Prescription Opioid Addiction and Chronic Pain in Older Adults

Maria A. Sullivan, MD, PhD
Associate Professor of Clinical Psychiatry
Division on Substance Abuse
Columbia University/ New York State Psychiatric Institute
Disclosures

• Dr. Sullivan gratefully acknowledges support from NIDA for her research on the treatment of opioid dependence (DA030484, DA020448).

• Alkermes manufactures Vivitrol and provides medication samples for Dr. Sullivan’s DA030484. Reckitt manufactures Suboxone, which is a study medication in DA030484.

• No other conflicts to report.
Learning Objectives


2. Be able to discuss the risks of prescribing opioids.

3. Be able to identify risks for non-adherence in older patients.

4. Be able to describe and implement a risk assessment strategy for opioid prescribing.

5. Be able to describe and interpret aberrant behaviors which predict opioid misuse.
Narcotic Addiction: A Public Health Imperative

- Up to 1 million heroin users in need of treatment and nearly 2 million untreated prescription opioid addicts in the U.S. (*NSDUH 2011*)

- In past two decades, non-medical use and abuse of opioids has risen dramatically

- Prescription opioid abuse: more than 3 times prevalence of heroin dependence

- By 2006, number of new initiates to prescription opioid abuse exceeded those for marijuana and cocaine (*NSDUH, SAMHSA*)

- HCV prevalence among injecting heroin addicts: 75-95%

- Mortality: 2% (overdose deaths) - 3.5% (all causes) per year
Chronic Pain: Scope and Prevalence

Chronic pain persists or recurs for more than three months (Verhaak et al 1998). Affects more than 100 million Americans.

Prevalence of common types of pain conditions:

- Osteoarthritis: 13.9% of adults aged 25 + in the U.S.
- Low back pain: 25-50% of primary care populations (Reid et al. 2002)
- Musculoskeletal (14% in gen. pop.) myofascial, fibromyalgia
- Injury-related (10%-13% among chronic pain patients)
- Diabetic neuropathy (8-10%) Spinal stenosis (4-10%), headache (4-13%)
- Overall 1-month prevalence of moderate/severe non-cancer pain: 19% (Reid et al. 2011)

Decreased occupational functioning: most frequent cause of disability for Americans. Pain-related work absences: $61B annually (Stewart et al. 2003)

Psychiatric co-morbidity: depression, insomnia, anxiety (McCarburg et al. 2006) and alcohol or substance use
Epidemiology of Prescription Opioid Abuse in the United States

- 5.2 million Americans (2.1% of U.S. pop.) used prescription opioids non-medically in past month (*NSDUH 2011*)

- Prevalence: 30.4% chronic pain patients in a large (N=239) general practice reported taking extra narcotic doses (*Rosser et al. 2011*)

- Most common sources for misused opioids: free from friend or relative (60%), followed by obtaining prescriptions from one physician (17%) (*NSDUH 2011*)

- Prescription opioids are gateway drug: 17.1% of substance abusers cite pain medication as being the first substance they abused (*NSDUH 2009*)

- Efforts to more aggressively manage pain have resulted in sharp rises in prescribing and misuse of high-potency opioids such as hydrocodone and oxycodone
Non-Medical Use of Prescription Drugs

Illicit Drug Dependence or Abuse in the Past Year Among Persons Aged 12+

NSDUH, SAMHSA 2011
Opioid Prescribing Trends in the United States

- Events in late 1990s led to increased opioid prescribing: (1) state medical boards liberalized rules for prescribing for non-cancer pain (Manchikanti et al. 2010), (2) FDA approval of high-potency Oxycontin.

- Reimbursement for medical care linked to number of encounters; does not reward risk vs. benefit analyses (Gallagher and Rosenthal 2008)

- From 1997 to 2007, retail sales of oxycodone increased 866% and 1293% for methadone (Manchikanti et al. 2010)

- Physician offices: significant increase in visit rate for high-potency opioids (hydrocodone, oxycodone) (Mendelson et al. 2008).

