic processes that cause continuous pain or pain at intervals for months or years; 2) Persistent pain that is not amenable to routine pain control methods.

Trescott al. (2008) *Pain Phys* 11: S5-S62

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Chronic Non-Cancer Pain

Today we will focus on chronic non-cancer pain (CNCP). Cancer and other aggressive pain, as well as acute injury, require different approaches.

Approximately 40% of patients report inadequate pain control for their CNCP, resulting in significant disruptions of daily function

AND

Nearly half of CNCP caused visits are to PCPs, yet these providers express marked concerns regarding

1. ***how to best manage CNCP***
2. ***concern about prescription opioid abuse***
3. ***concern on the burden of care represented by CNCP patients***

Leverence et al. (2011) *J Am Board Fam Med* 24: *551-561.*

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Most studies support PCP discomfort with chronic pain management:

Per Vijayaraghavan et al., 54.% of PCPs felt less or much less confident with chronic pain management vs. a commonly encountered problem, and 84% felt less of much less satisfied in treating chronic pain versus common problems.

Vijayaraghavan M et al. (2012) *Pain med* **13:** 1141-1148

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Low Back Pain
Foot Pain
Headache

These are not diagnoses but symptoms – one must identify the pain generators and the type of pain to guide the where, what and how of treatment

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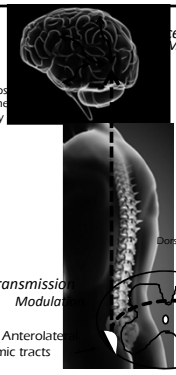
Thanks Seddon Savage MD



ception
Modulation

Nociceptive Pain

To Brain
- Multiple synaps
- Rich interconne
- Modulation by
  - Meaning
  - Thoughts
  - Feelings
  - Memories

Afferent nociceptive pathway
Afferent non-nociceptive sensory pathway

Spinal modulation
- norEpi, serotonin
+ glutamate, NDMA

Nociceptors:
Polymodal, high threshhold \

Dorsal Horn

Mixed fiber neuron

Transmissio
Modulat

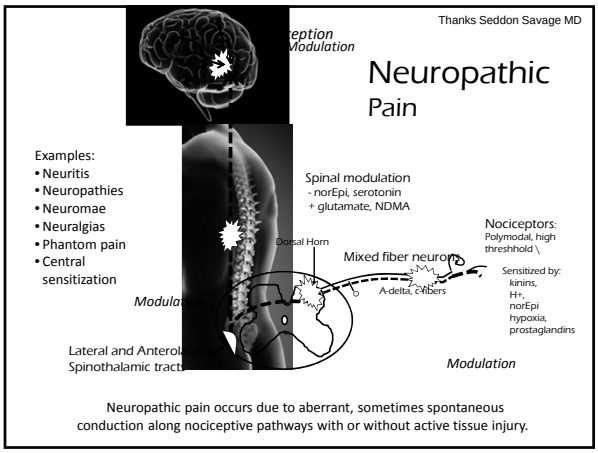
A-delta, c-fibers

Sensitized by:
kinins,
H+,
norEpi
hypoxia,
prostaglandins

Transduction
Modulation

Lateral and Anterolate
Spinothalamic tracts

In nocicpetion, high intensity stimulation transduces a pain signal in receptors which transmits along nerves across synapses in the spinal dorsal horn to the brain where it has rich synaptic interconnections and moves on to perception. Along the way modulation (physical, psychological, behavioral) can amplify or inhibit the signal.



Common Types of Pain

Neuropathic:

peripheral: diabetic, alcoholic, HIV and post-herpetic neuropathies, CPRS, trigemminal neuralgia

Central: post-stroke, spinal cord injury, fibromyalgia

Nociceptive:

low back pain, rheumatoid and osteoarthritis, myofascial

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Why Non-opioids?

