From:	Ecovi@cs.com
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Sent:	6/26/2001 11:46:02 PM
Subject:	Chronic Opioid Therapy Handout
Attachments:	Opioid Maintenance 2001 Handout.pdf

Hello -

It was good to see you again, and thanks again for sponsoring the talk. I hope that it went well.

You'd requested a copy of my handout, which is attached. I sent it to Dr Dobritt last week, and am not sure why it was not available at the lecture.

Ed Covington

Opioid Maintenance in Chronic Non-Malignant Pain

Edward C. Covington, M.D.
Cleveland Clinic Foundation

JAMA 1941

"The use of narcotics in the terminal cancer [patient] is to be condemned if it can possibly be avoided. Morphine and terminal cancer are in no way synonymous. Morphine usage is an unpleasant experience to the majority of human subjects because of undesirable side effects. Dominant in the list of these unfortunate effects is addiction."

Lee LE. Medication in the control of pain in terminal cancer. JAMA, 116(3): 216-220, 1941

Acute and Cancer Pain Undertreated

- Poor understanding
  - pharmacology
  - pharmacokinetic
- Failure to ask patients re pain
- Fear of creating addiction – even in terminal patients
- Regulatory fears

Addiction in Acute Pain

- 11,882 pts given narcotics for medical problems
  - None had a CD history
  - 4 subsequently abused drugs
  - This was a major problem only in 1

  Porter J, Jick H, NEJM 302(2), 1980
- 10,000 burn patients
  - Frequent opioids, usually parenteral, protracted
  - No iatrogenic dependence
  - 22 subsequently abused drugs
  - All had previously done so

  Perry, Heidrich:Pain 1982

Acute Pain Conclusions

- Iatrogenic addiction in treatment of acute pain is virtually nonexistent
- The appropriate opioid dose for postoperative /post traumatic pain is whatever it takes

Opioids in Chronic Non-malignant Pain – History

- Predictions:
  - Declining efficacy
  - Dose escalation – dependence
  - Promote regression
  - Reinforce pain behavior
  - Diversion
  - Toxicity
  - Impaired cognition, alertness, motor function
- Consequences:
  - Maintenance opioids rarely used, last resort, act of desperation, not a routine standard of care.

Beginning of Liberalization

Melzack: The Tragedy of Needless Pain

- People suffer not because their discomfort is untreatable but because physicians are reluctant to prescribe morphine.
- Care givers, afraid of turning patients into addicts, deliver amounts that are too small, spaced too widely to control pain.
- The fact is that when patients take morphine to combat pain, it is rare to see addiction.
- Addiction seems to arise only in users who take the drug for psychological effects, such as euphoria or to relieve tension.
- Patients who take morphine for pain do not develop the rapid tolerance that is often a sign of addiction.

The Pendulum Swings

- Enthusiasm for opioid maintenance has grown rapidly
- The condemnation of opioids has, in many places, been replaced with unbridled enthusiasm
- Headlines scream
- Patients develop unrealistic expectations

Damned if You Do – Damned if You Don't

- "Pain Patients' Bill of Rights" - California
  - Frees physicians to prescribe any dose of opioids they consider appropriate
  - Requires that opioid maintenance not be relegated to "after all else fails"
  - Requires physicians who do not prescribe opioids for chronic pain to notify the patient of physicians who will
- Litigation for pain undertreatment
  - Oregon
  - California

Current Controversy

- Considerable polarization

"There appears to be little hope for a rational outcome as the discussion is dominated by zealots at one extreme and nihilists at the other."

Peter Wilson, Clin J Pain 13(1), 1997

Origins of Controversy

- Lack of data on long term efficacy
- Vastly different experiences among experts
  - Improvement when opioids are given
  - Improvement when opioids are stopped
- Different pain syndromes
  - Headache, cancer, sickle cell
- Different patients
  - Injured workers, arthritics
- Non-nociceptive issues in CNMP

Medical Issues in Opioid Maintenance

- Risks
  - Toxicity
  - Functional impairment
  - Addiction/physical dependence
  - Hyperalgesia
- Potential Benefits
  - Analgesia
  - Function
  - Quality of life

Opioid Toxicity - A Non-issue?