- MD offices and EDs are important channels for abused opioids.
Prescribed Therapeutic Opioids in the U.S.

Based on data from US Drug Enforcement Administration. Automation of Reports and Consolidated Orders System (ARCOS); www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index/html
Prescription Opioid Morbidity and Mortality

• Substantial morbidity and mortality; ED visits have risen linearly with availability of opioids

• Deaths due to opioid analgesics in US (2008): 15,000, surpassing motor vehicle accidents as cause of death in some states (Paulozzi et al. 2008)

• Since 2003, opioid analgesics account for more deaths by overdose that cocaine and heroin combined (CDC, MMWR, January 13, 2012/61(01): 10-13.)

• Immunosuppressive effects of opioids may increase morbidity from infectious diseases, autoimmune diseases, and cancer (Pergolizzi et al. 2008)
CDC: Overdoses with Prescription Opioid Pain Relievers (OPR), 1999-2008: United States

- In 2008, drug overdoses in the U.S. caused 36,450 deaths.

- OPR were involved in 14,800 deaths (73.8%) of the 20,044 prescription drug overdose deaths.

- Overdose death rates ranged from 5.5 per 100,000 population in Nebraska to 27.0 in New Mexico.

- Highest sales rates were clustered in the SE and the NW.

- Among 27 states with overdose death rates above the national rate, 21 (77.8%) had rates of OPR sales above national rate. By contrast, of 24 states with death rates at or less than national rate, five (20.8%) had rates of OPR sales above national rate (p<0.001).
Challenges to Opioid Prescribing

Risks of Under-treating Pain due to:

a) inadequate training in pain management (Tousignant-Laflamme et al. 2012, Saroyan et al. 2011)

b) drug interactions affecting metabolism of opioids (Gallagher et al. 2008)

c) concerns regarding abuse liability (Webster & Fine 2010)

Risks of Prescribing Opioids include:

a) Overcoming opioid tolerance

b) Use of opioids for psychoactive properties

c) Opioid-induced hyperalgesia (Stanos 2012)

d) Diversion
Special Considerations in Opioid Management for Older Patients
Epidemiology of Older Pain Patients

• In 2011, “baby boomers” started turning 65

• By 2030, nearly 1 in 5 U.S. residents will be age 65+

• From 2008 to 2050, number of older (>65 yrs) adults will more than double, from 38.7 M to 88.5 M (Alliance for Aging Research 2006)

• Attitudes of stoicism and cautiousness to label pain mediate reduced pain perception and reporting in older age (Yong 2006)

• 40-50% of older adult report the presence of a chronic pain disorder (Soldato et al. 2007)

• Immunosuppressive effects of opioids may aggravate age-related decline in immune function
Screening for Persistent Pain in the Elderly

- Pain is common and under-diagnosed in older patients

- When an elderly patient presents for initial evaluation, qualitative and quantitative assessment for persistent pain should be documented

- If individual is cognitively impaired, a standardized pain scale, behavioral assessment, or proxy report of pain should be used (Etzioni et al. 2007)

- All elderly patients should be screened annually for persistent pain
Prescription Drug Abuse: Invisible Epidemic in Older Patients

- Polypharmacy is common in older (65+) adults, who have multiple underlying medical disorders (*Ballentine 2008*)

- Approximately one third of all prescription drugs in U.S. are used by older (65+) adults (*NIDA 2005*)

- Among individuals with substance use disorders, accelerated rate of biologic aging due to higher medical burden; older adults with substance use disorder: 50+ years

- Rising proportion of older adults will experience prescription substance abuse because of (1) aging cohort, and (2) increased accessibility of prescription drugs (*Dowling et al. 2008*)

- CONSORT study found older women have highest prevalence of long-term opioid use (8-9% in 2005) (*Campbell et al. 2010*)
Trends in long-term opioid analgesic use in the U.S. by gender and age, 1997-2005
Specific Risks for Non-adherence in Older Patients

- Prevalence of cognitive and functional impairment in elderly increases their risk of non-adherence to medication regimen (*DiMatteo et al. 2007*).

