Learning Objectives

1. Expand understanding of opioid receptor function and its role in pain and hyperalgesia

2. Increase awareness of discontinuation events from medications used in the treatment of pain

3. Define weaning and discontinuation strategies for medications used in the treatment of pain

Common Pain Related Pain Medication

- Most can be weaned successfully over 4-6 weeks
- Most without major adverse events
  - Gabapentin
  - Pregabalin
  - Topiramate
  - Tricyclic medication

SNRI Class medication

- Most patients can wean without discontinuation events
- Some have substantial challenges with stopping
- Symptoms of SNRI withdrawal:
  - Palpitations
  - Parasthesias
  - Diaphoresis
  - Irritability
  - “Electric shocks”

SNRI discontinuation Strategies

- Gradual Wean
  - Limited by dosing size
  - Consider alternating days of dose reduction
  - Last step is the hardest
- Bridge Therapy
  - Long acting SSRI (fluoxetine) prescribed to blunt discontinuation effects of SNRI
  - Maintain fluoxetine for 4-6 weeks, then stop.

Benzodiazepine Medication

- Discontinuation may be challenging
- Consider providing additional treatment for underlying disorders:
  - Anxiety
  - Depression
  - Sleep dysfunction

Benzodiapzepine Cessation

- Tools to consider:
  - Diet
  - Exercise
  - Pain psychologist
  - Sleep therapies
    - Melatonin
    - L-Theanine
    - Low dose naltrexone

Benzodiazepine Cessation

- Medications to treat underlying symptoms:
  - Psychiatric symptoms
    - SSRI
    - SNRI
    - Membrane stabilizers
  - Autonomic dysfunction
    - Clonidine
    - Beta blocker

Benzodiazepine Cessation

- Gradual wean over time
  - The longer someone has been on the benzodiazepine, the longer it might take to wean
  - The final stages may be most challening

Benzodiazepine Cessation

- Phenobarbital transition
  - Long duration of action
  - Similar (not same) mechanism as benzodiazepine
  - Well tolerated
  - Dosing:
    - Range of starting between 32.4mg qhs - 64.8mg twice daily


Have a seat Kermit. What I'm about to tell you might come as big shock...

OPIOID RECEPTOR PHARMACOLOGY

Agonists, antagonists, and partial agonists

Agonists: substances that bind to the receptor and produce full intrinsic activity

Antagonists: substances that bind to the receptor and do not have any intrinsic activity

