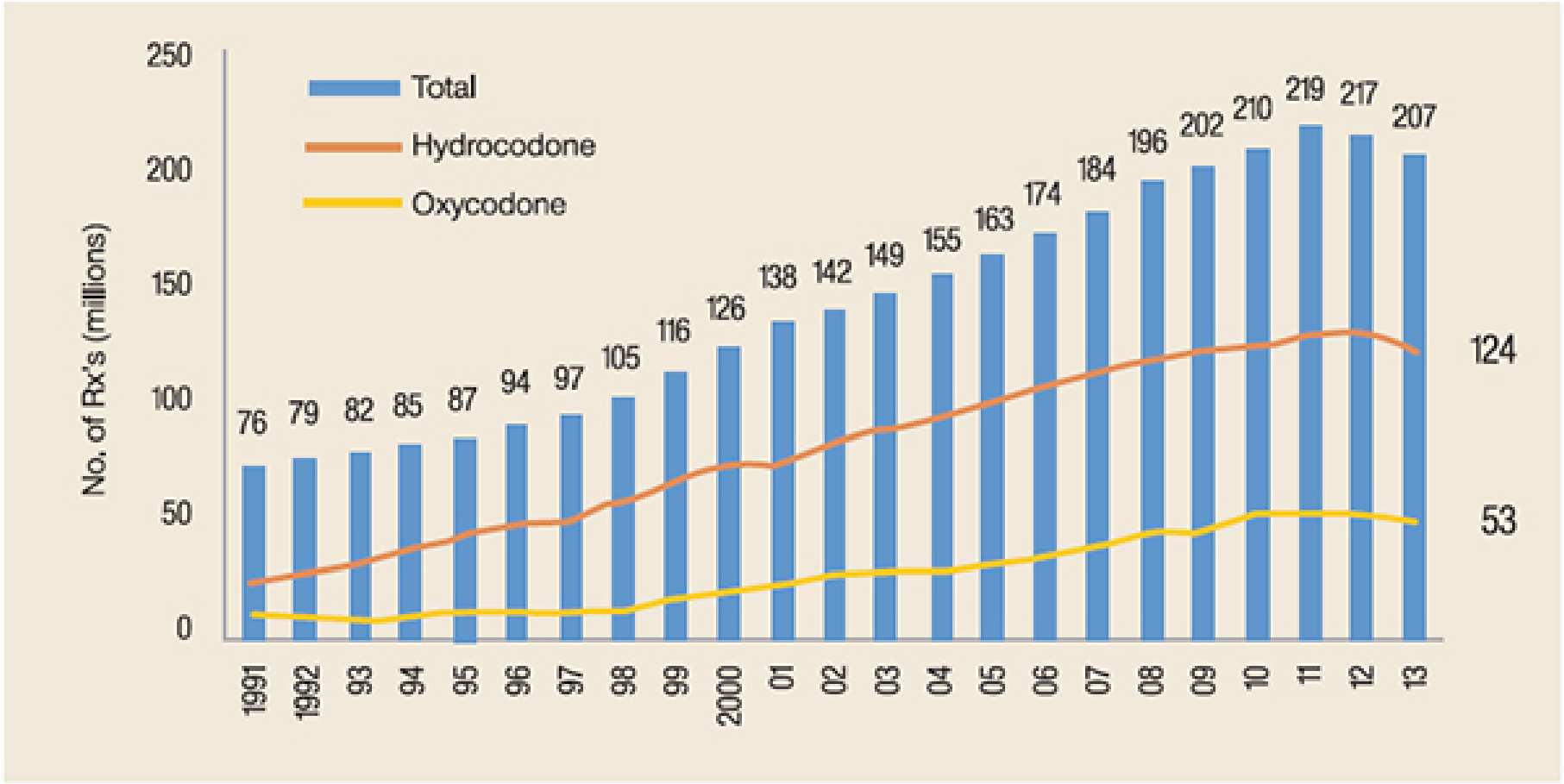
Reducing Adverse Drug Events from Opioids (RADEO)

shm
Society of Hospital Medicine

HOSPITALISTS, TRANSFORMING HEALTHCARE, REVOLUTIONIZING PATIENT CARE.

Opioid Prescribing Trends



Opioid Prescriptions Dispensed by US Retail Pharmacies IMS Health, Vector One: National, years 1991-1996, Data Extracted 2011. IMS Health, National Prescription Audit, years 1997-2013, Data Extracted 2014.

Opioid Prescribing Statistics

- Opioids are the **most commonly prescribed** class of medications in the hospital
- **Second** most common class of medications to cause adverse patient events
- **700 patient deaths** directly attributed to PCA between 2005 and 2009. (AAMI/FDA Infusion Device Summit, 2010)
- Approximately **1 in 200** hospitalized post-operative surgical patients experience post-operative respiratory depression (Dahan, 2010)
- Post-operative respiratory failure cost estimated at **$2 billion** per year (Reed, 2011)
- Prescription opioid-related overdose deaths now outnumber overdose death involving all illicit drugs such as heroin and cocaine combined (CDC, 2013, Wonder database, http://wonder.cdc.gov)

Pain Control For Hospitalized Patients

- **1996** – Joint Commission and American Pain Society established the 5th vital sign
- **2001** – Joint Commission pain management standard - “pain undertreated in the hospital”
- **2002** – HCAHPS – “During your hospital stay how often was your pain well controlled?” Goal - ***always***
- **2011** – Medicare Value based Purchasing – HCAHPS tied to hospital reimbursement

Opioid use and opioid related adverse events have increased over this period of time

Patient Safety Movement

- **2000** - To Err is Human - Institute of Medicine
- **2004** - 100,000 lives campaign - Institute of Healthcare Improvement
- **2012** - The Joint Commission Sentinel Event Alert 49
  - recommends specific steps every hospital should take to reduce opioid-related respiratory depression which includes implementing effective processes, safe technology, education and training, and effective tools
- Adverse Drug Events (ADEs) - Institute for Safe Medication Practices (ISMP), Opioids are among “high-alert medications"
- ADEs affect nearly 5% of hospitalized patients,(Hauck, 2011)

Joint Commission's Sentinel Event Database 2004-2011

Opioid related adverse events, including death:

- 47% wrong dose medication errors
- 29% related to improper monitoring
- 11% related to excessive dosing, drug interactions and adverse drug reactions

Reporting

- Actual number of events may be higher then reported
- Health care worker concern about consequences
- Higher incidence of events noted in clinical trials

Objectives for Training

1. Review opioid pharmacology, physiology and potential adverse reactions and safety hazards associated with these medications
2. Review best practices for safe opioid prescribing, dispensing, opioid use risk assessment and monitoring for inpatients
3. Review quality improvement as it relates to safe use of opioids in the inpatient setting, and the role of RADEO and SHM Mentored Implementation

Case 1

- George is a 59 year-old male who is admitted to the hospital with acute onset severe abdominal pain
- PMH
  - DM for 20 years – recently started on insulin
  - CAD with DES to LAD 16 months ago
  - CRI stage III from his DM
  - Morbid Obesity with BMI of 36
- Diagnosis - gallstone pancreatitis, worsening renal failure, severe dehydration
- **Will this patient require opioids for pain management?**

Case 2

- Mary is 81 year old female admitted to the hospital after a fall with severe right hip pain
- PMH
  - Osteoporosis
  - HTN
  - Early cognitive decline / dementia
- Admission with right sub-trochanteric femur fracture, no other injuries
- **Will this patient require opioids?**

Opioids - Pharmacology, Physiology, Metabolism

Opioid Terminology

- Opiate naïve – not taking opioids
- Opioid tolerant - regular use of opioids
- Addiction – use despite negative social, psychological or physical consequences
- Physical addiction - chronic use, withdrawal, drug seeking
- Dependence - occurs after normal use, body adapts to chronic drug exposure, not the same as addiction

Opioid Receptors

Mu receptor

- Produces analgesia, sedation, euphoria, respiratory depression, constipation, and physical dependence

Delta receptor

- Produces analgesia
- Mu agonists potentiate effect
- Respiratory depression is limited except at high doses

Kappa receptor

- Mild analgesia effect
- Higher hallucinogenic potential
- Low respiratory depression

Opioid Receptor Locations

- Brain
  - increased sedation
- Spinal cord
- Organs
  - End organ effects
- Peripheral nerves

How Does this Relate to the Patient?

- Receptors can be activated - opioid receptor agonist
  - Morphine, methadone, buprenorphine, etc.

- Receptors can be blocked - opioid receptor antagonist
  - Naloxone, naltrexone

- Different medications work on different receptors
  - Understanding the type of medication you use, helps predict response and side-effect profile

Activity at Receptors = Clinical Effect of Medication

- Full agonist - strong analgesia effect
  - morphine, hydromophone, fentanyl, oxycodone
- Partial agonist - mild analgesia effect
  - buprenorphine, nalbuphine
- Antagonist–blocks receptor
  - naloxone and naltrexone
- Agonist/Antagonist combinations – reduces or does not allow diversion-crushing/dilution for IV injection
  - Suboxone

Opioid Metabolism

- All metabolized in the liver
  - CYP2D6 enzyme key in developing active metabolites.
- Some, especially Morphine and Meperidine have renal excretion of metabolites
- Half-lives widely varied

Opioid Metabolism

- Active Opioid Metabolites
  - Morphine Metabolites
    - morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G)
    - M6G causes CNS effects
      - respiratory depression
    - M3G can cause CNS agitation/excitation
  - Dilaudid Metabolites
    - Dilaudid-3-glucuronide 95%, reduced excretion
  - Codiene and Tramadol Metabolites
    - Metabolized to become active
    - Morphine and O-desmethyltramadol

Opioid Metabolism

- Active Opioid Metabolites (Cont.)
  - Oxycodone metabolite
    - Noroxycodone – very weak effect
- Opioids without active Metabolites
  - Fentanyl, oxymorphone, methadone
    - Unlikely to have metabolites causing analgesia or side effects.

