Side Effects and Drug Abuse: Managing Opioid Risk

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Side Effects and Drug Abuse: Managing Opioid Risk

- Safe and effective opioid prescribing requires
  - Skills to optimize pain relief
  - Skills to minimize risk
    - Risk of side effects and toxicities
    - Risk of abuse-related outcomes

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Opioid Side Effects

- Most common side effects
  - Gastrointestinal effects
  - Neurological effects
    - Neurocognitive effects
    - Neuroendocrine effects
- Other concerns
  - Itch
  - Urinary retention
  - Sleep-disordered breathing
  - QTc prolongation

Opioid-Induced Constipation

- Prevalence of OIC is uncertain because multiple causes often co-exist
  - Estimates vary
    - 23% to 63% of cancer patients receiving opioids
    - 15% to 90% of non-cancer patients receiving opioids
- OIC may cause distress, increase cost of care, and lead to discontinuation of analgesics

Nelson AD, Camilleri M. Ther Adv Chronic Dis 2016;7:121-134; Bell TJ, et al, Pain Med 2009;10:35-42.

Opioid-Induced Constipation

- Contributing factors
  - Advanced age
  - Dietary change
  - Poor hydration status
  - Decreased physical activity
  - Premorbid gastrointestinal disease, e.g., IBS
  - Comorbid gastrointestinal disease
    - Structural pathology
    - Autonomic neuropathy
  - Comorbid systemic disease, e.g., hypercalcemia
  - Drugs with constipating effects
  - Psychosocial factors, e.g., loss of privacy

Opioid-Induced Constipation

- Mechanisms
  - Central effects mediated by multiple brainstem receptors
  - But peripheral effects predominate
    - Mediated by mu and other receptors in gut wall
- Effects
  - Increased non-propulsive motility
  - Decreased peristalsis
  - Decreased secretions

Mori T, et al. J Pharmacolo Exp Ther 2013;347:91-99

Opioid-Induced Constipation

- Management
  - Consider treatment of contributing factors
  - Consider opioid rotation
    - Oral to transdermal route may be useful
  - Non-pharmacologic interventions
    - Improve hydration
    - Dietary changes

Opioid-Induced Constipation

- Management
  - "Routine" use of laxative therapy recommended in most cases
  - No data on dose finding, combination therapy, laxative rotation

Nelson AD, Camilleri M. Ther Adv Chronic Dis 2016;7:121-134

Opioid-Induced Constipation: First-line Therapy

Type	Effects	Examples
Bulk laxatives	Dietary fiber; causes water retention in the colon and increase stool bulk	Psyllium husk, methylcellulose
Osmotic laxatives	Salt content retains fluid retention and increased intestinal secretion	**Polyethylene glycol**, **lactulose**, sorbitol, magnesium citrate
Stool softeners	Decrease surface tension to lubricate and soften fecal matter	**Docusate**
Stimulants	Increased colonic motility and electrolyte transport; stimulate fluid secretion	**Senna**, bisacodyl, cascara

Wald A. JAMA 2016;315:185-191; Candy B, et al. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD003448

Opioid-Induced Constipation: New Treatments

- Probiotics
- Peripherally-acting mu opioid antagonists
  - Oral and injectable methylnaltrexone
  - Oral naloxegol
  - Oral naloxone, alone or in opioid combination drug
- Chloride channel stimulants
  - Linaclotide acts via agonism at guanylate cyclase C
  - Lubiprostone acts via activation of a prostaglandin receptor
- Prokinetics
  - Metoclopramide used occasionally
- Others—5HT4 modulators and bile acid transport inhibitors—in development

Davis M, Gamier P. Curr Oncol Rep 2015;17(12):55. doi:10.1007/s11912-015-0481-x; Wald A. JAMA 2016;315:185-191

Opioid-Induced Somnolence/Mental Clouding

- Prevalence is uncertain because multiple causes often co-exist
- Management
  - Psychostimulants
    - Methylphenidate most studied
      - 10 mg/day resulted in 35% improvement in sedation compared to 8% in placebo
      - 15 mg/day resulted in 61% reduction in sedation versus 21% in placebo

