Opioids: History & Pharmacology

Thomas A. Coury, DO
Physical Medicine & Rehabilitation
Desert Sky Spine & Sports Medicine

October 17, 2020

2018 AZ Law, Part 1 of 4

- 5-day limit on initial prescriptions, 14-day limit on post-surgical prescriptions
- Defined as no rx in the past 60 days
- Exceptions: cancer, neonatal withdrawal, trauma, substance abuse disorder maintenance, burns, SNF, hospice, end-of-life care

2018 AZ Law, Part 2 of 4

- 90 MME limit
  - New prescriptions
  - Exceptions
    - Post-surgical rx
    - Permission from a board certified pain physician
    - Any of the exceptions on the previous slide
- Prohibition against physicians dispensing opioids
- 3 hours of opioid education

2018 AZ Law, Part 3 of 4

- You must reference the Controlled Substances Prescription Monitoring Program database (CSPMP)
- Prescriptions must be sent electronically (not written, not "called in")
  - Our EMR requires double authentication
- Complete History and Physical examination, documenting diagnosis and reason for medical necessity of opioids

2018 AZ Law, Part 4 of 4

Utilize non-narcotic methods of pain relief first

Avoid use of benzodiazepines and opioids

Prescribe naloxone for anyone over 90 MME

Good Samaritan Law – Anyone reporting an overdose cannot be charged with narcotic-related crimes.

Opioids: History and Pharmacology

- History of Opioid Use
- History of Opioid Legal Regulation
- Classification of Opioids
- Opioid Mechanism of Action
- Routes of Administration, Short acting, Long acting

A Brief Tour through the History of Opioids

Papaver somniferum

Papaver somniferum

- Native range was probably eastern Mediterranean, but has been cultivated by humans throughout the ancient world, its true native origins have been lost to time.

- Medicinal and culinary uses predate written history, and are found ubiquitously throughout the ancient world.

- Poppy seeds and poppyseed oil continue to be used for culinary purposes.

Q: Why don't we see opium poppy plant busts as frequently as marijuana busts?

A: Economics. It takes 1 acre of poppy to yield 600 mg of heroin. Much cheaper to import heroin from other countries.

Papaver somniferum

- Three primary uses of the opium poppy plant
  - Poppy Seed Cultivation
  - Extracting opioids (morphine, codeine)
  - Extracting alkaloids for manufacturing other opiates (hydrocodone)

Nutritional Value of Poppy Seeds

Nutrition Facts
Serving Size 100 Grams of seed
Servings Per Container Approx 1.7

Amount Per Serving
Calories 533 Calories from fat 374

		% Daily Value*
Total Fat	450G	69%
Saturated Fat	5G	24%
Trans Fat	0MG	
Cholesterol	0MG	0%
Sodium	21MG	1%
TTL Carbohydrate	24G	8%
Dietary Fiber	10G	40%
Sugars	14G	
Protein	118G	
Vitamin A		0%
Vitamin C		0%
Calcium		145%
Iron		52%

*based on 2000 calorie diet

CONTAINS: POPPY SEED

Opium Etymology

- Opos – Juice (Greek)
- Opion – Poppy Juice (Greek)
- Opium (Middle English)
- Opioids – any substance derived from opium
- Opiate – chemicals that can be isolated from opium without further manipulation/synthesis

Opium den

- Popular in the 1800s
- Often, more frequented than saloons
- Associated with Chinese immigrants in the US, one of the few businesses the Chinese were allowed to operate
- High-class and low-class dens were present, based on socioeconomic status

History: Laudanum

- Paracelsus (1600s)
  - Swiss physician; coined the term for a tincture of opium mixed with other substances
- Thomas Syndenham (1700s)
  - British physician; Mixed opium and alcohol to make laudanum
- A.T. Still
  - "Shall we benumb the writhing intestines with **opium**, and poison the organs" (Journal of Osteopathy, December 1897)
- Today
  - Also known as tincture of opium
  - Only FDA indication is diarrhea, but used off-label for neonatal withdrawal syndrome