Hospital Responsibility

Care Team Responsibility

- Assess, monitor and treat pain
  - Identify type, location and severity of pain
  - Treat pain based on quality and severity
  - Monitor response
- Identify potential patient risks
  - History of high risk conditions
  - History of previous opioid use
  - Allergies

Care Team Responsibility

- Monitor for and treat adverse reactions
  - Sedation assessment, vital signs, ins and outs
- Partner with others to improve patient safety environment with reference to opioid prescribing and dispensing in their hospital or health system
  - Develop systems based practices
  - QI with multidisciplinary team

Adverse Events

Opioids and Allergies

- Side effects and pseudo-allergies versus “true allergies”
- Pseudo-allergic reactions - itching, rash, troubles breathing, and hypotension, caused by mast cell activation → histamine release, not immunologic reactions
- Natural opioids cause more common / pronounced pseudo-allergic reactions than synthetic
- Anaphylaxis (IgE mediated) anaphylactoid reactions and rare but can be severe - nasal congestion, flushing, pruritus, angioedema, nausea, vomiting, diarrhea, urinary urgency, bronchospasm, hypotension and death

Opioid Classification

Phenanthrenes

- Morphine, codeine, oxycodone, hydrocodone, and hydromorphone

Phenylpiperidine

- Fentanyl and meperidine

Diphenylheptanes

- Methadone

Patients with an allergy to a specific class can be switched to a different class, although cross-sensitivity still may occur

Respiratory Depression

- Decreased minute ventilation

- Opioids depress/alter all phases of respiration
  - Rate
  - Rhythm
  - Minute volume
  - Tidal exchange

Types of Respiratory Failure

Table 1—The 3 Clinical Pattern Types of Unexpected Hospital Death (PUHD)	
TYPE I	**Hyperventilation Compensated Respiratory Distress (e.g., Sepsis, PE, CHF)** Stable SPO_2 with progressively falling $PaCO_2$ eventually yields to slow SPO_2 decline (mitigated by respiratory alkalosis), which is followed by precipitous SPO_2 decline when metabolic acidosis dominates.
TYPE II	**Progressive Unidirectional Hypoventilation (CO_2 Narcosis)** Progressive rise in $PaCO_2$ (and $etCO_2$) and fall in SPO_2 over 15 minutes to many hours. (Often due to overdosing of narcotics or sedatives)
TYPE III	**Sentinel Rapid Airflow/SPO_2 Reductions Followed by Precipitous SPO_2 Fall** A state of "arousal dependent survival" that occurs only during sleep. Arousal failure allows precipitous hypoxemia during apnea causing terminal arousal arrest.

Type I Respiratory Failure

- Metabolic acidosis mediated hyperventilation
  - Sepsis
  - Pulmonary embolus
  - CHF
  - Trauma
- Compensatory hyperventilation and respiratory distress
- Eventual inability to compensate and respiratory failure and death
- Opioids can exacerbate

Respiratory Failure Type I

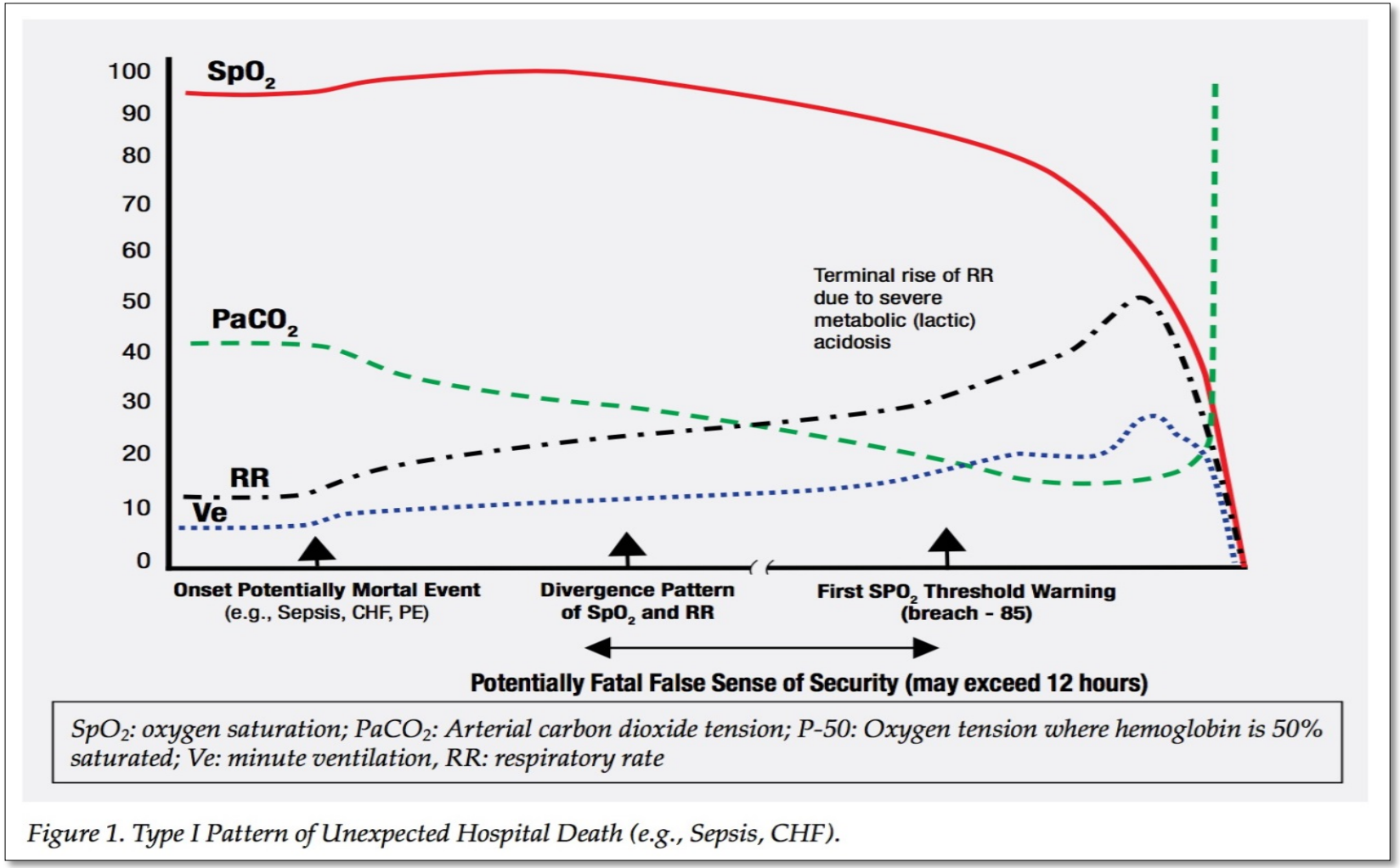


Figure 1. Type I Pattern of Unexpected Hospital Death (e.g., Sepsis, CHF).

(Curry JP, Lynn LA. Threshold Monitoring, Alarm Fatigue, and the Patterns of Unexpected Hospital Death. Anesthesia Patient Safety Foundation Newsletter. 2011;26(2):32-35.)

Type II Respiratory Failure

- Progressive unidirectional hypoventilation and respiratory acidosis - CO_2 narcosis
- Sedative or narcotic overdose
- “Shut down” the breathing center
- *Eventual* develops low oxygenation, respiratory failure and death
- **Low O_2 saturation / PaO_2 is a late sign**

Respiratory Failure Type II

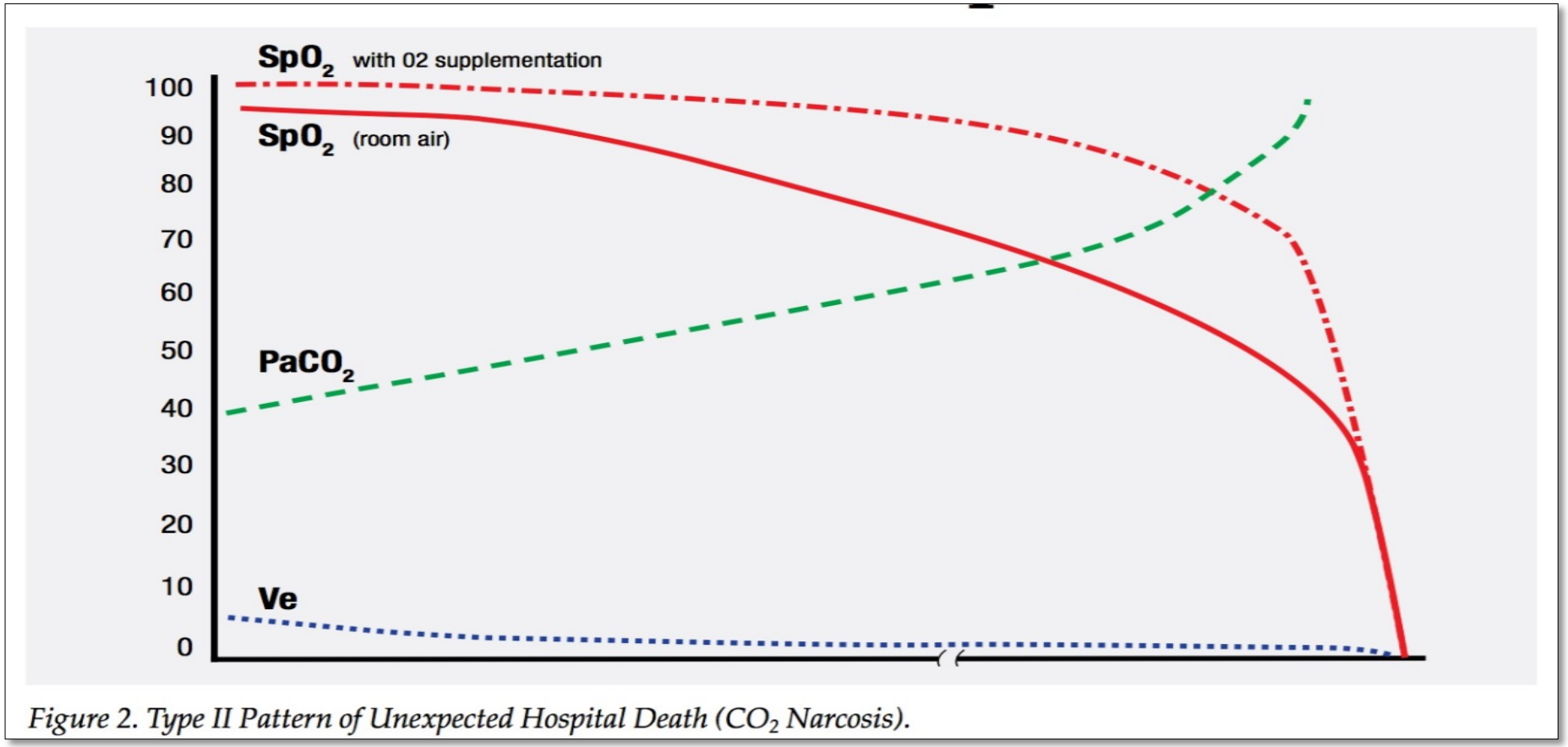


Figure 2. Type II Pattern of Unexpected Hospital Death (CO_2 Narcosis).

