

# Update in Palliative Care

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Recertification

# Disclosure

- Mary Lynn McPherson, PharmD, BCPS has received consulting fees from Alpharma

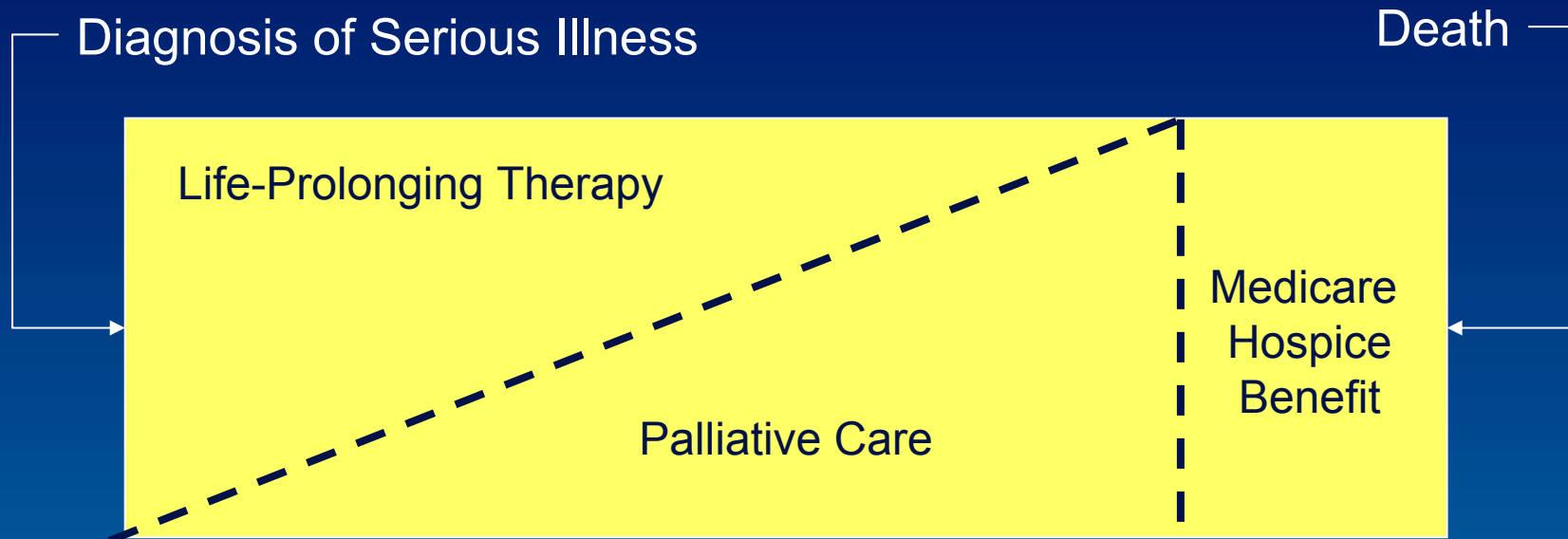
# Learning Objectives

- Differentiate between levels of hospice care (routine home care, continuous home care, and inpatient care) and reimbursement levels throughout the United States
- Describe the process of effective medication management for patients with advanced illness
- Describe controversial therapeutic dilemmas in caring for patients with advanced illness, such as the potential for opioids to hasten death, withdrawal of ventilatory support, and the use of anticoagulants
- Develop a strategy for dosing methadone safely and effectively to control pain in advanced cancer patients

# What Is Palliative Care?

- Goal is to prevent and relieve suffering and to support the best possible quality of life (QOL) for patients and their families
  - Regardless of the stage of the disease or the need for other therapies
- Philosophy of care and an organized, highly structured system for delivering care
- Can occur with life-prolonging care or as the main focus of care

# Palliative Care's Place in the Course of Illness



# What Is Hospice Care?

- Compassionate care for people facing a life-limiting illness or injury
  - Prognosis of 6 months or less
- Team-oriented approach to expert medical care, pain management, and emotional and spiritual support expressly tailored to the person's needs and wishes
- Support provided to the person's loved ones as well

# Hospice Admissions by Primary Diagnosis

Primary Diagnosis	2006	2005
Cancer	44.1%	46.4%
Noncancer diagnoses	55.9%	53.6%
Heart disease	12.2%	12.05
Debility unspecified	11.8%	9.2%
Dementia, including Alzheimer disease	10.0%	9.8%
Lung disease	7.7%	7.5%
Stroke or coma	3.4%	3.3%
Kidney disease	2.9%	2.9%
Motor neuron diseases	2.0%	2.1%
Liver disease	1.8%	1.7%
HIV/AIDS	0.5%	0.5%
Other diagnoses	3.7%	4.7%

