ANALGESICS: SCIENCE OR DOGMA?

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Agenda for Today's Presentation

An evidence-based approach to medications for pain.

We will discuss medications that are most common to treat pain?

We will discuss the evidence to support use of these medications.

What's the Problem with Pain Medicine?

A mountain of information makes it difficult to identify facts and develop effective plans.

What We Really Know (facts)

What We Think We Know

Multimillion-Dollar Marketing Campaigns

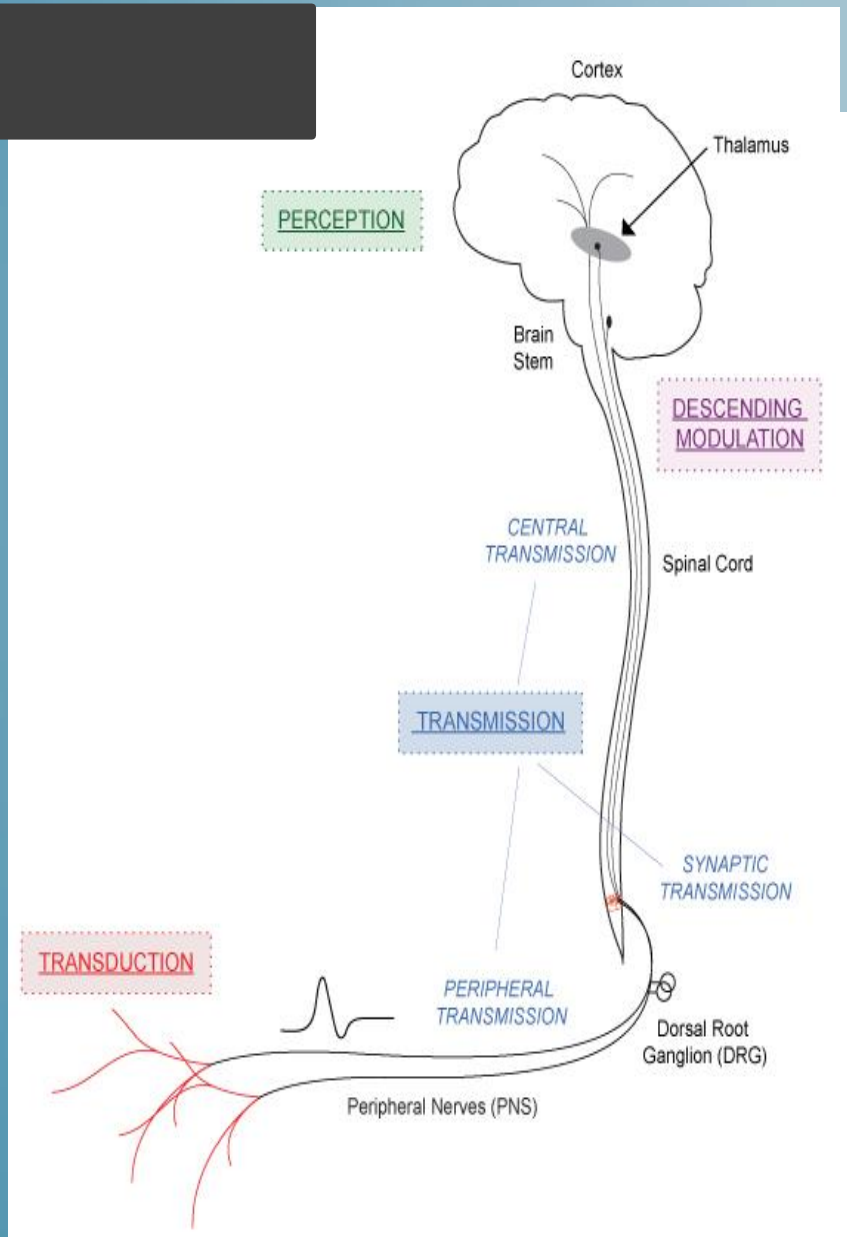
Image from Flickr user Cheryl Leong