(Curry JP, Lynn LA. Threshold Monitoring, Alarm Fatigue, and the Patterns of Unexpected Hospital Death. Anesthesia Patient Safety Foundation Newsletter. 2011;26(2):32-35.)

Type III Respiratory Failure

- Individuals with *arousal dependent* respiration, oxygenation and ventilation
- Obstructive Sleep Apnea (OSA)
- Apnea → failure to arouse → rapid respiratory failure (hypoxemia and hypercapnia) → death

Type III Respiratory Failure

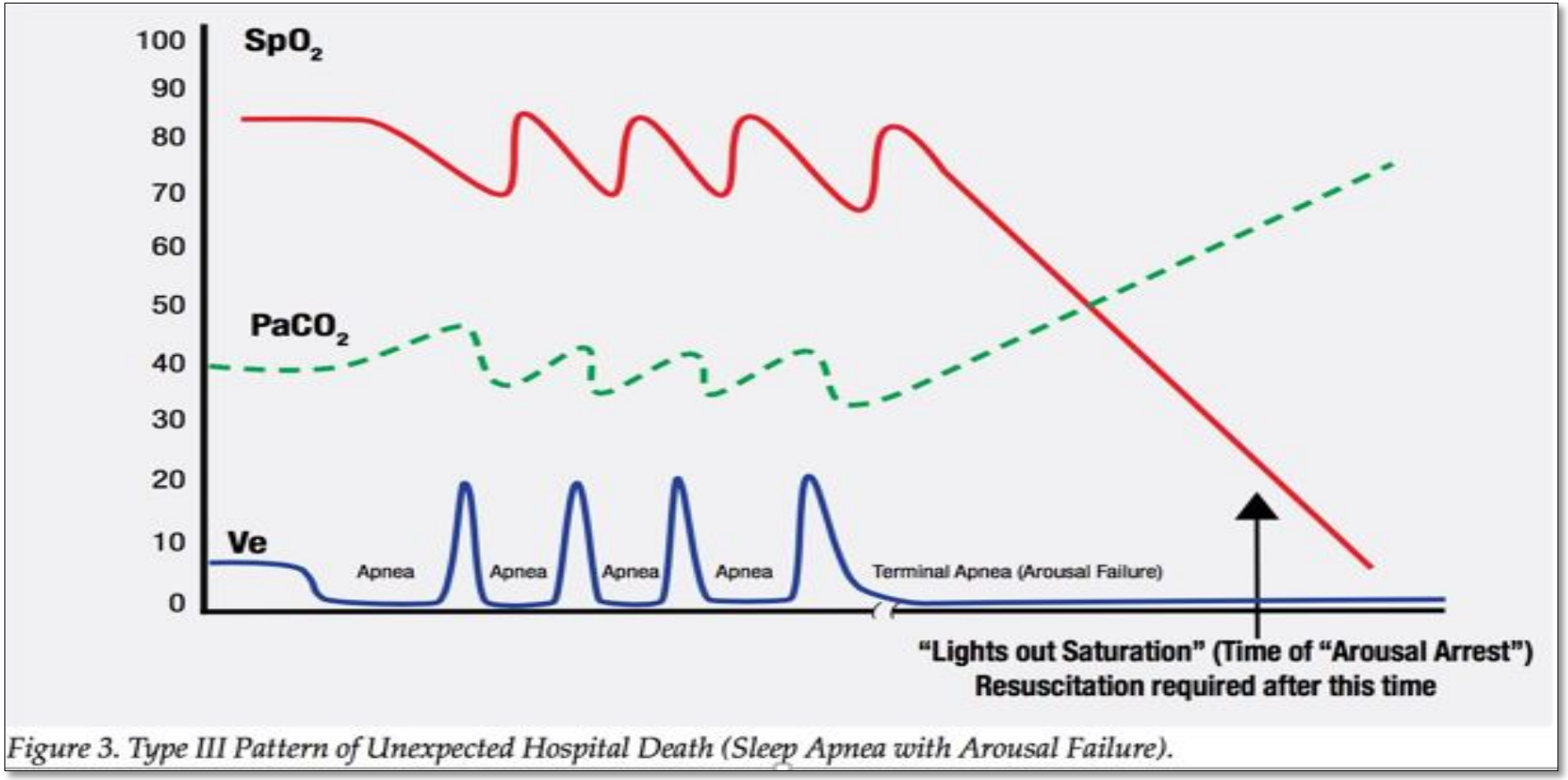


Figure 3. Type III Pattern of Unexpected Hospital Death (Sleep Apnea with Arousal Failure).

(Curry JP, Lynn LA. Threshold Monitoring, Alarm Fatigue, and the Patterns of Unexpected Hospital Death. Anesthesia Patient Safety Foundation Newsletter. 2011;26(2):32-35.)

Strategies to Opioid Associated Respiratory Failure

- Reduce poly-pharmacy
- Prescribing and administration guidance
- Multi-modal strategies
- High-risk assessment
- Sedation assessment
- Monitoring

Delirium

- Definition – acute onset decline in cerebral function
- Hallmarks – Inattention, alteration in arousal (agitation, somnolence or both), decline in cognition
- Opioids are associated with delirium
  - Opioids and metabolites can cause CNS excitation or depression
  - Pain, constipation, respiratory insufficiency are associated with delirium
- Delirium is associated with increased morbidity and mortality

GI Adverse Events from Opioids

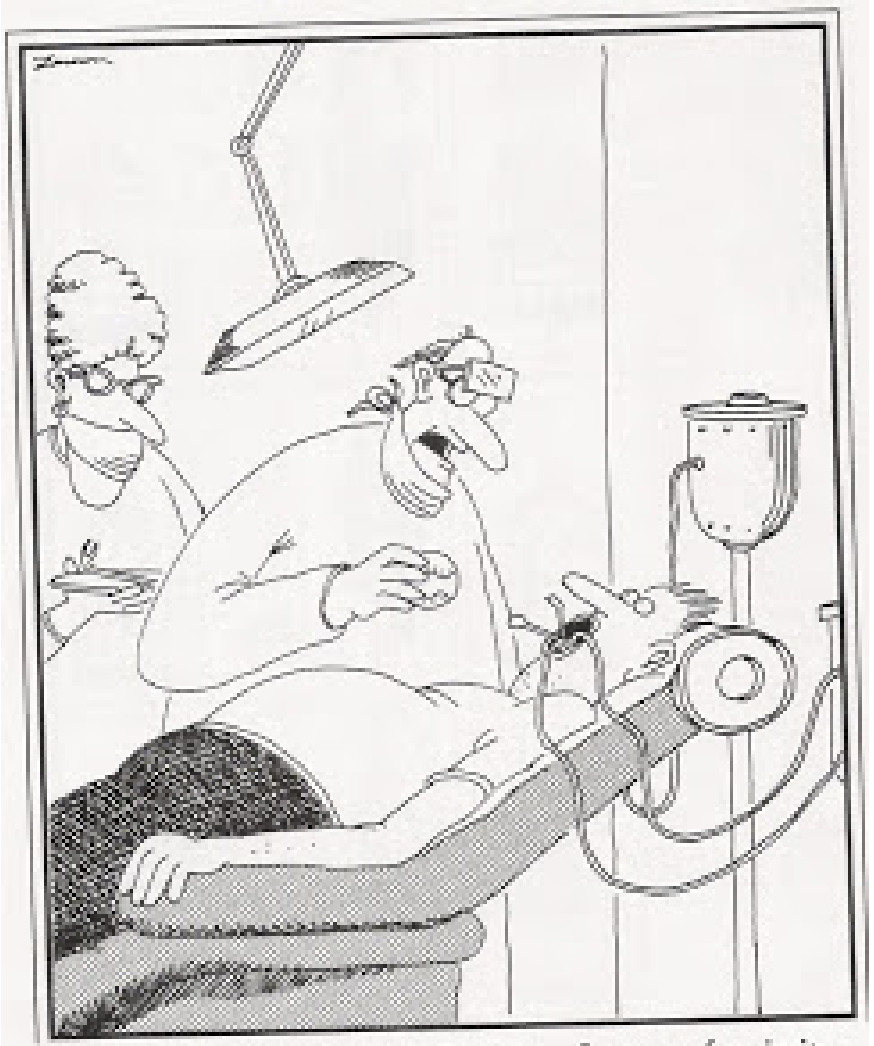
- Constipation – 50-80%
- Nausea
- Vomiting

Avoiding Adverse Events - Best Practices

Policies, caregiver education, standards, work flows and procedures to support:

- Safe prescribing and administration
- Appropriate monitoring
- Risk assessment
- Care transitions
- Patient education

High Risk Patients and Screening



"Now open even wider, Mr. Stevens.... Just out of curiosity, we're going to see if we can also cram in this tennis ball."

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Remember George!

- 59 year-old male who is admitted to the hospital with acute onset severe abdominal pain
- PMH
  - DM 2 for 20 years recently started insulin
  - CAD with DES to LAD 16 months earlier
  - CRI stage 3 from his DM
  - Morbid obesity with a BMI of 36
- Diagnosis - gallstone pancreatitis, worsening renal failure, severe dehydration
- More Details: VS – RR 28 and HR 111
- Placed on Morphine PCA due to severe pain
- What are your concerns?