# Levels of Hospice Care

- **Routine home care** – 93% of hospice care
  - Home, skilled nursing or assisted living facility
  - Patient not in crisis
  - Physicians, nursing care, PT/OT/speech, medical social services, HHA, medical supplies (drugs, biologicals, medical appliances), counseling (dietary and bereavement)
  - \$135.11 (FFY '08)

# Levels of Hospice Care

## ■ Continuous home care

- Occurs where patient resides
- In the event of a medical crisis
- Hospice team provides up to around-the-clock care
- Hospice bills Medicare by the hour
- \$788.55/\$32.86 per hour (FFY '08)

# Levels of Hospice Care

## ■ General inpatient care

- Occurs in an inpatient facility because care cannot be managed where patient resides
- Includes room and board payment
- \$601.02 (FFY '08)

# Levels of Hospice Care

## ■ Inpatient respite care

- Occurs in an inpatient facility
- Designed to give caregiver a rest
- Available for up to 5 consecutive days
- Includes room and board payment
- \$139.76 (FFY '08)

# Medication Management in Hospice

- Medication Reconciliation (MR)
- Medication Regimen Review
- Providing the Medication

# Can I See Your Medications, Please?



# Medication Reconciliation

- The practice of obtaining the most accurate list of ALL the patient's medications at each transitional point of care, including admission, transfer, discharge, and involvement of a new service
- The process of comparing a patient's medication orders to all of the medications that the patient has been taking
- Performed to avoid medication errors such as:
  - Omissions, duplications, dosing errors, or drug interactions

# Medication Reconciliation

MR process involves five steps:

1. Develop a list of current medications
2. Develop a list of medications to be prescribed
3. Compare the medications on the two lists
4. Make clinical decisions based on the comparison
5. Communicate the new list to the appropriate health care providers and to the patient/caregiver

MR



# Obtaining the Medication History

- Organization must implement a standardized method for creating an accurate list of medications at admission/entry and transfer
- The list should include the full range of medications

MR



# Obtaining the Medication History

- Prescription medications
- Sample medications
- Vitamins
- Nutraceuticals
- Over-the-counter (OTC) drugs
- Vaccines
- Diagnostic and contrast agents
- Radioactive medications
- Respiratory-therapy-related medications
- Parenteral nutrition
- Blood derivatives
- IV solutions (plain or with additives)
- Any product designated by the FDA as a drug

# List of What Patient SHOULD Be Receiving ...

- Confirm list of medications with primary care physician
  - Review with each admission?
  - Sending plan of care?
- May require discussion with specialist prescribers as well (eg, cardiologist, pulmonologist, neurologist, etc)

# COMPARE the Two Lists

- Chances are SUPERB that you will have medications on your list that the patient is taking, that the primary care physician has no idea about
  - Other Rx meds, OTC, CAM
  - Home remedies, etc

MR



# Make Clinical Decisions ...

- Based on the comparison of the two lists
- Based on your clinical knowledge and the patient's therapeutic goals

MR



# Drug-Related Problems

## *Hepler and Strand*

- Untreated indication
- Improper drug selection
- Subtherapeutic dose
- Failure to receive or take medications
- Overdose
- Adverse drug events
- Drug interactions
- Drug use without indication

# Untreated Indication

- Failure to recognize pain or distinguish pains
  - Behavioral disturbances
  - 80% of cancer patients have more than one pain; one third have  $\geq 4$  pains
- Failure to optimize drug therapy in noncancer diagnoses (eg, heart failure)
- Prophylaxis
  - Opioid-induced constipation
  - Cytoprotection with NSAID/CCS therapy

NSAID = nonsteroidal anti-inflammatory drugs; CCS = corticosteroid.

# Improper Drug Selection

- Using “one size fits all” mentality in analgesic selection
  - Opioids, nonopioids
  - Coanalgesics (NSAIDs for bone pain, agents for neuropathic pain)
- Morphine (opioid) “allergy”
- Inappropriate dosage formulations
  - Long-acting (LA), short-acting, rapid-acting opioids
  - TDF, LA opioids in ostomy patients

# Drug Use Without Indication

- Taking medications no longer necessary
- Medications with no clear therapeutic goal
  - Therapeutic goal no longer relevant/changed
- Antilipemic agents
- Antihypertensive agents
- Antidiabetes therapies
- HOW to stop medications?

