

# **CHRONIC OPIOID RX FOR NON-MALIGNANT PAIN**

Gerald M. Aronoff, M.D., DABPM  
Med. Dir., Carolina Pain Assoc  
Charlotte, North Carolina, USA

## **Pain**



“Pain is a more terrible  
Lord of mankind  
than even death itself.”

Albert Schweitzer

## **Goals for Treating CP**

- Decrease or eliminate c/o Pain
- Decrease or eliminate Suffering
- Improve Functional Daily Activities
- Improve Quality of Life
- Absence of significant adverse side effects

## **PAIN-PATHOPHYSIOLOGY**

- NOCICEPTIVE
- NEUROPATHIC
- MIXED
- UNCERTAIN
- PSYCHOGENIC

# Pharmacologic Management

---

- Non-opioid analgesics
- Opiate analgesics
- Adjuvant analgesics

## CRITICAL REEVALUATION OF OPIOIDS BASED ON

---

- LONG-TERM OPIOID TREATMENT WITH CANCER PATIENTS

# INSIGHTS FROM THE CANCER POPULATION

---

- UNRELIEVED PAIN IS ASSOCIATED WITH:1) INCREASED MORBIDITY 2)PSYCHOSOCIAL DISTRESS
- EFFECTIVE ANALGESIA CAN REVERSE THESE AND IMPROVE QUALITY OF LIFE

## Tolerance

---

- May occur to both the desired and undesired effects of drugs
- May develop at different rates for different effects
  - Tolerance to opioids usually develops more slowly to analgesia than respiratory depression
  - Tolerance to constipation may not occur at all
  - Tolerance to the analgesic effect of opioids is variable but never absolute
- No upper limit to dosage of pure opioid agonists can be established

# Opioid Analgesics

- Mainstay of cancer pain management<sup>1</sup>
- Guidelines published by
  - World Health Organization, 1996
  - United States Agency for Health Care Policy and Research, 1994
  - American Pain Society, 1992

<sup>1</sup> Foley KM. *Cancer*. 1989;63(11 Suppl):2257-2265.

# Efficacy of Opioid Therapy

- Efficacy of oxycodone in neuropathic pain. A randomized trial in postherpetic neuralgia<sup>1</sup>
- Dose-response relationship of opioids in nociceptive and neuropathic postoperative pain<sup>2</sup>
- Randomized double-blind active placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain<sup>3</sup>

<sup>1</sup> Watson CP, Babul N. *Neurology*. 1998;50(6):1837-1841; <sup>2</sup> Benedetti F, et al. *Pain*. 1998;74(2-3):205-211; <sup>3</sup> DelleMijn PL, et al. *Lancet*. 1997;349(9054):753-758.

# Opioids in Chronic Nonmalignant Pain

---

- In a study by Zenz, et al. of 100 patients with diverse pain states treated with various opioids, 3 out of 4 had good or partial pain reduction
- Allan, et al. reported significantly reduced pain intensity scores in 256 patients using sustained-release oral morphine or transdermal fentanyl
- In 68 patients with chronic low back pain, Simpson et al. reported that use of transdermal fentanyl resulted in significantly improved pain intensity scores and activities of daily living
- Data suggest favorable outcomes with careful patient monitoring

Zenz M, et al. *J Pain Symptom Manage.* 1992;7(2):69-77; Allan L, et al. *BMJ.* 2001;322(7295):1154-1158; Simpson RK Jr, et al. *J Pain Symptom Manage.* 1997;14(4):218-224.

## PUBLISHED STUDIES

---

- PORTENOY-1992
- ZENZ et al -1992
- TAUB-1992
- TENNANT & UELMAN-1983
- BROOKOFF & PALOMANO-1992

## **Opioids and the treatment of chronic pain: Controversies, current status, and future directions**

- Focuses on the complex issues at the interface between analgesia and abuse, including terminology, clinical challenges and the potential for new agents, such as acute morphine, to influence practice

Rosenblum A, Marsch A, Joseph H, and Portenoy R. Exp Clin Psychopharm 2008 Oct; 16(5):405-416

## **Occupational Medicine Practice Guidelines Second Edition: Chronic Pain 2008**

- No good long-term studies documenting efficacy to support recommendation for long-term use of opioids for chronic pain in injured workers (Recommended, Insufficient Evidence)

## **Pure Agonists**

---

- Preferred agents – especially for cancer pain
- Many different agents available in the U.S.
- Tramadol – not officially an opioid
  - Weak mu agonist
  - Monoamine reuptake inhibition