Obstructive Sleep Apnea (OSA)

- Number one risk factor for opioid-induced respiratory depression and failure
- Increased risk of respiratory depression and hypercarbia/hypoxia due to sedating medications
  - General Anesthesia
  - Opioids
  - Benzodiazepines
  - Others
- Prevalence is about 7 to 22%
- About 75% of these patients are undiagnosed

Obstructive Sleep Apnea (OSA) and Obesity

- Obesity is most common risk factor for OSA (BMI >30 kg/m^2)
- Morbid obesity (BMI>35 kg/m^2) associated with more post operative:
  - Complications
  - Increased length of stay
  - Venous thromboembolism
  - Death
- Obese patients may have obese hypoventilation syndrome (OHS)

Sleep Apnea – Hospital Respiratory Failure and Death

- Medical or Surgical Insult or Trauma (subject to Type I RF)
- Sedating medication (subject to Type II RF)
- Fall asleep unobserved
- Dependent on waking mechanism to keep breathing
- Mechanism suppressed by opioids and/or other medications
- Become apneic and have a rapid respiratory failure and death (Type III RF)

Screening for OSA

- Screening can guide in-hospital pain management and monitoring needs
- Tools
  - **STOP-Bang -** highest sensitivity at 96%, but has a low specificity at 16%
    - Over estimates the likelihood of OSA
    - The most widely used screening tool in the pre-operative area
  - Berlin Questionnaire has better specificity of 35%, lower sensitivity
  - Epworth Sleepiness Scale has lower sensitivity 50% but better specificity at 67%

STOP-Bang

1. **S**noring – do you snore loudly?
2. **T**ired – do you often have daytime tiredness, fatigue or sleepiness?
3. **O**bserved – has anyone observed you stop breathing while you sleep?
4. Blood **P**ressure – do you have or are you being treated for high blood pressure?
5. **B**MI > 35 kg/m^2?
6. **A**ge > 50 years?
7. **N**eck Circumference > 17 in or 40 cm?
8. **G**ender – Male?

Three or more of 8 is a positive screen

High Risk Patients
Chronic Medical Conditions

Remember George!

- 59 year-old male who is admitted to the hospital with acute onset severe abdominal pain
- PMH
  - DM 2 for 20 years recently started insulin
  - CAD with DES to LAD 16 months earlier
  - CRI stage 3 from his DM
  - Morbid obesity with a BMI of 36
- Diagnosis - gallstone pancreatitis, worsening renal failure, severe dehydration
- More Details: VS – RR 28 and HR 111
- Placed on Morphine PCA due to severe pain
- Which of his chronic medical conditions put him at risk for opioid related adverse events?

Peri-operative Patients and Anesthesia

- **ASA Classification**
  - Effectively predict perioperative risk of morbidity and mortality
  - 5 categories
  - 3 thru 5 - increased risk of perioperative morbidity and mortality
  - 3 thru 5 have increased risk of opioid-related sedation and respiratory depression
    - **ASA 3** - severe systemic disease
    - **ASA 4** - severe systemic disease that is a constant threat to life
    - **ASA 5** - moribund and not expected to survive without the operation

High Risk Medical Conditions

- Increase the risk of opioid-induced respiratory depression or other opioid-related adverse events
  - Obesity
  - Pulmonary disease
  - Cardiac disease
  - Renal disease
  - Chronic pain
  - Hepatic disease
  - Substance abuse
  - Major mental illness

Pulmonary Disease

- OSA and OHS
- Patients at increased risk include:
  - Chronic obstructive pulmonary disease (COPD)
  - Restrictive lung disease
  - History of smoking
- Increased risk is due to reduced oxygen reserves and higher retained CO_2 levels

Elderly

Increased risk for opioid-related respiratory depression, sedation and other adverse effects

- Especially with poor health status
- Males higher risk
- Higher risk for hepatic and renal failure
- Higher risk of delirium and other cognitive side effects

Heart Disease

At increased risk for opioid related adverse events

- Poorly controlled heart failure
- Pulmonary edema related to heart failure
- Cardiac disease can compromise hepatic and renal function
- Decreased metabolism and slow metabolite excretion

Renal Disease

At increased risk for opioid related adverse events

- Active metabolites are renally eliminated
- Increased the risk of respiratory depression, sedation and other adverse events related to opioid administration
- Renal failure has risk for respiratory depression, sedation and delirium, **adding opioids will compound the risk**
- Morphine doses should be reduced or not used
- Hydromorphone lower risk but still has active metabolites that can be problematic
- Fentanyl is the safest opioid to use in renal failure for acute pain management

Hepatic Disease

At increased risk for opioid related adverse events

- Increased sedation and respiratory depression from opioids
- Patients with severe hepatic impairment have slower opioid metabolism and accumulation can occur
- Reduced opioid doses and increasing the interval
- Patients with a history of ETOH abuse, ascites and evidence of hepatic failure have been shown to have a higher risk of developing respiratory failure in the hospital, **adding opioids will compound the risk**

Remember Mary!

- 81 year old female admitted to the hospital after a fall with severe right hip pain
- PHM
  - Osteoporosis
  - HTN
  - Early cognitive decline / dementia
- Admission with right sub-trochanteric femur fracture, no other injuries
- More information – received 8 mg morphine in the ED with good pain control
- Upon arrival to medical floor was asleep, easy to arise, and had a RR of 7 while sleeping
- **What chronic medical conditions put Mary at risk for opioid related adverse events?**

Neurologic Disease

At increased risk for opioid related adverse events

- Central nervous system (CNS) injury (trauma, bleed, stroke) makes patients more prone to the adverse effects of multiple drugs including opioids
- Pre-existing cognitive impairment increases the risk of postoperative **delirium** from opioids
- Reducing the dose may be necessary
- PCA or continuous administration of opioids may not be appropriate due to decreased comprehension
- Pain and sedations scales are less reliable

Delirium

- Clinical syndrome marked by a fluctuating acute decline in cognitive function
- Typical are
  - Hallucinations
  - Disorientation
  - Agitation and/or somnolence
- Many causes including disease processes, medications including opioids, pain, urinary retention, constipation
- Treatment is symptomatic and removing insults
- Doubles mortality
- Patients often do not return to baseline

Patients with Chronic Pain

- Chronic pain is a risk factor for difficult-to-control acute pain
- Screen of pre-hospital opioid use
- Previous use and tolerance
- Generally require higher doses
- Considerations:
  - multimodal approach
  - pain specialist
  - monitoring if high dosages of opioids are needed

Substance Abuse History

- Obtain history of current or past legitimate and illicit substance use
- Have the right to have pain management
- Patients with substance abuse currently or history present a pain management challenge
- Tolerance, withdrawal and addiction behavior complicate the acute pain management
- Hospital policies needed to help guide treatment of such patients

Substance Abuse History

- Examples of drug seeking behaviors in the inpatient setting:
  - Use of opioids from outside the hospital
  - Resisting changes to medication dose, route, or drug despite adverse effects
  - Hording opioid medications
  - Injection of an oral opioid formulation
  - Seeking over-sedation
  - Use of opioids for sleep or anxiety management
  - Requesting IV antihistamine administration
  - Altering or tampering with PCA pump

Psychiatric Illness

- Not a reason to withhold treatment
- Under treatment of pain will increase anxiety, depression, psychosis, other symptoms
- Increased risk for comorbid substance disorder
- May experience adverse psychological effects from opioid administration
- Opioid use may mask or mimic mental illness
- Psychiatric consultation may help differentiate opioid intoxication, abuse or dependence from psychiatric illness
- Malingering a diagnosis of exclusion

Safe Prescribing and Administration

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When to Avoid Opioids

- Chronic pain treatment
- Some specific conditions:
  - Pelvic pain
  - Fibromyalgia,
  - Headaches, migraine
  - Low back pain
  - Temporomandibular disease
  - Irritable bowel syndrome
  - Ill-defined pain syndromes
- Consider avoiding when potential present for secondary gain or diversion

Reference: Prescribers Letter. Appropriate Opioid Use. 2016, August 2012

Non-preferred Agents – Hospital/Acute Pain

- Codeine – Risk for toxicity
- Tramadol – Lowers seizure threshold, multiple drug interactions
- Meperidine – Risk for seizures, accumulation in renal insufficiency
- Fentanyl patch – Not for acute pain

Reference: Prescribers Letter. Appropriate Opioid Use. 2016, August 2012

Hospitalized Patient with Uncontrolled Pain – Opioid Naïve

General Considerations:

- Oral route is preferred – slower/safer onset
- Clear Orders
- Pharmacy and Nursing Review
- Use a standard stepwise approach
- Pay attention to dosing intervals

Stepwise approach to uncontrolled acute pain:

PO

> Acetaminophen 1 g PO q 6 hrs scheduled, max 4g/day
- Reduce 50% if patient is >70 yrs

> Ibuprofen 400-800 mg PO q 8 hrs scheduled
- Alternative: Ketorolac 15 mg IV q 6hrs X 24 hrs unless contraindicated
- Reduce/Omit: if patient is >70 yrs, renal insufficiency, coagulopathy, bleeding

> Gabapentin 300-600 mg PO q 6 hrs

> Oxycodone 5-10 mg PO q 3hrs PRN
> Alternative: Hydromorphone (Dilaudid) PO 2-4 mg q 3hrs PRN

> Oxycodone 10-20 mg q 3hrs PRN
> Alternative: Hydromorphone (Dilaudid) 4-8 mg PO q 3hrs PRN

> Consider Pain Service consult

Stepwise approach to uncontrolled acute pain:

IV

> Ketorolac
15-30 mg IV q6 hrs X 24-48 hrs scheduled unless contraindicated

> Provide time limited (e.g. 6-12 hrs) PRN IV rescue doses:

- Hydromorphone

0.2-0.8 mg q 1-2 hours

- Morphine

1-4 mg q 1-2 hours

> Institute IV PCA X 24 hours

- Hydromorphone

0.2-0.3 mg with 6 minutes lockout

- Morphine

1-1.5 mg with 6 minutes lockout

> Consider Pain Service consult

Hospitalized Patient with Uncontrolled Pain – Opioid Tolerant

General Considerations:

- Confirm home dosages
  - Outpatient pharmacy records
  - Opioid prescriber(s)
  - Family members
  - State prescription drug monitoring program database
- Continue home dosages if not at risk and can take PO
- Continue long acting oral opioids
- Be careful with fentanyl patches – do skin exam
- If switching opioids or switching to IV start at 30-50% equianelgesic dose
- If new acute pain may require high dosages

Opioid Conversions

Table 11: Equianalgesic Table (based on single immediate-release dosage forms)

Drug	Parenteral	PO	Parenteral:PO Ratio	Duration of Action (hr)
Morphine	10	30	1:3	3-4
Hydromorphone				
	1.5	7.5	1:5	3-4
Oxymorphone				
	1	10	1:10	3-4
Oxycodone				
	N/A	20-30	—	3-4
Codeine	130	200 NA	1:1.5	3-4
Hydrocodone				
	—	30	—	3-4
Meperidine				
	75	300**	1:4	2-3
Fentanyl				
	0.1	—	—	1-3

Duration of action based on use of short-acting formulations.