History: Morphine

- Friedrich Wilhelm Adam Sertürner (1804)
  - German Physician and alkaloid chemist
  - First to isolate the alkaloid he named Morpheum
- Morpheus – Greek god of dreams
- Commercially produced by Merck in the 1800s

"I consider it my duty to attract attention to the terrible effects of this new substance I called morphium in order that calamity may be averted. (Sertürner)

History: Heroin

- Diacetylmorphine, or diamorphine
- Synthesized by Charles Romley Alder White (1874)
- Purported to be the “hero” that would save you from your morphine addiction

History: Methadone

- Synthesized in Germany in 1937
- Trade name Dolophin, contrary to urban legend, is not coined from Adolph Hitler. Instead “Dolos” means “pain” and “fin” means “end”, and was coined after WWII
- Used to for opioid addiction maintenance, although this is not universal throughout the world

A Brief Tour through Opioid Regulation in the US

History of Opioid Regulation

- **1906 – Pure Food and Drug Act**
  Preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, and for other purposes. Punishment included fines and prison time.

- **1909 – Smoking Opium Exclusion Act**
  Banned the importation, possession and use of "smoking opium". Did not regulate opium-based "medications". First Federal law banning the non-medical use of a substance.

- **1914 – The Harrison Act**
  In summary, The Harrison Act of 1914 was written more to have all parties involved in importing, exporting, manufacturing and distributing opium or cocaine to register with the Federal Government and have taxes levied upon them. Exempt from the law were physicians operating “in the course of his professional practice”

- **1919 – Supreme Court** ratified the Harrison Anti-Narcotic Act in Webb et al., v. United States and United States v. Doremus, then again in Jin Fuey Moy v. United States, in 1920, holding that doctors may not prescribe maintenance supplies of narcotics to people addicted to narcotics. However, it does not prohibit doctors from prescribing narcotics to wean a patient off of the drug. It was also the opinion of the court that prescribing narcotics to habitual users was not considered “professional practice” hence it then was considered illegal for doctors to prescribe opioids for the purposes of maintaining an addiction. It can be argued that today’s addiction medications are not intended to *maintain an addiction* but to facilitate addiction remission. In which case, this opinion of the court should not preclude practitioners from prescribing buprenorphine or methadone to patients suffering from an addictive disorder.

- **1924 – Heroin Act**
  Prohibited manufacture, importation and possession of heroin illegal – even for medicinal use.

History of Opioid Regulation

- **1922 -- Narcotic Drug Import and Export Act**
  Enacted to assure proper control of importation, sale, possession, production and consumption of narcotics.
- **1927 -- Bureau of Prohibition**
  The Bureau of Prohibition was responsible for tracking bootleggers and organized crime leaders. They focused primarily on interstate and international cases and those cases where local law enforcement official would not or could not act.
- **1932 -- Uniform State Narcotic Act**
  Encouraged states to pass uniform state laws matching the federal Narcotic Drug Import and Export Act. Suggested prohibiting cannabis use at the state level.
- **1938 -- Food, Drug, and Cosmetic Act**
  The new law brought cosmetics and medical devices under control, and it required that drugs be labeled with adequate directions for safe use. Moreover, it mandated pre-market approval of all new drugs, such that a manufacturer would have to prove to FDA that a drug were safe before it could be sold
- **1951 -- Boggs Act**
  Imposed maximum criminal penalties for violations of the import/export and internal revenue laws related to drugs and also established mandatory minimum prison sentences.
- **1956 -- Narcotics Control Act**
  Increased Boggs Act penalties and mandatory prison sentence minimums for violations of existing drug laws.
- **1965 -- Drug Abuse Control Amendment**
  Enacted to deal with problems caused by abuse of depressants, stimulants and hallucinogens. Restricted research into psychoactive drugs such as LSD by requiring FDA approval.

History of Opioid Regulation

- **1970 -- Controlled Substance Act | Controlled Substances Import and Export Act**
  These laws are a consolidation of numerous laws regulating the manufacture and distribution of narcotics, stimulants, depressants, hallucinogens, anabolic steroids, and chemicals used in the illicit production of controlled substances. The CSA places all substances that are regulated under existing federal law into one of five schedules. This placement is based upon the substance's medicinal value, harmfulness, and potential for abuse or addiction. Schedule I is reserved for the most dangerous drugs that have no recognized medical use, while Schedule V is the classification used for the least dangerous drugs. The act also provides a mechanism for substances to be controlled, added to a schedule, decontrolled, removed from control, rescheduled, or transferred from one schedule to another.