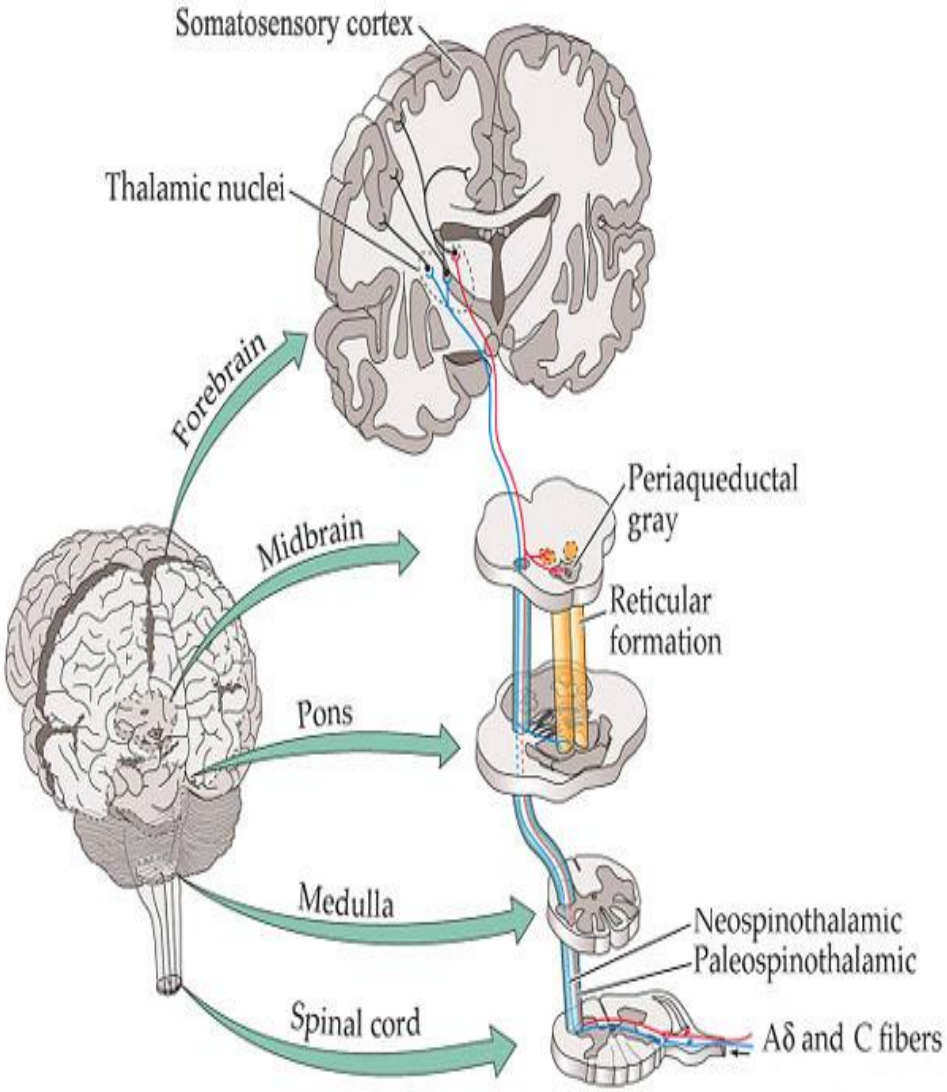
ECONOMICS

- Pharmaceutical agents represents a significant portion of the total cost of managing chronic pain.
- Many of these agents are very expensive.
- A typical chronic pain patient's life-time medical cost estimate will cost more than $1,000,000.00 with 70-80% of the cost derived from pharmaceutical agents.
- The cost of ineffective medications drives cost containment measures across the healthcare industry including physician reimbursements.

- SOC is moving toward evidenced based medicine.
- Solid knowledge of the evidence is necessary to practice within this emerging SOC.