# Adverse Drug Effects

## ■ Opioids

- Nausea, vomiting, constipation, sedation, confusion, respiratory depression
- Codeine, opioids with active metabolites

## ■ NSAIDs

- GI upset/bleeding, fluid retention, renal failure

## ■ Coanalgesics

- TCAs – amitriptyline vs desipramine

# Other Drug-Related Problems

- Subtherapeutic dosing
- Overdose
- Drug interactions
- Failure to receive or take medications

# Rational Drug Therapy

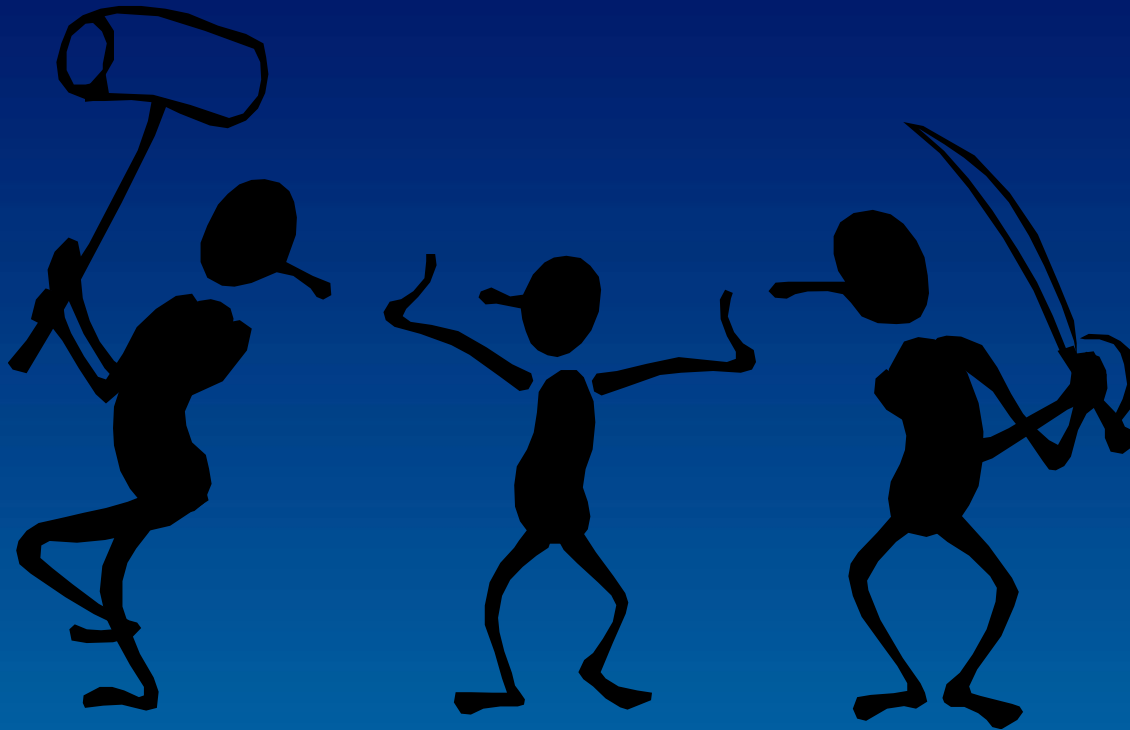
- Now you have the list of appropriate medications for the patient to be taking
- Who provides each medication?
- Medicare hospice benefit stipulates:
  - “Medical supplies and appliances, including drugs and biologicals, must be provided as needed for the palliation and management of the terminal illness and related conditions.”

# Hospice Provided Medications

- Analgesics
- Bowel regimen
- Symptom management (cough, nausea, insomnia)
- Disease-specific therapies related to terminal diagnosis
  - CHF (diuretics, ACE inhibitors, beta blockers)
  - Parkinson's disease (levodopa/carbidopa)
  - COPD (albuterol, ipratropium, morphine)

Will this make the patient  
feel more comfortable?

# Controversies in Palliative Care



# Do Opioids Hasten Death?

- Concern may be a reason why pain is not adequately treated in patients with advanced illness
- National Hospice Outcomes Project
  - To determine whether survival after last opioid dose change is associated with opioids dosing characteristics or other factors
- 13 US Hospice programs (1306 patients; 725 on opioids with at least one dose change prior to death)
- Mean  $\pm$  SD survival after last dose change was 12.46  $\pm$  23.11 days

US = United States; SD = standard deviation.

Portenoy RK, et al. *J Pain Symptom Manage.* 2006;32:532-40.

# Do Opioids Hasten Death?

- Multivariate models demonstrated a significant association between shorter survival and:
  - Higher opioid dose
  - Cancer diagnosis
  - Nonresponsiveness
  - Pain <5 on a 0 to 10 scale
- None of these models explained >10% of the variance in time until death
- Concern about opioids hastening death does not justify withholding opioid therapy

# Management of Neuropathic Pain

- First-line medications in neuropathic pain
  - Gabapentin
  - 5% lidocaine patch
  - Opioid analgesics
  - Tramadol hydrochloride
  - Tricyclic antidepressants

# Lidocaine for Neuropathic Pain

- Question – Are intravenous lidocaine and oral mexiletine effective and safe for the treatment of neuropathic pain?
  - Lidocaine produces analgesia by blocking peripheral and central sodium ion gate channels, including in the spinal dorsal horn (IV – can alleviate deafferentation pain or central pain)
- Systematic review and meta-analysis
- 706 patients with neuropathic pain in 19 trials (10 with IV lidocaine and 9 with oral mexiletine)
- Both superior to placebo
- Consider for refractory neuropathic pain

# Initiation/Monitoring Infusional Lidocaine for Neuropathic Pain

- Pre-infusional assessment
  - Pain history, physical examination
  - History of “caine” allergy
  - History of heart failure or liver disease
- Lidocaine challenge
  - 1 to 3 mg/kg (100 mg often used) given IV (as 8 mg/mL) over 20 to 30 minutes
  - May be given SQ over 30 to 60 minutes (as up to 40 mg/mL)

SQ = subcutaneous.