- **1973 – Drug Enforcement Agency**
  By Executive Order, the DEA was formed to take place of the Bureau of Narcotics and Dangerous Drugs.

- **1974 –Narcotic Addict Treatment Act of 1974 - Public Law 93-281**
  Amends the Controlled Substance Act of 1970 to provide for the registration of practitioners conducting narcotic treatment programs. [methadone clinics] It also provides legal definitions for the phrases “maintenance treatment” and “detoxification treatment”.

- **1986 -- Anti-Drug Abuse Act of 1986**
  Strengthened Federal efforts to encourage foreign cooperation in eradicating illicit drug crops and in halting international drug traffic, to improve enforcement of Federal drug laws and enhance interdiction of illicit drug shipments, to provide strong Federal leadership in establishing effective drug abuse prevention and education programs, to expand Federal support for drug abuse treatment and rehabilitation efforts, and for other purposes. It also re-imposed mandatory sentencing minimums depending on which drug and how much was involved.

- **1988 -- Anti-Drug Abuse Act of 1988**
  Established the Office of National Drug Control Policy (ONDCP) in the Executive Office of the President; authorized funds for Federal, state and local drug enforcement activities, school-based drug prevention efforts, and drug abuse treatment with special emphasis on injecting drug abusers at high risk for AIDS.

History of Opioid Regulation

- **2000 -- Federal – The Drug Addiction Treatment Act of 2000 (DATA 2000)**
  It enables qualified physicians to prescribe and/or dispense narcotics for the purpose of treating opioid dependency. For the first time, physicians are able to treat this disease from their private offices or other clinical settings. This presents a very desirable treatment option for those who are unwilling or unable to seek help in drug treatment clinics. Patients can now be treated in the privacy of their doctor's office, as are other people being treated for any other type of medical condition. One medicine doctors may now prescribe is Buprenorphine. The major downfall of this Act is the limitation of 30 patients per practice – which means that large facilities, no matter how many physicians are there, can only treat 30 patients at a time.

Arizona Opioid Epidemic Act (2018)

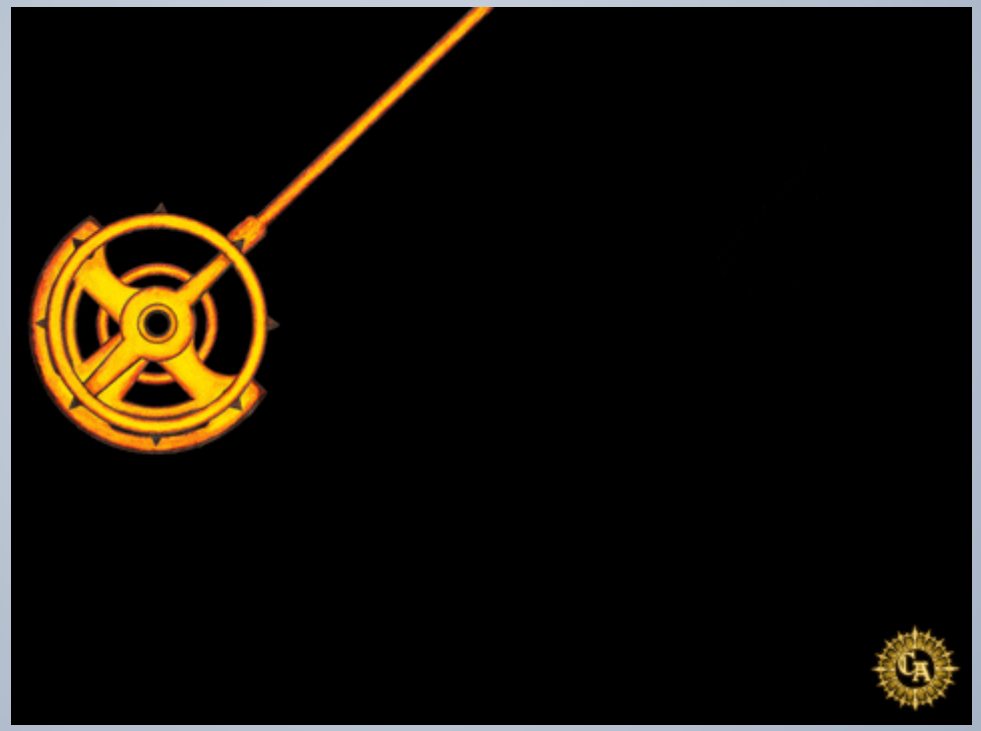
Verbiage of the Bill itself:

https://www.azleg.gov/legtext/53leg/1S/laws/0001.pdf

AZDHS document summarizing the guidelines:

https://www.azdhs.gov/documents/audiences/clinicians/clinical-guidelines-recommendations/prescribing-guidelines/az-opioid-prescribing-guidelines.pdf

Pendulum of Addiction Crises vs Opioid Demonization



Opioid epidemic vs COVID-19 pandemic

- March 2020, DEA drops face-to-face encounter for opioid prescription

- Opioid usage continues to escalate, amidst isolation, fear, socioeconomic factors

Routes of Administration

- Inhaled
  - End-of-life palliation of dyspnea
- Mucosal
  - Fentanyl (cancer); Bupenorphine (chronic)
- Oral / GI
  - Tablets, Pills, Liquids
- Intravenous

- Epidural/intrathecal
  - Intrathecal pump therapy for chronic pain
- Rectal
  - Admittedly, overlooked route of opioid administration

Short vs Long Acting

- Pharmacokinetics of an opioid is dependent on multiple factors
  - Chemical composition
  - Route of administration
  - Hydrophilic/hydrophobic properties (BBB)
  - Dose
  - How it is released

Short Acting

- Examples of Short-Acting Opioids
  - Oral Hydrocodone
  - Oral Oxycodone
  - Oral Morphine
  - Oral Tramadol

- Examples of Very Short-Acting Opioids
  - IV Fentanyl
  - IV hydromorphone
  - Oral hydromorphone

Long Acting

- Examples of Long-Acting Opioids
  - Oxycontin, Oxycodone ER, Xtampza
  - MS Contin
  - Ultram, Tramadol ER
- Examples of Very Long-Acting Opioids
  - Fentanyl patch
  - Buprenorphine patch (Butrans)
  - Intrathecal pump therapies*

Same molecule, different pharmacokinetics

- Morphine IR
  - Morphine ER, MS Contin
- Tramadol
  - Tramadol ER, Ultram
- Hydromorphone (Dilaudid)
  - Hydromorphone ER, Exalgo
- Oxycodone
  - Oxycodone ER, Oxycontin
- Hydrocodone
  - Zohydro ER, Hysingla ER
- Tapentadol (Nucynta)
  - Nucynta ER

Conclusions & Recommendations

- New Rx need to be 5 days or less
- Complete H&P includes diagnosis, medical justification for opioids, patient education regarding the dangers of opioids, and a physical examination
- Utilize non-narcotic methods of pain relief, before, during, and after opioid therapies
- Check the CSPMP and perform random UDS
- Like any classification of medication, understand any drug-drug interactions, metabolism, and elimination
- Keep Rx at 90 MME or lower
- Avoid Benzodiazepines and opioids
- Consider Rx Narcan for anyone on chronic opioid therapy

Treating Chronic Pain without Narcotics

Thomas A. Coury, DO
Physical Medicine & Rehabilitation
Desert Sky Spine & Sports Medicine
October 17, 2020

Non-opioid treatments for chronic pain

- We will utilize low back pain as a model for how to treat without the use of opioids.
- The first step in the treatment of any chronic painful condition is to get an appropriate diagnosis.
- Treat “pain” as a symptom, not a diagnosis.
  - Myofascial, degenerative, inflammatory, biomechanical, psychological

Treatment: Reassurance & Education

- Reassurance should include information about the underlying pathology, the fact that the prognosis is good, and that they should return to regular activity