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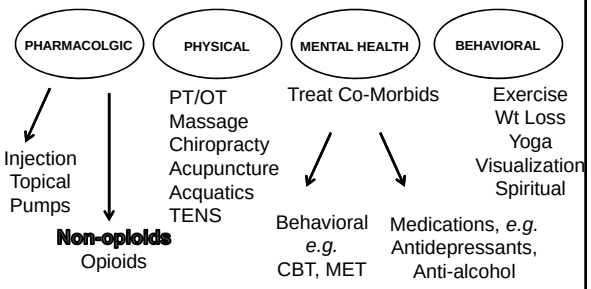
Medications are just one part of a multipronged approach to pain management – the one we focus on today



MANY Reviews Conclude There is Little or No Evidence for Improved Function on Chronic Opioids

Papaleontiou M, Henderson CR, Turner BJ, Moore AA, Olkhovskaya Y, Amanfo L, Reid MC. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. JAGS 2010; 58:1353-1369.

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Rethinking Opioid Use

From 1991 to 2010 the number of opioid prescriptions increased sixfold, from 30 million to 180 million prescriptions. Concurrent with this growth in opioid prescriptions has been an increase in diversion and nonmedical opioid use.

NIDA Research Report Series, 2011, NIH Publication Number 11-4881

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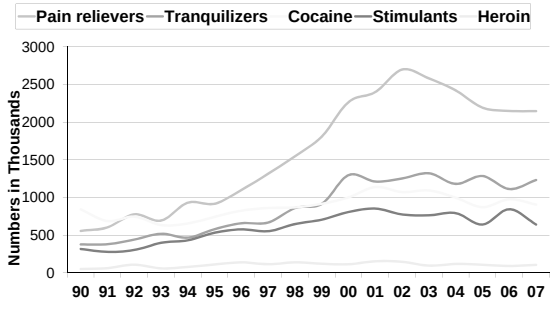
Estimated numbers of *new* nonmedical users in past year by type of drug, U.S., 1990-2007



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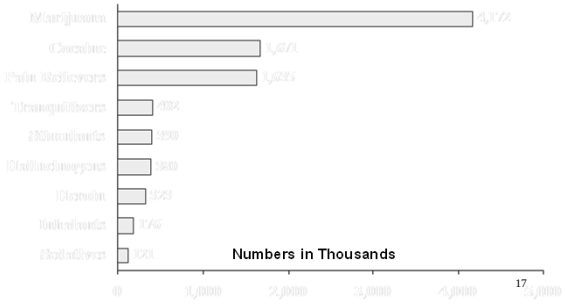
Source: SAMHSA NSDUH, 2006 and 2007

Fig 7.2

Dependence on or Abuse of Specific Illicit Drugs in the Past Year among Persons Aged 12 or Older: 2006



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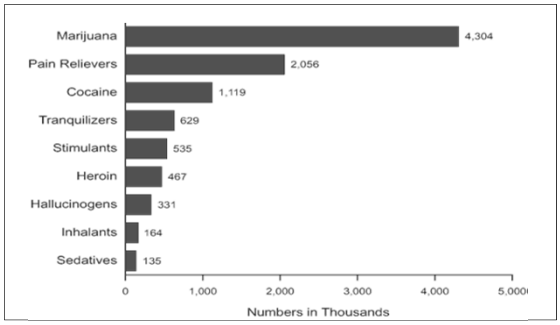
Specific Illicit Drug Use Disorder in Past Year among Persons Aged 12+: 2012



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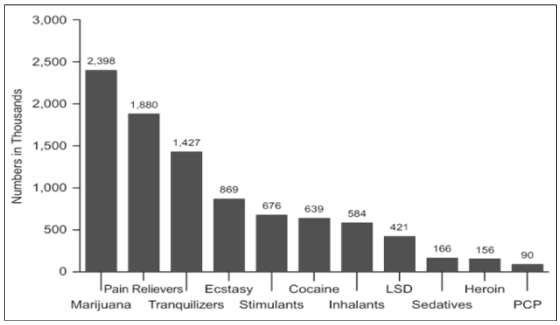
Source: SAMHSA NSDUH 2012, Fig. 7.2

Past Year Initiates for Specific Illicit Drugs among Persons Aged 12+: 2012



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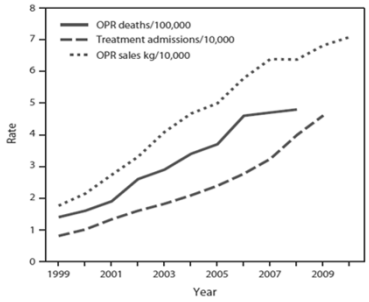
Source: SAMHSA NSDUH 2012, Fig. 5.2