Ferrini R, Paice JA. *J Support Oncol.* 2004;2:90-4.

# Initiation/Monitoring Infusional Lidocaine for Neuropathic Pain

## ■ Lidocaine infusion

- Start on continuous infusion, SQ or IV at 0.5 to 2 mg/kg per hour, using lowest possible dose to control pain
- Titrate down until pain returns
- Doses above 2 mg/kg/hour rarely indicated
  - Toxicity rare with doses of 1 to 2 mg/kg/hr
  - AE – lightheadedness, numbness around tongue/mouth, dizziness, metallic taste in mouth, increase in BP, redness/erythema at SQ infusion site
- Titrate opioid dose down as indicated

AE = adverse event; BP = blood pressure.

Ferrini F, Pace JA. *J Supportive Oncol.* 2004;2:90-94

# Opioids for Dyspnea

- Prognosis: years – years to months – months to weeks
  - Assess symptom intensity
  - Treat underlying causes/comorbid conditions
    - Radiation, chemotherapy, thoracentesis, pleurodesis, bronchoscopic therapy, bronchodilators, diuretics, steroids, antibiotics, transfusions
  - Relieve symptoms
    - Temporary ventilation, O<sub>2</sub>, BZD, opioids, non-pharmacologic, education, psychosocial, emotional support

O<sub>2</sub> = oxygen; BZD = benzodiazepine.

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# Opioids for Dyspnea

- Prognosis: Weeks to days (dying patient)
  - Assess symptom intensity (physical signs of distress in noncommunicative patients)
  - Focus on comfort (tx underlying condition as appropriate)
  - Relieve symptoms
    - Opioids for cough or dyspnea
    - BZD for anxiety/agitation/air hunger
    - Nonpharmacologic
    - Reduce excessive secretions
    - O<sub>2</sub> if subjective report of relief

# Opioids for Dyspnea

- Prognosis: Weeks to days (dying patient)
  - Withhold/withdraw/time-limited trial of mechanical ventilation as indicated
  - DC fluid support/consider low-dose diuretics if fluid overload may be contributing factor
  - Anticipatory guidance for patient/family on dying process, treatment of respiratory crisis
  - Provide emotional support

DC = discontinue.

# Opioids for Dyspnea

- Breathlessness in terminal illness
- 18 studies identified
  - Nine involved non-nebulized route of administration
    - Statistically significant improvement
    - Oral or parenteral opioids
  - Nine involved nebulized route of administration
    - No evidence to support use

# Withdrawing Ventilatory Support

- Death in ICU typically follows a decision to withhold/withdraw life-sustaining therapies
  - Including ventilatory support
- Critical competency for palliative care and hospice clinicians
- Controversial issues in literature include:
  - Need for premedication
  - Extubation vs rapid terminal wean ± extubation
  - Accepted drugs/dosing regimens

ICU = intensive care unit.

Campbell ML. *AACN Adv Crit Care*. 2007;18:397-403.

# Withdrawing Ventilatory Support

- Clinical bottom line
  - Clinicians should use consistent and objective measures of respiratory distress
  - Premedication and initial dosing should be guided by potential for distress, while dose escalation should be based on objective, documented markers of distress
  - Endotracheal tube removal is preferred in most but not all cases

# Anticoagulation in Advanced Cancer Patients

- Challenges of managing cancer-related venous thromboembolism (VTE) in the palliative care setting
  - Defining the population
  - Recognition of the VTE
  - Confirmation of the VTE
  - Treatment of the VTE
  - How long to continue anticoagulation?

# Anticoagulation in Advanced Cancer Patients

- Cancer patients fall into one of three groups
  - Patients previously established on oral anticoagulation
  - Patients not on anticoagulation and with no evidence of DVT
  - Patients not on anticoagulation and found to have DVT

# Anticoagulation in Advanced Cancer Patients

Patients previously established on oral anticoagulation:  
Continue oral warfarin unless:

- Evidence of bleeding
- INR >5 on repetition
- Thrombocytopenia
- Hepatic failure
- Serious risk of falls
- High alcohol intake
- Dysphagia
- Drug interactions
- Difficulty monitoring INR

**Benefit vs Burden**

# Anticoagulation in Advanced Cancer Patients

- Patients not on anticoagulation and with no evidence of DVT
  - Prophylactic LMWH?
  - Compression hosiery or TED stockings for patients at risk (eg, spinal cord compression)