- Even very mild cognitive impairment in healthy elderly living independently has significant negative impact on adherence (*Hayes et al. 2009*).

- Polypharmacy: among patients age 65+, 19% of men and 23% of women take at least 5 prescription drugs (*Kaufman et al. 2013*).

- Older adults are less adherent to analgesics than to other medications; most frequent deviation is reducing frequency and dose (*Sale et al. 2006*). Despite physical limitations, minimize pain and claim high tolerance.

- Attitudes toward analgesics: Fear of addiction, desire to reduce number of pills taken daily, belief that pain is natural part of aging (*Markotic et al. 2013*).
Prescription Opioid-dependent Patients Entering Treatment: Modes of Diversion as a Function of Age

Side Effects of Opioid Analgesics in Older Patients

- Most common adverse events: constipation (30%), nausea (28%), dizziness (22%); these prompted opioid discontinuation in 25% of cases (Papaleontiou et al. 2010)

- Reduced volume of distribution for water-soluble drugs such as morphine

- Use of opioids, especially codeine combinations, increases the risk of falls (Huang et al. 2012)

- Given that most previous pain treatment studies have excluded for advanced age and significant co-morbidity, it is unclear whether older adults with functional/cognitive impairment benefit from long-term opioid therapy.
Co-occurring Depression and Substance Abuse in Elderly

• Substance dependence: often unrecognized, untreated problem in elderly

• Distinctive pattern of substances abused: more alcohol and prescription drugs (Weintraub et al. 2002)

• Increased prescription of tranquilizers and narcotic analgesics for insomnia and painful medical conditions

• Limited research to date on treatment of substance use disorders and co-occurring substance use and depression in elderly

• Treatment methods developed for young and middle-aged patients can be cautiously extrapolated to elderly
Percent of male and female patients of various ages with co-morbid bodily pain, psychiatric disorders, alcoholism, and nicotine dependence

Cicero et al., JSAT 42(1): 87-94, 2012
Dementia and Pain

• Dementia represents serious impediment to evaluation and management of pain

• Compared to cognitively intact patients, individuals with dementia receive fewer analgesics for the same condition (Feldt et al. 1998, Morrison & Siu 2000)

• Cannot assume older patients will automatically report pain

• Systematic use of 3 pain assessment scales (VAS, faces, pain descriptive scale) increased detection of pain (30% vs. 15%, p<0.001) (Etzioni et al. 2007)

• Under-treatment of pain can lead to chronic pain syndromes, adversely affecting long-term QOL (Catananti et al. 2010)
Chronic Pain and Opioid Abuse: Neurobiological and Psychiatric Features
Neurobiology of Opioid Addiction

• Compulsive drug-taking mediated by reward pathways from ventral tegmental area (VTA) to nucleus accumbens (NA), amygdala, prefrontal cortex (Ballantyne et al. 2007)

• Opioids release dopamine directly via in NA and indirectly by decreasing GABA-inhibition in the VTA (Nestler 1996, Cami and Farre 2003)

• Neuropathological changes in opioid abusers: (1) reduced gray matter in prefrontal and temporal cortices; (2) low levels of N-acetylaspartate (Lyoo et al. 2006, Yucel et al. 2007)
Overlapping Neural Circuitry: Pain and Addiction

*Chronic pain serves as pathway for problematic opioid use/addiction:*

- Several brain regions involved in both pain processing and opioid addiction: NA, amygdala, ACC, hypothalamus

- Pain and analgesia alter levels in reward system (*Becerra et al. 2001, Wagner et al. 2004*)

- Final common pathway involves glutamate as: (1) major neurotransmitter in pain response; (2) role in drug- and cue-induced reinstatement (*Kalivas et al. 2003*)
Cognitive Deficits in Pain and Opioid Addiction

Chronic pain patients demonstrate:

- Decision-making abnormalities \((Apkarian\ et\ al.\ 2004)\)
- Impaired prospective short-term memory \((Ling\ et\ al.\ 2007)\)
- Reduced hippocampal volume; observed learning and emotional deficits \((Mutso\ et\ al.\ 2012)\)