NA = equianalgesic data unavailable. Codeine doses should not exceed 1.5mg/kg because of an increased incidence of side effects with higher doses.

** Avoid multiple dosing with meperidine (no more than 48 hrs or at doses greater than 600mg/24hrs). Accumulation of toxic metabolite normeperidine (half-life 12-16 hrs) can lead to CNS excitability and convulsions. Contraindicated in patients receiving MAO inhibitors. Oral meperidine is not recommended due to very poor oral bioavailability.

Adapted from Gordon DB, Stevenson KK, Griffie J, et al. Opioid equianalgesic calculations. J Palliat Med. 1999;2(2):209-218.

Patient Controlled Analgesia (PCA)

- Allows patients to self-administer small doses of opioids intravenously via programed pump
- Drug delivered by patient at timed intervals – Patient Initiated Dose (PID)
- Allows patients to have control over their opioid delivery without waiting for the nurse to administer it
- Designed to maintain a desired level of analgesia with minimal side effects
- Improves patient satisfaction
- Not demonstrated to improve pain control or safety
- Multiple respiratory failure deaths due to poor patient selection, improper prescribing and inadequate monitoring

PCA Safety Considerations

- Careful patient selection
- High risk screening
- Administration policies and procedures
- Monitoring policies and protocols
- Nursing education
- Require prescribing via protocol via protocol
- Consider pharmacy and/or anesthesia oversight
- Basal rate – not for opioid naïve
- Not for patients with cognitive impairment
- Family education
- Conversion to PO when can take PO

PCA Starting Parameters

Doses, lockouts and limits must be adjusted based on the required loading dose, age, state of health and presence of opioid tolerance

Patient Population	Drug	Usual Starting Dose after Load	Usual Dose Range	Usual Lockout (Minutes)
Pediatric (less than 50kg)	Morphine (1mg/mL)	0.02mg/kg/dose	0.01-0.03 mg/kg/dose	10
	Hydromorphone (0.2mg/mL)	0.003-0.004 mg/kg/dose	0.003-0.005 mg/kg/dose	10
	Fentanyl (50mcg/mL)	0.5-1 mcg/kg/dose	0.5-1 mcg/kg/dose	10
Adult – opioid naïve	Morphine (1mg/mL)	1mg	0.5-2.5mg	10
	Hydromorphone (0.2mg/mL)	0.2mg	0.05-0.4mg	10
	Fentanyl (50mcg/mL)	25mcg	10-25mcg	10
Adult – opioid tolerant*	Morphine (1mg/mL)	2mg	0.5-5mg	10
	Hydromorphone (0.2mg/mL)	0.4-0.5mg	0.2-0.5mg	10
	Fentanyl (50mcg/mL)	25mcg	10-50mcg	6

**This dose may vary based on a person's chronic opioid regimen. Consider restarting a person's long-acting opioid regimen ASAP or replace it with the use of a basal rate (continuous infusion).*

Safe Prescribing
Interactions with Other Medications

Additive Sedation Risk

- Be aware of the sedation potential of other medication classes
- Combinations can cause additive sedation and respiratory depression
- Awareness of the sedating potential of different medications and classes
- Frequent monitoring of sedation level is necessary in these patients

Benzodiazepines with Opioids

- GABAA receptors concentrated in the brainstem respiratory center
- Combined with opioids → synergistic respiratory inhibition, many cases of fatal respiratory failure
- Chronic benzodiazepine therapy prior to coming into the hospital maintained because of potential for withdrawal
- In the hospital indications include preoperatively, as a premedication, anxiety, sleep, muscle spasm
- Exercise caution with opioids, especially if naïve to both classes of medications

Benzodiazepines

- Alprazolam
- Lorazepam
- Clonazepam
- Diazepam
- Temazepam
- Midazolam

Gabapentinoids with Opioids

- Indications: Anticonvulsant, neuropathic pain, multimodal pain regimens and other off label usages
- Can lead to significant postoperative sedation
- Can contribute to delirium
- Care must be taken during initiation and titration
- Situations that call for aggressive monitoring include:
  - Immediately after surgery when other sedatives are used
  - Effects of anesthesia are lingering, elderly, renal failure

Muscle Relaxants with Opioids

- All muscle relaxants have sedative effects
- Additive sedation with opioids and other sedating medications
- Higher risk patients include:
  - Elderly
  - Opioid-naïve patients
- Common muscle relaxants include:
  - Cyclobenzaprine
  - Baclofen
  - Methocarbamol
  - Tizanidine
- Carisoprodol is a precursor to a barbituate and should be avoided

Antidepressants with Opioids

- All have some sedation potential, especially with initiation of therapy
- Tricyclic antidepressants are most sedating and can be used for neuropathic pain
- Additive sedation with opioids
- Duloxetine and venlafaxine may have less sedative effects as pain adjuncts
- SSRIs lack analgesia effects and are not generally used as pain adjuncts

Antipsychotics with Opioids

- Very Sedating “Major Tranquilizers”
- Common antipsychotics that are used in the hospital include:
  - Haloperidol
  - Risperidone
  - Olanzapine
- Many in hospital indications other than psychosis
- These medications should be used carefully in conjunction with opioids

Pain Adjuvants

- Ketamine is often used for perioperative pain
  - No respiratory depression
  - Dose dependent sedation
- Clonidine or dexmedetomidine
  - Dose dependent sedation
  - Can induce delirium

Antihistamines with Opioids

- Diphenhydramine and hydroxyzine - itching, sleep, nausea and medication reactions
- Very sedating
- Combined respiratory depressant effect with opioids
- Commonly prescribed for opioid related pruritus - little clinical evidence

Antiemetics with Opioids

- Nausea is a common opioid adverse event
- Commonly prescribed hospital agents include:
  - Promethazine
  - Prochlorperazine
  - Droperidol and Haldoperidol
  - Both very sedating with potential respiratory depression
- Ondansetron may be an alternate for nausea and vomiting due to its less sedative properties

Safe Prescribing
Multi-Modal Approaches

Remember Mary!

- 81 year old female admitted to the hospital after a fall with severe right hip pain
- PHM
  - Osteoporosis
  - HTN
  - Early cognitive decline / dementia
- Admission with right sub-trochanteric femur fracture, no other injuries
- More information – received 8 mg morphine in the ED with good pain control
- Upon arrival to medical floor was asleep, easy to arose, and had a RR of 7 while sleeping
- **What post op pain control strategies can be employed to decrease risk of opioid related adverse events?**

Multimodal **Analgesia**

- Combine analgesic agents or techniques
- Take advantage different mechanisms to:
  - Improve pain control
  - Reduce opioid requirements
  - Reduce opioid-related adverse effects
- Multimodal analgesia utilizes non-opioid pain medications, regional anesthesia, alternative delivery techniques and non-pharmacologic adjuvants
- Allows lowest acceptable dose of opioid
- Consider especially in opioid naïve patients

Case Example

A 46 year old male with PHM of DM II is admitted for left toe infection and cellulitis

- He complains of lower leg pain
- The patient received IV morphine in the ER , the patient indicates it relieved his pain.
- Acetaminophen/hydrocodone started by hospitalist

Case Continued – more history

- The patient is diabetic and has had numbness in his hands and feet for a long time. He also reports that he has had tingling and pain in his legs and feet for a long time
- He has a history of alcohol abuse

Case Continued – Treatment Plan

- Patient indicated pain was not controlled
- Is this untreated neuropathic pain?
- Gabapentin was added to his regimen
- Patient’s pain was controlled

Multimodal Pain Strategies
Anesthesia Society of America Task Force 2012

Post-surgical patient recommendations:

- Scheduled acetaminophen and NSAID be used unless contraindicated
- Regional anesthesia should be used
- Gabapentin or Pregabalin can be added

Stepwise Multimodal Pain Therapy

Pasero C. *Pain Manag Nurs*. 2012;13(2):107-124.

Step 1	Mild Postoperative Pain	Nonopioid analgesics (acetaminophen, NSAID) and Local anesthetic infiltration
Step 2	Moderate Postoperative Pain	Nonopioid analgesics (acetaminophen, NSAID) and Local anesthetic infiltration and Intermittent doses of opioid analgesics
Step 3	Severe Postoperative Pain	Nonopioid analgesics (acetaminophen and NSAID) and Local anesthetic infiltration and Intermittent doses of opioid analgesics for breakthrough pain and Local anesthetic peripheral nerve block (with or without catheter) for continuous severe pain or Modified-release opioid analgesics for continuous pain

Multimodal Pain Strategies: Non-opioid alternatives

Before or in conjunctions with opioids

Antidepressants

- Tricyclics, amitriptyline
- SNRIs, Duloxetine

Anticonvulsants

- Gabapentin and Pregabalin

Muscle relaxants

- Baclofen
- Tizanidine

Interdisciplinary Care and Multimodal Pain Strategies

- Physical and occupation therapy
- Manipulation
- Massage
- Ice
- Music therapy
- Acupuncture

Key Interventions to Reduce Adverse Events Associated with Opioids in the Hospital – Patient Monitoring

Systems/Team Based Approach

- Making the Subjective Objective
- Safety is the First Goal
  - Reassess after Adverse Events
  - Develop Recurring Education for Staff
- Team Based Approach to Assessment
  - Nurses, Techs, Physicians, Pharmacists
  - Equal Responsibility for Patient Safety
  - Communication Bidirectional
- Prevention of Adverse Events
  - Know the local complication rates
  - Prevention is better than Forgiveness
- Visible warning for Rapid Response Teams

Objective Assessments

- Vital signs (blood pressure, temperature, pulse, respiratory rate)
- Pain level “5th vital sign”
- Respiratory effort/quality
- Sedation level
- Functional level

Functional Goals

- Establish functional goals from the patient for pain control
  - Complete ADLs independently
  - Tolerate physical therapy
  - Tolerate dressing changes/wound care
  - Transition to outpatient treatment modalities
- Limit opioid use based on functional goals, not just pain scores.