## **Agonist-Antagonists and Partial Agonists**

---

- Little clinical indication for use
- May precipitate withdrawal in opioid tolerant patients



## Opioid Titration and Maintenance

---

- No analgesic “ceiling” dose
- Drug titration until satisfactory pain relief or unmanageable side effects occur
- Maintenance doses vary considerably according to individual factors and nature of pain

## Therapeutic Use of Opioids

---

When given at stable doses for long-term therapy, opioids do not significantly impair cognition, attention, mood, driving ability, or general functioning

Portenoy RK. *Ann Acad Med Singapore*. 1994;23(2):160-170; Vainio A, et al. *Lancet*. 1995;346(8976):667-670; Haythornthwaite JA, et al. *J Pain Symptom Manage*. 1998;15(3):185-194.

# Management of Common Opioid Side Effects

- Constipation
  - Prophylactic use of laxatives and stool softeners
- Nausea and vomiting
  - Neuroleptics, metoclopramide, cisapride, antivertiginous drugs
- Sedation
  - Discontinue other CNS depressants
  - Add psychostimulants
- Respiratory depression
  - Extremely rare. Monitor if not severe; carefully titrate naloxone if severe

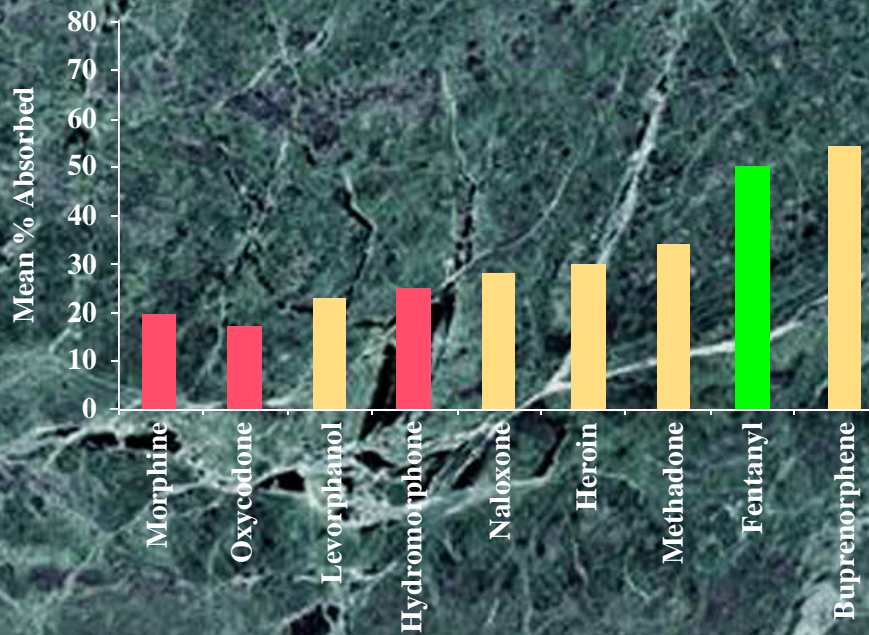
CNS: Central nervous system

# Opioid Selection

## Pure Agonists

- |   |   |
|---|---|
| <ul style="list-style-type: none"><li>■ Immediate-release preparations<ul style="list-style-type: none"><li>■ MSO<sub>4</sub></li><li>■ Oxycodone</li><li>■ Oxymorphone</li><li>■ Hydromorphone</li><li>■ Fentanyl</li><li>■ Methadone</li><li>■ Levorphanol</li><li>■ Meperidine ☹</li></ul></li></ul> | <ul style="list-style-type: none"><li>■ Controlled-release preparations<ul style="list-style-type: none"><li>■ MSO<sub>4</sub></li><li>■ Oxycodone</li><li>■ Fentanyl</li><li>■ Oxymorphone</li><li>■ Hydromorphone (soon...)</li></ul></li></ul> |
|---|---|

# Absorption of Opioids from Oral Cavity



From Weinberg DS, et al. *Clin Pharm Ther* 1988;44:337.

