Muscle Relaxants OMM

AOASM OMED15
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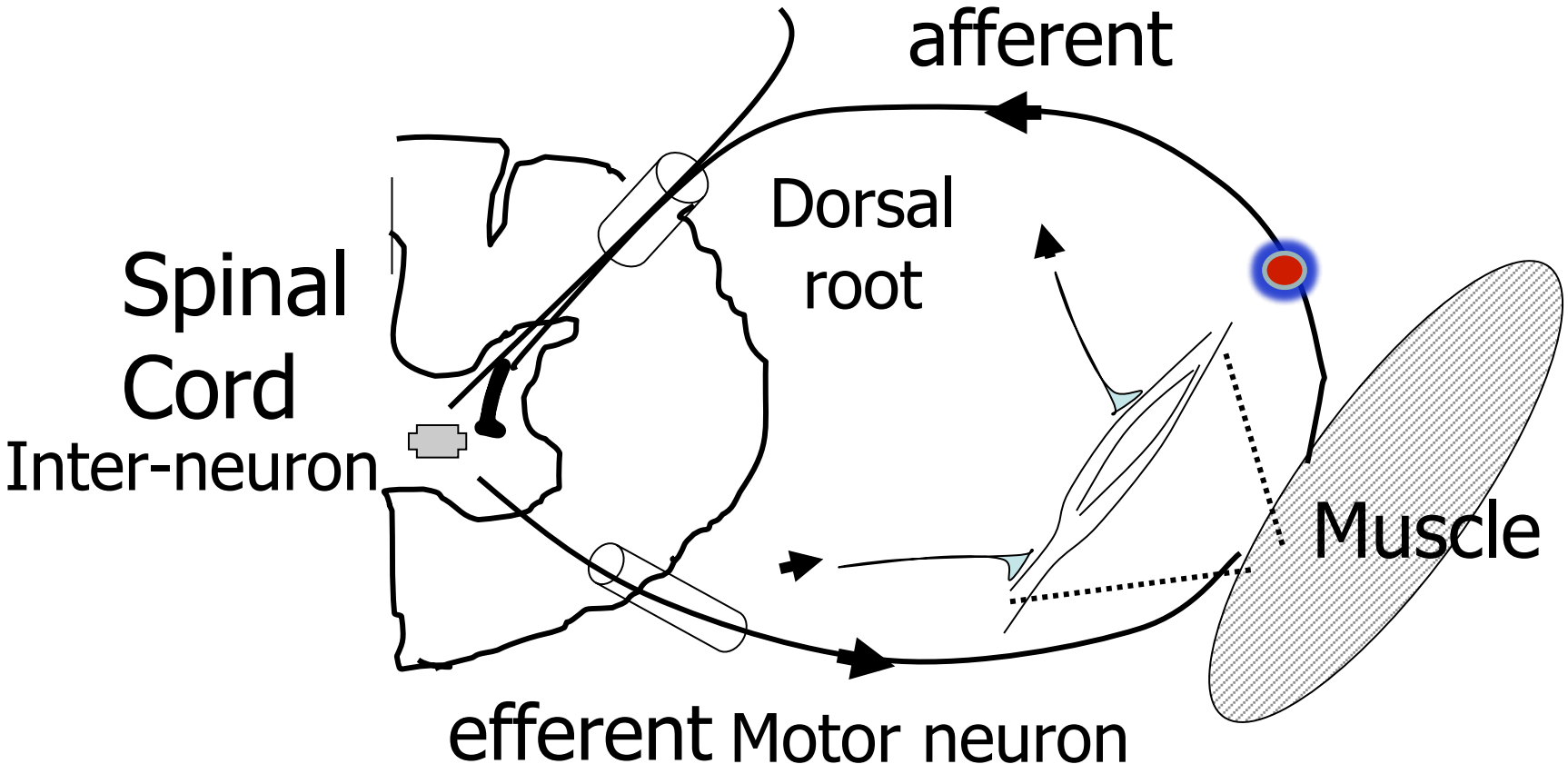
OF MEDICINE AND BIOSCIENCES

F.A. Fitzpatrick, Ph.D.

