Walking the Pain Management Line Between Palliative and Hospice Care

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Disclosures

- Advisory Board for Hisamitsu America, Inc.

Pharmacist Objectives

- Delineate the major definitions and goals between palliative and hospice care
- Analyze the various roles pharmacists can play in both deprescribing and optimizing pain management medication regimens in palliative and hospice care patient populations
- Assess the ethical and legal ramifications of mismanaging palliative and hospice care patient populations

Pharmacy Technician Objectives

- Delineate the major definitions and goals between palliative and hospice care
- Describe the importance of medication checks when filling outpatient and inpatient medication orders
- Assess the ethical and legal ramifications of mismanaging palliative and hospice care patient populations

Pre-Question One

What best highlights a difference between palliative and hospice care?

A. Hospice care is a wider range of care services that includes palliative care which is usually reserved for those with a life expectancy of 6 months or less.
B. Palliative care is a wider range of care services that includes hospice care which is usually reserved for those with a life expectancy of 6 months or less.
C. Neither palliative nor hospice care are concerned with the management of pain.
D. Palliative care services would be inappropriate for someone suffering from end stage renal disease.

Pre-Question Two

Which of the following is true regarding opioid use in palliative care services?

A. Opioids are still considered the mainstay in treatment of pain in those suffering from palliative conditions.
B. Opioids should only be used in hospice care settings and are not recommended for pain in palliative care settings.
C. Opioids should not be prescribed at daily doses greater than 90mg morphine equivalence.
D. Opioids have only shown to increase incidence of death in those in hospice care and have not shown any benefits.

What is Palliative Care?

Palliative care attends to the physical, functional, psychological, practical, and spiritual consequences of a serious illness.

Palliative care focuses on expert assessment and management of pain and other symptoms, assessment, and support of caregiver needs, and coordination of care.

Palliative care is interdisciplinary to attend to the holistic care needs of the patient and their identified family and caregivers.

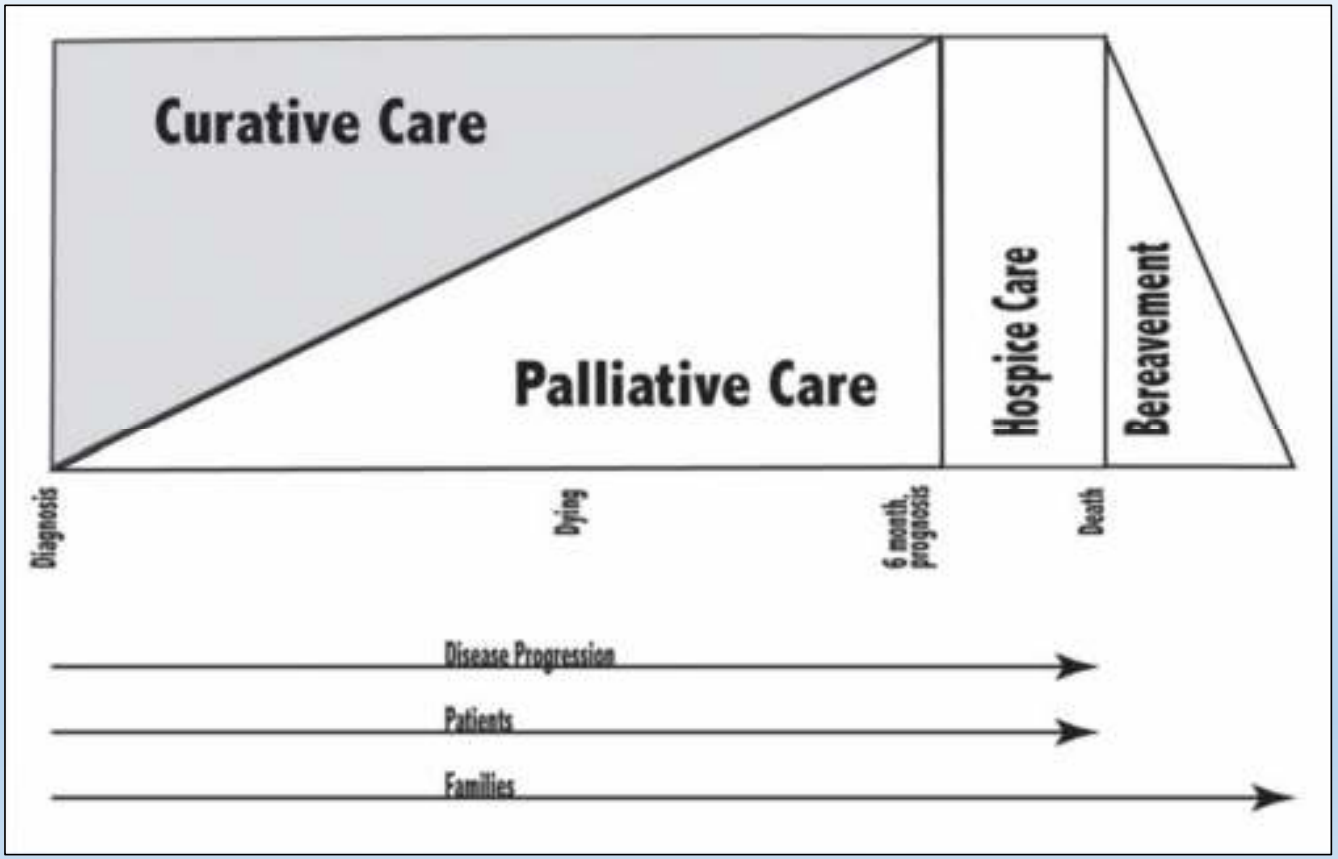
National Consensus Project for Quality Palliative Care. Clinical Practice Guidelines for Quality Palliative Care, 4th Edition. 2018.