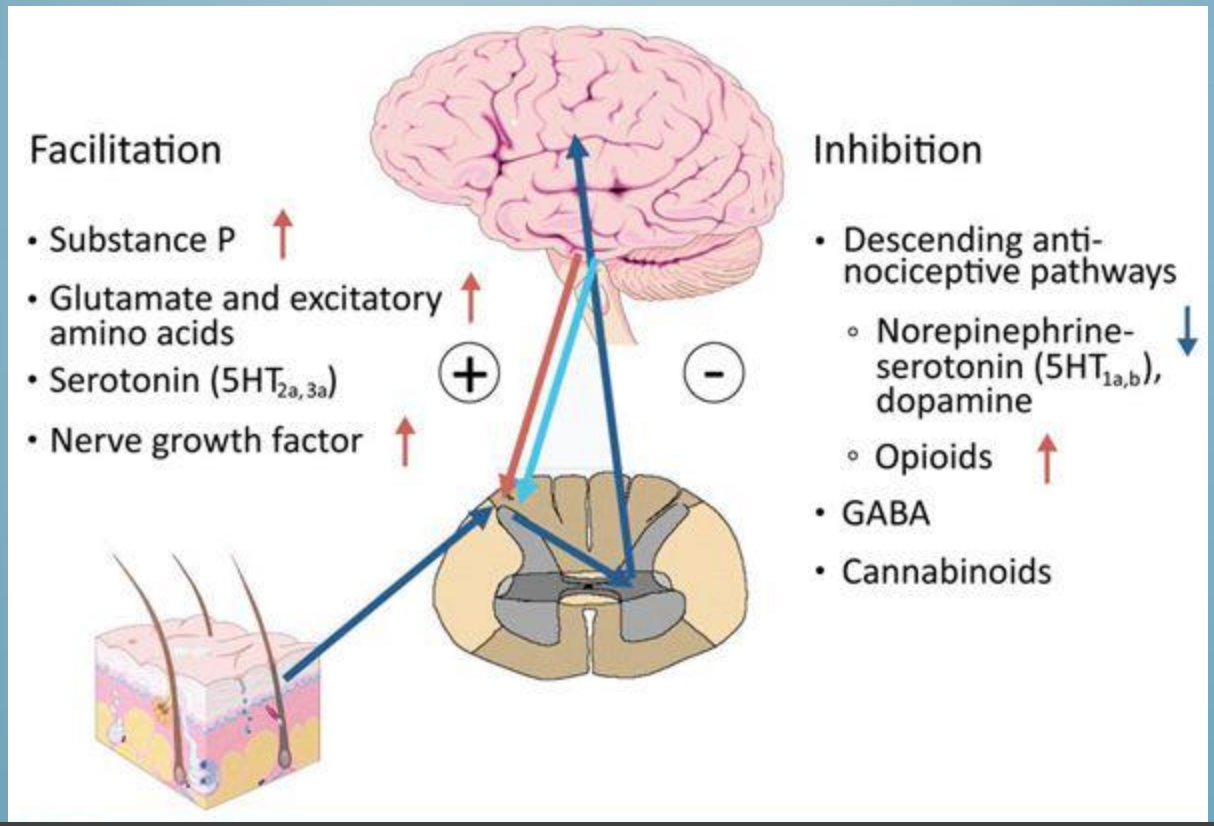
What is Pain?





BIOLOGICAL PSYCHOLOGY, Fourth Edition, Figure 8.24 © 2004 Sinauer Associates, Inc.

The Molecular Basis for Pain Medications



NNT

- *Number needed to treat is defined as the number of patients that must be treated with a given pharmaceutical agent in order for one patient produce a given response.*

- *Typically defined in the pharmaceutical industry as a greater than or equal to 50% reduction in pain.*

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)/COX-2 Inhibitors

"Anti-inflammatories": Is there validated evidence of inflammation?