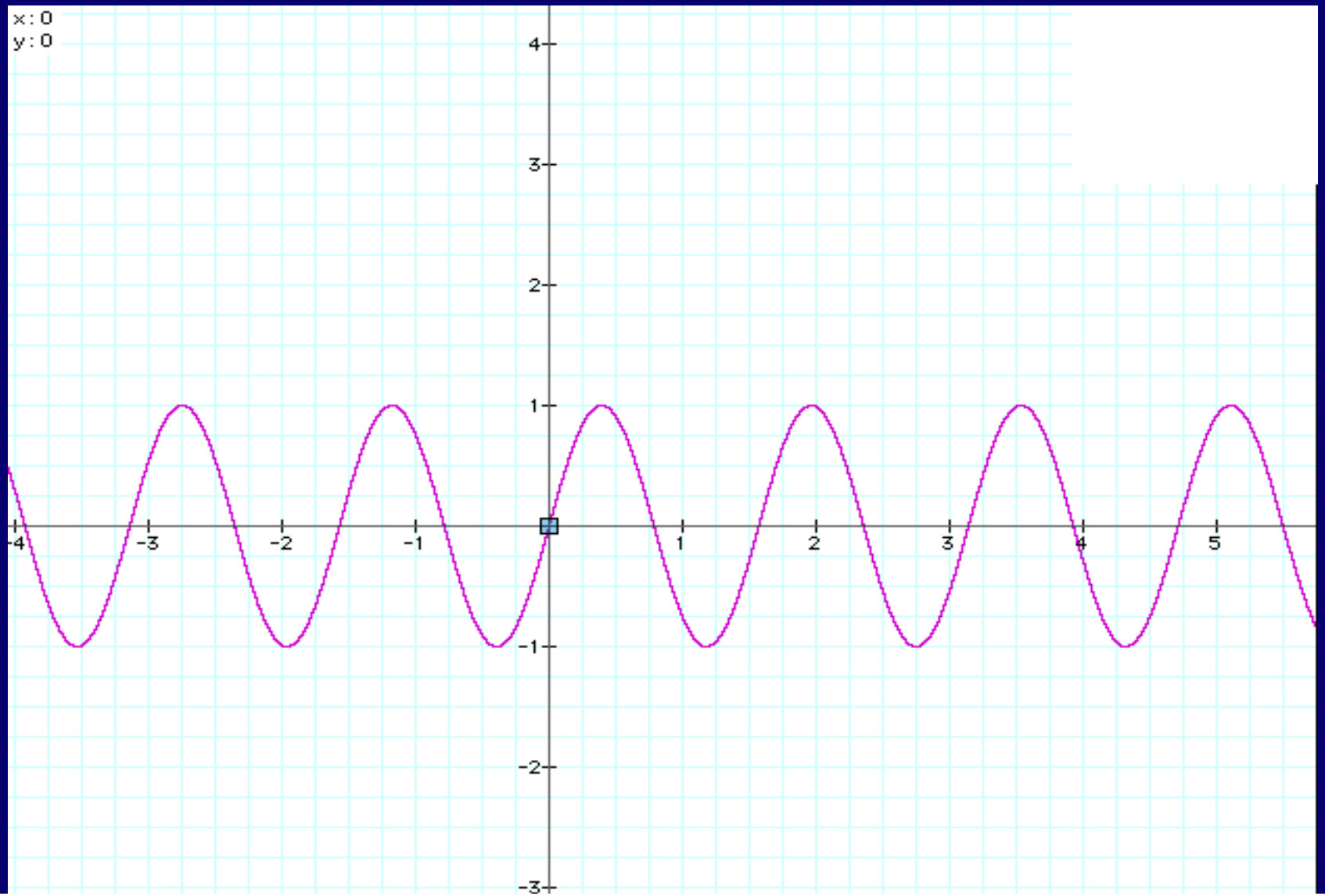
Partial agonists: substances that bind to the receptor and produce some intrinsic activity – less than the response produced a full agonist

RECEPTOR PHARMACOLOGY

- Different types of opioid receptors

Receptor	Response on activation
μ (mu)	Analgesia, respiratory depression, miosis (constriction of the pupil), euphoria, reduced gastrointestinal motility
κ (kappa)	Analgesia, dysphoria (restlessness, depression, anxiety), psychotomimetic effects (mental processes), respiratory depression
δ (delta)	Analgesia