What is Palliative Care?

- Arose originally from modern hospice movement
  - Various evolutions, became medical subspecialty in 2006
- Focuses on patient-centered and family-centered approach to care
  - World Health Organization and US Department of HHS
- Optimize quality of life by addressing:
  - Physical, intellectual, emotional, social, and spiritual needs
- Care coordination by an interdisciplinary team
- Terms *palliative care, hospice care, and supportive care* all are very different

(1) National Consensus Project for Quality Palliative Care. Clinical Practice Guidelines for Quality Palliative Care, 4th Edition. 2018. (2) Herndon CM, et al. Am J Health Syst Pharm. 2016;73(17):1351-67.

Continuum of Palliative Care



Guo Q, et al. J Palliat Care Med. 2012;2:1-6.

What is Defined as a Palliative Condition?

- More than just cancer…

- WHO defines this as care for life-threatening illness:
  - Cardiovascular diseases
  - Chronic respiratory diseases
  - AIDS
  - Kidney failure
  - Chronic liver disease
  - Multiple sclerosis
  - Parkinson's Disease
  - Many others

Palliative Care. World Health Organization. 2020. https://www.who.int/news-room/fact-sheets/detail/palliative-care#:~:text=Many%20other%20conditions%20may%20require,anomalies%20and%20drug%2Dresistant%20tuberculosis.

Major Goals of Palliative Care Treatment

- Addressing physical symptoms
    - Pain, fatigue, appetite, sleep, mood
- Maximizing functional status
- Enhancing quality of life

National Consensus Project for Quality Palliative Care. Clinical Practice Guidelines for Quality Palliative Care, 4th Edition. 2018.

Pain Management in Palliative Care

- Continuous frequent re-evaluation of physical pain symptoms
- Document functional and symptom goals
- Ensure patients are meeting those goals
- Risk of all medications should be assessed

National Consensus Project for Quality Palliative Care. Clinical Practice Guidelines for Quality Palliative Care, 4th Edition. 2018.

What is Hospice Care?

What is Hospice Care?

- A specific subtype of palliative care: recognized as the ”best care for patients nearing end of life”
- When life expectancy is measured in months, not years
    - Defined, time-limited prognosis (certified by two physicians) six months or less
- Much more frequent telephone and in-person contact with patient and caregivers before death
- Addressing same physical symptoms: Focus on comfort
    - Pain, dyspnea, nausea, agitation, delirium, and terminal secretions
- Counseling, spiritual/emotional support, planning around approach to death and coordinating of care

National Consensus Project for Quality Palliative Care. Clinical Practice Guidelines for Quality Palliative Care, 4th Edition. 2018.