Serial Sedation Assessments

- A standard scale/policy/process is recommended when assessing patients on opioids
- Validated scales:
  - Pasero Opioid-induced Sedation Scale (POSS)
  - Richmond Agitation Sedation Scale
  - Ramsey Sedation Scale and Comfort Scale.
- POSS most common:
  - Easier to use
  - High nursing confidence
  - More usefulness for clinical decision-making
  - Easy to place in EHR

POSS

5-point nursing assessment of opioid-related sedation

- S = Asleep but easy to arouse
- Level 1 = Awake and alert
- Level 2 = Slightly drowsy, easily aroused
- Level 3 = Frequently drowsy, arousable, drifts off to sleep during conversation
- Level 4 = Somnolent, minimal or no response to verbal or physical stimulation

POSS

POSS – Suggested Actions

- S = Asleep but easy to arouse – *Acceptable; no action necessary; may increase opioid dose if needed*
- Level 1 = Awake and alert – *Acceptable; no action necessary; may increase opioid dose if needed*
- Level 2 = Slightly drowsy, easily aroused – *Acceptable; no action necessary; may increase opioid dose if needed*

POSS – Suggested Actions

- Level 3 = Frequently drowsy, arousable, drifts off to sleep during conversation – *Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25 percent to 50 percent or notify prescriber or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing non-opioid, such as acetaminophen or an NSAID, if not contraindicated.*
- Level 4 = Somnolent, minimal or no response to verbal or physical stimulation – *Unacceptable; stop opioid; consider administering naloxone; notify prescriber or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.*

Serial Sedation Assessments: Best Practices

- Paucity of good studies/evidence
- When to initiate assessment
  - Coincide with the time to achieve peak effects
  - 15 to 30 minutes after an initial parental opioid
  - One hour after an initial oral dose
- Consider “dose stacking” and need for continued assessment

Serial Sedation Assessment

Policy and procedure considerations include

- Type of pain
- Opioid delivery – oral, parental, PCA
- Implement POSS and actions – empower nurses
- Other sedating medications
- Naive or tolerant patient
- Adequacy of initial pain relief
- Presence of side effects
- Comorbidities – especially OSA
- Changes in clinical status
- Other monitoring modalities employed
- Respiratory status
- When to notify providers

Serial Sedation Assessment

Policy and Procedure considerations include (continued):

- Frequency – less frequently after patient has exhibited good pain control without adverse effects after 24 hours
- Shift changes to establish a baseline and promote continuity of care
- Assess along with VS, pain level, respiratory effort/quality, hypoxia, other opioid related adverse events
- Consider continuous monitoring of oxygenation (pulse oximetry) rather then intermittent measurement

Clear Communication

- TeamSTEPPS
- Always Safe Culture

Clear Communication

- TeamSTEPPS
- Always Safe Culture
- Develop scripting for nurses
- Involve pharmacy in screening dose conversion
- Share the responsibility so burden doesn’t fall on the provider alone

Case

A 40 year old female was admitted for acute on chronic pancreatitis.

- Chronic opioid therapy,
- Pain is a 10 out of 10 in the ER
- Admitted for IV fluids and pain control
- Late in the evening you get a call from the patient’s nurse
- Rapid response called because patient was not arousable
- RR is difficult to determine
- Non-responsive to voice and touch
- You immediately ask for a oximeter to be placed
- Oxygen Saturation is 70%

What do you do next?

Case Continued

Having excellent clinical knowledge and training you order:

- High flow oxygen via venti mask
- “Naloxone 2mg IV stat!”

Patient awoke, oxygen saturations improved and patient became agitated

- This was a real case of a medication error
- Patient was on Morphine SR 30 mg bid at home
- Transcribed wrong in hospital as 300 mg bid

Naloxone

- Opioid antagonist:
  - Reverses opioid sedation and respiratory depression
  - Treat opioid side effects as a continuous infusion
  - Sometimes used to rule out opioid as a cause of decreased level of consciousness and respiratory depression
  - Examination of naloxone administration may uncover deficits in processes and provide targets for improvement in opioid safety

Guidelines - Naloxone Administration

- Patients should meet 2 of the 3 criteria
  - Sedation scale = 3 (Somnolent; Difficult to arouse)
  - RR <8
  - Pinpoint pupils

Naloxone – Review of Cases

- In your facility you might uncover:
  - Improper prescribing and administration
  - Inadequate policies, procedures or compliance
  - Lack of pharmacy safety checks
  - Lack of provider knowledge about potency
  - Lack of nursing knowledge of sedation and respiratory assessment
  - Lack of high risk screening

Naloxone – Review of Cases

- In your facility you might uncover (continued):
  - Deficits in sedation monitoring
  - Excess co-administration of CNS depressants
  - Breakdowns in communication
    - Medication reconciliation
    - Opioid tolerance
  - Overreliance on opioids for pain control
  - Inadequate use of multimodal analgesia

Pulse Oximetry

- Measures the oxygen saturation of the patient
- Useful - but major limitations, and can be misleading
- **Limitations**
  - **Oxygen saturation is a late indicator of respiratory compromise**
  - Patient can have normal values but have compromised ventilation
  - A patient may have poor minute ventilation – respiratory compromise - and normal oxygen saturation
  - Patient may continue to be given pain medication and eventually have respiratory arrest/failure
  - **Supplemental oxygen make this situation worse**
  - Alarms are not specific – alarm fatigue

Supplemental Oxygen

- Routine use of supplemental oxygen is discouraged
- Hypoxia is a late sign of respiratory compromise
- Indication for supplemental oxygen is hypoxia, this makes the patient high risk!
- Hypoxia is further delayed by supplemental oxygen
- When supplemental oxygen is needed consider monitoring of ventilation – earlier sigh of respiratory deterioration
  - Assess breathing
  - Estimate arterial carbon dioxide concentrations
- The nursing assessment should include respiratory rate, quality and depth of respiration for a full minute and serial sedation assessments

Interventions to Reduce Adverse Events:

Type II Pattern of Unexpected Hospital Death – Limitations of Oximetry

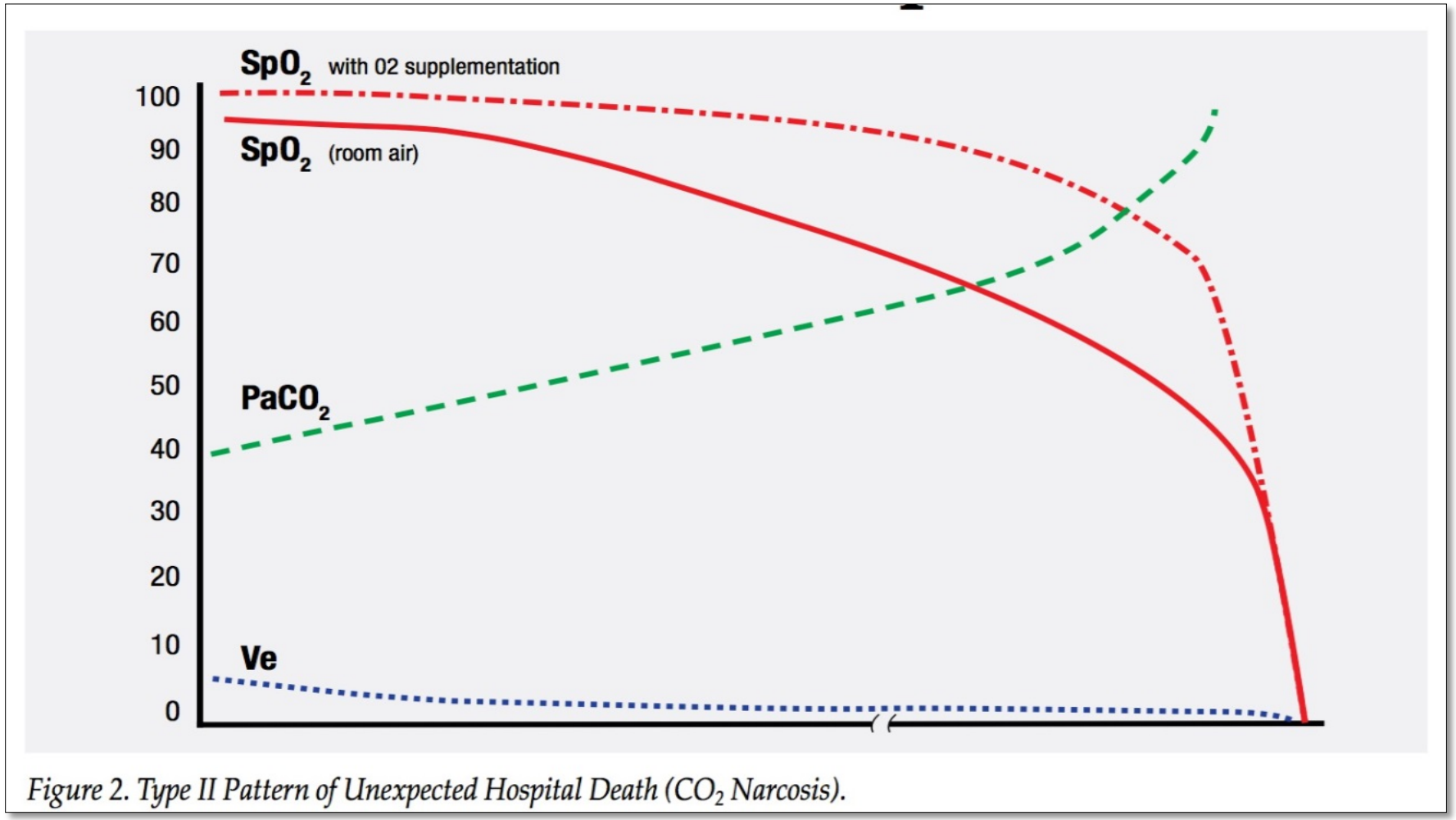


Figure 2. Type II Pattern of Unexpected Hospital Death (CO_2 Narcosis).

(Curry JP, Lynn LA. Threshold Monitoring, Alarm Fatigue, and the Patterns of Unexpected Hospital Death. *Anesthesia Patient Safety Foundation Newsletter*. 2011;26(2):32-35.)