Opiate users demonstrate:

- Diminished error-related activation in anterior cingulate cortex and higher apathy \((Pluck\ et\ al.\ 2012,\ Yucel\ et\ al.\ 2007)\)
- Prolonged deliberation times in making risky decisions \((Fishbein\ et\ al.\ 2007)\)
Psychiatric Co-morbidities in Chronic Pain Patients

- Frequently co-occurring diagnoses: depression (37%), anxiety (25%), substance use disorders (12%) (Knaster et al. 2012), somatization, borderline personality disorder (McWilliams et al. 2013)

- Prevalence of drug or alcohol abuse in chronic pain patients: 3-19% (Fishbain et al. 1992, Chabal et al. 1997)

- Patients with significant psychiatric co-morbidity and substance abuse are more likely to stay on opioids and to receive higher doses (Krashin et al. 2013)

- Patients with pain are more prone to a chronic course of depressive and anxiety disorders (Gerrits et al. 2012)
Assessment and Treatment of Opioid Abuse in Chronic Pain Patients
Case #1

- Margaret, a 65-year-old woman, reports chronic low back pain that resulted from a motor vehicle accident 2 years ago. Under the care of another physician, she has been taking hydromorphone (Dilaudid®) 8 mg PO 3 times/day for the past year. From the beginning, she has required higher than prescribed doses to control her pain, and she has sought early refills from her physician and pharmacist. She is anxious and preoccupied with obtaining a prescription on initial consultation. She reports that she has been out of drugs for the past 2 days, is having worsening pain, and is very concerned about withdrawal.
Case #2

- Roger, a 58-year-old man, had a skiing injury 6 years ago involving a dislocated shoulder. His rotator cuff was repaired, and in the postop period he was treated with Vicodin®, but had difficulty tapering from the medication. He currently receives Vicodin 7.5/750 1-2 tabs qid from his internist and also consults a rheumatologist, who prescribes Oxycodone 10 mg q 4 hrs for osteoarthritis. He finds the Oxycodone helpful at night for falling asleep, especially if he has had a stressful day. His wife notes that he is drowsy in the evening and sometimes has difficulty getting to work on time. On presentation, he is somewhat irritable and cannot recall the contact information for his rheumatologist.
Recognizing Nonmedical Users of Prescription Drugs

- Unusual behavior in the waiting room
- Assertive personality, demanding immediate action
- Unusual appearance: extremes of slovenliness or overdressed
- Shows unusual knowledge of controlled substances and/or gives textbook symptoms or vague, evasive medical history
- No regular doctor, often no health insurance
- Has no interest in diagnosis
- Fails to keep appointments for further diagnostic tests or refuses to see another practitioner for consultation

Assessment of Opioid Abuse in Opioid Maintenance Therapy

Aberrant drug-related behaviors suggesting addiction in pain patients (Portenoy & Payne 1997):

• Selling or forging prescriptions
• Altering route of administration
• Obtaining prescriptions from non-medical sources
• Dose escalations or failure to comply with regimen
• “Losing” medication
• Seeking Rx from other MDs
• Deterioration in function
• Resisting changes despite adverse effects
Assessment of Opioid Abuse (cont:)

Prescription Drug Use Questionnaire (PDUQ) (Compton et al. 1998):

- Hoarding pills
- Using analgesics to relieve symptoms other than pain
- Supplementing with alcohol or drugs

Pain Assessment and Documentation Tool (PADT) (Passik et al. 2004) assesses 4 domains: (1) pain relief, (2) patient functioning, (3) adverse events, (4) drug-related behaviors

30.4% of chronic pain patients in a large (N=239) general practice reported taking extra narcotic doses (Rosser et al. 2011)
Steps Taken by Physicians to Avoid Diversion

- Limit 30-day supply to those compliant – 75%
- Prescribe lowest effective dose – 64%
- Require drug screening – 62%
- Highly selective of patients – 49%
- Require counseling if indicated -- 43%
- Require more than monthly visits – 35%
- Random pill counts – 32%
- Ask family to observe ingestion