Byas-Smith MG, et al. Clin J Pain. 21:345-352 2005; Wilwerding MB, et al. Support Care Cancer 1995;3:135-138; Bruera E, et al. JPSM 2003;26;5:1049-54; Webster L. et al. Pain Med 2003;2:135-40 Kurita GP, et al. J Clin Oncol 2011;29:1297-1303

Opioid-Induced Somnolence/Mental Clouding

- Management
  - Other psychostimulants
    - Modafinil has limited data
      - Retrospective trial data resulted in a 40% reduction in sedation scores
    - Dextroamphetamine, amphetamine, others
  - Cholinesterase inhibitors
    - Donepezil 5 mg daily for 1 week improved sedation and fatigue in cancer patients in a small open-label trial

Byas-Smith MG, et al. Clin J Pain. 21:345-352 2005; Wilwerding MB, et al. Support Care Cancer 1995;3:135-138; Bruera E, et al. JPSM 2003;26;5:1049-54; Webster L. et al. Pain Med 2003;2:135-40.

Opioid-Induced Neuroendocrine Effects

- Opioids inhibit GnRH, LHRH, FSH and LH
  - Reduce testosterone and estrogen by inhibiting GnRH, LHRH, FSH, and LH
  - Reduce testosterone production by stimulating prolactin release
- Potential effects
  - Sexual dysfunction, infertility, galactorrhea, fatigue, depressed mood, hot flashes, night sweats
  - May worsen osteoporosis or sarcopenia

Smith HS, et al. Pain Physician 2012;15:ES145-ES156; De Maddalena C, et al.. Pain Physician 2012;15:ES111-ES118

Opioid-Induced Neuroendocrine Effects

- Management
  - Depends on analysis of risk-to-benefit
    - Assess symptoms—depressed mood, weakness, fatigue, sexual dysfunction—and other risks
    - If benefits possible, measure testosterone and consider treating male hypogonadism with replacement therapy
    - If benefits possible, measure estradiol and consider treating premenopausal women with estrogen therapy

Smith HS, et al. Pain Physician 2012;15:ES145-ES156; De Maddalena C, et al.. Pain Physician 2012;15:ES111-ES118

Opioid-Induced Itch

- Prevalence: 2%-10%
- May worsen itch from other factors
- Management
  - Skin care and treatment of contributing factors
  - Consider opioid rotation
  - Drugs for opioid-related itch
    - Opioid antagonists effective but difficult to use
    - Others tried based on limited evidence and use in other forms of itch

Ko MC, et al. J Pharmacol Exp Ther. 2004; 310:169-76;
Siemens W et al. Dtsch Arztebl Int 2014;111:863-870;
Reich A, Szepietowski JC. Clin Exp Dermatol 2010;35:2-6

Opioid-Induced Itch

- Drug therapy for itch
  - H1 antagonists, e.g. diphenhydramine
  - H2 antagonists, e.g. ranitidine
  - 5-HT3 antagonists, e.g. ondansetron
  - SSRI antidepressant, e.g. paroxetine or sertraline
  - Atypical antidepressant: mirtazapine
  - Gabapentinoid, e.g. gabapentin or pregabalin

Siemens W et al. Dtsch Arztebl Int 2014;111:863-870; Reich A, Szepietowski JC. Clin Exp Dermatol 2010;35:2-6

Opioid-Induced Urinary Retention

- Prevalence unknown
- Mechanisms poorly understood
  - Decreased detrusor muscle tone and contraction
  - Sensation of fullness
  - Voiding reflex diminished
- Management
  - Consider opioid rotation
  - Opioid antagonists work but difficult to use
  - Consider alpha-1 adrenergic blocker, e.g., tamsulosin

Rawal N. An experimental study of urodynamic effects of epidural morphine and of naloxone reversal. Anesthesia & Analgesia. 62;7:641-7. 1983

Opioid-Induced Sleep-Disordered Breathing

- Opioids may worsen pre-existing obstructive or central sleep apnea
- Opioids may precipitate a new sleep apnea synodrome—central or both central and obstructive
- Risk may be higher with methadone and when benzodiazepines are co-administered

