“Opiate Overuse”: Pain Management Strategies for Care Coordination

16th Annual Case Management Conference: Navigating the Future Course of Case Management
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Kellogg Hotel & Conference Center

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Declarations of Potential Conflicts of Interest

• I have no financial relationship with any pharmaceutical company
• The content of this presentation is non-commercial and does not represent any conflict of interest or commercial bias
• I will mention the use of medications for indications that are not FDA approved (but you will be informed when that happens)
Objectives

• Very brief discussion of the problem
• What is addiction anyway?
• Neurobiology of Addiction
• Problems with opiates
• Management Strategies for this population
What is the Problem?

• Reported opiate overdose deaths are currently between 40,000 – 50,000
• Annual opiate overdose deaths exceed traffic fatalities since 2008 and continue to rise
• A significant proportion involve prescription medications
• Philosophy regarding the treatment of chronic painful conditions is undergoing a complete revision
What is the REAL Problem?  
(i.e., Why am I here?)

• This patient population is poorly understood by health care providers, insurers, legislators, the media, etc.

• Some people dying from opiate overdose have Substance Use Disorder (SUD)

• Many do not have SUD

• Which patient is which?

• The old plan for treating chronic pain, makes patients worse, not better
Doctors Training in Addiction

• National survey of residency training directors found that 56.3% had addiction in required curriculum which ranged from 3-12 hours

• National Center on Addiction and Substance Abuse at Columbia University reviewed board certification exams in 6 medical specialties that interact most often and regularly with patients who may have SUD issues and found that it ranged from 0-2% of the exams.
• 94% of primary care physicians failed to diagnose substance abuse when presented with early symptoms of alcohol abuse in an adult patient.

www.centerforhealthandjustice.org/BOSUDsandPrimaryCare.pdf
• 29.5% of patients (in treatment for addiction) said their physicians knew about their addiction and prescribed psychoactive drugs such as sedatives or Valium.

www.centerforhealthandjustice.org/BOSUDsandPrimaryCare.pdf
Public Policy Statement on Measures to Counteract Prescription Drug Diversion, Misuse and Addiction - ASAM BOD, 01/25/12.

• “Studies have shown that physicians have not received adequate education about the potential psychiatric and addiction consequences of the decision to prescribe scheduled medication”

• “Most practicing physicians have had little if any formal training in addiction.”

• “Confusion still exists whereby some clinicians mistake physical dependence (tolerance and withdrawal) for addiction”
Effects of Opiate Exposure

• Everyone
  – Short Term
    • Pain relief
  – Long Term (varied individual progression)
    • Tolerance
    • Dependence
    • Hyperalgesia
    • Risk of Medication Toxicity to the CNS

• Genetically predisposed to addictive illness
  – All of the above plus…
  – Profound decision making alterations
Annals of Internal Medicine

Opioid Prescriptions for Chronic Pain and Overdose
A Cohort Study
Kate M. Dunn, PhD; Kathleen W. Saunders, JD; Carolyn M. Rutter, PhD; Caleb J. Banta-Green, MSW, MPH, PhD; Joseph O. Merrill, MD, MPH; Mark D. Sullivan, MD, PhD; Constance M. Weisner, DrPH, MSW; Michael J. Silverberg, PhD, MPH; Cynthia I. Campbell, PhD; Bruce M. Psaty, MD, PhD; and Michael Von Korff, ScD

Primary Funding Source: National Institute of Drug Abuse.

Dunn, et al. 2010

- 9940 patients; 1997-2005
- Results

<table>
<thead>
<tr>
<th>Morphine Dose</th>
<th>Hazard Ratio of Serious Overdose</th>
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<tbody>
<tr>
<td>None</td>
<td>0.19</td>
</tr>
<tr>
<td>1 - &lt;20 mg /day</td>
<td>1.00</td>
</tr>
<tr>
<td>20 - &lt;50 mg/day</td>
<td>1.19</td>
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<tr>
<td>50 - &lt;100 mg/day</td>
<td>3.11</td>
</tr>
<tr>
<td>100 + mg/day</td>
<td>11.18</td>
</tr>
</tbody>
</table>
ADDICTION 101
What is an Addict?