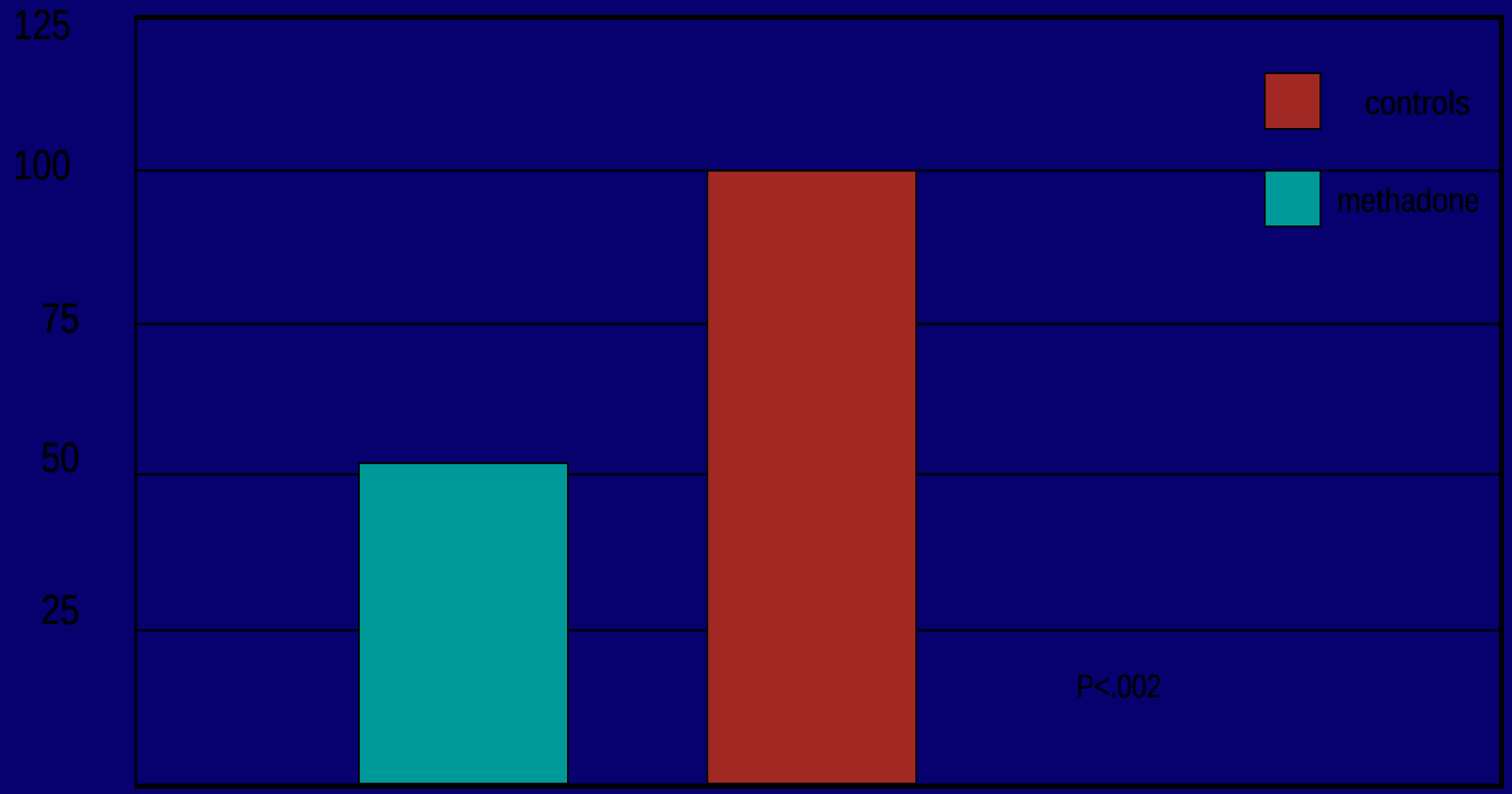
Cycles of Intoxication and Withdrawal



OPIOID HYPERALGESIA

If any man wants to learn sympathetic charity, let him keep pain subdued for six months by morphia, and then make the experiment of giving up the drug. By this time he will have become irritable, nervous and cowardly. The nerves, muffled, so to speak, by narcotics, will have grown to be not less sensitive, but *acutely, abnormally capable of feeling pain* and of *feeling as pain a multitude of things not usually competent to cause it.* *S.W. Mitchell*

Diminished Pain Tolerance in Methadone-Maintained Patients



Compton M, et al. *J Pain Symptom Manage*, 2000. 20(4) 237-245.

THE TROUBLE WITH OPIOIDS

- Tolerance/Withdrawal
- Addiction Potential
- Hyperalgesia (Central Sensitization)
- Unpleasant Effects
- Regulatory Fears

CME

Daily scheduled opioids for intractable head pain

Long-term observations of a treatment program

J.R. Saper, MD, FACP, FAAN; A.E. Lake III, PhD; R.L. Hamel, PA-C; T.E. Lutz, BA; B. Branca, PhD; D.B. Sims, RN; and M.M. Kroll, RN, BSN