# Anticoagulation in Advanced Cancer Patients

- Patients not on an anticoagulant and suspected to have VTE
  - Defining the population
  - Recognition of the VTE (incidence 1%-5%)
    - Natural history of asymptomatic VTE in palliative care patient is unknown
    - Underappreciation of risk factors of advanced malignancy among palliative care practitioners
    - Nonspecific presenting symptoms

# Anticoagulation in Advanced Cancer Patients

- Burden or benefit
  - Investigation or treatments vs
  - Treating solely symptomatically
- Nihilistic view that “a large PE might be a nice way to go” – not supported by evidence
  - Cancer deaths from PE are rarely sudden, quick and symptom-free
  - Patients symptomatic for an average of 2 hours prior to death

PE = pulmonary embolism.

Noble S. *Postgrad Med J*. 2007;83:671-4.

# Anticoagulation in Advanced Cancer Patients

## Common causes of swollen legs in palliative care patient

### Unilateral

- Deep vein thrombosis
- Cellulitis
- Nodal disease in groin
- Lymphedema

### Bilateral

- Deep vein thrombosis
- Hypoalbuminemia
- Heart failure
- Medications (steroids, nifedipine)
- Lymphedema
- Pelvic disease causing reduced venous outflow

# Anticoagulation in Advanced Cancer Patients

## Common causes of dyspnea in advanced cancer patients

- Pneumonia
- Pulmonary edema
- Pleural effusion
- Anemia
- Lung metastases
- Lymphangitis
- Muscle fatigue
- Concurrent pulmonary illness
  - COPD
  - Emphysema
  - Interstitial lung disease
  - Congestive cardiac fx

# Anticoagulation in Advanced Cancer Patients

- Confirmation of VTE
  - Use of D-dimers
  - Confirmation of suspected DVT
  - Confirmation of suspected pulmonary embolus

# Anticoagulation in Advanced Cancer Patients

## Imaging Tests Available for the Diagnosis of Pulmonary Embolus

Investigation	Accuracy in dx PE	Burden on Patient	Usefulness in Pall Care
Pulmonary angiography	++++	++++	++
V/Q scan	++	+	+
CTPA	+++	+	+++

CTPA = computed tomography pulmonary angiogram; V/Q = ventilation/perfusion.

Reproduced from Noble S. *Postgrad Med J.* 2007;83:671-4 with permission from the BMJ Publishing Group.

# Anticoagulation in Advanced Cancer Patients

- Treatment of VTE
  - Patients become more prothrombotic as malignancy advances
  - Patients tend to be anticoagulated at subtherapeutic levels to minimize the risk of bleeding
  - Cancer patients have higher bleeding rates on warfarin (up to 21.6%); greater in palliative care patients

# Anticoagulation in Advanced Cancer Patients

- LMWH benefits over warfarin
  - Dose is calculated according to patient weight; no need to monitor anticoagulation
  - Efficacy is not altered by changes in nutritional status
  - Not affected by absorption problems or poor oral intake
  - Efficacy not altered by new medicines

# Anticoagulation in Advanced Cancer Patients

- Meyer, et al compared cancer patients with VTE receiving LMWH or warfarin
  - Bleeding and recurrent VTE
    - 21.1% warfarin patients
    - 10.5% LMWH patients
- LITE Trial – 200 cancer patients with acute VTE
  - VTE at 3 months was 6% in LMWH group vs 10% in warfarin group, and 7% vs 16% at one year

# Anticoagulation in Advanced Cancer Patients – CLOT

	Dalteparin Only group	Oral AC group
Recurrent DVT or PE	9% (SS)	17%
Rates of major bleeding	6%	4%
Any bleeding	14%	19%
Mortality	39%	40%

- Long-term LMWH more effective than long-term oral anticoagulation for preventing DVT or PE in cancer patients and did not cause excessive bleeding
- Unclear if results translated into a meaningful difference in quality of life

# Anticoagulation in Advanced Cancer Patients – Learning Points

- VTE is common in advanced cancer patients
- The management of VTE in this patient group needs to take into account the impact of investigations and treatments on overall QOL
- Involvement of patients in the decision-making process is essential
- Anticoagulated cancer patients are at higher risk of bleeding complications than noncancer patients
- Cancer patients are more likely to develop further thrombotic events on warfarin than noncancer patients
- LMWHs are more efficacious and have a better impact on QOL than warfarin in the advanced cancer patient
- Warfarin is not advised in the treatment of VTE in the advanced cancer patient

**FDA Public Health Advisory  
Methadone Use for Pain Control  
May Result in Death and  
Life-Threatening Changes in  
Breathing and Heart Beat**