• Someone who says they are an addict
• Someone who asks for pills all the time
• Someone with weak will power
• Someone who is not smart enough to stop
• The last patient you ever want to deal with
What is Addiction

General Idea:
Continued use of a substance or engagement in an activity despite obvious harm.
What is Addiction

• A primary, chronic disease of brain reward, motivation, memory and related circuitry

• Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations.

• This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.
What is Addiction

• Like other chronic diseases, addiction often involves cycles of relapse and remission.

• Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

American Society of Addiction Medicine, Public Policy Statement: Definition of Addiction
VTA (Ventral Tegmental Area, midbrain) is a central component in the "Pleasure Circuit." It is involved in the reward system and is activated by various substances including amphetamines, cocaine, opioids, cannabinoids, and phencyclidine (PCP).

Key areas and pathways in the diagram include:
- **FCX (Frontal Cortex)**
- **AMYG (Amygdala)**
- **HIPP (Hippocampus)**
- **CRF (Corticotropin-Releasing Factor)**
- **GLU (Glutamate)**
- **GABA (Gamma-Amino Butyric Acid)**
- **OPIOID (Opioid)**
- **DYN (Dopamine)**
- **5HT (Serotonin)**
- **NE (Norepinephrine)**
- **DA (Dopamine)**
- **BNST (Bilateral Nucleus of the Amygdala)**
- **HYPOTHAL (Hypothalamus)**
- **OFT (Olfactory Tubercle)**
- **ABN (Arcuate Nucleus)**
- **ICSS (Induced Conditioned Stimulus)**
- **RETIC (Reticular Activating System)**

Neurotransmitters and pathways such as GABA, NE, 5HT, and DA are crucial in the reward circuit and are influenced by substances like opioids, cannabinoids, and amphetamines. The complex network of these neurotransmitters and circuits plays a vital role in the regulation of pleasure and reward.
“Pleasure Circuit”

- Cortex (logic)
- Amygdala (emotions)
- Hippocampus (memory)
- Ventral Pallidum (motivation)
- Nucleus Accumbens (striatum)
- VTA
- Ventral Tegmental Area (midbrain)
“Pleasure Circuit”

VTA

Cortex (logic)

Amygdala (emotions)

Hippocampus (memory)

Ventral Pallidum (motivation)

Nucleus Accumbens (striatum)

Ventral Tegmental Area (midbrain)

Amphetamine

Cocaine

Opiates

Cannabinoids

Phencyclidine

Ketamine

Opiates

Ethanol

Barbiturates

Benzodiazepines

Nicotine

Cannabinoids

DOPAMINE!!!
How To Assess Addiction

• Ask about current addiction
  • Nicotine addiction (aka “Smoking”)
  • Alcohol use (Heavy Drinking)
  • Illicit Drugs
  • Prescription Drug aberrancy

• Ask about past history of addictive behavior and consequences
  • DUI, MIP’s, incarceration, job loss, marital and family problems, treatment centers

• Family History of Addiction
Formalized Assessment Tools

- CAGE – (originally for alcohol only)
- DSM-IV Checklist
- AUDIT – short, 10 items, 5min
- MAST – oldest, 22 items, alcohol only
- DAST – MAST for drugs
What to do if you find addiction?

• Be supportive and non-judgemental
• Share what you know about addiction
• Refer to a specialist for assessment
• Refer to mutual self-help group (patient and family)
• Avoid mood altering substances (esp. benzodiazepines and opiates)
Summary ("Take Home Points")

• Addiction is a brain disease
• There are treatments that work
• Treat your addicted patients with kindness and respect understanding they are ill (just like cancer or diabetes)
• Get help with your addicted patients – this is not easy.
Why Did I Just Talk About Addiction?