## Not Recommended

- Mixed agonist-antagonists
  - Pentazocine, butorphanol, nalbuphine, dezocine
    - Compete with agonists → withdrawal
    - Analgesic ceiling effect
    - High risk of psychotomimetic effects
- Meperidine
  - Toxic metabolite → normeperidine
  - Lowers seizure threshold
- Propoxyphene
  - No better than placebo in controlled trials

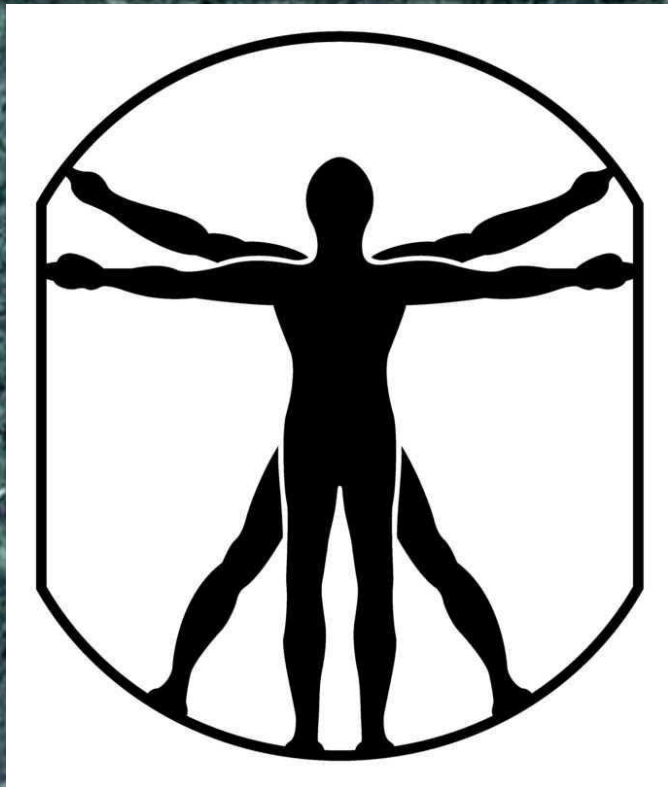
## Initiating an Opioid Trial

- Establish opioid requirements with a short-acting preparation
  - Consider half-life
  - Alert patients to the risk of acetaminophen toxicity with combined formulations

## Initiating an Opioid Trial

- Once utilization has stabilized, switch to an extended release formulation
  - Calculate total daily dose
  - Divide by the dosing interval of the long-acting preparation
  - Establish the appropriate rescue dose

## Breakthrough Pain



## Prevalence of Breakthrough Pain

- 52 - 64% of inpatients referred to cancer pain service
  - Memorial Sloan-Kettering surveys
- 67% of outpatients in multi-national study
  - IASP Task Force on Cancer Pain
- 61% of chronic non-cancer pain sufferers
  - APS survey

Portenoy RK, Hagen NA. *Pain*. 1990;41(3):273-281; Portenoy RK. Symposium on Breakthrough Pain, 15th Annual Scientific Meeting of the American Pain Society, November 14-17, 1996, Washington DC. Abstract.; APS. *Chronic Pain in America: Roadblocks to Relief*. Roper Starch Worldwide Inc. January 1999.

# Types of Breakthrough Pain

---

- Incident
- Idiopathic/ spontaneous
- End-of-dose failure

# Clinical Issues in Long-Term Opioid Treatment

---

- OPIOID RESPONSIVENESS
- THERAPEUTIC EFFICACY
- DRUG MISUSE
- DRUG ABUSE
- TOLERANCE
- DEPENDENCE
- ADDICTION

# ADVERSE OUTCOMES

- RISK OF MAJOR ORGAN TOXICITY:  
NOT SUPPORTED BY STUDIES  
Exception is Endocrine
- SIDE EFFECTS:  
CONSTIPATION > COGNITIVE  
DYSFUNCTION

## American Society of Addiction Medicine (ASAM)

### Addiction

“A primary, chronic neurobiological disease with genetic, psychosocial and environmental factors influencing its development and manifestation”

# DEPENDENCE AND ADDICTION

---

- PHYSICAL DEPENDENCE IS A PHYSIOLOGICAL PROCESS
- ADDICTION IS A PSYCHOLOGICAL AND BEHAVIORAL PROCESS WHICH INVOLVES: a) loss of control over drug use, b) compulsive drug use, and c) continued use despite harm

# PSEUDOADDICTION

---

- WEISSMAN & HADDOX(1989)
- “In the setting of under treated pain, some patients develop aberrant behaviors that may be quite similar to those associated with addiction. When pain is relieved, the behaviors cease and opioids and other drugs are used responsibly.”



# DRUG ABUSE

“All potent medications that act on the CNS and influence our feelings and behaviors have abuse potential. They were developed because of a therapeutic benefit to a select population. However, there are always some people who will divert drugs for non-therapeutic uses.”