- Respiratory depression
  - Only with sedating doses
  - Tolerance develops quickly
- Liver, kidneys, heart, brain, GI
  - < NSAIDs, acetaminophen, 'atypical analgesics'
- Toxic metabolites
  - Hyperexcitability, seizures
  - Avoid meperidine, propoxyphene
- Exception
  - Lethal in overdose

Opioid Induced Impairment

- Controlled studies, years of experience
- Methadone maintenance in heroin addicts produces minimal functional impairment
- Patients are safe to drive and work
- Options
  - Benzodiazepines impair cognition and driving
  - Anticonvulsants, antidepressants may impair performance
  - Unrelieved pain impairs function on cognitive testing

Opioid Induced Impairment

Extensive review of opioid effects on cognition, psychomotor function

Conclusions:

- Impairment mostly in opioid naïve
- Much less in recreational users, pain patients
- In healthy volunteers, cognition is effected < speed. Behavior tends to be slower, not more erratic.
- Several studies show accidents are likely with alcohol, benzodiazepines, marijuana, cocaine, not opioids

Zacny, JP. Exp Clin Psychopharmacol, 1995.

Physical Dependence

- Universal
- Also with α_2 agonists, anticonvulsants
- Significance:
  - Inconvenience
  - Dose/response curve shifts right
  - Necessitates special arrangements for absences
  - Increased pain with short acting drugs?
  - Abstinence during troughs $\rightarrow$ tension, autonomic arousal

Addiction

- Most feared consequence of opioid maintenance
- Surveys of addicts introduced to drugs medically
- Misunderstanding of pseudoaddiction
- Argument: Studies demonstrate the rarity of addictive disorder in those with no prior addiction
- Weakness – most studies short term
- Conclusion
  - Without long term (years) studies, the risk of producing addiction by opioid maintenance will remain unknown

Criteria for Addiction

- DSM-IV criteria not helpful in chronic pain
  - Include tolerance and withdrawal
  - Universal in opioid maintenance
- Important indicators of addictive disorder
  - Loss of control – inability to ration
  - Preoccupation – multiple sources, spends time thinking about, obtaining, and taking the drug
  - Use despite adverse consequences – personality changes, regression, intoxication

Efficacy

- Not all pains are equally opioid responsive
- More responsive
  - Dull, aching, visceral pains
- Less responsive
  - Neuropathic
  - Skin
  - Sharp pain
  - Incident pain

Tolerance

- Animal studies – inconclusive
  Almost all address acute rather than chronic tolerance
- Cancer patients – opioid requirements generally stable until disease progression
- CNMP – most report several weeks' dose titration, then stability for months - years

Opioid Efficacy in CNMP

- 1996 review found no controlled studies
- Case series – 566 patients
- Supported opioids for chronic LBP

Relative contraindications:

- Substance use disorders
- Personality disorders (ASP, BPD)
- Renal, hepatic, pulmonary insufficiency, slow gut, urinary retention
- Occupations (e.g., transportation, law enforcement)

Brown RL, et al. J Amer Bd Fam Prac, 1996

Methadone Maintenance in CNMP

- 124 outpatients, 11 yrs mean pain
- Methadone 70-100 mg/d
- Duration: $\bar{X}$ = 20 mo.
- 90% good response
- 20 mo mean f/u
- No significant tolerance
- No change in acute pains (menses, injury)

Kell M. APM 4(1), 10-16, 1994

Long-Term Opioids in CNMP

- N = 100, mean treatment 7 mo.
- MS dose = 255 mg/d (20-2000)
- Mostly neuropathic, LBP
- Dihydrocodone, MS, buprenorphine
- Doses stabilized after 14-21 days
- Good relief (≥ 50%) in 51
- Partial relief (≥ 25%) in 28
- Relief correlated with performance improvement
- No addiction
- Poor relief in 6/8 face, head pain

Zenz, M, et al, J Pain Sympt Mgt 7(2) 1992

Morphine in Chronic Soft Tissue Pain

- 9 wk, randomized, crossover, MPC patients
- Myofascial, musculoskeletal, rheumatic pain
- Excluded: substance abuse, depression, neuropathic pain, headache
- Morphine, ≤ 60 mg bid (x 83.5 mg/d) vs. placebo (benztropine)
- After titration, MS → substantial pain reduction
- At end of evaluation phase, small pain reduction, no change in function, POMS, SIP, SCL-90, or Pain Disability Index

Moulin DE et al, Lancet 347:143-7, 1996

COT by CL Psychiatry

- CNMP, N = 59, f/u $\bar{X}$ = 36 mo
- 90% some psychopathology, not drug abuse/addiction
- "Good candidates" for opioids per primary, psychiatrist
- 34% complete relief, 20% none
- 69% some tolerance (treatment limiting in 22%)
- Depression negatively associated with efficacy
- 56% abused opioids
  - Serious in 27%
  - 24% developed opioid addiction
  - 8% possible addiction
- 34% overall good response