Released November 27, 2006

# Methadone

- Synthetic opioid
- Widespread use for MMT
- Variable pharmacokinetics
  - Conversion from other opioids
- Multi-compartment modeling
- Numerous drug interactions
- Very effective, low cost, long half-life, convenient dosing schedule

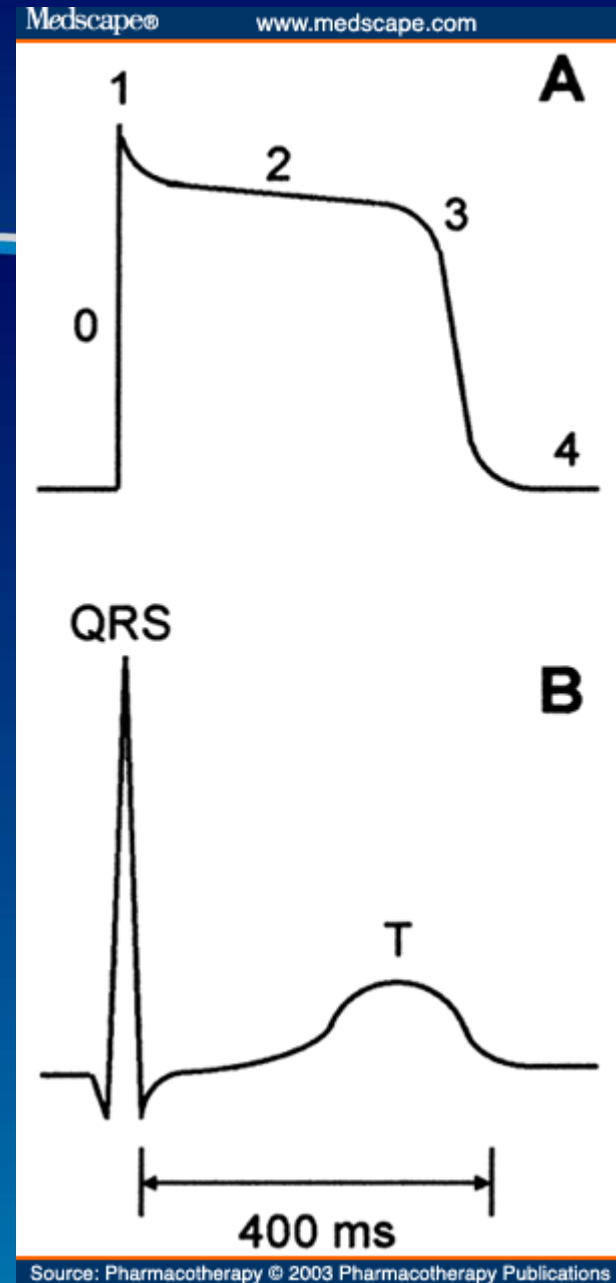
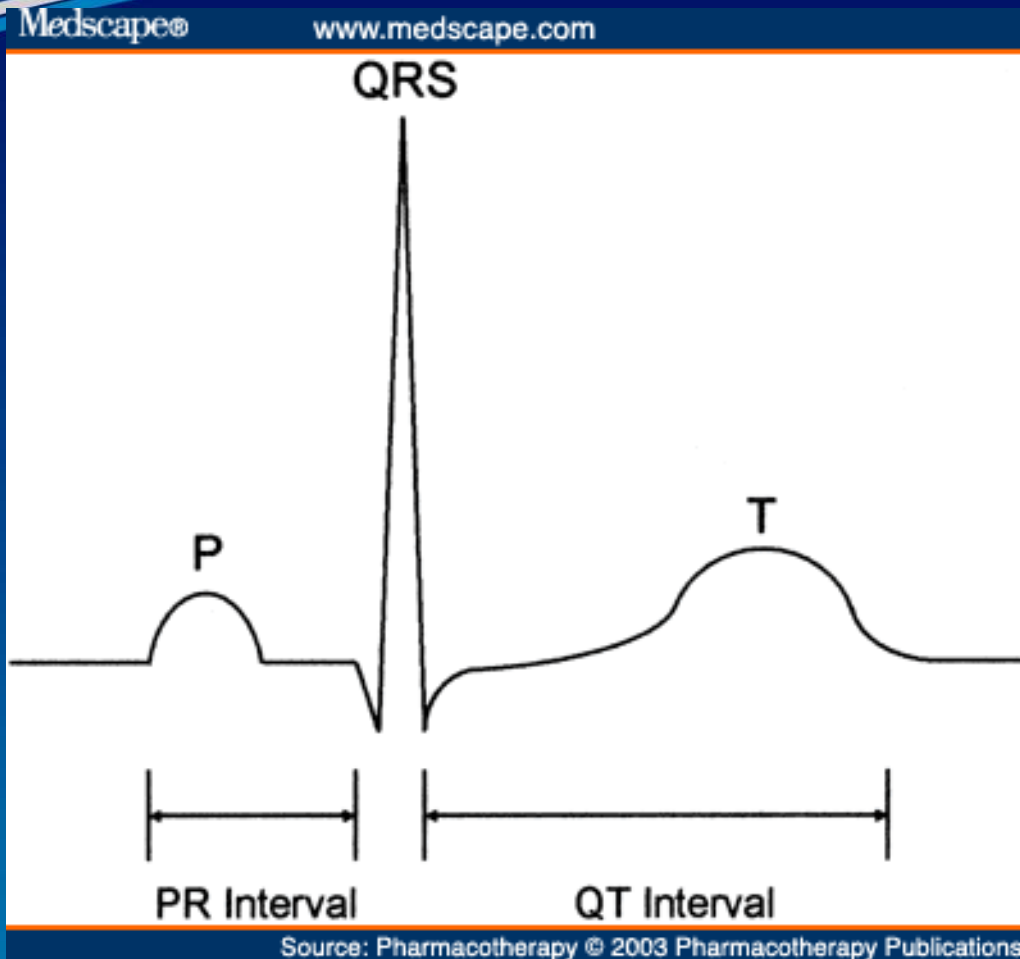
# Methadone Pharmacokinetics