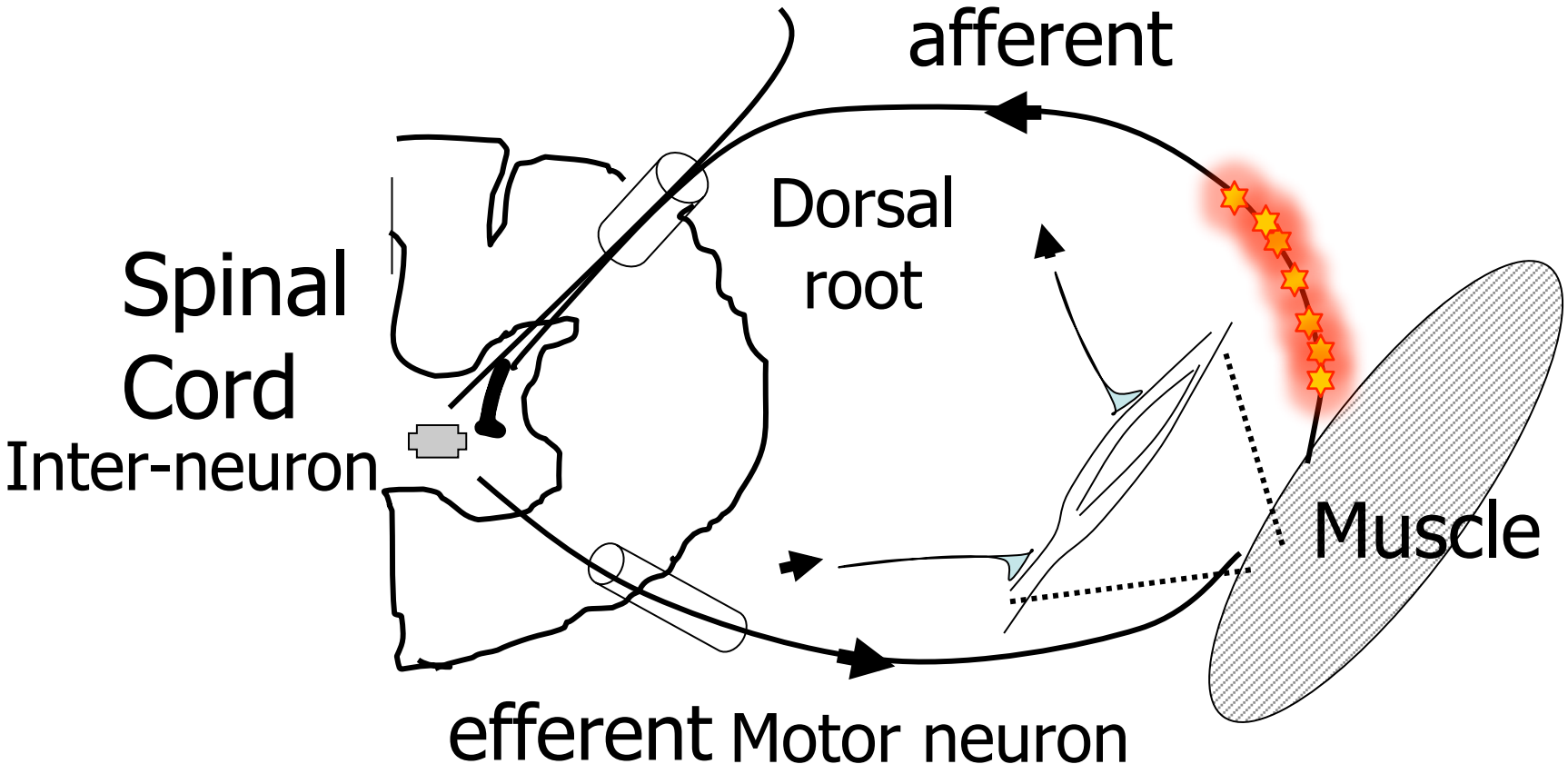
Normal muscle activation occurs
~ 10-15 events sec^{-1}.