- Occasionally, this is all that a patient may need

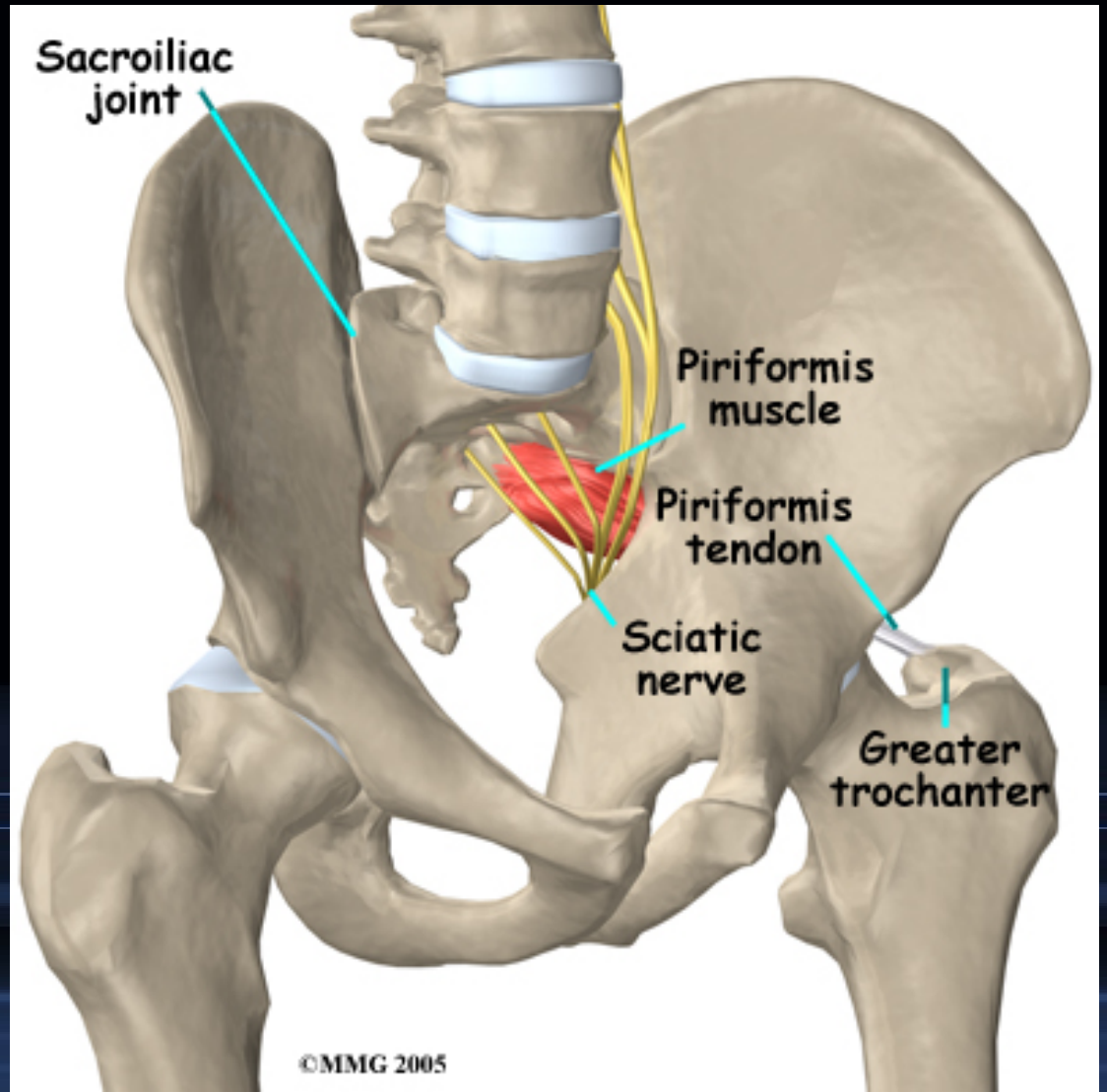
Treatment: Chronic, nonfocal pain

- Assess previous hx of trauma
  - Physical, emotional, sexual
  - Encourage counseling for these
- Labs to monitor
  - Vitamin D, thyroid, testosterone
- Sleep hygiene
- Gentle aerobic exercise daily
- Try to eliminate stressors that exacerbate the pain, without decreasing activity