What is the Pharmacist's Role?

Functions of the Palliative Care Pharmacist

- May support administrative roles
- Consultative roles
- Advanced clinical practice roles

Herndon CM, et al. Am J Health Syst Pharm. 2016;73(17):1351-67.

Role of the Pharmacist in Palliative Care

- Clinical Practice Roles:
  - Symptom assessment/palliation
  - Laboratory monitoring
  - Medication management (including resolving/preventing drug-related toxicities)
  - Dose adjustments/deprescribing → Even prescribing
  - Communication and counseling on medication-related changes

Herndon CM, et al. Am J Health Syst Pharm. 2016;73(17):1351-67.

Role of the Pharmacist in Hospice care?

- Part of conditions of participation in CMS, programs responsible for all services including those related to medications…
    - Thus, medication reviews are essential aspects of these conditions
    - Also essential in reducing risk of analgesic and symptom control gaps
- Similar to roles in palliative care, however closer f/u
- Also, more aggressive dosing of certain analgesics
    - Still has to be appropriate!

National Consensus Project for Quality Palliative Care. Clinical Practice Guidelines for Quality Palliative Care, 4th Edition. 2018.

Deprescribing?

The Polypharmacy Problem

- Polypharmacy is common in palliative care populations
  - Sera et al in 2014 found on average hospice patients were on 15.7 meds[1]
- Consequences of polypharmacy?
  - Increased risk of adverse events[2]
  - Increased pill burden[2]
  - Increased costs[2]
  - Higher symptom burden and lower quality of life[3]

(1) Sera L et al. Am J Hosp Palliat Care. 2014 Mar; 31(2):126-31. (2) Lindsay J et al. Support Care Cancer. 2014; 22(4):1113-9. (3) Schenker Y et al. J Gen Intern Med. 2019 Apr; 34(4):559-566.

What About Deprescribing?

- Deprescribing:
  - Stepwise, patient-centered process about reducing risks and burden of taking multiple meds
  - NOT DENYING EFFECTIVE TREATMENT
- Considers age, life expectancy, co-morbidities, duration of impact of medications
- Prioritize one at a time and monitor closely

Thompson J. Clin Med (Lon). 2019;19(4):311-314.

‘OncPal’ Deprescribing Guideline

Class of Medication	Situations of Limited Benefit
Aspirin	Primary Cardiovascular Prevention*
Lipid lowering agents	All indications
Anti-hypertensives	Mild to moderate HTN* Secondary Cardiovascular Prevention* Management of CAD*
Anti-ulcer Medications	All indications
Oral Hypoglycemics	Mild hyperglycemia*
Osteoporosis Medications	All indications besides hypercalcemia*
Vitamins	All indications
Minerals	All indications

*Depends on life expectancy prognosis

Lindsay J, et al. Support Care Cancer. 2015;23:71-78.

How do we Manage Pain?

Goals of Pain Management?

- Reducing pain
- Increasing comfortability
- Increasing functionality
    - Not so much hospice
- Enhancing quality of life
- All through the optimization of pharmacologic and non-pharmacologic modalities

Non-Steroidal Anti-Inflammatories

- Mechanism:
  - Inhibition of cyclooxygenase (COX) to reduce thromboxane, prostaglandin, and prostacyclin production
- Common and used in a wide variety of pain conditions
- HOWEVER:
  - Increase risk of peptic ulcer disease and GI bleeding
  - Elevation of blood pressure
  - Can worsen congestive heart failure
  - Increases risk of acute renal failure, nephrotic syndrome, and renal papillary necrosis
  - Increases risk of thrombotic/cardiovascular events
- OVERALL: NOT A GREAT CHOICE!

Bettinger JJ, et al. Practical Pain Management. 2017;17(3).