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

Muscle Reflex Arc



Pain-Spasm Reflex Arc



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, α 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	**<u>High abuse potential</u>** **<u>meprobromate metabolite</u>**

Cyclobenzaprine (Flexeril)	Reduces tonic somatic motor activity in brain stem	Clinical trials establish efficacy at low, non-sedating dose
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).		

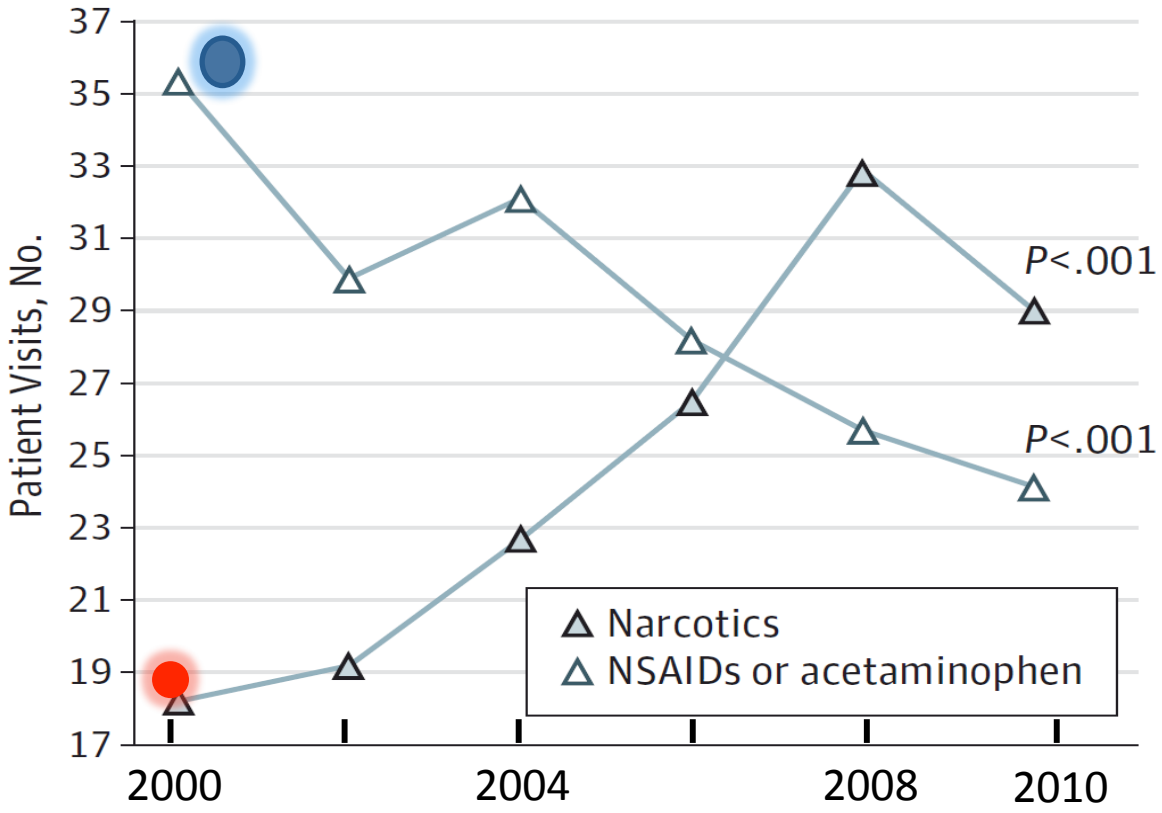
Trends in Management

Original Investigation *JAMA Intern Med.* 2013;173(17):1573-1581.|September 23, 2013

Worsening Trends in the Management and Treatment of Back Pain

John N. Mafi, MD; Ellen P. McCarthy, PhD, MPH; Roger B. Davis, ScD; Bruce E. Landon, MD, MBA, MSc