Abstract—*Background:* Daily scheduled opioids (DSO) have been employed in some instances to remediate intractable headache. However, long-term studies of effectiveness, sequelae over several years, predictors of long-term benefit, comparisons of pain-related outcome measures, and prevalence of problematic drug behavior are not available. *Methods:* The authors evaluated the results of a treatment program at their institution designed to treat and monitor intractable headache patients administered DSO. Of 160 sequential patients participating in the program, 70 who remained on DSO for at least 3 years qualified for inclusion in an efficacy analysis. Patients completed structured questionnaires at each medical visit as part of routine clinical care. The authors assessed medical records during treatment, and during the 2 years before starting DSO. The primary clinical efficacy variable was percentage improvement in the severe headache index (frequency x severity of severe headaches/week). *Results:* Analysis of the medical records found 41 (26%) of the original 160 patients with >50% improvement. Patients reported larger improvements on a visual analog scale (mean improvement = 70%) than shown by the medical record (mean improvement = 46%), $p < 0.00001$. Problem drug behavior (dose violations, lost prescriptions, multisourcing) occurred in 50% of patients, usually involving dose violations. *Conclusions:* For a select group of intractable headache patients, DSO can offer significant benefit. However, 74% of those treated either failed to show significant improvement or were discontinued from the program for clinical reasons. The relatively low percentage of patients with demonstrated efficacy and unexpectedly high prevalence of misuse have clinical relevance.

NEUROLOGY 2004;62:1687–1694

The role of opioids in the acute treatment of intermittent headache is complex and controversial.[1] Parenteral, rectal, or oral narcotics can be an effective rescue therapy for patients requiring acute relief from a very severe and otherwise refractory headache episode.[2,3] However, the overuse of narcotic analgesics (more than two times/week) can contribute to the intractability of chronic daily headache (analgesic rebound, medication overuse headache[4]), and can be a barrier to effective prophylaxis.[4,5] Even when used for reasons other than pain control, such as slowing bowel motility after colectomy, frequent use of opioids may induce the development of chronic daily headache (transformed migraine) in patients with a previous history of episodic migraine.[6]

The appropriateness of daily scheduled opioid

ments are contraindicated (as in the senior population), chronic opioid medication is justified[8] and useful.[9,10] Assays of CSF enkephalins from migraine patients during and between attacks, compared with assays from nonheadache control patients, suggest that an intermittent failure in the endogenous opioid system could be a factor in the mechanism of migraine.[11] If this were the case, then prophylaxis of chronic migraine with opioid medication could be a means of regulating this aspect of migraine pathophysiology for some patients—analogous to replacement therapy in any one of several well recognized medical disorders.

This article reports data from a large number of patients who participated in a structured scheduled-opioid program we initiated in 1992 to treat selected

Systematic Review: Opioid Treatment for Chronic Back Pain: Prevalence, Efficacy, and Association with Addiction

Bridget A. Martell, MD, MA; Patrick G. O'Connor, MD, MPH; Robert D. Kerns, PhD; William C. Becker, MD; Knashawn H. Morales, ScD; Thomas R. Kosten, MD; and David A. Fiellin, MD

Background: The prevalence, efficacy, and risk for addiction for persons receiving opioids for chronic back pain are unclear.

Purpose: To determine the prevalence of opioid treatment, whether opioid medications are effective, and the prevalence of substance use disorders among patients receiving opioid medications for chronic back pain.

Data Sources: English-language studies from MEDLINE (1966–March 2005), EMBASE (1966–March 2005), Cochrane Central Register of Controlled Clinical Trials (to 4th quarter 2004), PsychInfo (1966–March 2005), and retrieved references.

Study Selection: Articles that studied an adult, nonobstetric sample; used oral, topical, or transdermal opioids; and focused on treatment for chronic back pain.

Data Extraction: Two investigators independently extracted data and determined study quality.

Data Synthesis: Opioid prescribing varied by treatment setting (range, 3% to 66%). Meta-analysis of the 4 studies assessing the efficacy of opioids compared with placebo or a nonopioid control did not show reduced pain with opioids (g, −0.199 composite standardized mean difference [95% CI, −0.49 to 0.11]; $P = 0.136$). Meta-analysis of the 5 studies directly comparing the efficacy of different opioids demonstrated a nonsignificant reduction in pain from baseline (g, −0.93 composite standardized mean difference [CI, −1.89 to −0.03]; $P = 0.059$). The prevalence of lifetime substance use disorders ranged from 36% to 56%, and the estimates of the prevalence of current substance use disorders were as high as 43%. Aberrant medication-taking behaviors ranged from 5% to 24%.

Limitations: Retrieval and publication biases and poor study quality. No trial evaluating the efficacy of opioids was longer than 16 weeks.

Conclusions: Opioids are commonly prescribed for chronic back pain and may be efficacious for short-term pain relief. Long-term efficacy (≥16 weeks) is unclear. Substance use disorders are common in patients taking opioids for back pain, and aberrant medication-taking behaviors occur in up to 24% of cases.