Bouckoms AJ, et al. Ann Clin Psychiatry 1992

Methadone in Chronic Daily Headache

- Retrospective, headache clinic patients, n=42
- Original n = 148, 106 dropped out (efficacy or side effects)
- Refractory to standard headache therapies
- 6 mo methadone
  - Mean 12.5 mg/d, Max 40 mg/d

Improved	% of 42	% of 148
Work/housework	86	24
Marriage	71	20
Other relationships	81	23
Sex	60	17

Robbins R. Headache Quarterly 1997

Continuous Opioid Therapy (for Pain) in Addicts

- N = 20
- CNMP + history of substance abuse
- Patients treated for > 1 year
- Those who abused treatment did so early.
- Non-abusers
  - more likely to be active in AA
  - stable support systems.
  - less likely to be recent polysubstance abusers

Dunbar SA, Katz NP. J Pain & Symptom Mgt , 1996

Opioid Failure

- 32/50 CNMP pts treated in CD unit – improved pain, work, family relationships, sexual function Finlayson RE, et al, Pain 26, 1986
- Detoxification, relaxation training, 3 session therapy: ↓ pain Taylor CMB, et al, Pain 8, 1980
- 4 CNMP patients detoxified → reduced pain, return to work Brodner RA. Taub a, Mt Sinai Med J 45, 1978
- 200 mixed HA patients – Prophylaxis most effective in those weaned from opioids Kudrow L, Adv Neurol 33, 1982
- Behavioral programs – Patients taking opioids in severe pain, severely dysfunctional, seeking higher doses, more comfortable after weaning.

Morphine Causes Pain

- Spinal dynorphin produced in response to sustained opioid exposure is pronociceptive
- Lidocaine to the RVM blocks opioid induced hyperalgesia
- DLF lesions block development of morphine tolerance
- Suggests the descending facilitatory tract is the mechanism

Vanderah TW, et al. Pain 2001
Vanderah TW et al. J. Neuroscience 2001

Hyperalgesia

- Opioids can increase pain
- Neurophysiologic changes after high dose opioids are similar to those in hyperalgesic/sensitization
- Addicts on methadone may have lower pain thresholds
- Extreme hyperalgesia
  - terminal cancer, massive doses
  - High dose intrathecal opioids

Success ≠ Satisfaction

- Intrathecal opioids, retrospective, n = 38
- ≥ 36 months ($\bar{X}$ = 50 months)
- OUTCOME
  - Dose escalation = 6 X
  - Δ pain – small but significant decrease
  - high pain levels on the McGill
  - severe disability per Oswestry
  - mild depression per Beck
  - multiple side effects and system complications

Brown J, Klapow J, Doleys D, et al. Clin J Pain 1999

Success ≠ Satisfaction

- Retrospective questioning, patient reported improvement:
  - 64% pain
  - 48% functioning
- Family reported 61% improvement in pain.
- Quality of Well-Being Scale:
  - lower health-related quality of life than rheumatoid arthritis
  - lower physical functioning than CHF
  - Mental function comparable to U.S. population
- 81% reported good to excellent satisfaction

Brown J, Klapow J, Doleys D, et al. Clin J Pain 1999

Reinforcement of Pain Behavior

- Pain behavior increases with reinforcement
- Behavior, function, comfort improve with elimination of reinforcement for pain behavior
- Opioids are quintessential reinforcers
- If one receives meperidine when he goes to bed and moans, will these behaviors increase?
- Contingency management may minimize this risk
  - Medicate by the clock
  - Medicate for activities (before a walk)
  - Not prn

1992 Survey of State Medical Board Members

	Lawful, generally acceptable	Lawful, generally not acceptable - discourage	Prob violation of med practice laws / regs - investigate	Prob violation of fed / state laws; investigate
Ca pain	75%	14%	5%	5%
Ca pain + hx opioid abuse	46%	22%	14%	12%
CNMP	12%	47%	32%	27%
CNMP + hx opioid abuse	1%	25%	58%	50%

Joranson DE, et al. Federation Bulletin 1992

Federal Regulatory Concerns

- Federal law does not impede prescribing opioids for intractable pain
- Controlled Substances Act: "Many of the drugs included within this title have a useful and legitimate medical purpose and are necessary to maintain the health and general welfare of the American people."
- DEA Administrator: patients and pharmacies should be able to obtain sufficient quantities of *any schedule II drug*. A therapeutic drug should be available to patients when they need it.