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

Retail	Dosing
Ibuprofen	$t^{1/2}$ = 2 hrs, 2-3 tablets, tid, qid
Naproxen	$t^{1/2}$= 14 hrs, 1-2 tablets,bid

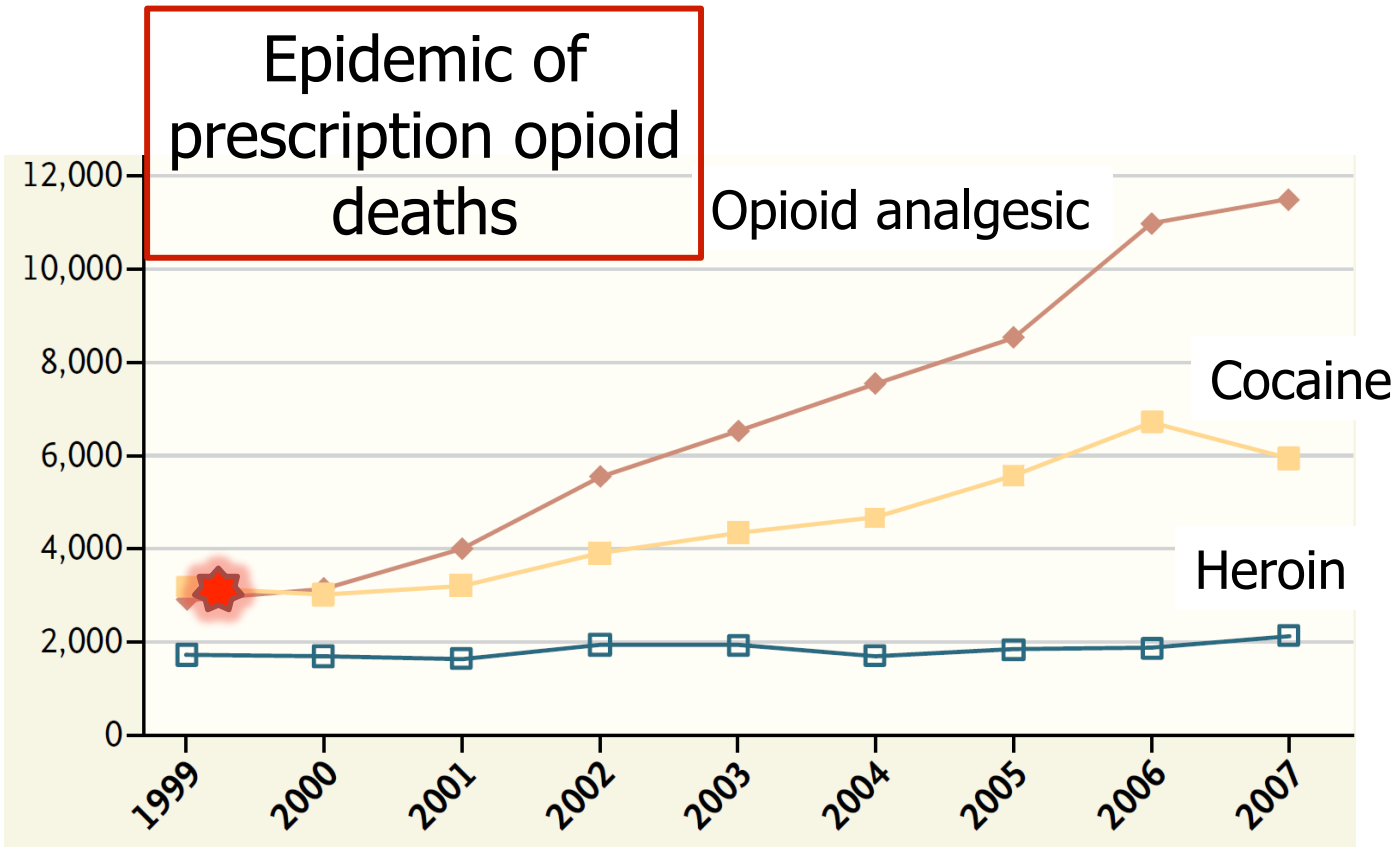
Rapid increase in narcotic prescriptions raises significant concerns.