- *Mechanism: inhibit an enzyme in the inflammatory pathways called cyclooxygenase (COX-1 and COX-2)*
  - *Non-specific inhibitors*
  - *Selective COX-2 inhibitors*
  - *Selective inhibitors have fewer gastrointestinal side effects.*
  - *NSAID class NNT = 2.9*
- *Adverse Events*
  - *COX-2 inhibitors cause fewer GI side effects than NSAIDs, but increased cardiovascular risks*
  - *GI bleed rate are similar between COX-2 and NSAIDs*
  - *Cardiovascular risks with NSAIDs*
  - *Naproxen is one of the safest NSAIDs*
  - *Delay of healing in all soft tissues (muscle, ligaments, tendons, cartilage) with NSAIDs*

Non-Specific Inhibitors

- Aleve
- Motrin/Advil
- Voltaren/Cataflam

Selective COX-2 Inhibitors

- Vioxx
- Bextra
- Prexige

NSAIDs and COX-2 Inhibitors

Generally supported	
Osteoarthritis	– Appear superior to acetaminophen – No difference between NSAID and COX-2 inhibitors – No evidence of long-term effectiveness for pain or function
Equivocally supported	
Back Pain	– Not more effective than acetaminophen
Chronic lower back pain	– Cochrane Review: NSAIDs not more effective than acetaminophen, muscle relaxers, opioids – NSAIDs have more side effects than placebo and acetaminophen, but fewer than muscle relaxers and opioids – No NSAID or COX-2 is more effective
Generally not supported	
Axial lower back pain (no leg pain)	– Cochrane Review: No difference between NSAID and acetaminophen – Acetaminophen had fewer side effects – NSAIDs did not shorten the recovery period
Lower back pain with Sciatica	– Cochrane Review: No difference between NSAID and placebo
Neuropathic pain	– Inconsistent evidence for long term use

Opioids

"Have the potential to produce profound analgesia, mood changes, physical dependence, tolerance and a hedonic ('rewarding') effect which may lead to compulsive drug use."[1]

- *Mechanism of action: affect naturally occurring opioid receptors on nerve cells in the brain and spinal cord (and elsewhere)*
  - *Effect of an opioid drug can stimulate or antagonize a receptor*
- *Lethal accidental overdoses from opioids now exceed deaths from motor vehicle accidents, the previous leading cause of accidental deaths*

Examples

- Tramadol
- Codeine
- Hydrocodone
- Hydromorphone
- Oxymorphone
- Morphine
- Fentanyl
- Oxycodone
- Methadone
  Buprenorphine
- Naloxone
- Naltrexone

1. Report of the International Narcotics Control Board for 2007. United Nations, New York, 2008.

Opioids for Chronic Pain

Limitations on evidence.

- *No long-term outcome studies*
- *Existing short-term outcome studies exclude risk factors for abuse commonly seen in pain clinics*
  - *Risk factors: personal and family history of substance abuse, nicotine abuse, age less than 45, depression, anxiety, impulse control problems like personality disorders, ADD, OCD, and hyper-vigilant states such as PTSD, abuse history*
  - *Few of the short-term outcome studies looked at function*
  - *Pain relief is typically reported at about 30% at best*
  - *Studies had high drop-out rates due to intolerable side effects or lack of efficacy*
- *When function was measured, function declined despite a reported analgesic response*
  - *Disconnect between function and analgesia is not understood and probably is result of chemically coping*
- *Adverse effects*

Opioids

Indications and evidence.

Generally supported	
Nociceptive pain	– Defined as pain from ongoing tissue damage. Example: cancer, post-surgical – Recommended as a first line of treatment, wean off asap
Equivocally supported	
Osteoarthritis/Neuropathic pain/Back pain	– Not a first line therapy
Chronic lower back pain	– Not recommended as a first line treatment – Must produce a functional improvement to continue with this treatment
Generally not supported	
Headaches	– Not recommended because of analgesic rebound headaches (also a risk with NSAID , acetaminophen, and migraine specific analgesics with use > 2 days per week).

Muscle Relaxants

Is there objective evidence of muscle spasm?