• So you can differentiate it from dependence
• To understand that the treatment of dependence is not the same as the treatment of addiction
• The treatment of addiction requires a great deal more than prescribing drugs (topic of another talk)
PAIN 101
Simple Approach to Treating Non-Malignant Pain

- If it hurts.....
- If it hurts a lot...
- If it REALLY hurts...
- If it still REALLY hurts...
  “Hmmm. Something is just not right.”
  “If it REALLY hurts for a long time....
  “If it’s getting worse no matter what I prescribe...
- Give ibuprofen
- Give hydrocodone
- Give something stronger
- Give more
- Keep giving more
- Discharge patient
Pain

Clinical definition:

“Whatever the patient states it is unless proven otherwise by poor adherence to the agreed upon medical regimen.”

“No kind of sensation is keener and more active than that of pain, its impressions are unmistakable.”

The Marquis de Sade
Pain is the Most Highly Modulated Sensory Experience

- Central Modulation (e.g., stimulation of periaqueductal gray)
- Inhibitory or facilitatory processes in spinal cord (ascending) or brain (descending)
- Opioid analgesics enhance inhibition initially, may facilitate as late phenomena (hyperalgesia)
- Addictive illness facilitates via multiple mechanisms

Chronic Pain Syndrome

“Under such torments, the temper changes, the most amiable grow irritable, the bravest soldier becomes a coward…….”

Dr. S. Weir Mitchell, 1872
Chronic Pain Syndrome

• Intractable pain of more than 6 months duration
• Marked alteration in behavior, restriction in daily activities
• Excessive use of medication and medical services
• No clear relationship to organic disorder - multiple nonproductive tests/treatments/surgeries
Summary Of Current Chronic Pain Theory

Neuroplasticity influenced by:
- excito-toxicity
- central sensitization (allergy to pain?)
- genetic predisposition
- trauma/abuse
- addiction/psychiatric co-morbidities
- with resulting neurochemical and neurohormonal derangements
Chronic Pain Responds Differently than Acute Pain

• Some of the treatments that work well for acute pain, may worsen chronic pain

• Examples:
  • Short acting opiates
  • “muscle relaxers” / sedatives
  • Medical procedures
Goals of Treating Chronic Pain

• Increase function!!!
• Decrease pain
• Use medications that do not have unacceptable side effects
Take Home Point

Chronic Pain is Different than Acute Pain
Conclusions. Evidence on long-term opioid therapy for chronic pain is very limited but suggests an increased risk of serious harms that appears to be dose-dependent. More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies.
## Randomized Trial Evidence for Commonly Used Medications from Recent Meta-Analyses

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Number of trials</th>
<th>Number of patients</th>
<th>Person-years (est.)</th>
<th>Number US adults using long-term</th>
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</thead>
<tbody>
<tr>
<td>Antihypertensives(^a)</td>
<td>147</td>
<td>~464,000</td>
<td>~1,857,000</td>
<td>48 million</td>
</tr>
<tr>
<td>Statins(^b)</td>
<td>26</td>
<td>~169,000</td>
<td>~753,000</td>
<td>34 million</td>
</tr>
<tr>
<td>NSAIDs(^c)</td>
<td>31</td>
<td>~116,000</td>
<td>~117,000</td>
<td>6 million</td>
</tr>
<tr>
<td>Opioids(^d)</td>
<td>62</td>
<td>~12,000</td>
<td>~1,500</td>
<td>7-9 million</td>
</tr>
</tbody>
</table>

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\(^a\) Law et al., BMJ 2009.
\(^b\) CTT Collaboration, Lancet 2010.
\(^c\) Trelle et al., BMJ 2011.