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.

Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med*. 2007;146(2):116-127.

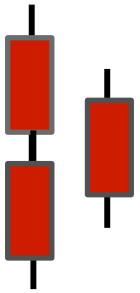


Okie S. N Engl J Med 2010;363:1981-1985.

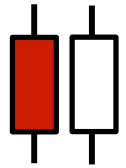
Codeine Pharmacogenetics…. A Concern?

CYP2D6 Pharmacogenetics

Ultrafast metabolizer
CYP2D6 gene duplication
& 'ultrafast' allele

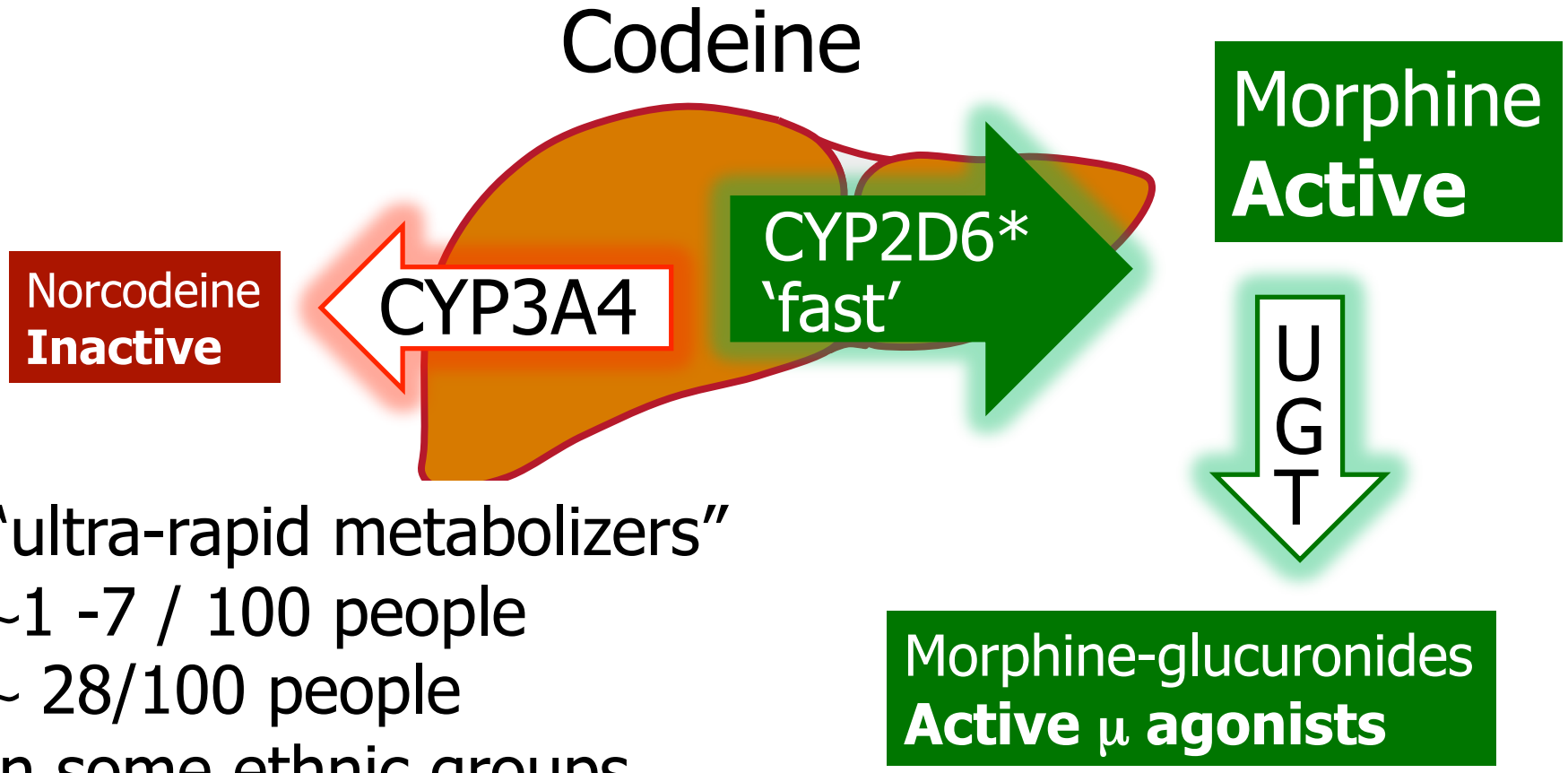