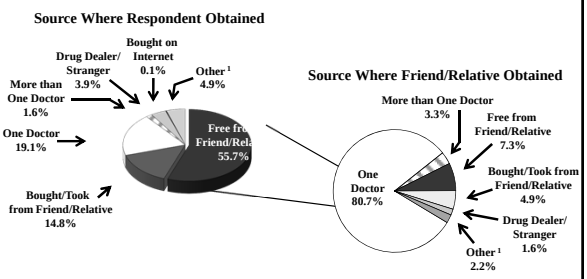
Opioid Overdose Deaths & Opioid Sales



The figure above shows rates of opioid pain reliever (OPR) overdose death, OPR treatment admissions, and kilograms of OPR sold in the United States during 1999-2010. During 1999-2008, overdose death rates, sales, and substance abuse treatment admissions related to OPR all increased substantially.

CDC MMWR November 4, 2011 / 60(43);1487-1492

Source Where Pain Relievers Were Obtained for Most Recent Nonmedical Use among Past Year Users Aged 12 or Older: 2006



Note: Totals may not sum to 100% because of rounding or because suppressed estimates are not shown.

[1] The Other category includes the sources: "Wrote Fake Prescription," "Stole from Doctor's Office/Clinic/Hospital/Pharmacy," and "Some Other Way."

Opioids are only one small piece of the CNCP puzzle AND …

- Opioid Prescribing is correlated with the risk of addiction and misuse
- Opioid Prescribing has not been the answer to improving relief of CNCP
- Opioid Prescribing is a major source of anxiety and dissatisfaction for PCPs (and at least for this consulting psychiatrist)

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So if not Opioids, What?

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Non-opioid Analgesics

- Acetominophen – most prescribed, hepatoxic in doses >3 to 3.5 g/day; probably less effective than NSAIDS
- Non-Selective COX inhibitors – cardiac, GI, renal and liver toxicity, platelet inhibition; naproxyn less cardiotoxic than others; gastropathy the most limiting issue.
- COX-2 Selective inhibitors – when GI symptoms don't allow use of non-selective agents but more cardiotoxic.

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Non-opioid Analgesics (2)

- May lower total opioid requirement
- Effective for nociceptive pain, anti-inflammatory properties; little use in neuropathic pain.
- Naproxyn least cardiotoxic – good first choice.
- May interfere with ASA antithrombotic effect – take at least 1/2 hr before the ASA
- Martell et al. (2007) Ann Int Med 146: 116 showed superior efficacy of NSAIDS over opioids for low back pain

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Gabapentin and Pregabalin

- Bind to alpha 2-delta subunit of voltage-gated calcium-channels, thus inhibiting neurotransmitter release (glutamate and norepinephrine).
- Proven efficacy for tx of neuropathic pain: first line agents
- Often used off-label in US for anxiolysis and/or insomnia

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Gabapentin

- ✧ Best studied for post-herpetic and diabetic neuropathies
- ✧ Titrate slowly up to 3600+ mg qd in divided doses (bid to qid)
- ✧ Poorly absorbed and may take 2 months for adequate trial
- ✧ Complaints: sedation, weight gain, dizziness, frequency of dosing
- ✧ Risks: overuse in substance use disorder populations; adjust for renal insufficiency.

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Pregabalin

- FDA-approved for use in fibromyalgia
- Can be more quickly titrated to max recommended dose (600 mg) than gabapentin
- 300-600 mg efficacy for post-herpetic and diabetic neuropathy > than for fibromylagia and central neuropathic pain
- Similar side effects to gabapentin, perhaps less sedation
- Schedule V due to reports of euphoria

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Other Anticonvulsants

- Long history of use for neuropathic pain since the 1960s
- Direct analgesic effects PLUS calming/ mood stabilizing effects BUT these are second or third-line agents
- Exception is carbmamazepine indicated for trigemminal neuralgia, used in post-herpetic neuralgia; oxcarbazepine similar - complicated interactions

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Other Anticonvulsants (2)

Some evidence for lamotrigine in low back pain

Phenytoin, valproric acid, clonazepam etc.
? proGABA-ergic or anti-glutmatergic

Blood levels do not correlate with pain efficacy follow normal prescribing precautions, such as checking LFTs, blood counts etc.