Courtesy Michael Von Korff

OPIOIDS COMPARED WITH PLACEBO OR OTHER TREATMENTS FOR CHRONIC LOW BACK PAIN: AN UPDATE OF THE COCHRANE REVIEW
Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review

- 15 trials, 5540 participants
- “…short-term efficacy (moderate for pain and small for function) of opioids to treat CLBP compared with placebo”
- The effectiveness and safety of long-term opioid therapy for treatment of CLBP remains unproven
Problems with Opioids And Pain

• Tolerance
• Dependence/Withdrawal
• Opiate-Induced Hyperalgesia (OIH)
Hyperalgesia

• A heightened pain state
• Minor painful stimuli produce an intense and miserable pain state ("heightened misery state")
• Universal at chronic high doses of opioids
• Central facilitatory/excitatory mechanisms responsible
• CNS pain filtering mechanisms are essentially absent

J Mao, DD Price and DJ MayeThermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acid receptors and protein kinase C Journal of Neuroscience, Vol 14, 2301-2312
Mechanisms of Opioid Induced Hyperalgesia

• Dynorphine System Activation
  – Kappa receptor overstimulation

• Descending Facilitation
  – CCK upregulation in rostral ventromedial medulla (Mitchell et al, 1998)
Diminished Pain Tolerance in Methadone-Maintained Patients

Cold-Pressor Withdrawal Latency Test

Centralized Pain Syndromes

- Pain “generator” is in the CNS
- Always made worse with opiates and sedatives
- Examples:
  - Complex Regional Pain Syndrome (formerly RSD)
  - Fibromyalgia
  - Migraine
  - Interstitial Cystitis
  - Burning Mouth Syndrome
BENZODIAZEPINES

Maybe Not Mother’s Little Helper
Instead, we found evidence that benzodiazepine use was significantly associated with activity level, medical visitation, domestic disability, and to a lesser degree, disability days. With respect to illness behavior, therefore, benzodiazepine use appears to offer an alternative explanation for the observed “downhill spiral” thought to be associated with opioid use.
Management of generalised anxiety disorder in adults: summary of NICE guidance

Tim Kendall,1,2,3 John Cape,4,2 Melissa Chan,1 Clare Taylor,1 on behalf of the Guideline Development Group

Do not offer a benzodiazepine to treat generalised anxiety disorder in primary or secondary care except as a short term measure during crises. (New recommendation.)
Benzodiazepine use and risk of dementia: prospective population based study

Sophie Billioti de Gage PhD student\textsuperscript{1,2}, Bernard Bégad professor\textsuperscript{1,2,3}, Fabienne Bazin researcher\textsuperscript{1,2}, Hélène Verdoux professor\textsuperscript{1,2,4}, Jean-François Dartigues professor\textsuperscript{1,5,3}, Karine Pérès researcher\textsuperscript{1,5}, Tobias Kurth director of research\textsuperscript{1,6,7}, Antoine Pariente associate professor\textsuperscript{1,2,3}
Discussion

In this large, prospective, population based study of elderly people who were free of dementia and did not use benzodiazepines until at least the third year of follow-up, new use of benzodiazepines was associated with a significant, approximately 50% increase in the risk of dementia. This result remained stable after adjustment for potential confounding factors, including cognitive decline before starting benzodiazepine and clinically significant symptoms of depression. It also remained robust when we pooled five cohorts of new benzodiazepine users throughout the 15 year follow-up period and in a complementary nested case-control study.
EXIT STRATEGIES:

A return to safety
The Answer!

- Medication Transition
  - Opiates
    - using a partial opioid agonist
      (i.e., buprenorphine)
  - Benzodiazepines
    - Using GABA receptor modifying agents
Disclaimer

• There are often circumstances where patients are so dependent that it is necessary to refer to a specialist in treating medication toxicity and or addiction

• In certain cases, hospitalization is necessary (yes, it is covered as long as it is not addiction treatment)
“If you can’t land, don’t take off.”