Intermediate Metabolizer
CYP 2D6 heterozygous



Poor metabolizer
CYP2D6 gene deletion
& 'slow' allele

Codeine Disposition: Ultra-fast Metabolizer



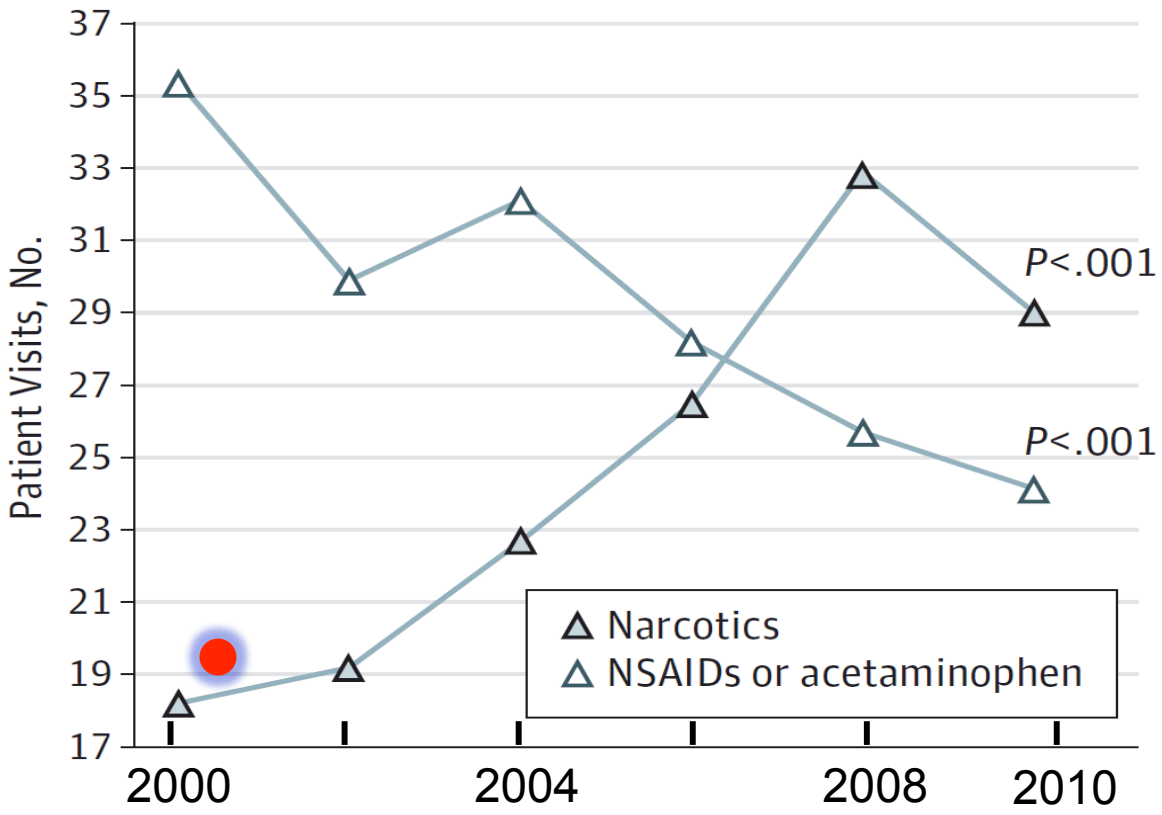
"ultra-rapid metabolizers"
~1 -7 / 100 people
~ 28/100 people
in some ethnic groups

So far, concern about codeine & the influence of pharmacogenetics on its metabolic disposition is limited to certain situations….