Federal Regulatory Concerns

- Prescribing for 'addicts' is sharply limited
- Ambiguity results: 'pain patients' and 'addicts' are not mutually exclusive
- Prevalence of addiction in CNMP
  - 414 chronic pain patients
  - Swedish rehabilitation hospital
  - Structured interviews, DSM-III-R criteria
  - Active misuse or dependency in 23.4%
  - Additional 9.4% met criteria for remission

Hoffmann NG, et al. *Int J Addict*. 1995

Methadone Programs
Narcotic Addict Treatment Act of 1974

Narcotic Treatment Programs

- Task: maintaining or detoxifying addicts with opioids
- Only licensed NTPs may use opioids for detoxification
- They are limited to methadone or LAAM
- They can only dispense, not prescribe

Distinction from pain management:

"This section is not intended to impose any limitation on a physician... to... administer or dispense (including prescribe) narcotic drugs to persons with intractable pain in which no relief or cure is possible or none has been found after reasonable efforts." (Code of Federal Regulations)

Model Guidelines for the Use of Controlled Substances for the Treatment of Pain

Federation of State Medical Boards of the United States, Inc.

May 1998

Model Guidelines

- Opioids may be essential in chronic cancer or non-malignant pain.
- Tolerance / physical dependence are normal in sustained use and are not synonymous with addiction.
- Physicians should be diligent in preventing diversion
- Physicians should not fear discipline for prescribing for a legitimate purpose.
- The board will not take action for failing to adhere strictly to these provisions, if good cause is shown for deviation.
- Physicians' conduct will be evaluated to a great extent by treatment outcome.
- The board will judge prescribing based on overall treatment and documentation rather than quantity and chronicity.

Model Guidelines

Requirements

- Documentation of complete H&P, including effects of pain on physical and psychological function, history of substance abuse.
- Treatment plan must contain objectives that will be criteria of success.
- There must be informed consent with discussion of risks and benefits, ± a written agreement.
- Treatment should be periodically reviewed.
- Comorbid chemical dependency or psychiatric illness may require extra care and consultation.
- Documentation must be complete.

Up-to-date Regulatory Information

University of Wisconsin Pain and Policy Studies Group

http://www.medsch.wisc.edu/painpolicy/

Reasonable Conclusions

- Acute, Ca, AIDS pain are undertreated. The goal is comfort. Failure to treat acute pain may predispose to chronic pain.
- Physicians can Rx opioids for pain without reprisal, assuming excellent documentation, frequent f/u, evidence of benefit
- Some patients experience an improved quality of life, less suffering, increased function on maintenance opioids.
- Others, even with pain thought to be opioid sensitive, have little analgesia, reduced function, lowered quality of life
- It is difficult to predict outcome

Reasonable Conclusions

- It is rare for acute opioids to cause addiction where none existed (though patients switch addictions.)
- The risk of addiction with maintenance opioids is unclear but apparently low.
- Thus a closely monitored trial with good accountability is low risk, if not continued beyond the point of obvious failure.
- Risk factors for addiction include personal and family history of chemical dependence.

Reasonable Conclusions

- Opioid maintenance is less helpful if inordinate regression, 'abnormal illness behavior.'
- Those with 'chronic pain syndrome' are probably poor candidates.
- This is intuitive, given that opioids are primarily effective for nociception, and nociception is not the predominant problem in this syndrome.
- Use of opioids for psychoactive effects – to reduce fear, anger, boredom, sadness – may cause rapid dose escalation and unsatisfactory analgesia.

Practical Application

Attend to three constituencies

- Patient
- Society
- Yourself

The Federation of State Medical Boards Guidelines are an excellent, common sense start.

Taking Care of the Patient

- Risk/benefit assessment
  - Is the pain opioid responsive?
  - Physiologic exam
  - Is there high risk of addictive disorder?
  - Is the patient reliable?
- Plan, objectives clear to patient and physician
  - Opioids are to have a life, not to hide from life.
- Opioids - occasionally necessary, rarely sufficient
  - PT, other medications, counseling, relaxation training
- Give stool softeners

Drug Choice

- Fast in, fast out – most addicting
  Nicotine, cocaine, heroin, barbiturates
- Slow onset/long acting
  Methadone is cheapest by far
  Usually by the clock.
- Avoid prolonged use of drugs with toxic metabolites
  meperidine, propoxyphene
- Avoid mixed agonist-antagonists
  therapeutic ceilings, psychotomimetic, mostly IM
- Change drugs when one is/becomes ineffective
  Individual variability
  Incomplete cross tolerance

Outcome Monitoring is Essential

- Analgesia
  - Pain level – 0 -10
- Affect
  - Beck Depression Inventory
- Activity level
  - Pain Disability Index
- Adverse effects
  - Cognition, alertness
- Aberrant behaviors
  - Multisourcing, lost drugs

If not effective, stop.