Parameter	Average	Range
Bioavailability	70%-80%	36%-100%
T <sub>max</sub>	2.5-4 hours	1-5 hours
Vd ( $\beta$ )	4.0 L/kg	1.9-8.0 L/kg
Protein binding	87%	81-97%
Half-life	20-35 hours	5-130 hours

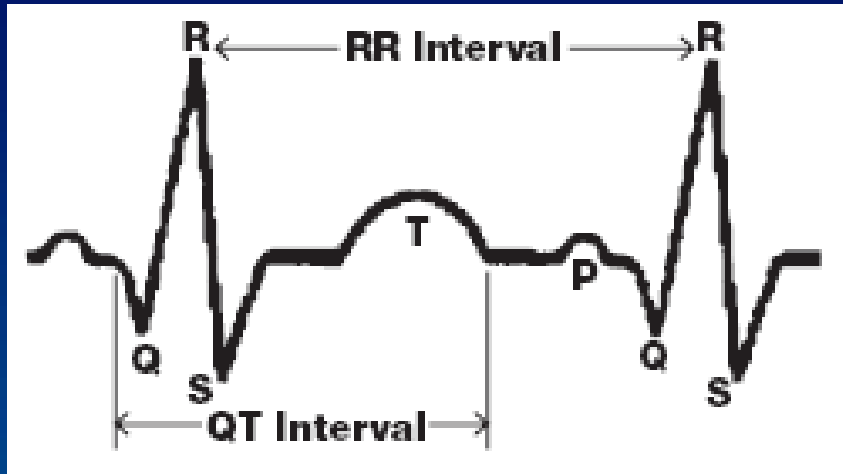
# Drug Interactions

- Methadone undergoes hepatic N-demethylation by 3A4, 2B6, 2C19, 2C9, 2D6
- Opioid antagonists, mixed, partial agonists
- Enzyme inducers – rifampin, phenytoin, St. John's wort, phenobarbital, CBZ
  - Antiretrovirals – reduce plasma level of methadone
  - Efavirenz, nelfinavir, nevirapine, ritonavir, etc
- Enzyme inhibitors – azole antifungals, macrolide antibiotics, SSRIs, voriconazole
- Prolongation of QT interval

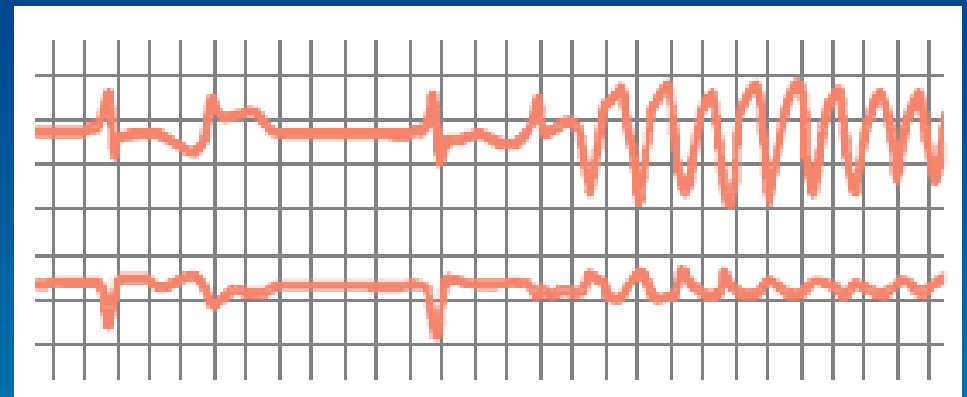
# QT Prolongation



# Drug-Induced Prolonged QTc Interval



Criteria for significant QTc prolongation is 500 ms



# QT Interval Prolongation

- In methadone patients, QTc length associated with dose, 3A4 drug interactions, hypokalemia, altered liver function
- Routine ECG screening not warranted
- Consider screening for:
  - Structural heart disease (left vent. dysfunction)
  - Above associated factors
  - Multiple QTc prolonging drugs
- Common medications: class I and III antiarrhythmics, some neuroleptics and TCAs, some CCB