PERSPECTIVE

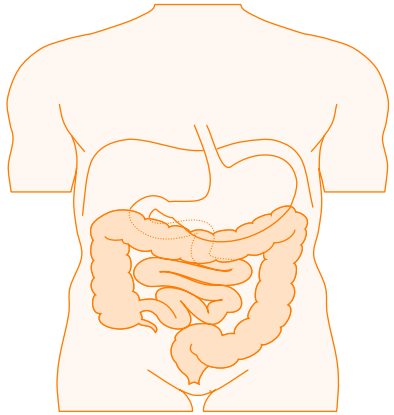
New Evidence about an Old Drug — Risk with Codeine after Adenotonsillectomy

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.

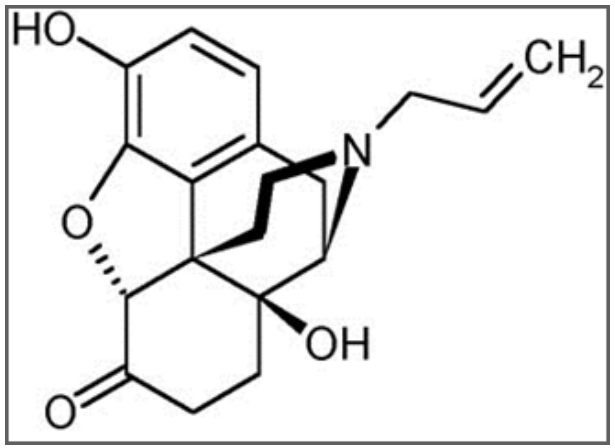


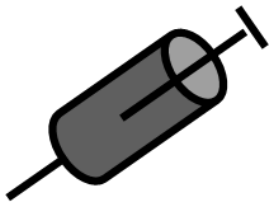
Narcotic use per visit increased from 19.3% to 29.1%.

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?**

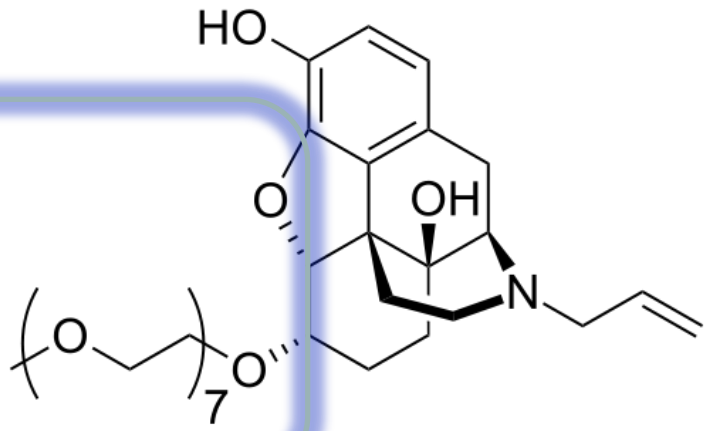


Naloxone





Naloxogol



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.

Prinsen JK, Hensel KL, Snow RJ. ***J Am Osteopath Assoc***. 114:90-8 (2014). OMT associated with reduced analgesic prescribing and fewer missed work days in patients with low back pain: an observational study.

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

Muscle Relaxants	Usual Dosage Range
Carisoprodol	350 mg, 4 times daily
Chlorzoxazone	250–500 mg, 3–4 times daily
Cyclobenzaprine	5–10 mg, 3–4 times daily
Diazepam	2–10 mg, 3–4 times daily
Methocarbamol	4,000–4,500 mg/day in divided doses
Metaxalone	400–800 mg, 3–4 times daily
Orphenadrine	100 mg twice daily