Capnography

- Capnography is meant to assess ventilation
- Ventilation is a earlier marker for respiratory compromise
- Capnography measures end tidal CO_2
- Estimate of arterial CO_2 concentration
- Limitations
  - Inconsistent results
  - Alarm fatigue
  - Uncomfortable for patients
  - Staff lack of familiarity
  - Difficult to interpret
  - Type III respiratory failure can be a late finding
  - Alarm fatigue

Type III Pattern of Unexpected Hospital Death – Limitation of Capnography

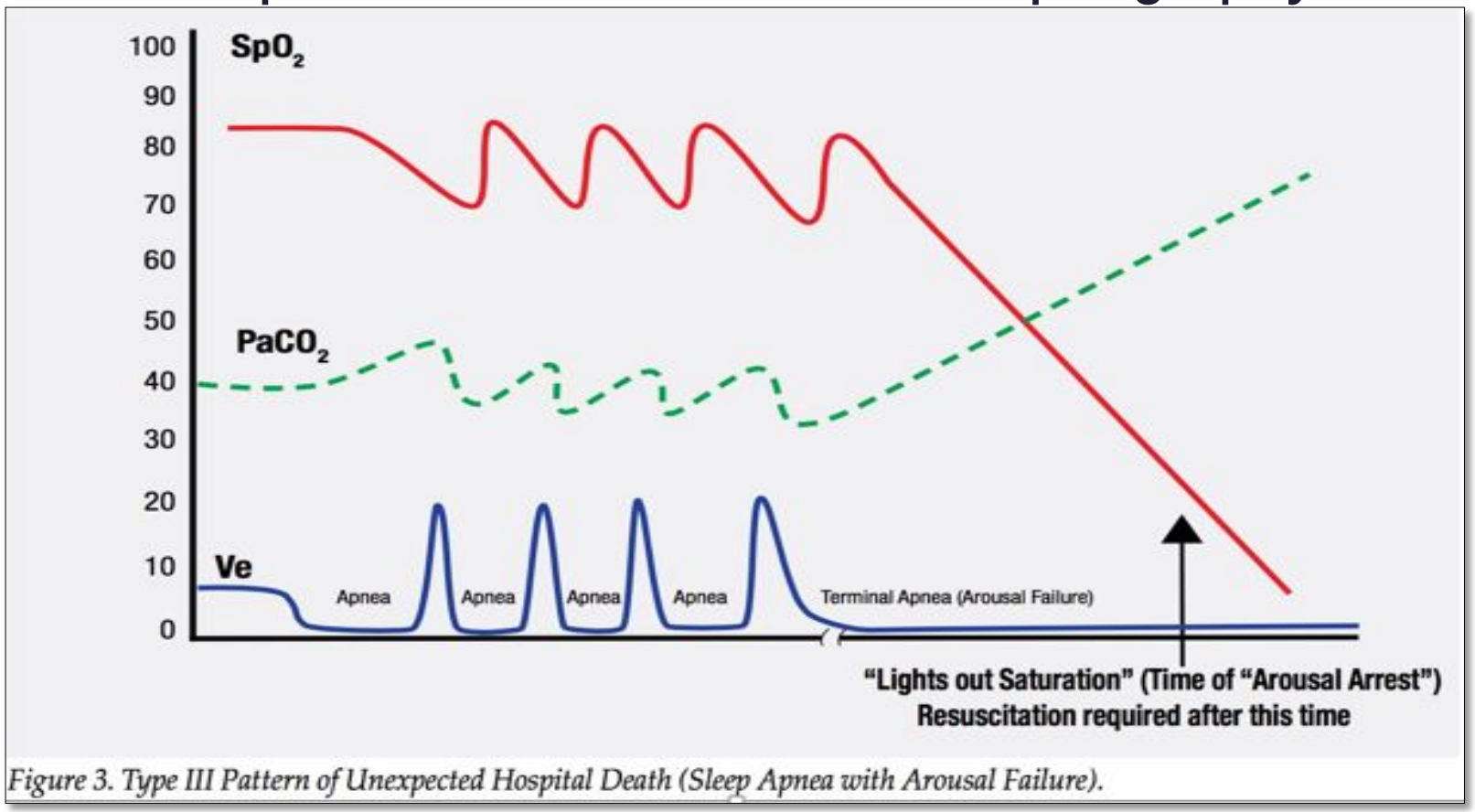


Figure 3. Type III Pattern of Unexpected Hospital Death (Sleep Apnea with Arousal Failure).

(Curry JP, Lynn LA. Threshold Monitoring, Alarm Fatigue, and the Patterns of Unexpected Hospital Death. Anesthesia Patient Safety Foundation Newsletter. 2011;26(2):32-35.)

Alarm Fatigue

- Pattern:
  - Care provider responds to multiple alarms multiple times in a short time frame No significant clinical event is noted and the alarm is reset
  - After a certain number of events, complacency sets in and the response to an alarm is delayed or ignored
  - Can be precipitated by incorrect or “one size fits all” thresholds.
- Can lead to a respiratory event

Alarm Fatigue Leading to Type III Respiratory Failure

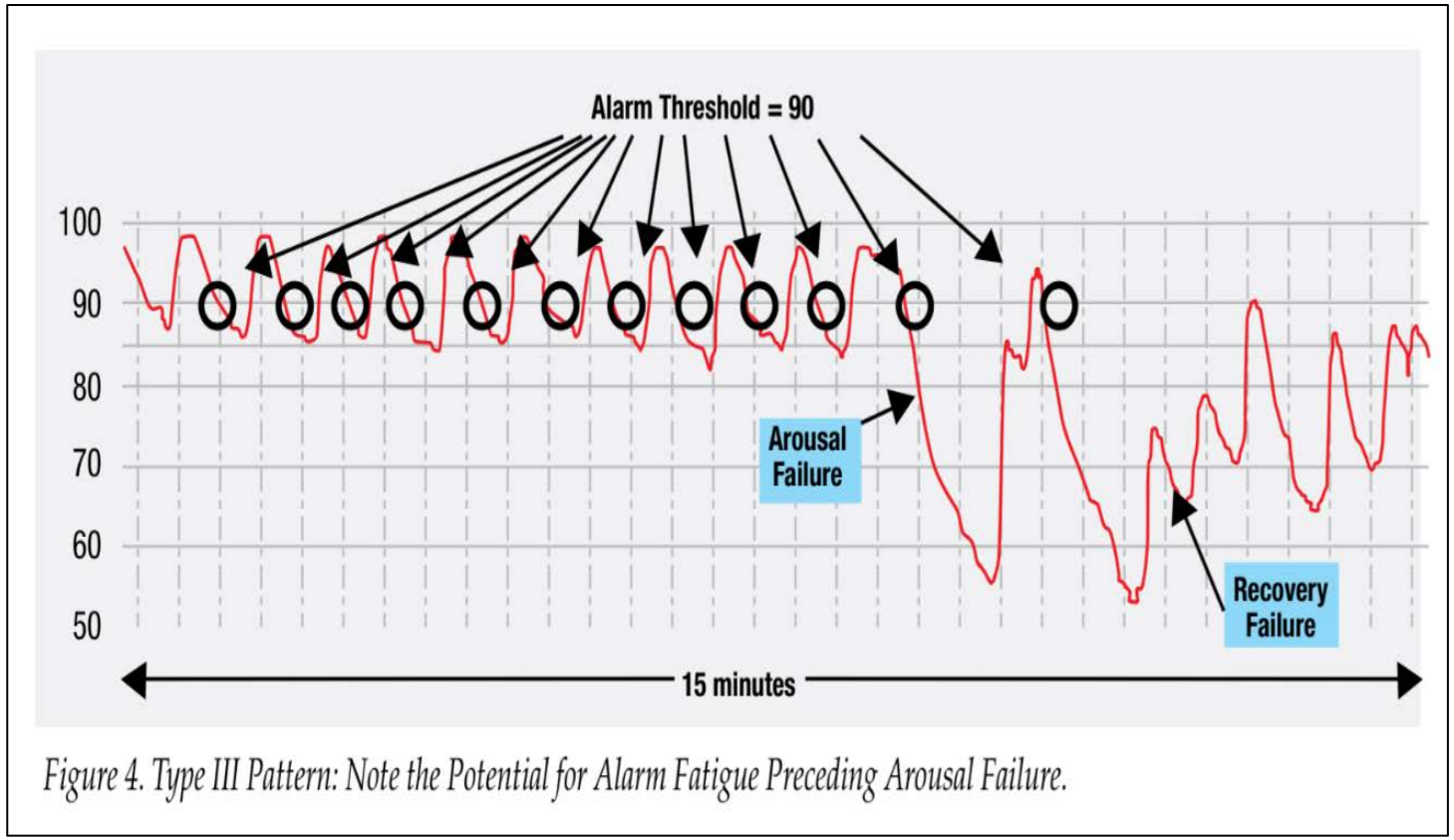


Figure 4. Type III Pattern: Note the Potential for Alarm Fatigue Preceding Arousal Failure.

(Curry JP, Lynn LA. Threshold Monitoring, Alarm Fatigue, and the Patterns of Unexpected Hospital Death. Anesthesia Patient Safety Foundation Newsletter. 2011;26(2):32-35.)