Ann Intern Med. 2007;146:116-127. www.annals.org

For author affiliations, see end of text.

Back pain is the second leading symptom seen by physicians in the United States (1). Chronic back pain (that is, pain lasting more than 3 months) (2) occurs in 5% to 8% of community-dwelling persons (3, 4) and is reported in 19% of working adults (5).

Clinicians treating chronic back pain choose from a

March 2005), Cochrane Central Register of Controlled Clinical Trials (through the fourth quarter of 2004), and PsychInfo (1966–March 2005) and limited the search to English-language and human studies. We used Medical Subject Headings (MeSH) and text words in MEDLINE (**Appendix Table 1**, available at www.annals.org). Separate

Ann Int Med 2007

Why Use Opioids in the First Place???

TO IMPROVE FUNCTION!!

(and relieve pain)

OPIOIDS SHOULD BE STOPPED

- If they are not clearly beneficial
- Just like any other medication

Covington E, MiSAM Update in Addiction Medicine 2004

Once dependent, why isn't it easy to stop?

- Withdrawal from opioids is associated with an extremely unpleasant syndrome:
  - ✓ Physical pain (muscle aches, cramps)
  - ✓ Nausea and vomiting
  - ✓ Diarrhea
  - ✓ Dysphoria
  - ✓ Depression
  - ✓ Irritability and anxiety
  - ✓ Dysregulation of brain reward systems

- Pharmacologic intervention proven to help relieve symptoms of withdrawal

Remember:

"If you can't land, don't take off."

When you initiate a trial of opioid therapy, have an 'exit strategy'.

Covington, E. "Weaning Drugs in Patients With Chronic Pain" Presented at *Pain and Addiction, Common Threads IV*, 2003


EXIT

‘Weaning’, ‘Detoxing’, and the DEA

- Opioid dependent patients may be tapered and weaned in the office (think buprenorphine).
- Opioid addicted patients must be referred to licensed clinics (methadone) or DATA-waivered physicians (buprenorphine) for detoxification.

Buprenorphine

- A synthetic opioid
- Partial agonist at the μ receptor
  - Low intrinsic activity only partially activating opiate receptors
  - Exhibits 'ceiling' effects on respiratory depression
- High affinity for the μ receptor
  - Binds more tightly to opiate receptors than other opiates or opiate antagonists
- Slow dissociation from the receptor
  - ✓milder withdrawal
- Antagonist at the κ receptor
  - ✓May be responsible for effects on chronic pain

Buprenorphine in Chronic Pain

- Sublingual Buprenorphine Is Effective in the Treatment of Chronic Pain Syndrome
  - *Am J Therapeutics* 12; 379-384 (2005)

- Herbert Malinoff, Robert L. Barkin, and Geoffrey Wilson

SLB in Chronic Pain: Response

- Patients were evaluated with VAS (1-5)
- Before treatment: 3.9 +/- 0.4
- After treatment: 2.2 +/- 0.5

- Patients who reported “substantial” improvement: 86%
- Duration of treatment: 8.8 months (2.4-16.6)

Three Years Later…….

350+ chronic pain, opioid dependent non-addicted patients weaned from pure opioid agonist therapy

Similar (70%) positive response rate

Malinoff HL, Christensen CW, Thielking P, et al. Manuscript in preparation

SLB in Chronic Pain: Conclusions

- "The use of buprenorphine and buprenorphine/naloxone to treat chronic pain patients refractory to LTOA therapy in this study was safe, effective, and well tolerated by these patients."

What Medications Are You Taking?