Cheatle M. Pain Medicine 2015;16, Suppl 1:S22-S26

Opioid-Induced Sleep-Disordered Breathing

- Management
  - Assess for existing sleep apnea syndrome or its risk factors
  - Avoid methadone in those at high risk
  - Avoid benzodiazepines in those at high risk
  - Use co-analgesic approaches to reduce needed opioid dose
  - Consider primary treatment of sleep disorder if risk vs. benefit warrant

Cheatle M. Pain Medicine 2015;16, Suppl 1:S22-S26

Opioid-Induced QTc Prolongation

- Dose-dependent effect of methadone
- Management
  - Assess and manage other risk factors, e.g., hypokalemia
  - Review baseline ECG should be reviewed in most cases
    - With rare exceptions, do not use methadone if QTc >500 ms
    - Consider alternatives if the QTc >450 ms and <500 ms
  - Repeat the ECG after 2 weeks or after increasing the dose, at least once or twice
  - Consider repeat ECG if dose goes above 100 mg/day

Krantz M, et al. Ann Intern Med. 2009;150(6):387-395.

Side Effects and Drug Abuse: Managing Opioid Risk

- Safe and effective opioid prescribing requires
  - Skills to optimize pharmacological outcomes
  - Skills to minimize risk
    - Risk of side effects and toxicities
    - Risk of abuse related outcomes

Drug Abuse: Importance in Palliative Care

- Drug abuse is associated with serious illnesses
  - HIV/AIDs, some cancers, cirrhosis, heart failure, others
  - Smoking co-exists with drug abuse and independently increases risk of serious illness
- Palliative care specialists frequently prescribe drugs that may be abused or diverted
- Clinicians have an obligation to help address a public health problem

Drug Abuse: Importance in Palliative Care

- Prescription drug abuse has increased sharply in the US and is increasing in other countries
- Adverse consequences include rise in heroin addiction and opioid mortality
- Patients with pain due to serious illness can be harmed
  - Directly, by the development of abuse or addiction
  - Indirectly, by the unintended impact of regulations that target abuse and diversion

Drug Abuse in Palliative Care: Management

- All clinicians should be able to recognize, assess, diagnose, and manage the phenomena related to drug abuse
- Definitions must be understood
  - Physical dependence
  - Tolerance
  - Drug abuse
  - Addiction
  - Aberrant drug-related behavior
  - Pseudoaddiction
  - Diversion

Definitions of Substance Abuse Phenomena

- Physical dependence
  - *Abstinence on abrupt discontinuation or dose reduction, or administration of an antagonist*
    - Not an overt problem if abstinence is avoided
    - May or may not be present in drug abusers
    - *Should never be labeled "addiction"*
- Dependence
  - Meanings vary
  - Term should not be used

Definitions of Substance Abuse Phenomena

- Tolerance
  - *Declining drug effect induced by exposure to the drug*
    - Tolerance to a side effect is desirable
    - Tolerance to a favorable effect is problematic
    - May or may not be present in drug abusers or those with addiction
    - *Should never be labeled "addiction"*

Definitions of Substance Abuse Phenomena

- Abuse
  - *Any drug use outside of socially accepted norms*
    - Use of an illicit drug OR significant non-adherence during the use of a controlled prescription drug
    - *Caution*: Norms vary, reflecting culture and laws
    - *Caution*: Imprecise term—"*drug abuse*" may be called "*misuse*", "*nonadherence*" or "*aberrant drug-related behavior*"

Definitions of Substance Abuse Phenomena

- Addiction
  - *A disease whose manifestations are best understood as a complex interaction between biological, psychological, and psychosocial phenomena*
  - DSM-V now includes a group of "Substance Related and Addictive Disorders", e.g., opioid use disorder
    - A *problematic pattern of use leading to clinically significant impairment or distress,* as manifested by at least two of 11 characteristics during a 12-month period

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, 2013

Definitions of Substance Abuse Phenomena

- Addiction
  - *Another definition: A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations*
  - Characterized by the "4C's"