- *Mechanism:*
  - *Varied, depending on medication.*
  - *Act on nervous system and/or muscle to decrease muscle tone or spasm*
- *Three general types*
  - *Antispasticity Drugs: decrease neurological spasticity from MS, CP, spinal cord injury)*
  - *Antispasmodics: decrease muscle spasms such may occur with lower back pain*
  - *Mixed Antispasticity/antispasmodics*
- *Adverse effects vary: sedation, dependence, dry mouth, liver impairment*

Antispasticity

- Lioresal

Antispasmodics

- Flexeril
- Robaxin
- Skelaxin
- Parafon Forte
- Norflex
- Soma

Mixed Antispasticity Antispasmodics

- Zanaflex
- Benzodiazepines

Muscle Relaxants

Equivocally supported	
Cyclobenzaprine (Flexeril)	– Limited, mixed evidence; not recommended for chronic use – More effective than placebo for back pain; modest effect with significant side effects – Best effect in first 4 days after injury, best benefits observed when treating fibromyalgia)
Chlorzoxazone (Parafon Forte)	– Advantages over other muscle relaxants include less sedation and less evidence of abuse
Tizanidine (Zanaflex)	– Efficacy demonstrated in several studies for low back pain – FDA approved for spasticity, one study demonstrated significant decrease in pain and was recommended as a first line treatment – Side Effects: Somnolence, hepatotoxicity (Liver function test recommended at baseline, 1, 3, and 6 months)
Generally not supported	
Baclofen (Lioresal)	– Not indicated for non-neurological spasm; has also shown potential in treating lancinating, paroxysmal neuropathic pain (trigeminal neuralgia) (not FDA approved)
Carisoprodol (Soma)	– Well known abuse potential; controlled substance in all 50 States
Benzodiazepines	– Not recommended due to rapid tolerance and dependency issues

Adjunctive Analgesics

Medications commonly used for neuropathic pain and select musculoskeletal conditions.

Two general categories:

- *Antidepressants*
  - *Tricyclic Antidepressants (TCA)*
  - *Selective serotonin and norepinephrine reuptake inhibitors (SNRI)*
- *Anticonvulsants*
  - *Neuromembrane Stabilizers*

Tricyclic Antidepressants

- Elavil
- Pamelor
- Norpramin

Selective Serotonin and Norepinephrine Reuptake Inhibitors

- Cymbalta
- Savella
- Effexor

Anticonvulsants/ Neuromembrane Stabilizers

- Neurontin
- Lyrica
- Topamax

Tricyclic Antidepressants

Indications and evidence.

- *Neuropathic pain:*
  - *Considered a first line treatment for neuropathic pain, supported by both meta-analysis and systematic reviews*
    - *Demonstrated to be helpful in central post-stroke pain, post-herpetic neuralgia, painful diabetic and non-diabetic neuropathy, and post-mastectomy syndrome. NNT = 3 but NNH =14*
    - *Negative results in spinal cord pain and phantom limb pain (possible poor study design), HIV neuropathy, cisplatinum neuropathy, neuropathic cancer pain or chronic root pain*
  - *Side Effects:*
    - *Contraindicated with cardiac arrhythmias or epilepsy (baseline EKG recommended)*
    - *Narrow therapeutic window and low threshold for toxicity (blood levels should be checked)*
    - *Dry mouth, constipation, sweating, dizziness, orthostatic hypotension, urinary retention*

Serotonin and Norepinephrine Reuptake Inhibitors

Indications and evidence.

Equivocally supported	
Duloxetine (Cymbalta) and milnacipran (Savella)	– Approved for diabetic neuropathy, chronic musculoskeletal pain (Cymbalta), anxiety (Cymbalta only), fibromyalgia (Cymbalta and Savella) and depression – Savella should be used with caution in epileptic patients, narrow angle glaucoma, alcohol abuse or liver impairment – Use with caution in bipolar disorder (Cymbalta and Savella) – **Cymbalta NNT: OA =7, DM =6, Fibro =6-8** – **Savella NNT: Fibro =12**
Pregabalin (Lryica)	– Approved for fibromyalgia and diabetic neuropathy – **NNT: Fibro =12, DM =4**
Bupropion (Wellbutrin)	– Small study (n = 41) showed efficacy in neuropathic pain
Generally not supported	
Venlafaxine (Effexor)	– Use for pain is off label