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

Twelve Reasons for Considering Buprenorphine as a Frontline Analgesic in the Management of Pain

Mellar P. Davis, MD, FCCP, FAAHPM

Buprenorphine

• Available in several forms:
  – Buprenex injection
  – Generic SL buprenorphine
  – Transdermal Patch (Butrans®)
  – Suboxone Film*: naloxone added
  – Generic SL Buprenorphine/naloxone

• Dosing for chronic pain is often different than for chemical dependency

• *not FDA approved for pain
Buprenorphine

• Acts as a mu agonist:
  – Partial agonist; ceiling effect for analgesia and respiratory depression
  – Slower dissociation = milder withdrawal
  – High affinity: will displace some other µ agonists and precipitate withdrawal
  – Antagonist at the kappa receptor
Clinically Observed Affinity

Morphine
Oxycodone/hydrocodone
Buprenorphine
Hydromorphone
Methadone
Fentanyl(s)
Work-up For Chronic Pain Patients

- Take a complete medical history
- Review psychiatric history
- Review substance abuse history (including alcohol and tobacco use)
- Get a complete list of all medications (current and historical) MAPS (and repeat regularly)
- Urine Drug Screen
- Basic Labs (CBC, Chem profile, Thyroid fxn, etc)
- Carefully educate the patient as to risks, benefits and expectations.
Work-up For Chronic Pain Patients

• Consider all of the following:
  – Pain Psychology Consult
  – Psychiatry consult
  – Nutritional consult
  – Medicine / Cardiology consult
Indications For Change

• Worsening pain despite increasing doses of opiates (i.e., emergence of hyperalgesia)

• Emergence of intolerable side effects (esp. mood disorder and cognitive impairment)

• Lack of improvement in activity or social interaction

• Safety concerns (falls, MVA, unintentional overdose)
# Guidelines For Appropriate Use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum Appropriate</th>
<th>Possible Hyperalgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>30 – 40 mg/day</td>
<td>&gt; 40 mg/ day</td>
</tr>
<tr>
<td>Morphine</td>
<td>15 – 60 mg/day</td>
<td>&gt; 100 mg/day</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>30 – 40 mg/day</td>
<td>&gt; 90 mg/day</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>12 – 50 mcg/hr</td>
<td>&gt;50 mcg/hr</td>
</tr>
<tr>
<td>Methadone</td>
<td>10 – 40 mg/ day</td>
<td>&gt; 40 mg/day</td>
</tr>
</tbody>
</table>
Buprenorphine Induction

• Office-based **Stratification**
  – Lower doses of opioids
  – Low risk / little comorbidity
  – 3-4 hour observed visit

• Hospital Based
  – Toxic doses of opioids (i.e., medication toxicity)
  – High comorbidity
  – Hospital stay 3-5 days
Keys To Success

• Experience using buprenorphine for pain
  – The training for addiction does not provide this and often leads to poor pain control and side effect limitations

• Pain psychology counseling
  – Very high incidence of trauma, abuse and unresolved grief in the chronic pain population

• Interdisciplinary Care Team Meetings

• Identification and simultaneous treatment of SUD and other medical and psychological comorbidities
Success Rates

- Patients report reduced pain and improvement in quality of life in 69\(^2\) – 84\(^1\)%
- Family members frequently say “Thank you for giving me my [wife/husband/parent/child] back
- Patient usually “comes to” by the second month
- This is the beginning of a long process

Take Home Points

• Not every patient who overuses medication is an addict
• Medication toxicity is can be the result of over prescribing
• Medication-assisted withdrawal requires some expertise and patience but can dramatically improve quality of life and safety
• Do not forget to treat your patient with compassion and understanding
Thank You!

• How to reach me:
  – IHA Pain Management Consultants
    • 734 622-5016
  – Email
    • mark_weiner@ihacares.com
References


www.centerforhealthandjustice.org/BOSUDsandPrimaryCare.pdf


American Society of Addiction Medicine, Public Policy Statement: Definition of Addiction


J Mao, DD Price, and DJ Mayer Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acid receptors and protein kinase The Journal of Neuroscience, 1 April 1994, 14(4): 2301-2312;


N Hendler, C Cimini, T Ma, D Long A comparison of cognitive impairment due to benzodiazepines and to narcotics *Am J Psychiatry*, 1980