Alarm Fatigue and Single Threshold Alarms

- Most current patient monitoring systems have single-value threshold alarms
- For example - pulse oximetry that is set to alarm below 90%
- Single-value threshold alarms often have difficulty distinguishing between meaningful and non-meaningful declines → nuisance alarms
- Multiple monitor systems in concert may help improve the reliability / specificity of the alarm system
- However, more alerts will also correlate with more false alarms and alarm fatigue

Potential Solutions to Alarm Fatigue

- Modified Early Warning Score (MEWS)
  - Physiologic score for post surgical patients
  - Prevent delay in intervention or transfer of critically ill patients
  - Combine the threshold from multiple monitors and physiologic parameters to maintain sensitivity but reduce false positives
  - Limitation – simple addition may still not adequately represent the complex physiologic process that is occurring in respiratory depression, static
- **Future development** – Technologies that monitor for patterns of changes in physiologic parameters over time to predict declines based on trend analysis

Rapid Response System (RRS)

- 3 components:
  - Afferent Limb – criteria for activating the system
    - Hospital set triggers – include vital signs, decreased urine output, change in mental status, chest pain, change in mental status
    - Empowerment of bedside care givers and families
    - **Limitation**: It requires clinicians to proactively identify deteriorating patients

Rapid Response System (RRS)

- 3 components continued:
  - Efferent Limb – Response, Medical Emergency (MET) Team Activation
    - Team members based on hospital preferences, usually critical care experienced nurses
    - Respond with standardized assessment and care protocols
  - Quality Improvement based on data analysis and interventions

Patient Education & Care Transitions

Patient Education: Basics for Clinicians

Key Elements to Discuss When Prescribing Opioids at Discharge

- Name of the medication, brand and generic
- Route, Dose, Schedule, Tapering, Duration
- Principle Risks
- Side effects and what the patient needs to do to lessen them

Empower a multidisciplinary approach to help patients make the transition at discharge

- Physicians
- Pharmacy
- Nursing

Discuss Key Risks

- Potential for tolerance
- Physical dependency
- Addiction
- Withdrawal symptoms
- Discuss their home situation/Safety
  - Children and their ages
  - Discuss storage and security

What Patients Need to Know

- Address 2 key questions:
  - How will this medication effect…?”
  - “What are the Goals for therapy?”
- Cognition, ask patients:
  - How do you get to work?
  - What do you do at work?
- Alert them to the cognitive and sedatory side effects
- Confirm that the patient has a good understanding – use “teach-back”
- Give time for patients to ask questions
- Give them a way to contact you

Age Specific Risks

- Elderly
  - Risks of falls
  - Memory issues
  - Hallucinations - Delirium
  - Bladder and bowel changes/monitoring
- Young Adults
  - Risk of misuse
  - Nausea and vomiting
  - Sedation

Hospitalist Handoff to Primary Care Physician

- Opioids are High Risk Medication
- PCP needs to know
  - Indication
  - Medication, douse, route, duration
  - Tapering schedule
  - Your concerns for risks of adverse events
  - Need for refills
  - Need for specialty referral

Overview of Quality Improvement and Methodologies for Implementation

Quality Improvement (QI) in Healthcare - Overview

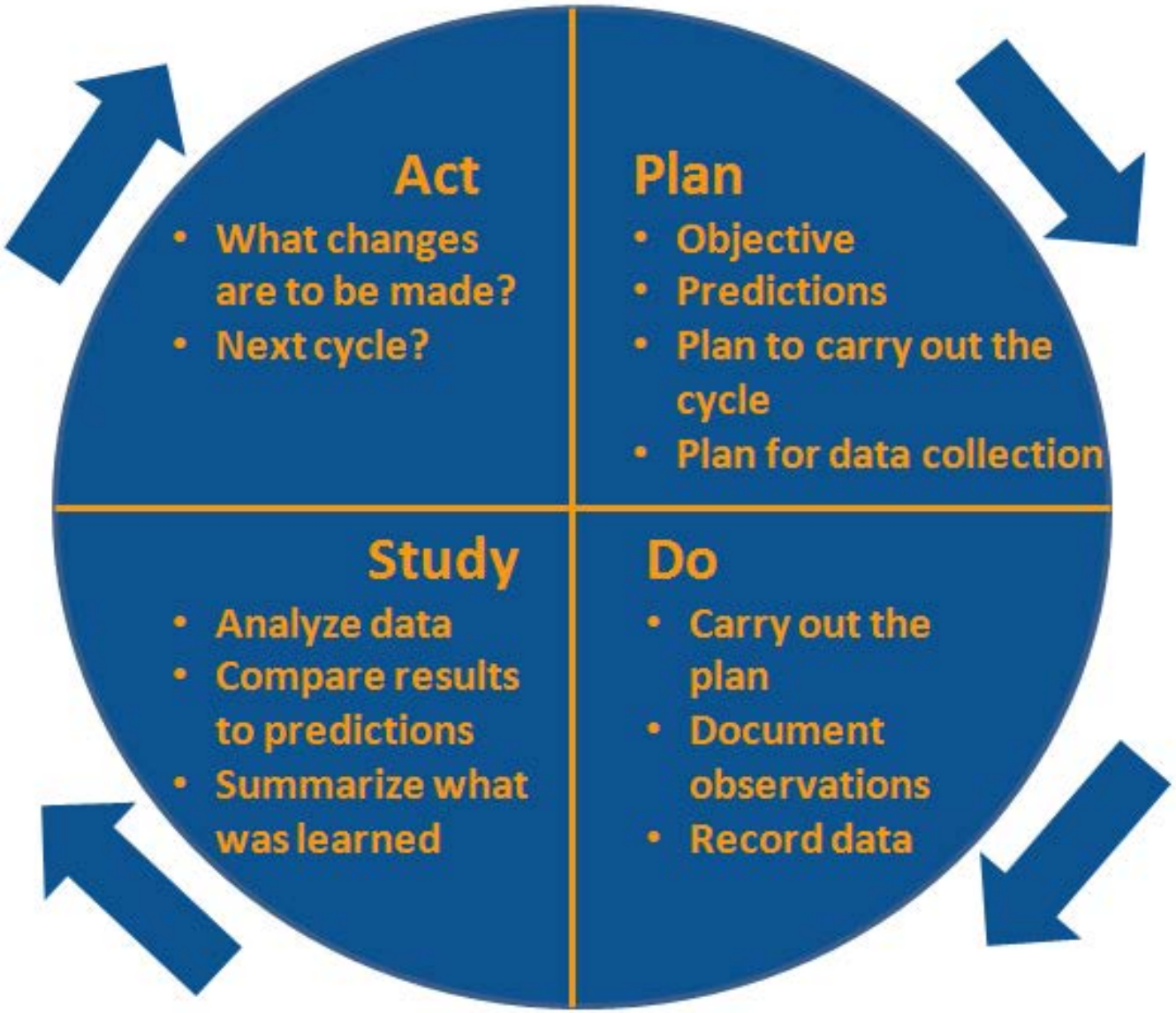
- QI is a systemic approach to planning and implementing continuous improvement in patient care)
- Requirements:
  - Organizational support
  - Sustained leadership
  - Training and support
  - Measurement and data collection systems
  - Aligned incentives
  - Cultural receptivity to change

Weiner, 2016

QI Overview (Continued)

- Successful QI program will focus on:
  - QI work as systems and processes
  - Focus on patients
  - Focus on being part of the team
  - Focus on use of the data
- Challenges:
  - Finite resources
  - Lack of institutional leadership support
  - Limitation in an ability to collect data
  - A deficit in staffing expertise

QI Process


Act
What changes are to be made?
Next cycle?
Plan
Objective
Predictions
Plan to carry out the cycle
Plan for data collection
Study
Analyze data
Compare results to predictions
Summarize what was learned
Do
Carry out the plan
Document observations
Record data

Development of RADEO Implementation Guide

Development of the RADEO Guide

- SHM received funding to develop the RADEO guide
- Step-by-step QI to improve opioid prescribing in the hospital
- SHM Assembled the Expert Panel
  - Interviewed candidates about their expertise/experience in quality improvement and pain management
  - Contributors/co-authors - diverse interdisciplinary team
    - Nurse Anesthetist
    - Anesthesiologist
    - Pain Management Physician
    - Hospitalist
    - Nurse Practitioner

Development of the RADEO Guide

Process

- The panel developed a thorough outline to inform the organization of the text
- The expert panel conducted extensive literature review

Development of the RADEO Guide

RADEO

- Reviews the key components of a quality improvement
- Suggests specific applications with reference to RADEO
- Suggests specific QI steps including assembling a project team, gaining support and identifying metrics
- Defines key interventions
- Defines accompanying metrics to measure interventions
- Provides evidence review and evidence-based tools

Lessons Learned from Implementation to Date

Lessons learned from the pilot program will inform the implementation of the program at 10 additional sites beginning in November 2016

SHM has identified several lessons to date:

- Institutional support is essential for success
- Sites may leverage existing interventions and use mentored support to build on those initiatives to achieve additional outcomes
- Gaining approval for implementation of processes or interventions can be slow and incremental
- The data collection process can be arduous and timely
- The site visit is a critical component for solidifying the mentor/mentee relationship and building momentum for program implementation
- Order sets implementation can be an extensive process and timelines can be unpredictable for approval. When approved and loaded into the EMR; there is potential for providing improved standard care

Key Takeaways

Key Takeaways from Todays' Training

- Opioids are most frequently prescribed medication in the hospital, and second most common cause of adverse events in the hospital
- ADEs affect nearly 5% of hospitalized patients
- Adverse events related to opioids are costly, estimated at $2 billion
- Many systems have shown a decrease in patient-related harm with the implementation of rigorous quality improvement programs to improve opioid prescribing and administration

Key Takeaways from Todays' Training

- OSA is the number one risk factor for opioid-induced respiratory depression
- Screening for OSA can guide in-hospital pain management and monitoring
- STOP-Bang is the best screening instrument for OSA
- OSA is associated with arousal dependent respiratory failure (Type III) - sudden onset with and rapid decline and death

Key Takeaways from Todays' Training

- Chronic medical conditions increase the risk of opioid-induced respiratory depression and adverse events
  - Obesity
  - Cognitive impairment
  - Pulmonary disease
  - Cardiac disease
  - Renal disease
  - Chronic pain
  - Hepatic disease
  - Substance abuse
  - Psychiatric illness

Key Takeaways from Todays' Training

- Use the lowest acceptable dose to limit the risk of adverse events
- Assess additive sedation risk when combining opioids with other sedating non-opioid medications
- Multimodal techniques improve analgesia and reduce opioid requirements and the resulting opioid-related adverse effects

Society of Hospital Medicine

Key Takeaways from Todays' Training

- POSS is the most commonly used sedation scale
- Monitoring has limitations including
  - Alarm Fatigue
  - Single thresholds
  - Static
- Hypoxia is a late indicator of respiratory failure
- Avoid non-indicated supplemental oxygen
- Multiple monitor systems, in concert, even when each is set to a single threshold

Key Takeaways from Todays' Training

- An overall risk assessment for opioid-related respiratory depression in a hospitalized patient is not well studied
- New technologies may focus on physiologic trends for early identification
- Early identification of high risk patients can inform prescribing and monitoring
- Communication, policies, standardized processes and care coordination are essential to the safe care of these complex patients
- Multi-disciplinary patient education and discharge should discuss key items when prescribing opioids

Questions?

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