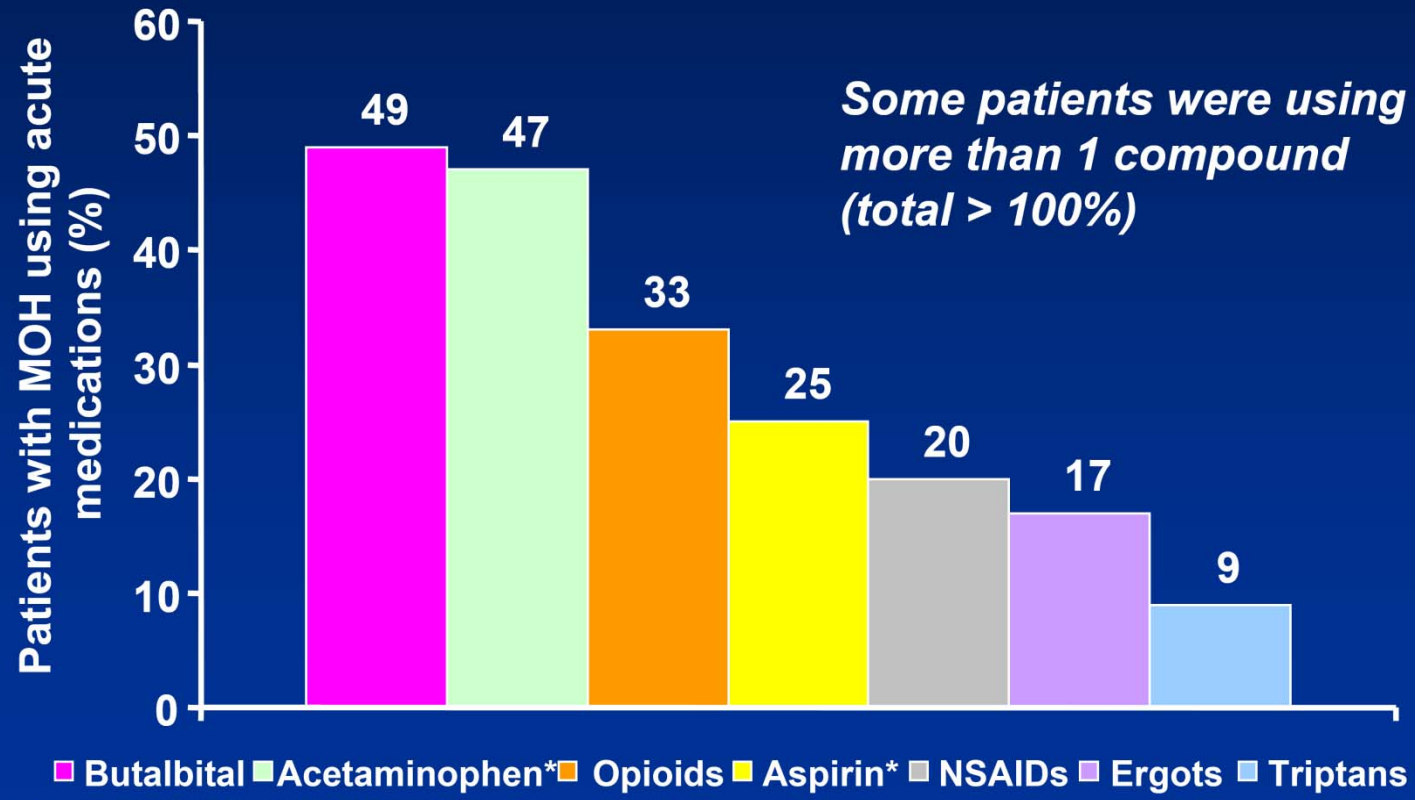
Michigan Automated Prescription Service (MAPS)

Medication Overuse Headache
"Rebound Headaches"

- Usually previous headache history
- Pain is typically bifrontal location
- Refractory to treatments
- Pain worsens when medication stopped
- Awaken with headache

Patients with MOH Were More Likely to Have Overused a Nonmigraine-Specific Medication

Acute medications used by patients with MOH



* Alone or in combination compounds

Data from a tertiary headache center (N = 436).
Data collection period 1980–2001, including the period prior to 1993 when triptans were not available.
Bigal ME et al. *Cephalalgia.* 2004;24:483–490.

Medication Overuse Headache

Butalbutal (fioricet, [illegible]gic)

- Not FDA approved [illegible]dache
- Chronic use may le[illegible]prolonged "rebound" durati[illegible]
- May need inpat[illegible] detox[illegible]tion

Daily Opioid Ther[illegible]

- Despite reportin[illegible]50%[illegible]rovement, disability remained
- Significant noncom[illegible]e, even in highly controlled program

(Sap[illegible]al., 2004)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