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Antidepressants

- First-line agents for neuropathic pain
- Best studied in neuropathic pain, fibromyalgia and headaches
- Action through re-uptake blockade of NE and 5-HT, but also effects on NMDA, opioid and adenosine receptors, and sodium channels
- Efficacy for neuropathic pain does not correlate with antidepressant response

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Tricyclic Antidepressants (TCAs)

- Efficacy in neuropathic pain, fibromyalgia, low back pain, headaches, irritable bowel syndrome
- Side effect profile favors secondary amines (nortriptyline, desipramine) over tertiary amines (amitriptyline, imipramine), but tertiary amines may be more effective

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TCAs (2)

- Tolerability Issues: sedation, weight gain, urinary retention, blurred vision
- Safety issues: lethal in overdose, cardiac conduction effects, glaucoma
- Usually effective at lower daily doses (25 - 50 mg) than used for depression (150 - 200 mg); titrate to effect

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5HT/NE Reuptake Inhibitors (SNRIs)

- Think of them as kinder-gentler TCAs
- Lack the adrenergic cholinergic and sodium channel effects of TCAs
- Much better tolerability and better safety profile
- Venlafaxine, duloxetine and milnacipran in this class
- First or second line agents for neuropathic pain

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SNRIs (2)

- Duloxetine has FDA indication for fibromyalgia, diabetic neuropathy and chronic musculoskeletal pain.
- Pain efficacy may be no better for 120 mg as 60 mg; antidepressant efficacy may require the higher dose
- Milnacipran has FDA-indication for fibromylagia
- No head-to heads comparing the SNRIs
- Tolerability may vary – venlafaxine associated with hypertension

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Anti-spasmodics

- Cyclobenzaprine, a TCA, efficacious in fibromyalgia, and commonly used in musculoskeletal disorders – calming and sedating.
- Baclofen, a GABA-B agonist, has limited support
- Most anti-spasmodics have a third-line role in CNCP control.

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Topicals

- A number of agents are now available, including topical lidocaine, topical NSAIDS, topical salicylates and topical capsaicin.
- All appear to have efficacy in regional control of neuropathic & nociceptive pain.
- Mechanisms include local anti-inflammation, depletion of substance P, neural desensitization.

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AND

- SSRIs appear less effective than SNRIs and TCAs
- Corticosteroids
- α2-adrenergic agonists (tizanidine)
- NMDA antagonists (dextromethorphan, memantine)
- Na^+-channel blockers (mexiletine)
- CB1/CB2 agonists

Please see references for more extensive discussion

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Combination Therapy

- Because no one drug is a “magic bullet” polypharmacy is the norm
- Few studies have examined efficacy of drug combinations (*e.g.* Tesfaye et al. (2013) *Pain* **154:** 2616-2625)
- Non-opioid analgesic combinations with opioids are common

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Treatment Approach for Chronic Pain (1)

1. Gather history exam and physical data, collaborate with treating MD
2. Perform psychiatric assessment
3. If on opiates, are they effective or a problem

Treatment Approach for Chronic Pain (2)

1. If not on opiates, treat psychiatric co-morbidity
2. Suggest non-opiate approaches, or give support to MD where opiates are appropriate.

Treatment Approach for Chronic Pain (3)

1. If on opiates, and ineffective:
2. Treat psychiatric co-morbidity AND
3. Begin (or recommend) non-opiate adjuncts
4. Refer for behavioral pain intervention

Treatment Approach for Chronic Pain (4)

1. **If on opiates, and problematic:**
2. **Orchestrate opiate taper and/or detox**
3. **Aggressively begin (or recommend) non-opiate adjuncts**
4. **Refer for substance abuse treatment and behavioral pain intervention**

Take Home Message

- Pharmacological pain management is only one arm of a multifactorial approach.
- With proper diagnosis, risk assessment and monitoring opioids may be indicated, BUT if they fail and/or function does not improve, there are options.
- Pain control usually requires a TEAM approach of many disciplines – use what you have available.

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