--*Craving*
--*Compulsive use*
--*Loss of Control*
--*Continued use despite harm*

1997 joint statement of APS, AAPM and ASAN: Savage SR, et al: J Pain Symptom Manage 2003;26(1):655-67

Definitions of Substance Abuse Phenomena

- Aberrant Drug-Related Behavior
  - *Behaviors during treatment that raise concerns about abuse, addiction, or diversion*
    - *Caution*: Reflects culture and laws
    - *Caution*: Imprecise term—"*aberrant drug-related behavior"* may be called "*drug abuse", "misuse", "nonadherence", "problematic drug-related behavior,"* or *"red flag behavior"*

Aberrant Drug-Related Behavior: Examples

- **More serious**
  - Selling prescription drugs
  - Prescription forgery
  - "Doctor shopping"
  - Stealing or borrowing another patient's drugs
  - Injecting oral formulation
  - Obtaining prescription drugs from nonmedical sources
  - Concurrent abuse of related illicit drugs
  - Multiple dose escalations
- **Less serious**
  - Repeated asking for higher doses
  - Drug hoarding
  - Requesting specific drugs
  - Occasional temporary dose escalation without permission
  - Use of the drug to treat another symptom
  - Reporting euphoria or other psychic effects

Passik SD, Portenoy RK: In Holland J, et al: Handbook of Psycho-oncology, 2nd ed, 1998, pp 576-586

Definitions of Substance Abuse Phenomena

- Pseudoaddiction
  - *Aberrant drug-related behavior driven by uncontrolled symptoms, which resolve when symptoms are better controlled*
    - Originally used in a case report of an inpatient with cancer who became difficult to manage
    - *Should not be used to avoid a primary diagnosis of addiction, or avoid the label of drug abuse*
    - Can co-exist with addiction—reminder that abuse and addiction are worsened by unrelieved symptoms and other stressors

Weissman DE, Haddox JD, Pain 1989;36:363-366;
Passik SD et al, Pain Manag 2011;1:239-248

Definitions of Substance Abuse Phenomena

- Diversion
  - *Unlawful channeling of controlled drugs to the illicit marketplace due to theft or unlawful activity of physicians, pharmacists, or patients*
    - If clinician behavior is perceived as facilitating diversion, an individual may be prosecuted

Inciardi JA, et al. Subst Use Misuse 2006;41:1–10

Drug Abuse in Palliative Care: Management

- Universal Precautions
  - *A set of practices intended to assess and minimize the risk of abuse, addiction, or diversion*
    - Model developed for opioid treatment of chronic pain
    - Can be applied to *all patients receiving any controlled substance*

Gourlay DL, Heit HA, Almahrezi A: Pain Med 2005;6(2):107–12

“Universal Precautions” in Palliative Care

- 5-step approach
  - Assess and stratify risk
  - Choose to prescribe or not to prescribe
  - Monitor adherence to minimize risk
  - Monitor drug-related behaviors over time
  - Respond to aberrant drug-related behaviors
- At all steps, document and communicate

Portenoy RK, Ahmed E: 2014;32(16):1662-70

Step 1: Assess and Stratify Risk

- Assess and stratify risk
  - *Very low or negligible*
    - A bedbound patient residing in a controlled environment
    - A patient with advanced dementia

Step 1: Assess and Stratify Risk

- Assess and stratify risk
  - *Lower or higher based on history*
    - Personal history of alcohol abuse or drug abuse
    - Family history of alcohol or drug abuse
    - Any significant psychiatric history

Michna E, et al. J Pain Symptom Manage 2004;28:250-258

Step 1: Assess and Stratify Risk

- Assess and stratify risk
  - *Other relevant history*
    - Smoking history
    - Younger age
    - Better performance status
    - Some medical conditions
    - Poor social adjustment
    - History of physical/sexual abuse
    - History of incarceration
    - Prior involvement in drug abuse culture
  - *Findings on examination, e.g. needle marks, sometimes helpful*

Michna E, et al. J Pain Symptom Manage 2004;28:250-258

Step 1: Assess and Stratify Risk

- Assess and stratify risk
  - *Some tools may be helpful*
    - Computerized prescription drug monitoring
    - Laboratory tests, e.g., urine drug screening
    - Simple tool, e.g., CAGE-AID

Have you felt you ought to Cut down on your alcohol or drug use?