Treatment: Biomechanics

- Postural retraining is important for two primary reasons
  - Exercises are more effective if they are done from a position of proper alignment
  - Virtually all patients will spend much more time in habitual postures such as sitting and standing than will ever be spent exercising

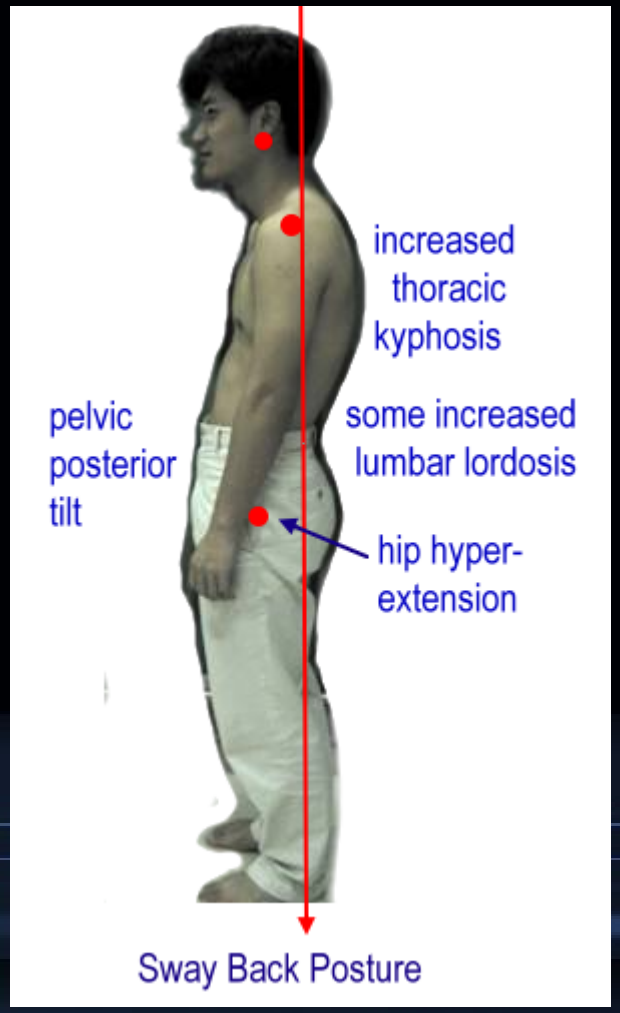
Biomechanics: Posture



Biomechanics: Anterior Pelvic Tilt

- Weak anterior abdominals
- Tight one-joint hip flexors
- Tight two-joint hip flexors
- Tight paraspinals
- Weak hip extensors

Biomechanics: Posterior Pelvic Tilt



- Weak iliopsoas
- Weak external obliques
- Tight hamstrings

Biomechanics: Lateral Pelvic Tilt

- Weak gluteus medius
- Tight unilateral trunk muscles
- Slight heel lift may correct by allowing the tight muscles to relax

Treatment: Aerobic Activity

- Studies have found that group classes that combine low-impact aerobics with strengthening and stretching floor exercises can be as effective in reducing pain and decreasing disability as individualized PT and strengthening with weight machines
- No particular type of aerobic activity has been found to be more effective for gaining fitness or decreasing pain than another for pts w/ back pain
- Slow walking reduces spine motion and causes overall higher spine loading, and therefore more pain than faster walking with arm swings

Treatment: Aquatic exercise

- Buoyancy effects
- Decreased pain via gate theory
  - Sensory input from water temperature, hydrostatic pressure and turbulence

Treatment: Manipulation

- Types of manipulation
  - High Velocity, Low Amplitude (HVLA)
  - Soft tissue techniques
  - Muscle Energy Techniques
  - Strain/Counterstrain

Treatment: Manipulation

- Most countries recommend spinal manipulation for treatment of acute low back pain
- Metaanalysis reveals manipulation to be as effective as other treatments (analgesics, exercise, physical therapy), but not more effective