Antidepressants

- Mechanism:
  - Inhibition of reuptake of NE and serotonin in the descending pain pathway within the CNS, with the primary mediator being NE
- Tricyclic antidepressants (TCAs) and selective serotonin-NE reuptake inhibitors (SNRIs)
- Antinociceptive effects generally take up to two weeks*

Sindrup SH, et al. Basic Clin Pharmacol Toxicol. 2005; 96(6):399-409.

TCAs

- Specific medications:
  - Amitriptyline, desipramine, doxepin, imipramine, nortriptyline, and trimipramine
- Well established efficacy for different neuropathic pain conditions, however none carry FDA approval for neuropathic pain conditions
- Non-selective binding:
  - Tricyclic structure allows them to bind and inhibit histaminergic-1, alpha-adrenergic, and muscarinic receptors
  - This “sloppiness” leads to a profusion of adverse effects:
    - Cardiac conduction abnormalities, orthostatic hypotension, fatigue, dry mouth, constipation, sweating, dizziness, etc
- Generally, not the most ideal for palliative/hospice care!

Sindrup SH, et al. Basic Clin Pharmacol Toxicol. 2005; 96(6):399-409.

SNRIs

- Specific medications:
  - Venlafaxine, desvenlafaxine, duloxetine, milnacipran, and levomilnacipran
- FDA approved neuropathic pain indications:
  - *Duloxetine:* diabetic peripheral neuropathy and fibromyalgia
  - *Milnacipran:* fibromyalgia
- Selective binding:
  - Unlike TCAs, SNRIs bind selectively, producing much fewer side effects:
    - Nausea, vomiting, dry mouth, increased risk of serotonin syndrome, and hypertension; minimal influence on cardiac conduction
- Potential pain and mood benefits?

Sindrup SH, et al. Basic Clin Pharmacol Toxicol. 2005; 96(6):399-409.

Overview of SNRIs

Drug Name (Brand)	FDA-Approved Neuropathic Pain Condition	Metabolism/Elimination	General Dosing Range
Venlafaxine (Effexor®)	None	• Primarily metabolism through CYP2D6 into active metabolites	37.5mg to 300mg daily
Desvenlafaxine (Pristiq®)	None	• 50% renally • 50% phase II metabolism	50mg daily
Duloxetine (Cymbalta®)	• Diabetic neuropathy • Fibromyalgia	• Almost entirely through CYP1A2 and CYP2D6	20mg to 120mg daily
Milnacipran (Savella®)	• Fibromyalgia	• 55% renally • 45% hepatically	12.5mg to 100mg daily (divided doses)
Levomilnacipran (Fetzima®)	None	• 58% renally • 42% hepatically	40mg to 120mg daily

Sindrup SH, et al. Basic Clin Pharmacol Toxicol. 2005; 96(6):399-409.

Anticonvulsants

- Gabapentinoids:
  - Gabapentin and pregabalin
- Mechanism in neuropathic pain:
  - Antagonism of α_2-δ subunit of N-type voltage-dependent calcium channels presynaptically, reducing excitatory neurotransmitter release
  - Pregabalin has linear absorption and 6 times higher binding affinity
- FDA approved neuropathic pain indications:
  - Gabapentin: postherpetic neuralgia
  - Pregabalin: fibromyalgia, diabetic peripheral neuropathy, neuropathic pain associated with spinal cord injury, postherpetic neuralgia
- Common adverse events:
  - Dizziness, somnolence, confusion, and peripheral edema.

Eisenberg E, et al. Drugs. 2007; 67(9): 1265-1289.

Other Anticonvulsants

- Specific medications:
  - Carbamazepine, oxcarbazepine, topiramate, lamotrigine
- Mechanisms:
  - Inhibition of voltage-dependent sodium channels
  - Topiramate: prolongation of voltage sensitive sodium channel inactivation, GABA agonism, and NMDA antagonism
- FDA approved neuropathic pain indications:
  - Carbamazepine: trigeminal neuralgia and glossopharyngeal neuralgia
  - Topiramate: prophylaxis of migraines
- Common side effects:
  - Dizziness, somnolence, nausea, blurred vision, ataxia, dermatologic reactions

Eisenberg E, et al. Drugs. 2007; 67(9): 1265-1289.