Have people Annoyed you by criticizing your alcohol or drug use?

Have you felt bad or Guilty about your alcohol or drug use?

Have you had a drink or used drugs first thing in the morning to steady your nerves, treat a hangover, or get the day started? (Eye-opener)

Passik S, et al, Pain Med 2008;suppl s2:s145-s166; Ewing JA. JAMA.1984;252:1905-1907; Kwon JH, et al. Oncologist 2015;20:692-697

Step 1: Assess and Stratify Risk

- Questionnaires are seldom used
  - Screening tool for Addiction Risk (STAR) (Friedman et al, Pain Med, 2003)
  - Screener and Opioid Assessment for Patients with Pain (SOAPP) (Butler et al, Pain, 2004)
  - Pain Medicine Questionnaire (Adams et al, J Pain Symptom Manage, 2004)
  - Screening Instrument for Substance Abuse Potential (SISAP) (Coambs et al, Pain Res Manage, 1996)
  - Substance Abuse Subtle Screening Inventory (SASSI) (www.sassi.com)

Step 2:
To Prescribe or Not

- In palliative care, the usual response is to prescribe
- However, some scenarios require caution
  - If risk of *diversion* is high, do not prescribe unless the risk can be eliminated
  - If risk of *drug abuse* is high, consider reasonable alternatives, proceed only with appropriate adherence monitoring in place

Step 3: Monitor Adherence to Minimize Risk

- If the decision is made to prescribe, implement adherence monitoring as necessary to reduce risk and help some patients maintain control
  - If the risk is negligible, no specific approach may be needed
  - If the risk is *not* neglible, implement strategies appropriate to the level of risk

Step 3: Monitor Adherence to Minimize Risk

- Options
  - Use an opioid with a low street value
  - Do not use short-acting opioids
  - Prescribe small quantities
  - Require consultations
  - Require use of one pharmacy
  - Perform pill counts when the patient is seen
  - Use a written agreement
  - Implement biofluid drug concentration monitoring

Step 3: Monitor Adherence to Minimize Risk

- Role of drug concentration monitoring
  - Usually urine or saliva; hair testing also used
  - If appropriately interpreted, can be used to verify that a prescribed medication is taken and that other drugs are not
  - Interpretation requires understanding of potential for false positives and false negatives

Step 4: Monitor Drug-Related Behaviors

- Drug-related behavior should be monitored like any other effect
  - From history obtained from patient or family
  - From findings on examination
  - From objective evidence, e.g. result of pill counts,
    drug screening, etc.

Step 4: Monitor Drug-Related Behaviors

- Differential diagnosis of aberrant behavior
  - Addiction
  - Pseudo-addiction
  - Other psychiatric diagnosis
    - Organic brain syndrome
    - Personality disorder
    - Chemical coping
    - Depression/anxiety/situational
  - Family issues
  - Criminal intent

Step 5: Respond To Aberrant Behaviors

- Management depends on the seriousness of the behavior and the diagnosis
  - If diversion is occurring, it must be stopped or prescribing must stop
  - Consider whether stopping the controlled drug is an option in managing other types of abuse
  - If treatment is continuing, consider increasing adherence monitoring
  - If behavior is very serious, consider inpatient stay to achieve control and decide on next steps, if possible

“Universal Precautions” in Palliative Care

- At all steps of a “Universal Precautions” approach
  - *Document and communicate*

Portenoy RK, Ahmed E, J Clin Oncol 2014;32(16):1662-70

Side Effects and Drug Abuse: Managing Opioid Risk

- Conclusion
  - Safe and effective prescribing of controlled drugs requires the skills to assess and manage risk
  - Managing risk involves assessing and reducing the harm potentially caused by
    - Side effects and toxicities
    - Abuse-related outcomes