Johanson et al. *Drug and Alcohol Depend.* 2012
Treatment Strategies for Prescribing Narcotics to Pain Patients

- Need to monitor carefully for signs of abuse or misuse of medications; dependence and analgesic tolerance often present without behavioral change\(^1\)

- Narcotic protocol consists of medication contract, consent, psychological evaluation, random urine toxicology\(^2\)

- Monitoring both urine toxicology and aberrant drug-related behavior (ADRB) will detect more inappropriate drug-taking than either alone\(^3\)

- Highest sensitivity (.90) for predicting ADRB: clinical interview combined with Screener and Opioid Assessment for Patients with Pain (SOAPP)\(^4\)

---

Universal Precautions in Opioid Analgesic Therapy

• Uniform approach reduces stigma and risk, improves care

• Ask patients about personal and family history of substance abuse (often with screening tools)

• Obtain consent with formal written treatment agreement

• Medication agreements specify parameters for adherence, means of testing compliance, goals

• Ongoing reassessment of benefits from trial of opioid therapy and complete documentation

Risk Assessment for Patients on Opioid Therapy for Pain

Low-risk patients:
• No history of substance abuse
• Lack any major psychiatric co-morbidity
• No indication of aberrant behaviors
• Can be managed in primary care setting

Medium risk:
• Prior history or family history of substance abuse
• May have psychiatric co-morbidity
• Can be managed in primary care setting with consultation from specialist

High risk:
• Active addictive disorders
• At increased risk for aberrant behaviors
• Should be referred to a pain management clinic

Buprenorphine for Opioid Dependence and Pain: Pros and Cons

Advantages:
- Quick onset of action via sublingual absorption: 30-60 min, peak effect in 1-4 hrs, duration 2+ days
- Partial agonist structure increases safety profile; ceiling effect protects against overdose
- Minimal subjective effects; limited abuse potential when used sublingually (dissolvable film replacing tablet)
- Maintained patients describe “clear-headedness,” improved energy and sleep
- Much lower likelihood of ventricular arrhythmias than with methadone
- May be best alternative for most prescription opioid abusers: well tolerated, high retention, few side effects.

Disadvantages:
- Ceiling on agonist effects at 32 mg
- Risk of abuse by injection (Subutex > Suboxone)
- Induction: wait 12-18 hrs after heroin, 24-36 hrs after methadone; give 2-4 mg initial dose, repeat after 1-2 hrs until symptomatic relief: usually 8-16 mg
- When used for outpatient detoxification, difficulty tapering often leads to unanticipated maintenance
Buprenorphine: Empirical Findings

- Detoxification taper often unsuccessful, and no advantage to longer taper. Abstinence at end of taper: 44% (7 days), 30% (28 days) (Ling et al. 2009)

- Intravenous high-dose (8 mg) buprenorphine under experimental conditions: (1) few changes in oxygen saturation, confirming clinical safety, and (2) serves as a reinforcer under laboratory conditions (Comer et al. 2005)

- Combination tablet (Suboxone) reduces but does not eliminate intravenous misuse (Mammen & Bell 2009, Comer et al. 2010)

- For chronic pain patients seeking treatment for opioid dependence, 2/3 experience clinically meaningful reduction in pain (Weiss et al. 2010, POATS study)

- Safety profile of buprenorphine in combination with benzodiazepines is not well understood. Overdose deaths have been reported involving this combination.
Methadone: Risks to Prescribing for Pain

- Methadone-related mortality increased by: (1) genetic variants (CYP2B6*6, OPRM1 A118G)) (Bunten et al. 2011), and (2) concomitant benzodiazepine abuse (Cai et al. 2010)

- Accumulation possible because of long T1/2 and high fat solubility; increased risk of overdose

- Analgesic effects last only 6-9 hrs, leading to potentially fatal trap when prescribed to chronic pain patients.