Aronoff 2001



# **CLINICAL STUDIES SUGGEST**

---

- THERE IS A SUBGROUP OF CP PTS WHO CAN BE RX WITH CHRONIC OPIOIDS. ON THESE THEY REMAIN FUNCTIONAL AND PRODUCTIVE. WITHOUT ADEQUATE ANALGESIA PAIN BECOMES AN IMPAIRMENT AND COMPROMISES THE QUALITY OF THEIR LIVES.(Aronoff,1992)

# **Federation of State Medical Boards of the US**

---

- Model Policy for the Use of Controlled Substances for the Treatment of Pain (1998, 2004)
  1. To address the under treatment of both acute and chronic pain
  2. To provide guidelines for physicians for safe and appropriate use of opioids
  3. To discuss risk factors for misuse, abuse or diversion

## **APS & AAPM Opioid Treatment Guidelines**

---

- Chou R, Fanciullo GJ, Fine PG, et al. Opioid Treatment Guidelines. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. *J. Pain* 2009; 10 (2): 113-30.

## **Opioids in the Management of Chronic Noncancer Pain: An update of the ASIPP Guidelines**

---

- Trescot AM, Helm S, Hansen H, et al. *Pain Physician* 2008: Opioids Special Issue: 11: S5-S62

## **Guidelines for Maintenance Opioid Use in Chronic Pain**

- Documented medical condition as the cause of the pain
- Prior systematic therapeutic trials of alternative pain control regimens (analgesics, adjuvants, psychosocial interventions, appropriate medical rxs, and behavioral approaches) have been unsuccessful

## **Guidelines for Maintenance Opioid Use in Chronic Pain**

- Documentation that nonopioid rxs have resulted in (a) inadequate analgesia impairing functional ADL and (b) continued suffering
- Document detailed discussion of short and long term effects and risks. Signed informed consent is suggested.

## **Guidelines for Maintenance Opioid Use in Chronic Pain**

---

- Prior to initiating opioid maintenance, (a) obtain consultation with a Pain Med. MD or (b) consult with a specialist in management of the specific problem being rx. Consultation report should document concurrence with opioid rx.

## **Guidelines for Maintenance Opioid use in Chronic Pain**

---

- One physician should be responsible for writing prescriptions (which should be on a time contingent rather than a pain contingent basis) and monitoring clinical progress. Recommended initial frequency of appointments is at least monthly. Pts must be seen and records must document reasons for continuing opioids

## **Guidelines for Maintenance Opioids in Chronic Pain**

---

- Document (at each visit) that maintenance opioids improve analgesia, functional ADL, and diminish suffering. Note side effects, drug seeking behaviors, physical and psychosocial status.

## **Guidelines for Maintenance Opioid Use in Chronic Pain**

---

- Use lowest clinically effective dose. Peripherally acting non-opioids and adjuvants used concurrently may allow lower dose opioid usage. Cognitive-behavioral and physical medicine techniques may assist with analgesia

## **Guidelines for Maintenance Opioid Use in Chronic Pain**

- If pain/suffering persist, with little change despite appropriate opioid trial, consider possibility that pain may not be opioid responsive
- A history of substance abuse or addiction is a relative contraindication. Before proceeding, consider addiction medicine consultation.

## **Guidelines for Maintenance Opioid Use in Chronic Pain**

- Any evidence of drug-seeking behavior, obtaining opioids from multiple sources, or frequent requests for dose escalation without documentation of significant worsening of the clinical condition should be a cause for careful review and reconsideration of maintenance opioid use.

# **WORK, DRIVING & USE OF OPIOIDS**

---

- Are patients at increased risk for MVA's or work injuries?
- Should they be restricted?
- Do they need special monitoring?
- Are you at risk if they have a MVA or work injury?

## **Effects of Opioids on Driving Ability in Pts with CP-2**

---

- Two important factors to consider:
  1. period of time since the last dose
  2. duration of time since the pt started opioid therapy

Bruera et al, *Pain*, 39,13-16,1989



# **WORK, DRIVING AND USE OF OPIOIDS**

---

- Emerging research suggesting that pts on stable doses of opioids with a normal mental status are not at increased risk for MVA's or work injuries
- Monitor concurrent meds (incl OTC) especially those centrally acting
- Monitor reaction time(Aronoff test) and mental status
- Caution when opioids are increased

# **PHARMACOLOGIC INTERVENTIONS**

---

- Elderly require lower initial analgesic dosages
- common opioid side effects are sedation, dizziness, n/v,constipation
- less common are respiratory depression, excitatory responses, urinary retention, and orthostasis

# CONCLUSION

---

- It is the responsibility of the entire healthcare team to evaluate the patient as a whole, physically, psychosocially and spiritually.
- Relief of pain and suffering and improvement in QOL should be the ultimate treatments goals