Overview of Gabapentinoids

Drug Name (Brand)	FDA-Approved Neuropathic Pain Condition	Metabolism and Elimination	General Dosing Range
Gabapentin (Neurontin®)	• Postherpetic neuralgia	• 100% renally	100mg to 3600mg daily (divided doses)
Pregabalin (Lyrica®)	• Fibromyalgia • Diabetic neuropathy • Neuropathic pain associated with spinal cord injury • Postherpetic neuralgia	• 90% renally	25mg to 600mg daily (divided doses)

Eisenberg E, et al. Drugs. 2007; 67(9): 1265-1289.

Overview of Other Anticonvulsants:

Drug Name (Brand)	FDA-Approved Neuropathic Pain Condition	Metabolism/Elimination	General Dosing Range
Carbamazepine (Tegretol®)	• Trigeminal neuralgia • Glossopharyngeal neuralgia	• Primarily metabolism through CYP3A4 into active metabolites	100mg to 1600mg daily (divided doses)
Oxcarbazepine (Trileptal®)	None	• Primarily phase II metabolism into active metabolites	150mg to 1200mg daily (divided doses)
Topiramate (Topamax®)	• Prophylaxis of migraines	• 70% renally • 30% phase II metabolism	25mg to 200mg daily (divided doses)
Lamotrigine (Lamictal®)	None	• 10% renally • 90% phase II metabolism	25mg to 400mg daily (divided doses)

Eisenberg E, et al. Drugs. 2007; 67(9): 1265-1289.

What About Opioids?

Opioids

- Main analgesic mechanism:
  - Agonize mu-opioid receptors throughout both peripheral and central nervous system
- Still considered the mainstay of pain management in palliative and hospice care
  - Big difference in how quickly to titrate
  - Multiple studies have shown opioids do not affect survival in hospice[2-4]
- Specific opioids with neuropathic pain-relieving properties:
  - Tramadol, tapentadol, methadone, and levorphanol

(1) Smith HS. Pain Physician. 2012; 15(3 Suppl):ES93-110. (2) Portenoy RK et al. J Pain Symptom Manage. 2006;32:532-540.
(3) Good PD et al. Intern Med J. 2005;35:512-517. (4) Morita T et al. J Pain Symptom Manage. 2001;21:282-289.

Risks with Opioids

- Physical addiction, abuse, and misuse
  - Can still be an important issue in palliative care patients, or even their caretakers
- Respiratory depression
- Constipation, somnolence, nausea, vomiting
- Specific risks:
  - QTc prolongation with methadone
  - Serotonin syndrome with tramadol, methadone, and levorphanol

Smith HS. Pain Physician. 2012; 15(3 Suppl):ES93-110.
Pham TC, et al. Pain Med. 2015; 16(9):1673-9.

Wait… What About those Respiratory Effects?

- Refractory dyspnea is prominent and disabling among patients with advanced lung and heart disease
    - Experience of dyspnea can be quite distressing and typically evokes anxiety, panic, and/or fear

- Opioids:
    - Depress respiratory drive
    - Modulate central processing of dyspnea
    - Alter activity of peripheral opioid receptors located in the lung
    - Reducing anxiety

Mahler DA. Expert Rev Respir Med. 2013;7(2):123-135.

Dosing Equivalence?

Opioid	Equianalgesic Doses: Parenteral (IV, IM, SQ, TD)	Equianalgesic Doses: Oral
Morphine	10mg	30mg
Codeine	100mg	165mg
Fentanyl	0.1mg	N/a
Hydrocodone	N/a	30mg
Hydromorphone	1.5mg	7.5mg
Levorphanol	N/a	4mg
Meperidine	100mg	300mg
Methadone	N/a	Depends on formula
Oxycodone	Not determined	20mg
Oxymorphone	1mg	10mg
Tapentadol	N/a	100mg
Tramadol	N/a	N/a