Treatment: Traction

- Studies have varied in weight, frequency, and length of treatment
- Multiple randomized controlled trials using different doses of traction have not found traction to be effective for treatment of back pain

Treatment:
Lumbar supports

- One study showed that patients who wore a lumbar support plus rigid insert had more subjective improvement than those who wore a brace without support
- No evidence that lumbar supports actually increase intraabdominal pressure, decrease muscle forces and fatigue, or limit ROM

Treatment: Heel lifts

- Must differentiate if leg length discrepancy is anatomic or functional
- Correct foot biomechanics prior to using lift
- Small unblinded studies have found that correction of leg length discrepancy decreases low back pain
- No large controlled trials

Treatment:

Transcutaneus electrical nerve stimulation

- Metaanalyses of TENS outcomes show trends toward better pain reduction, better function, and satisfaction with treatment as compared with placebo, but these trends do not reach statistical significance

Treatment: Massage

- Mechanism of action thought to include relaxation and stress reduction; theraputic benefits of touch, and beneficial effects on the structure of function of tissues and pain sensation
- High-quality studies have found massage to be effective for improving symptoms and functions in subacute and chronic low back pain

Treatment: Yoga/Pilates

- Have been found helpful in case series but have not been subjected to stringent randomized controlled trials

Treatment: Medication

- NSAIDs
- Muscle Relaxants
- Antidepressants
- Anticonvulsants
- Topical treatments
  - Lidoderm
  - Capsacin
- Opioids

Treatment:
Trigger Point Injections

- Useful for myofascial component of mechanical low back pain
- Cochrane review of injection therapy found trigger point injections to be effective in treatment of low back pain

Treatment: Acupuncture

- The general consensus in multiple reviews is that evidence for acupuncture in relieving low back pain is either positive or inconclusive.
  - In Britain, the BMA analysis found it to be effective
  - In Canada, the Canadian/Alberta Health Authorities found the results inconclusive
- Most studies are poorly designed or controlled

Treatment:
Botulinum toxin

- Increasingly being used to treat low back pain.
- Mechanism of action could be through changes in sympathetic tone, reduction of muscle spasms
- Studies at this point are small, and results are inconclusive

Treatment: Prolotherapy

- Consists of series of injections into spinal ligaments to cause inflammation and thickening of ligaments
- Still controversial, with inconclusive results at this point

Interventional Techniques

- Epidural injections
- Facet Joint Injections/Medial Branch Blocks/RFA
- SI joint injections
- Selective Nerve Root Blocks

Interventional Techniques

- Hip Injections
- Spinal Cord Stimulator Trials
- Pump Trials
  - Pain pump; Baclofen pump
- Provocative Discography
  - IDET; Percutaneous Disc Decompression

Treatment: General Approach

- September 2007 Archives of PM&R Article
- Set in Switzerland
- Compared Function-Centered vs Pain-Centered Rehabiliation Program
  - FCT emphasized activity despite pain by using work simulation, strength, endurance, and cardiovascular training
  - PCT emphasized pain reduction and included passive and active mobilization, stretching, strength training
- Compared with PCT, FCT significantly increased average number of work days during the follow-up year (primary outcome)
  - Did not affect unemployment rate or number of patients receiving permanent disability allowance

Sources

Barr, K., Harrast, M. Low Back Pain, Physical Medicine & Rehabilitation, 3rd ed, Braddom

Falco, et. al, Peripheral Joint, Soft Tissue and Spinal Injection Techniques and Interventional Pain Management Procedures, Physical Medicine & Rehabilitation, 3rd ed, Braddom

Kendall, F., McCreary E., Muscles: Testing and Function with Posture and Pain, 5th Ed

Kool, J., et. al, Function-Centered Rehabilitation Increases Work Days in Patients with Nonacute Nonspecific Low Back Pain: 1-year Results from a Randomized Controlled Trial, Archives of Physical Medicine and Rehabilitation, Sept 2007, Vol 88, No 9

Lehrich, J., Sheon, R., Treatment of subacute and chronic low back pain, www.uptodateonline.com , May 1, 2007

Levin, K., Lumbar Spinal Stenosis, www.uptodateonline.com , May 10, 2007.