Topical Agents and Compound Topical Creams

Equivocally supported	
Topical Nonsteroidal Anti-inflammatory Drugs (NSAIDs)	– Examples: Ketoprofen gel, Flector patch – Limited efficacy – Low back pain, osteoarthritis of the shoulder, hip, neuropathic pain no indication – Osteoarthritis of the knee, some evidence of effectiveness for 12 weeks then wears off
Generally not supported	
Lidoderm Patch	– No pharmaceutical rationale that it would be effective for any conditions below skin level (90% of lidocaine is rapidly metabolized by liver and plasma cholinesterase). – Approved for post-herpetic neuralgia
Compounded Topical Creams	– Typically involve a cocktail of various drugs including an NSAID, ketamine, muscle relaxer, local anesthetic, other "analgesics," and a carrier chemical to carry the drugs across the skin barrier – There no evidenced based literature to support the use of these compounded creams which can be very expensive

In Summary

Use evidence to determine the diagnosis and to prescribe appropriately.

- *Medications that may be effective for acute pain often do not have proven long-term effectiveness*
- *NSAIDs may be helpful in arthritic conditions such as post-traumatic arthritis*
  - *Significant gastrointestinal and cardiovascular side effect profile*
  - *If prescribed for inflammation, there should be physical evidence of inflammation*
- *Chronic use of opioids, particularly at high doses, is not supported by evidence . Objective functional measures must be used to determine a therapeutic benefit. Opioid abuse is at epidemic levels.*
  - *Consider the significant risk of physical dependence , chemical coping, and substance use disorders*
- *Muscle relaxants may be helpful for short-term use for acute conditions; not supported for long-term use*
  - *Some muscle relaxants have known abuse potential (avoid Soma)*
  - *Zanaflex has some evidence for benefit.*
- *Adjunctive medications for neuropathic pain and select musculoskeletal conditions can be effective when used for a clear-cut indication. NNT is high.*
  - *Less effective when used for non-specific indications*
- *Topical agents have little evidence for use .*

Defining a Therapeutic Benefit

Chronic pain does not have an on/off switch.

- *Meds must be applied in context of the overall rehabilitation plan*
- *Blind prescription of meds to treat "pain" is less likely to be effective*
- *A pain assessment should clarify what objective measures you are trying to improve: Bio, Psycho, Social*
- *Know what problem a medication is prescribed for*
  - *Inflammation, nerve pain, spasm, muscle joint pain, emotional distress*
- *The concept of "carefully selected"*

An accurate diagnosis and clear treatment plan prevent a snowball from becoming an avalanche

Measuring Effectiveness

Examples from Official Disability Guidelines (ODG).

- *Work functions and/or activities of daily living, self report of disability*
  - *Walking, driving, keyboard or lifting tolerance, Oswestry, pain scales*
- *Physical impairments*
  - *Joint range of motion, muscle flexibility, strength, or endurance deficits*
- *Approach to self-care and education*
  - *Reduced reliance on other treatments, modalities, or medications*
- *Return to normal quality of life*
  - *Go to work/volunteer each day, normal daily activities each day, have a social life outside of work, take an active part in family life.*
- *Behavioral*
  - *Fear avoidance, catastrophizing, symptom magnification*

Key Points

Keep your focus on asking the right questions, making evidence-based decisions, and providing education/informed consent.

- *There are no magic bullets: effectiveness depends on careful selection*
- *Other medications suffer the same issues as treatment with opioids*
  - *Lack of evidence basis for widespread or long-term use*
  - *Used outside carefully selected indications, trial-and-error, polypharmacy*
  - *Risk of side effects, risk of misuse*
- *The solution lies in developing a treatment strategy that:*
  - *Assesses the biological aspect of the pain symptoms, the psychosocial factors of the pain experience*
  - *Chooses medications as part of a more compressive treatment plan*
  - *Includes both symptoms and functional measures of response to medications*
  - *Deemphasizes the quick fix, magic bullet expectations of medications*
  - *Educate the injured worker to make better personal health decisions and choices*

CONCLUSIONS

- *Analgesics have limited evidence to support long term use*
- *Many of the medications are expensive*
- *Without objective and clinically meaningful therapeutic changes (functional), the medications should be discontinued to avoid potential dependence, abuse, diversion, and risk of death.*
- *The $ bucket is finite.*
- *Continued prescribing of expensive and ineffective medications will result in decrease reimbursement for procedures and E&M coding.*