https://opioidcalculator.practicalpainmanagement.com/methods.php

Pain Medicine 2016; 17: 892–898
doi: 10.1111/pme.12920

OXFORD

OPIOIDS, SUBSTANCE ABUSE & ADDICTIONS SECTION

Original Research Articles

Variability in Opioid Equivalence Calculations

Amanda Rennick, PharmD,* Timothy Atkinson, PharmD,† Nina M. Cimino, PharmD,‡ Scott A. Strassels, PharmD, PhD,§ Mary Lynn McPherson, PharmD, MA, BCPS, CPE,‡ and Jeffrey Fudin, PharmD, DAAPM, FCCP, FASHP¶‖,‖‖

result, patients are at risk for undertreated pain and serious adverse events. The purpose of this survey was to compare the equianalgesic conversion estimates between nurse practitioners, pharmacists, and physicians for commonly prescribed opioids.

Rennick et al. Pain Medicine. 2016;17:892-898

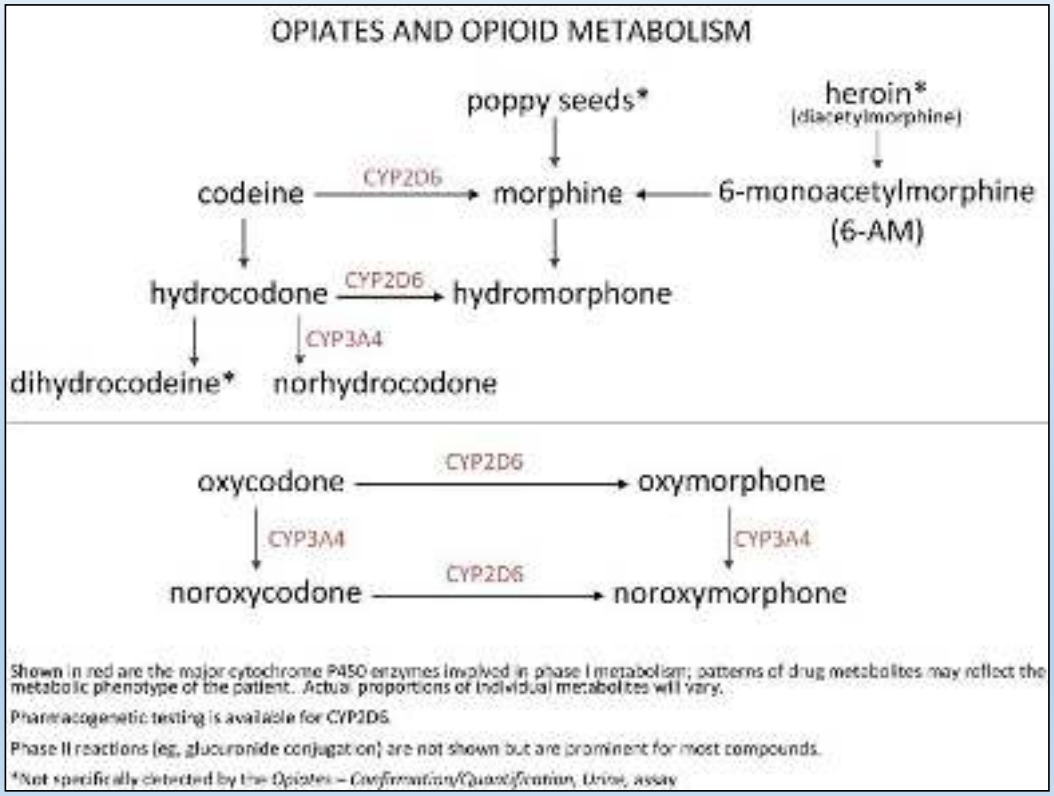
Rennick et al Results

Morphine equivalent doses (mg) for each opioid medication by specialty:

Practice Specialty	Fentanyl	Hydrocodone	Hydromorphone	Methadone	Oxycodone
Pain Management (n = 39)	166 ± 115 (150)	85 ± 43 (80)	191 ± 68 (192)	162 ± 111 (120)	167 ± 45 (180)
Palliative Care (n = 35)	168 ± 57 (150)	84 ± 17 (80)	188 ± 67 (192)	251 ± 166 (240)	154 ± 38 (180)
None of the Above (n = 247)	177 ± 124 (150)	88 ± 43 (80)	191 ± 50 (192)	169 ± 115 (160)	177 ± 37 (180)