- Potential cardiac arrhythmias led to black-box warning in 2006:
  - QT prolongation – prevalence 9.2% (Fonseca et al. 2009)
  - Torsades de Pointes (Mayet et al. 2010), more likely at doses of >120 mg/day

- In a study of 2112 fatal unintentional prescription opioid overdoses, methadone was associated with highest number of deaths per equianalgesic dose sold (23.3) (Piercefield et al. 2010)

- Not a first-line agent for opioid analgesic therapy. Should not be used in opioid-naïve patients.
Abuse-deterrent Formulations

• Emerging pharmaco-technology designed to deter abuse

• Abuse-resistant formulations (ARFs) use a physical barrier:
  – (1) makes it difficult to extract core opioid, or
  – (2) renders tampered tablets unsuitable for injecting or snorting

• Abuse-deterrent formulations (ADFs) use a “chemical deterrent” which:
  – (1) contains aversive agents (e.g. niacin) that cause unpleasant reaction if taken in high doses, or
  – (2) uses an antagonist (e.g. naltrexone) that cancels the active drug’s effect if the formulation is tampered with

1 Schneider JP et al. CNS Drugs 2010; 24(10): 805-10.
Clinical Trial Data: Current and Emerging Treatment Options

• 11.5% of patients reported abuse of at least 1 opioid analgesic in the 30 days prior to entering substance abuse treatment¹

• New oral formulation of morphine sulfate has been developed based on an abuse-deterrent, prolonged-release erodible matrix (ADPREM). In a randomized study, 24-hr dosing with ADPREM was therapeutically equivalent to morphine (CRM) at 12-hour intervals² in patients with cancer pain

• Two new abuse-deterrent opioid products have been approved for marketing:
  – Embeda® (morphine sulfate with naltrexone) and
  – New formulation of extended-release oxycodone (OxyContin)³
  – FDA has not yet approved explicit label claims of abuse deterrence

• Oxycodone does not produce reinforcing subjective effects in opioid-abusing chronic pain patients maintained on buprenorphine/naloxone⁴

³ Schneider JD et al. CNS Drugs. 2010;24:806-810.
Case #1: Suggested Approach

• Aberrant behavior: Margaret’s need for pain medication has exceeded the prescribed amount

• But the frequency of dosing Dilaudid has been sub-therapeutic (q 8 hours vs. q 4-6 hrs). Requests for early refills and preoccupation with obtaining analgesic prescriptions can be understood as “pseudo-addiction” – that is, apparent aberrant behaviors explained by inadequate dosing and subsequent fear of pain and opioid withdrawal symptoms

• Management should include a medical workup to look for progression of disease (because her medication regimen is unsatisfactory). With appropriate pain management, aberrant behaviors are expected to abate.
Case #2: Suggested Approach

- Aberrant behaviors include: dose escalations, using multiple MDs, impaired functioning, and resisting change in regimen
- On risk stratification, this patient is “high risk” for opioid abuse
- Requires medication contract specifying single MD prescribing opioid, consequences of nonadherence, consent, psychological evaluation, random urine toxicology
- Consider role for buprenorphine/naloxone or ADF
Conclusions

• Prescription opioids remains safe and effective pharmacotherapies for chronic non-malignant pain

• Over the last decade, marked increase in abuse of prescription opioids has occurred in U.S.

• Addiction involves impaired control over drug use, continued use despite harm, craving

• Aberrant drug behaviors may signal abuse / addiction

• Such behaviors may also reflect inadequate analgesia (pseudoaddiction) or opioid misuse to treat anxiety, depression, or personality disorders
Conclusions (cont.)

• To date, predictive factors for opioid abuse among chronic pain patients have not been clearly identified

• For patients who do develop addiction:
  – (1) opioid substitution with buprenorphine/naloxone
  – (2) medical management of addiction through medication agreements and adherence monitoring

• Clear imperative to develop analgesics with lower abuse liability

• Research efforts targeted at developing better methods to detect patients at risk for addiction
Please Click the Link Below to Access the Post Test for the Online Module

Upon completion of the Post Test:

• You will receive an email detailing correct answers, explanations, and references for each question.

• You will be directed to a module evaluation, upon completion of which you will be emailed your module Certificate of Completion.

http://www.cvent.com/d/04q8bp