# Beginning Methadone Therapy ...

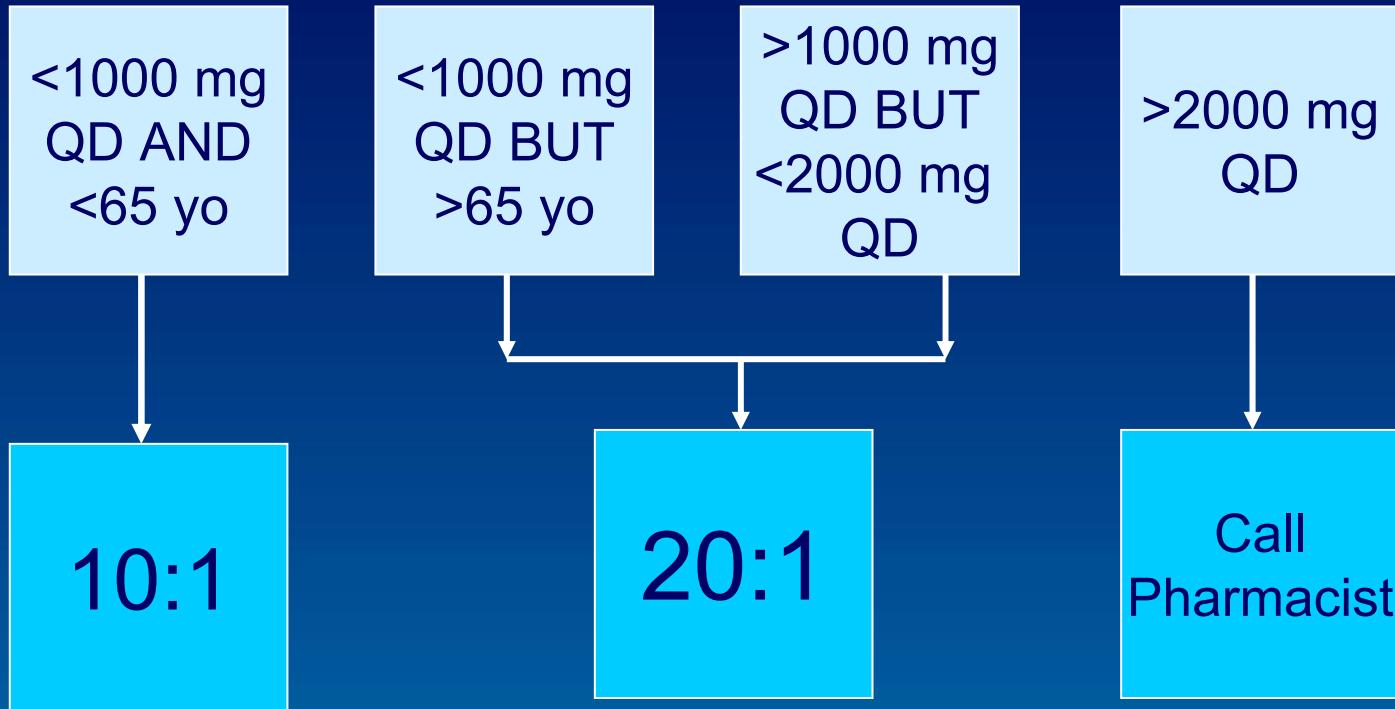
- 2.5 to 5 mg PO qhs – q12 – q8h
- Breakthrough analgesia?
  - Methadone
  - More linear opioids
    - Morphine
    - Oxycodone
- Conversion from other opioids?



# Conversion From Other Opioids

<b>TDD Oral Morphine</b>	<b>EPERC Conversion (morphine:meth) (reduce by 50%)</b>	<b>% of Morphine dose (FDA)</b>
<100 mg	3:1	20-30%
101-300 mg	5:1	10-20%
300-600 mg	10:1	8-12%
600-800 mg	12:1	600-1000 mg
800-1000 mg	15:1	5-10%
>1000 mg	20:1	<5%

# Friedman Method



# Further Notes on Methadone

- After determining total daily dose, divide into every 8- or 12-hour dosing
- Rapid switch or one cheek sneak?
- What to use for breakthrough dosing?
- When to adjust dose – NO SOONER than every 5 days (preferably every 7 days)
- After achieving steady state – breakthrough?

# Methadone References

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# **HOPA/ISOPP 2008**

**Thursday, June 19**

***HOPA/ISOPP 2008  
Joint Annual Conference  
Anaheim, California  
June 18-21, 2008***

**BCOP**  
Recertification