Rennick et al. Pain Medicine. 2016;17:892-898

Review of Opioid Metabolism



http://www.arupconsult.com/assets/graphics/OpiatesAndOpiodMetabolism.jpg

Alternative Opioid Metabolism

Drug Name (Brand)	FDA-Approved Neuropathic Pain Condition	Metabolism/Elimination
Tramadol (Ultram®)	• Moderate to severe pain	• 30% renally • 60% metabolism via CYP2D6 into active and 3A4 into inactive metabolites
Tapentadol (Nucynta®)	• Moderate to severe pain • Diabetic neuropathy	• Primarily phase II metabolism into inactive metabolites
Methadone (Dolophine®)	• Chronic pain	• Primarily CYP3A4, 2B6, and 2C19 metabolism into inactive metabolites
Levorphanol	• Moderate to severe pain	• Primarily phase II metabolism into inactive metabolites
Fentanyl	• Moderate to severe pain	• Primarily via CYP3A4 into inactive metabolite (norfentanyl)

Smith HS. Pain Physician. 2012; 15(3 Suppl):ES93-110.
Pham TC, et al. Pain Med. 2015; 16(9):1673-9.

What Could Go Wrong??

Some legal cases… Food for thought!

- Prescribing excessive doses of any drug is reckless, harmful, and potentially lethal… Opioids are no different
- This is true even in palliative care and hospice settings
- Mistakes at the prescribing, dispensing, and/or administration level can result in patient harm and legal consequences

Some legal cases… Food for thought!

10INVESTIGATES

Mount Carmel fined $477,000 in settlement agreement with board of pharmacy

—

Two Mount Carmel pharmacists will also have to pay fines and receive continuing education courses in areas like palliative care, end of life therapy and medication safety.

https://www.10tv.com/article/news/investigations/10-investigates/mount-carmel-fined-477000-settlement-agreement-board-pharmacy-2020-mar/530-50b37295-e5e6-468a-bcab-190a70431200

Some legal cases… Food for thought!

WATCHDOG REPORTS

After botched prescription refill, Wisconsin pharmacist settles with widower for $325,0000

Cary Spivak Milwaukee Journal Sentinel

Published 8:00 a.m. CT Feb. 8, 2018 | **Updated 8:27 p.m. CT Feb. 11, 2018**

https://www.jsonline.com/story/news/investigations/reports/2018/02/08/did-pharmacistunusual-legal-fight-occurs-after-pharmacists-error-followed-womans-death-spouse-collec/1077047001/

Post-Question One

What best highlights a difference between palliative and hospice care?

A. Hospice care is a wider range of care services that includes palliative care which is usually reserved for those with a life expectancy of 6 months or less.
B. Palliative care is a wider range of care services that includes hospice care which is usually reserved for those with a life expectancy of 6 months or less.
C. Neither palliative nor hospice care are concerned with the management of pain.
D. Palliative care services would be inappropriate for someone suffering from end stage renal disease.

Post-Question Two

Which of the following is true regarding opioid use in palliative care services?

A. Opioids are still considered the mainstay in treatment of pain in those suffering from palliative conditions.
B. Opioids should only be used in hospice care settings and are not recommended for pain in palliative care settings.
C. Opioids should not be prescribed at daily doses greater than 90mg morphine equivalence.
D. Opioids have only shown to increase incidence of death in those in hospice care and have not shown any benefits.

Summary

- Understanding patient populations who may benefit from palliative care and/or hospice services can be essential in ensuring proper symptomatic management and enhancing quality of life.

- It is important to understand the multitude of medications available to treat pain in palliative and hospice care, as well as subtle differences between them that can allow for optimization of pain management in those with serious illnesses.

- Identifying the differences and nuances between agents can also be essential in allowing for appropriate care to not only protect patient safety, but also to protect yourselves and providers from legal and ethical shortcomings.

Thank you!

Questions?