Protecting Society

- Diversion is a serious concern
- Physicians are not detectives, but should not be naïve
- Chronic pain patients are often poor
- Street value >>>> legitimate price
- A patient convicted of diversion should obtain opioids from methadone centers, if at all
- Toxicology screen should be positive. If not, consider diversion, or false sample

Be Financially Responsible

- Prolonged high dose opioids can be costly
- Expensive analgesics are not more effective, only more convenient - sometimes.
- IV infusions, pumps, intrathecal agents
  - Mostly useful in acute pain and terminal care
  - Short gut, emesis, impaired consciousness, impaired swallowing
- Most opioids are well absorbed sublingually, rectally, vaginally

Retail Opioid Prices

Drug	Tabs/Mg/d	Daily Cost
Morphine 10 mg	10/100	3.31
Percodan	24/120	20.40
Oxycodone/acet	24/100	9.60
Vicodin	24/100	12.40
Levorphanol	16/32	2.02
MS Contin 15	6.7/100	6.67
Methadone 5	13/66	2.00
Methadone 10	6.5/33	1.61
Duragesic 25	2 patches 8.25	2.75

Cleveland 1999

Protect Yourself

- Document sufficient work-up to establish diagnosis
- Delay COT until confirm:
  - There isn't a better method of pain control
  - Pain is intractable - pathology is not correctable
  - These may require consultation
- Document
  - Decision making process
  - Patient's agreement to responsible use and accountability
  - Written description of risks is useful.
  - Patients must be held accountable.

Paradoxes and Conflicts

Tolerance

- Tolerance develops minimally, analgesic effect is retained for years.
- Addicts on methadone maintenance obtain no analgesia
- How does methadone control visceral pain in chronic use, yet not effect dysmenorrhea?

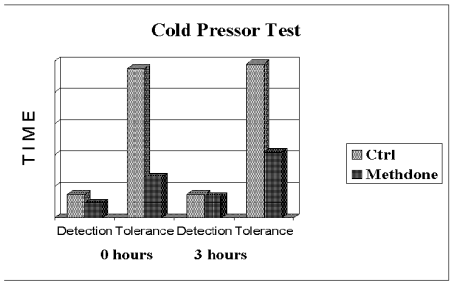
Paradoxes and Conflicts

The Illusion of Benefit

- Patients may be unable to determine the effect of opioid treatment on pain and quality of life.
- The patient who is devastated by opioids reports, "They take the edge off."
- This may reflect only that peak levels are more comfortable than trough.
- These patients frequently have pain reduction with opioid elimination.
- Analogous to alcoholism

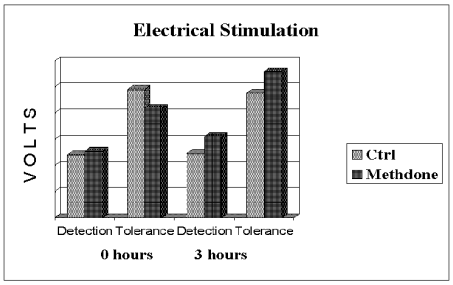
Hyperalgesia in Methadone Maintenance

Doverty M, et al, Pain 2001



Hyperalgesia in Methadone Maintenance

Doverty M, et al, Pain 2001



Chronic Methadone and Pain

- Opioid tolerant rats are hyperalgesic
- Former heroin addicts – methadone maintained vs. opioid free
  - Those on methadone are less tolerant to cold pressor

    Compton P, Ling W
- Intra-subject comparison on / off naltrexone maintenance
  - Cold pressor test
  - 8/10 had better pain tolerance on naltrexone

    Compton P, Ling , J Pain Sympt Management, 1998

Paradoxes and Conflicts

- Confusion
  - Morphine and methadone do not cause confusion in chronic use.
  - Patients commonly describe coming out of a haze when they are detoxified from opioids.
- Function vs. Comfort Puzzle:
  - Some patients don't function due to pain
  - Report relief from opioids
  - Still don't function

Opioid Maintenance

- It is not possible to accurately predict who will be helped/harmed
- Assess risk factors
- Get informed consent
- Monitor compliance
- Monitor efficacy
  - Pain score
  - Functional status

The Future

- The role of opioids in CNMP will evolve as we learn from the current massive social experiment
- Research may produce ways to prevent / reverse tolerance (NMDA antagonists)
- Opioid usefulness may be greatly enhanced by them.
- Alternative opioids, such as κ–agonists, with minimal cross tolerance
- Prediction:
  - Opioids will be established as an answer to the problem of chronic pain
  - They will never be *the* answer