Muscle Relaxants OMM

AOASM OMED15
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Normal muscle activation occurs \( \sim 10-15 \text{ events sec}^{-1} \).

Brain senses a "normal" rate of activity, suited for coordinating motor reflex response to painful stimuli.
Muscle Reflex Arc

- Spinal Cord
- Inter-neuron
- Dorsal root
- afferent
- efferent Motor neuron
- Muscle
Pain-Spasm Reflex Arc

Spinal Cord
Inter-neuron

Muscle

Dorsal root

afferent

efferent Motor neuron
Muscle in ‘spasm’ sends signals to the brain 200-300 events-sec\(^{-1}\) (20 x faster).

If ‘spasms’ persists beyond 2-3 weeks, muscle can start to shorten, hypoxic damage occur, scars form that perpetuate this cycle of reflex arc... with further stimulation, increased muscle tone, spasm, & pain.
Symptomatic Relief With Non-Narcotic Analgesics (NSAIDs or Acetaminophen)
Therapy can provide temporary symptomatic relief.

**Short-term treatment:**

**NSAID or acetaminophen.** NSAIDs for younger patients without significant renal, gastric, or cardiovascular comorbidity.

Acetaminophen for patients without hepatic compromise who cannot tolerate NSAIDs.
Centrally Acting Smooth Muscle Relaxants
Central Acting Muscle Relaxants
Patients age <65 years who can tolerate the sedating effects may also benefit from a non-benzodiazepine muscle relaxant (such as cyclobenzaprine).

Cyclobenzaprine is a reasonable first choice drug, based on the volume of evidence.
Non-Specific inhibition of polysynaptic reflex pathways in brain stem, spinal cord, $\alpha$ motor neurons decreases excitability and causes muscle relaxation (accompanied by CNS depression, sedation)
Carisoprodol [Soma®]
Chlorzoxazone [Paraflex®]
Cyclobenzaprine [Flexeril®]
Orphenadrine [Norflex®]
Methocarbamol [Robaxin®]
Metaxolone [Skelaxin®]
| Carisoprodol (Soma) | Blocks interneuronal activity in descending reticular formation & spinal cord | High abuse potential meprobromate metabolite |
Cyclobenzaprine is a tricyclic anti-depressant analog. It can interact with anti-depressants that block re-uptake of norepinephrine or serotonin causing serotonin syndrome (potentially life threatening).
Trends in Management
Despite numerous published clinical guidelines, management of back pain has relied increasingly on guideline discordant care.
Narcotic use per visit increased from 19.3% to 29.1%.

NSAID or acetaminophen use per visit decreased from 36.9% to 24.5%.
These results are not explained by:

- Change in short-term vs long-term presentations.
- Type of physician prescribing.

The marked decrease in use of first-line therapies accompanied by the rapid increase in narcotic prescriptions raises significant concerns.
The decline in NSAIDs use may derive from FDA warnings.

Most recent one issued July 09, 2015
FDA strengthens warning that non-aspirin anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes.

<table>
<thead>
<tr>
<th>Retail</th>
<th>Dosing</th>
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<tbody>
<tr>
<td>Ibuprofen</td>
<td>$t^{1/2} = 2$ hrs, 2-3 tablets, tid, qid</td>
</tr>
<tr>
<td>Naproxen</td>
<td>$t^{1/2} = 14$ hrs, 1-2 tablets, bid</td>
</tr>
</tbody>
</table>
Rapid increase in narcotic prescriptions raises significant concerns.

What Are the Concerns?
Meta-analysis: Narcotics provide little to no benefit in acute back pain, they have no proven efficacy in chronic back pain.

43% of patients have concurrent substance abuse disorders.


- Epidemic of prescription opioid deaths
- Opioid analgesic
- Cocaine
- Heroin

Graph: Trends in drug-related deaths from 1999 to 2007.
Codeine Pharmacogenetics…. A Concern?
CYP2D6 Pharmacogenetics

Ultrafast metabolizer
CYP2D6 gene duplication & ‘ultrafast’ allele

Intermediate Metabolizer
CYP 2D6 heterozygous

Poor metabolizer
CYP2D6 gene deletion & ‘slow’ allele
Codeine Disposition: Ultra-fast Metabolizer

- Codeine
- Norcodeine: Inactive
- CYP3A4: 'fast'
- CYP2D6*: 'fast' ("ultra-rapid metabolizers")
- ∼1 -7 / 100 people
- ∼28/100 people in some ethnic groups
- Morphine-glucuronides: Active μ agonists
So far, concern about codeine & the influence of pharmacogenetics on its metabolic disposition is limited to certain situations....

New Evidence about an Old Drug — Risk with Codeine after Adenotonsillectomy

Judith A. Racoosin, M.D., M.P.H., David W. Roberson, M.D., Michael A. Pacanowski, Pharm.D., M.P.H., and David R. Nielsen, M.D.
If opioid prescription trends continue, what other challenges will emerge?

Narcotic use per visit increased from 19.3% to 29.1%.
Opioids increase smooth-muscle tone and inhibit the coordinated peristalsis required for propulsion, which contributes to nausea & vomiting as well as constipation. **What strategies might work for opioid-induced side effects such as constipation?**
FDA approved MOVANTIK™ (naloxegol) as a once-daily orally administered, peripherally-acting μ opioid receptor antagonist for the treatment of opioid-induced constipation (OIC), in adult patients with chronic, non-cancer pain. Opioids relieve chronic pain relief by binding to spinal & supra-spinal μ opioid receptors, but they also bind to μ-receptors in the gastrointestinal tract, which may result in opioid induced constipation.
CAUTION

Cases of GI perforation have occurred with other peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract.
Osteopathic Manipulative Treatment
Recent observational findings ...suggest that analgesic medication use is lower in patients who receive OMT, align with previous findings of RCTs and support the generalizability of these findings.

Other Central Acting Non-Specific Muscle Relaxers
GABA_A Receptor Agonists
Central Acting Muscle Relaxants

Benzodiazepines: Not first line because of less evidence to support their use and concern about abuse potential. Muscle relaxants should generally be limited to relatively short-term therapy (one to three weeks).
LAST SLIDE
Grateful thanks to

Dr. John Dougherty, DO, FACOFP, FAOASM, FAODME
Senior Associate Dean for Clinical Affairs & GME, Professor
Clinical Education/GME for inviting me to speak.

W. Joshua Cox, DO, FACOFP
Chairman, Primary Care Medicine for helpful comments.
Table I: Mechanisms of action of skeletal muscle relaxants

- Antihistamines
  Diphenhydramine
- CNS depressants (sedatives)
  Carisoprodol, chlorzoxazone, metaxalone, methocarbamol
- Central α2-adrenergic agonists
  Tizanidine
- γ-aminobutyric acid (GABA) agonists
  Baclofen, benzodiazepines
- Tricyclic antidepressant compounds
  Cyclobenzaprine

<table>
<thead>
<tr>
<th>Muscle Relaxants</th>
<th>Usual Dosage Range</th>
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<tbody>
<tr>
<td>Carisoprodol</td>
<td>350 mg, 4 times daily</td>
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<tr>
<td>Chlorzoxazone</td>
<td>250–500 mg, 3–4 doses daily</td>
</tr>
<tr>
<td>Cyclobenzapine</td>
<td>5–10 mg, 3–4 times daily</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2–10 mg, 3–4 times daily</td>
</tr>
<tr>
<td>Metaxalone</td>
<td>4,000–4,200 mg/day in divided doses</td>
</tr>
<tr>
<td>Methocarbamol</td>
<td>400–800 mg, 3–4 times daily</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>100 mg twice daily</td>
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